Janssen Research & Development *

Clinical Protocol

A Phase 2, Multicohort Open-Label Study of JNJ-68284528, a Chimeric Antigen Receptor T cell (CAR-T) Therapy Directed Against BCMA in Subjects with Multiple Myeloma

CARTITUDE-2

Protocol 68284528MMY2003; Phase 2
AMENDMENT 6/USA-1

JNJ-68284528(ciltacabtagene autoleucel)

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US sites of this study will be conducted under US Food & Drug Administration IND regulations (21 CFR Part 312).

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GCP Compliance: This study will be conducted in compliance with Good Clinical Practice, and applicable regulatory requirements.

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PROTOCOL AMENDMENTS

DOCUMENT HISTORY	
Document	**Date**
Amendment 6/USA-1	23 October 2023
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Amendment 6	14 June 2022
Amendment 5	31 January 2022
Amendment 4	24 May 2021
Amendment 3	13 July 2020
Amendment 2	23 March 2020
Amendment 1	31 October 2019
Original Protocol	07 June 2019

Amendment 6/USA-1 (23 October 2023)

Overall Rationale for the Amendment: The reason for this amendment is to incorporate all relevant information pertaining to Cohort G and Cohort H, with the goal to supplement USA enrollment in these populations and generate key data with daratumumab-based on induction regimens prior to cilta-cel. These cohorts of subjects with NDMM are similar to those existing in the current protocol Cohorts F and E, as well as to those in CARTITUDE-5 and CARTITUDE-6 studies, registered as NCT04923893 and NCT05257083, respectively.

Information related to these 2 new cohorts is not added in the main body of the Amendment, but rather can be found in Part B, under Section 18 of the current protocol. Therefore, unlike in Amendments 1 to 6/EEA-1, no Amendment Table for Part B is provided in the Protocol Amendment Section. Only the Synopsis in the main body includes information related to Cohort G and Cohort H.

If a subsection in Section 18 contains general information that is applicable to all cohorts of this study, ie, Cohort A through Cohort F, as well as Cohorts G and H, a link is provided back to the text in the main body of the protocol.

- All attachments specific to Cohort G and Cohort H have a modifier “B”, ie, Attachment B 1, etc. They can be found in the *Attachments Specific to PART B* section.
- All Attachments that are applied to all cohorts of this protocol, ie, Cohort A though Cohort H, are provided in the *Attachment* section that follows the References section.

Only selected United States sites will participate in Part B.

Amendment 6/EEA-1 (17 August 2023)

Overall Rationale for the Amendment: The reason for this amendment is to update targeted sections of the protocol to comply with EU CTR requirements and to update the neurologic toxicities language in Table 9 as per health authority request. Additionally, to adjust the protocol for EU CTR transition, country-specific requirements were consolidated within corresponding country/territory-specific attachments, namely requirements for France.

Section Number and Name	Description of Change	Brief Rationale
Title Page	Added study EU CTR number.	To comply with EU CTR requirements.
Synopsis	Added reference to protocol version and date, EudraCT number, EU CTR number, and a benefit-risk assessment subsection.	To comply with EU CTR requirements.
1.3 Potential Safety Risks and Mitigation Strategies, Table 9	Table 9 updated.	To align with the cilta-cel IB and with other cilta-cel study protocols.
6.1 Study Treatment Administration, Table 10	Text and Table 10 added to provide the designations (IMP, AxIMP) and authorization status in the EU/EEA of the study medicinal products.	To comply with EU CTR requirements.
Table 10 to Table 25	Tables renumbered as a result of the addition of Table 10.	To ensure the internal consistency of the protocol.
17.2 Recruitment Strategy	Section added.	To comply with EU CTR requirements although recruitment is complete.
Attachment 27: Country/Territory-specific Requirements	Attachment added to consolidate the country/territory-specific requirements for France.	To comply with EU CTR requirements.
Throughout the protocol	Added cross-references within the body of the document to country-specific requirements listed in Attachment 27 (Country/Territory-specific Requirements).	To refer to the country/territory-specific requirements listed in the attachment, in compliance with EU CTR requirements and the current sponsor protocol template.
Throughout the protocol	Minor formatting changes were made.	Minor errors were noted.

Amendment 6 (14 June 2022)

Overall Rationale for the Amendment: The reason for the amendment is to inform investigators that patients receiving cilta-cel are possibly at a higher risk of severe/fatal outcomes from COVID-19 infection compared with patients who are receiving standard of care therapy, and to provide additional guidance for prevention and mitigation. Additional guidance for HLH and additional clarifications were also incorporated.

Section Number and Name	Description of Change	Brief Rationale
1.3. Potential Safety Risks and Mitigation Strategies (Table 9) 6.2.7. Serious Infection Attachment 20: COVID-19 Guidance on Study Conduct and Vaccine Timing; 8.1. Prophylaxis for Infections	Added guidance on measures to prevent and mitigate COVID-19 infection, including the importance of vaccines and other preventative measures, the use of prophylaxis therapy (eg, Evusheld, if available), and the use of antiviral therapy (eg, Paxlovid, if available) for COVID-19 infection.	To provide additional prevention and mitigation guidelines for COVID-19 infections in patients treated with cilta-cel.
Time and Events Schedules (Table 1, Table 3, Table 6); 9.7.1. Adverse Events; 12.3.1. All Adverse Events	Added text to indicate that events of COVID-19 infection will be reported during the first-year post-infusion of cilta-cel.	To expand the reporting timeframe for COVID-19 infections.

Section Number and Name	Description of Change	Brief Rationale
Time and Events Schedules (Table 1, Table 3, Table 5, Table 6); 8. Prestudy and Concomitant Therapy; Attachment 20: COVID-19 Guidance on Study Conduct and Vaccine Timing	Specified that medications for the prevention and treatment of COVID-19, including vaccinations against COVID-19, will be reported until 1 year after cilta-cel infusion.	To expand the reporting timeframe for COVID-19 medications.
1.3. Potential Safety Risks and Mitigation Strategies (Table 9); 6.2.1. Management of Cytokine Release Syndrome	Added language regarding features of HLH that may put subjects at high risk of bleeding and included additional measures to be taken if HLH is suspected.	To increase awareness and provide additional guidance about the risk of HLH, consistent with health authority feedback.
12.3.3. Adverse Events of Special Interest	Removed statement that "Grade 1 or 2 AEs of CRS and neurotoxicity would not qualify for expedited reporting unless they meet SAE criteria".	For clarity.
12.3.3. Adverse Events of Special Interest; 12.3.4. Delayed Adverse Events	Rephrased reporting requirement for any grade movement and neurocognitive toxicity (ie, "Parkinson-like syndrome" changed to "parkinsonism").	To ensure this risk is communicated in an expedited fashion, consistent with health authority feedback.
Time and Events Schedules (Tables 1, 3, 5, 6); 1.3. Potential Safety Risks and Mitigation Strategies (Table 9)	Clarification was added that CMV and EBV testing performed prior to cilta-cel infusion includes both serology and PCR. Post-infusion CMV and EBV testing includes PCR only. The testing schedule was revised to give specific Study Days for post-infusion testing, with a ±6-week window added.	Clarification of guidance on required testing.
Time and Events Schedules (Tables 1, 3, 6)	The sample collection schedule for MRD (bone marrow aspirate) was reworded for clarity.	To help ensure that all required bone marrow aspirate samples are collected.
Time and Events Schedules (Tables 1, 5)	Table 1 (footnote v) and Table 5 (footnote c) were revised to acknowledge that stem cell mobilization may be performed using the specified agents (cyclophosphamide, G-CSF, Plerixafor) or per local standard of care.	To allow for treatment flexibility.
3.1.5. Cohort E Study Design	Text was added that subjects may receive 1 cycle of anti-myeloma therapy (physician's choice) any time before enrollment. Enrollment was defined as the start of D-VRd induction.	To clarify guidance regarding allowed anti-myeloma therapy prior to enrollment.
4.5.1. Cohort E Inclusion Criteria	The "Note" for Inclusion Criterion 4e.2 was revised. Reference to "VRd therapy prior to enrollment" was changed to "anti-myeloma therapy prior to enrollment".	To align text with acceptable use of prior anti-myeloma therapy.
4.5.2. Cohort E Exclusion Criteria	Exclusion Criterion 2e.2 was clarified to add that 1 cycle of anti-myeloma therapy is acceptable if administered at any time before enrollment.	

Section Number and Name	Description of Change	Brief Rationale
3.1.6. Cohort F Study Design	Text was added to describe acceptable limited use of alternative (physician's choice) anti-myeloma therapy prior to the start of the protocol-specified initial regimens. Guidance was added for acceptable protocol-specified regimens prior to enrollment.	To define allowable flexibility regarding the use of protocol-specific regimens.
4.6.1. Cohort F Inclusion Criteria	Inclusion Criterion 12f.1 was revised to clarify that subjects may receive 1 cycle of alternative anti-myeloma therapy prior to the protocol-specified initial therapy regimens.	
3.1.6 Cohort F Study Design	Timing of peripheral stem cell mobilization and harvesting (eg, to allow for salvage ASCT after disease progression is confirmed).	To clarify requirements for the timing of peripheral stem cell mobilization and harvesting.
3.1.6. Cohort F Study Design; 4.6.1. Cohort F Inclusion Criteria	Figure 7 (Schematic Overview of the Study, Cohort F) and Inclusion criterion 3f.2 were revised for clarity. The number of required cycles for each protocol-specified regimen was specified.	To clarify requirements for the protocol-specified regimens.
6.2.1. Management of Cytokine Release Syndrome	Table 22 (Guidelines for the Management of Cytokine Release Syndrome) reorganized and modified to include organ toxicity.	Revised based on health authority feedback.
6.2.2.1. CAR-T Cell-related Neurotoxicity (Immune Effector Cell-Associated Neurotoxicity Syndrome [ICANS])	Added guidance in text for treatment if concurrent CRS is suspected during a neurologic event.	Added for clarity.
6.2.2.1. CAR-T Cell-related Neurotoxicity (Immune Effector Cell-Associated Neurotoxicity Syndrome [ICANS])	Table 23 (Guidelines for the Management of Immune Effector Cell-Associated Neurotoxicity Syndrome [ICANS]) reorganized and modified based on ASTCT consensus criteria.	Revised based on health authority feedback.
6.1.5.1.5. Dose Modification Guidelines	For non-blistering rash, ≥Grade 3 or 4: Added lenalidomide to therapies that should be on hold. Corrected the following sentence: For Grade 4 toxicity ~~permanently~~ discontinue bortezomib and lenalidomide permanently.	Correction of error.
6.1.5.1.5. Dose Modification Guidelines	Added to Grade 1 peripheral neuropathy guidance: No action required, **however, changing frequency to weekly may be considered based on clinical judgement and/or institutional practice.**	Guidance for Grade 1 peripheral neuropathy added to be consistent with site instructions.
6.1.5.1.5. Dose Modification Guidelines	Added maximum dose for bortezomib dose reductions for peripheral neuropathy Grade 1 with pain or Grade 2 and Grade 2 with pain or Grade 3.	Revised for clarity.
6.1.5.1.5 Dose Modification Guidelines	Clarified that change in the schedule of bortezomib administration to once per week should occur on Days 1, 8, and 15.	Revised for clarity.

Section Number and Name	Description of Change	Brief Rationale
11.3. Efficacy Analyses	Revised MRD negative rate definition for subjects in Cohorts D and F to remove the reference to retreatment of JNJ-68284528.	To provide a definition of MRD negative rate consistent with the eligibility of each cohort for retreatment.
Synopsis (Overview of Study Design); Time and Events Schedules (Tables 1, 3, 6)	Text defining when each cohort will be completed was restated for clarity. Table 1 (footnote c), Table 3 (footnote c), and Table 6 (footnote a) were revised accordingly.	To provide consistent definitions of cohort completion for all cohorts.
Synopsis (Overview of Study Design) Time and Events Schedules (Table 1) Time and Events Schedules (Tables 5, 6)	Eligibility for retreatment was specified for each cohort. Footnote c was revised to state that retreatment is permitted for Cohorts A, B, and C; retreatment is not permitted for Cohort F. Text under the heading Serum and Urine Disease Evaluations related to retreatment with cilta-cel was deleted.	To clarify which cohorts are eligible for retreatment.
6.1.2.1. Criteria for Conditioning Regimen	Transfusion support is permitted to maintain hemoglobin at ≥8 g/L (previously >8 g/L).	Hemoglobin requirement corrected.
Time and Events Schedule (Table 6)	Footnote a was revised. Subjects who discontinue the study before Day 100 should have Day 100 assessments performed before withdrawal, if feasible.	To provide additional guidance on timing of study procedures.
4.4.1. Cohort D Inclusion Criteria (7d.3); 4.5.1. Cohort E Inclusion Criteria (8e.2); 6.1.4. Lenalidomide (Cohort D); 12.3.5. Pregnancy	Reference to the Revlimid Risk Minimization Program or Revlimid labeling was broadened to include lenalidomide (e.g., Revlimid/lenalidomide Risk Minimization Program).	Revision to clarify that generic lenalidomide can be used.
8.1. Prophylaxis for Infections	The heading was changed from “Prophylaxis for Herpes Zoster Reactivation” to Prophylaxis for Infections” to reflect additional text added to the section.	To accurately reflect section content.
9.7.5 Clinical Laboratory Tests	Added a request to provide COVID-19 antibody titers, if available, post cilta-cel infusion for up to 1 year.	Request for clarity regarding COVID-19 antibody reporting, including timeframe
9.7.5. Clinical Laboratory Tests	The in-text table summarizing clinical laboratory testing was reorganized by type of test.	Investigators should refer to the appropriate Time and Events schedule for the timing of clinical laboratory testing.
Attachment 26: Adverse Event Reporting Guidance	Attachment was added to summarize requirements for adverse event and expedited adverse event reporting.	To help ensure adverse events are collected and reported as required.
15. Study-Specific Materials	Reference to the SIPPM was replaced with reference to the CTPPM.	Terminology updated.
Throughout the protocol	Minor grammatical, formatting, or spelling changes were made.	Minor errors were noted.

Amendment 5 (31 January 2022)

Overall Rationale for the Amendment: The overall reason for the amendment is to adjust the sample size in Cohort D and to change the consolidation treatment in Cohort E from daratumumab plus lenalidomide to lenalidomide.

Section number and Name	Description of Change	Brief Rationale
Synopsis, Overview of Study Design; 1.2. Overall Rationale for the Study; 3.1. Overview of Study Design; 3.1.4. Cohort D Study Design;	Decrease the target number of subjects enrolled in Cohort D from approximately 20 subjects to approximately 17 subjects.	Data from 17 subjects was determined to be adequate for Cohort D.
Synopsis, Overview of Study Design; Synopsis, Dosage and Administration; Time and Events Schedule (Table 6); 1.2. Overall Rationale for the Study; 3.1. Overview of Study Design; 3.1.5. Cohort E Study Design; 3.3. Study Design Rationale; 6.1.5. Cohort E: Induction and Post JNJ-68284528 Therapy 6.1.5.2. Cohort E: Lenalidomide Consolidation Treatment; 7. Treatment Compliance; 8. Pre-study and Concomitant Therapy; 8.4. Subsequent Anticancer Therapy; 9.1.6.4. Lenalidomide Consolidation Treatment Period after JNJ-68284528 Infusion (Cohort E); 9.7.1. Adverse Events; 10.2. Discontinuation of Study Treatment; 12.3.1. All Adverse Events; Attachment 16, Contraception and Barrier Guidance and Collection of Pregnancy Information	Cohort E: Change in consolidation treatment from daratumumab plus lenalidomide to lenalidomide alone. Removal of reference to daratumumab in the context of consolidation including dosing information and pre-medications.	Consolidation treatment with daratumumab was removed based on emerging preclinical data suggesting that daratumumab may not provide synergistic effects after CAR-T therapy.
6.1.5.1.4. Dexamethasone 6.1.5.2. Cohort E: Lenalidomide Consolidation Treatment	Removed guidance for dexamethasone dosing as premedication for D+R consolidation as only lenalidomide will be used as consolidation therapy. Added that lenalidomide will be dispensed on Day 1 of each cycle for self administration and removed daratumumab dosing information. Deleted platelet and ANC required for daratumumab dosing. Deleted Table 22.	

Section number and Name	Description of Change	Brief Rationale
Synopsis, Dosage and Administration; 3.1.4. Cohort D Study Design; 3.1.5. Cohort E Study Design; 6.1.4. Lenalidomide (Cohort D); 9.1.6.4. Lenalidomide Consolidation Treatment Period after JNJ-68284528 Infusion (Cohort E)	Removed qualifiers to resolution of neurological toxicities 'per ASTCT criteria' and 'associated with JNJ-68284528'	Resolution of neurotoxicity regardless of causality is required before the start of lenalidomide administration post JNJ-68284528 in Cohorts D and E
Synopsis, Dosage and Administration; 3.1.4. Cohort D Study Design; 3.1.5. Cohort E Study Design;	Added to the description of Cohort D and Cohort E: Additionally, initiation of lenalidomide treatment is dependent on no additional safety concerns by investigator or sponsor.	Addition for clarity
Synopsis, Dosage and Administration; 6.1.5.2. Cohort E: Lenalidomide Consolidation Treatment	Revised guidance for subjects with eGFR <60 mL/min/1.73m^2 in Cohort E to match guidance from Cohort D	Revision for consistency
Time and Events Schedule (Table 1); Time and Events Schedule (Table 3); Time and Events Schedule (Table 5); Time and Events Schedule (Table 6)	Added separate entry for CMV and EBV testing.	Added at the recommendation of the DMC
1.3. Potential Safety Risks and Mitigation Strategies	In Table 9, added that CMV and **EBV** serology **should be performed** at baseline.	
Attachment 18 (Anti-microbial Prophylaxis Recommendations)	Removed table footnote as it is no longer applicable due the addition of the new CMV entry in the Time and Events Schedules.	
Time and Events Schedule (Table 1) Time and Events Schedule (Table 3); Time and Events Schedule (Table 5)	Added ECOG assessment at apheresis	For consistency with language in Section 6.1.1.
Time and Events Schedule (Table 1); Time and Events Schedule (Table 3); Time and Events Schedule (Table 6)	Windows added for MRD assessments. Study Days corresponding to 6 and 12 months were added.	Addition made for clarity
Time and Events Schedule (Table 1)	Addition of footnote 'w': **For Cohort F only. β2 microglobulin assessed by local lab prior to initiation of any anti-myeloma therapy will be collected as the screening values for determination of ISS staging**	To allow for the use of laboratory values collected prior to initial therapy
Time and Events Schedule (Table 2); Time and Events Schedule (Table 4); Time and Events Schedule (Table 8); 9.5. Biomarker Evaluations	Added that if post-treatment assays are negative for RCL during the first year, collection of follow-up samples may be discontinued and yearly review of medical history will be sufficient for the patient. If any post-treatment samples are positive, further analysis of the RCL, and more extensive patient follow-up should be undertaken.	Revised guidance for RCL to be consistent with current recommendations across the cilta-cel program

Section number and Name	Description of Change	Brief Rationale
Time and Events Schedule (Table 3); Time and Events Schedule (Table 6)	Aligned footnote (Table 3) and footnote (Table 6) with language below, as stated in Section 9.2.1 (Bone Marrow Examination for MRD Assessment). "Bone marrow aspirate for MRD should be taken from first or second aspiration attempt, if feasible. If for any reason a bone marrow aspirate is not performed at pre-dose, or if a baseline clone cannot be established from the pre-dose bone marrow aspirate collection, then non-decalcified diagnostic tissue will be requested or perform MRD assessment using NGF."	Addition for consistency
Time and Events Schedule (Table 8); 9.3.1. Evaluations; 9.3.3. Pharmacokinetic Parameters; 11.4. Pharmacokinetic Analyses; 11.6. Pharmacokinetic/ Pharmacodynamic Analyses	For Cohort E, deleted all daratumumab PK sample collections on and after cilta-cel infusion.	Change in collection of daratumumab PK samples due to removal of daratumumab from consolidation therapy
2. Objectives, Endpoints, and Hypothesis	Deleted exploratory objectives/endpoints to assess and characterize the PK and immunogenicity of daratumumab	
Time and Events Schedule (Table 1); Time and Events Schedule (Table 3)	Window for post-treatment assessments changed from 'up to 12 months' to 'up to Day 352' to clarify that it is 1 year after infusion.	Changes for clarity
Time and Events Schedule (Table 2); Time and Events Schedule (Table 4); Time and Events Schedule (Table 8)	Added window (1 to 56 days) to assessments collected at PD	
Time and Events Schedule (Table 2); Time and Events Schedule (Table 4); Time and Events Schedule (Table 8)	Added footnotes (to PK CAR transgene levels and Immunogenicity) stating the following: **After 1 year, CAR+ T cell counts and CAR transgene levels will be measured at least annually until EOS, PD, or until the LLOQ of the cilta-cel transgene is reached, whichever is earlier. Additional event-triggered testing for PK CAR transgene levels and CAR+ T cell counts may be conducted as clinically indicated.**	
Time and Events Schedule (Table 5)	Added footnote 's' to disease characteristics for clarity	
Time and Events Schedule (Table 6)	Added window for lenalidomide consolidation treatment	
Time and Events Schedule (Table 7)	Footnote 'a' added to clarify that cytogenetics at screening can be performed from a bone marrow sample at the time of initial diagnosis.	
3.1.1. Cohort A Study Design	Clarified that Cohort A will have 2 separate end of cohort dates	

Section number and Name	Description of Change	Brief Rationale
3.1.7. Retreatment with JNJ-68284528	Clarified that Inclusion criterion 2 is not relevant for retreatment as there is no restriction on the maximum time required between dosing with JNJ-68284528 and PD.	
4.5.1. Cohort E Inclusion Criteria	Added clarification to definition of high-risk cytogenetics. Added Bisht 2021 citation.	
9.2.6. Documentation of Extramedullary Disease/ Extramedullary Plasmacytomas	Added that evaluation of extramedullary plasmacytomas may be done **on Day 78, Day 156, and then** every 12 weeks to align with language in T&E Schedules.	
Time and Events Schedule (Table 7)	ADA testing to coincide with daratumumab PK sample	Clarification of ADA sample collection
Time and Events Schedule (Table 8)	Footnotes 'f' and 'g' were deleted in Amendment 4 in error. Added back in Amendment 5	Correction of error
1.3. Potential Safety Risks and Mitigation Strategies	Tumor Lysis Syndrome added to Table 9 – Risks associated with cilta-cel.	Addition made in response to Health Authority Feedback
1.3. Potential Safety Risks and Mitigation Strategies	In Table 9 added guidance for other cytokine-targeting therapies that may be used for cases that do not respond to tocilizumab and corticosteroids.	Change for consistency with current guidance across the cilta-cel program.
3.1. Overview of Study Design; 17.9.1. Study Completion/End of Cohort	The sponsor will continue to monitor subjects for 15 years in a long-term follow-up study	Clarify continued monitoring in separate long term follow-up study
3.1.5. Cohort E Study Design 6.1.5.1. Cohort E: D-VRd Induction Treatment	Added to footnote 'a' of Cohort E study schema: Eligible subjects will receive 4 cycles of D-VRd induction therapy as tolerated, **additional cycles permitted with sponsor approval.** Added that additional cycles may be given with sponsor approval if an unanticipated delay in JNJ-68284528 occurs.	Added for flexibility to ensure subsequent subjects enrolled do not go without therapy if their dosing is delayed.
4.5.1. Cohort E Inclusion Criteria	Added age criterion (≥18 years of age) as 11e.	Correction of error
4.6.1. Cohort F Inclusion Criteria	Added age criterion (≥18 years of age) as 11f	
4.5.1. Cohort E Inclusion Criteria	Added the following note: Note: For subjects that have received 1 cycle of VRd therapy prior to enrollment (as allowed by Exclusion Criterion 2e.1) measurable disease must be assessed by local laboratory on the most recent evaluation prior to the start of the VRd therapy.	Addition for clarity

Section number and Name	Description of Change	Brief Rationale
4.5.2. Cohort E Exclusion Criteria	Deleted exclusion criterion 22e.	Correction of error. The criteria for prior therapy are not applicable to this cohort of subjects with newly diagnosed multiple myeloma.
4.6.1. Cohort F Inclusion Criteria	Added to criterion 3.f subjects who received at least 5 to 8 cycles of initial therapy with D-VRd as acceptable combination therapy.	To obtain data for D-VRd pretreated patients in advance of initiation of a Phase 3 study, as requested per health authority feedback.
4.6.1. Cohort F Inclusion Criteria	Added criterion 12f to state that subjects may receive up to 1 cycle of alternative anti-myeloma therapy prior to the specified initial therapy regimens	To improve subject recruitment by allowing a single cycle of therapy prior to cohort enrollment.
6.1.3.1. Exceptional Release Criteria	Added: **If required, approval from the relevant local health authorities for use of the product will be obtained in compliance with local regulations regarding notification and approval**	Added to comply with requirements from local health authorities.
6.2.2. Neurologic Toxicities; 6.2.2.1. CAR-T Cell-related Neurotoxicity (ICANS); 9.7.1. Adverse Events; 9.7.11. Neurologic Examination; 11.7. Safety Analyses; 12.1.3. Severity Criteria; 12.3.3. Adverse Events of Special Interest	Changes made regarding how ICANS is referenced	Changes made to the nomenclature for CAR-T cell neurotoxicity to align with current language used in IB and other study protocols
6.2.2. Neurologic Toxicities	Changed the length of time subjects should be monitored for neurotoxicity from 1 year post infusion to '**end of study**'.	Align with current guidance
12.3.3. Adverse Events of Special Interest	Added to events that must be reported to the sponsor following the SAE reporting process: '**any grade movement and neurocognitive toxicity (ie, Parkinson-like syndrome)**'.	
12.3.4. Delayed Adverse Events	Added: **any grade movement and neurocognitive toxicity (ie, Parkinson-like syndrome)** to events that must be reported to the sponsor within 24 hours of awareness of the event for the duration of the study.	
6.2.3. Tumor Lysis Syndrome	Removed reference to exact frequency of TLS as that could change over time.	Change for clarity
8.3. Prohibited Therapies	Vaccination recommendations updated	Update with current guidelines
8.3. Prohibited Therapies	Added strong inhibitors and inducers of CYP3A4 and MDR1 should be avoided.	Added for guidance when considering COVID therapeutics

Section number and Name	Description of Change	Brief Rationale
9.2. Efficacy Evaluations	Only subjects in Cohorts A, B, and C (not Cohort F) can be enrolled in the study based on disease that is followed by PET/CT or whole body MRI	Correction
9.2.2. Myeloma Protein Measurements in Serum and Urine 9.7.5. Clinical Laboratory Tests	Added that for subjects in Cohort F only, serum β2-microglobulin will also be required from local laboratory assessment prior to initiation of any anti-myeloma therapy Added β2-microglobulin/albumin for Cohort F only	Change for clarity
10.2. Discontinuation of Study Treatment	Clarified that a subject will be discontinued if they received concurrent (non-protocol) anti-cancer treatment (with the exception of sponsor-approved bridging therapy) **prior to initial infusion of JNJ-68284528**.	Revision for clarity
Throughout the protocol	Minor grammatical, formatting, or spelling changes were made.	Minor errors were noted

Amendment 4 (24 May 2021)

Overall Rationale for the Amendment: The overall reason for the amendment is to add a new cohort of subjects with multiple myeloma representing an additional subject population of unmet medical need and to increase the sample size in Cohort A to obtain safety and efficacy data in subjects receiving ciltacabtagene autoleucel (cilta-cel) manufactured with the commercial process. The rationale for the changes, the description of the changes, and the affected section numbers are provided below. Revisions noted below are representative of the changes. In some cases, new text is displayed in bold font and deleted text noted with strikethrough.

Section Number and Name	Description of Change	Brief Rationale
Title page; Synopsis; 1. Introduction	Added generic name (cilta-cel) to the document and removed JNJ-68284528.	Added generic name
Synopsis (Primary Objective, Endpoint); 2.1. Objectives and Endpoints	Added next generation flow (NGF).	Revised for consistency with other studies in the program
Synopsis (Overview of Study Design); 1.2. Overall Rationale for the Study; 3.1. Overview of Study Design; 3.1.1. Cohort A Study Design; Figure 2	The number of subjects enrolled in Cohort A increased from 20 to 40. The size of all other cohorts remains unchanged.	To obtain safety and efficacy data in subjects receiving cilta-cel manufactured with the commercial process and due to the addition of country-specific amendment (Amendment 3/USA-1) into Global Amendment 4. Country specific amendment will be retired.

Section Number and Name	Description of Change	Brief Rationale
Synopsis (Overview of Study Design); 11.3. Efficacy Analysis	Clarified the timeline for primary analysis of Cohort A subjects including initial vs newly added in the expansion cohort.	Revised for clarity based on the increase in the size of Cohort A.
Synopsis (Overview of Study Design); 1.2. Overall Rationale for the Study; 3.1. Overview of Study Design; 3.1.6. Cohort F Study Design and Figure 7; 3.1.7. Retreatment with JNJ-68284528; 4. Subject Population	Added description of the study design for Cohort F and new Figure 7.	Addition of new Cohort F.
Synopsis (Dosage and Administration)	Dosing information provided for Cohort F. Additionally, clarified that subjects in Cohort A, B, C and F who do not receive an infusion of cilta-cel will be replaced.	
Time and Events Schedule (Table 1 and Table 2)	Updated to include Cohort F.	
3.3. Study Design Rationale	Added a rationale for the design of Cohort F.	
4.6. Cohort F Eligibility Criteria 4.6.1 Cohort F Inclusion Criteria 4.6.2 Cohort F Exclusion Criteria	Added inclusion and exclusion criteria for subjects to be enrolled in Cohort F.	
8. Pre-study and Concomitant Therapy	Added Cohort F.	
9.1.6.2. Post-treatment period	Added Cohort F.	
9.2 Efficacy Evaluations 9.2.6 Documentation of Extramedullary Disease/ Extramedullary Plasmacytomas	Added Cohort F.	
11. Statistical Methods	Added Cohort F.	
17.9.1 Study Completion/End of Cohort	Added Cohort F	
Time and Events Schedule (Table 1)	• Adjusted timings for PET/CT or MRI assessments and added that it is applicable for Cohort A, B and C. • Clarified the timing for MRD (bone marrow aspirate) sample collection. • Modified footnote ‘g’ and added reference of Attachment 10 for details. • Modified footnote ‘m’ to add MRD assessment using NGF. • Modified footnote ‘q’ to indicate the references for more details about immunoglobulin levels. • Added a new row with footnote ‘u’ for collecting delayed adverse events.	Revised for clarity and correction of errors.

Section Number and Name	Description of Change	Brief Rationale
	• Added a new footnote 'v' clarifying that for Cohort F only, stem cell harvest after apheresis may occur based on PI discretion. • For MRD (bone marrow aspirate) and extramedullary plasmacytomas assessments, clarified sample collection timepoints. • Clarified the timing for adverse events collection.	
Time and Events Schedule (Table 2)	• For PK CAR transgene levels clarified that cyclophosphamide conditioning regimen sample will be collected for A, B and C Cohorts only. Provided flexible windows for RCL and added a window for cytokine profiling.	
Time and Events Schedule (Table 3)	• Modified footnote 'g' and added reference of Attachment 10 for details. • For MRD and extramedullary plasmacytomas assessments, clarified the timing for the sample collection. • Clarified the timing for adverse events collection. • Added the timing for collecting delayed adverse events. • Modified footnote 'q' to indicate when immunoglobulin levels will be monitored. • Added a new row with footnote 'x' for collecting delayed adverse events.	
Time and Events Schedule (Table 4)	Clarified the timing for replication competent lentivirus (RCL) and added a window for cytokine profiling.	
Time and Events Schedule (Table 5)	• Added text for serology in the table and provided reference of Attachment 10 for details. • Clarified that on D15, vital signs including oxygen saturation, hematology and chemistry will be done for Cycle 1 and 2. • Modified footnote 'c' to clarify details for stem cell mobilization and harvesting. • Added footnote 'p' to indicate when immunoglobulin levels will be monitored. • Added a new row with footnote 'q' for collecting delayed adverse events.	

Section Number and Name	Description of Change	Brief Rationale
	• Added a new footnote 'r' indicating vital signs should be done before and after daratumumab administration.	
Time and Events Schedule (Table 6)	• Revised text for serology in the table, footnote 'f' and provided reference of Attachment 10 r details. • For MRD and extramedullary plasmacytomas assessments, clarified the timing for the sample collection. • Added a new row with footnote 'm' for collecting delayed adverse events. • Clarified the timing for adverse events collection. • Added footnote 'n' to indicate that immunoglobulin levels will be monitored.	
Time and Events Schedule (Table 7)	• Deleted footnotes 'a-d' as required. • Removed the predose flow cytometry sample collection timepoint for Cycle 1 Day 1.	Revised for clarity and due to the addition of country-specific amendment (Amendment 3/USA-1) into Global Amendment 4. Country specific amendment will be retired.
Time and Events Schedule (Table 8)	• Provided window for BCMA, ADA and PK/immunogenicity sample collection at the Day 1 infusion. • Clarified the timing for replication competent lentivirus (RCL) and added a window for cytokine profiling. • Deleted footnotes d and e as required.	
Abbreviations	Removed and added abbreviations as required.	Revised for consistency
1.1.4. JNJ-68284528 3.1.1. Cohort A Study Design	Added to clarify that 20 additional subjects of Cohort A will receive cilta-cel manufactured using the commercial process.	Revised for clarity based on the increase in the size of Cohort A.
1.1.5. Clinical Studies 1.3. Potential Safety Risks and Mitigation Strategies and Table 9 3.2. Rationale of Dose and Administration Schedule Selection 6.2.2.2. Other Neurotoxicities	Updated this section per current safety and efficacy data.	Updated based on current clinical data and to align with other studies in the program.
3.3. Study Design Rationale	Provided current published data for Cohort E.	
2.1. Objectives and Endpoints 6.1.1. Criteria for Apheresis 9.3 Pharmacokinetics and Immunogenicity 11.1. Subject Information 11.4. Pharmacokinetic Analyses 11.5. Immunogenicity Analyses 11.6. Pharmacokinetic/ Pharmacodynamic Analyses	Additional exploratory objectives to characterize the pharmacokinetics and immunogenicity of daratumumab added.	Changes to align with newly added exploratory objectives.

Section Number and Name	Description of Change	Brief Rationale
4.1.1, Cohort A Inclusion Criteria	Modified criterion 5 indicating that patients in Cohort A, B and C will require a minimum of one lesion with a bi-dimensional measurement of at least 1cm × 1cm.	Revised for clarity
4.1.2, Cohort A Exclusion Criteria 4.2.2., Cohort B Exclusion Criteria 4.3.2., Cohort C Exclusion Criteria 4.4.1., Cohort D Exclusion Criteria	For Cohort A B, and D criterion 4 and for Cohort C criterion 3, modified as following: Targeted therapy, epigenetic therapy, ~~or~~ treatment with an investigational drug ~~or~~, **investigational intervention (including investigational vaccines)** used an invasive investigational medical device within 14 days or at least 5 half-lives, whichever is less, **or currently enrolled in an investigational study.**	Updated based on current clinical data
4.5.1. Cohort E Inclusion Criteria	• Revised criterion 1e to include patients with high-risk by ISS stage III criteria and any of the cytogenetics feature. • Revised criterion 8e to include effective methods of contraception until 3 months after daratumumab.	
4.5.2. Cohort E Exclusion Criteria	• Revised criterion 2e as following: Prior therapy for plasma cell disorder-multiple myeloma ~~other that a short course~~ of ~~corticosteroids (not to exceed 40 mg of dexamethasone, or equivalent per day for a maximum of 4 days, total of 160 mg dexamethasone or equivalent) with the exception~~ **with the exception of one cycle of chemotherapy**. • Revised criterion 17e to exclude patients with any history of Parkinson's disease or other neurodegenerative disorder. • Revised criterion as 22e to exclude patients with certain prior therapies including investigational drug, vaccine or vaccine.	
6.1.2.1. Criteria for Conditioning Regimen	Revised a bullet point as following: "No live, attenuated vaccines within ~~4~~ **6** weeks prior to conditioning regimen dosing."	Revised for consistency with other studies in the program
6.1.3. JNJ-68284528 Administration	Added that product will be manufactured based on weight at apheresis.	Revised for clarity
6.1.3.1 Exceptional Release Criteria	Revised to clarify the product release criteria.	
6.1.5.1.1.2. Daratumumab Administration	Clarified collection timepoints for vital signs.	

Section Number and Name	Description of Change	Brief Rationale
6.2.1. Management of Cytokine Release Syndrome	Revised as following: "Other **cytokine** ~~monoclonal antibodies~~ targeting **therapies** ~~cytokines~~ (for example, ~~anti-~~ IL1 and/or anti-TNFα) may be used based on institutional practice, especially for cases of **neurotoxicity** ~~CRS~~ which does not respond to tocilizumab **and corticosteroids."**	
6.2.2.2. Other Neurotoxicities	Section revised to update list of other Neurotoxicities	Updated based on current clinical data
6.2.3. Tumor Lysis Syndrome	Deleted the sentence indicating "~~TLS will be captured as an adverse event of special interest (see Section 12.3.3)~~."	Revised for consistency with other studies in the program
6.2.5 Prolonged Cytopenia	Updated the title to add prolonged before cytopenia.	
6.2.6 Hypogammaglobulinemia	Updated that vaccination with live attenuated virus vaccines is not permitted for at least 6 weeks	
6.2.7. Serious Infections	Updated the title to add serious before infections. Reference to Attachment 10 added.	
6.2.8. Hypersensitivity Reactions	Ampicillin was deleted.	
6.3. Treatment of Overdose	Added this new sub-section about treatment overdose	
8.3. Prohibited therapies	Revised as following: Vaccination with live, attenuated vaccine after signing consent and in the ≤ 4 **6** weeks prior to the ~~infusion~~ **start** of ~~JNJ-68284528~~ the conditioning regimen, and for 100 days after infusion of JNJ-68284528.	
9.1.1. Study procedures (Overview)	Updated the blood volumes for existing cohorts and added the blood volume for Cohort E and F.	
9.1.2 Screening Phase/Post treatment Phase	Added that for Cohort E only, local laboratory β-2 microglobulin measurement prior to treatment with dexamethasone (or equivalent steroid) may be used to determine eligibility.	
9.1.3 Apheresis	Removed the range of PBMCs collection and clarified that apheresis should be performed according to the institutional standards.	
9.1.6.3. Lenalidomide Treatment Period after JNJ-68284528 Infusion (Cohort D)	Added the option for remote visits via telemedicine technology.	Revised for consistency in the protocol.

Section Number and Name	Description of Change	Brief Rationale
9.1.6.4. D+R Consolidation Treatment Period after JNJ-68284528 Infusion (Cohort E)		
9.1.6.5. Long-term Follow-up	Revised to indicate that assessment of other delayed AEs will be collected for the duration of the study and up to 15 years after the last dose of the study drug. Also, clarified that after subject's death, the date and cause of death will be documented in the eCRF.	
9.2.1. Bone Marrow Examination for MRD Assessment	Added next generation flow (NGF) and clarified assessment timing.	
9.2.2. Myeloma Protein Measurement in Serum and Urine 9.6. Patient-reported outcome assessments 9.9. Medical Resource Utilization	Reference for Table 9 added.	
9.2.7. Local Laboratory Assessments	Clarified that if local and central laboratory data are collected on the same day, the central laboratory results will take precedence.	Revised to allow for flexibility in collecting PBMCs
9.7. Safety Evaluations	• Clarified adverse event reporting language and provided cross reference for the adverse events of special interest, delayed adverse events and serious adverse events. • Added additional clinical laboratory tests plus clarified definition for the HCV infection.	Revised to be consistent with other studies in the program.
9.8. Sample Collection and Handling	Reference for Table 10 added.	Revised for clarity.
10.3. Withdrawal from the study	Added that a 3rd apheresis attempt may be permitted if an immediately rectifiable cause is identified (eg, product shipped improperly) and with sponsor approval.	Revised to ensure transport issues do not preclude study participation.
11.7 Safety Analyses	Clarified to indicate that parameters with pre-defined NCI-CTCAE toxicity grades will be summarized except for CRS and CAR-T cell-related neurotoxicity (eg, ICANS).	Revised to be consistent with other studies in the program.
12.1.3. Severity Criteria	Added CAR-T related neurotoxicity and clarified that changes in handwriting should be graded using the criteria outlined in Attachment 17.	
12.2. Special Reporting Situations	Clarification to existing text per current safety data.	
12.3.1. All Adverse Events		
12.3.2. Serious Adverse Events		
12.3.3. Adverse Events of Special Interest		
12.3.4. Delayed Adverse Events	Added this new sub-section to specify delayed adverse events	
References	Added five new references.	

Section Number and Name	Description of Change	Brief Rationale
Attachment 10: Hepatis B Virus Screening	Revised the existing text to clarify the details for serology for HBV reactivation.	
Attachment 18: Anti-Microbial Prophylaxis Recommendations	Revised recommendations for anti-microbial prophylaxis including pentamidine administration for pneumocystis pneumonia.	
Attachment 20: COVID-19 Guidance on Study Conduct and Vaccine Timing	Updated guidance on study conducts to include vaccine timing for cilta-cel recipients. Added that testing for COVID-19 should be performed according to local guidance.	To be consistent with newly added text in the protocol.
Throughout the protocol	• Minor grammatical, formatting, or spelling changes were made. • ASBMT has been replaced with ASTCT. • CTPPM has been added. • References to the Attachments added in the relevant sections.	Revised for clarity.

Amendment 3 (13 July 2020)

Overall Rationale for the Amendment: The overall reason for the amendment is to add a new cohort of subjects with multiple myeloma representing an additional patient population of unmet medical need.

Section Number and Name	Description of Change	Brief Rationale
Title page; Synopsis; 1. Introduction	Added generic name (ciltacabtagene autoleucel) to the document.	Added generic name
Synopsis (Overview of Study Design); 1.2. Overall Rationale for the Study; 3.1. Overview of Study Design; 3.1.5. Cohort E Study Design	Added description of the study design for Cohort E	Addition of Cohort E
Synopsis (Dosage and Administration); 6. Dosage and Administration; 6.1.5. Cohort E: Induction and Post JNJ-68284528 Therapy	Dosing information provided for D-VRd induction therapy and post JNJ-68284528 administration of daratumumab, lenalidomide, and dexamethasone.	
Time and Events Schedule	Time and Events Tables 5 to 8 added for Cohort E	
3.3. Study Design Rationale	Added a rationale for the design of Cohort E	
4.5. Cohort E Eligibility Criteria	Added inclusion and exclusion criteria for subjects to be enrolled in Cohort E	
6.1.1. Criteria for Apheresis (all cohorts unless otherwise specified)	Added timing of apheresis with respect to D-VRd induction treatment	

Section Number and Name	Description of Change	Brief Rationale
6.2.9. Cohort E: Management of Infusion-related Reactions and Local Injection-site Reactions of Daratumumab SC	Added management guidelines specific to daratumumab	
7. Treatment Compliance	Added D-VRd and D+R	
8. Prestudy and Concomitant Therapy	Added concomitant medication recording period for Cohort E	
8.3.1. Additional Prohibited Therapies for Cohort E	Added prohibited therapies with the use of bortezomib	
9.1.2. Screening Phase	Added that subjects in Cohort E will receive induction treatment with D-VRd after screening and prior to apheresis	
9.1.6.4. D+R Consolidation Treatment Period after JNJ-68284528 (Cohort E)	Added section for Cohort E post-treatment period	
9.5.1 Pharmacodynamic/Predictive Markers	Added that data review by the DMC will determine if there are any potential pharmacodynamic interactions between D-VRd and JNJ-68284528.	
9.7. Safety Evaluations	Added a subsection for Indirect Antiglobulin Test (IAT) to be performed before the first dose of daratumumab in Cohort E.	
10.2. Discontinuation of Study Treatment	Added discontinuation of study treatment information for Cohort E	
11.1. Subject Information	Added description of Cohort E analysis population	
Attachment 19: International Staging System (ISS)	Added Revised International Staging System (R-ISS)	
Attachment 21: Myeloma Frailty Score Calculator	Addition of Myeloma Frailty Score Calculator	
Attachment 24: Asthma Guidelines	Added asthma guidelines for daratumumab	
Attachment 25: Antihistamine That May Be Used Predose	Added antihistamines that may be used predose for daratumumab	
Synopsis (Overview of Study Design); 3.1. Overview of Study Design; 9.1.6.3. Lenalidomide Treatment Period after JNJ-68284528 Infusion (Cohort D) 17.9.1. Study Completion/End of Cohort	Cohort D (and Cohort E) will be considered complete **2 ½ years** after the last subject receives their initial dose of JNJ-68284528.	Clarification on definition of study completion
Synopsis (Statistical Methods)	Sample size language revised to be consistent with Section 11.2.	Revision for consistency
Synopsis (Dosage and Administration); 3.1.4. Cohort D Study Design (Figure 5)	One **or more cycles** of lenalidomide bridging therapy are permitted.	Revision made for clarity

Section Number and Name	Description of Change	Brief Rationale
Synopsis (Dosage and Administration); 3.1.4. Cohort D Study Design; 6.1.4. Lenalidomide (Cohort D)	Clarified that initiation of lenalidomide post-JNJ-68284528 infusion requires resolution of CRS or neurotoxicities **per ASTCT criteria**.	
Time and Events Schedule (Table 1)	Added (under screening assessments) PET/CT or MRI whole body scan from screening to apheresis for subjects without measurable disease in serum or urine. Moved from MRD assessment by imaging (optional)	
Time and Events Schedule (Table 2 and Table 4)	Aligned window for collection of biomarker samples at apheresis with hematology and chemistry sample collection (≤72 hour window)	
Time and Events Schedule (Table 3)	Moved details of hematology collection in lenalidomide treatment period into footnote (w).	
Time and Events Schedule (Table 3)	Clarified that chemistry laboratory assessment should be performed at the start of each lenalidomide cycle during bridging.	
Time and Events Schedule (Table 3)	Added window for collection of hematology and chemistry on Day 1 with Cohorts A, B, and C. Added window for bone marrow aspirate and extramedullary plasmacytomas at conditioning regimen. Added MRD assessment by imaging at screening for subjects without measurable disease in urine or serum at baseline Added window for assessment of extramedullary plasmacytomas	
3.1. Overview of Study Design	Added the following: For all cohorts, at select sites ~~within the US~~ and at investigator discretion with sponsor approval, study visits in the post-treatment part of the study, as early as after Day 100 after JNJ-68284528 infusion, may be performed remotely via telemedicine technology that connects study subjects to their research coordinators and investigators **if not using the sponsor's telemedicine solution**.	
6.1.4. Lenalidomide (Cohort D)	Labeled Table 12 as Cohort D. Added cross reference to Table 15 in footnote.	
6.1.4. Lenalidomide (Cohort D)	Added that lenalidomide pill counts should be performed every cycle.	
14.5. Drug Accountability	Clarified that the investigator is responsible for ensuring that all **sponsor-provided** study treatment received at the site is inventoried and accounted for throughout the study.	
Attachment 1: Criteria for Response to Multiple Myeloma treatment	In footnote 'a' added the following: CR in such subjects indicates a normal FLC ratio of 0.26 to 1.65 **(or reference range in testing laboratory)** in addition to CR criteria listed above.	

Section Number and Name	Description of Change	Brief Rationale
Synopsis (Evaluations)	Added: For subjects with disease, but neither serum nor urine measurable disease, baseline PET/CT, or whole body MRI may be used to satisfy the measurable disease criteria.	Revisions for allow for PET/CT or whole body MRI to satisfy the measurable disease criteria.
Time and Events Schedule (Table 1)	For subjects with baseline measurable disease by PET/CT, added MRD assessment by imaging at screening, apheresis, and at 6 months, 12 months, and then yearly after infusion	
4.1.1. Cohort A Inclusion Criteria; 4.2.1. Cohort B Inclusion Criteria; 4.3.1. Cohort C Inclusion Criteria	Revised inclusion criterion to state that: For subjects with neither serum nor urine measurable disease, baseline PET/CT, or whole body MRI may be used to satisfy the measurable disease criteria	
9.2. Efficacy Evaluations	Added: Subjects who did not meet the definition of measurable disease per inclusion criterion and were enrolled in the study based on disease that is followed by PET/CT or whole body MRI must also follow the efficacy assessments for all other disease compartments (ie, serum, urine, bone marrow, skeletal (bone) lesions) as described in the Time and Events Schedule.	
9.2.6. Documentation of Extramedullary Disease/ Extramedullary Plasmacytomas	Added: These response criteria are applicable only to patients screened with measurable disease in serum or urine. For patients screened without measurable disease in serum or urine, via PET/CT or whole body MRI refer to Attachment 22 for response characterization.	
10.2. Discontinuation of Study Treatment	Revised bullet #4 as follows: Confirmed disease progression per IMWG criteria (Attachment 1) either between the time of conditioning therapy and infusion of JNJ-68284528, or during the post-JNJ-68284528 infusion ~~lenalidomide~~ treatment phase of Cohort D **with lenalidomide (as applicable) and Cohort E with daratumumab and lenalidomide. For subjects in Cohorts A, B, and C without measurable disease in serum or urine at screening, progression on either PET/CT scan or Whole Body MRI (see Attachment 22 for imaging response criteria) will be used.**	
11.3. Efficacy Analyses	Revised MRD negative rate definition for subjects without measurable disease in Cohorts A, B, and C. For ORR added: For subjects with neither serum nor urine measurable disease and using PET/CT or whole body MRI to satisfy the measurable disease criteria (Cohorts A, B, and C), see Attachment 22 for adjudication of response criteria and Attachment 23 for reporting considerations.	

Section Number and Name	Description of Change	Brief Rationale
	For PFS added: For subjects in Cohorts A, B, and C without measurable disease in serum or urine at screening disease, PFS is defined as the time from the date of the initial infusion of JNJ-68284528 to the date of disease progression as identified by imaging response criteria in Attachment 22 or death due to any cause, whichever occurs first.	
Attachment 22: Characterization of Imaging Response	Addition of Characterization of Imaging Response via PET/CT or Whole Body MRI	
Attachment 23: Recommendations for the Reporting of Imaging Results	Addition of Recommendations for the Reporting of Imaging Results	
Synopsis (Overview of Study Design); 1.2. Overall Rationale for the Study; 3.1. Overview of Study Design; 4.2.1. Cohort B Inclusion Criteria	For Cohort B: Disease progression per IMWG criteria ≤12 months after ASCT or disease progression ≤12 months from the start of anti-myeloma therapy for subjects who have not had an ASCT. Confirmation may be from either central or local testing.	Correction to window
Time and Events Schedule (Table 1, Table 3)	Revised timing of skeletal survey to allow it to be performed at screening or ≤14 days prior to the first dose of conditioning regimen.	Change made to allow for flexibility to allow skeletal survey to be performed in parallel with other disease evaluations.
Time and Events Schedule (Table 2)	Footnote 'g': deleted "For subjects in US" as PK and biomarker sample collection at the subject's home is not limited to only the US.	Correction
Time and Events Schedule (Table 3)	For Cohort D, added MRD assessment by imaging (optional) at screening.	Revision to align with common medical practice
Time and Events Schedule (Table 3)	Deleted duplicate information stating lenalidomide dosing is dependent on adequate hematologic recovery	Deletion of redundant information
4.3.1. Cohort C Inclusion Criteria	Criterion 7c revised to allow for transfusion within 3 days (reduced from 7 days) before hemoglobin and platelet testing.	Subjects in this cohort may have poor bone marrow reserve and require additional support
4.4.1. Cohort D Inclusion Criteria	Criterion 7d revised to state that women of childbearing potential must follow the contraception criteria outlined in the global REVLIMID® pregnancy prevention program **or equivalent local REMS as applicable in their region, whichever is more stringent.**	Clarification to inclusion criterion
4.1.2. Cohort A Exclusion Criteria; 4.2.2. Cohort B Exclusion Criteria; 4.3.2. Cohort C Exclusion Criteria; 4.4.2. Cohort D Exclusion Criteria	Added 'Contraindications' to exclusion criterion 16a (Cohort A), exclusion criterion 16b (Cohort B), exclusion criterion 15c (Cohort C), and exclusion criterion 14d (Cohort D).	Clarification to exclusion criteria
6. Dosage and Administration	For Cohort D, lenalidomide **given post JNJ-68284528** is also considered a study treatment.	Clarification on the definition of study treatment for Cohort D

Section Number and Name	Description of Change	Brief Rationale
6.1.4. Lenalidomide (Cohort D)	Consistent with the synopsis and Section 3.1.4, revised to state that subjects will receive lenalidomide at a dose of 10 mg per day upon adequate hematologic recovery from ASCT (absolute neutrophil count [ANC] ≥ 1 x 10^9/L and platelet count ≥ 75 x 10^9/L)	Clarification of lenalidomide dose after apheresis and prior to conditioning regimen
6.1.4. Lenalidomide (Cohort D)	In Table 14, Dose level -1; corrected starting dose (5 mg) as Days 1-21 every **28 day cycle.**	Correction of error
12.1.1. Adverse Event Definitions and Classifications	For determination of the expectedness of an adverse event, the daratumumab Investigator's Brochure should be used in regions without marketing authorization. For dexamethasone, bortezomib, and lenalidomide with marketing authorization, expectedness of an adverse event will be determined by the prescribing information.	Revisions include daratumumab, lenalidomide, bortezomib, and dexamethasone
12.3.1. All Adverse Events	Revised language for exceptions	Revised for consistency with current template language
12.3.1. All Adverse Events; 12.3.3. Adverse Events of Special Interest	The sponsor assumes responsibility for appropriate reporting of RCL positive test results to regulatory authorities and will notify the investigator of positive RCL test results in a timely manner. RCL positive test results will not be collected as an adverse event in the eCRF.	Revision to clarify testing and reporting of replication competent lentivirus (RCL)
12.3.3. Adverse Events of Special Interest; 12.3.4. Pregnancy	Revised text to clarify that all subjects must adhere to the global REVLIMID® pregnancy prevention program or equivalent local lenalidomide pregnancy prevention program applicable in their region, whichever is more stringent	Revisions to provide additional guidance on lenalidomide Global Pregnancy Prevention Plan
Attachment 16: Contraceptive and Barrier Guidance and Collection of Pregnancy Information	Renamed attachment from "Definition of Woman of Childbearing Potential" to "Contraceptive and Barrier Guidance and Collection of Pregnancy Information". Added examples of contraceptives.	
12.3.1. All Adverse Events; Attachment 13: Anticipated Events	Deleted as anticipated events are considered not applicable for non-randomized studies	Correction in response to latest recommendations
Attachment 20: COVID-19 Guidance on Study Conduct	Added guidance on study conduct during the COVID-19 pandemic	COVID-19 Appendix
Throughout the protocol	Minor grammatical, formatting, or spelling changes were made.	Minor errors were noted

Amendment 2 (23 March 2020)

Overall Rationale for the Amendment: The overall reason for the amendment is to add other neurotoxicities as a safety risk and implement additional monitoring and risk minimization measures for JNJ-68284528.

Section number and Name	Description of Change	Brief Rationale
Time and Events Schedule: Cohort A, Cohort B, and Cohort C (Table 1) Time and Events Schedule: Cohort D (Table 3)	Collection of a handwriting sample and frequency of testing was added to the study procedures. Study Day 35 was added to the table as additional assessment days for collection of handwriting samples. Added that collection of medical history should include neurologic history	Update of safety information to include other neurotoxicities
	Added that ICE neurologic test should be performed at least until **ICANS is** resolved.	
	Added: Reporting of neurologic adverse events or exacerbation of existing neurologic adverse events will be extended to up to 12 months after JNJ-8284528 infusion	
1.1.5. Clinical Studies	Added to summary of data for Study 68284528MMY2001 a description of 6 cases of other neurotoxicities.	
1.3. Potential Safety Risks and Mitigation Strategies	Added other neurotoxicities to Table 5 (Risks Associated with JNJ-68284528 and Mitigation Strategies) as a subsection of neurologic toxicities	
2. Objectives and Endpoints	Added exploratory objective and endpoints to characterize potential early predictive markers for neurotoxicity	
4.1.2. Cohort A Exclusion Criteria (criterion 17a); 4.2.2. Cohort B Exclusion Criteria (criterion 17b); 4.3.2. Cohort C Exclusion Criteria (criterion 16c); 4.4.2. Cohort D Exclusion Criteria (criterion 17d)	Added the following to the list of serious underlying medical conditions: Any history of Parkinson's disease or other neurodegenerative disorder	
6.1.3. JNJ-68284528 Administration	Table 6 – Added: 'Hospitalization is required for Grade 2, 3, or 4 CAR-T cell-related neurotoxicity (eg, ICANS) **temporally associated to CRS**.' **Hospitalization for neurotoxicity that is not temporally associated with CRS, or any other neurologic adverse events, is at the discretion of the investigator.**	
6.2.2. Neurologic Adverse events	Divided section into overall neurologic adverse events with sub-sections of CAR-T cell related neurotoxicity (ICANS) (Section 6.2.2.1) and other neurotoxicities (Section 6.2.2.2). Added that subjects should be monitored for neurotoxicity for 1 year post JNJ-68284528 infusion.	

Section number and Name	Description of Change	Brief Rationale
6.2.2.1. CAR-T Cell-related Neurotoxicity (ICANS)	Added "Consider performing neuroimaging (eg, MRI)." Clarified that hospitalization is required for Grade 2, 3, or 4 CAR-T cell-related neurotoxicity temporally associated to CRS. Added recommendation to rule out alternative etiologies at first sign of neurotoxicity. Table 13 (Guidelines for Management of ICANS) – added to row 1 (ICE score 7-9) when no concurrent CRS dexamethasone can be considered	
6.2.2.2. Other Neurotoxicities	New section with guidance to monitor for other neurotoxicities	
9.7. Safety Evaluations	Text updated to include additional guidance regarding the reporting of neurotoxicity events. To neurologic examination subsection, Added the following: For subjects with prior pertinent neurologic disease (eg, stroke, encephalitis) consider baseline MRI of the brain and an EEG. Added a section describing the assessment for qualitative changes in handwriting.	
12.3.1. All Adverse Events	Added that changes in handwriting using criteria in Attachment 17 should be reported as an adverse event in the eCRF.	
Attachment 17: Handwriting Adverse Event Toxicity Grading Criteria	Table for added for qualitative grading of handwriting sample	
Time and Events Schedule: Cohort A, Cohort B, and Cohort C (Table 1) Time and Events Schedule: Cohort D (Table 3)	Table 1 (footnote g) and Table 3 (footnote g), Added that Serology results performed as standard of care within 28 days prior to apheresis are acceptableHepatitis B recommendation revised as follows: HBsAg, anti-HBc, anti-HBs, HBV DNA quantification (for subjects who are anti-HBs positive without history of vaccination or for subjects who are **anti-HBc positive with or without** anti-HBs positive ~~and anti-HBc positive~~).	Revisions to enrich the clinical trial population by allowing inclusion of subjects who are anti-HBc positive with or without anti-HBs positive
9.7. Safety Evaluations	Revisions made to Hepatitis B serology: Hepatitis B: HBsAg, anti-HBc, anti-HBs, HBV DNA quantification (for subjects who are anti-HBs positive without history of vaccination or for subjects who are **anti-HBc positive with or without** anti-HBs positive ~~and anti-HBc positive~~)	

Section number and Name	Description of Change	Brief Rationale
Attachment 10: Hepatitis B Virus Screening	Revised hepatitis B screening guide to allow subjects who are anti-HBc positive only to participate in the study Added "If there is evidence of HBV reactivation initiate treatment as appropriate per institutional guidance".	
Synopsis	Subheadings added to dosage and administration to separate individual cohorts	Revisions made for clarity
	Repeated dosage information in Cohort D rather than cross referencing to another cohort to group information for clarity	
Time and Events Schedule (Table 1, Table 3)	Added window to clarify timing of collection of hematology samples at apheresis	
	For infectious disease testing, merged screening and apheresis columns and added collection window	
	Clarified timing of sample collections for MRD	
	MySIm-Q changed from optional to 'unless translation not available'	
Time and Events Schedule (Table 1, Table 3)	For concomitant medications, added that collection is continuous '..until **at least** 100 days…'. Also added "Thereafter, continue to report concomitant therapy given for any Adverse Events considered related to study drug until the end of the study".	
4.1.1. Cohort A Inclusion Criteria	Clarified criteria for lenalidomide refractory includes patients with non-responsive disease while on lenalidomide for at least 1 cycle	
4.3.2. Cohort C Exclusion Criteria	Revised prior antitumor therapy as follows: Targeted therapy, epigenetic therapy, or treatment with an investigational drug or used an invasive investigational medical device within 14 days ~~or at least 5 half-lives, whichever is longer~~	
7. Treatment Compliance	Added that site specific methods to ensure compliance with outpatient medication is permissible.	
9.5. Biomarkers Evaluations	Defined that additional biomarker samples include but are not limited to serum or PBMCs from whole blood. Clarified that a tumor sample should be collected from subjects diagnosed with a SPM.	
9.5. Biomarkers Evaluations	Added that if a subject dies and an autopsy is preformed, specimens may be requested by the sponsor for analysis.	
9.9. Medical Resource Utilization	Added that costs associated with the medical encounters will be collected separately from the eCRF. All health economic data will be used only in a de-identified manner.	
9.7. Safety Evaluations; 12.1.3. Safety Criteria	Defined grading criteria for ICANS and CRS.	
11.3. Efficacy Analyses	Added: A sensitivity analysis of overall MRD negative rate will be performed based on the subjects in the mITT analysis set who received the JNJ-68284528 product that met all of the pre-specified release criteria	

Section number and Name	Description of Change	Brief Rationale
Time and Events Schedule (Table 1)	Revised collection of disease characteristics from screening phase, to occur between screening and the conditioning regimen.	Change made to avoid additional bone marrow collections
Time and Events Schedule (Table 1, Table 3)	Day 21 visit window changed from ±1 day to ±2 days for consistency with the PK/biomarker assessments in Tables 2 and 4.	Revised visit window for consistency
Time and Events Schedule (Table 3)	Revised language for pregnancy testing during lenalidomide treatment: to be 'repeated' ~~and repeated at a maximum of~~ at least every 28 days.	Revised pregnancy testing guidelines to be consistent with lenalidomide REMS
4.4.1. Cohort D Inclusion Criteria	Criterion 7d revised to state that subject must agree to practice 2 methods of reliable birth control simultaneously from **4 weeks prior to initiating treatment with lenalidomide** ~~the time of signing the ICF~~ until 1 year after receiving JNJ-68284528 infusion	
Attachment 16: Definition of Woman of Childbearing Potential	Postmenopausal state definition changed from 12 months with no menses to 24 months with no menses	
Time and Events Schedule (Table 3)	Added serum FLC and serum/urine immunofixation, MRD (bone marrow aspirate) collections and assess extramedullary plasmacytomas at conditioning regimen	Change for consistency with other cohorts
4.3.1. Cohort C Exclusion Criteria	Criterion 3c modified as follows: Targeted therapy, epigenetic therapy, or treatment with an investigational drug or used an invasive investigational medical device within 14 days ~~or at least 5 half-lives, whichever is longer~~.	
Time and Events Schedule (Table 4)	Added collection of PBMCs for functional in vitro assays	Correction of error
4.1.2. Cohort A Exclusion Criteria; 4.2.2. Cohort B Exclusion Criteria; 4.3.2. Cohort C Exclusion Criteria 4.4.2. Cohort D Exclusion Criteria	Localized prostate cancer with a Gleason score of 6 corrected to "Gleason score of ≤6".	
Time and Events Schedule (Cohort D, Table 4)	Added collection of PBMCs for functional in vitro assays (omitted in error in Amendment 1)	
9.1.6.2. Post-treatment Period (Cohorts A, B, and C)	Paper PROs will be used in this study. Deleted the following: "PRO assessments may be captured via smart phone based application and electronic patient reported outcomes (ePRO) instruments".	
1.1.5. Clinical Studies	Added an update to Study 68284528MMY2002	Updated study information added
1.3. Potential Safety Risks and Mitigation Strategies (Table 5)	Added that sponsor should be notified if a subject is experiencing Grade 2 or higher CRS Added that sponsor should be notified if a subject is experiencing any grade ICANS	Revised risk language

Section number and Name	Description of Change	Brief Rationale
1.3. Potential Safety Risks and Mitigation Strategies (Table 5); 6.2.7. Infections	Added that JNJ-68284528 should not be administered to subjects with active infections Added recommendation for extended use of anti-microbial therapies	Revised guidance for infections
Attachment 18	Added table with anti-microbial prophylaxis recommendations	
3.1. Overview of Study Design	Data Monitoring Committee (DMC) added for periodic review of all safety data.	Data Monitoring Committee added
3.1. Overview of Study Design; 9.1.6.2. Post-treatment Period (Cohorts A, B, and C)	Added that 'with sponsor approval' study visits in the post-treatment part of the study 'as early as' after Day 100 may be performed remotely via telemedicine technology.	Revisions to allow telemedicine visits to occur earlier for some subjects
3.1.1. Cohort A Study Design; 3.1.2. Cohort B Study Design; 3.1.3. Cohort C Study Design; 3.1.4. Cohort D Study Design	Revised bridging therapy options to include therapies to which a subject has not been previously exposed.	Revisions to bridging therapy recommendations
Time and Events Schedule (Cohort D, Table 3); Synopsis (Overview of Study Design); 3.1.4. Cohort D Study Design	Added that alternative bridging therapy instead of, or in addition to, lenalidomide is permissible with sponsor approval.	
Time and Events Schedule (Cohort D, Table 3);	Added that Cycle 2 of bridging therapy is permitted with sponsor approval.	
3.1.5. Retreatment with JNJ-68284528	Bridging therapy is allowed for subjects receiving retreatment with permission from the sponsor.	
Synopsis (Dosage and Administration); 3.1.4. Cohort D Study Design; 6.1.4. Lenalidomide (Cohort D)	The first 5 subjects in Cohort D will be treated with JNJ-68284528 only, there will be no lenalidomide after JNJ-68284528. The DMC will review the data from these 5 subjects and recommend if treating with lenalidomide should proceed. Once dosing of subjects with lenalidomide is initiated, a stagger of at least 4 weeks between subjects will continue for the next 5 subjects.	Revised staggered dosing strategy for Cohort D
6.1.4. Lenalidomide (Cohort D)	Added: **Initiation and continuation of lenalidomide treatment is dependent on no additional safety concerns by investigator or sponsor**	
6.1.3. JNJ-68284528 Administration (All Cohorts)	Target dose statement in Table 6 revised as follows: The target dose will be the RP2D ~~which is anticipated to be~~ **of** 0.75 x 10^6 CAR-positive viable T cells/kg (range: 0.5-1.0 x 10^6 CAR-positive viable T cells/kg) as described in Section 3.3	Clarification that RP2D is known (no longer anticipated to be)

Section number and Name	Description of Change	Brief Rationale
1.3. Potential Safety Risks and Mitigation Strategies (Table 5); 6.2.5. Cytopenia	Added consideration of parvovirus B19 monitoring	Additional guidance for cytopenia and hypogammaglobulinemia
1.3. Potential Safety Risks and Mitigation Strategies (Table 5); 6.2.6. Hypogammaglobulinemia	Added that subjects IgG <400 mg/dL and recurrent infections may receive prophylactic IVIG	
9.1.6.3. Lenalidomide Treatment Period after JNJ-68284528 Infusion (Cohort D)	Lenalidomide treatment period lasts until study completion defined as: ~~2 years~~ after the last subject in Cohort D has discontinued **lenalidomide for 4 weeks or has had 2 years of follow-up after receiving** ~~received~~ his or her initial dose of JNJ-68284528, **whichever is later**	Revised definition of lenalidomide treatment period.
9.2.7. Local Laboratory Assessments; 9.2. Efficacy Evaluations Time and Events Schedule (Table 1 and Table 3),	Added a section to allow for local laboratory data to be collected if central laboratory data is not available. Added footnote 's' (Table 1) and footnote 'u' (Table 3)	Addition to allow for flexibility in collecting laboratory data
Attachment 14 (JNJ-68284528 Outpatient Administration Guidelines)	Added that sponsor approval is required when evaluating for the suitability of outpatient administration	Revised for consistency
Throughout the protocol	Minor grammatical, formatting, or spelling changes were made.	Minor errors were noted

Amendment 1 (31 October 2019)

Overall Rationale for the Amendment: The overall reason for the amendment is to add 2 new cohorts of subjects with multiple myeloma representing different populations of unmet medical need.

Section number and Name	Description of Change	Brief Rationale
Synopsis, Overview of Study Design; 1.2. Overall Rationale for the Study; 3.1. Overview of Study Design; 3.1.3. Cohort C Study Design	Added description of the study design for Cohort C	Addition of Cohort C, which consists of subjects with relapsed refractory disease previously treated with a PI, IMiD, anti-CD38 monoclonal antibody, and BCMA-directed therapy.
Time and Events Schedule	Cohort C assessments to be collected per Table 1 and Table 2	
3.3. Study Design Rationale	Added rationale for the design of Cohort C	
4.3. Cohort C Eligibility Criteria	Added inclusion and exclusion criteria for subjects to be enrolled in Cohort C	

Section number and Name	Description of Change	Brief Rationale
Synopsis, Overview of Study Design; 1.2. Overall Rationale for the Study; 3.1. Overview of Study Design; 3.1.4. Cohort D Study Design	Added description of the study design for Cohort D	Addition of Cohort D, which consists of subjects with recently diagnosed multiple myeloma who did not achieve CR after 4-8 total cycles of initial therapy, including induction, high-dose chemotherapy, and ASCT with or without consolidation.
Synopsis, Dosage and Administration;	Subjects in Cohort D will receive 1 cycle of lenalidomide after apheresis and before conditioning regimen. At least 21 days post infusion of JNJ-68284528, and after adequate hematologic recovery, subjects will receive lenalidomide treatment.	
Time and Events Schedule	Time and Events Tables 3 and 4 added for Cohort D	
3.1.5. Retreatment with JNJ-68284528	Added "Subjects in Cohort D will not be allowed to receive retreatment".	
3.3. Study Design Rationale	Added rationale for the design of Cohort D	
4.4. Cohort D Eligibility Criteria	Added inclusion and exclusion criteria for subjects to be enrolled in Cohort D	
6.1.4. Lenalidomide (Cohort D)	Section added to provide dosing information for lenalidomide.	
7. Treatment Compliance	Added that pill counts will be used to assess compliance to lenalidomide	
8.2. Permitted Medications	Added cross reference to lenalidomide prescribing information for subjects in Cohort D	
8.3. Prohibited Therapies	Added cross reference to lenalidomide prescribing information for subjects in Cohort D	
9.1.7.2. Post-treatment Period (Cohort D)	Added separate description for the post-treatment period for Cohort D.	
10.2. Discontinuation of Study Treatment	Added that criteria apply to discontinuation of lenalidomide.	
12.3.3. Adverse Events of Special Interest	Added reference to the REMS program for lenalidomide with regards to the embryo-fetal risks to ensure compliance with the guidance on subject education	
Synopsis, Dosage and Administration; 3.1.1. Cohort A Study Design; 3.1.2. Cohort B Study Design; 3.1.3. Cohort C Study Design; 3.1.4. Cohort D Study Design; 3.2. Rationale of Dose and Administration Schedule Selection; 6.1.2. Administration of Conditioning Regimen; 9.1.4. Cyclophosphamide and Fludarabine Conditioning Regimen	Added "The dose of fludarabine should be reduced to 24 mg/m^2 for subjects with an estimated glomerular filtration rate of 30 to 70 $mL/min/1.73m^2$."	Added guidance to reduce the recommended dose of fludarabine in subjects with renal dysfunction.

Section number and Name	Description of Change	Brief Rationale
Synopsis, Statistical Methods; 11.2. Sample Size Determination	Deleted "For Cohort A and Cohort B, an MRD negative rate of less than 10% is deemed not clinically meaningful. With 20 subjects, the lower bound of 90% CI will be ≥10% if more than 4 subjects achieve MRD negativity."	Removed language referring to specific MRD negative rates in individual cohorts as sample size is not driven by statistics.
Synopsis, Study Hypotheses; 2.2. Hypotheses	Removed specific statistical language for MRD negative rate.	Aligned hypothesis statement with changes to statistical methods section
Time and Events Schedule (Table 1); 9.7. Safety Evaluations	Added an ocular examination for subjects in Cohort C who received prior ADC treatment Footnote 'r' specifies requirements of ocular examination.	Addition for safety monitoring
Time and Events Schedule (Table 1); 6.1.3. JNJ-68284528 Administration (All Cohorts); 9.1.7. Post-treatment Phase; 16.1. Study-specific Design Considerations; Attachment 14; Attachment 15	Added guidance for screening subjects for outpatient suitability and monitoring for subjects receiving JNJ-68284528 as an outpatient	Addition of guidance to evaluate subjects for outpatient suitability
Time and Events Schedule (Table 1); 2.1. Objectives and Endpoints; 9.6. Patient Reported Outcomes; 11.8. Patient-reported Outcome Assessments; Attachment 11	The EQ-5D-5L measure was replaced with the Multiple Myeloma Symptom and Impact Questionnaire (MySIm-Q). The MySIm-Q is an optional assessment. Added endpoint for worsening of symptoms using MySIm-Q	Change made in response to evolving PRO strategy
Time and Events Schedule (Table 1); 2.1. Objectives and Endpoints; 9.9. Medical Resource Utilization	MRU assessments will be collected for subjects in all cohorts	Addition for consistency with other studies in the program
Time and Events Schedule (Table 1)	Added ≤24-hour window to hematology and chemistry assessments collected pre-dose (JNJ-68284528 infusion) and for assessment criteria to be collected prior to JNJ-68284528 infusion. Windows added for assessment of extramedullary plasmacytomas Footnote 'i' (vital signs): added window of ±10 minutes	Added collection windows for clarity and consistency across subjects
Time and Events Schedule (Table 2)	Added a window of ≤4 hours for pre-dose PK and biomarker samples not previously defined with collection window	

Section number and Name	Description of Change	Brief Rationale
Time and Events Schedule (Table 1)	Frequency of serology testing expressed in weeks instead of months Added that adverse events considered related to study drug need to be reported until the end of study Footnote 'g': added additional guidance around testing for subjects who are positive for antibodies to hepatitis B and subjects with HBV vaccination.	Revisions incorporated to harmonize language within this protocol and across studies
4.1.1. Cohort A Inclusion Criteria	Criterion 1a: Revised language to clarify lenalidomide refractory requirement	
4.1.1. Cohort A Inclusion Criteria; 4.2.1. Cohort B Inclusion Criteria	Criterion 7a and 7b: Replaced laboratory criteria of 'creatinine clearance' with 'estimated glomerular filtration rate'	
4.1.2. Cohort A Exclusion Criteria; 4.2.2. Cohort B Exclusion Criteria	Revised criterion 15a and 15b regarding requirement of supplemental oxygen Criterion 17a and 17b: clarified that bacterial infection 'requiring systemic antimicrobial therapy' as a serious underlying medical condition.	
6.1.1. Criteria for Apheresis; 6.1.2.1 Criteria for Conditioning Regimen	Harmonized language across JNJ-68284528 protocols has been incorporated	
9.7. Safety Evaluations	Added "Beyond the adverse event reporting period, adverse events that are considered related to study drug need to be reported until the end of the study" Added guidance regarding collection of follow-up data for Grade 3 or higher laboratory abnormalities	
Time and Events Schedule (Table 1)	Day 56 MRD evaluation added	To harmonize with bone marrow collections for PK and biomarkers
Time and Events Schedule (Table 1)	During the JNJ-68284528 infusion period, post-infusion period, and post-treatment phase added that pregnancy testing should be performed as clinically indicated 'or as mandated by local regulations, whichever is more stringent'	Revision to pregnancy testing to accommodate local regulations
Time and Events Schedule (Table 1)	Timing of the MRD (bone marrow aspirate) assessment changed from Day 28 to Day 56	Change made to more accurately capture the depth of response
Time and Events Schedule (Table 1)	Added PRO assessments (EORTC QLQ-C30, MySIm-Q, and PGIS) at apheresis	Assessment at apheresis added in order to obtain 2 timepoints before subjects receive treatment.
Time and Events Schedule (Table 2)	Footnote 'h' (whole blood immunophenotyping) and 'i' (flow cytometry, bone marrow) to specify when additional samples may be collected at the discretion of the investigator.	Footnotes added for guidance regarding additional sample collections

Section number and Name	Description of Change	Brief Rationale
Synopsis, Dosage and Administration; 6.1.4. Lenalidomide (Cohort D)	Added that subjects will continue to receive lenalidomide for 2 years post JNJ-68284528 infusion	Duration of lenalidomide treatment added.
Synopsis, Overview of Study Design; 1.2. Overall Rationale for Study Design	Added that subjects who have received prior therapy that is targeted to BCMA are excluded from Cohorts G and H; and that subjects who met eligibility criteria for Cohort A and Cohort B must be enrolled in Cohort B.	Additions for clarity
Time and Events Schedule (Table 1)	Table 1, added entry for criteria for JNJ-68284528 administration	
Time and Events Schedule (Table 1)	Added footnote 'e' to clarify the collection window for disease characteristics cytogenetics.	
Time and Events Schedule (Table 1)	The placement of footnote 'k' for quantitative immunoglobulins was updated as it applies to the entire duration of the study. Added footnote 'q' to indicate that additional immunoglobulin samples may be collected as clinically indicated for safety	
Time and Events Schedule (Table 1)	The description of extramedullary Plasmacytomas was updated to: 'By physical examination (if applicable): measurable sites at D28, D56, D78, D100 and then every 4 weeks. By radiologic imaging: D78, D156 then every 12 weeks (for all subjects with a history of plasmacytomas or as clinically indicated for others)' ~~Measurable sites Day 28, Day 56, Day 78, Day 100 then every 4 weeks for physical examination (if applicable) and Day 78 and Day 156 then every 12 weeks for radiologic assessment (for subjects with a history of plasmacytomas or as clinically indicated for others).~~	
Time and Events Schedule (Table 1); 1.3. Potential Safety Risks and Mitigation Strategies; 6.2.4. Second Primary Malignancy; 9.1.7.3. Long-term Follow-up	Added language to indicate that a tumor sample should be collected for any second primary malignancies in text and footnote 'p'.	
Time and Events Schedule (Table 1); 9.1.7.1. Post-treatment Period (Cohorts A, B, and C)	Added to survival follow-up that survival status will also be collected prior to the any planned efficacy analysis	
1.3. Potential Safety Risks and Mitigations	Added cross references from Table 5 to management guidelines in the document	
3.1.1. Cohort A Study Design; 3.1.2. Cohort B Study Design	Removed 'anticipated to be' from the recommended Phase 2 dose as the dose has now been established.	

Section number and Name	Description of Change	Brief Rationale
4.1.2. Cohort A Exclusion Criteria; 4.2.2. Cohort B Exclusion Criteria	Criterion 5a and 5b modified to state "Ongoing" toxicity from previous anticancer therapy…	
6.1.3.1. Exceptional Release Criteria	Added text stating that the investigator will discuss with the subject if product does not meet pre-specified release criteria	
6.2.7. Infections	Clarified that HBV reactivation has occurred "in subjects receiving other CAR-T products"	
6.2.8. Hypersensitivity Reactions	Added reference to lenalidomide prescribing information for subjects in Cohort D	
8.3. Prohibited Therapies	Added that 'systemic' corticosteroids' should be avoided.	
9.2.1. Bone Marrow Examination for MRD Assessment	Added "In case the myeloma clone is not be identified successfully from the baseline fresh bone marrow aspirate, the sponsor will ask for non-decalcified diagnostic tissue."	
9.7. Safety Evaluations	Added for Cohort D: adverse events will be collected 100 days after JNJ-68284528 infusion or 30 days after the last dose of lenalidomide (whichever is later).	
12.1.1. Adverse Event Definitions and Classifications	Clarified definition of a serious adverse event as inpatient hospitalization **that was not required by the protocol**.	
12.3.1. All Adverse Events; 12.3.3. Adverse Events of Special Interest	Clarified the time period for reporting adverse events and serious adverse events as 100 days after infusion of JNJ-68284528 (Cohorts A, B, and C), and 100 days after infusion of JNJ-68284528 or 30 days after the last dose of lenalidomide, whichever is later (for Cohort D)	
12.3.2. Serious Adverse Events	Added, for clarity: Events that require an escalation of care when the subject is already hospitalized should be recorded as an SAE. Examples of such events were added in text.	
Throughout the document	Revised reference to 'Cohort A and Cohort B' to state 'all Cohorts' where applicable or reference to specific individual Cohorts, as applicable.	
Time and Events Schedule (Table 1)	PRO-CTCAE is no longer optional.	Updates to PRO-CTCAE
Time and Events Schedule (Table 1); 9.7. Safety Evaluations; 12.1.3. Severity Criteria; Attachment 2; Attachment 4	Updated reference for ASBMT criteria and added incorporated change in name (to ASTCT).	Update to ASBMT criteria
Time and Events Schedule (Table 2)	Added footnote 'g' to state that PK and biomarker collections may be performed at the subject's home by mobile study personnel	Revisions to include the capability for nursing home visits

Section number and Name	Description of Change	Brief Rationale
3.1. Overview of Study Design; 9.1.7.1. Post-treatment period (Cohorts A, B, and C)	Added that, at the discretion of the investigator, study visits in the post treatment phase may be performed remotely via telemedicine technology and that blood sample collection may be performed in the subject's home by mobile study personnel. PRO assessments may be captured via smart-phone based application and ePRO instruments.	
1.1.5. Clinical Studies	Updated summary of preliminary data for Study 68284528MMY2001 Added a brief summary of preliminary data for Study 68284528MMY2002 Consolidated summary of data from the Legend-2 study	Updated data provided for ongoing studies
1.3. Potential Safety Risks and Mitigation Strategies	In Table 5, additional guidance added for CRS, SPM, cytopenias, and hypogammaglobulinemia	Updates in response to evolving safety information
3.1.1 Cohort A Study Design; 3.1.2 Cohort B Study Design	Guidance provided on dose reduction for fludarabine in subjects with renal dysfunction.	
6.2.5. Cytopenia	Added text stating that "severe thrombocytopenia may increase the risk of bleeding" Added precaution for neutropenia and thrombocytopenia for subjects in Cohort D upon receiving lenalidomide after JNJ-68284528	
6.2.6. Hypogammaglobulinemia	Added that vaccination with live virus is not permitted for at least 4 weeks prior to the start of conditioning regimen "and for 100 days after infusion of JNJ-68284528"	
3.1.2. Cohort B Study Design	Deleted text stating that the medical monitor must be contact before administration of bridging therapy and replaced with more specific guidance regarding when bridging therapy will be allowed	Guidance added for use of bridging therapy in Cohort B
3.1.5. Retreatment with JNJ-68284528	Revised criteria to state that to be eligible for retreatment the subject must have no ongoing Grade 2 non-hematologic toxicity (except for nausea, vomiting, hair loss) and no ongoing Grade 3 or higher hematologic toxicity.	Refined retreatment criteria
3.2. Rationale of Dose and Administration Schedule Selection	Added brief summary of data from Study 68284528MMY2001 used to form the decision of the Safety Evaluation Team	Recommended Phase 2 dose has been determined

Section number and Name	Description of Change	Brief Rationale
3.3. Study Design Rationale	Deleted "Further, the sponsor will assess whether a fixed-timepoint at 1 year for evaluation of MRD negativity is as predictive of long-term outcome as the overall MRD negative rate."	Correction to MRD analysis
4.1.1. Cohort A Inclusion Criteria	Criterion 1a – deleted text for smoldering myeloma Criterion 2a – revised evidence of progressive disease within 6 months of the last regimen Criterion 8a – correction to timing of pregnancy testing (deleted prior to first dose of conditioning regimen)	Revision for consistency in language with protocols from other JNJ-68284528 studies
4.2.1. Cohort B Inclusion Criteria	Criterion 1b - removed mention of smoldering myeloma Criterion 8b – correction to timing of pregnancy testing (deleted prior to first dose of conditioning regimen)	
4.1.1. Cohort A Inclusion Criterion; 4.1.2. Cohort A Exclusion Criteria; 4.2.1. Cohort B Inclusion Criterion; 4.2.2. Cohort B Exclusion Criterion	The amount of time that a subject must agree to remain on a highly effective method of contraception, planning to become pregnant, or father a child, changed from 'at least 100 days' to '1 year' after receiving an infusion of JNJ-68284528	Updates to the length of time subjects must remain on a highly effective method of contraception
4.1.2. Cohort A Exclusion Criteria; 4.2.2. Cohort B Exclusion Criteria	Criteria 3a revised with updated list of exceptions to active malignancies.	Revision to be consistent with current template language
6.1.3.1. Exceptional Release Criteria	Added that notification and approval for use of the product will be obtained "in compliance with local regulations Changed "investigators **should** inform the study subject" to "investigators **will** inform the study subject" Deleted text stating that subjects must sign an ICF to consent to receive product as that is no longer a requirement	Corrections to exceptional release criteria
8. Prestudy and Concomitant Therapy	Added requirements for Cohorts C and D	Revision to accommodate the addition of new cohorts
9.1.1 Overview	Updated volume of blood required for all cohorts	
9.1.6.2. Post-treatment Period	Specified in the section header that language in this section is applicable to Cohorts A, B, and C	
8. Prestudy and Concomitant Therapy	A list of medications given for adverse events (to be recorded) has been added	Added guidance to concomitant medications that should be recorded
9.1.7.1. Post-treatment Phase	Removed text that is repetitive with other sections of the protocol	Consolidated text to remove redundancy

Section number and Name	Description of Change	Brief Rationale
11.3. Efficacy Analyses	Added "For time-to-event endpoints, such as DOR, PFS, and OS, the distributions will be provided using Kaplan-Meier estimates. Detailed analysis methods will be provided in the Statistical Analysis Plan."	Added methods for analysis of time-to-event endpoints
12.3.1. All Adverse Events	Added that all deaths at any time not related to disease progression occurring at any time of the study should be reported to the sponsor following expedited reporting procedures.	Revised in response to health authority feedback
12.3.3. Adverse Events of Special Interest	Added that the following events must be reported to the sponsor using the Serious Adverse Event Form within 24-hours of awareness: ≥Grade 3 CRS, ≥Grade 3 neurotoxicity, ≥Grade 3 tumor lysis syndrome second primary malignancies	
Attachment 16	Woman of Childbearing Potential and Woman of Not of Childbearing Potential has been defined in detail	Provided a definition of women of childbearing potential
Throughout the protocol	Minor grammatical, formatting, or spelling changes were made.	Minor errors were noted

SYNOPSIS

A Phase 2, Multicohort Open-Label Study of JNJ-68284528, a Chimeric Antigen Receptor T cell (CAR-T) Therapy Directed Against BCMA in Subjects with Multiple Myeloma

Synopsis is based on Protocol 68284528MMY2003 Amendment 6/EEA-1, finalized on 17 August 2023.

EudraCT NUMBER: 2018-004124-10

EU CTR NUMBER: 2023-506587-13-00

Ciltacabtagene autoleucel (cilta-cel) is an autologous chimeric antigen receptor T cell (CAR-T) therapy that targets B cell maturation antigen (BCMA), a molecule expressed on the surface of mature B-lymphocytes and malignant plasma cells. The cilta-cel drug product used in this study and the LCAR-B38M CAR-T cell drug product used in the first-in-human Legend-2 study express an identical CAR protein. The cilta-cel drug product will be produced using modified manufacturing and scale-up processes. Results from the Phase 1b portion of Study 68284528MMY2001 and the Legend-2 study indicate that cilta-cel and LCAR-B38M CAR-T cells have significant anti-myeloma activity and a safety profile consistent with the known mechanism of action of the product.

The objective of Study 68284528MMY2003 is to determine the safety and efficacy of cilta-cel in various MM treatment settings. Multiple cohorts will run in parallel for enrollment of unique patient populations of unmet medical need. Details of each cohorts A though F are provided in the Overview of Study Design section 3.1.

BENEFIT-RISK ASSESSMENT

Despite the success of current treatments and of new triplet regimens that include daratumumab and other novel agents in prolonging progression-free survival (PFS) and overall survival (OS) in multiple myeloma (MM) patients, the disease remains incurable. Subgroups of MM patients, particularly those with high-risk disease characteristics, who are lenalidomide refractory, have had an early relapse, or are heavily pretreated are especially at need for new treatment options. Experience with cilta-cel in Study 68284528MMY2001 and LCAR-B38M CAR-T cells in the Legend-2 study demonstrates high response rates, MRD negative rates, and acceptable toxicity in a heavily pre-treated population of subjects with MM. Further, as the efficacy of CAR-T therapy is dependent on a patient's immune response, cilta-cel has the potential to be more efficacious and produce more durable responses in the frontline MM setting for patients whose immune systems have experienced very limited exposure to immunomodulatory and cytotoxic therapy.

Potential safety risks for cilta-cel include neurologic toxicity, prolonged and recurrent cytopenia, serious infection, second primary malignancies, tumor lysis syndrome, hypogammaglobulinemia, and hypersensitivity reactions. Mitigation measures for these potential risks have been planned for and are included in this protocol, including close monitoring of safety data of all patients by an interdisciplinary medical team during the conduct of the study as well as by the study's Data Monitoring Committee (DMC). Considering the risk minimization measures, the potential risks identified in association with cilta-cel are justified by the anticipated benefits that may be afforded to subjects with both newly diagnosed (NDMM) and relapsed refractory MM (RRMM).

PRIMARY OBJECTIVE, ENDPOINT

For Cohorts A – F

Objective	Endpoint
Primary	
To evaluate the overall minimal residual disease (MRD) negative rate of subjects who receive cilta-cel	MRD negative rate (10^{-5} threshold) as defined by the International Myeloma Working Group (IMWG) criteria using next generation sequencing (NGS) or next generation flow (NGF)

For Cohorts G and H

Objective	Endpoint
Primary	
• Cohort G: To evaluate the efficacy of DRd followed by cilta-cel in subjects for whom transplant is not planned • Cohort H: To evaluate the efficacy of D-VRd followed by cilta-cel in subjects who are transplant eligible	Sustained MRD-negative CR, defined as MRD-negative CR for a minimum 12 month duration, with MRD status determined by NGS with a sensitivity of at least 10^{-5}

STUDY HYPOTHESES

For Cohorts A – F

The primary hypothesis is that cilta-cel will induce a deep-response, measured by MRD negative rate in the clinical settings investigated.

For Cohorts G and H

There is no statistical hypothesis testing in these study cohorts. The clinical hypothesis is that cilta-cel will induce a deep and durable response, measured by sustained MRD negative CR in the clinical settings investigated.

OVERVIEW OF STUDY DESIGN

For Cohorts A – F

This is a Phase 2, multicohort, open-label, multicenter study to determine whether treatment with cilta-cel (alone or with other treatment regimens) results in MRD negativity in adult subjects with multiple myeloma. Multiple patient populations of unmet medical need will be studied. Approximately 40 subjects will be enrolled in Cohort A and Cohort F, and approximately 17 subjects in Cohort D. Approximately 20 subjects will be enrolled in all other Cohorts. The primary endpoint for all Cohorts will be overall MRD negative rate at a 10^{-5} threshold.

Subjects will be enrolled into one of the following cohorts based on eligibility criteria.

- Cohort A: progressive disease after 1 to 3 prior lines of therapy, including a proteasome inhibitor (PI) and immunomodulatory drug (IMiD) either individually or in combination. Subjects are required to be refractory to lenalidomide. Subjects who have received prior therapy that is targeted to BCMA are excluded from this cohort.

- Cohort B: one line of previous therapy containing a PI and an IMiD and early relapse defined as disease progression ≤12 months after an autologous stem cell transplantation (ASCT) or ≤12 months after the start of front-line therapy for subjects who have not had an ASCT. Subjects who have received prior therapy that is targeted to BCMA are excluded from this cohort.
- Cohort C: relapsed or refractory disease in subjects previously treated with a PI, IMiD, anti-CD38 monoclonal antibody, and BCMA-directed therapy (excluding cellular immunotherapy).
- Cohort D (cilta-cel plus lenalidomide): multiple myeloma without complete response after 4 to 8 total cycles of initial therapy, including induction, high-dose chemotherapy and ASCT with or without consolidation.
- Cohort E (daratumumab, bortezomib, lenalidomide, and dexamethasone [D-VRd] induction, cilta-cel, then lenalidomide): high risk newly diagnosed and untreated multiple myeloma (hr-NDMM) subjects for whom stem cell transplant is not planned as initial therapy.
- Cohort F will include newly diagnosed multiple myeloma subjects with standard risk disease and an overall response ≥VGPR after 4 to 8 total cycles of initial therapy.

Subjects who meet the eligibility criteria for Cohort A and Cohort B, must be enrolled in Cohort B.

All enrolled subjects will undergo apheresis to acquire peripheral blood mononuclear cells (PBMCs). Cilta-cel will be generated from the subject's T cells selected from the apheresis product. After cilta-cel production and product release, subjects will receive a conditioning regimen of cyclophosphamide and fludarabine. Cilta-cel will be administered 5 days to 7 days after the start of the conditioning regimen. The primary analysis for each cohort will occur approximately 1 year after the last subject in each cohort has received his or her initial dose of cilta-cel. For Cohort A, primary analysis of the initial subjects (prior to Cohort A expansion) will occur approximately 1 year after the last subject is dosed. A primary analysis for subjects in the expanded cohort will occur approximately 1 year after the last subject is dosed in the expanded cohort.

Cohort completion for Cohorts A, B, and C is defined as 2 years after last cohort subject receives initial cilta-cel dose (retreatment is permitted for Cohorts A, B and C).

Cohort completion for Cohorts D and E is defined as 2½ years after last cohort subject receives cilta-cel dose (retreatment is not permitted for Cohorts D and E).

Cohort completion for Cohort F is defined as 2 years after last cohort subject receives cilta-cel dose (retreatment is not permitted for Cohort F).

For Cohorts G and H

These study cohorts aim to enroll a subject population that is racially representative of the overall prevalence of this disease in the US. Approximately 40 and up to 100 subjects will be enrolled in each cohort.

The study will include screening, apheresis, induction therapy, lymphodepleting chemotherapy, cilta-cel infusion, and post-treatment periods.

All enrolled subjects will undergo apheresis to acquire PBMCs. Cilta-cel will be generated from the subjects' T cells selected from the apheresis product.

In both cohorts, induction therapy will be followed by cyclophosphamide and fludarabine lymphodepletion (Day -7 to -5) after which cilta-cel will be administered.

In either cohort, subjects who are potential candidates for ASCT may have stem cell collection during study conduct. Collection and storage of stem cells will be considered an allowed, off-protocol procedure. In addition, subjects who have had between 1 to 2 cycles of induction therapy prior to enrollment will be eligible to enroll onto the study if treatment was provided with either DRd (for Cohort G) or D-VRd (for Cohort H), respectively. In this case, they will complete the remainder of induction cycles on study for a total of 4 cycles.

After cilta-cel infusion, subjects will remain in the study and will be followed for efficacy, MRD-status, safety, and occurrence of PD. After confirmed PD, subjects will be followed for survival, subsequent anti-myeloma therapies, SPMs, and other delayed adverse events.

For both Cohorts G and H, the primary analysis will be conducted approximately at 1.5 year after the last subject in that cohort started their study treatment. The final analysis will be conducted at cohort completion, which is defined as approximately 2.5 years after the last subject in that cohort has started their study treatment. In addition, for Cohort G only, a first analysis may be conducted at approximately 6 to 12 months after the last subject in that cohort started their study treatment. If the first analysis is performed, it may become the primary analysis.

All subjects who receive cilta-cel will continue to be monitored for long-term safety under a separate study for up to 15 years after cilta-cel administration.

DOSAGE AND ADMINISTRATION

For Cohort A, Cohort B, and Cohort C, and Cohort F

All subjects in Cohorts A, B, C and F will receive a conditioning regimen consisting of cyclophosphamide 300 mg/m^2 intravenously (IV) daily and fludarabine 30 mg/m^2 IV daily for 3 days. The dose of fludarabine should be reduced to 24 mg/m^2 for subjects with an estimated glomerular filtration rate (eGFR) of 30 to 70 mL/min/1.73m^2. Cilta-cel IV infusion will take place 5 to 7 days after the start of the conditioning regimen. The target dose is 0.75 x 10^6 CAR-positive viable T cells/kg (range: 0.5-1.0 x 10^6 CAR-positive viable T cells/kg). Subjects in Cohort A, B, C and F who do not receive an infusion of cilta-cel will be replaced.

Cohort D

Subjects in Cohort D will receive the following:

- After apheresis and prior to administration of cyclophosphamide and fludarabine (conditioning regimen prior to cilta-cel infusion): 1 or more cycles of lenalidomide at a dose of 10 mg per day upon adequate hematologic recovery from ASCT (absolute neutrophil count [ANC] ≥ 1 x 10^9/L and platelet count ≥ 75 x 10^9/L). Alternative bridging therapy regimen is permissible with sponsor approval.
- After cilta-cel production and product release, subjects will receive a conditioning regimen consisting of cyclophosphamide 300 mg/m^2 IV daily and fludarabine 30 mg/m^2 IV daily for 3 days. The dose of fludarabine should be reduced to 24 mg/m^2 for subjects with an estimated glomerular filtration rate (eGFR) of 30 to 70 mL/min/1.73m^2. Cilta-cel IV infusion will take place 5 to 7 days after the start of the conditioning regimen. The target dose is 0.75 x 10^6 CAR-positive viable T cells/kg (range: 0.5-1.0 x 10^6 CAR-positive viable T cells/kg).
- A strategy of staggered dosing with cilta-cel will be applied at the start of enrollment to Cohort D. There must be an observation period of at least 4 weeks between administration of cilta-cel to the first 5 subjects to allow for subject 28-day safety review prior to next subject dosing. In addition, the first 5 subjects will not receive lenalidomide after cilta-cel therapy. After the first 5 subjects are dosed with cilta-cel, the Data Monitoring Committee (DMC) will convene to review safety and any other relevant data.

- Based on recommendation of the DMC, subsequent subjects in this cohort will be eligible to receive lenalidomide after cilta-cel. The same strategy of staggered dosing will also be applied to the first 5 subjects receiving lenalidomide after cilta-cel (ie, the 6th through 10th subject enrolled in Cohort D). There must be an observation period of at least 4 weeks between administration of cilta-cel (followed by lenalidomide) to these 5 subjects. The DMC will review safety and any other relevant data from the first 5 subjects who receive cilta-cel followed by lenalidomide before a decision is made regarding the treatment plan for further subjects enrolled in Cohort D.

  Cilta-cel plus lenalidomide treatment: Subjects will initiate lenalidomide maintenance therapy at a minimum of 21 days post cilta-cel infusion and after resolution of any cytokine release syndrome (CRS) or neurologic toxicities. Subjects will continue to receive lenalidomide until confirmed PD, unacceptable toxicity, or for 2 years post cilta-cel infusion, whichever occurs first. The initial dose of lenalidomide post- cilta-cel infusion will depend on the level of hematologic recovery. Additionally, initiation of lenalidomide treatment is dependent on no additional safety concerns by investigator or sponsor.

  - Criteria for lenalidomide administration after cilta-cel infusion depend on the level of hematologic recovery and are summarized in the table below.

Hematologic Parameter			
ANC		**Platelet Count**	**Starting Dose of Lenalidomide**
$\geq 1.0 \times 10^9$/L	AND	$\geq 75 \times 10^9$/L	10 mg daily
0.75×10^9/L to $<1.0 \times 10^9$/L	AND	$\geq 50 \times 10^9$/L	Start 5 mg daily, increase to 10 mg per day when ANC is $\geq 1.0 \times 10^9$/L and the platelet count is $\geq 75 \times 10^9$/L
$\geq 0.75 \times 10^9$/L	AND	50×10^9/L to $<75 \times 10^9$/L	
$<0.75 \times 10^9$/L	OR	$<50 \times 10^9$/L	Lenalidomide must be held if either one of these criteria are present

  - If well tolerated after 3 cycles of lenalidomide treatment at 10 mg, the dose of lenalidomide may be increased to 15 mg per day at the discretion of the investigator.
  - For subjects with an eGFR <60 mL/min/1.73m^2, the lenalidomide dose should be reduced to 5 mg per day. Other dose adjustments should be performed based on local prescribing information consistent with the protocol guidance for dose reductions.

Cohort E

Subjects in Cohort E will receive the following:

- Eligible subjects will receive 4 cycles of D-VRd induction therapy as tolerated. The apheresis will be performed after Cycle 1 or Cycle 2.
- After cilta-cel production and product release, subjects will receive a conditioning regimen consisting of cyclophosphamide 300 mg/m^2 intravenously (IV) daily and fludarabine 30 mg/m^2 IV daily for 3 days. The dose of fludarabine should be reduced to 24 mg/m^2 for subjects with an estimated glomerular filtration rate (eGFR) of 30 to 70 mL/min/1.73m^2. The conditioning regimen will be initiated a minimum of 21 days after the last dose of D-VRd. Cilta-cel IV infusion will take place 5 to 7 days after the start of the conditioning regimen. The target dose is 0.75×10^6 CAR-positive viable T cells/kg (range: $0.5\text{-}1.0 \times 10^6$ CAR-positive viable T cells/kg).

- After infusion of cilta-cel: All subjects will receive treatment with lenalidomide consolidation therapy until confirmed PD, unacceptable toxicity, or for 2 years post cilta-cel infusion, whichever occurs first. Lenalidomide should be started when the following conditions are met:
  - Lenalidomide will be initiated at a minimum of 21 days post cilta-cel infusion and will only start after resolution of any grade cytokine release syndrome (CRS) or neurological toxicities. The initial dose of lenalidomide will depend on the level of hematologic recovery. Additionally, initiation of lenalidomide treatment is dependent on no additional safety concerns by investigator or sponsor.

Hematologic Parameter			
ANC		**Platelet Count**	**Starting Dose of Lenalidomide**
$\geq 1.0 \times 10^9$/L	AND	$\geq 75 \times 10^9$/L	10 mg daily
0.75×10^9/L to $<1.0 \times 10^9$/L	AND	$\geq 50 \times 10^9$/L	Start 5 mg daily, increase to 10 mg per day when ANC is $\geq 1.0 \times 10^9$/L and the platelet count is $\geq 75 \times 10^9$/L
$\geq 0.75 \times 10^9$/L	AND	50×10^9/L to $<75 \times 10^9$/L	
$<0.75 \times 10^9$/L	OR	$<50 \times 10^9$/L	Lenalidomide must be held if either one of these criteria are present

    - For subjects with an eGFR <60 mL/min/1.73m^2, the lenalidomide dose should be reduced to 5 mg per day. Other dose adjustments should be performed based on local prescribing information consistent with protocol guidance for dose reduction.
    - If well tolerated after 3 cycles of 10 mg lenalidomide treatment, the dose of lenalidomide may be increased to 15 mg per day at the discretion of the investigator.
    - Further up-titration by 5 mg increments may proceed after 6 cycles until a maximum dose of 25 mg daily (eg, lenalidomide Cycle 1: 10 mg, Cycle 2: 10 mg, Cycle 3: 10 mg, Cycle 4: 15 mg, Cycle 5: 15 mg, Cycle 6: 15 mg, Cycle 7: 20 mg, Cycle 8: 25 mg).

For Cohorts G and H

INDUCTION THERAPY

Daratumumab, Lenalidomide, and Dexamethasone – Cohort G

Subjects enrolled in Cohort G will receive 4 cycles of DRd prior to cilta-cel infusion. If a subject has already received 1 to 2 cycles of DRd before apheresis they should receive additional cycles for a total of 4 cycles of DRd. Subjects should aim to start induction (or resume induction if 1-2 cycles were already received) within 7 days of apheresis.

After completion of 4 cycles of DRd, all subjects will receive a conditioning regimen of cyclophosphamide and fludarabine, followed by cilta-cel infusion. Thereafter, subjects will be in observation (no treatment) until confirmed PD.

Description of DRd Induction Regimen for Cohort G

Study Treatment	Dose/Route of Administration	Schedule
Daratumumab	1,800 mg SC	Weekly (Days 1, 8, 15, 22) for Cycles 1 to 2 Every 2 weeks (Days 1 and 15) for Cycles 3 to 4
Lenalidomide (dose and regimen can be adjusted	25 mg PO[a]	Days 1 to 21 of each 28-day cycle from Cycles 1 to 4
Dexamethasone (dose and regimen can be adjusted	40 mg [b,c]	Days 1, 8, 15, and 22 of each 28-day cycle from Cycles 1 to 4

DRd=daratumumab, lenalidomide, and dexamethasone; PO=oral, SC=subcutaneous.

a. Lenalidomide should be dosed based on renal function and dose should be re-evaluated (and increased) in case of improved renal function for subsequent cycles.
b. The dexamethasone dose of 40 mg may be split over 2 days (20 mg/day x 2 days), if necessary.
c. For underweight subjects (BMI <18.5 kg/m^2) and subjects ≥75 years of age, dexamethasone may be administered at a dose of 20 mg on Days 1, 8, 15, and 22. Subjects receiving 20 mg weekly dexamethasone, can receive the entire weekly dose (20 mg) of dexamethasone on Days 1, 8, 15, and 22. Dexamethasone may be split over 2 days: Day 1, 2, 8, 9, 15, 16, 22 and 23, as clinically indicated.

Description of DVRd Induction Regimen for Cohort H

Subjects enrolled in Cohort H will receive 4 cycles of D-VRd prior to cilta-cel infusion. If a subject has already received 1 to 2 cycles of D-VRd before apheresis, they should receive additional cycles for a total of 4 cycles of D-VRd. Subjects should aim to start induction (or resume induction if 1-2 cycles were already received) within 7 days of apheresis.

After completion of 4 cycles of D-VRd, all subjects will receive a conditioning regimen of cyclophosphamide and fludarabine, followed by cilta-cel infusion. Thereafter, subjects will be in observation (no treatment) until confirmed PD.

Description of D-VRd Induction Regimen for Cohort H

Study Treatment	Dose/Route of Administration	Schedule
Daratumumab	1,800 mg SC	Weekly (Days 1, 8, 15, 22) for Cycles 1 to 2 Every 2 weeks (Days 1 and 15) for Cycles 3 to 4
Bortezomib (dose and regimen can be adjusted.)	1.3 mg/m^2 SC	Days 1, 8 and 15 of Cycles 1 to 4
Lenalidomide **(**dose and regimen can be adjusted	25 mg PO[a]	Days 1 to 21 of each 28-day cycle from Cycles 1 to 4
Dexamethasone **(**dose and regimen can be adjusted.)	40 mg [b,c]	Days 1, 8, 15, and 22 of each 28-day cycle from Cycles 1 to 4

D-VRd=daratumumab, bortezomib, lenalidomide, and dexamethasone; PO=oral, SC=subcutaneous.

a. Lenalidomide should be dosed based on renal function and dose should be re-evaluated (and increased) in case of improved renal function for subsequent cycles.
b. The dexamethasone dose of 40 mg may be split over 2 days (20 mg/day x 2 days), if necessary.
c. For underweight subjects (BMI <18.5 kg/m2) and subjects ≥75 years of age, dexamethasone may be administered at a dose of 20 mg on Days 1, 8, 15, and 22. Subjects receiving 20 mg weekly dexamethasone, should receive the entire weekly dose (20 mg) of dexamethasone on Days 1, 8, 15, and 22. Dexamethasone may be split over 2 days: Day 1, 2, 8, 9, 15, 16, 22 and 23, as clinically indicated.

EVALUATIONS

For Cohorts A – F

Disease status will be evaluated according to the IMWG consensus recommendations for multiple myeloma. Efficacy evaluations will include measurements of tumor burden/residual disease, myeloma proteins, bone marrow examinations, skeletal surveys, extramedullary plasmacytomas, and serum calcium corrected for albumin. For subjects in Cohorts A, B, and C with neither serum nor urine measurable disease, baseline PET/CT, or whole-body MRI may be used to satisfy the measurable disease criteria.

Blood and serum samples will be collected for assessment of cilta-cel pharmacokinetics, immunogenicity (antibodies to cilta-cel), and predictive biomarkers of response or resistance to cilta-cel.

Data regarding subjects' health-related quality of life (HRQoL), symptoms, functioning, and general well-being will be captured using patient-reported outcome (PRO) measures.

Safety will be evaluated by adverse events, laboratory test results, vital sign measurements, physical examination findings (including neurologic examination), assessments of cardiac function, Immune Effector Cell-associated Encephalopathy (ICE) score. Performance status will be assessed with the ECOG scale.

For Cohorts G and H

Disease status will be evaluated for response and disease progression according to the IMWG consensus criteria for multiple myeloma based on local laboratory testing. Efficacy evaluations will include measurements of myeloma protein, imaging of lytic lesions, assessment of extramedullary and bone-based soft tissue plasmacytomas, bone marrow examinations, and MRD evaluations. MRD will be monitored centrally using NGS (and with NGF if a clone cannot be identified for NGS), and PET/CT (for PET/CT MRD negativity) if locally available.

In both treatment cohorts all subjects will have whole blood and may have tumor or other tissue collected for PK/PD assessments, cilta-cel specific assessments and safety assessments. Whole blood will also be collected for exploratory biomarkers.

Safety evaluations will include a review of AEs, laboratory test results, vital sign measurements, physical examination findings (including neurologic examination), assessment of cardiac function and assessment of ECOG performance status grade. Subjects will also receive an ICE assessment. All study evaluations will be conducted according to the Time and Event Schedules. Additional samples including but not limited to blood, bone marrow or tissue samples may be collected for safety work-up of AEs.

STATISTICAL METHODS

For Cohorts A – F

No formal statistical hypothesis testing will be performed. The sample size of each cohort is selected to collect necessary data on preliminary efficacy and safety information.

For Cohorts G and H

No formal statistical hypotheses are planned to be tested in these study cohorts.

Assuming the true underlying sustained (≥12 months) MRD negative CR rate is 65%, the probability of observing a sustained MRD negative CR rate ≥ 55% is at least 90% with a sample size of 40.

TIME AND EVENTS SCHEDULES: COHORT A, COHORT B, COHORT C, AND COHORT F (TABLE 1 AND TABLE 2)

Table 1: Cohort A, Cohort B, Cohort C, and Cohort F: Time and Events Schedule for Study Procedures/Assessments

	Screening Phase	**Apheresis**	**Cyclophos-phamide and fludarabine conditioning regimen**	**JNJ-68284528 Infusion**	**Post Infusion (Day 1 to Day 100) (any subject who received an infusion of JNJ-68284528 should continue all subsequent assessments)[c]**											**Post-treatment (Day 101 and up to End of Cohort)[c]**
	≤28 days prior to apheresis[a]	**Upon enrollment[v]**	**Day -5,* -4, -3[b] *Window of Day -7 to Day -5**	**Day 1 (Infusion)**	**Day 3**	**Day 7 (± 1 day)**	**Day 10 (± 1 day)**	**Day 14 (± 1 day)**	**Day 21 (± 1 day)**	**Day 28 (± 2 days)**	**Day 35 (± 2 days)**	**Day 42 (± 2 days)**	**Day 56 (± 2 days)**	**Day 78 (± 2 days)**	**Day 100 (± 2 days)[c]**	**(every 28 days up to Day 352 then every 56 days)[d] (± 7 days)**
Screening Assessments																
Informed consent[a]	X (Before the 1st study related procedure)															
Eligibility criteria (See Section 4)	X															
Demography, Medical History (including neurologic history)	X															
Disease Characteristics[e]	X Disease characteristics to be collected prior to start of conditioning regimen															
PET/CT or MRI whole body scan (if without measurable disease in serum or urine) Cohorts A, B, or C only	X		X[t] (≤72-hour window)		Perform at 6 months, 12 months, and then yearly (±16 days) after infusion of JNJ-68284528)											
ECOG performance status	X	X (≤72 hrs prior to apheresis)	Prior to 1st dose only	X									X		X	
12-lead ECG	X		As clinically indicated													
Physical Examination Refer to Attachment 27 for the schedule of neurologic examinations specific to France	X		A symptom-directed physical examination should be performed as clinically indicated													

Table 1: Cohort A, Cohort B, Cohort C, and Cohort F: Time and Events Schedule for Study Procedures/Assessments

	Screening Phase	**Apheresis**	**Cyclophos-phamide and fludarabine conditioning regimen**	**JNJ-68284528 Infusion**	**Post Infusion (Day 1 to Day 100) (any subject who received an infusion of JNJ-68284528 should continue all subsequent assessments)** [c]											**Post-treatment (Day 101 and up to End of Cohort)**[c]
	≤28 days prior to apheresis[a]	**Upon enrollment** [v]	**Day -5,* -4, -3** [b] ***Window of Day -7 to Day -5**	**Day 1 (Infusion)**	**Day 3**	**Day 7 (± 1 day)**	**Day 10 (± 1 day)**	**Day 14 (± 1 day)**	**Day 21 (± 1 day)**	**Day 28 (± 2 days)**	**Day 35 (± 2 days)**	**Day 42 (± 2 days)**	**Day 56 (± 2 days)**	**Day 78 (± 2 days)**	**Day 100 (± 2 days)**[c]	**(every 28 days up to Day 352 then every 56 days)**[d] **(± 7 days)**
Height	X															
Echocardiogram or MUGA scan	X (≤8 weeks of apheresis)		For subjects who receive bridging therapy that includes agents with known cardiac toxicity (per prescribing information), assessment of cardiac function should be repeated within 7 days prior to the start of the conditioning regimen then again as clinically indicated if the subject develops signs/symptoms of heart failure													
ICE neurologic test				X (≤24 hours prior to infusion)[f]	ICE test must be repeated at any incidence of suspected CAR-T cell-related neurotoxicity (eg, ICANS). Perform at least daily until ICANS is resolved.											
Handwriting sample Refer to Attachment 27 for the schedule of handwriting sample collection specific to France				X (≤24 hours prior to infusion)[f]	X	X	X	X	X	X	X	X	X	X	X	Perform monthly up to Day 184
Ocular Exam; subjects who received prior ADC (Cohort C Only)[r]	X			As clinically indicated												
Outpatient Administration: In consultation with and approval of the sponsor. See Attachment 15 for outpatient monitoring																
Evaluation for outpatient suitability (See Attachment 14)		X		X (pre-dose)												
All Subjects with hospital discharge on Day 10							Daily phone calls during business hours from site staff, Days 11-14									

Table 1: Cohort A, Cohort B, Cohort C, and Cohort F: Time and Events Schedule for Study Procedures/Assessments

	Screening Phase	**Apheresis**	**Cyclophos-phamide and fludarabine conditioning regimen**	**JNJ-68284528 Infusion**	**Post Infusion (Day 1 to Day 100) (any subject who received an infusion of JNJ-68284528 should continue all subsequent assessments)** [c]											**Post-treatment (Day 101 and up to End of Cohort)**[c]
	≤28 days prior to apheresis[a]	**Upon enrollment** [v]	**Day -5,* -4, -3** [b] ***Window of Day -7 to Day -5**	**Day 1 (Infusion)**	**Day 3**	**Day 7 (± 1 day)**	**Day 10 (± 1 day)**	**Day 14 (± 1 day)**	**Day 21 (± 1 day)**	**Day 28 (± 2 days)**	**Day 35 (± 2 days)**	**Day 42 (± 2 days)**	**Day 56 (± 2 days)**	**Day 78 (± 2 days)**	**Day 100 (± 2 days)**[c]	**(every 28 days up to Day 352 then every 56 days)**[d] **(± 7 days)**
Assessments Prior to Apheresis and Conditioning Regimen																
Criteria for Apheresis (See Section 6.1.1)		X														
Criteria for Conditioning Regimen (See Section 6.1.2)			≤72 hours of the 1st dose only													
Criteria for JNJ-68284528 Administration (See Section 6.1.3)				X (pre-dose) ≤24-hour window												
Laboratory Assessments (See Section 9.7). To be performed by the local laboratory except for the calcium and albumin-adjusted calcium, which will be performed at the central laboratory (local labs may be used to assess eligibility). Blood samples collection may be performed at the subject's home by mobile study personnel (ie, nurses and mobile phlebotomist) in the post-treatment period, after the Day 100.																
Hematology (see Section 9.7.5)	X	X (≤72 hours prior to apheresis)	Prior to 1st dose only (≤72 hour window)	X (pre-dose) ≤24-hour window	X	X	X	X	X	X		X	X	X	X	
Chemistry (see Section 9.7.5)	X	X (≤72 hour window)	Prior to 1st dose only (≤72 hour window)	X (pre-dose) ≤24-hour window	X	X	X	X	X	X		X	X	X	X	
Serology [g]	X				For subjects at risk for HBV reactivation monitor HBV DNA and AST/ALT every 3 months for 12 months post cilta-cel dose (see Attachment 10)											
Coagulation (PT/INR, aPTT, fibrinogen, D-dimer)	X			As clinically indicated for subjects who have fever or other signs of potential CRS												
Serum Pregnancy test (in subjects with childbearing potential)	X	X (≤72 hour window)	Prior to 1st dose only (≤72 hour window)	As clinically indicated or as mandated by local regulations, whichever is more stringent												

Table 1: Cohort A, Cohort B, Cohort C, and Cohort F: Time and Events Schedule for Study Procedures/Assessments

	Screening Phase	**Apheresis**	**Cyclophos-phamide and fludarabine conditioning regimen**	**JNJ-68284528 Infusion**	**Post Infusion (Day 1 to Day 100) (any subject who received an infusion of JNJ-68284528 should continue all subsequent assessments)** [c]											**Post-treatment (Day 101 and up to End of Cohort)**[c]
	≤28 days prior to apheresis[a]	**Upon enrollment** [v]	**Day -5,* -4, -3** [b] ***Window of Day -7 to Day -5**	**Day 1 (Infusion)**	**Day 3**	**Day 7 (± 1 day)**	**Day 10 (± 1 day)**	**Day 14 (± 1 day)**	**Day 21 (± 1 day)**	**Day 28 (± 2 days)**	**Day 35 (± 2 days)**	**Day 42 (± 2 days)**	**Day 56 (± 2 days)**	**Day 78 (± 2 days)**	**Day 100 (± 2 days)**[c]	**(every 28 days up to Day 352 then every 56 days)**[d] **(± 7 days)**
Infectious Disease Testing[h]	X (within 60 days prior to apheresis, as applicable per local regulations)															
CMV and EBV Testing	X (serology and PCR within 60 days prior to apheresis)				PCR to be collected at visit Days 100, 184, 268, 352 and repeated as clinically indicated. A window of +/- 6 weeks will be allowed.											
Study Intervention Administration																
Weight	X	X (for JNJ-68284528 dose calculation)	Prior to 1st dose only	X												
Vital signs, including oxygen saturation	X	X	X	X[i]	X	X	X	X	X	X			X			
Temperature				Measure at least twice a day[j]												
Apheresis		X														
Cyclophosphamide and fludarabine			X													
Pre-infusion medication (see Section 6.1.3.3 for requirements prior to dosing with JNJ-68284528)				X												
JNJ-68284528 (See CTPPM and IPPI for administration of JNJ-68284528)				X												
Serum and Urine Disease Evaluations (See Section 9.2 for efficacy assessments. Blood and 24-hour urine: to be sent to the central laboratory[s]. Disease evaluation should continue to be performed until confirmed disease progression, death, start of a new anticancer treatment, withdrawal of consent for study participation, or study completion, whichever occurs first.). Subjects with disease progression who receive retreatment with JNJ-68284528 must continue with disease evaluation visits. For subjects at select sites, blood samples collection may be performed at the subject's home by mobile study personnel (i.e. nurses and mobile phlebotomist) in the post-treatment period, after the Day 100.															

Table 1: Cohort A, Cohort B, Cohort C, and Cohort F: Time and Events Schedule for Study Procedures/Assessments

	Screening Phase	**Apheresis**	**Cyclophos-phamide and fludarabine conditioning regimen**	**JNJ-68284528 Infusion**	**Post Infusion (Day 1 to Day 100) (any subject who received an infusion of JNJ-68284528 should continue all subsequent assessments) [c]**											**Post-treatment (Day 101 and up to End of Cohort)[c]**
	≤28 days prior to apheresis[a]	**Upon enrollment [v]**	**Day -5,* -4, -3 [b] *Window of Day -7 to Day -5**	**Day 1 (Infusion)**	**Day 3**	**Day 7 (± 1 day)**	**Day 10 (± 1 day)**	**Day 14 (± 1 day)**	**Day 21 (± 1 day)**	**Day 28 (± 2 days)**	**Day 35 (± 2 days)**	**Day 42 (± 2 days)**	**Day 56 (± 2 days)**	**Day 78 (± 2 days)**	**Day 100 (± 2 days)[c]**	**(every 28 days up to Day 352 then every 56 days)[d] (± 7 days)**
Serum β2-microglobulin[w]			X (prior to first dose [≤7 days])													
Quantitative Immunoglobulins [k, q]	X		X (prior to first dose [≤7 days])							X			X	X	X	X
Serum M-protein quantitation by electrophoresis	X		X (prior to first dose [≤7 days])							X			X	X	X	X
24-hour urine protein electrophoresis sample	X [l]		X (prior to first dose [≤7 days])							X			X	X	X	X
Serum calcium corrected for albumin	X		X (prior to first dose [≤7 days])							X			X	X	X	X
Serum FLC and serum/urine immunofixation	X		Serum FLC and serum/urine immunofixation are to be performed prior to the start of conditioning regimen (Day -5 [≤7 days]) and when CR is suspected or maintained; for subjects with measurable disease only by light chain criteria serum FLC will also be performed at every assessment when an SPEP is performed													
Other Disease Evaluations																
MRD (bone marrow aspirate)[m]			X (prior to first dose [≤7 days])	Sample should be collected: • At time of suspected CR or sCR • For all dosed subjects at Day 56 (±2 days), and at 6-month (Day 184), 12 month (Day 352), 18 month (Day 520), 24 month (Day 744), with a window of ± 16 days. • Yearly (±3 months) thereafter for subjects in CR or sCR.. All timepoints are relative to Day 1 (cilta-cel infusion) and continue until disease progression.											
Bone marrow aspirate and core biopsy for disease evaluation			X (prior to first dose [≤7 days])	To confirm CR, sCR, and at disease progression (immunohistochemistry or immunofluorescence). Can be taken at the same time as the MRD sample if needed.												
Skeletal Survey [n]	X (at screening or ≤14 days prior to first dose of conditioning regimen)			As clinically indicated to document disease progression or response.												

Table 1: Cohort A, Cohort B, Cohort C, and Cohort F: Time and Events Schedule for Study Procedures/Assessments

	Screening Phase	**Apheresis**	**Cyclophos-phamide and fludarabine conditioning regimen**	**JNJ-68284528 Infusion**	**Post Infusion (Day 1 to Day 100) (any subject who received an infusion of JNJ-68284528 should continue all subsequent assessments)** [c]											**Post-treatment (Day 101 and up to End of Cohort)**[c]
	≤28 days prior to apheresis[a]	**Upon enrollment** [v]	**Day -5,* -4, -3** [b] ***Window of Day -7 to Day -5**	**Day 1 (Infusion)**	**Day 3**	**Day 7 (± 1 day)**	**Day 10 (± 1 day)**	**Day 14 (± 1 day)**	**Day 21 (± 1 day)**	**Day 28 (± 2 days)**	**Day 35 (± 2 days)**	**Day 42 (± 2 days)**	**Day 56 (± 2 days)**	**Day 78 (± 2 days)**	**Day 100 (± 2 days)**[c]	**(every 28 days up to Day 352 then every 56 days)**[d] **(± 7 days)**
Assess extramedullary Plasmacytomas	X [o]		X (≤14 days prior to first dose)	By physical examination (if applicable): measurable sites at D28, D56, D78, D100 and then every 4 weeks. By radiologic imaging: D78, D156 then every 12 weeks [± 4 weeks window] (for all subjects with a history of plasmacytomas or as clinically indicated for others) Day 28 to 100 (±2 days window), Day 101 and later (±7 days window).													
MRD assessment by imaging (optional)				If performed, must be recorded in the CRF												
Biomarker evaluations	See Biomarker Time & Events Schedule (**Table 2**)															
Patient Reported Outcomes (PRO) and Medical Resource Utilization (MRU): PRO assessments to be completed before any clinical tests or procedures scheduled for the same day as the PRO assessments that would influence the subject's perceptions of their current health																
EORTC QLQ-C30	X	X (≤72 hour window)				X				X			X	X	X	X; every 112 days (±7 days)
MySIm-Q (Unless translation not available)	X	X (≤72 hour window)				X				X			X	X	X	X; every 112 days (±7 days)
PGIS	X	X (≤72 hour window)				X				X			X	X	X	X; every 112 days (±7 days)
PGIC										X			X	X	X	
PRO CTCAE	X					X				X			X	X	X	
MRU				X				X		X			X		X	X; every 28 days until Day 180 (±7 days)

Table 1: Cohort A, Cohort B, Cohort C, and Cohort F: Time and Events Schedule for Study Procedures/Assessments

	Screening Phase	**Apheresis**	**Cyclophos-phamide and fludarabine conditioning regimen**	**JNJ-68284528 Infusion**	**Post Infusion (Day 1 to Day 100) (any subject who received an infusion of JNJ-68284528 should continue all subsequent assessments)** [c]											**Post-treatment (Day 101 and up to End of Cohort)**[c]
	≤28 days prior to apheresis[a]	**Upon enrollment** [v]	**Day -5,* -4, -3** [b] ***Window of Day -7 to Day -5**	**Day 1 (Infusion)**	**Day 3**	**Day 7 (± 1 day)**	**Day 10 (± 1 day)**	**Day 14 (± 1 day)**	**Day 21 (± 1 day)**	**Day 28 (± 2 days)**	**Day 35 (± 2 days)**	**Day 42 (± 2 days)**	**Day 56 (± 2 days)**	**Day 78 (± 2 days)**	**Day 100 (± 2 days)**[c]	**(every 28 days up to Day 352 then every 56 days)**[d] **(± 7 days)**
Ongoing Subject Review																
Adverse Events	Continuous from the time of signing ICF until 100 days after cilta-cel dosing; thereafter, continue to report all SAEs regardless of causality, and any nonserious adverse events considered related to study treatment until EOS. Events of HBV reactivations and COVID-19 infection should be reported during the first-year post-dosing of cilta-cel. Also, refer to section 12.3.4 for additional details regarding reporting of delayed AEs.															
Delayed Adverse Events[p, u]	Continuous from Day 1 CAR-T infusion until EOS															
Concomitant medication	Continuous from the time of signing of ICF until at least 100 days after last administration of any study treatment. Thereafter, continue to report concomitant therapy given for any Adverse Events considered related to study drug until the end of the study. Medications for the prevention and treatment of COVID-19 (including vaccines) and HBV reactivation should be reported until 1 year after cilta-cel infusion (Attachment 20).															
Survival Follow-up	After disease progression is documented, survival status will be obtained every 16 weeks until study completion. Survival status will also be collected prior to any planned efficacy analysis.															
Subsequent Anticancer Therapy	After disease progression is confirmed, subsequent anticancer therapy will be obtained every 16 weeks until study completion															

Abbreviations: ADC=antibody-drug conjugate; aPTT=activated partial thromboplastin time; ASBMT=American Society for Blood and Bone Marrow Transplantation; ASTCT=American Society for Transplantation and Cellular Therapy; CAR-T=chimeric antigen receptor T (cells); CMV=cytomegalovirus; CR=complete response; sCR=stringent complete response; CRS=cytokine release syndrome; CT=computed tomography; CTCAE=Common Terminology Criteria for Adverse Events; CTPPM=cell therapy product procedures manual; D=Day; EBV=Epstein-Barr Virus; ECOG=Eastern Cooperative Oncology Group; EORTC-QLQ=European Organization for Research and Treatment of Cancer Quality of Life Questionnaire; FISH=fluorescence in situ hybridization; FLC=free light chain; HBV=hepatitis B virus; ICANS=Immune-effector Cell-associated Neurotoxicity Syndrome; ICE=Immune effector Cell-associated Encephalopathy; ICF=informed consent form; INR=international normalized ratio; IPPI=investigational product preparation instructions; MRD=minimal residual disease; MRI=magnetic resonance imaging; MRU=Medical Resource Utilization; MUGA=multiple-gated acquisition; MySIm-Q=Multiple Myeloma Symptom and Impact Questionnaire; PGIC=Patient Global Impression of Change; PGIS=Patient Global Impression of Severity; PRO=patient reported outcome; PT=prothrombin time; SPEP=serum protein electrophoresis; UPEP=urine protein electrophoresis.

[a] ICF must be signed before any study-related procedures are performed and remains in effect even if the screening evaluation is not performed within the 28-day Screening Phase. Evaluations for eligibility determination performed outside the screening window may need to be repeated. For subjects who require a repeat apheresis see Section 9.1.3 for assessments that should be collected before the second apheresis. If the second apheresis falls outside of the 28-day window, all screening assessments (except bone marrow collection) must be repeated.

[b] Assessments may be conducted ≤72 hours predose unless otherwise noted.

Table 1: Cohort A, Cohort B, Cohort C, and Cohort F: Time and Events Schedule for Study Procedures/Assessments

	Screening Phase	Apheresis	Cyclophos-phamide and fludarabine conditioning regimen	JNJ-68284528 Infusion	Post Infusion (Day 1 to Day 100) (any subject who received an infusion of JNJ-68284528 should continue all subsequent assessments) [c]											Post-treatment (Day 101 and up to End of Cohort)[c]
	≤28 days prior to apheresis[a]	Upon enrollment [v]	Day -5,* -4, -3 [b] *Window of Day -7 to Day -5	Day 1 (Infusion)	Day 3	Day 7 (± 1 day)	Day 10 (± 1 day)	Day 14 (± 1 day)	Day 21 (± 1 day)	Day 28 (± 2 days)	Day 35 (± 2 days)	Day 42 (± 2 days)	Day 56 (± 2 days)	Day 78 (± 2 days)	Day 100 (± 2 days)[c]	(every 28 days up to Day 352 then every 56 days)[d] (± 7 days)

[c] For subjects who discontinue the study before Day 100, the Day 100 assessments should be performed prior to withdrawal if feasible. Subjects who discontinue after Day 100 but before study completion should have urine and serum disease assessments performed prior to withdrawal if feasible at the time of discontinuation, unless performed within 14 days prior to discontinuation. Completion of Cohorts A, B, and C is defined as 2 years after the last cohort subject received initial cilta-cel dose (retreatment is permitted for Cohorts A, B, and C). Completion of Cohort F is defined as 2 years after the last Cohort F subject received their cilta-cel dose retreatment is not permitted for Cohort F).

[d] Post-treatment assessments to be obtained until progressive disease is documented or the start of subsequent anticancer therapy, with the exception of survival status and subsequent anticancer therapy, which are to be collected until study completion. PRO assessments are collected until study completion (continued after disease progression or subsequent anticancer therapy).

[e] Disease characteristics cytogenetics (full karyotyping or FISH as well as molecular genetics [if applicable], both of which may originate from a bone marrow assessment performed prior to or during the screening period until the start of the conditioning regimen) and information on extra-medullary disease, as applicable. A pathologist/cytogeneticist should complete the cytogenetics data collection worksheet.

[f] Pre-infusion ICE test and handwriting sample should be performed before pre-medication with diphenhydramine

[g] See Attachment 10 for details.

[h] HIV, hepatitis B, hepatitis C, HTLV, and other infectious diseases will be performed within 60 days of apheresis or as applicable per local regulations, whichever is more stringent

[i] Immediately before the start of infusion, at the end of infusion, and 0.5, 1, 2 hours after end of infusion (window ±10 minutes). Monitor until normalized after a CRS event.

[j] Temperature will be checked at least twice a day up to Day 28. Subjects will be provided with a thermometer and instructed on the use of the thermometer and entering 2 temperatures including their maximum daily temperature in a diary. Diary will be reviewed at each visit, then collected on Day 28 and stored with patient source documents.

[k] All subjects will be evaluated for IgG, IgA, IgM. Testing for IgD and IgE will only be performed for subjects with IgD and IgE-type myeloma.

[l] UPEP sample collected as part of the standard of care and prior to the subject signing ICF may be used for analysis at the central laboratory.

[m] Bone marrow morphology from an aspirate and core biopsy to be assessed locally at all time points. Additional bone marrow aspirate samples will be collected for biomarkers (see Table 2). Bone marrow aspirate for MRD should be taken from first or second aspiration attempt, if feasible. If for any reason a bone marrow aspirate is not performed at pre-dose, or if a baseline clone cannot be established from the pre-dose bone marrow aspirate collection, then non-decalcified diagnostic tissue will be requested or perform MRD assessment using NGF.

[n] Results from skeletal survey performed as routine follow-up within 42 days before start of apheresis may be used without these tests being repeated. Additional imaging (X-ray, CT, or MRI) will be performed as clinically indicated (eg, to document response or progression) (Section 9.2.5).

[o] Results from radiologic plasmacytoma assessments performed ≤14 days prior to the first dose of the conditioning as routine follow-up for subject's disease may be used. Extramedullary plasmacytomas should be assessed for all subjects with a history of plasmacytomas or if clinically indicated at screening, by clinical examination or radiologic imaging (Section 9.2.6).

[p] A tumor sample should be collected and sent to the sponsor for DNA, RNA, or protein analysis to investigate the presence of lentiviral elements

[q] Additional immunoglobulin samples may be collected as clinically indicated for safety. Refer to Section 1.3 and Section 6.2.6.

Table 1: Cohort A, Cohort B, Cohort C, and Cohort F: Time and Events Schedule for Study Procedures/Assessments

	Screening Phase	Apheresis	Cyclophos-phamide and fludarabine conditioning regimen	JNJ-68284528 Infusion	Post Infusion (Day 1 to Day 100) (any subject who received an infusion of JNJ-68284528 should continue all subsequent assessments) [c]											Post-treatment (Day 101 and up to End of Cohort)[c]
	≤28 days prior to apheresis[a]	Upon enrollment [v]	Day -5,* -4, -3 [b] *Window of Day -7 to Day -5	Day 1 (Infusion)	Day 3	Day 7 (± 1 day)	Day 10 (± 1 day)	Day 14 (± 1 day)	Day 21 (± 1 day)	Day 28 (± 2 days)	Day 35 (± 2 days)	Day 42 (± 2 days)	Day 56 (± 2 days)	Day 78 (± 2 days)	Day 100 (± 2 days)[c]	(every 28 days up to Day 352 then every 56 days)[d] (± 7 days)

[r] For Cohort C, subjects who have received prior antibody-drug conjugate (ADC), ocular exam is to include best-corrected visual acuity (BCVA), slit lamp examination (with special focus on cornea), intraocular pressure, and dilated fundoscopic examination.

[s] Local laboratory assessments may be used under specified circumstances (See Section 9.2.7)

[t] Only if screening assessment was performed using whole body MRI. Not required if PET/CT imaging is utilized.

[u] Delayed AEs will be collected regardless of causality from the time of JNJ-68284528 administration until the end of study, and subsequently in a separate long-term follow-up study for up to 15 years after last administration of cilta-cel. Delayed AEs include new malignancies or recurrence of pre-existing malignancy (all grades), new incidence or exacerbation of pre-existing neurologic AEs (all grades), new incidence or exacerbation of a pre-existing rheumatologic or other autoimmune disorder (all grades), new incidence of Grade ≥ 3 hematologic disorder, and new incidence of Grade ≥ 3 infections.

[v] Cohort F Only: Stem cell mobilization and harvesting is optional and per investigator preference. If chosen, stem cell mobilization may be performed using cyclophosphamide, G-CSF, Plerixafor, or per local standard of care after apheresis and stem cells will be harvested based on response to mobilization per institutional practice.

[w] For Cohort F only. β2 microglobulin assessed by local lab prior to initiation of any anti-myeloma therapy will be collected as the screening values for determination of International Staging System (ISS) staging

Table 2: Cohort A, Cohort B, Cohort C, and Cohort F: Time and Events Schedule for Pharmacokinetic and Biomarker Sampling

	Screening Phase	Apheresis	Cyclophos-phamide and fludarabine conditioning regimen	JNJ-68284528 Infusion	Post Infusion (any subject who received infusion of JNJ-68284528 should continue all subsequent assessments) [a] and Post-treatment (Day 101 up to study completion)[g]													At PD	At Study Completion for subjects without PD
	≤28 days prior to apheresis	Upon enrollment	Day -5,* -4, -3 *Window of Day -7 to Day -5	Day 1 (Infusion)	Day 2 (± 2 hour)	Day 3 (± 4 hour)	Day 7 (± 1 day)	Day 10 (± 1 day)	Day 14 (± 1 day)	Day 21 (± 1 day)	Day 28 (± 2 days)	Day 35 (± 2 days)	Day 42 (± 2 days)	Day 56 (± 2 days)	Day 78 (± 2 days)	Day 100 (± 2 days)	Day 184 (±7 days)	Window of 1 to 56 days	
Pharmacokinetics																			
PK CAR transgene levels blood sample[b, j]			X (prior to first dose [≤7 days])	Pre-dose (≤4 hr window); Post EOI (within 30 minutes)	24-hour post-EOI	X	X	X	X	X	X		X	X	X	X; then every 8 weeks up to 1 year		X	X
Soluble serum BCMA sample			X (prior to first dose [≤7 days])	Pre-dose (≤4 hr window); Post EOI (within 30 minutes)	24-hour post-EOI	X	X	X	X	X	X		X	X	X	X; then every 8 weeks up to 1 year		X	X
PK CAR transgene levels bone marrow sample			X (prior to first dose [≤7 days]) (Except Cohort F)								X			X			X		

Table 2: Cohort A, Cohort B, Cohort C, and Cohort F: Time and Events Schedule for Pharmacokinetic and Biomarker Sampling

	Screening Phase	Apheresis	Cyclophos-phamide and fludarabine conditioning regimen	JNJ-68284528 Infusion	Post Infusion (any subject who received infusion of JNJ-68284528 should continue all subsequent assessments) [a] and Post-treatment (Day 101 up to study completion)[g]													At PD	At Study Completion for subjects without PD
	≤28 days prior to apheresis	Upon enrollment	Day -5,* -4, -3 *Window of Day -7 to Day -5	Day 1 (Infusion)	Day 2 (± 2 hour)	Day 3 (± 4 hour)	Day 7 (± 1 day)	Day 10 (± 1 day)	Day 14 (± 1 day)	Day 21 (± 1 day)	Day 28 (± 2 days)	Day 35 (± 2 days)	Day 42 (± 2 days)	Day 56 (± 2 days)	Day 78 (± 2 days)	Day 100 (± 2 days)	Day 184 (±7 days)	Window of 1 to 56 days	
ADA sample (serum)[b,c]				Pre-dose ≤4 hour window					X		X			X	X	X	X	X	X
Biomarker Sampling																			
Immuno-phenotyping (whole blood)[d, f, j] Includes the flow PK		X (≤72 hour window)	X (prior to first dose [≤7 days])	Pre-dose ≤4 hour window	24-hour post EOI		X	X	X	X	X	X	X	X	X	X; then every 8 weeks up to 1 year[h,]		X	X[d]
Flow cytometry, (aspirate) (bone marrow)[d, i]			X (prior to first dose [≤7 days])								X			X			X	X	X
CyTOF (aspirate) (bone marrow) [d,e]			X (prior to first dose [≤7 days])								X			X			X	X	X
CyTOF/ PBMC/ Plasma (whole blood) [d,e]		X (≤72 hour window)					X	X	X	X	X	X	X	X		X	X	X	X

Table 2: Cohort A, Cohort B, Cohort C, and Cohort F: Time and Events Schedule for Pharmacokinetic and Biomarker Sampling

	Screening Phase	Apheresis	Cyclophos-phamide and fludarabine conditioning regimen	JNJ-68284528 Infusion	Post Infusion (any subject who received infusion of JNJ-68284528 should continue all subsequent assessments) [a] and Post-treatment (Day 101 up to study completion)[g]												At PD	At Study Completion for subjects without PD
	≤28 days prior to apheresis	Upon enrollment	Day -5,* -4, -3 *Window of Day -7 to Day -5	Day 1 (Infusion)	Day 2 (± 2 hour)	Day 3 (± 4 hour)	Day 7 (± 1 day)	Day 10 (± 1 day)	Day 14 (± 1 day)	Day 21 (± 1 day)	Day 28 (± 2 days)	Day 35 (± 2 days)	Day 42 (± 2 days)	Day 56 (± 2 days)	Day 78 (± 2 days)	Day 100 (± 2 days)	Day 184 (±7 days)	Window of 1 to 56 days	
PBMCs for functional in vitro assays		X (≤72 hour window)						X			X			X		X; then every 8 weeks up to 1 year			
Cytogenetics (bone marrow)			X (prior to first dose [≤7 days])															X	
Replication Competent Lentivirus (RCL) (whole blood)			X Prior to 1st dose only (≤7 day window)	Pre-dose (≤4 hour window)		At approximately 3 months (Day 100), 6 months (Day 184), and 12 months (Day 352) (±1 month); then yearly (±3 months) for 15 years post infusion. Yearly collection of RCL samples is not required if assessments within the first year are negative. Additional samples may be collected triggered by events which may be relevant to RCL per clinical assessment.											
Serum protein analysis			X (prior to first dose [≤7 days])	Pre-dose (≤4 hour window)	Additional serum protein sample will be taken at each SIFE/SPEP evaluation, as well as at each MRD sample collection														

Table 2: Cohort A, Cohort B, Cohort C, and Cohort F: Time and Events Schedule for Pharmacokinetic and Biomarker Sampling

	Screening Phase	Apheresis	Cyclophos-phamide and fludarabine conditioning regimen	JNJ-68284528 Infusion	Post Infusion (any subject who received infusion of JNJ-68284528 should continue all subsequent assessments)[a] and Post-treatment (Day 101 up to study completion)[g]													At PD	At Study Completion for subjects without PD
	≤28 days prior to apheresis	Upon enrollment	Day -5,* -4, -3 *Window of Day -7 to Day -5	Day 1 (Infusion)	Day 2 (± 2 hour)	Day 3 (± 4 hour)	Day 7 (± 1 day)	Day 10 (± 1 day)	Day 14 (± 1 day)	Day 21 (± 1 day)	Day 28 (± 2 days)	Day 35 (± 2 days)	Day 42 (± 2 days)	Day 56 (± 2 days)	Day 78 (± 2 days)	Day 100 (± 2 days)	Day 184 (±7 days)	Window of 1 to 56 days	
Cytokine profiling[f] (serum)			X Prior to 1st dose only (≤7 day window)	Pre-dose (≤4 hour window); 2hrs Post-dose (±10 minutes)	X	X	X	X	X	X	X		X	X	X	X			

Abbreviations: ADA=anti-drug antibody; BCMA=B-cell maturation antigen; CAR=chimeric antigen receptor; CR = complete response; CRS=cytokine release syndrome; CyTOF=cytometry by time of flight; EOI=end of infusion; EOS=end of study; MRD=minimal residual disease; PBMC=peripheral blood mononuclear cell; PD=progressive disease; PK=pharmacokinetic; sCR=stringent complete response

[a] For subjects who discontinue the study before Day 100, the Day 100 assessments should be performed if feasible.

[b] Collect additional samples when any of the following are suspected or reported: 1) CRS or CAR-T cell-related neurotoxicity (eg, ICANS) Grade ≥2 (at onset of the event, and 24 and 72 hours after) or as clinically indicated; and 2) as indicated based on emerging data

[c] ADA sample should be collected if a subject withdraws from the study afterJNJ-68284528 administration but prior to disease progression or study completion.

[d] Sample should be collected at suspected CR.

[e] Sample should be collected at 12 months, relative to Day 1, for subjects that achieve CR/sCR and remain on study

[f] Collect additional samples when any of the following are suspected or reported: 1) CRS or CAR-T cell-related neurotoxicity (eg, ICANS) (any grade) (at onset of the event, and then every 24 hours until CRS or ICANS event has stabilized or is resolving at which time additional collections should occur at 24, 48, and 72 hours) or as clinically indicated; and 2) as indicated based on emerging data.

[g] Pharmacokinetic and biomarker samples collection (serum samples only) may be performed at the subject's home by mobile study personnel (i.e. nurses and mobile phlebotomist) in the post-treatment period, after the Day 100.

[h] If the 1-year immunophenotyping sample has detectable levels of CAR+ T cells, additional samples may be collected for central laboratory assessment at the discretion of the investigator

Table 2: Cohort A, Cohort B, Cohort C, and Cohort F: Time and Events Schedule for Pharmacokinetic and Biomarker Sampling

	Screening Phase	Apheresis	Cyclophos-phamide and fludarabine conditioning regimen	JNJ-68284528 Infusion	Post Infusion (any subject who received infusion of JNJ-68284528 should continue all subsequent assessments) [a] and Post-treatment (Day 101 up to study completion)[g]													At PD	At Study Completion for subjects without PD
	≤28 days prior to apheresis	Upon enrollment	Day -5,* -4, -3 *Window of Day -7 to Day -5	Day 1 (Infusion)	Day 2 (± 2 hour)	Day 3 (± 4 hour)	Day 7 (± 1 day)	Day 10 (± 1 day)	Day 14 (± 1 day)	Day 21 (± 1 day)	Day 28 (± 2 days)	Day 35 (± 2 days)	Day 42 (± 2 days)	Day 56 (± 2 days)	Day 78 (± 2 days)	Day 100 (± 2 days)	Day 184 (±7 days)	Window of 1 to 56 days	

[i] If the last post-D100 immunophenotyping samples has detectable levels of CAR+ T cells an additional bone marrow sample may be collected at the discretion of the investigator for central laboratory assessment

[j] After 1 year, CAR+ T cell counts and CAR transgene levels will be measured at least annually until end of study (EOS), progressive disease (PD), or until the lower limit of quantitation (LLOQ) of the cilta-cel transgene is reached, whichever is earlier. Additional event-triggered testing for PK CAR transgene levels and CAR+ T cell counts may be conducted as clinically indicated.

TIME AND EVENTS SCHEDULES: COHORT D (TABLE 3 AND TABLE 4)

Table 3: Cohort D: Time and Events Schedule for Study Procedures/Assessments

	Screening Phase	**Apheresis**	**Lenalidomide (upon adequate hematologic recovery from ASCT)[y]**	**Cyclophosph-amide and fludarabine conditioning regimen**	**JNJ-68284528 Infusion**	**Post Infusion (Day 1 to Day 100) (any subject who received an infusion of JNJ-68284528 should continue all subsequent assessments) [c]**											**Lenalidomide Treatment Period (As early as Day 22 and up to End of Cohort)[c]**
	≤28 days prior to apheresis [a]	**Upon enrollment**	**Cycle 1 (Additional Cycles permitted with Sponsor approval)**	**Day -5,* -4, -3[b] *Window of Day -7 to Day -5**	**Day 1 (Infusion)**	**Day 3**	**Day 7 (± 1 day)**	**Day 10 (± 1 day)**	**Day 14 (± 1 day)**	**Day 21 (± 1 day)**	**Day 28 (± 2 days)**	**Day 35 (± 2 days)**	**Day 42 (± 2 days)**	**Day 56 (± 2 days)**	**Day 78 (± 2 days)**	**Day 100 (± 2 days) [c]**	**(every 28 days up to Day 352 then every 56 days)[d, t] (± 7 days)**
Screening Assessments																	
Informed consent[a]	X (Before the 1st study related procedure)																
Eligibility criteria (See Section 4)	X																
Demography, Medical History (including neurologic history)	X																
Disease Characteristics[e]	X																
ECOG performance status	X	X (≤72 hrs prior to apheresis)		Prior to 1st dose only	X									X		X	
12-lead ECG	X		As clinically indicated														
Physical Examination Refer to Attachment 27 for the schedule of neurologic examinations specific to France	X		A symptom-directed physical examination should be performed as clinically indicated														

Table 3: Cohort D: Time and Events Schedule for Study Procedures/Assessments

	Screening Phase	**Apheresis**	**Lenalidomide (upon adequate hematologic recovery from ASCT)[y]**	**Cyclophosph-amide and fludarabine conditioning regimen**	**JNJ-68284528 Infusion**	**Post Infusion (Day 1 to Day 100) (any subject who received an infusion of JNJ-68284528 should continue all subsequent assessments)[c]**											**Lenalidomide Treatment Period (As early as Day 22 and up to End of Cohort)[c]**
	≤28 days prior to apheresis[a]	**Upon enrollment**	**Cycle 1 (Additional Cycles permitted with Sponsor approval)**	**Day -5,* -4, -3[b] *Window of Day -7 to Day -5**	**Day 1 (Infusion)**	**Day 3**	**Day 7 (± 1 day)**	**Day 10 (± 1 day)**	**Day 14 (± 1 day)**	**Day 21 (± 1 day)**	**Day 28 (± 2 days)**	**Day 35 (± 2 days)**	**Day 42 (± 2 days)**	**Day 56 (± 2 days)**	**Day 78 (± 2 days)**	**Day 100 (± 2 days)[c]**	**(every 28 days up to Day 352 then every 56 days)[d, t] (± 7 days)**
Height	X																
Echocardiogram or MUGA scan	X (≤8 weeks of apheresis)		For subjects who receive bridging therapy that includes agents with known cardiac toxicity (per prescribing information), assessment of cardiac function should be repeated within 7 days prior to the start of the conditioning regimen then again as clinically indicated if the subject develops signs/symptoms of heart failure														
ICE neurologic test					X (≤24 hours prior to infusion)[f]	ICE test must be repeated at any incidence of suspected CAR-T cell-related neurotoxicity (eg, ICANS). Perform at least daily until ICANS is resolved.											
Handwriting sample Refer to Attachment 27 for the schedule of handwriting sample collection specific to France					X (≤24 hours prior to infusion)[f]	X	X	X	X	X	X	X	X	X	X	X	Perform monthly up to Day 184
Outpatient Administration: In consultation with and approval of the sponsor. See Attachment 15 for outpatient monitoring																	
Evaluation for outpatient suitability (See Attachment 14)		X			X (predose)												
All Subjects with hospital discharge on Day 10								Daily phone calls during business hours from site staff, Days 11-14									

Table 3: Cohort D: Time and Events Schedule for Study Procedures/Assessments

	Screening Phase	**Apheresis**	**Lenalidomide (upon adequate hematologic recovery from ASCT)[v]**	**Cyclophosph-amide and fludarabine conditioning regimen**	**JNJ-68284528 Infusion**	**Post Infusion (Day 1 to Day 100) (any subject who received an infusion of JNJ-68284528 should continue all subsequent assessments)[c]**											**Lenalidomide Treatment Period (As early as Day 22 and up to End of Cohort)[c]**
	≤28 days prior to apheresis[a]	**Upon enrollment**	**Cycle 1 (Additional Cycles permitted with Sponsor approval)**	**Day -5,* -4, -3[b] *Window of Day -7 to Day -5**	**Day 1 (Infusion)**	**Day 3**	**Day 7 (± 1 day)**	**Day 10 (± 1 day)**	**Day 14 (± 1 day)**	**Day 21 (± 1 day)**	**Day 28 (± 2 days)**	**Day 35 (± 2 days)**	**Day 42 (± 2 days)**	**Day 56 (± 2 days)**	**Day 78 (± 2 days)**	**Day 100 (± 2 days)[c]**	**(every 28 days up to Day 352 then every 56 days)[d, t] (± 7 days)**
Assessments Prior to Apheresis and Conditioning Regimen																	
Criteria for Apheresis (See Section 6.1.1)		X															
Criteria for Conditioning Regimen (See Section 6.1.2.1)				≤72 hours of the 1st dose only													
Criteria for JNJ-68284528 Administration (See Section 6.1.3.2)					X (predose)												
Laboratory Assessments (See Section 9.7). To be performed by the local laboratory except for the calcium and albumin-adjusted calcium, which will be performed at the central laboratory (local labs may be used to assess eligibility). Blood samples collection may be performed at the subject's home by mobile study personnel (i.e. nurses and mobile phlebotomist) in the post-treatment period, after the Day 100.																	
Hematology[s] (See section 9.7.5)	X	X (≤72 hours prior to apheresis)	X[w] (within 24 hrs prior to 1st dose)	Prior to 1st dose only (≤72 hour window)	X (predose) (≤24 hour window)	X	X	X	X	X	X		X	X	X	X	
Chemistry[s] (see Section 9.7.5)	X	X (≤72 hour window)	X (within 24 hrs prior to 1st dose and at the start of each Len cycle)	Prior to 1st dose only (≤72 hour window)	X (predose) (≤24 hour window)	X	X	X	X	X	X		X	X	X	X	X (at start of each Len cycle)
Serology[g]	X					For subjects at risk for HBV reactivation monitor HBV DNA and AST/ALT every 3 months for 12 months post cilta-cel dose (see Attachment 10)											

Table 3: Cohort D: Time and Events Schedule for Study Procedures/Assessments

	Screening Phase	**Apheresis**	**Lenalidomide (upon adequate hematologic recovery from ASCT)[v]**	**Cyclophosph-amide and fludarabine conditioning regimen**	**JNJ-68284528 Infusion**	**Post Infusion (Day 1 to Day 100) (any subject who received an infusion of JNJ-68284528 should continue all subsequent assessments)[c]**										**Lenalidomide Treatment Period (As early as Day 22 and up to End of Cohort)[c]**
	≤28 days prior to apheresis[a]	**Upon enrollment**	**Cycle 1 (Additional Cycles permitted with Sponsor approval)**	**Day -5,* -4, -3[b] *Window of Day -7 to Day -5**	**Day 1 (Infusion)**	**Day 3**	**Day 7 (± 1 day)**	**Day 10 (± 1 day)**	**Day 14 (± 1 day)**	**Day 21 (± 1 day)**	**Day 28 (± 2 days)**	**Day 35 (± 2 days)**	**Day 42 (± 2 days)**	**Day 56 (± 2 days)**	**Day 78 (± 2 days)**	**Day 100 (± 2 days)[c]**	**(every 28 days up to Day 352 then every 56 days)[d, t] (± 7 days)**
Coagulation (PT/INR, aPTT, fibrinogen, D-dimer)	X				As clinically indicated for subjects who have fever or other signs of potential CRS												
Thyroid assessment (via local laboratory)[r]	X			Every 6 months or more frequently, as clinically necessary													
Serum Pregnancy test (in subjects with childbearing potential)	X	X (≤72 hour window)	10-14 d prior to 1st dose and within 24 hrs prior to 1st dose	Prior to 1st dose only (≤72 hour window)	Within 24 hours prior to start of lenalidomide, every week for the first 4 weeks, then repeated at least every 28 days Pregnancy testing must be performed 4 weeks after stopping lenalidomide. Additional pregnancy testing is done as clinically indicated or consistent with any country specific requirements listed in the local prescribing information for lenalidomide, whichever is more stringent												
Infectious Disease Testing[h]	X (within 60 days prior to apheresis, as applicable per local regulations)																
CMV and EBV Testing	X (serology and PCR within 60 days prior to apheresis)				PCR to be collected at visit Days 100, 184, 268, 352 and repeated as clinically indicated. A window of +/- 6 weeks will be allowed.												
Study Intervention Administration																	
Weight	X	X (for JNJ-68284528 dose calculation)		Prior to 1st dose only	X												
Vital signs, including oxygen saturation	X	X		X	X[i]	X	X	X	X	X	X			X			
Temperature[i]					Measure at least twice a day[j]												
Apheresis		X															

Table 3: Cohort D: Time and Events Schedule for Study Procedures/Assessments

	Screening Phase	Apheresis	Lenalidomide (upon adequate hematologic recovery from ASCT)[v]	Cyclophosph-amide and fludarabine conditioning regimen	JNJ-68284528 Infusion	Post Infusion (Day 1 to Day 100) (any subject who received an infusion of JNJ-68284528 should continue all subsequent assessments)[c]											Lenalidomide Treatment Period (As early as Day 22 and up to End of Cohort)[c]
	≤28 days prior to apheresis[a]	Upon enrollment	Cycle 1 (Additional Cycles permitted with Sponsor approval)	Day -5,* -4, -3[b] *Window of Day -7 to Day -5	Day 1 (Infusion)	Day 3	Day 7 (± 1 day)	Day 10 (± 1 day)	Day 14 (± 1 day)	Day 21 (± 1 day)	Day 28 (± 2 days)	Day 35 (± 2 days)	Day 42 (± 2 days)	Day 56 (± 2 days)	Day 78 (± 2 days)	Day 100 (± 2 days)[c]	(every 28 days up to Day 352 then every 56 days)[d, t] (± 7 days)
Cyclophosphamide and fludarabine				X													
Pre-infusion medication (see Section 6.1.3.3 for requirements prior to dosing with JNJ-68284528)					X												
JNJ-68284528 (See CTPPM and IPPI for administration of JNJ-68284528)					X												
Lenalidomide			X			Initiate lenalidomide a minimum of 21 days post JNJ-68284528 after resolution of associated CRS or neurologic toxicities. Refer to Table 13 and Section 6.1.4 for additional dosing considerations Lenalidomide will be taken daily (continuously) in 28-day cycles, until PD											
Accountability/Exposure Check																	
Pill count for Lenalidomide[s]			X								X			X	X	X	X
Serum and Urine Disease Evaluations (See Section 9.2 for efficacy assessments. Blood and 24-hour urine: to be sent to the central laboratory[u]. Disease evaluation should continue to be performed until confirmed disease progression, death, start of a new anticancer treatment, withdrawal of consent for study participation, or study completion, whichever occurs first.). Disease evaluation for subjects that discontinue lenalidomide treatment due to adverse events should continue until disease progression. For subjects at select sites within the US, blood samples collection may be performed at the subject's home by mobile study personnel (i.e. nurses and mobile phlebotomist) in the post-treatment period, after the Day 100																	
Serum β2-microglobulin				X (prior to first dose [≤7 days])													
Quantitative Immunoglobulins[k, q]	X			X (prior to first dose [≤7 days])							X			X	X	X	X

Table 3: Cohort D: Time and Events Schedule for Study Procedures/Assessments

	Screening Phase	**Apheresis**	**Lenalidomide (upon adequate hematologic recovery from ASCT)[v]**	**Cyclophosph-amide and fludarabine conditioning regimen**	**JNJ-68284528 Infusion**	**Post Infusion (Day 1 to Day 100) (any subject who received an infusion of JNJ-68284528 should continue all subsequent assessments)[c]**											**Lenalidomide Treatment Period (As early as Day 22 and up to End of Cohort)[c]**
	≤28 days prior to apheresis[a]	**Upon enrollment**	**Cycle 1 (Additional Cycles permitted with Sponsor approval)**	**Day -5,* -4, -3[b] *Window of Day -7 to Day -5**	**Day 1 (Infusion)**	**Day 3**	**Day 7 (± 1 day)**	**Day 10 (± 1 day)**	**Day 14 (± 1 day)**	**Day 21 (± 1 day)**	**Day 28 (± 2 days)**	**Day 35 (± 2 days)**	**Day 42 (± 2 days)**	**Day 56 (± 2 days)**	**Day 78 (± 2 days)**	**Day 100 (± 2 days)[c]**	**(every 28 days up to Day 352 then every 56 days)[d, t] (± 7 days)**
Serum M-protein quantitation by electrophoresis	X			X (prior to first dose [≤7 days])							X			X	X	X	X
24-hour urine protein electrophoresis sample	X[l]			X (prior to first dose [≤7 days])							X			X	X	X	X
Serum calcium corrected for albumin	X			X (prior to first dose [≤7 days])							X			X	X	X	X
Serum FLC and serum/urine immunofixation	X			Serum FLC and serum/urine immunofixation are to be performed prior to the start of conditioning regimen (Day -5 [≤7 days]) and when CR is suspected or maintained; for subjects with measurable disease only by light chain criteria serum FLC will also be performed at every assessment when an SPEP is performed													
Other Disease Evaluations																	
MRD (bone marrow aspirate)[m]	X				Sample should be collected: • At time of suspected CR or sCR • For all dosed subjects at Day 56 (±2 days), and at 6-month (Day 184), 12-month (Day 352), 18 month (Day 520), 24 month (Day 744), with a window of ± 16 days • Yearly (±3 months) thereafter for subjects in CR or sCR, All timepoints are relative to Day 1 (cilta-cel infusion) and continue until disease progression.													
Bone marrow aspirate and core biopsy for disease evaluation	X			X (prior to first dose [≤7 days])	To confirm CR, sCR, and at disease progression (immunohistochemistry or immunofluorescence). Can be taken at the same time as MRD sample if needed.												
Skeletal Survey[n]	X (at screening or ≤14 days prior to the first dose of conditioning regimen)				As clinically indicated to document disease progression or response.												
Assess extramedullary Plasmacytomas	X[o]			X (≤14 days prior to first dose)	By physical examination (if applicable): measurable sites at D28, D56, D78, D100 and then every 4 weeks. By radiologic imaging: D78, D156 then every 12 weeks [± 4 weeks window] (for all subjects with a history of plasmacytomas or as clinically indicated for others) Day 28 to 100 (±2 days window), Day 101 and later (±7 days window).												

Table 3: Cohort D: Time and Events Schedule for Study Procedures/Assessments

	Screening Phase	**Apheresis**	**Lenalidomide (upon adequate hematologic recovery from ASCT)[y]**	**Cyclophosph-amide and fludarabine conditioning regimen**	**JNJ-68284528 Infusion**	**Post Infusion (Day 1 to Day 100) (any subject who received an infusion of JNJ-68284528 should continue all subsequent assessments)[c]**											**Lenalidomide Treatment Period (As early as Day 22 and up to End of Cohort)[c]**
	≤28 days prior to apheresis[a]	**Upon enrollment**	**Cycle 1 (Additional Cycles permitted with Sponsor approval)**	**Day -5,* -4, -3[b] *Window of Day -7 to Day -5**	**Day 1 (Infusion)**	**Day 3**	**Day 7 (± 1 day)**	**Day 10 (± 1 day)**	**Day 14 (± 1 day)**	**Day 21 (± 1 day)**	**Day 28 (± 2 days)**	**Day 35 (± 2 days)**	**Day 42 (± 2 days)**	**Day 56 (± 2 days)**	**Day 78 (± 2 days)**	**Day 100 (± 2 days)[c]**	**(every 28 days up to Day 352 then every 56 days)[d, t] (± 7 days)**
MRD assessment by imaging (optional)	X				If performed, must be recorded in the CRF												
Biomarker evaluations	See Biomarker Time & Events Schedule (Table 2)																
Patient Reported Outcomes (PRO) and Medical Resource Utilization (MRU): PRO assessments to be completed before any clinical tests or procedures scheduled for the same day as the PRO assessments that would influence the subject's perceptions of their current health																	
EORTC QLQ-C30	X	X (≤72 hour window)					X				X			X	X	X	X; every 112 days (±7 days)
MySIm-Q (Unless translation not available)	X	X ≤2 hour window)					X				X			X	X	X	X; every 112 days (±7 days)
PGIS	X	X (≤72 hour window)					X				X			X	X	X	X; every 112 days (±7 days)
PGIC											X			X	X	X	
PRO CTCAE	X						X				X			X	X	X	
MRU					X				X		X			X		X	X; every 28 days until Day 180 (±7 days)

Table 3: Cohort D: Time and Events Schedule for Study Procedures/Assessments

	Screening Phase	Apheresis	Lenalidomide (upon adequate hematologic recovery from ASCT)[y]	Cyclophosph-amide and fludarabine conditioning regimen	JNJ-68284528 Infusion	Post Infusion (Day 1 to Day 100) (any subject who received an infusion of JNJ-68284528 should continue all subsequent assessments)[c]										Lenalidomide Treatment Period (As early as Day 22 and up to End of Cohort)[c]
	≤28 days prior to apheresis [a]	Upon enrollment	Cycle 1 (Additional Cycles permitted with Sponsor approval)	Day -5,* -4, -3[b] *Window of Day -7 to Day -5	Day 1 (Infusion)	Day 3	Day 7 (± 1 day)	Day 10 (± 1 day)	Day 14 (± 1 day)	Day 21 (± 1 day)	Day 28 (± 2 days)	Day 35 (± 2 days)	Day 42 (± 2 days)	Day 56 (± 2 days)	Day 78 (± 2 days)	Day 100 (± 2 days)[c]	(every 28 days up to Day 352 then every 56 days)[d, t] (± 7 days)
Ongoing Subject Review																	
Adverse Events	Continuous from the time of signing ICF until 100 days after cilta-cel dosing; thereafter, continue to report all SAEs regardless of causality, and any nonserious adverse events considered related to study treatment until EOS. Events of HBV reactivations and COVID-19 infection should be reported during the first-year post-dosing of cilta-cel. Also, refer to section 12.3.4 for additional details regarding reporting of delayed AEs.																
Delayed Adverse Events[p, x]	Continuous from Day1 CAR-T infusion until EOS																
Concomitant medication	Continuous from the time of signing of ICF until at least 100 days after administration of JNJ-68284528, or 30 days after last dose of lenalidomide, whichever is later. Thereafter, continue to report concomitant therapy given for any Adverse Events considered related to study drug until the end of the study. Medications for the prevention and treatment of COVID-19 (including vaccines) and HBV reactivation should be reported until 1 year after cilta-cel infusion (Attachment 20).																
Survival Follow-up	After disease progression is documented, survival status will be obtained every 16 weeks until study completion. Survival status will also be collected prior to any planned efficacy analysis.																
Subsequent Anticancer Therapy	After disease progression is confirmed, subsequent anticancer therapy will be obtained every 16 weeks until study completion																

Abbreviations: ANC=absolute neutrophil count; aPTT=activated partial thromboplastin time; ASBMT=American Society for Blood and Bone Marrow Transplantation; ASTCT=American Society for Transplantation and Cellular Therapy; CAR-T=chimeric antigen receptor T (cells); CAR-T=chimeric antigen receptor T (cells); CR=complete response; sCR=stringent complete response; CMV=cytomegalovirus; CRS= cytokine release syndrome; CT=computed tomography; CTCAE=Common Terminology Criteria for Adverse Events; CTPPM=cell therapy product procedures manual; D=Day; EBV=Epstein-Barr Virus; ECOG=Eastern Cooperative Oncology Group; EORTC-QLQ=European Organization for Research and Treatment of Cancer Quality of Life Questionnaire; FISH=fluorescence in situ hybridization; FLC=free light chain; HBV=hepatitis B virus; ICANS=Immune-effector Cell-Associated Neurotoxicity Syndrome; ICE=Immune effector Cell-associated Encephalopathy; ICF=informed consent form; INR=international normalized ratio; IPPI=investigational product preparation instructions; Len=lenalidomide; MRD=minimal residual disease; MRI=magnetic resonance imaging; MUGA=multiple-gated acquisition; MySim-Q=Multiple Myeloma Symptom and Impact Questionnaire; PGIC=Patient Global Impression of Change; PGIS=Patient Global Impression of Severity; PRO=patient reported outcome; PT=prothrombin time; SIPPM=site investigational product procedures manual; SPEP=serum protein electrophoresis; UPEP=urine protein electrophoresis.

[a] ICF must be signed before any study-related procedures are performed and remains in effect even if the screening evaluation is not performed within the 28-day Screening Phase. Evaluations for eligibility determination performed outside the screening window may need to be repeated. For subjects who require a repeat apheresis see Section 9.1.3 for assessments that should be collected before the second apheresis. If the second apheresis falls outside of the 28 day window, all screening assessments (except bone marrow collection) must be repeated.

[b] Assessments may be conducted ≤72 hours predose unless otherwise noted. Window for the start of the conditioning regimen is Day -7 to Day -5.

Table 3: Cohort D: Time and Events Schedule for Study Procedures/Assessments

	Screening Phase	Apheresis	Lenalidomide (upon adequate hematologic recovery from ASCT)[v]	Cyclophosph-amide and fludarabine conditioning regimen	JNJ-68284528 Infusion	Post Infusion (Day 1 to Day 100) (any subject who received an infusion of JNJ-68284528 should continue all subsequent assessments)[c]										Lenalidomide Treatment Period (As early as Day 22 and up to End of Cohort)[c]
	≤28 days prior to apheresis[a]	Upon enrollment	Cycle 1 (Additional Cycles permitted with Sponsor approval)	Day -5,* -4, -3[b] *Window of Day -7 to Day -5	Day 1 (Infusion)	Day 3	Day 7 (± 1 day)	Day 10 (± 1 day)	Day 14 (± 1 day)	Day 21 (± 1 day)	Day 28 (± 2 days)	Day 35 (± 2 days)	Day 42 (± 2 days)	Day 56 (± 2 days)	Day 78 (± 2 days)	Day 100 (± 2 days)[c]	(every 28 days up to Day 352 then every 56 days)[d, t] (± 7 days)

c For subjects who discontinue the study before Day 100, the Day 100 assessments should be performed prior to withdrawal if feasible. Subjects who discontinue after Day 100 but before study completion should have urine and serum disease assessments performed prior to withdrawal if feasible at the time of discontinuation, unless performed within 14 days prior to discontinuation. Cohort D completion is defined as 2 ½ years after the last Cohort D subject receives their cilta-cel dose.

d Post-treatment assessments to be obtained until progressive disease is documented or the start of subsequent anticancer therapy, with the exception of survival status and subsequent anticancer therapy, which are to be collected until study completion. PRO assessments are collected until study completion (continued after disease progression or subsequent anticancer therapy).

e Disease characteristics cytogenetics (full karyotyping or FISH as well as molecular genetics [if applicable]), both of which may originate from prior to or during the screening period and information on extra-medullary disease, as applicable. A pathologist/cytogeneticist should complete the cytogenetics data collection worksheet.

f Pre-infusion ICE test and handwriting sample should be performed before pre-medication with diphenhydramine

g See Attachment 10 for details.

h HIV, hepatitis B, hepatitis C, HTLV, and other infectious diseases will be performed within 60 days of apheresis or as applicable per local regulations, whichever is more stringent

i Immediately before the start of infusion, at the end of infusion, and 0.5, 1, 2 hours after end of infusion (window ±10 minutes). Monitor until normalized after a CRS event.

j Temperature will be checked at least twice a day up to Day 28. Subjects will be provided with a thermometer and instructed on the use of the thermometer and entering 2 temperatures including their maximum daily temperature in a diary. Diary will be reviewed at each visit, then collected on Day 28 and stored with patient source documents.

k All subjects will be evaluated for IgG, IgA, IgM. Testing for IgD and IgE will only be performed for subjects with IgD and IgE-type myeloma.

l UPEP sample collected as part of the standard of care and prior to the subject signing ICF may be used for analysis at the central laboratory.

m Bone marrow morphology from an aspirate and core biopsy to be assessed locally at all time points. Additional bone marrow aspirate samples will be collected for biomarkers (see Table 2). Bone marrow aspirate for MRD should be taken from first or second aspiration attempt, if feasible. If for any reason a bone marrow aspirate is not performed at pre-dose, or if a baseline clone cannot be established from the pre-dose bone marrow aspirate collection, then non-decalcified diagnostic tissue will be requested or perform MRD assessment using NGF.

n Results from skeletal survey performed as routine follow-up within 42 days before start of apheresis may be used without these tests being repeated. Additional imaging (X-ray, CT, or MRI) will be performed as clinically indicated (eg, to document response or progression) (Section 9.2.5).

o Results from radiologic plasmacytoma assessments performed ≤14 days prior to the first dose of the conditioning as routine follow-up for subject's disease may be used. Extramedullary plasmacytomas should be assessed for all subjects with a history of plasmacytomas or if clinically indicated at screening, by clinical examination or radiologic imaging (Section 9.2.6).

p A tumor sample should be collected, and DNA, RNA, or protein analysis may be performed to investigate the presence of lentiviral elements

Table 3: Cohort D: Time and Events Schedule for Study Procedures/Assessments

	Screening Phase	Apheresis	Lenalidomide (upon adequate hematologic recovery from ASCT)[v]	Cyclophosph-amide and fludarabine conditioning regimen	JNJ-68284528 Infusion	Post Infusion (Day 1 to Day 100) (any subject who received an infusion of JNJ-68284528 should continue all subsequent assessments)[c]										Lenalidomide Treatment Period (As early as Day 22 and up to End of Cohort)[c]
	≤28 days prior to apheresis [a]	Upon enrollment	Cycle 1 (Additional Cycles permitted with Sponsor approval)	Day -5,* -4, -3[b] *Window of Day -7 to Day -5	Day 1 (Infusion)	Day 3	Day 7 (± 1 day)	Day 10 (± 1 day)	Day 14 (± 1 day)	Day 21 (± 1 day)	Day 28 (± 2 days)	Day 35 (± 2 days)	Day 42 (± 2 days)	Day 56 (± 2 days)	Day 78 (± 2 days)	Day 100 (± 2 days)[c]	(every 28 days up to Day 352 then every 56 days)[d, t] (± 7 days)

q Monitor immunoglobulin levels after treatment and treat according to local guidelines (see section 1.3 and 6.2.6). Additional immunoglobulin samples may be collected as clinically indicated for safety

r Thyroid assessment: TSH only, if TSH is <LLN or >ULN need free T3 and free T4 testing

s Hematology, chemistry and pill count are to be done every 28 days past 12 months; all other assessments will be collected every 56 days or as otherwise noted.

t Hematology and chemistry samples will continue to be collected every 28 days for subjects receiving lenalidomide beyond 12 months.

u Local laboratory assessments may be used under specified circumstances (see Section 9.2.7)

v If an alternative bridging therapy is used, assessments specified for lenalidomide toxicity do not apply

w Weekly for the first 2 cycles, twice a month for Cycle 3 then once a month at start of each lenalidomide cycle

x Delayed AEs will be collected regardless of causality from the time of JNJ-68284528 administration until the end of study, and subsequently in a separate long-term follow-up study for up to 15 years after last administration of JNJ-68284528. Delayed AEs include new malignancies or recurrence of pre-existing malignancy (all grades), new incidence or exacerbation of pre-existing neurologic AEs (all grades), new incidence or exacerbation of a pre-existing rheumatologic or other autoimmune disorder (all grades), new incidence of Grade ≥ 3 hematologic disorder, and new incidence of Grade ≥ 3 infections.

Table 4: Cohort D: Time and Events Schedule for Pharmacokinetic and Biomarker Sampling

	Screening Phase	Apheresis	Lenalido-mide	Cyclophos-phamide and fludarabine conditioning regimen	JNJ-68284528 Infusion	Post Infusion (any subject who received infusion of JNJ-68284528 should continue all subsequent assessments) [a] and Post-treatment (Day 101 up to study completion)[g]													At PD	At Study Completion for subjects without PD
	≤28 days prior to apheresis	Upon enroll-ment	Cycle 1 (Additional Cycles permitted with Sponsor approval)	Day -5,* -4, -3 *Window of Day -7 to Day -5	Day 1 (Infusion)	Day 2 (± 2 hour)	Day 3 (± 4 hour)	Day 7 (± 1 day)	Day 10 (± 1 day)	Day 14 (± 1 day)	Day 21 (± 1 day)	Day 28 (± 2 days)	Day 35 (± 2 days)	Day 42 (± 2 days)	Day 56 (± 2 days)	Day 78 (± 2 days)	Day 100 (± 2 days)	Day 184 (±7 days)	1 to 56 days	
Pharmacokinetics																				
PK CAR transgene levels blood sample[b, j]				X (prior to first dose [≤7 days])	Pre-dose (≤4 hr window); Post EOI (within 30 minutes)	24-hour post-EOI	X	X	X	X	X	X		X	X	X	X; then every 8 weeks up to 1 year		X	X
Soluble serum BCMA sample				X (prior to first dose [≤7 days])	Pre-dose (≤4 hr window); Post EOI (within 30 minutes)	24-hour post-EOI	X	X	X	X	X	X		X	X	X	X; then every 8 weeks up to 1 year		X	X
PK CAR transgene levels bone marrow sample				X (prior to first dose [≤7 days])								X			X			X		
ADA sample (serum)[b,c]					Pre-dose (≤4 hour window)					X		X			X	X	X	X	X	X

Table 4: Cohort D: Time and Events Schedule for Pharmacokinetic and Biomarker Sampling

	Screening Phase	Apheresis	Lenalido-mide	Cyclophos-phamide and fludarabine conditioning regimen	JNJ-68284528 Infusion	Post Infusion (any subject who received infusion of JNJ-68284528 should continue all subsequent assessments) [a] and Post-treatment (Day 101 up to study completion)[g]													At PD	At Study Completion for subjects without PD
	≤28 days prior to apheresis	Upon enroll-ment	Cycle 1 (Additional Cycles permitted with Sponsor approval)	Day -5,* -4, -3 *Window of Day -7 to Day -5	Day 1 (Infusion)	Day 2 (± 2 hour)	Day 3 (± 4 hour)	Day 7 (± 1 day)	Day 10 (± 1 day)	Day 14 (± 1 day)	Day 21 (± 1 day)	Day 28 (± 2 days)	Day 35 (± 2 days)	Day 42 (± 2 days)	Day 56 (± 2 days)	Day 78 (± 2 days)	Day 100 (± 2 days)	Day 184 (±7 days)	1 to 56 days	
Biomarker Sampling																				
Immuno-phenotyping (whole blood) [d,f, j] Includes the flow PK		X (≤72 hour window)		X (prior to first dose [≤7 days])	Pre-dose (≤4 hour window)	24 hour post EOI		X	X	X	X	X	X	X	X	X	X	X; then every 8 weeks up to 1 year[h]		X	X[e]
Flow cytometry, (aspirate) (bone marrow)[d, i]				X (prior to first dose [≤7 days])								X			X			X	X	X
CyTOF (aspirate) (bone marrow) [d,e]				X (prior to first dose [≤7 days])								X			X			X	X	X
CyTOF/ PBMC/ Plasma (whole blood) [d,e]		X (≤72 hour window)						X	X	X	X	X	X	X	X		X	X	X	X
PBMCs for functional in vitro assays		X (≤72 hour window)							X			X			X		X; then every 8 weeks up to 1 year			

Table 4: Cohort D: Time and Events Schedule for Pharmacokinetic and Biomarker Sampling

	Screening Phase	Apheresis	Lenalido-mide	Cyclophos-phamide and fludarabine conditioning regimen	JNJ-68284528 Infusion	Post Infusion (any subject who received infusion of JNJ-68284528 should continue all subsequent assessments)[a] and Post-treatment (Day 101 up to study completion)[g]												At PD	At Study Completion for subjects without PD
	≤28 days prior to apheresis	Upon enroll-ment	Cycle 1 (Additional Cycles permitted with Sponsor approval)	Day -5,* -4, -3 *Window of Day -7 to Day -5	Day 1 (Infusion)	Day 2 (± 2 hour)	Day 3 (± 4 hour)	Day 7 (± 1 day)	Day 10 (± 1 day)	Day 14 (± 1 day)	Day 21 (± 1 day)	Day 28 (± 2 days)	Day 35 (± 2 days)	Day 42 (± 2 days)	Day 56 (± 2 days)	Day 78 (± 2 days)	Day 100 (± 2 days)	Day 184 (±7 days)	1 to 56 days	
Cytogenetics (bone marrow)				X (prior to first dose [≤7 days])														X	
Replication Competent Lentivirus (RCL) (whole blood)				X Prior to 1st dose only (≤7 day window)	Pre-dose (≤4 hour window)		At approximately 3 months (Day 100), 6 months (Day 184), and 12 months (Day 352) (±1 month); then yearly (±3 months) for 15 years post infusion. Yearly collection of RCL samples is not required if assessments within the first year are negative. Additional samples may be collected triggered by events which may be relevant to RCL per clinical assessment.												
Serum protein analysis				X (prior to first dose [≤7 days])	Pre-dose (≤4 hour window)	Additional serum protein sample will be taken at each SIFE/SPEP evaluation, as well as at each MRD sample collection													
Cytokine profiling[f] (serum)				X Prior to 1st dose only (≤7 day window)	Pre-dose (≤4 hour window); 2hrs Post-dose (±10 minutes)	X	X	X	X	X	X	X		X	X	X	X		

Abbreviations: ADA=anti-drug antibody; BCMA=B-cell maturation antigen; CAR=chimeric antigen receptor; CR = complete response; CRS=cytokine release syndrome; CyTOF=cytometry by time of flight; EOI=end of infusion; MRD=minimal residual disease; PBMC=peripheral blood mononuclear cell; PD=progressive disease; PK=pharmacokinetic; sCR=stringent complete response

[a] For subjects who discontinue the study before Day 100, the Day 100 assessments should be performed if feasible.

[b] Collect additional samples when any of the following are suspected or reported: 1) CRS or CAR-T cell-related neurotoxicity (eg, ICANS) Grade ≥2 (at onset of the event, and 24 and 72 hours after) or as clinically indicated; and 2) as indicated based on emerging data

[c] ADA sample should be collected if a subject withdraws from the study after JNJ-68284528 administration but prior to disease progression or study completion.

[d] Sample should be collected at suspected CR.

[e] Sample should be collected at 12 months, relative to Day 1, for subjects that achieve CR/sCR and remain on study

Table 4: Cohort D: Time and Events Schedule for Pharmacokinetic and Biomarker Sampling

	Screening Phase	Apheresis	Lenalido-mide	Cyclophos-phamide and fludarabine conditioning regimen	JNJ-68284528 Infusion	Post Infusion (any subject who received infusion of JNJ-68284528 should continue all subsequent assessments) [a] and Post-treatment (Day 101 up to study completion)[g]												At PD	At Study Completion for subjects without PD
	≤28 days prior to apheresis	Upon enroll-ment	Cycle 1 (Additional Cycles permitted with Sponsor approval)	Day -5,* -4, -3 *Window of Day -7 to Day -5	Day 1 (Infusion)	Day 2 (± 2 hour)	Day 3 (± 4 hour)	Day 7 (± 1 day)	Day 10 (± 1 day)	Day 14 (± 1 day)	Day 21 (± 1 day)	Day 28 (± 2 days)	Day 35 (± 2 days)	Day 42 (± 2 days)	Day 56 (± 2 days)	Day 78 (± 2 days)	Day 100 (± 2 days)	Day 184 (±7 days)	1 to 56 days	

[f] Collect additional samples when any of the following are suspected or reported: 1) CRS or CAR-T cell-related neurotoxicity (eg, ICANS) (any grade) (at onset of the event, and then every 24 hours until CRS or ICANS event has stabilized or is resolving at which time additional collections should occur at 24, 48, and 72 hours) or as clinically indicated; and 2) as indicated based on emerging data.

[g] Pharmacokinetic and biomarker samples collection (serum samples only) may be performed at the subject's home by mobile study personnel (i.e. nurses and mobile phlebotomist) in the post-treatment period, after the Day 100.

[h] If the 1-year immunophenotyping sample has detectable CAR+ T cells, additional samples may be collected for central laboratory assessment at the discretion of the investigator

[i] If the last post-D100 immunophenotyping samples has detectable levels of CAR+ T cells and additional bone marrow sample may be collected at the discretion of the investigator for central laboratory assessment

[j] After 1 year, CAR+ T cell counts and CAR transgene levels will be measured at least annually until end of study (EOS), progressive disease (PD), or until the lower limit of quantitation (LLOQ) of the cilta-cel transgene is reached, whichever is earlier. Additional event-triggered testing for PK CAR transgene levels and CAR+ T cell counts may be conducted as clinically indicated.

TIME AND EVENTS SCHEDULES: COHORT E (TABLE 5, TABLE 6, TABLE 7, AND TABLE 8)

Table 5: Cohort E: Time and Events Schedule for Study Procedures/Assessments (Screening to Conditioning Regimen)

	Screening Phase	**Induction Treatment D-VRd** (Cycles 1-4, 21-Day Cycle) Upon enrollment			**Apheresis** *Note: Occurs after Cycle 1 or 2, before Cycle 3* Minimum of 21 days after last dose of D-VRd	Peripheral Stem Cell Mobilization and Harvesting (Optional)[c]	**Cyclophosphamide and fludarabine conditioning regimen** Upon recovery from C4 Induction therapy; Minimum of 21 days after last dose of D-VRd
	≤28 days prior to Induction Treatment[a]	D1	D8 (±2 days)	D15 (±2 days)		After apheresis (Post-Induction Cycle 2, 3 or 4)	**Day -5,* -4, -3 [b] *Window of Day -7 to Day -5**
Screening Assessments							
Informed consent[a]	X Before the 1st study related procedure						
Eligibility criteria	X						
Demography, Medical History (including neurological history)	X						
Disease Characteristics[s]	X						
ECOG performance status	X	C3 only			X (≤72 hrs prior to apheresis)		Prior to 1st dose only
Myeloma Frailty Index	X						
12-lead ECG	X	As clinically indicated					
Physical examination Refer to Attachment 27 for the schedule of neurologic examinations specific to France	X	Symptom and disease directed examination as clinically indicated					
Height	X						
Spirometry (subjects with known COPD only)	X						
Echocardiogram or MUGA scan	X (≤8 weeks before induction treatment)						As clinically indicated if the subject develops signs/symptoms of heart failure
Outpatient Administration In consultation with and approval of the sponsor. See Attachment 15 for outpatient monitoring							
Evaluation for outpatient suitability (See Attachment 14)					X		
Assessments Prior to Apheresis and Conditioning Regimen							
Criteria for Apheresis (See Section 6.1.1)					X; After recovery from 1 or 2 cycles of D-VRd induction and ≤72 hours prior to apheresis		

Table 5: Cohort E: Time and Events Schedule for Study Procedures/Assessments (Screening to Conditioning Regimen)

	Screening Phase	**Induction Treatment D-VRd** (Cycles 1-4, 21-Day Cycle) Upon enrollment			**Apheresis** *Note: Occurs after Cycle 1 or 2, before Cycle 3* Minimum of 21 days after last dose of D-VRd	Peripheral Stem Cell Mobilization and Harvesting (Optional)[c]	**Cyclophosphamide and fludarabine conditioning regimen** Upon recovery from C4 Induction therapy; Minimum of 21 days after last dose of D-VRd
	≤28 days prior to Induction Treatment[a]	D1	D8 (±2 days)	D15 (±2 days)		After apheresis (Post-Induction Cycle 2, 3 or 4)	**Day -5,* -4, -3 [b] *Window of Day -7 to Day -5**
Criteria for Conditioning Regimen (See Section 6.1.2.1)							≤ 72 hours of the 1st dose only
Study Intervention and Administration							
Weight	X	X			X (for JNJ-68284528 dose calculation)		Prior to 1st dose only
Vital signs, including oxygen saturation[r]	X	X	X	C1-2 only	X	As clinically indicated; per investigator discretion or local guidelines	X
Apheresis					X		
Cyclophosphamide and G-CSF[c]						For stem cell mobilization per local standard of care	
Cyclophosphamide and fludarabine							X
D-VRd Induction Regimen							
Pre-Daratumumab Medications (administer 1-3 hours before daratumumab)							
Dexamethasone 20 mg [d]		X	C1-2 only	C1-2 only			
Diphenhydramine 25-50 mg (or equivalent)		X	C1-2 only	C1-2 only			
Paracetamol 650-1000 mg;		X	C1-2 only	C1-2 only			
Montelukast 10 mg (recommended prior to daratumumab C1D1 and is optional before all other doses)		Recom-mended for C1 only					
D-VRd							
Dexamethasone 20 mg, oral or intravenous[m]		On Days 1, 2, 4, 5, 8, 9, 11, 12					

Table 5: Cohort E: Time and Events Schedule for Study Procedures/Assessments (Screening to Conditioning Regimen)

	Screening Phase	**Induction Treatment D-VRd** (Cycles 1-4, 21-Day Cycle) Upon enrollment			**Apheresis** *Note: Occurs after Cycle 1 or 2, before Cycle 3* Minimum of 21 days after last dose of D-VRd	Peripheral Stem Cell Mobilization and Harvesting (Optional)[c]	**Cyclophosphamide and fludarabine conditioning regimen** Upon recovery from C4 Induction therapy; Minimum of 21 days after last dose of D-VRd
	≤28 days prior to Induction Treatment[a]	D1	D8 (±2 days)	D15 (±2 days)		After apheresis (Post-Induction Cycle 2, 3 or 4)	**Day -5,* -4, -3 [b] *Window of Day -7 to Day -5**
Bortezomib 1.3 mg/m^2; administer by subcutaneous injection		On Days 1, 4, 8, 11 of each cycle					
Lenalidomide 25 mg, oral		On Day 1-14 of each cycle					
Daratumumab 1800 mg SC; Refer to SIPPM or approved prescribing information for drug preparation and administration recommendations		On Days 1, 8, 15 for Cycles 1-2 [weekly] then Day 1 of Cycles 3-4					
Pill count for lenalidomide[o]		X					
Pill count for dexamethasone[o]		X					
Laboratory Assessments (Section 9.7) To be performed by the local laboratory except for the calcium and albumin-adjusted calcium, which will be performed at the central laboratory (local labs may be used to assess eligibility). Blood samples collection may be performed at the subject's home by mobile study personnel (i.e. nurses and mobile phlebotomist).							
Blood group and type and indirect antiglobulin test (IAT) results		Pre-dose C1D1[e]					
Hematology[o]	X	X	X	C1-2 only	X (≤72 hours prior to apheresis)		Prior to 1st dose only (≤72 hour window)
Chemistry (see section 9.7)	X	X		C1-2 only	X (≤72 hours window)		Prior to 1st dose only (≤72 hour window)
Serology[f,]	X	For subjects at risk for HBV reactivation monitor HBV DNA and AST/ALT every 3 months for 12 months post cilta-cel dose See Attachment 10					
Coagulation (PT/INR, aPTT, fibrinogen, D-dimer)	X						
Serum Pregnancy test (in subjects with childbearing potential)	X	Within 24 hours prior to C1D1	Weekly during Cycle 1 and then monthly in women with regular menstrual cycles or every 2 weeks in women with irregular menstrual cycles		X (≤72 hour window)		Prior to 1st dose only (≤72 hour window)

Table 5: Cohort E: Time and Events Schedule for Study Procedures/Assessments (Screening to Conditioning Regimen)

	Screening Phase	**Induction Treatment D-VRd** (Cycles 1-4, 21-Day Cycle) Upon enrollment			**Apheresis** *Note: Occurs after Cycle 1 or 2, before Cycle 3* Minimum of 21 days after last dose of D-VRd	Peripheral Stem Cell Mobilization and Harvesting (Optional)[c]	**Cyclophosphamide and fludarabine conditioning regimen** Upon recovery from C4 Induction therapy; Minimum of 21 days after last dose of D-VRd
	≤28 days prior to Induction Treatment[a]	D1	D8 (±2 days)	D15 (±2 days)		After apheresis (Post-Induction Cycle 2, 3 or 4)	**Day -5,* -4, -3 [b] *Window of Day -7 to Day -5**
Infectious Disease Testing[g]					X (within 60 days of apheresis, as applicable per local regulations)		
CMV and EBV Testing							Serology and PCR prior to 1st dose only (≤72 hour window)
Serum and Urine Disease Evaluations (See Section 9.2 for efficacy assessments. Blood and 24-hour urine: to be sent to the central laboratory. Disease evaluation should continue to be performed until confirmed disease progression, death, start of a new anticancer treatment, withdrawal of consent for study participation, or study completion, whichever occurs first.).							
Serum β2-microglobulin	X						
Quantitative Immunoglobulins[p]	X[h]						X (prior to first dose [≤7 days])[h]
Serum M-protein quantitation by electrophoresis	X	X					X (prior to first dose [≤7 days])
24-hour urine protein electrophoresis sample	X[i]	X					X (prior to first dose [≤7 days])
Serum calcium corrected for albumin	X	X					X (prior to first dose [≤7 days])
Serum FLC and serum/urine immunofixation	X	X					Serum FLC and serum/urine immunofixation are to be performed prior to the start of conditioning regimen (Day -5 [≤7 days]) and when CR is suspected or maintained; for subjects with measurable disease only by light chain criteria serum FLC will also be performed at every assessment when an SPEP is performed
Other Disease Evaluations							
MRD (bone marrow aspirate)[j]	X (performed during screening)						X (prior to first dose [≤7 days])
Bone marrow aspirate and biopsy for disease evaluation	X						X (prior to first dose [≤7 days])
Skeletal Survey[k]	X (at screening, or within 14 days prior to the first dose of conditioning regimen)						

Table 5: Cohort E: Time and Events Schedule for Study Procedures/Assessments (Screening to Conditioning Regimen)

	Screening Phase	**Induction Treatment D-VRd** (Cycles 1-4, 21-Day Cycle) Upon enrollment			**Apheresis** *Note: Occurs after Cycle 1 or 2, before Cycle 3* Minimum of 21 days after last dose of D-VRd	Peripheral Stem Cell Mobilization and Harvesting (Optional)[c]	**Cyclophosphamide and fludarabine conditioning regimen** Upon recovery from C4 Induction therapy; Minimum of 21 days after last dose of D-VRd
	≤28 days prior to Induction Treatment[a]	D1	D8 (±2 days)	D15 (±2 days)		After apheresis (Post-Induction Cycle 2, 3 or 4)	**Day -5,* -4, -3 [b] *Window of Day -7 to Day -5**
Assess extramedullary Plasmacytomas	X	If applicable, by physical exam Q4W, by radiologic exam (if required) Q12W					X (≤14 days prior to first dose)[l]
Biomarker evaluations	See Biomarker Time & Events Schedule (Table 7)						
Patient Reported Outcomes (PRO): To be completed before any clinical tests or procedures scheduled for the same day as the PRO assessments that would influence the subject's perceptions of their current health							
EORTC QLQ-C30	X				X (≤72 hour window)		
MySim-Q (Unless translation not available)	X				X (≤72 hour window)		
PGIS	X				X (≤72 hour window)		
PGIC							
PRO CTCAE Items	X						
MRU		X					
Ongoing Subject Review							
Adverse Events	Continuous from the time of signing ICF until 100 days after cilta-cel dosing; thereafter, continue to report all SAEs regardless of causality, and any nonserious adverse events considered related to study treatment until EOS. Events of HBV reactivations and COVID-19 infection should be reported during the first year postdosing of cilta-cel. Also, refer to section 12.3.4 for additional details regarding reporting of delayed AEs.						
Delayed Adverse Events[q]	Continuous from Day1 CAR-T infusion until EOS						
Concomitant medication	Continuous from the time of signing of ICF[t]						
Survival Follow-up	After disease progression is documented, survival status will be obtained every 16 weeks until study completion						
Subsequent Anticancer Therapy	After disease progression is confirmed, subsequent anticancer therapy will be obtained every 16 weeks until study completion						

Abbreviations: aPTT=activated partial thromboplastin time; CR=complete response; sCR=stringent complete response; CMV=cytomegalovirus; CRS= cytokine release syndrome; CT=computed tomography; C=Cycle; D=Day; EBV=Epstein-Barr Virus; ECOG=Eastern Cooperative Oncology Group; ECG=electrocardiogram; EORTC-QLQ=European Organization for Research and Treatment of Cancer Quality of Life Questionnaire; FISH=fluorescence in situ hybridization; FLC=free light chain; IAT=indirect antiglobulin test; ICF=informed consent form; INR=international normalized ratio; IPPI=investigational product preparation instructions; MRD=minimal residual disease; MRI=magnetic resonance imaging; MUGA=multiple-gated acquisition; MySIm-Q=Multiple Myeloma Symptom and Impact Questionnaire; PGIC=Patient Global Impression of Change; PGIS=Patient Global Impression of Severity; PRO=patient reported outcome; PT=prothrombin time; SC=subcutaneous; SIPPM=site investigational product procedures manual; w=weeks.

[a] ICF must be signed before any study-related procedures are performed, and remains in effect even if the screening evaluation is not performed within the 28-day Screening Phase. Evaluations for eligibility determination performed outside the screening window may need to be repeated. For subjects who require a repeat apheresis see Section 9.1.3 for assessments should be collected before the second apheresis.

[b] Window for the start of the conditioning regimen is Day -7 to Day -5.

[c] Stem cell mobilization and harvesting is optional and per investigator preference. If chosen, stem cell mobilization may be performed using cyclophosphamide, G-CSF, Plerixafor, or per local standard of care after apheresis and stem cells will be harvested based on response to mobilization per institutional practice.

[d] On daratumumab dosing days, dexamethasone pre-medication for daratumumab injection will replace the daily dose of dexamethasone (and should be administered 1 hour before the daratumumab infusion).
[e] Blood type, Rh, and Indirect Antiglobulin Test (IAT) should be done before the first dose of daratumumab
[f] See Attachment 10 for details.
[g] HIV, hepatitis B, hepatitis C, HTLV, and other infectious diseases will be performed within 60 days of apheresis or as applicable per local regulations, whichever is more stringent
[h] All subjects will be evaluated for IgG, IgA, IgM. Testing for IgD and IgE will only be performed for subjects with IgD and IgE-type myeloma.
[i] UPEP sample collected as part of the standard of care and prior to the subject signing ICF may be used for analysis at the central laboratory.
[j] Bone marrow morphology from an aspirate and core biopsy to be assessed locally at all time points. Additional bone marrow aspirate samples will be collected for biomarkers (See Table 8)
[k] Results from skeletal survey performed as routine follow-up within 42 days before start of induction therapy may be used without these tests being repeated (Section 9.2.5). Additional imaging (X-ray, CT, or MRI) will be performed as clinically indicated (eg, to document response or progression).
[l] Results from radiologic plasmacytoma assessments performed ≤14 days prior to the first dose of the conditioning as routine follow-up for subject's disease may be used. Extramedullary plasmacytomas should be assessed for all subjects with a history of plasmacytomas or if clinically indicated at screening, by clinical examination or radiologic imaging (Section 9.2.6).
[m] For subjects older than 75 years or underweight (BMI <18.5), the dexamethasone dose may be administered at a dose of 20 mg on days 1, 4, 8, and 11.
[n] A tumor sample should be collected, and DNA, RNA, or protein analysis may be performed to investigate the presence of lentiviral elements
[o] Hematology, chemistry and pill count are to be done every 28 days past 12 months; all other assessments will be collected every 56 days or as otherwise noted
[p] Monitor immunoglobulin levels after treatment and treat according to local guidelines (see section 1.3 and 6.2.6). Additional immunoglobulin samples may be collected as clinically indicated for safety
[q] Delayed AEs will be collected regardless of causality from the time of cilta-cel administration until the end of study, and subsequently in a separate long-term follow-up study for up to 15 years after last administration of cilta-cel. Delayed AEs include new malignancies or recurrence of pre-existing malignancy (all grades), new incidence or exacerbation of pre-existing neurologic AEs (all grades), new incidence or exacerbation of a pre-existing rheumatologic or other autoimmune disorder (all grades), new incidence of Grade ≥ 3 hematologic disorder, and new incidence of Grade ≥ 3 infections
[r] It should be done before and after daratumumab administration.
[s] Disease characteristics cytogenetics (full karyotyping or FISH as well as molecular genetics [if applicable], both of which may originate from a bone marrow assessment performed prior to or during the screening period until the start of the induction regimen) and information on extra-medullary disease, as applicable. A pathologist/cytogeneticist should complete the cytogenetics data collection worksheet.
[t] Medications for the prevention and treatment of COVID-19 (including vaccines) and HBV reactivation should be reported until 1 year after cilta-cel infusion (Attachment 20).

Table 6: Cohort E: Time and Events Schedule for Study Procedures/Assessments (JNJ-68284528 Infusion to Post-treatment)

	JNJ-68284528 Infusion	Post Infusion (Day 1 to Day 100) (any subject who received an infusion of JNJ-68284528 should continue all subsequent assessments) [a]											Consolidation Lenalidomide Treatment (As early as day 21 and up to End of Cohort)[a, b]
	Day 1 (Infusion)	Day 3	Day 7 (± 1 day)	Day 10 (± 1 day)	Day 14 (± 1 day)	Day 21 (± 1 day)	Day 28 (± 2 days)	Day 35 (± 2 days)	Day 42 (± 2 days)	Day 56 (± 2 days)	Day 78 (± 2 days)	Day 100 (± 2 days)[a]	(every 28 days)[d] (± 7 days)
Screening Assessments													
ECOG performance status	X									X		X	
12-lead ECG	As clinically indicated												
Physical Examination Refer to Attachment 27 for the schedule of neurologic examinations specific to France	A symptom-directed physical examination should be performed as clinically indicated												
Echocardiogram or MUGA scan	As clinically indicated if the subject develops signs/symptoms of heart failure												
ICE neurologic test	X (≤24 hours prior to infusion)[c]	ICE test must be repeated at any incidence of suspected CAR-T cell-related neurotoxicity (eg, ICANS). Perform at least daily until resolved.											
Handwriting sample Refer to Attachment 27 for the schedule of handwriting sample collection specific to France	X (≤24 hours prior to infusion)[c]	X	X	X	X	X	X	X	X	X	X	X	Perform monthly up to Day 184
Outpatient Administration In consultation with and approval of the sponsor. See Attachment 15 for outpatient monitoring													
Evaluation for outpatient suitability (See Attachment 14)	X (predose)												
All Subjects with hospital discharge on Day 10				Daily phone calls during business hours from site staff, Days 11-14									
Assessments Prior to Apheresis and Conditioning Regimen													
Criteria for JNJ-68284528 Administration (See Section 6.1.3.2)	X (predose)												
Study Intervention and Administration													
Weight	X												

Table 6: Cohort E: Time and Events Schedule for Study Procedures/Assessments (JNJ-68284528 Infusion to Post-treatment)

	JNJ-68284528 Infusion	Post Infusion (Day 1 to Day 100) (any subject who received an infusion of JNJ-68284528 should continue all subsequent assessments) [a]											Consolidation Lenalidomide Treatment (As early as day 21 and up to End of Cohort)[a, b]
	Day 1 (Infusion)	Day 3	Day 7 (± 1 day)	Day 10 (± 1 day)	Day 14 (± 1 day)	Day 21 (± 1 day)	Day 28 (± 2 days)	Day 35 (± 2 days)	Day 42 (± 2 days)	Day 56 (± 2 days)	Day 78 (± 2 days)	Day 100 (± 2 days)[a]	(every 28 days)[d] (± 7 days)
Vital signs, including oxygen saturation	X[d]	X	X	X	X	X	X			X			X
Temperature	Measure at least twice a day[e]												
Pre-infusion medication (see Section 6.1.3.3 for requirements prior to dosing with JNJ-68284528)	X												
JNJ-68284528 (See CTPPM and IPPI for administration of JNJ-68284528)	X												
Lenalidomide Continued Treatment													
Lenalidomide						Initiate lenalidomide a minimum of 21 days post JNJ-68284528 after resolution of associated CRS or neurological toxicities. Refer to Table 22 and Section 6.1.5.2 for additional dosing considerations Lenalidomide will be taken daily (21 days on, 7 days off) in 28-day cycles, until PD, unacceptable toxicities or until a maximum of 2 years.							
Pill count for lenalidomide[k]													X
Laboratory Assessments (See Section 9.7). To be performed by the local laboratory except for the calcium and albumin-adjusted calcium, which will be performed at the central laboratory (local labs may be used to assess eligibility). Blood samples collection may be performed at the subject's home by mobile study personnel (i.e. nurses and mobile phlebotomist) in the post-treatment period, after the Day 100.													
Hematology[k] (see section 9.7.5)	X (predose)	X	X	X	X	X	X		X	X	X	X	X (prior to each cycle of lenalidomide) (also see section 9.7.5)
Chemistry[k] (see section9.7.5)	X (predose)	X	X	X	X	X	X		X	X	X	X	X (prior to each cycle)
Serology [f]		For subjects at risk for HBV reactivation monitor HBV DNA and AST/ALT every 3 months for 12 months post cilta-cel dose (see Attachment 10)											
CMV and EBV Testing		PCR to be collected at visit Days 100, 184, 268, 352 and repeated as clinically indicated. A window of +/- 6 weeks will be allowed.											
Coagulation (PT/INR, aPTT, fibrinogen, D-dimer)	As clinically indicated for subjects who have fever or other signs of potential CRS												

Table 6: Cohort E: Time and Events Schedule for Study Procedures/Assessments (JNJ-68284528 Infusion to Post-treatment)

	JNJ-68284528 Infusion	Post Infusion (Day 1 to Day 100) (any subject who received an infusion of JNJ-68284528 should continue all subsequent assessments) [a]											Consolidation Lenalidomide Treatment (As early as day 21 and up to End of Cohort)[a, b]
	Day 1 (Infusion)	Day 3	Day 7 (± 1 day)	Day 10 (± 1 day)	Day 14 (± 1 day)	Day 21 (± 1 day)	Day 28 (± 2 days)	Day 35 (± 2 days)	Day 42 (± 2 days)	Day 56 (± 2 days)	Day 78 (± 2 days)	Day 100 (± 2 days)[a]	(every 28 days)[d] (± 7 days)
Serum Pregnancy test (in subjects with childbearing potential)		Within 24 hours prior to start of lenalidomide, every week for the first 4 weeks and repeated at a maximum of at least every 28 days (or every 14 days for women of childbearing potential with irregular menses) Pregnancy testing must be performed 4 weeks after stopping lenalidomide. Additional pregnancy testing is done as clinically indicated or consistent with any country specific requirements listed in the local prescribing information for lenalidomide, whichever is more stringent											
Serum and Urine Disease Evaluations (See Section 9.2 for efficacy assessments. Blood and 24-hour urine: to be sent to the central laboratory. Disease evaluation should continue to be performed until confirmed disease progression, death, start of a new anticancer treatment, withdrawal of consent for study participation, or study completion, whichever occurs first.).													
Quantitative Immunoglobulins[n]							X			X	X	X	X
Serum M-protein quantitation by electrophoresis							X			X	X	X	X
24-hour urine protein electrophoresis sample							X			X	X	X	X
Serum calcium corrected for albumin							X			X	X	X	X
Serum FLC and serum/urine immunofixation	Serum FLC and serum/urine immunofixation are to be performed prior to the start of conditioning regimen (Day -5 [≤7 days]) and when CR is suspected or maintained; for subjects with measurable disease only by light chain criteria serum FLC will also be performed at every assessment when an SPEP is performed												
Other Disease Evaluations													
MRD (bone marrow aspirate)[g]	Sample should be collected: • At time of suspected CR or sCR • For all dosed subjects at Day 56 (±2 days), and at 6-month (Day 184), 12-month (Day 352), 18 month (Day 520), 24 month (Day 744), with a window of ± 16 days. • Yearly (±3 months) thereafter for subjects in CR or sCR.. All time points are relative to Day 1 (cilta-cel infusion) and continue until disease progression.												
Bone marrow aspirate and core biopsy for disease evaluation	To confirm CR, sCR, and at disease progression (immunohistochemistry or immunofluorescence). Can be taken at the same time at MRD sample if needed.												
Skeletal Survey [h]	As clinically indicated to document disease progression or response.												
Assess extramedullary Plasmacytomas [i]	Measurable sites Day 28, Day 56, Day 78, Day 100 then every 4 weeks for physical examination (if applicable) and Day 78 and Day 156 then every 12 weeks for radiologic assessment (with ± 4 weeks window for subjects with a history of plasmacytomas or as clinically indicated for others).												
MRD assessment by imaging (optional)	Must be recorded in the CRF												

Table 6: Cohort E: Time and Events Schedule for Study Procedures/Assessments (JNJ-68284528 Infusion to Post-treatment)

	JNJ-68284528 Infusion	Post Infusion (Day 1 to Day 100) (any subject who received an infusion of JNJ-68284528 should continue all subsequent assessments) [a]											Consolidation Lenalidomide Treatment (As early as day 21 and up to End of Cohort)[a, b]
	Day 1 (Infusion)	Day 3	Day 7 (± 1 day)	Day 10 (± 1 day)	Day 14 (± 1 day)	Day 21 (± 1 day)	Day 28 (± 2 days)	Day 35 (± 2 days)	Day 42 (± 2 days)	Day 56 (± 2 days)	Day 78 (± 2 days)	Day 100 (± 2 days)[a]	(every 28 days)[d] (± 7 days)
Biomarker evaluations	See Biomarker Time & Events Schedule (Table 7 and Table 8)												
Patient Reported Outcomes (PRO): To be completed before any clinical tests or procedures scheduled for the same day as the PRO assessments that would influence the subject's perceptions of their current health													
EORTC QLQ-C30			X				X			X	X	X	X; every 112 days (±7days)
MySIm-Q (Unless translation not available)			X				X			X	X	X	X; every 112 days(±7days)
PGIS			X				X			X	X	X	X; every 112 days (±7days)
PGIC							X			X	X	X	
PRO CTCAE			X				X			X	X	X	
MRU	X				X		X			X		X	X; every 28 days until Day 180 (±7 days)
Ongoing Subject Review													
Adverse Events	Continuous from the time of signing ICF until 100 days after cilta-cel dosing; thereafter, continue to report all SAEs regardless of causality, and any nonserious adverse events considered related to study treatment until EOS. Events of HBV reactivations and COVID-19 infection should be reported during the first year postdosing of cilta-cel. Also, refer to section 12.3.4 for additional details regarding reporting of delayed AEs.												
Delayed Adverse Events [l,m]	Continuous from Day1 CAR-T infusion until EOS												
Concomitant medication	Continuous from the time of signing of ICF until at least 100 days after administration of JNJ-68284528, or 30 days after last dose of lenalidomide, whichever is later. Thereafter, continue to report concomitant therapy given for any Adverse Events considered related to study drug until the end of the study. Medications for the prevention and treatment of COVID-19 (including vaccines) and HBV reactivation should be reported until 1 year after cilta-cel infusion (Attachment 20).												
Survival Follow-up	After disease progression is documented, survival status will be obtained every 16 weeks until study completion												
Subsequent Anticancer Therapy	After disease progression is documented, subsequent anticancer therapy will be obtained every 16 weeks until study completion												

Abbreviations: aPTT=activated partial thromboplastin time; CMV=cytomegalovirus; CR=complete response; sCR=stringent complete response; CRS= cytokine release syndrome; CT=computed tomography; CTPPM=cell therapy product procedures manual; EBV=Epstein-Barr Virus; ECOG=Eastern Cooperative Oncology Group; ECG=electrocardiogram; EORTC-QLQ=European Organization for Research and Treatment of Cancer Quality of Life Questionnaire; FISH=fluorescence in situ hybridization; FLC=free light chain; ICF=informed consent form; INR=international normalized ratio; IPPI=investigational product preparation instructions; MRD=minimal residual disease; MRI=magnetic resonance imaging; MUGA=multiple-gated acquisition; MySIm-Q=Multiple Myeloma Symptom and Impact Questionnaire; PGIC=Patient Global Impression of Change; PGIS=Patient Global Impression of Severity; PRO=patient reported outcome; PT=prothrombin time; SC=subcutaneous; SIPPM=site investigational product procedures manual; w=weeks.

[a] For subjects who discontinue the study before Day 100, the Day 100 assessments should be performed prior to withdrawal, if feasible. Subjects who discontinue after Day 100 but before study completion should have urine and serum disease assessments performed prior to withdrawal if feasible at the time of discontinuation, unless performed within 14 days prior to discontinuation. Cohort E completion is defined as 2½ years after the last Cohort E subject receives their cilta-cel dose.

[b] Post-treatment assessments to be obtained until progressive disease is documented or the start of subsequent anticancer therapy, with the exception of survival status and subsequent anticancer therapy, which are to be collected until study completion. PRO assessments are collected until study completion (continued after disease progression or subsequent anticancer therapy).

[c] Pre-infusion ICE test and handwriting sample should be performed before pre-medication with diphenhydramine.

[d] Immediately before the start of infusion, at the end of infusion, and 0.5, 1, 2 hours after end of infusion. Monitor until normalized after a CRS event.

[e] Temperature will be checked at least twice a day up to Day 28. Subjects will be provided with a thermometer and instructed on the use of the thermometer and entering 2 temperatures including their maximum daily temperature in a diary. Diary will be reviewed at each visit, then collected on Day 28 and stored with subject source documents.

[f] See Attachment 10 for details

[g] Bone marrow morphology from an aspirate and core biopsy to be assessed locally at all time points. Additional bone marrow aspirate samples will be collected for biomarkers (See Table 8). Bone marrow aspirate for MRD should be taken from first or second aspiration attempt, if feasible. If for any reason a bone marrow aspirate is not performed at pre-dose, or if a baseline clone cannot be established from the pre-dose bone marrow aspirate collection, then non-decalcified diagnostic tissue will be requested or perform MRD assessment using NGF.

[h] Results from skeletal survey performed as routine follow-up within 42 days before start of induction therapy may be used without these tests being repeated (Section 9.2.5). Additional imaging (X-ray, CT, or MRI) will be performed as clinically indicated (eg, to document response or progression).

[i] Results from radiologic plasmacytoma assessments performed ≤14 days prior to the first dose of the conditioning as routine follow-up for subject's disease may be used. Extramedullary plasmacytomas should be assessed for all subjects with a history of plasmacytomas or if clinically indicated at screening, by clinical examination or radiologic imaging (Section 9.2.6).

[j] Footnote deleted in Amendment 5

[k] Hematology, chemistry and pill count are to be done every 28 days past 12 months; all other assessments will be collected every 56 days or as otherwise noted.

[l] A tumor sample should be collected, and DNA, RNA, or protein analysis may be performed to investigate the presence of lentiviral elements.

[m] Delayed AEs will be collected regardless of causality from the time of cilta-cel administration until the end of study, and subsequently in a separate long-term follow-up study for up to 15 years after last administration of cilta-cel. Delayed AEs include new malignancies or recurrence of pre-existing malignancy (all grades), new incidence or exacerbation of pre-existing neurologic AEs (all grades), new incidence or exacerbation of a pre-existing rheumatologic or other autoimmune disorder (all grades), new incidence of Grade ≥ 3 hematologic disorder, and new incidence of Grade ≥ 3 infections.

[n] Additional immunoglobulin samples may be collected as clinically indicated for safety. Refer to section 1.3 and 6.2.6.

Table 7: Cohort E: Time and Events Schedule for Pharmacokinetic and Biomarker Sampling (Screening to Conditioning Regimen)

	Screening Phase	**Induction Treatment D-VRd** (Cycles 1-4, 21-Day Cycle) *Note: Cycle 4 will be administered during CAR-T cell manufacturing.* T = Induction treatment			**Apheresis** *Note: Occurs after Cycle 1 or 2, before Cycle 3* Minimum of 21 days after last dose of D-VRd	**Cyclophosphamide and fludarabine conditioning regimen** (Upon recovery from C4 Induction therapy)
	≤28 days Prior to Induction Treatment	D1T	D8T (±2 days)	D15T (±2 days)		**Day -5,* -4, -3** Assessments may be conducted ≤72 hours predose. ***Window of Day -7 to Day -5**
Pharmacokinetics						
PK CAR transgene levels blood sample						X (prior to first dose [≤7 days]
Soluble serum BCMA sample						X (prior to first dose [≤7 days]
PK CAR transgene levels bone marrow sample						X (prior to first dose [≤7 days]
Daratumumab PK sample and ADA (serum)		Pre-dose C1D1T; Pre-dose C3D1T			X (≤72 hours window)	
Biomarker Sampling						
Immuno-phenotyping (whole blood)	X	Pre-dose Day 1 of each cycle			X (≤72 hours window)	X (prior to first dose [≤7 days])
Flow cytometry, (aspirate) (bone marrow)	X (done during screening)					X (prior to first dose [≤7 days])
CyTOF (aspirate) (bone marrow)						X (prior to first dose [≤7 days])
CyTOF/ PBMC/ Plasma (whole blood)	X				X(≤72 hours window)	
PBMCs for functional in vitro assays					X (≤72 hours window)	
Cytogenetics (bone marrow)	X[a]					
Whole Exome Sequencing (bone marrow)	X					
Replication Competent Lentivirus (RCL) (whole blood)						X (prior to first dose [≤7 days])
Serum protein analysis		Pre-dose C1D1T				X (prior to first dose [≤7 days])
Cytokine profiling (serum)						X (prior to first dose [≤7 days])

Abbreviations: ADA=antidrug antibody; BCMA=B-cell maturation antigen; C=cycle; CAR=chimeric antigen receptor; CR = complete response; CRS=cytokine release syndrome; CyTOF=cytometry by time of flight; D=day; PBMC=peripheral blood mononuclear cell; PD=progressive disease; PK=pharmacokinetic; sCR=stringent complete response

[a] Cytogenetics can be performed on prior bone marrow sample eg bone marrow sample at time of initial diagnosis.

Table 8: Cohort E: Time and Events Schedule for Pharmacokinetic and Biomarker Sampling (JNJ-68284528 Infusion to Disease Progression or Study Completion)

	JNJ-68284528 Infusion	Post Infusion (any subject who received infusion of JNJ-68284528 should continue all subsequent assessments) [a] and Post-treatment (Day 101 up to study completion)[e]													At PD	At Study Completion for subjects without PD
	Day 1 (Infusion)	Day 2 (± 2 hour)	Day 3 (± 4 hour)	Day 7 (± 1 day)	Day 10 (± 1 day)	Day 14 (± 1 day)	Day 21 (± 1 day)	Day 28 (± 2 days)	Day 35 (± 2 days)	Day 42 (± 2 days)	Day 56 (± 2 days)	Day 78 (± 2 days)	Day 100 (± 2 days)	Day 184 (±7 days)	Window of 1 to 56 days	
Pharmacokinetics																
PK CAR transgene levels blood sample[b, h]	Pre-dose (≤4 hr window); Post end of infusion (within 30 minutes)	24-hour post-end of infusion	X	X	X	X	X	X		X	X	X	X; then every 8 weeks up to 1 year		X	X
Soluble serum BCMA sample	Pre-dose (≤4 hr window); Post end of infusion (within 30 minutes)	24-hour post-end of infusion	X	X	X	X	X	X		X	X	X	X; then every 8 weeks up to 1 year		X	X
PK CAR transgene levels bone marrow sample								X			X			X		
ADA sample (serum)[b,c]	Pre-dose (≤4 hour window)					X		X			X	X	X	X	X	X
Biomarker Sampling																
Immuno-phenotyping (whole blood) [d, f, , h] Includes the flow PK	X Pre-dose (≤4 hour window)	24-hour post end of infusion		X	X	X	X	X	X	X	X	X	X; then every 8 weeks up to 1 year		X	X

Table 8: Cohort E: Time and Events Schedule for Pharmacokinetic and Biomarker Sampling (JNJ-68284528 Infusion to Disease Progression or Study Completion)

	JNJ-68284528 Infusion	Post Infusion (any subject who received infusion of JNJ-68284528 should continue all subsequent assessments) [a] and Post-treatment (Day 101 up to study completion)[e]													At PD	At Study Completion for subjects without PD
	Day 1 (Infusion)	Day 2 (± 2 hour)	Day 3 (± 4 hour)	Day 7 (± 1 day)	Day 10 (± 1 day)	Day 14 (± 1 day)	Day 21 (± 1 day)	Day 28 (± 2 days)	Day 35 (± 2 days)	Day 42 (± 2 days)	Day 56 (± 2 days)	Day 78 (± 2 days)	Day 100 (± 2 days)	Day 184 (±7 days)	Window of 1 to 56 days	
Flow cytometry, (aspirate) (bone marrow)[f]								X			X			X	X	X
CyTOF (aspirate) (bone marrow)[f, g]								X			X			X	X	X
CyTOF/ PBMC/ Plasma (whole blood)[g]				X	X	X	X	X	X	X	X		X	X	X	X
PBMCs for functional in vitro assays					X			X		X	X		X; then every 8 weeks up to 1 year			
Cytogenetics (bone marrow)															X	
Whole Exome Sequencing (bone marrow)															X	
Replication Competent Lentivirus (RCL) (whole blood)	Pre-dose (≤4 hour window)		At approximately 3 months (Day 100), 6 months (Day 184), and 12 months (Day 352) (±1 month); then yearly (±3 months) for 15 years post infusion. Yearly collection of RCL samples is not required if assessments within the first year are negative. Additional samples may be collected triggered by events which may be relevant to RCL per clinical assessment.													
Serum protein analysis	Pre-dose (≤4 hour window)	Additional serum protein sample will be taken at each SIFE/SPEP evaluation, as well as at each MRD sample collection														
Cytokine profiling[d] (serum)	Pre-dose (≤4 hour window), 2hrs Post (±10 minutes)	X	X	X	X	X	X	X		X	X	X	X			

Abbreviations: ADA=anti-drug antibody; BCMA=B-cell maturation antigen; CAR=chimeric antigen receptor; CR = complete response; CRS=cytokine release syndrome; CyTOF=cytometry by time of flight; ICANS= immune effector cell-associated neurotoxicity syndrome; MRD=minimal residual disease; PBMC=peripheral blood mononuclear cell; PD=progressive disease; PK=pharmacokinetic; sCR=stringent complete response; SIFE=serum immunofixation electrophoresis; SPEP=serum protein electrophoresis

[a] For subjects who discontinue the study before Day 100, the Day 100 assessments should be performed if feasible.
[b] Collect additional samples when any of the following are observed or reported: 1) CRS or neurotoxicity event Grade ≥2 (at onset of the event, and 24 and 72 hours after) or as clinically indicated; and 2) as indicated based on emerging data
[c] ADA sample should be collected if a subject withdraws from the study after JNJ-68284528 administration but prior to disease progression or study completion.
[d] Collect additional samples when any of the following are suspected or reported: 1) CRS or CAR-T cell-related neurotoxicity (eg, ICANS) (any grade) (at onset of the event, and then every 24 hours until CRS or ICANS event has stabilized or is resolving at which time additional collections should occur at 24, 48, and 72 hours) or as clinically indicated; and 2) as indicated based on emerging data.
[e] Pharmacokinetic and biomarker samples collection (serum samples only) may be performed at the subject's home by mobile study personnel (i.e. nurses and mobile phlebotomist) in the post-treatment period, after the Day 100.
[f] Sample should be collected at suspected CR
[g] Sample should be collected at 12 months, relative to Day 1, for subjects that achieve CR/sCR and remain on study.
[h] After 1 year, CAR+ T cell counts and CAR transgene levels will be measured at least annually until end of study (EOS), progressive disease (PD), or until the lower limit of quantitation (LLOQ) of the cilta-cel transgene is reached, whichever is earlier. Additional event-triggered testing for PK CAR transgene levels and CAR+ T cell counts may be conducted as clinically indicated.

ABBREVIATIONS

ADC	antibody-drug conjugate
ADL	Activities of Daily Living
AL	amyloid light-chain
ALC	absolute lymphocyte count
ALL	acute lymphocytic leukemia
ALT	alanine aminotransferase
ANC	absolute neutrophil count
APRIL	a proliferation inducing ligand
ASBMT	American Society for Blood and Marrow Transplantation
ASCT	autologous stem cell transplantation
AST	aspartate aminotransferase
ASTCT	American Society for Transplantation and Cellular Therapy
AUC	area under the curve
BAFF	B-cell activating factor
BCMA	B-cell maturation antigen
β2M	beta 2 microglobulin
β-hCG	β human chorionic gonadotropin
BiPAP	Bilevel Positive Airway Pressure
BiTE	bispecific T-cell engager
BMI	body mass index
BNP	B-type natriuretic peptide
CABG	coronary artery bypass graft
CAR-T	chimeric antigen receptor T (cells)
CBC	complete blood count
CBR	clinical benefit rate
CI	confidence interval
CNS	central nervous system
COPD	chronic obstructive pulmonary disease
CPAP	Continuous Positive Airway Pressure
CR	complete response
CRF	case report form
CRS	cytokine release syndrome
CSR	clinical study report
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTPPM	Cell therapy product procedures manual
CyTOF	cytometry by time of flight
DMSO	dimethyl sulfoxide
DIC	disseminated intravascular coagulation
DOR	duration of response
DTT	dithiothreitol
D-VRd	daratumumab, bortezomib, lenalidomide, dexamethasone
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
eDC	electronic data capture
eGFR	estimated glomerular filtration rate
EORTC	European Organization for Research and Treatment of Cancer
FLC	free light chain
FOIA	Freedom of Information Act
GCP	Good Clinical Practice
G-CSF	granulocyte colony-stimulating factor
GVHD	graft-versus-host disease
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus

HCV	hepatitis C virus
HLH/MAS	hemophagocytic lymphohistiocytosis/macrophage activation syndrome
HIV	human immunodeficiency virus
HRQoL	health-related quality of life
hr-NDMM	high risk, newly diagnosed multiple myeloma
IAT	Indirect Antiglobulin Test
ICANS	immune effector cell-associated neurotoxicity syndrome
ICE	immune effector cell-associated encephalopathy
ICF	informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ICP	intracranial pressure
IEC	independent ethics committee
Ig	immunoglobulins
IL	interleukin
IMiD	immunomodulatory drug
IMWG	International Myeloma Working Group
IPPI	investigational product preparation instructions
IRB	Institutional Review Board
IRR	infusion-related reaction
ISS	International Staging System
IV	intravenous(ly)
LDH	lactate dehydrogenase
LVEF	left ventricular ejection fraction
MedDRA	Medical Dictionary for Regulatory Activities
MR	minimal response
MRD	minimal residual disease
MRI	magnetic resonance imaging
MUGA	multiple-gated acquisition
MySIm-Q	Multiple Myeloma Symptom and Impact Questionnaire
NGF	next generation flowcytometry
NGS	next generation sequencing
NYHA	New York Heart Association
ORR	overall response rate
OS	overall survival
PBMC	peripheral blood mononuclear cell
PD	progressive disease
PET	positron emission tomography
PFS	progression-free survival
PGIC	Patient Global Impression of Change
PGIS	Patient Global Impression of Severity
PI	proteasome inhibitor
POEMS	polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, and skin changes
PQC	product quality complaint
PR	partial response
PRO	patient reported outcomes
QIg	quantitative immunoglobulin
RBC	red blood cell
RCL	replication competent lentivirus
REMS	Risk Evaluation and Mitigation Strategy
rHuPH20	recombinant human hyaluronidase
RP2D	recommended Phase 2 dose
sBCMA	soluble BCMA
SC	subcutaneous
sCR	stringent complete response
SET	safety evaluation team
SIPPM	site investigational product procedures manual
SPEP	serum protein electrophoresis

SPM	second primary malignancy
SVR	sustained virologic response
TCR	T cell receptor
TEAE	treatment-emergent adverse event
TLS	tumor lysis syndrome
TNF-R	tumor necrosis factor receptor
TTR	time to response
ULN	upper limit of normal
UPEP	urine M-protein quantitation by electrophoresis
VGPR	very good partial response

1. INTRODUCTION

JNJ-68284528 (ciltacabtagene autoleucel) is an autologous chimeric antigen receptor T cell (CAR-T) therapy that targets B cell maturation antigen (BCMA), a molecule expressed on the surface of mature B lymphocytes and malignant plasma cells. Results from the Phase 1b portion of study 68284528MMY2001 indicate that JNJ-68284528 has a safety profile consistent with the known mechanism of action of the product and compelling efficacy in a population of heavily pre-treated subjects.

For the most comprehensive nonclinical and clinical information regarding JNJ-68284528, refer to the latest version of the Investigator's Brochure and Addenda for JNJ-68284528.

The term "sponsor" used throughout this document refers to the entities listed in the Contact Information page(s), which will be provided as a separate document.

1.1. Background

1.1.1. Multiple Myeloma

Multiple myeloma is characterized by the production of monoclonal immunoglobulin (Ig) proteins or protein fragments (M proteins) that have lost their function (Kyle 2009; Palumbo 2011). The proliferation of multiple myeloma cells leads to subsequent displacement of normal bone marrow hematopoietic precursors and overproduction of M-proteins. Hallmarks of multiple myeloma include osteolytic lesions, anemia, increased susceptibility to infections, hypercalcemia, renal insufficiency or failure, and neurologic complications (Korde 2011; Palumbo 2011).

Treatment options for multiple myeloma have substantially improved over time and vary depending on the aggressiveness of the disease, underlying prognostic factors, physical condition of the patient, and existing co-morbidities. Therapeutic options include agents such as proteasome inhibitors (PIs), immunomodulatory drugs (IMiDs), monoclonal antibodies, and stem cell transplantation.

Despite these therapeutic achievements, the disease recurs and remains incurable. Thus, there is a need for novel therapeutic approaches.

1.1.2. B cell Maturation Antigen

B cell maturation antigen (BCMA, also known as CD269 and TNFRSF17) is a 20 kilodalton, type III membrane protein that is part of the tumor necrosis receptor superfamily (Tai 2015). BCMA is predominantly expressed in B-lineage cells and plays a critical role in B cell maturation and subsequent differentiation into plasma cells (Tai 2015). BCMA binds 2 ligands that induce B cell proliferation: a proliferation inducing ligand (APRIL; CD256) and B-cell activating factor (BAFF; CD257) (Avery 2003; Darce 2007; Patel 2004). Upon binding of BCMA monomers to the APRIL trimer, activation and phosphorylation of p38MAPK, ELK, and NF-κB are triggered through intracellular tumor necrosis factor receptor (TNF-R)-associated factor (TRAF) molecules leading to pro-survival gene regulation (Bossen 2006; Hatzoglou 2000; Kimberley 2009).

In multiple myeloma cell lines and patient samples, BCMA is more stably expressed specifically on the B cell lineage than CD138, a key plasma cell marker which is also expressed on normal fibroblasts and epithelial cells (Palaiologou 2014). The expression characteristics of BCMA make it an ideal therapeutic target in the treatment of multiple myeloma (Frigyesi 2014; Tai 2015).

1.1.3. CAR-T Therapy

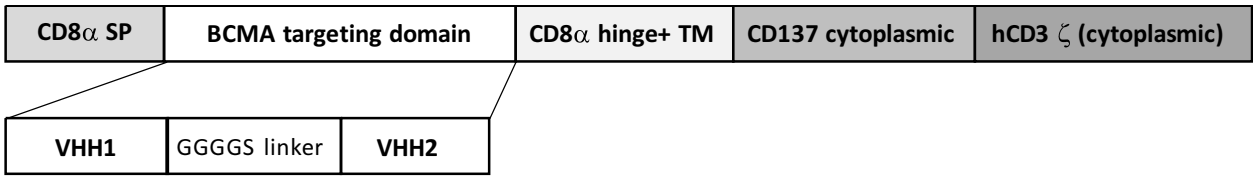
Chimeric antigen receptor T (CAR-T) cell therapy uses modified autologous T cells that are activated in a MHC-independent manner upon binding to their target. This results in lysis of the targeted cells. An ongoing Phase 1 clinical study with bb2121, a BCMA-directed CAR-T immunotherapy, demonstrated promising results for this strategy in relapsed/refractory multiple myeloma (Raje 2019). Of the first 33 consecutive subjects to receive an infusion of bb2121 76% experienced cytokine release syndrome (CRS), which was Grade 1 or 2 in 23 subjects (70%) and Grade 3 in 2 subjects (6%). Neurologic toxicity occurred in 42% of subjects. The objective response rate (partial response or better) was 85%, including 15 subjects (45%) with complete responses. A median progression-free survival (PFS) of 11.8 months was observed for the 30 subjects who received $\geq 15 \times 10^7$ CAR-positive T-cells and 2.6 months for the 3 subjects who received $<15 \times 10^7$ CAR-positive T-cells. Sixteen subjects with a partial response or better and who could be evaluated for minimal residual disease (MRD), were MRD negative at the sensitivity threshold of 10^{-4}.

1.1.4. JNJ-68284528

JNJ-68284528, consists of autologous CAR-T cells and the target antigen is BCMA. The novel design features dual targeting domains on BCMA, enabling tight binding of LCAR-B38M to the BCMA-expressing cells.

The LCAR-B38M coding sequence is comprised of a human CD8 alpha signal peptide (CD8α SP), BCMA targeting domain consisting of 2 different VHH (single domain antibody, clone VHH1 and VHH2), human CD8 alpha hinge and transmembrane domain (CD8α hinge+TM), human CD137 cytoplasmic domain, and a human CD3 zeta cytoplasmic domain (CD3ζ) (Figure 1). The expression of LCAR-B38M is driven and controlled by a human elongation factor 1 alpha promoter (hEF1α promoter).

Figure 1: LCAR-B38M Coding Region



The JNJ-68284528 drug product used in this study and the LCAR-B38M CAR-T cell drug product used in the first-in-human Legend-2 study (See Section 1.1.5) express an identical CAR protein. The JNJ-68284528 drug product is produced using modified manufacturing and scale-up processes compared with the Legend-2 study material. The LCAR-B38M CAR-T cell designation will be used when referring to results from the Legend-2 study. JNJ-68284528 will be used to reference the drug product in Study 68284528MMY2003 (CARTITUDE-2). A similar manufacturing process will be utilized to generate the commercial product used in Cohort A of Study 68284528MMY2003.

1.1.5. Clinical Studies

Study 68284528MMY2001

Study 68284528MMY2001 is a Phase 1b/2, open-label, multicenter study to evaluate the safety and efficacy of cilta-cel in adult subjects with relapsed or refractory multiple myeloma. For the 97 subjects who received cilta-cel (Phase 1b: 29 subjects; Phase 2: 68 subjects) the median duration of follow-up was 12.4 months (range: 1.5 to 24.9 months) as of the 1 September 2020 clinical cutoff date.

- All 97 subjects had at least 1 treatment-emergent adverse event (TEAE). The most frequently reported TEAEs were neutropenia (95.9%), CRS (94.8%), anemia (81.4%), thrombocytopenia (79.4%), leukopenia (61.9%), and lymphopenia (52.6%).
- Serious TEAEs were reported for 53 subjects (54.6%). Serious TEAEs of Grade 3 or 4 toxicity were reported for 29 subjects (29.9%). Serious TEAE reported in >5% of subjects were CRS (20.6%) and ICANS, pneumonia, and sepsis (5.2% each).
- Fifty-six subjects (57.7%) developed infections, most commonly upper respiratory tract infection (15.5%), rhinovirus infection (6.2%), pneumonia (8.2%), sepsis (5.2%), sinusitis (4.1%), and influenza (5.2%).
- Fourteen deaths were reported for Phase 1b and Phase 2 studies combined as of the 1 September 2020 clinical cutoff for safety. Five deaths were attributed to PD. The 9 remaining deaths were attributed to adverse events (AEs) with 6 (6.2%) related to cilta-cel (3 infections, 1 respiratory failure, 1 cytokine release syndrome (CRS)/hemophagocytic lymphohistiocytosis (HLH), 1 neurotoxicity).
- Ninety-two subjects (94.8%) experienced CRS. Most subjects (87 subjects [89.7%]) experienced CRS TEAEs that were Grade 1 or 2; 5 subjects had CRS Grade >3: 3 Grade 3 (3.1%), 1 Grade 4 (1.0%) and 1 Grade 5 (1.0%) The median time from cilta-cel infusion to first onset of CRS was 7.0 days (range: 1 to 12 days), and the median duration of CRS was 4.0 days (range: 1 to 14 days) with the exception of the subject who experienced Grade 5 CRS (97-day duration).
- CAR-T cell neurotoxicity is categorized as immune effector cell-associated neurotoxicity syndrome (ICANS) as well as other neurotoxicity determined by the investigator to be related to CAR-T therapy and occurring after recovery from CRS and/or ICANS. Twenty subjects (20.6%) experienced a treatment-emergent CAR-T cell neurotoxicity event.

- All-grade ICANS were reported for 16 subjects (16.5%). Of these, 2 subjects (2.1%) developed maximum Grade 3 or 4 ICANS. Median time from cilta-cel infusion to ICANS onset was 8 days (range: 3 to 12 days), and the median duration of ICANS was 4 days (range: 1 to 12 days). Fifteen subjects experienced ICANS concurrent with CRS and 1 subject experienced ICANS 4 days after the recovery of CRS.
- Twelve subjects (12.4%) experienced other CAR-T cell neurotoxicity not defined as ICANS as assessed by the Investigator either due to symptoms or time of onset (ie, occurring after period of recovery from CRS and/or ICANS). These events included a variety of symptoms with varying severity including disturbances in consciousness, coordination and balance, movement disorders, mental impairment, cranial nerve disorders, and peripheral neuropathies.
    - Five of these 12 subjects experienced a similar presentation of movement and neurocognitive TEAEs. These included a cluster of movement (eg, micrographia, tremors, etc), cognitive (eg, memory loss, disturbance in attention, etc) and personality change (eg, reduced facial expression, flat affect, etc) TEAEs that were observed to progress to an inability to work or care for oneself (disabling). This cluster of movement and neurocognitive TEAEs appears potentially to be associated with a combination of 2 or more factors such as higher tumor burden, prior Grade 2 or higher CRS, prior ICANS, and high CAR-T cell expansion and persistence.
    - The neurotoxicity was Grade 1 or 2 in 3 subjects (3.1%), Grade 3 or 4 in 8 subjects (8.2%) and Grade 5 in 1 subject (1.0%). These events had a median onset of 26.5 days from cilta-cel infusion (range: 11 to 108 days) with a median duration of 74.5 days (range: 2 to 160 days). At the time of clinical data cutoff, 6 (50%) had resolved, 4 (33%) were ongoing at the time of death due to other causes, and 1 is ongoing in a subject still in follow-up; one case (8.3%) was fatal.

At the time of the 11 February 2021 data cutoff for the efficacy update, the median duration of follow-up was 18.0 months.

Treatment of these subjects with cilta-cel resulted in an overall response rate (ORR) of 97.9% with 95 of 97 subjects in the Alltreated analysis set achieving a partial response (PR) or better as assessed by Independent Review Committee (IRC) (based on International Myeloma Working Group [IMWG] criteria). Notably, the stringent complete response (sCR) rate was 80.4%. The responses occurred rapidly, with the median time to first response of 0.95 month (range: 0.9 to 1.9). The overall median progression-free survival (PFS) based on the IRC response assessment was 22.8 months. Please see IB for most current information regarding clinical studies.

Study 68284528MMY2002

Study 68284528MMY2002 is a Phase 2, open-label, multicenter study in China (sponsored by Legend Biotech HK Limited and Janssen R&D; Investigational New Drug holder is Legend Biotech) to evaluate the efficacy and safety of cilta-cel in adult Chinese subjects with relapsed or refractory multiple myeloma. Subjects must have received at least 3 lines of treatment for multiple myeloma, have undergone at least 1 complete cycle of treatment for each line of treatment (unless PD was the best response), and have received a PI and an IMiD. The primary objective is to evaluate the efficacy of LCAR-B38M CAR-T cells. The first subject was dosed on 22 March 2019.

As of March 2021, enrollment and treatment in this study were completed; 48 subjects received cilta-cel. Safety and efficacy findings were consistent with Study 68284528MMY2001. Further details are provided in the most recent edition of the cilta-cel Investigator's Brochure.

Legend-2

Legend-2 is a first-in-human, single-arm, open-label, multicenter study to determine the safety and efficacy of LCAR-B38M CAR-T cells used to treat subjects with relapsed or refractory multiple myeloma. This study was conducted in China. Study enrollment was completed in November 2017; 74 subjects with relapsed or refractory Multiple Myeloma treated with LCAR-B38M CAR-T cell therapy. Further details are provided in the most recent edition of the Cilta-cel Investigator's Brochure

1.2. Overall Rationale for the Study

BCMA is a cell surface antigen highly expressed on cells of the B cell lineage. Comparative studies show a lack of BCMA in most normal tissues and absence of expression on CD34-positive hematopoietic stem cells (Carpenter 2013; Hsi 2008). This selective expression and the biological importance for the proliferation and survival of myeloma cells makes BCMA a promising target for CAR-T based immunotherapy, JNJ-68284528. Results in 74 subjects from the Legend-2 study (Section 1.1.5) indicate an ORR of 87.8% with a CR rate of 64.9%. The observed response rates and the reversible adverse events for most subjects, support further investigation of this approach in the current study.

The safety and efficacy of JNJ-68284528 in heavily pretreated patients with multiple myeloma is being evaluated in the Phase 1b/2 Study 68284528MMY2001. As the degree of benefit of the CAR-T therapy is dependent on a patient's immune response, JNJ-68284528 could provide potentially meaningful efficacy and durability when administered to patients with multiple myeloma who have had less exposure to immunomodulatory and cytotoxic therapy. The objective of Study 68284528MMY2003 is to determine the safety and efficacy of JNJ-68284528 in various clinical settings. Multiple cohorts will run in parallel with unique patient populations of unmet medical need enrolled. Approximately 40 subjects will be enrolled in Cohort A and Cohort F, and approximately 17 subjects in Cohort D. Approximately 20 subjects each will be enrolled in all other cohorts. The subject population for each of the cohorts is described below.

- Cohort A: Subjects with progressive disease after 1 to 3 prior lines of therapy for multiple myeloma including a proteasome inhibitor (PI) and immunomodulatory drug (IMiD) either individually or in combination. Subjects are required to be refractory to lenalidomide. Subjects who have received prior therapy that is targeted to BCMA are excluded from this cohort.
- Cohort B: Subjects who have received one line of previous therapy containing a PI and an IMiD and who have early relapse defined as disease progression ≤12 months after an ASCT or ≤12 months after the start of front-line therapy for subjects who have not had an ASCT. Subjects who have received prior therapy that is targeted to BCMA are excluded from this cohort.

- Cohort C: Relapsed or refractory disease in subjects previously treated with a proteasome inhibitor (PI), immunomodulatory drug (IMiD), anti-CD38 monoclonal antibody and BCMA-directed therapy (excluding cellular immunotherapy).
- Cohort D (JNJ-68284528 plus lenalidomide): Subjects with multiple myeloma who did not achieve a complete response after 4 to 8 total cycles of initial therapy, including induction, high-dose therapy and ASCT with or without consolidation induction.
- Cohort E (daratumumab, bortezomib, lenalidomide, and dexamethasone [D-VRd] induction, then JNJ-68284528, followed by consolidation treatment with lenalidomide: Subjects with high risk, newly diagnosed and untreated multiple myeloma (hr-NDMM) for whom hematopoietic stem cell transplant is not planned as initial therapy.
- Cohort F will include newly diagnosed multiple myeloma subjects with standard risk disease and an overall response ≥VGPR after 4 to 8 total cycles of initial therapy.

Subjects who meet the eligibility criteria for Cohort A and Cohort B, must be enrolled in Cohort B.

1.3. Potential Safety Risks and Mitigation Strategies

JNJ-68284528 (All Cohorts)

The potential risks of JNJ-68284528 are identified from the following: 1) results of nonclinical studies; 2) mechanism of action; and 3) previous clinical experience with JNJ-68284528 and LCAR-B38M CAR-T cells. Treatment of additional subjects and prolonged follow-up may reveal additional risks.

By stimulating an inflammatory cascade, there is potential for toxicity in other tissues or organs by non-specific immune cell activation. Therefore, special attention will be given to both immunological and immunogenicity-related toxicities. Safety risks and mitigation strategies are outlined in Table 9.

Table 9: Risks Associated with JNJ-68284528 and Mitigation Strategies

Risk	Mitigation Strategies
Cytokine release syndrome (CRS) [a]	Monitor closely for CRS and follow guidance for management in Section 6.2.1. Body temperature should be monitored twice daily for 28 days post infusion. At the first sign of CRS (such as fever) subjects should be immediately hospitalized for evaluation. See Table 11 for other hospitalization requirements. Potentially life-threatening complications of CRS may include cardiac dysfunction, adult respiratory distress syndrome, neurologic toxicity, renal failure, hepatic failure, and disseminated intravascular coagulation. Rarely, severe CRS can evolve into a presentation consistent with hemophagocytic lymphohistiocytosis/macrophage activation syndrome (HLH/MAS) that may require additional therapy. Severe thrombocytopenia, low fibrinogen, and often disseminated intravascular coagulation (DIC) may be features of HLH, all of which combined may increase the risk of severe bleeding in these subjects. Section 6.2.1 describes measures to be taken if HLH is suspected. The use of myeloid growth factors, particularly granulocyte colony-stimulating factor (G-CSF), should be avoided during CRS. Tocilizumab intervention may be considered with presenting symptom of fever in the absence of clear infectious etiology. Early tocilizumab should be considered in subjects at high risk of severe CRS. Section 6.2.1 provides management guidelines for CRS. Notify the sponsor if subject is experiencing Grade 2 or higher CRS.

Table 9: Risks Associated with JNJ-68284528 and Mitigation Strategies

Risk	Mitigation Strategies
Neurologic toxicities [a]	Immune effector cell-associated neurotoxicity syndrome (ICANS): Monitor closely for neurologic AEs, including CAR-T cell-related neurotoxicity (eg, ICANS) and raised intracranial pressure/cerebral edema; follow guidance for management in protocol. Subjects should be advised to seek medical evaluation if they notice new onset of headache, convulsions, speech disorders, visual disorders, disturbances in consciousness, confusion and disorientation, and coordination and balance disorders, or mental status changes. Notify the sponsor if subject is experiencing any grade ICANS. At the first sign of neurotoxicity, neurology consultation and evaluation should be considered. The immune effector cell-associated encephalopathy (ICE) Assessment Tool (ICE-Tool) should be performed at baseline and daily after the first symptoms of neurotoxicity are suspected and until resolution. Hospitalization is required for ≥ Grade 2 CAR-T cell-related neurotoxicity (eg, ICANS). Section 6.2.2 provides management guidelines for neurotoxicity. Consider non-sedating, anti-seizure medicines (eg, levetiracetam) for seizure prophylaxis for any Grade 1 or higher neurologic toxicities. Other cytokine-targeting therapies (for example, IL-1) may be used based on institutional practice, especially for cases of neurotoxicity which does not respond to tocilizumab or corticosteroids. Therapy directed at reduction or elimination of CAR-T cells, including chemotherapy, may be considered in consultation with the sponsor for subjects who develop neurotoxicity that remains severe or life-threatening following prior therapies, including tocilizumab and corticosteroids.
	Movement and Neurocognitive Toxicity (ie, Parkinsonism): A cluster of symptoms with variable onset spanning more than one symptom domain was observed, including: changes in movement (eg, micrographia or changes in handwriting, tremors, bradykinesia, rigidity, shuffling gait, impaired balance and coordination, difficulty writing, difficulty performing activities of daily living like dressing or feeding oneself), cognitive impairments (eg, memory loss or forgetfulness, disturbance in attention, mental slowness or fogginess, difficulty speaking or slurred speech, difficulty reading or understanding words), and personality changes (eg, reduced facial expression, flat affect, reduced ability to express emotion, less communicative, disinterest in activities). A cluster of movement and neurocognitive TEAEs were observed at a higher frequency in subjects with high burden of disease and in subjects experiencing higher grade CRS (Grade 2 and above) and any grade ICANS. This may be indicative that ≥Grade 2 CRS or any grade ICANS are early indicators for the development of other neurotoxicity after a period of recovery from CRS and/or ICANS. Therefore, ≥Grade 2 CRS or any grade ICANS may represent an opportunity for early intervention and more aggressive supportive care (including steroids), especially in patients treated with a high tumor burden, that may mitigate the risk for developing late, other neurotoxicity. Infection and sepsis were seen concurrently in many of these patients. Mitigation strategies for other neurotoxicity include enhanced bridging therapy to reduce baseline tumor burden, early aggressive treatment of CRS and ICANS, handwriting assessments for early detection of neurotoxicity symptoms, and extended monitoring and reporting time for neurotoxicity for the duration of the study. Monitor closely for other neurotoxicities with clinical presentation for the duration the study after infusion. If those neurologic or psychiatric symptoms are noted, contact the medical monitor, and refer the subject immediately to a neurologist for a full evaluation. Section 6.2.2.2 provides further details for management guidelines for neurotoxicity.

Table 9: Risks Associated with JNJ-68284528 and Mitigation Strategies

Risk	Mitigation Strategies
	Cranial Nerve Palsies: Monitor patients for signs and symptoms of cranial nerve palsies (eg, facial paralysis, facial numbness). Consider management with short-course systemic corticosteroids, depending on the severity and progression of signs and symptoms. Peripheral Neuropathy: Monitor patients for signs and symptoms of peripheral neuropathies (eg, sensory, motor, or sensorimotor neuropathies). Consider management with short-course systemic corticosteroids, depending on the severity and progression of signs and symptoms. Guillain-Barré Syndrome: Monitor for signs and symptoms of GBS after cilta-cel infusion. Symptoms reported include those consistent with Miller-Fisher variant of GBS (encephalopathy, motor weakness, speech disturbances, and polyradiculoneuritis). Consider treatment with IVIG and escalate to plasmapheresis, depending on toxicity severity.
Second primary malignancies (SPMs)[a]	Second primary malignancies may occur in subjects receiving JNJ-68284528. SPMs should be managed per institutional standards. Second primary malignancies must be reported during the duration of the study, irrespective of when they occur, and subsequently will be collected in a long-term follow-up study yearly until 15 years post dosing of JNJ-68284528. A tumor sample should be collected, and DNA, RNA, or protein analysis may be performed to investigate the presence of lentiviral elements if an SPM develops. Section 6.2.4 provides management guidelines for SPMs.
Prolonged Cytopenia	Frequent monitoring of hematological parameters and provide supportive care (eg, radiated blood and thrombocyte concentrates, granulocyte-colony stimulating factor for neutropenia) as outlined by institutional guidelines. Pegylated myeloid growth factors (ie, pegfilgrastim) are prohibited. Prolonged neutropenia may increase the risk of infection. Severe thrombocytopenia may increase the risk of bleeding. Initiating lenalidomide after JNJ-68284528 might cause significant neutropenia and thrombocytopenia. Monitor complete blood counts (CBC) weekly for first 2 cycles, biweekly for cycle 3 and every 28 days thereafter. A dose interruption and reduction may be required (refer to local prescription information and guidance in Table 13, Table 14, and Table 15). Subjects should be monitored frequently for infection and bleeding. Supportive care should be provided per institutional standards. Section 6.2.5 provides management guidelines for cytopenia. Parvovirus B19 monitoring by PCR should be considered in subjects experiencing prolonged neutropenia or a decline in neutrophil counts following recovery.
Hypogammaglobulinemia	Monitor immunoglobulin levels after treatment and treat according to local guidelines, including administration of immunoglobulin replacement and monitoring for infection. Additional assessments of immunoglobulin levels may be done as per local standards of care. Section 6.2.6 provides management guidelines for hypogammaglobulinemia. Subjects with IgG < 400 mg/dL or recurrent infections (including HBV reactivation) should be considered for prophylactic IV or subcutaneous IgG as per institutional guidelines.
Serious Infections	Do not administer JNJ-68284528 to patients with active infection. Frequent monitoring for the presence of infections, with cultures or implementation of empiric antibiotic therapy as appropriate, based on clinical judgment and institutional standards. Extended use of anti-microbial therapies for at least 6 month (or longer as per institutional guidelines) or consistent with post ASCT consensus guidelines after JNJ-68284528 dosing is recommended (See Attachment 18).

Table 9: Risks Associated with JNJ-68284528 and Mitigation Strategies

Risk	Mitigation Strategies
	Perform screening for hepatitis B virus (HBV), hepatitis C virus (HCV), and human immunodeficiency virus (HIV) and monitor as clinically indicated, and initiate treatment as appropriate. Perform CMV and EBV serology (at baseline only) and PCR at baseline and according to the Time and Events Schedules (Table 1, Table 3, and Table 6), and as clinically indicated per institutional guidance. HBV reactivation, in some cases resulting in fulminant hepatitis, hepatic failure and death, may occur in subjects treated with drugs directed against B cells such as JNJ-68284528. HBV reactivation has occurred in subjects who appear to have resolved hepatitis B infection. Prophylaxis for herpes zoster reactivation is recommended during study treatment as clinically indicated. Routinely monitor HBV DNA and AST/ALT for subjects with risk of HBV reactivation (Attachment 10). Subjects receiving cilta-cel are possibly at a higher risk of severe/fatal outcomes from COVID-19 infection compared with patients who are receiving standard of care therapy. Subjects should be reminded of the importance of vaccines and other preventative measures. Investigators should consider prophylaxis (eg, Evusheld, if available) and antiviral medications (eg, Paxlovid, if available) for patients diagnosed with COVID-19 infection, as noted in (Attachment 20).
Hypersensitivity reactions	Allergic reactions may occur with the infusion of JNJ-68284528. Serious hypersensitivity reactions including anaphylaxis, may be due to dimethyl sulfoxide (DMSO), dextran 40, or residual ampicillin or kanamycin in JNJ-68284528. Subjects should be treated urgently per institutional standards, avoiding corticosteroid use if possible. Subjects should receive premedication prior to JNJ-68284528 dosing as noted in Section 6.1.3.3.
Tumor lysis syndrome	Monitor closely for TLS with frequent monitoring of chemistry parameters and follow guidance for management in protocol. Subjects with high tumor burden or multiple extramedullary disease sites or plasmacytomas should be treated prophylactically in accordance with local standards (eg, extra hydration; diuretics; allopurinol; and primary or secondary uricosuric agents, as indicated).

ALT=alanine aminotransferase; AST=aspartate aminotransferase; CMV=cytomegalovirus; DMSO=dimethyl sulfoxide; EBV=Epstein-Barr virus; G-CSF=granulocyte colony-stimulating factor; HBV=hepatitis B virus; HCV=hepatitis C virus; HIV=human immunodeficiency virus; HLH=hemophagocytic lymphohistiocytosis; ICE=immune effector cell-associated encephalopathy; MAS=macrophage activation syndrome; PCR=polymerase chain reaction; SPM=second primary malignancy; TEAE=treatment-emergent adverse event; TLS=tumor lysis syndrome.

[a] Adverse event of special interest (see Section 12.3.3)

2. OBJECTIVES, ENDPOINTS, AND HYPOTHESIS

2.1. Objectives and Endpoints

Objectives	Endpoints
Primary	
• To evaluate the overall minimal residual disease (MRD) negative rate of subjects who receive JNJ-68284528	• MRD negative rate at a 10^{-5} threshold as defined by the International Myeloma Working Group (IMWG) criteria using next generation sequencing (NGS) or next generation flow (NGF)
Secondary	
• To evaluate the efficacy of JNJ-68284528	• Overall Response Rate (ORR) (partial response [PR] or better) as defined by the IMWG response criteria • VGPR, CR, sCR rate as defined by the IMWG response criteria, clinical benefit rate (CBR; CBR = ORR [sCR + CR + VGPR + PR] + minimal response [MR]) • Duration of response (DOR) and time to response (TTR)

Objectives	Endpoints
• To further characterize MRD negativity	• MRD negative rate at 12 months for subjects who achieved a complete response (CR MRD neg 12 month) • Time to MRD negativity, duration of MRD negativity, • MRD negative rate across clinical response groups (CR, stringent complete response [sCR], very good partial response [VGPR])
• To characterize the safety of JNJ-68284528	• Incidence and severity of adverse events, laboratory results, and other safety parameters
• To characterize the pharmacokinetics and pharmacodynamics of JNJ-68284528	• Pharmacokinetic and pharmacodynamic markers including but not limited to depletion of soluble BCMA and BCMA expressing cells, systemic inflammatory cytokine concentrations and immune related proteins, and markers of CAR-T cell activation, expansion (proliferation), and persistence via monitoring CAR-T positive cell counts and CAR transgene level.
• To assess the immunogenicity of JNJ-68284528	• Presence of anti- JNJ-68284528 antibodies
Exploratory	
• To further characterize the efficacy of JNJ-68284528	• Progression-free survival (PFS), overall survival (OS) • Imaging plus MRD negative rate (if positron emission tomography [PET] is locally available)
• To explore changes in patient-reported outcomes (PRO) after treatment with JNJ-68284528	• Time to worsening of symptoms using the MySIm-Q total symptom score • Change from baseline in HRQoL (symptoms, functioning, and well-being) using the European Organization for Research and Treatment of Cancer (EORTC) QLQ-C30, MySIm-Q (Multiple Myeloma Symptom and Impact Questionnaire), Patient Global Impression of Change (PGIC), and Patient Global Impression of Severity (PGIS).
• To assess symptomatic adverse events from the patient perspective via patient reported outcomes of the Common Terminology Criteria for Adverse Events (PRO-CTCAE).	• PRO-CTCAE report using validated questions.
• To characterize the impact of JNJ-68284528 CAR-T process on medical resource utilization	• Number of subjects with type and length of inpatient stay and overall medical encounters
• To characterize potential early clinical, translational, and imaging markers for neurotoxicity (predictive markers)	• Qualitative changes in handwriting assessment • T_{max}, C_{max}, and phenotypic analysis of CAR-T cells • Neuroimaging (CT/MRI/PET)

2.2. Hypotheses

The primary hypothesis is that JNJ-68284528 will induce a deep-response, measured by MRD negative rate in the clinical settings investigated.

3. STUDY DESIGN AND RATIONALE

3.1. Overview of Study Design

This is a Phase 2, multicohort, open-label, multicenter study to determine whether treatment with JNJ-68284528 results in MRD negativity in adult subjects with multiple myeloma in various clinical settings. Multiple cohorts will run in parallel. Approximately 40 subjects will be enrolled in each Cohort A and Cohort F and approximately 17 subjects in Cohort D. Approximately

20 subjects each will be enrolled in all other cohorts. The primary endpoint for all cohorts will be overall MRD negative rate.

Subjects will participate in one of the following cohorts based on eligibility criteria defined in Section 4.1 to Section 4.5, and summarized below:

- Cohort A will include subjects with progressive disease after 1 to 3 prior lines of therapy for multiple myeloma including a proteasome inhibitor (PI) and immunomodulatory therapy (IMiD) either individually or in combination. In addition, all study subjects will be lenalidomide refractory. Subjects who have received prior therapy that is targeted to BCMA are excluded from this cohort.
- Cohort B will include subjects who have had one line of previous therapy containing a PI and an IMiD and who have early relapse defined as having disease progression ≤12 months after an ASCT or ≤12 months after the start of front-line therapy for subjects who have not had an ASCT. Subjects who have received prior therapy that is targeted to BCMA are excluded from this cohort.
- Cohort C will include subjects with relapsed or refractory disease in subjects previously treated with a PI, IMiD, anti-CD38 monoclonal antibody and BCMA-directed therapy (excluding cellular immunotherapy).
- Cohort D (JNJ-68284528 plus lenalidomide) will include subjects with multiple myeloma who did not achieve a complete response after 4 to 8 total cycles of initial therapy, including induction, high-dose chemotherapy and ASCT with or without consolidation.
- Cohort E (D-VRd induction, JNJ-68284528, then lenalidomide consolidation) will include subjects with high risk newly diagnosed and untreated multiple myeloma (hr-NDMM) for whom hematopoietic stem cell transplant is not planned as initial therapy.
- Cohort F will include newly diagnosed multiple myeloma subjects with standard risk disease and an overall response ≥VGPR after 4 to 8 total cycles of initial therapy

Subjects who meet the eligibility criteria for Cohort A and Cohort B, must be enrolled in Cohort B.

Assessment of MRD negativity and all response assessments will be performed by central laboratory. Disease status will be evaluated according to the IMWG consensus recommendations for multiple myeloma treatment response criteria (Attachment 1). Response will be determined using a validated computer algorithm.

Safety evaluations will include a review of adverse events, laboratory test results, vital sign measurements, physical examination findings (including neurologic examination), assessment of cardiac function, Immune Effector Cell-associated Encephalopathy (ICE) score, handwriting assessment, and assessment of Eastern Cooperative Oncology Group (ECOG) performance status grade. Follow up of subjects for disease progression and survival will continue during the Post-treatment Phase. All study evaluations will be conducted according to the Time and Events Schedules (Table 1 to Table 8). At the investigator discretion and with sponsor approval, study visits (for all cohorts) in the post-treatment part of the study, as early as after Day 100 after JNJ-68284528 infusion, may be performed remotely via telemedicine technology that connects study subjects to their research coordinators and investigators, if not using the sponsor's telemedicine solution. Blood sample collection may also be performed at the subject's home by mobile study personnel (ie, nurses and mobile phlebotomist), if not using the sponsor's home health nursing solution in the post-treatment period, as early as after Day 100 after JNJ-68284528 infusion.

The sponsor will establish a data cutoff date for the clinical study report (CSR) analyses. The primary analysis for each cohort will be conducted approximately 1 year after the last subject in each cohort receives their initial dose of JNJ-68284528. Subjects will be followed for survival after the clinical cutoff for the primary CSR. For Cohort A, B, and C, the cohort completion will be defined as no later than 2 years after the last subject in each cohort has received their initial dose of JNJ-68284528. For Cohort D and Cohort E, cohort completion will be defined as 2 ½ years after the last subject receives their initial dose of JNJ-68284528. However, the sponsor will monitor subjects treated with JNJ-68284528 for 15 years for complications of lentiviral integration, including second primary malignancies on a long-term follow-up study (See Section 9.5).

Data Monitoring Committee

A Data Monitoring Committee (DMC) will periodically review all safety and other relevant data collected in this study as well as data obtained in other JNJ-68284528 protocols. The DMC will provide recommendations to ensure subject safety and mitigate risk for all study subjects. Stopping rules based on safety signals will also be provided and maintained by the DMC. The roles and responsibilities of the DMC are to be specified in the DMC charter.

3.1.1. Cohort A Study Design

Subjects enrolled in Cohort A will undergo apheresis after screening to acquire peripheral blood mononuclear cells (PBMCs). For all subjects, JNJ-68284528 will be generated from the subject's T cells selected from the apheresis product. Subjects for whom apheresis or manufacturing fails will be allowed a second attempt at apheresis.

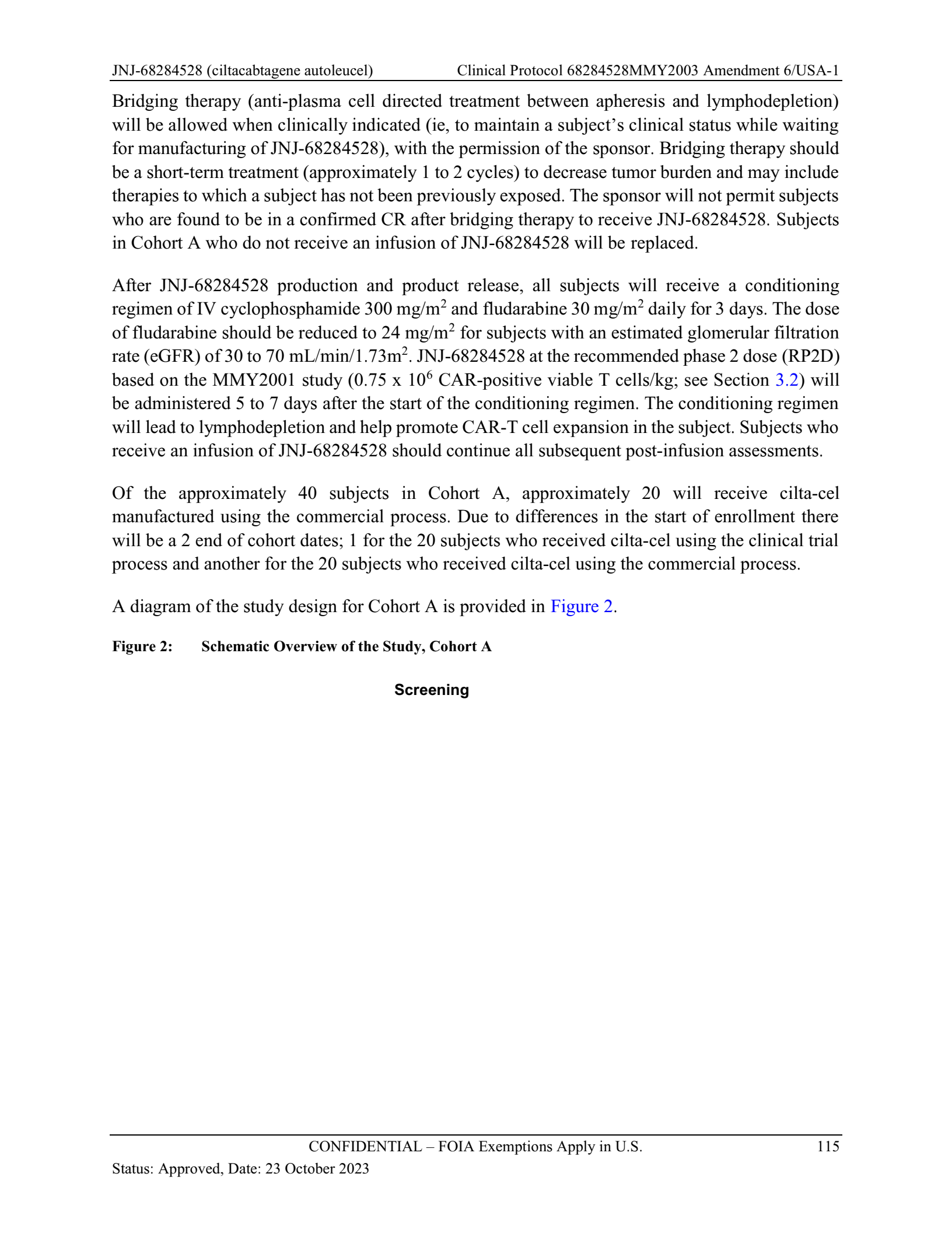
Bridging therapy (anti-plasma cell directed treatment between apheresis and lymphodepletion) will be allowed when clinically indicated (ie, to maintain a subject's clinical status while waiting for manufacturing of JNJ-68284528), with the permission of the sponsor. Bridging therapy should be a short-term treatment (approximately 1 to 2 cycles) to decrease tumor burden and may include therapies to which a subject has not been previously exposed. The sponsor will not permit subjects who are found to be in a confirmed CR after bridging therapy to receive JNJ-68284528. Subjects in Cohort A who do not receive an infusion of JNJ-68284528 will be replaced.

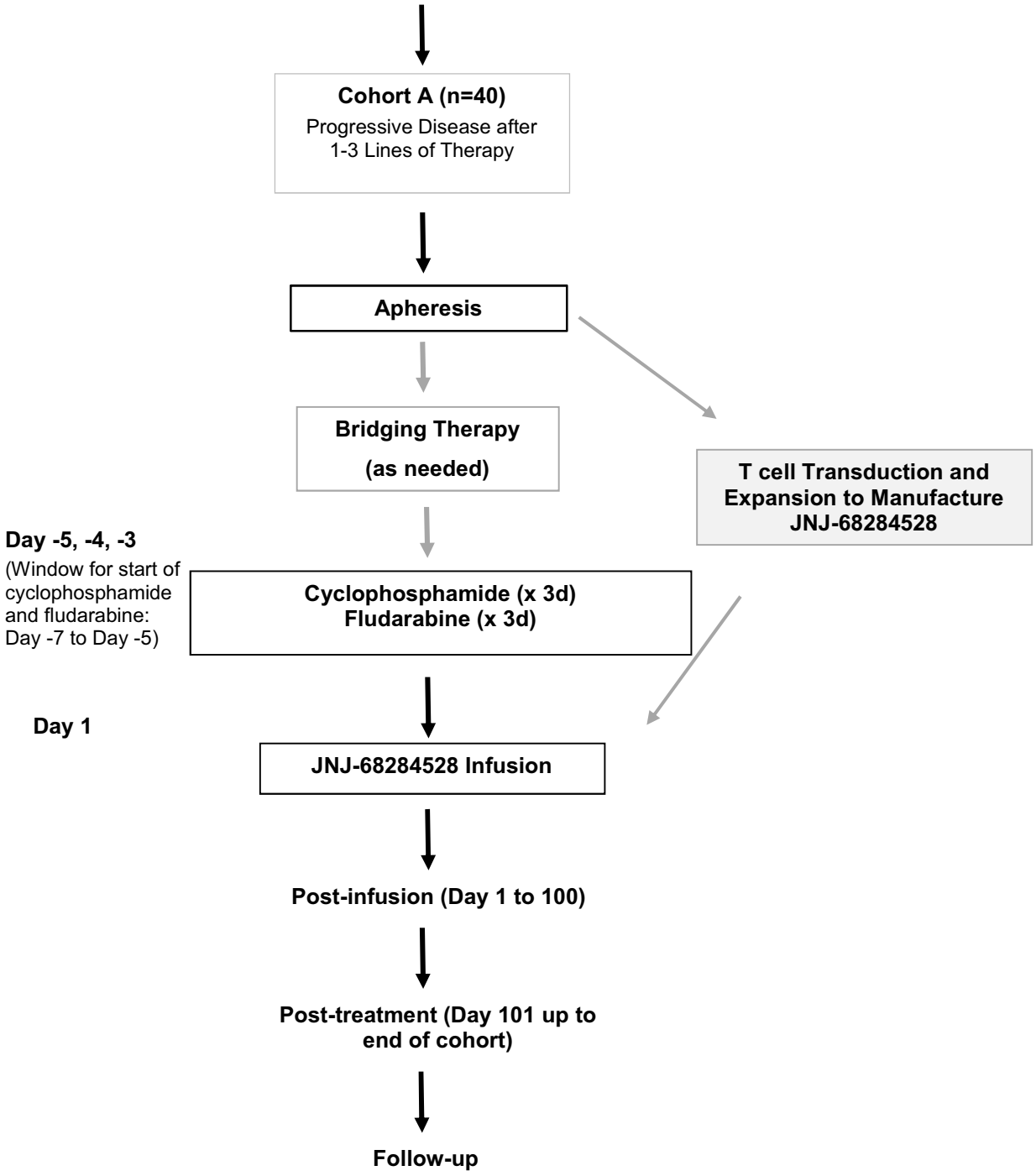
After JNJ-68284528 production and product release, all subjects will receive a conditioning regimen of IV cyclophosphamide 300 mg/m^2 and fludarabine 30 mg/m^2 daily for 3 days. The dose of fludarabine should be reduced to 24 mg/m^2 for subjects with an estimated glomerular filtration rate (eGFR) of 30 to 70 mL/min/1.73m^2. JNJ-68284528 at the recommended phase 2 dose (RP2D) based on the MMY2001 study (0.75 x 10^6 CAR-positive viable T cells/kg; see Section 3.2) will be administered 5 to 7 days after the start of the conditioning regimen. The conditioning regimen will lead to lymphodepletion and help promote CAR-T cell expansion in the subject. Subjects who receive an infusion of JNJ-68284528 should continue all subsequent post-infusion assessments.

Of the approximately 40 subjects in Cohort A, approximately 20 will receive cilta-cel manufactured using the commercial process. Due to differences in the start of enrollment there will be a 2 end of cohort dates; 1 for the 20 subjects who received cilta-cel using the clinical trial process and another for the 20 subjects who received cilta-cel using the commercial process.

A diagram of the study design for Cohort A is provided in Figure 2.

Figure 2: Schematic Overview of the Study, Cohort A




Cohort A (n=40)
Progressive Disease after 1-3 Lines of Therapy
Apheresis
Bridging Therapy
(as needed)
T cell Transduction and Expansion to Manufacture JNJ-68284528
Day -5, -4, -3
(Window for start of cyclophosphamide and fludarabine: Day -7 to Day -5)
Cyclophosphamide (x 3d)
Fludarabine (x 3d)
Day 1
JNJ-68284528 Infusion
Post-infusion (Day 1 to 100)
Post-treatment (Day 101 up to end of cohort)
Follow-up

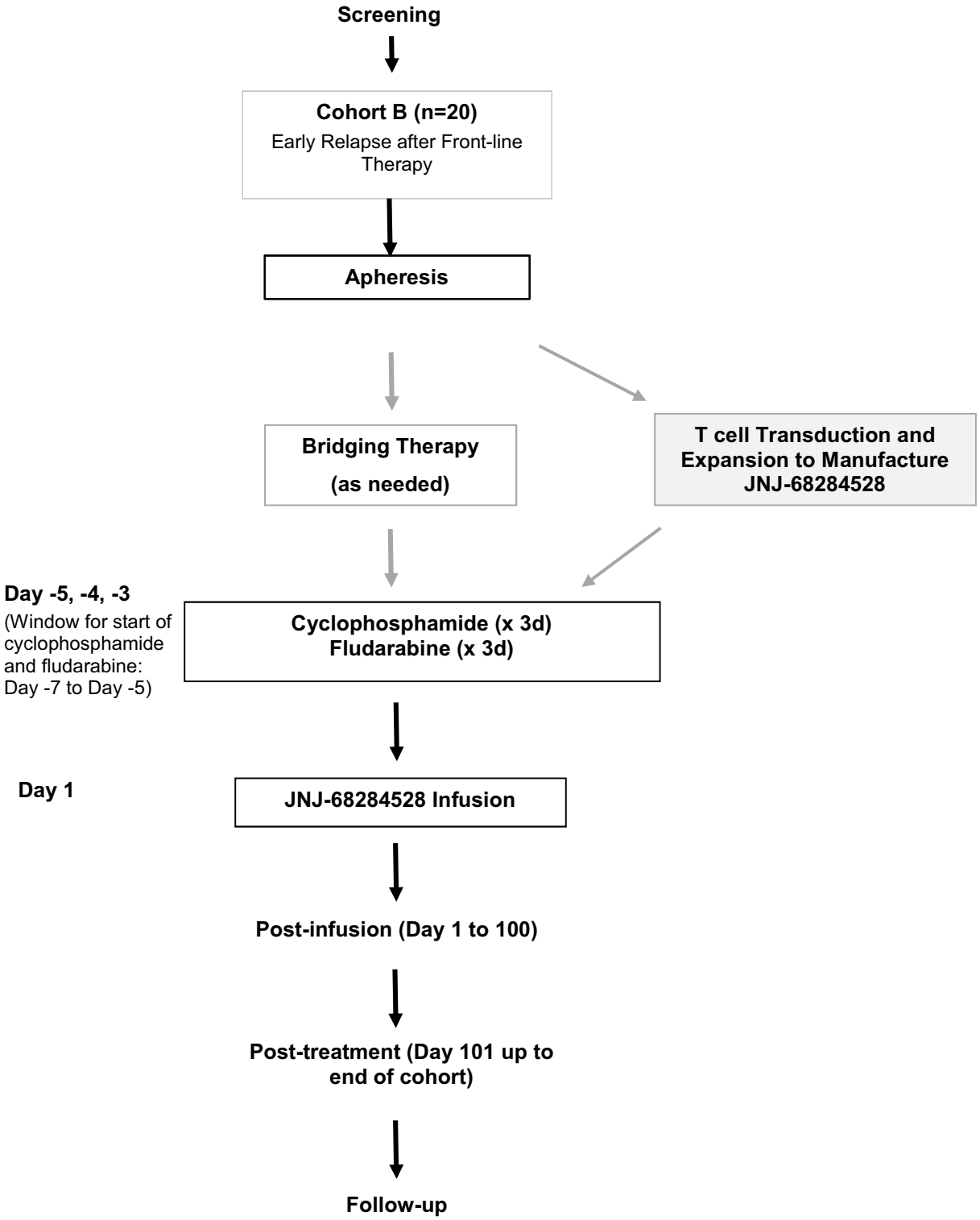
3.1.2. Cohort B Study Design

Subjects enrolled in Cohort B will undergo apheresis after screening to acquire peripheral blood mononuclear cells (PBMC). For all subjects JNJ-68284528 will be generated from the subject's T cells selected from the apheresis product. Subjects for whom apheresis or manufacturing fails will be allowed a second attempt at apheresis. Bridging therapy (anti-plasma cell directed treatment between apheresis and lymphodepletion) will be allowed when clinically indicated (ie, to maintain a subject's clinical status while waiting for manufacturing of JNJ-68284528), with the permission of the sponsor. Bridging therapy should be a short-term treatment (approximately 1 to 2 cycles) to decrease tumor burden and may include therapies to which a subject has not been previously exposed. The sponsor will not permit subjects who are found to be in a confirmed CR after bridging therapy to receive JNJ-68284528. Subjects in Cohort B who do not receive an infusion of JNJ-68284528 will be replaced.

After JNJ-68284528 production and product release, all subjects will receive a conditioning regimen of IV cyclophosphamide 300 mg/m^2 and fludarabine 30 mg/m^2 daily for 3 days. The dose of fludarabine should be reduced to 24 mg/m^2 for subjects with an eGFR of 30 to 70 $mL/min/1.73m^2$. JNJ-68284528 at the RP2D based on the MMY2001 study (0.75×10^6 CAR-positive viable T cells/kg) will be administered 5 to 7 days after the start of the conditioning regimen. The conditioning regimen will lead to lymphodepletion and help promote CAR-T cell expansion in the subject. Subjects who receive an infusion of JNJ-68284528 should continue all subsequent post-infusion assessments. Subjects in Cohort B who do not receive an infusion of JNJ-68284528 will be replaced.

A diagram of the study design for Cohort B is provided in Figure 3.

Figure 3: Schematic Overview of the Study, Cohort B



3.1.3. Cohort C Study Design

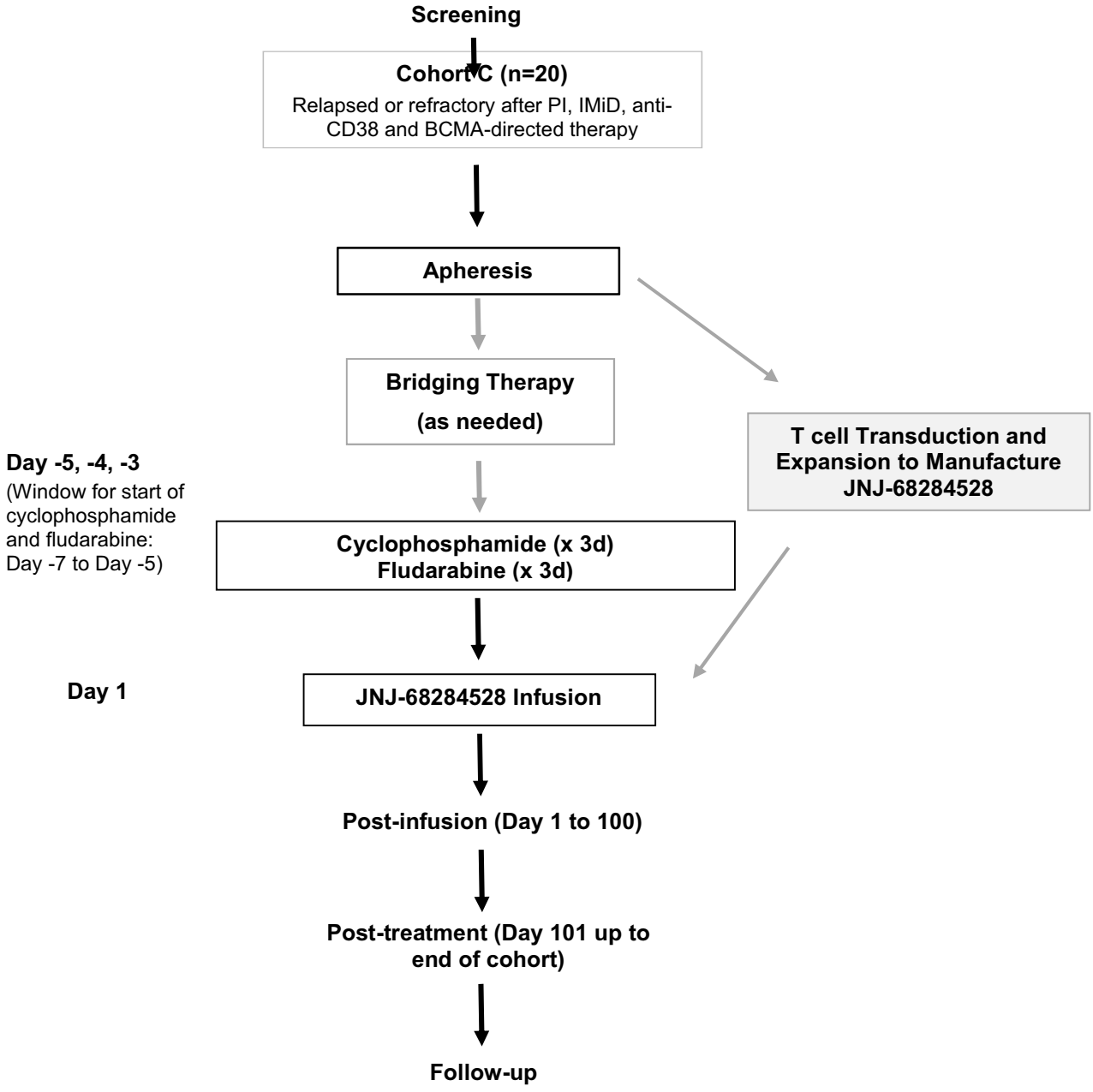
Subjects enrolled in Cohort C will undergo apheresis after screening to acquire peripheral blood mononuclear cells (PBMC). For all subjects, JNJ-68284528 will be generated from the subject's T cells selected from the apheresis product. Subjects for whom apheresis or manufacturing fails will be allowed a second attempt at apheresis.

Bridging therapy (anti-plasma cell directed treatment between apheresis and lymphodepletion) will be allowed when clinically indicated (ie, to maintain a subject's clinical status while waiting for manufacturing of JNJ-68284528), with the permission of the sponsor. Bridging therapy should be a short-term treatment (approximately 1 to 2 cycles) to decrease tumor burden and may include therapies to which a subject has not been previously exposed. The sponsor will not permit subjects who are found to be in CR after bridging therapy to receive JNJ-68284528. Subjects in Cohort C who do not receive an infusion of JNJ-68284528 will be replaced.

After JNJ-68284528 production and product release, all subjects will receive a conditioning regimen of IV cyclophosphamide 300 mg/m^2 and fludarabine 30 mg/m^2 daily for 3 days. The dose of fludarabine should be reduced to 24 mg/m^2 for subjects with an eGFR of 30 to 70 $mL/min/1.73m^2$. JNJ-68284528 at the recommended phase 2 dose (RP2D) of 0.75×10^6 CAR-positive viable T cells/kg based on the 68284528MMY2001 study will be administered 5 to 7 days after the start of the conditioning regimen. The conditioning regimen will lead to lymphodepletion and help promote CAR-T cell expansion in the subject. Subjects who receive an infusion of JNJ-68284528 should continue all subsequent post-infusion assessments.

A diagram of the study design for Cohort C is provided in Figure 4.

Figure 4: Schematic Overview of the Study, Cohort C



3.1.4. Cohort D Study Design

Subjects enrolled in Cohort D will undergo apheresis after screening to acquire peripheral blood mononuclear cells (PBMC). For all subjects, JNJ-68284528 will be generated from the subject's T cells selected from the apheresis product. Subjects for whom apheresis or manufacturing fails will be allowed a second attempt at apheresis. After apheresis and prior to administration of cyclophosphamide and fludarabine (conditioning regimen prior to JNJ-68284528 infusion) subjects will receive 1 or more cycles of lenalidomide at a dose of 10 mg per day upon adequate hematologic recovery from ASCT (absolute neutrophil count [ANC] $\geq 1 \times 10^9$/L and platelet count $\geq 75 \times 10^9$/L) when minimum laboratory requirements are met. Alternative bridging therapy instead of, or in addition to, lenalidomide is permissible with sponsor approval. Additionally, if an alternative bridging therapy is used, assessments to address lenalidomide toxicity will not be required in Table 3 (footnote v). The purpose of bridging therapy is to reduce the myeloma burden prior to lymphodepletion chemotherapy and JNJ-68284528 administration.

After JNJ-68284528 production and product release, all subjects will receive a conditioning regimen of IV cyclophosphamide 300 mg/m^2 and fludarabine 30 mg/m^2 daily for 3 days. The dose of fludarabine should be reduced to 24 mg/m^2 for subjects with an eGFR of 30 to 70 mL/min/1.73m^2. JNJ-68284528 at the RP2D based on the MMY2001 study (0.75×10^6 CAR-positive viable T cells/kg) will be administered 5 to 7 days after the start of the conditioning regimen. The conditioning regimen will lead to lymphodepletion and help promote CAR-T cell expansion in the subject.

A strategy of staggered dosing with JNJ-68284528 will be applied to Cohort D. There must be an observation period of at least 4 weeks between administration of JNJ-68284528 to the first 5 subjects to allow for subject 28-day safety review prior to next subject dosing. In addition, the first 5 subjects will not receive lenalidomide after JNJ-68284528 therapy to allow time for the Data Monitoring Committee (described in Section 3.1) to review safety data. After the first 5 subjects are dosed with JNJ-68284528, the DMC will convene to review safety and any other relevant data.

Based on recommendation of the DMC, subsequent subjects in this cohort will be eligible to receive lenalidomide after JNJ-68284528. The same strategy of staggered dosing will also be applied to the first 5 subjects receiving lenalidomide after JNJ-68284528 (ie, the 6th through 10th subject enrolled in Cohort D). There must be an observation period of at least 4 weeks between administration of JNJ-68284528 (followed by lenalidomide) to these 5 subjects. The DMC will review safety and any other relevant data from the first 5 subjects who receive JNJ-68284528 followed by lenalidomide before a decision is made regarding the treatment plan for further subjects enrolled in Cohort D.

JNJ-68284528 plus lenalidomide treatment: Subjects will initiate lenalidomide maintenance therapy at a minimum of 21 days post JNJ-68284528 infusion and after resolution of any cytokine release syndrome (CRS) or neurologic toxicities. Subjects will continue to receive lenalidomide until confirmed PD, unacceptable toxicity, or for 2 years post JNJ-68284528 infusion, whichever occurs first. The initial dose of lenalidomide post-JNJ-68284528 infusion will depend on the level

of hematologic recovery. Additionally, initiation of lenalidomide treatment is dependent on no additional safety concerns by investigator or sponsor.

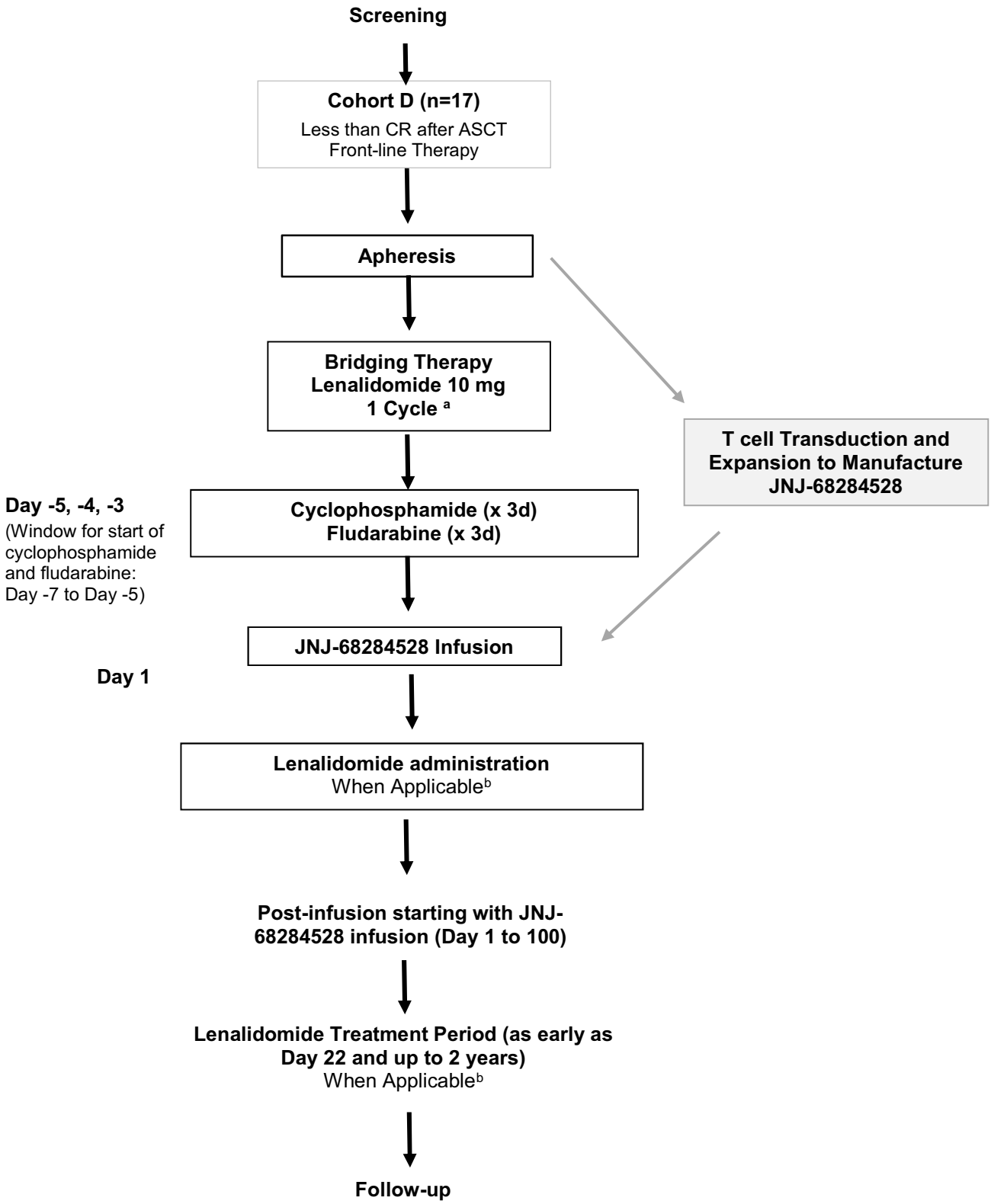
Lenalidomide after JNJ-68284528

A minimum of 21 days after infusion of JNJ-68284528, after resolution of CRS or neurologic toxicities, subjects in the cohort will receive lenalidomide treatment. The initial dose of lenalidomide will depend on the level of hematologic recovery as described in Section 6.1.4. Additionally, initiation of lenalidomide treatment is dependent on no additional safety concerns by investigator or sponsor.

Subjects should continue all subsequent post-infusion assessments after infusion of JNJ-68284528. Subjects will receive lenalidomide until confirmed PD, unacceptable toxicity, or for 2 years post JNJ-68284528 infusion, whichever occurs first. Subjects in Cohort D who do not receive an infusion of JNJ-68284528 will be replaced.

A diagram of the study design for Cohort D is provided in Figure 5.

Figure 5: Schematic Overview of the Study, Cohort D



a Additional cycles or alternative therapy permitted with sponsor approval
b See Section 3.1.4 for staggered dosing strategy

3.1.5. Cohort E Study Design

Subjects enrolled in Cohort E will receive 4 cycles of quadruplet induction regimen of daratumumab, bortezomib, lenalidomide and dexamethasone (D-VRd) as tolerated. All subjects in Cohort E will undergo apheresis after cycle 1 or 2 of the D-VRd induction regimen. At the investigator's discretion, subjects may undergo peripheral stem cell mobilization and harvesting after Cycle 3 or 4 of induction treatment (D-VRd) to allow for salvage ASCT after disease progression is confirmed. Subjects may receive one cycle of anti-myeloma therapy (physician's choice) any time before enrollment. Enrollment in Cohort E is defined as the start of D-VRd induction.

For all subjects JNJ-68284528 will be generated from the subject's T cells selected from the apheresis product. Subjects for whom apheresis or manufacturing fails will be allowed a second attempt at apheresis.

After JNJ-68284528 production and product release, all subjects will receive a conditioning regimen of IV cyclophosphamide 300 mg/m^2 and fludarabine 30 mg/m^2 daily for 3 days. The dose of fludarabine should be reduced to 24 mg/m^2 for subjects with an eGFR of 30 to 70 $mL/min/1.73m^2$. JNJ-68284528 at the recommended phase 2 dose (RP2D) of 0.75 x 10^6 CAR-positive viable T cells/kg based on the 68284528MMY2001 study will be administered 5 to 7 days after the start of the conditioning regimen. The conditioning regimen will lead to lymphodepletion and help promote CAR-T cell expansion in the subject. Subjects who receive an infusion of JNJ-68284528 should continue all subsequent post-infusion assessments.

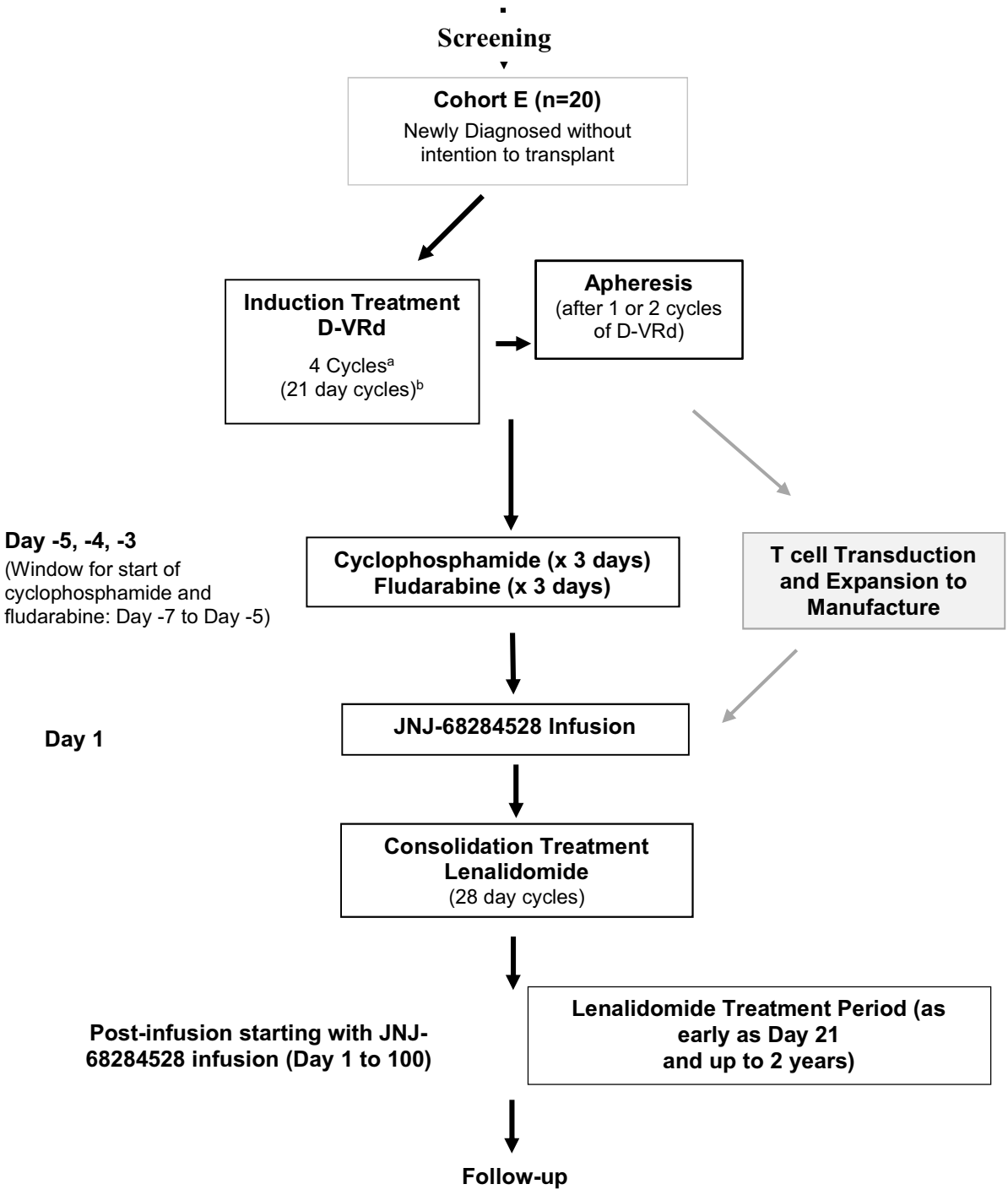
After the infusion of JNJ-68284528, subjects will receive consolidation treatment with lenalidomide until confirmed PD, unacceptable toxicity, or for 2 years post JNJ-68284528 infusion, whichever occurs first. Lenalidomide treatment will be initiated a minimum of 21 days after infusion of JNJ-68284528 and will only start after resolution of any grade CRS or neurologic toxicities. The initial dose of lenalidomide will depend on the level of hematologic recovery as described in Section 6.1.4. Additionally, initiation of lenalidomide treatment is dependent on no additional safety concerns by investigator or sponsor.

Subjects should continue all subsequent post-infusion assessments after infusion of JNJ-68284528. Subjects in Cohort E who do not receive an infusion of JNJ-68284528 will be replaced.

A strategy of staggered dosing will be applied to Cohort E. There will be a period of at least 2 weeks between administration of JNJ-68284528 to the first 5 subjects with periodic reviews by the DMC. After being treated with JNJ-68284528, the safety data of the first 5 subjects will be reviewed by the DMC to determine if there are any potential pharmacodynamic interactions between D-VRd induction treatment and JNJ-68284528. In addition, in order to evaluate the safety of adding lenalidomide consolidation treatment to JNJ-68284528 the DMC will also continue to review the safety data of these first 5 subjects after the start of consolidation therapy in a periodic basis. The composition of the committee and procedures will be provided in the DMC charter. The DMC will continue to evaluate safety throughout the duration of the cohort per the DMC charter.

A diagram of the study design for Cohort E is provided in Figure 6.

Figure 6: Schematic Overview of the Study, Cohort E



[a] Eligible subjects will receive 4 cycles of D-VRd induction therapy as tolerated, additional cycles permitted with sponsor approval

[b] Subjects in Cohort E may have peripheral stem cell mobilization and harvesting after Cycle 3 or 4 of induction therapy, at the investigator's discretion.

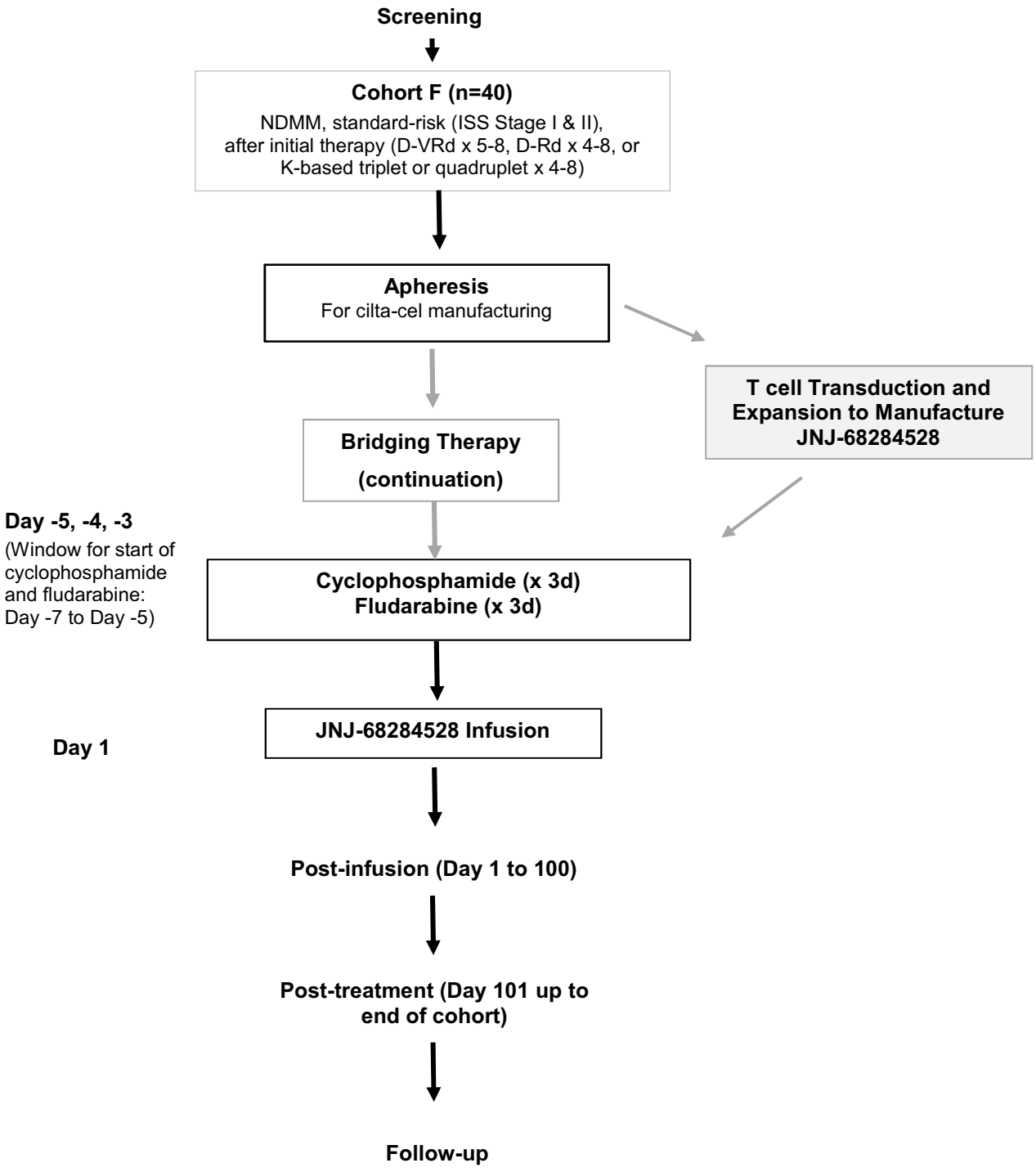
3.1.6. Cohort F Study Design

Subjects with standard risk multiple myeloma and an overall response ≥VGPR after 4 to 8 total cycles of initial therapy will be enrolled. A total of approximately 40 subjects will be enrolled and subjects must have received 1 of 3 protocol-allowed initial therapies, approximately 20 subjects who have had daratumumab, bortezomib, lenalidomide and dexamethasone (D-VRd), approximately 10 subjects who have had daratumumab + lenalidomide and dexamethasone (D-Rd) and approximately 10 subjects who have had a carfilzomib-based triplet or quadruplet regimen in the first line setting. With prior sponsor approval, it is acceptable for up to 1 cycle of the protocol-specified regimens to be missing one of the listed agents (eg, held due to toxicity). In addition, subjects may have received up to 1 cycle of alternative anti-myeloma therapy (physician's choice) prior to the start of protocol-specified initial therapy regimens. Of note, cyclophosphamide (if used) as mobilization prior to stem cell collection would be considered as 1 cycle of alternative anti-myeloma therapy. After screening, when all eligibility criteria are met, subjects will be apheresed (=enrollment) to acquire peripheral blood mononuclear cells (PBMCs). For all subjects, cilta-cel will be generated from the subject's T cells selected from this apheresis product. Subjects for whom apheresis or manufacturing fails will be allowed a second attempt at apheresis. When clinically indicated (ie, to maintain a subject's clinical status while waiting for manufacturing of cilta-cel) and with the permission of the sponsor, bridging therapy (anti myeloma treatment between apheresis and lymphodepletion) may be given. Bridging therapy (approximately 1 to 2 cycles) to decrease tumor burden should be a continuation of the initial therapy. Alternative bridging therapy may be permissible with sponsor approval. If at the investigator's discretion, subjects may need to undergo peripheral stem cell mobilization and harvesting (e.g., to allow for salvage ASCT after disease progression is confirmed), it is recommended that this occur either prior to study screening or after apheresis for cilta-cel manufacturing.

After cilta-cel production and product release, all subjects will receive a conditioning regimen of IV cyclophosphamide 300 mg/m^2 and fludarabine 30 mg/m^2 daily for 3 days. The dose of fludarabine should be reduced to 24 mg/m^2 for subjects with an eGFR of 30 to 70 mL/min/1.73m^2. cilta-cel at the RP2D based on the MMY2001 study (0.75 x 10^6 CAR-positive viable T cells/kg) will be administered 5 to 7 days after the start of the conditioning regimen. The conditioning regimen will lead to lymphodepletion and help promote CAR-T cell expansion in the subject. Subjects in Cohort F who do not receive an infusion of cilta-cel will be replaced.

A diagram of the study design for Cohort F is provided in Figure 7.

Figure 7: Schematic Overview of the Study, Cohort F



K= carfilzomib

3.1.7. Retreatment with JNJ-68284528

Subjects in Cohorts A, B, and C may be considered for retreatment with JNJ-68284528. Subjects in Cohort D, E and F will not be allowed to receive retreatment.

Subjects must satisfy the following criteria to be eligible for retreatment, with approval from the sponsor:

- Progressive disease (PD) after best response of minimal response (MR) or better
- No ongoing Grade 2 non-hematologic toxicity (except for nausea, vomiting, hair loss). No ongoing Grade 3 or higher hematologic toxicity
- At least 6 months between first JNJ-68284528 infusion and detection of PD

Subjects must satisfy all inclusion and exclusion criteria (Section 4), except for:

- Inclusion criterion 2 (Cohorts A, B, C), there is no restriction on the maximum time required between dosing with JNJ-68284528 and progressive disease.
- Exclusion criteria 1 (Cohorts A, B, C) and 2 (Cohorts A, B), to be eligible for retreatment.

A maximum of 1 retreatment may occur per subject. Bridging therapy is allowed for subjects receiving retreatment with permission from the sponsor.

Assessments for subjects receiving retreatment should follow the Time and Events schedules (Table 1 and Table 2 for Cohorts A, B, and C) with the following exceptions:

- Subjects do not have to sign an additional informed consent form
- Subject height does not need to be collected again
- Assessments scheduled prior to apheresis will only occur if it is necessary to collect a second apheresis sample
- PRO assessments will not be collected upon retreatment

Subjects who received retreatment with JNJ-68284528 and are in follow-up at the end of the study (2 years after the last subject in each cohort receives the initial dose of JNJ-68284528) will be monitored in the long-term follow-up study for 15 years from the time of last treatment (see Section 9.1.6.5). For subjects who receive retreatment, MRD negativity after retreatment with JNJ-68284528 will not be counted in the primary analysis for efficacy. The subject's best response before retreatment will be captured in the efficacy analysis.

3.2. Rationale of Dose and Administration Schedule Selection

The conditioning regimen of cyclophosphamide 300 mg/m^2 and fludarabine 30 mg/m^2 daily for 3 doses will lead to lymphodepletion and help promote CAR-T cell expansion in the subject. Cyclophosphamide 300 mg/m^2 and fludarabine 30 mg/m^2 before JNJ-68284528 infusion (Day 1) is consistent with the lymphodepletion regimen used in the marketed CAR-T products. The dose of fludarabine should be reduced to 24 mg/m^2 for subjects with an eGFR of 30 to 70 mL/min/1.73m^2.

JNJ-68284528 will be administered at a targeted infused dose of 0.75 x 10^6 CAR-positive viable T cells/kg (maximum dose: 1.0 x 10^8 CAR-positive viable T cells; doses above 1.0 x 10^8 CAR-positive viable T cells, but within the specified range of 0.5-1.0 x 10^6 CAR-positive viable T cells/kg, will be reviewed by the sponsor and will not be considered an overdose or an out-of-specification product). This dose was established in the Phase 1b part of Study 68284528MMY2001 (Section 1.1.5). Data from Study 68284528MMY2001 showed that a dose of 0.75 x 10^6 cells/kg of JNJ-68284528 CAR-T cell is highly efficacious with an acceptable safety profile in a patient population who had no alternative treatment options. Further discussion of the cilta-cel dose selection is provided in the cilta-cel Investigator's Brochure.

3.3. Study Design Rationale

Rationale for Study Cohorts

The safety and efficacy of JNJ-68284528 in heavily pretreated patients with multiple myeloma is being evaluated in the Phase 1b/2 Study 68285428MMY2001. The degree of benefit of CAR-T therapy may be dependent on the fitness of the patient's immune system at the time of T-cell apheresis (Fraietta 2018). This study includes subjects in varying stages of multiple myeloma treatment in order to assess the effect of prior exposure to immunomodulatory and cytotoxic therapy on the efficacy of JNJ-68284528:

- Cohort A includes subjects with progressive disease after 1 to 3 prior lines of therapy for multiple myeloma including a proteasome inhibitor (PI) and immunomodulatory therapy (IMiD) either individually or in combination. Subjects will be refractory to lenalidomide. There are many approved triplet regimens for patients with multiple myeloma that have relapsed after 1 to 3 prior lines of therapy. However, these regimens have largely been tested in lenalidomide naïve or lenalidomide non-refractory patients. Pivotal Phase 3 studies (ASPIRE, ELOQUENT-2, Tourmaline-MM1, POLLUX, etc.) excluded lenalidomide refractory patients because these studies randomized against lenalidomide plus dexamethasone control arms. Given that lenalidomide is now frequently administered in front-line maintenance, and relapse settings in both the US and EU, there are few options for patients with lenalidomide-refractory disease, resulting in a high unmet need for these patients. In fact, patients who are lenalidomide refractory have a poor median PFS ranging from 8.6 and 9.5 months when treated with bortezomib, pomalidomide and dexamethasone (Richardson 2019) or carfilzomib and dexamethasone (Moreau 2017). Thus, novel therapies such as BCMA directed CAR-T cells are a promising treatment alternative.

- Cohort B includes subjects who have had one line of previous therapy containing an IMiD and a PI and who have early relapse defined as having disease progression <12 months after an ASCT or <12 months after the start of front-line therapy for subjects who have not had an ASCT. Patients that have an early relapse after standard front-line therapies have a particularly poor prognosis and represent an area of unmet need. This group represents approximately 15% of all patients that receive their first line of therapy. Three centers have reported that patients who relapse within 1 year from start of initial therapy (with PI or IMiD-based induction) have a median OS of 22 months and patients that relapse within 1 year of ASCT have a median OS of approximately 20 months, which is substantially shorter than expected outcomes in multiple myeloma today (median OS not reached [NR]) for both groups of patients, HR 13.7) (Majithia 2016; Ong 2016; Jimenez-Zepeda 2015). New treatments, such as BCMA directed CAR-T cells may offer an alternative to currently available treatments which have failed to address this unmet medical need.

- Cohort C includes subjects with relapsed or refractory disease who have been previously treated with a PI, IMiD, anti-CD38 monoclonal antibody and BCMA-directed therapy (excluding cellular immunotherapy). In spite of recent advancement in the treatment of multiple myeloma, most patients still relapse or become refractory to the last line of therapy and new approaches are needed. BCMA is considered a promising target for anti-myeloma therapy, and currently multiple BCMA-directed platforms (eg, antibody-drug conjugate [ADC], bispecific T-cell engager [BiTE], CAR-T) are in the investigational phase (Cho 2018a; Cho 2018b). Recent data from belantamab mafodotin (GSK'916) (Trudel 2019) and AMG 420 (Topp 2019) have shown that patients still relapse after receiving these therapies and are left with limited options. Additionally, Gore et al (2018) reported that patients with ALL who relapsed after receiving blinatumomab (BiTE therapy), had an objective response to CAR-T therapy for the same target. The majority of other clinical trials for multiple myeloma patients receiving CAR-T have excluded patients who have previously received BCMA-directed therapy. There is an unmet need to address the sequence of treatments for BCMA-directed agents in multiple myeloma. Therefore, this cohort will determine whether BCMA CAR-T therapy remains effective after exposure to other BCMA-directed agents.

- Cohort D includes subjects with recently diagnosed multiple myeloma who did not achieve a CR after ASCT. This patient population does not achieve an optimal response to standard first line therapy including ASCT and is anticipated to have poorer clinical outcomes on standard lenalidomide maintenance treatment. Experience with JNJ-68284528 in Study 68284528MMY2001 and LCAR-B38M CAR-T cells in the Legend-2 study, demonstrates substantial response rates, MRD negative rates, and acceptable toxicity in a heavily pre-treated population of subjects. As the degree of benefit of CAR-T therapy is dependent on a patient's immune response, JNJ-68284528 could have potential meaningful efficacy and durability when administered to patients with multiple myeloma who have had less exposure to immunomodulatory and cytotoxic therapy. Therefore, addition of JNJ-68284528 to lenalidomide treatment could provide long-term benefit in this patient population compared to standard of care lenalidomide maintenance. In addition, lenalidomide has been shown to promote immunologic memory in T-cell populations. In a pre-clinical study, infusion of CS1 CAR-T followed by daily low dose of lenalidomide in myeloma tumor bearing mice preferentially expanded $CD8^{+}$CAR-T cells. Lenalidomide treatment also exerted a costimulatory effect on T-cell response by increasing production of IL-2 and IFN-γ and inhibiting production of anti-inflammatory cytokines; resulting in enhanced anti-myeloma

activity and persistence of CAR-T cells in vivo (Wang 2018). Similar effects have been observed in CD19 CAR-T and EGFRvIII CAR-T in-vitro and in-vivo studies (Kuramitsu 2015; Otahal 2016). The combination of anti-BCMA CAR-T cells and lenalidomide treatment is currently under study in patients with multiple myeloma (NCT03070327).

- Cohort E includes subjects with hr-NDMM for whom hematopoietic stem cell transplant is not planned as initial therapy. The treatment of high risk newly diagnosed patients with multiple myeloma is evolving. Induction therapy followed by transplant is not feasible in all patients due to age or patient frailty. Despite advances in treatment, including quadruplet therapies, patients with hr-NDMM still respond more poorly than patients with standard risk myeloma (Kurki 2016; Voorhees 2020; Sonneveld 2016). Therefore, novel strategies are needed.

  Due to the effectiveness of triplet and quadruplet therapies, some patients are deferring initial transplant. The most active combination to date is the VRd regimen. The superiority of the VRd regimen has been established by the results of the Phase 3 SWOG S0777 study (Durie 2017). This study demonstrated both increased PFS and OS in the VRd arm compared with Rd alone. Further, the Phase 3 study described by Attal (2017) showed that a deep level of response, CR and MRD negative status can be achieved with the VRd regimen without transplant.

  The sponsor has observed compelling clinical data with daratumumab in combination with either bortezomib or lenalidomide in the relapsed/refractory setting, and bortezomib in the frontline setting. The addition of daratumumab with VRd is anticipated to improve the response rates and the depth of response and may lead to improved long-term outcomes in newly diagnosed patients with multiple myeloma. The Phase 2 Study 54767414MMY2004 (NCT02874742), compared daratumumab with VRd (D-VRd) against VRd in patients with newly diagnosed multiple myeloma that were transplant eligible. The study found 42.4% of patients treated with D-VRd achieved a sCR, compared to 32.0% of patients who received VRd alone by the end of consolidation (Voorhees 2019). Overall, the safety profile of D-VRd was consistent with the safety profile for each therapy separately.

  The Phase 3 study of D-VRd (54767414MMY3014) in the same patient population described above utilizes the subcutaneous (SC) formulation of daratumumab instead of the IV formulation utilized in the Phase 2 VRd study 54767414MMY2004. This is expected to provide similar exposure and limit additional toxicity for patients treated with this quadruplet regimen, from infusion-related reactions due to daratumumab. The initial PK of SC daratumumab administration shows similar exposure to IV and improved safety with a lower IRR rate compared with the IV formulation (Usmani 2019). Additionally, another Phase 3 study of D-VRd is currently being conducted in newly diagnosed multiple myeloma patients in whom transplant is not intended, 54767414MMY3019 (NCT03652064).

Despite prolonging the PFS and OS in patients with newly diagnosed multiple myeloma who are transplant ineligible, the disease remains incurable, especially for patients with high-risk disease. Experience with JNJ-68284528 in Study 68284528MMY2001 and LCAR-B38M CAR-T cells in the Legend-2 study, demonstrates substantial response rates, MRD negative rates, and acceptable toxicity in a heavily pre-treated population of subjects. As the degree of benefit of CAR-T therapy is dependent on a patient's immune response, JNJ-68284528 could have potential meaningful efficacy and durability when administered in the frontline setting to patients with multiple myeloma who have had less exposure to immunomodulatory and cytotoxic therapy. In order to maximize disease control, lenalidomide will be given as consolidation therapy. The use of lenalidomide to potentiate the efficacy of JNJ-68284528 is addressed in the design rationale of Cohort D.

- Cohort F includes newly diagnosed multiple myeloma subjects with standard risk disease and an overall response ≥VGPR after 4 to 8 total cycles of initial induction therapy. Patients with standard risk myeloma are typically treated with ASCT (if eligible) and treatment until disease progression regardless of ASCT status (NCCN, ESMO Guidelines). Typically, maintenance therapy consists of lenalidomide alone, or in combination with other agents. The risks associated with chronic lenalidomide have been well documented and consist of bone marrow suppression, infections, thrombo-embolic disease, risk of secondary malignancy, fatigue, and GI intolerance (USPI). These potential toxicities and need for continued treatment may interfere with quality of life to such a degree that continuous maintenance therapy is not feasible in all patients (Dimopoulos 2020). An effective therapy with a finite duration may better avoid the toxicity and impact on quality of life of continuous therapy. Patients with standard risk myeloma have a longer PFS than patients with high-risk myeloma and are likely to receive maintenance therapy for a substantially prolonged period, while failure to support this maintenance therapy may lead to earlier relapse of the disease.

  Use of cilta-cel is hypothesized to result in greater response rates and duration of response when used in earlier lines of therapy due to improved immune function potentially resulting in a superior CAR-T product (Garfall 2019). Recent data also suggests that the strategy of delayed transplantation vs immediate transplant does not result in any differences in overall survival after 8+ years of follow-up. Thus, the strategy of deferring initial ASCT may be useful in patients receiving novel frontline therapy which offers a high response rate with finite duration of therapy (Perrot 2020). Therefore, there is interest in assessing the impact of cilta-cel in a "one and done" dosing for patients with standard risk myeloma to determine whether these patients will have a long disease-free survival without the need for chronic therapy until disease progression – as this is the current standard of care. Since all patients enrolled into this study will have received highly effective initial therapy (D-VRd, D+Rd, or carfilzomib containing triplets/quadruplets) and since the inclusion criteria requires that all patients have a response of VGPR or better (inclusion criteria 3F), it is anticipated that all subjects will have a very low tumor burden prior to lymphodepletion therapy and cilta-cel infusion. As higher tumor burden has been found to be a risk factor for neurotoxicity, it is therefore anticipated that this risk is greatly reduced for subjects enrolled in Cohort F.

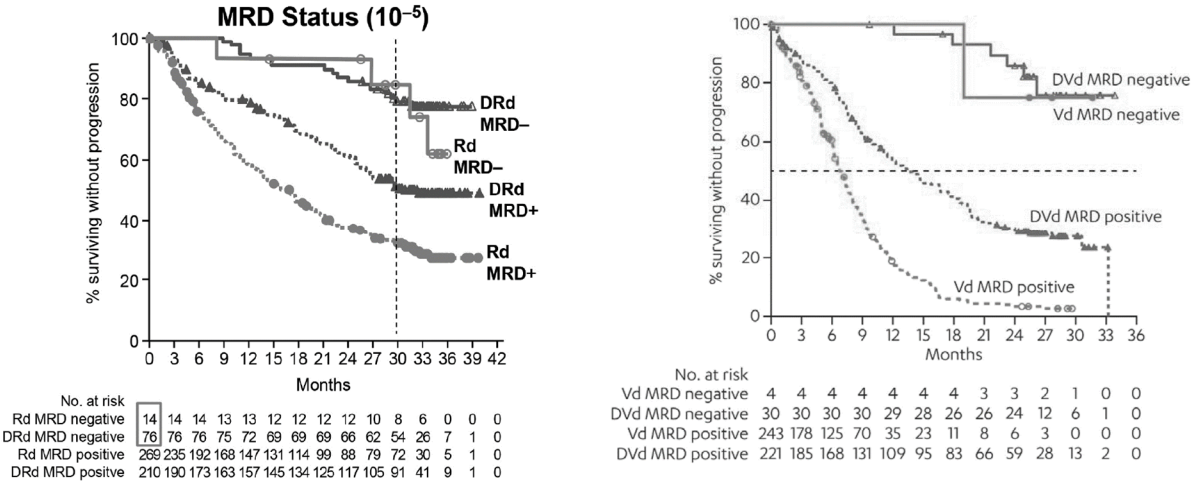
Rationale for MRD as Primary Endpoint

Achievement of MRD negativity by flow or next generation sequencing (NGS) at a cutoff of both 10^{-4} and 10^{-5} is associated with improvement of both PFS and OS (Lahuerta 2008; Landgren 2016; Munshi 2016). Meta- and pooled analyses of MRD data have demonstrated that MRD negative status is the strongest independent prognostic biomarker for PFS and OS in newly diagnosed multiple myeloma. Based upon the strength of these early analyses, the acceptance of MRD as a validated, clinical endpoint may be achieved in the near future.

Furthermore, data from 2 studies utilizing daratumumab in combination with either Rd (54767414MMY3003 [NCT02076009]) or Vd (54767414MMY3004 [NCT02136134]) in subjects with relapsed/refractory multiple myeloma have shown over a 3-fold increase in the number of subjects who achieved MRD negative status (Figure 8) (Avet 2016). Subjects achieving MRD negative status demonstrated improved PFS (Figure 8). These studies utilized the clonoSEQ MRD assay (Adaptive Biotechnology) that is an analytically validated NGS assay. The use of the clonoSEQ assay allows for centralized analysis and the consistent, accurate evaluation of MRD status that will support the primary endpoint.

Figure 8: Progression-free Survival According to MRD Status 10^{-5} in Studies 54767414MMY3003 and 54767414MMY3004

Study MMY3003 **Study MMY3004**



In this study, minimal residual disease will be evaluated at suspected CR when a subject has achieved a deep clinical response. Additional landmarked bone marrow aspirate samples will be obtained to allow for the statistical analysis of the association of MRD with PFS/OS and to evaluate the durability of MRD negativity in these subjects.

The primary endpoint will evaluate the overall MRD negative rate. Secondary endpoints will assess the durability of MRD negativity, thus assessing whether subjects who obtain MRD negativity are able to maintain that depth of response. The sponsor will assess the impact of this durability of MRD negativity on the long-term outcome of PFS.

4. SUBJECT POPULATION

The inclusion and exclusion criteria for enrolling subjects in this study are described in the following subsections. If there is a question about the inclusion or exclusion criteria below, the investigator must consult with the appropriate sponsor representative and resolve any issues before enrolling a subject in the study. Waivers are not allowed.

Eligibility criteria are grouped by cohort. Inclusion and exclusion criteria for Cohort A are described in Section 4.1, Cohort B in Section 4.2, Cohort C in Section 4.3, Cohort D in Section 4.4, Cohort E in Section 4.5, and Cohort F in Section 4.6.

Subjects who meet the eligibility criteria for both Cohort A and Cohort B, must be enrolled into Cohort B.

4.1. Cohort A Eligibility Criteria

4.1.1. Cohort A Inclusion Criteria

Each potential subject must satisfy all of the following criteria to be enrolled in Cohort A of the study:

1a. Criterion modified per Amendment 1

1a.1. Criterion modified per Amendment 2

1a.2. Have received a minimum of 1 to a maximum of 3 prior lines of therapy including a proteasome inhibitor (PI) and immunomodulatory therapy (IMiD) either individually or in combination.

- Undergone at least 1 complete cycle of treatment for each line of therapy, unless PD was the best response to that line of therapy.
- Lenalidomide refractory; confirmed PD, per IMWG consensus guidelines (Rajkumar 2011), during treatment or ≤60 days after cessation of treatment. Progression on lenalidomide maintenance or non-responsive disease while on lenalidomide for at least 1 cycle will meet this criterion. For subjects with more than 1 prior line of therapy, there is no requirement to be lenalidomide refractory to the most recent line of prior therapy.

2a. Criterion modified per Amendment 1

2a.1. Documented evidence of progressive disease based on investigator's determination of response by the IMWG criteria on or within 6 months of their last regimen (Attachment 1). Confirmation may be from either central or local testing.

3a. ≥18 years of age.

4a. Documented diagnosis of multiple myeloma according to IMWG diagnostic criteria (Attachment 5).

5a. Criterion modified per Amendment 3

5a.1. Criterion modified per Amendment 4

Measurable disease at Screening as defined by any of the following:

- Serum monoclonal paraprotein (M-protein) level ≥1.0 g/dL or urine M-protein level ≥200 mg/24 hours; or
- Light chain multiple myeloma in whom only measurable disease is by serum FLC levels in the serum: Serum immunoglobulin free light chain ≥10 mg/dL and abnormal serum immunoglobulin kappa lambda free light chain ratio.

Note: Local laboratory assessments may be used to establish measurable disease at Screening, with local laboratory result ≥125% of requirements (eg, M-protein ≥1.25 g/dL if using local labs).

- For subjects with neither serum nor urine measurable disease, baseline positron emission tomography/ computed tomography (PET/CT) or whole-body magnetic resonance imaging (MRI) may be used to satisfy the measurable disease criteria. A minimum of one lesion with a bi-dimensional measurement of at least 1cm × 1cm is required. See Attachment 22 for disease characterization of imaging and Attachment 23 for reporting requirements.

6a. ECOG Performance Status grade of 0 or 1 (Attachment 7).

7a. Criterion modified per Amendment 1

7a.1. Clinical laboratory values meeting the following criteria during the Screening Phase:

Hematology	
Hemoglobin	≥8.0 g/dL (≥5 mmol/L) (without prior red blood cell [RBC] transfusion within 7 days before the laboratory test; recombinant human erythropoietin use is permitted) *
Platelets	≥50 x 10^9/L (must be without transfusion support in the 7 days prior to the laboratory test)
Absolute Lymphocyte Count (ALC)	≥0.3 x 10^9/L
Absolute Neutrophil Count (ANC)	≥0.75×10^9/L (prior growth factor support is permitted but must be without support in the 7 days prior to the laboratory test)
Chemistry	
AST and ALT	≤3.0 × upper limit of normal (ULN)
Estimated Glomerular Filtration Rate	≥40 mL/min/1.73 m^2 based upon Modified Diet in Renal Disease formula calculation (Attachment 8) or a 24-hour urine collection.
Total bilirubin	≤2.0 × ULN; except in subjects with congenital bilirubinemia, such as Gilbert syndrome (in which case direct bilirubin ≤1.5 × ULN is required)
Corrected serum calcium	≤12.5 mg/dL (≤3.1 mmol/L) or free ionized calcium ≤6.5 mg/dL (≤1.6 mmol/L)

* For subjects who meet the inclusion criteria at screening, transfusion of RBCs is permitted after screening as needed to maintain a hemoglobin level ≥8.0 g/dL.

8a. Criterion modified per Amendment 1

8a.1. A woman of childbearing potential must have a negative highly sensitive serum pregnancy test (β-human chorionic gonadotropin [β-hCG]) at screening.

9a. Criterion modified per Amendment 1

9a.1. When a woman is of childbearing potential (See Attachment 16) the following are required:

- Subject must agree to practice a highly effective method of contraception (failure rate of <1% per year when used consistently and correctly) and agree to remain on a highly effective method of contraception from the time of signing the informed consent form (ICF) until 1 year after receiving a JNJ-68284528 infusion. Examples of highly effective contraceptives include:
  - user-independent methods: 1) implantable progestogen-only hormone contraception associated with inhibition of ovulation; 2) intrauterine device; intrauterine hormone-releasing system; 3) vasectomized partner;
  - user-dependent methods: 1) combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation: oral or intravaginal or transdermal; 2) progestogen-only hormone contraception associated with inhibition of ovulation (oral or injectable)

In addition to the highly effective method of contraception a man:

- Who is sexually active with a woman of childbearing potential must agree to use a barrier method of contraception (eg, condom with spermicidal foam/gel/film/cream/suppository) from the time of signing the ICF until 1 year after receiving a JNJ-68284528 infusion
- Who is sexually active with a woman who is pregnant must use a condom

Women and men must agree not to donate eggs (ova, oocytes) or sperm, respectively, during the study and for 1 year after receiving a JNJ-68284528 infusion.

Note: Hormonal contraception may be susceptible to interaction with the study treatment, which may reduce the efficacy of the contraceptive method.

10a. Subject must sign an ICF indicating that he or she understands the purpose of and procedures required for the study and is willing to participate in the study. Consent is to be obtained prior to the initiation of any study-related tests or procedures that are not part of standard-of-care for the subject's disease.

11a. Willing and able to adhere to the prohibitions and restrictions specified in this protocol.

4.1.2. Cohort A Exclusion Criteria

Any potential subject who meets any of the following criteria will be excluded from participating in Cohort A of the study:

1a. Prior treatment with CAR-T therapy directed at any target.

2a. Any therapy that is targeted to BCMA.

3a. Criterion modified per Amendment 1

3a.1. Criterion modified per Amendment 2

3a.2. Active malignancies (ie, progressing or requiring treatment change in the last 24 months) other than the disease being treated under study. The only allowed exceptions are:

- non-muscle invasive bladder cancer (NMIBC) treated within the last 24 months that is considered completely cured.
- skin cancer (non-melanoma or melanoma) treated within the last 24 months that is considered completely cured.
- non-invasive cervical cancer treated within the last 24 months that is considered completely cured.
- localized prostate cancer (N0M0):

  - with a Gleason score of ≤6, treated within the last 24 months or untreated and under surveillance,
  - with a Gleason score of 3+4 that has been treated more than 6 months prior to full study screening and considered to have a very low risk of recurrence, or
  - history of localized prostate cancer and receiving androgen deprivation therapy and considered to have a very low risk of recurrence.
- breast cancer: adequately treated lobular carcinoma in situ or ductal carcinoma in situ, or history of localized breast cancer and receiving antihormonal agents and considered to have a very low risk of recurrence.
- malignancy that is considered cured with minimal risk of recurrence.

4a. Criterion modified per Amendment 4

4a.1 Prior antitumor therapy as follows, prior to apheresis:

- Targeted therapy, epigenetic therapy, treatment with an investigational drug, investigational intervention (including investigational vaccines) or used an invasive investigational medical device within 14 days or at least 5 half-lives, whichever is less, or currently enrolled in an investigational study.
- Monoclonal antibody treatment for multiple myeloma within 21 days.
- Cytotoxic therapy within 14 days.
- Proteasome inhibitor therapy within 14 days.
- Immunomodulatory agent therapy within 7 days.
- Radiotherapy within 14 days. However, if the radiation portal covered ≤5% of the bone marrow reserve, the subject is eligible irrespective of the end date of radiotherapy.

5a. Criterion modified per Amendment 1

5a.1. Ongoing toxicity from previous anticancer therapy must resolve to baseline levels or to Grade 1 or less except for alopecia or peripheral neuropathy.

6a. The following cardiac conditions:

- New York Heart Association (NYHA) stage III or IV congestive heart failure
- Myocardial infarction or coronary artery bypass graft (CABG) ≤6 months prior to enrollment
- History of clinically significant ventricular arrhythmia or unexplained syncope, not believed to be vasovagal in nature or due to dehydration
- History of severe non-ischemic cardiomyopathy

- Impaired cardiac function (left ventricular ejection fraction [LVEF] <45%) as assessed by echocardiogram or multiple-gated acquisition (MUGA) scan (performed ≤8 weeks of apheresis)

7a. Received a cumulative dose of corticosteroids equivalent to ≥70 mg of prednisone within the 7 days prior to apheresis

8a. Known active, or prior history of central nervous system (CNS) involvement or exhibits clinical signs of meningeal involvement of multiple myeloma.

9a. Stroke or seizure within 6 months of signing ICF.

10a. Plasma cell leukemia at the time of screening (>2.0 x 10^9/L plasma cells by standard differential), Waldenström's macroglobulinemia, POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, and skin changes), or primary amyloid light-chain (AL) amyloidosis.

11a. Seropositive for human immunodeficiency virus (HIV).

12a. Vaccinated with live, attenuated vaccine within 4 weeks prior to apheresis.

13a. Hepatitis B infection as defined according to Attachment 10. In the event the infection status is unclear, quantitative levels are necessary to determine the infection status. (Hwang 2015)

14a. Hepatitis C infection defined as (anti-hepatitis C virus [HCV] antibody positive or HCV-RNA positive) or known to have a history of hepatitis C. For subjects with known history of HCV infection, confirmation of sustained virologic response [SVR] is required for study eligibility, defined as ≥24 weeks after completion of antiviral therapy.

15a. Criterion modified per Amendment 1

15a.1. Subject must not require continuous supplemental oxygen.

16a. Criterion modified per Amendment 3

16a.1. Contraindications, known life threatening allergies, hypersensitivity, or intolerance to cyclophosphamide, fludarabine, or JNJ-68284528 excipients, including DMSO (refer to Investigator's Brochure).

17a. Criterion modified per Amendment 1

17a.1. Criterion Modified per Amendment 2

17a.2. Serious underlying medical condition, such as:

- Evidence of active viral or bacterial infection requiring systemic antimicrobial therapy, or uncontrolled systemic fungal infection

- Active autoimmune disease or a history of autoimmune disease within 3 years
- Overt clinical evidence of dementia or altered mental status
- Any history of Parkinson's disease or other neurodegenerative disorder

18a. Any issue that would impair the ability of the subject to receive or tolerate the planned treatment at the investigational site, to understand informed consent or any condition for which, in the opinion of the investigator, participation would not be in the best interest of the subject (eg, compromise the well-being) or that could prevent, limit, or confound the protocol-specified assessments.

19a. Criterion modified per Amendment 1

19a.1. Pregnant or breast-feeding, or planning to become pregnant while enrolled in this study or within 1 year after receiving JNJ-68284528 infusion.

20a. Criterion modified per Amendment 1

20a.1. Plans to father a child while enrolled in this study or within 1 year after receiving a JNJ-68284528 infusion.

21a. Major surgery within 2 weeks prior to apheresis, or has surgery planned during the study or within 2 weeks after study treatment administration. (Note: subjects with planned surgical procedures to be conducted under local anesthesia may participate.)

22a. Received either of the following:

- An allogenic stem cell transplant within 6 months before apheresis. Subjects who received an allogeneic transplant must be off all immunosuppressive medications for 6 weeks without signs of graft-versus-host disease (GVHD).
- An autologous stem cell transplant ≤12 weeks before apheresis

23a. Received an investigational intervention (including investigational vaccines) or used an invasive investigational medical device within 15 days prior to apheresis or is currently enrolled in an investigational study

4.2. Cohort B Eligibility Criteria

4.2.1. Cohort B Inclusion Criteria

Each potential subject must satisfy all of the following criteria to be enrolled in Cohort B of the study:

1b. Criterion modified per Amendment 1

1b.1. Have undergone one line of prior therapy including a PI and an IMiD, per local standard of care.

2b. Criterion modified per Amendment 3

2b.1. Disease progression per IMWG criteria ≤12 months after ASCT or disease progression ≤12 months from the start of anti-myeloma therapy for subjects who have not had an ASCT. Confirmation may be from either central or local testing.

3b. ≥18 years of age.

4b. Documented diagnosis of multiple myeloma according to IMWG diagnostic criteria (Attachment 5).

5b. Criterion modified per Amendment 3.

5b.1. Measurable disease at Screening as defined by any of the following:

- Serum monoclonal paraprotein (M-protein) level ≥1.0 g/dL or urine M-protein level ≥200 mg/24 hours; or
- Light chain multiple myeloma in whom only measurable disease is by serum FLC levels in the serum: Serum immunoglobulin free light chain ≥10 mg/dL and abnormal serum immunoglobulin kappa lambda free light chain ratio.

Note: Local laboratory assessments may be used to establish measurable disease at Screening, with local laboratory result ≥125% of requirements (eg, M-protein ≥1.25 g/dL if using local labs).

- For subjects with neither serum nor urine measurable disease, baseline PET/CT or whole-body MRI may be used to satisfy the measurable disease criteria. See Attachment 22 for disease characterization of imaging and Attachment 23 for reporting requirements.

6b. ECOG Performance Status grade of 0 or 1 (Attachment 7).

7b. Criterion modified per Amendment 1

7b.1. Clinical laboratory values meeting the following criteria during the Screening Phase:

Hematology	
Hemoglobin	≥8.0 g/dL (≥5 mmol/L) (without prior red blood cell [RBC] transfusion within 7 days before the laboratory test; recombinant human erythropoietin use is permitted)*
Platelets	≥50 x 10^9/L (must be without transfusion support in the 7 days prior to the laboratory test)
Absolute Lymphocyte Count (ALC)	≥0.3 x 10^9/L
Absolute Neutrophil Count (ANC)	≥0.75×10^9/L (prior growth factor support is permitted but must be without support in the 7 days prior to the laboratory test)
Chemistry	
AST and ALT	≤3.0 × upper limit of normal (ULN)
Estimated Glomerular Filtration Rate	≥40 mL/min/1.73 m^2 based upon Modified Diet in Renal Disease formula calculation (Attachment 8) or a 24-hour urine collection.
Total bilirubin	≤2.0 × ULN; except in subjects with congenital bilirubinemia, such as Gilbert syndrome (in which case direct bilirubin ≤1.5 × ULN is required)
Corrected serum calcium	≤12.5 mg/dL (≤3.1 mmol/L) or free ionized calcium ≤6.5 mg/dL (≤1.6 mmol/L)

* For subjects who meet the inclusion criteria at screening, transfusion of RBCs is permitted after screening as needed to maintain a hemoglobin level ≥8.0 g/dL.

8b. Criterion modified per Amendment 1

8b.1. A woman of childbearing potential must have a negative highly sensitive serum pregnancy test (β-human chorionic gonadotropin [β-hCG]) at screening.

9b. Criterion modified per Amendment 1

9b.1. When a woman is of childbearing potential (See Attachment 16) the following are required:

- Subject must agree to practice a highly effective method of contraception (failure rate of <1% per year when used consistently and correctly) and agree to remain on a highly effective method of contraception from the time of signing the informed consent form (ICF) until 1 year after receiving a JNJ-68284528 infusion. Examples of highly effective contraceptives include:
  - user-independent methods: 1) implantable progestogen-only hormone contraception associated with inhibition of ovulation; 2) intrauterine device; intrauterine hormone-releasing system; 3) vasectomized partner;
  - user-dependent methods: 1) combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation: oral or intravaginal or transdermal; 2) progestogen-only hormone contraception associated with inhibition of ovulation (oral or injectable)

In addition to the highly effective method of contraception a man:

- Who is sexually active with a woman of childbearing potential must agree to use a barrier method of contraception (eg, condom with spermicidal foam/gel/film/cream/suppository) from the time of signing the ICF until 1 year after receiving JNJ-68284528 infusion.
- Who is sexually active with a woman who is pregnant must use a condom.

Women and men must agree not to donate eggs (ova, oocytes) or sperm, respectively, during the study and for 1 year after JNJ-68284528 infusion.

Note: Hormonal contraception may be susceptible to interaction with the study treatment, which may reduce the efficacy of the contraceptive method.

10b. Subject must sign an ICF indicating that he or she understands the purpose of and procedures required for the study and is willing to participate in the study. Consent is to be obtained prior to the initiation of any study-related tests or procedures that are not part of standard-of-care for the subject's disease.

11b. Willing and able to adhere to the prohibitions and restrictions specified in this protocol.

4.2.2. Cohort B Exclusion Criteria

Any potential subject who meets any of the following criteria will be excluded from participating in Cohort B of the study:

1b. Prior treatment with CAR-T therapy directed at any target.

2b. Any therapy that is targeted to BCMA.

3b. Criterion modified per Amendment 1

3b.1. Criterion modified per Amendment 2

3b.2. Active malignancies (ie, progressing or requiring treatment change in the last 24 months) other than the disease being treated under study. The only allowed exceptions are:

- non-muscle invasive bladder cancer (NMIBC) treated within the last 24 months that is considered completely cured.
- skin cancer (non-melanoma or melanoma) treated within the last 24 months that is considered completely cured.
- non-invasive cervical cancer treated within the last 24 months that is considered completely cured.

- localized prostate cancer (N0M0):
  - with a Gleason score of ≤6, treated within the last 24 months or untreated and under surveillance,
  - with a Gleason score of 3+4 that has been treated more than 6 months prior to full study screening and considered to have a very low risk of recurrence, or
  - history of localized prostate cancer and receiving androgen deprivation therapy and considered to have a very low risk of recurrence.
- breast cancer: adequately treated lobular carcinoma in situ or ductal carcinoma in situ, or history of localized breast cancer and receiving antihormonal agents and considered to have a very low risk of recurrence.
- malignancy that is considered cured with minimal risk of recurrence.

4b. Criterion modified per Amendment 4

4b.1. Prior antitumor therapy as follows, prior to apheresis:

- Targeted therapy, epigenetic therapy, treatment with an investigational drug, investigational intervention (including investigational vaccines) or used an invasive investigational medical device within 14 days or at least 5 half-lives, whichever is less, or currently enrolled in an investigational study.
- Monoclonal antibody treatment for multiple myeloma within 21 days.
- Cytotoxic therapy within 14 days.
- Proteasome inhibitor therapy within 14 days.
- Immunomodulatory agent therapy within 7 days.
- Radiotherapy within 14 days. However, if the radiation portal covered ≤5% of the bone marrow reserve, the subject is eligible irrespective of the end date of radiotherapy.

5b. Criterion modified per Amendment 1

5b.1. Ongoing toxicity from previous anticancer therapy must resolve to baseline levels or to Grade 1 or less except for alopecia or peripheral neuropathy.

6b. The following cardiac conditions:

- NYHA stage III or IV congestive heart failure
- Myocardial infarction or CABG ≤6 months prior to enrollment
- History of clinically significant ventricular arrhythmia or unexplained syncope, not believed to be vasovagal in nature or due to dehydration
- History of severe non-ischemic cardiomyopathy
- Impaired cardiac function (LVEF <45%) as assessed by echocardiogram or MUGA scan (performed ≤8 weeks of apheresis)

7b. Received a cumulative dose of corticosteroids equivalent to ≥70 mg of prednisone within the 7 days prior to apheresis

8b. Known active, or prior history of CNS involvement or exhibits clinical signs of meningeal involvement of multiple myeloma.

9b. Stroke or seizure within 6 months of signing ICF.

10b. Plasma cell leukemia at the time of screening (>2.0 x 10^9/L plasma cells by standard differential), Waldenström's macroglobulinemia, POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, and skin changes), or primary AL amyloidosis.

11b. Seropositive for HIV.

12b. Vaccinated with live, attenuated vaccine within 4 weeks prior to apheresis.

13b. Hepatitis B infection as defined according to Attachment 10. In the event the infection status is unclear, quantitative levels are necessary to determine the infection status. (Hwang 2015)

14b. Hepatitis C infection defined as (anti-hepatitis C virus [HCV] antibody positive or HCV-RNA positive) or known to have a history of hepatitis C. For subjects with known history of HCV infection, confirmation of sustained virologic response [SVR] is required for study eligibility, defined as ≥24 weeks after completion of antiviral therapy.

15b. Criterion modified per Amendment 1

15b.1. Subject must not require continuous supplemental oxygen.

16b. Criterion modified per Amendment 3

16b.1. Contraindications, known life threatening allergies, hypersensitivity, or intolerance to cyclophosphamide, fludarabine, or JNJ-68284528 excipients, including DMSO (refer to Investigator's Brochure).

17b. Criterion modified per Amendment 1

17b.1. Criterion modified per Amendment 2

17b.2. Serious underlying medical condition, such as:

- Evidence of active viral or bacterial infection requiring systemic antimicrobial therapy, or uncontrolled systemic fungal infection
- Active autoimmune disease or a history of autoimmune disease within 3 years

- Overt clinical evidence of dementia or altered mental status
- Any history of Parkinson's disease or other neurodegenerative disorder

18b. Any issue that would impair the ability of the subject to receive or tolerate the planned treatment at the investigational site, to understand informed consent or any condition for which, in the opinion of the investigator, participation would not be in the best interest of the subject (eg, compromise the well-being) or that could prevent, limit, or confound the protocol-specified assessments.

19b. Criterion modified per Amendment 1

19b.1. Pregnant or breast-feeding, or planning to become pregnant while enrolled in this study or within 1 year after receiving JNJ-68284528 infusion.

20b. Criterion modified per Amendment 1

20b.1. Plans to father a child while enrolled in this study or within 1 year after receiving JNJ-68284528 infusion.

21b. Major surgery within 2 weeks prior to apheresis, or has surgery planned during the study or within 2 weeks after study treatment administration. (Note: subjects with planned surgical procedures to be conducted under local anesthesia may participate.)

22b. Received either of the following:

- An allogenic stem cell transplant within 6 months before apheresis. Subjects who received an allogeneic transplant must be off all immunosuppressive medications for 6 weeks without signs of graft-versus-host disease (GVHD).
- An autologous stem cell transplant ≤12 weeks before apheresis

23b. Received an investigational intervention (including investigational vaccines) or used an invasive investigational medical device within 15 days prior to apheresis or is currently enrolled in an investigational study

4.3. Cohort C Eligibility Criteria

4.3.1. Cohort C Inclusion Criteria

Each potential subject must satisfy all of the following criteria to be enrolled in Cohort C of the study:

1c. Previously treated with a PI, an IMiD, an anti-CD38 monoclonal antibody and BCMA-directed therapy (prior exposure can be from different monotherapy or combination lines of therapy). Subjects may be enrolled in this cohort regardless of dose level/schedule or response obtained to prior BCMA directed therapy.

- Subject must have received prior therapy with at least one BCMA-directed agent (eg, ADC or BiTE), excluding cellular immunotherapy.

2c. Documented evidence of progressive disease based on investigator's determination of response by the IMWG criteria (Attachment 1), either:

- on or within 12 months of their last line of therapy, or.
- on or within 6 months of prior therapy, and refractory or non-responsive to their most recent line of therapy.

Confirmation may be from either central or local testing.

3c. ≥18 years of age.

4c. Documented diagnosis of multiple myeloma according to IMWG diagnostic criteria (Attachment 5).

5c. Criterion modified per Amendment 3

5c.1. Measurable disease at Screening as defined by any of the following:

- Serum monoclonal paraprotein (M-protein) level ≥1.0 g/dL or urine M-protein level ≥200 mg/24 hours; or
- Light chain multiple myeloma in whom only measurable disease is by serum FLC levels in the serum: Serum immunoglobulin free light chain ≥10 mg/dL and abnormal serum immunoglobulin kappa lambda free light chain ratio.

Note: Local laboratory assessments may be used to establish measurable disease at Screening, with local laboratory result ≥125% of requirements (eg, M-protein ≥1.25 g/dL if using local labs).

- For subjects with neither serum nor urine measurable disease, baseline PET/CT or whole body MRI may be used to satisfy the measurable disease criteria. See Attachment 22 for disease characterization of imaging response and Attachment 23 for reporting requirements.

6c. ECOG Performance Status grade of 0 or 1 Attachment 7).

7c. Criterion modified per Amendment 3

7c.1. Clinical laboratory values meeting the following criteria during the Screening Phase:

Hematology	
Hemoglobin	≥8.0 g/dL (≥5 mmol/L) (without prior red blood cell [RBC] transfusion within 3 days before the laboratory test; recombinant human erythropoietin use is permitted)*
Platelets	≥50 x 10^9/L (must be without transfusion support in the 3 days prior to the laboratory test)
Absolute Lymphocyte Count (ALC)	≥0.3 x 10^9/L
Absolute Neutrophil Count (ANC)	≥0.75×10^9/L (prior growth factor support is permitted but must be without support in the 7 days prior to the laboratory test)
Chemistry	
AST and ALT	≤3.0 × upper limit of normal (ULN)
Estimated Glomerular Filtration Rate	≥40 mL/min/1.73 m^2 based upon Modified Diet in Renal Disease formula calculation (Attachment 8) or a 24-hour urine collection.
Total bilirubin	≤2.0 × ULN; except in subjects with congenital bilirubinemia, such as Gilbert syndrome (in which case direct bilirubin ≤1.5 × ULN is required)
Corrected serum calcium	≤12.5 mg/dL (≤3.1 mmol/L) or free ionized calcium ≤6.5 mg/dL (≤1.6 mmol/L)

* For subjects who meet the inclusion criteria at screening, transfusion of RBCs is permitted after screening as needed to maintain a hemoglobin level ≥8.0 g/dL.

8c. Women of childbearing potential must have a negative pregnancy test at screening using a highly sensitive serum pregnancy test (β human chorionic gonadotropin [β-hCG]).

9c. When a woman is of childbearing potential (See Attachment 16) the following are required:

- Subject must agree to practice a highly effective method of contraception (failure rate of <1% per year when used consistently and correctly) and agree to remain on a highly effective method of contraception from the time of signing the informed consent form (ICF) until 1 year after receiving a JNJ-68284528 infusion. Examples of highly effective contraceptives include:
  - user-independent methods: 1) implantable progestogen-only hormone contraception associated with inhibition of ovulation; 2) intrauterine device; intrauterine hormone-releasing system; 3) vasectomized partner;
  - user-dependent methods: 1) combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation: oral or intravaginal or transdermal; 2) progestogen-only hormone contraception associated with inhibition of ovulation (oral or injectable)

In addition to the highly effective method of contraception a man:

- Who is sexually active with a woman of childbearing potential must agree to use a barrier method of contraception (eg, condom with spermicidal foam/gel/film/cream/suppository) from the time of signing the ICF until 1 year after receiving a JNJ-68284528 infusion.
- Who is sexually active with a woman who is pregnant must use a condom

Women and men must agree not to donate eggs (ova, oocytes) or sperm, respectively, during the study and for 1 year after JNJ-68284528 infusion.

Note: Hormonal contraception may be susceptible to interaction with the study treatment, which may reduce the efficacy of the contraceptive method.

10c. Subject must sign an ICF indicating that he or she understands the purpose of, and procedures required for the study and is willing to participate in the study. Consent is to be obtained prior to the initiation of any study-related tests or procedures that are not part of standard-of-care for the subject's disease.

11c. Willing and able to adhere to the prohibitions and restrictions specified in this protocol.

4.3.2. Cohort C Exclusion Criteria

Any potential subject who meets any of the following criteria will be excluded from participating in Cohort C of the study:

1c. Prior treatment with cellular immunotherapy (eg, CAR-T) directed at any target.

2c. Criterion modified per Amendment 2

2c.1. Active malignancies (ie, progressing or requiring treatment change in the last 24 months) other than the disease being treated under study. The only allowed exceptions are:

- non-muscle invasive bladder cancer (NMIBC) treated within the last 24 months that is considered completely cured.
- skin cancer (non-melanoma or melanoma) treated within the last 24 months that is considered completely cured.
- non-invasive cervical cancer treated within the last 24 months that is considered completely cured.
- localized prostate cancer (N0M0):
  - with a Gleason score of ≤6, treated within the last 24 months or untreated and under surveillance,
  - with a Gleason score of 3+4 that has been treated more than 6 months prior to full study screening and considered to have a very low risk of recurrence, or

  - history of localized prostate cancer and receiving androgen deprivation therapy and considered to have a very low risk of recurrence.

- breast cancer: adequately treated lobular carcinoma in situ or ductal carcinoma in situ, or history of localized breast cancer and receiving antihormonal agents and considered to have a very low risk of recurrence.
- malignancy that is considered cured with minimal risk of recurrence.

3c. Criterion modified per Amendment 2

3c.1. Criterion modified per Amendment 4

3c.2. Prior antitumor therapy as follows, prior to apheresis:

- Targeted therapy, epigenetic therapy, treatment with an investigational drug, investigational intervention (including investigational vaccines) or used an invasive investigational medical device within 14 days or at least 5 half-lives, whichever is less, or currently enrolled in an investigational study.
- Monoclonal antibody treatment for multiple myeloma within 21 days.
- BCMA-directed Antibody-drug Conjugate or Bispecific T-cell Engager Antibody therapy for multiple myeloma within 5 half-lives of the drug. However, if treated with belantamab mafodotin (GSK2857916) then within 21 days of the drug.
- Cytotoxic therapy within 14 days.
- Proteasome inhibitor therapy within 14 days.
- Immunomodulatory agent therapy within 7 days.
- Radiotherapy within 14 days. However, if the radiation portal covered ≤5% of the bone marrow reserve, the subject is eligible irrespective of the end date of radiotherapy.

4c. Ongoing toxicity from previous anticancer therapy must resolve to baseline levels or to Grade 1 or less except for alopecia or peripheral neuropathy.

5c. The following cardiac conditions:

- New York Heart Association (NYHA) stage III or IV congestive heart failure
- Myocardial infarction or coronary artery bypass graft (CABG) ≤6 months prior to enrollment
- History of clinically significant ventricular arrhythmia or unexplained syncope, not believed to be vasovagal in nature or due to dehydration
- History of severe non-ischemic cardiomyopathy
- Impaired cardiac function (left ventricular ejection fraction [LVEF] <45%) as assessed by echocardiogram or multiple-gated acquisition (MUGA) scan (performed ≤8 weeks of apheresis)

6c. Received a cumulative dose of corticosteroids equivalent to ≥70 mg of prednisone within the 7 days prior to apheresis

7c. Known active, or prior history of central nervous system (CNS) involvement or exhibits clinical signs of meningeal involvement of multiple myeloma.

8c. Stroke or seizure within 6 months of signing ICF.

9c. Plasma cell leukemia at the time of screening (>2.0 x 10^9/L plasma cells by standard differential), Waldenström's macroglobulinemia, POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, and skin changes), or primary AL amyloidosis.

10c. Seropositive for human immunodeficiency virus (HIV).

11c. Vaccinated with live, attenuated vaccine within 4 weeks prior to apheresis.

12c. Hepatitis B infection as defined according to Attachment 10. In the event the infection status is unclear, quantitative levels are necessary to determine the infection status. (Hwang 2015)

13c. Hepatitis C infection defined as (anti-hepatitis C virus [HCV] antibody positive or HCV-RNA positive) or known to have a history of hepatitis C. For subjects with known history of HCV infection, confirmation of sustained virologic response [SVR] is required for study eligibility, defined as ≥24 weeks after completion of antiviral therapy.

14c. Subject must not require continuous supplemental oxygen.

15c. Criterion modified per Amendment 3

15c.1. Contraindications, known life threatening allergies, hypersensitivity, or intolerance to cyclophosphamide, fludarabine, or JNJ-68284528 excipients, including DMSO (refer to Investigator's Brochure).

16c. Criterion modified per Amendment 2

16c.1. Serious underlying medical condition, such as:

- Evidence of active viral or bacterial infection requiring systemic antimicrobial therapy, or uncontrolled systemic fungal infection
- Active autoimmune disease or a history of autoimmune disease within 3 years
- Overt clinical evidence of dementia or altered mental status
- Any history of Parkinson's disease or other neurodegenerative disorder

17c. Any issue that would impair the ability of the subject to receive or tolerate the planned treatment at the investigational site, to understand informed consent or any condition for which, in the opinion of the investigator, participation would not be in the best interest of the subject (eg, compromise the well-being) or that could prevent, limit, or confound the protocol-specified assessments.

18c. Pregnant or breast-feeding, or planning to become pregnant while enrolled in this study or within 1 year after receiving JNJ-68284528 infusion.

19c. Plans to father a child while enrolled in this study or within 1 year after receiving JNJ-68284528 infusion.

20c. Major surgery within 2 weeks prior to apheresis, or has surgery planned during the study or within 2 weeks after study treatment administration. (Note: subjects with planned surgical procedures to be conducted under local anesthesia may participate.)

21c. Received either of the following:

- An allogenic stem cell transplant within 6 months before apheresis. Subjects who received an allogeneic transplant must be off all immunosuppressive medications for 6 weeks without signs of graft-versus-host disease (GVHD).
- An autologous stem cell transplant ≤12 weeks before apheresis

22c. Received an investigational intervention (including investigational vaccines) or used an invasive investigational medical device within 15 days prior to apheresis or is currently enrolled in an investigational study

4.4. Cohort D Eligibility Criteria

4.4.1. Cohort D Inclusion Criteria

Each potential subject must satisfy all of the following criteria to be enrolled in Cohort D of the study:

1d. Have newly diagnosed multiple myeloma per IMWG criteria (Rajkumar 2014) with a history of 4 to 8 total cycles of initial therapy, including induction, high-dose therapy, and ASCT with or without consolidation (Subjects previously treated for smoldering myeloma are not eligible).

Subject treated with consolidation must have received ≤2 cycles.

- Received an IMID or PI or both in combination with a steroid as a part of the induction or consolidation regimen
- Treatment with alkylating therapy (for example cyclophosphamide) and/or monoclonal antibodies (for example, daratumumab) during induction/consolidation is permitted

- Subjects who have not received consolidation therapy should be approximately 100 days post-ASCT during screening
- Subjects treated with consolidation therapy should be approximately 160 days post-ASCT during screening

2d. Have overall best response <CR and ≥stable disease, and have not yet evolved to Progressive Disease as assessed per IMWG 2016 criteria

3d. ≥18 years of age.

4d. ECOG Performance Status score of 0 or 1

5d. Clinical laboratory values meeting the following criteria during the Screening Phase:

Hematology	
Hemoglobin	≥8.0 g/dL (≥5 mmol/L) (without prior red blood cell [RBC] transfusion within 7 days before the laboratory test; recombinant human erythropoietin use is permitted)*
Platelets	≥75 x 10^9/L (must be without transfusion support in the 7 days prior to the laboratory test)
Absolute Lymphocyte Count (ALC)	≥0.3 x 10^9/L
Absolute Neutrophil Count (ANC)	≥1×10^9/L (prior growth factor support is permitted but must be without support in the 7 days prior to the laboratory test)
Chemistry	
AST and ALT	≤3.0 × upper limit of normal (ULN)
Estimated Glomerular Filtration Rate	≥40 mL/min/1.73 m^2 based upon Modified Diet in Renal Disease formula calculation (Attachment 8) or a 24-hour urine collection.
Total bilirubin	≤2.0 × ULN; except in subjects with congenital bilirubinemia, such as Gilbert syndrome (in which case direct bilirubin ≤1.5 × ULN is required)
Corrected serum calcium	≤12.5 mg/dL (≤3.1 mmol/L) or free ionized calcium ≤6.5 mg/dL (≤1.6 mmol/L)

* For subjects who meet the inclusion criteria at screening, transfusion of RBCs is permitted after screening as needed to maintain a hemoglobin level ≥8.0 g/dL

6d. Women of childbearing potential must have a negative highly sensitive serum pregnancy test (β-human chorionic gonadotropin [β-hCG]) at screening.

7d. Criterion modified per Amendment 2

7d.1. Criterion modified per Amendment 3

7d.2. Criterion modified per Amendment 6

7d.3. When a woman is of childbearing potential (See Attachment 16) the following are required:

- Subject must agree to practice 2 methods of reliable birth control simultaneously from 4 weeks prior to initiating treatment with lenalidomide until 1 year after receiving a JNJ-68284528 infusion or for 4 weeks following discontinuation of lenalidomide (whichever is later). One of the birth control methods should be a highly effective method of contraception (failure rate of <1% per year when used consistently and correctly; see examples below) and one other effective method (ie, male latex or synthetic condom, diaphragm, or cervical cap) and subject must agree to remain on both methods. Examples of highly effective contraceptives include:
  - user-independent methods: 1) implantable progestogen-only hormone contraception associated with inhibition of ovulation; 2) intrauterine device; intrauterine hormone-releasing system; 3) vasectomized partner;
  - user-dependent method: progestogen-only hormone contraception associated with inhibition of ovulation (oral or injectable). Estrogen-containing hormonal contraception is contraindicated due to increased risk of thromboembolic events with lenalidomide.
  - women of childbearing potential must follow the contraception criteria outlined in the global REVLIMID®/lenalidomide pregnancy prevention program or equivalent local Risk Evaluation and Mitigation Strategy (REMS), whichever is more stringent, as applicable in their region.

In addition to the highly effective method of contraception a man:

- Must always use a condom during any sexual contact with a woman of childbearing potential, even if they have undergone a successful vasectomy, from the time of signing the ICF until 1 year after receiving a JNJ-68284528 infusion or for 4 weeks after discontinuing lenalidomide (whichever is later).
- Who is sexually active with a woman who is pregnant must use a condom.
- Should agree to practice contraception according to and for the time frame specified in the global REVLIMID/lenalidomide pregnancy prevention program or equivalent local REMS, whichever is more stringent, as applicable in their region.

Women and men must agree not to donate eggs (ova, oocytes) or sperm, respectively, during the study and for 1 year after receiving a JNJ-68284528 infusion or for 4 weeks after discontinuing lenalidomide (whichever is later).

Note: Hormonal contraception may be susceptible to interaction with the study treatment, which may reduce the efficacy of the contraceptive method.

8d. Subject must sign an ICF indicating that he or she understands the purpose of and procedures required for the study and is willing to participate in the study. Consent is to be obtained prior to the initiation of any study-related tests or procedures that are not part of standard-of-care for the subject's disease.

9d. Willing and able to adhere to the prohibitions and restrictions specified in this protocol.

4.4.2. Cohort D Exclusion Criteria

Any potential subject who meets any of the following criteria will be excluded from participating in Cohort D of the study:

1d. Received prior treatment with CAR-T therapy directed at any target.

2d. Received any therapy that is targeted to BCMA.

3d. Criterion modified per Amendment 2

3d.1. Active malignancies (ie, progressing or requiring treatment change in the last 24 months) other than the disease being treated under study. The only allowed exceptions are:

- non-muscle invasive bladder cancer (NMIBC) treated within the last 24 months that is considered completely cured.
- skin cancer (non-melanoma or melanoma) treated within the last 24 months that is considered completely cured.
- non-invasive cervical cancer treated within the last 24 months that is considered completely cured.
- localized prostate cancer (N0M0):
  - with a Gleason score of ≤6, treated within the last 24 months or untreated and under surveillance,
  - with a Gleason score of 3+4 that has been treated more than 6 months prior to full study screening and considered to have a very low risk of recurrence, or
  - history of localized prostate cancer and receiving androgen deprivation therapy and considered to have a very low risk of recurrence.
- breast cancer: adequately treated lobular carcinoma in situ or ductal carcinoma in situ, or history of localized breast cancer and receiving antihormonal agents and considered to have a very low risk of recurrence.
- malignancy that is considered cured with minimal risk of recurrence.

4d. Criterion Modified per Amendment 4

4d.1. Prior anti-tumor therapy, as follows, prior to apheresis:

- Targeted therapy, epigenetic therapy, treatment with an investigational drug, investigational intervention (including investigational vaccines) or used an invasive investigational medical device within 14 days or at least 5 half-lives, whichever is less, or currently enrolled in an investigational study.
- Monoclonal antibody treatment for multiple myeloma within 21 days.
- Cytotoxic therapy within 14 days.

- Proteasome inhibitor therapy within 14 days.
- Immunomodulatory agent therapy within 7 days.
- Radiotherapy within 14 days. However, if the radiation portal covered ≤5% of the bone marrow reserve, the subject is eligible irrespective of the end date of radiotherapy.

5d. Ongoing toxicity from previous anticancer therapy must resolve to baseline levels or to Grade 1 or less, except for alopecia or peripheral neuropathy.

6d. Received a cumulative dose of corticosteroids equivalent to ≥70 mg of prednisone within the 14 days prior to apheresis.

7d. The following cardiac conditions:

- New York Heart Association (NYHA) stage III or IV congestive heart failure
- Myocardial infarction or coronary artery bypass graft ≤6 months prior to enrollment
- History of clinically significant ventricular arrhythmia or unexplained syncope, not believed to be vasovagal in nature or due to dehydration
- History of severe non-ischemic cardiomyopathy
- Impaired cardiac function (left ventricular ejection fraction <45%) as assessed by echocardiogram or multiple-gated acquisition (MUGA) scan (performed ≤8 weeks of apheresis)

8d. Known active, or prior history of central nervous system involvement of myeloma or exhibits clinical signs of meningeal involvement of multiple myeloma.

9d. Stroke or seizure within 6 months of signing ICF.

10d. Plasma cell leukemia at the time of screening (>2.0 x 10^9/L plasma cells by standard differential), Waldenström's macroglobulinemia, POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, and skin changes), or primary (AL) amyloidosis.

11d. Seropositive for human immunodeficiency virus (HIV).

12d. Vaccinated with live, attenuated vaccine within 4 weeks prior to apheresis.

13d. Subject must not require continuous supplemental oxygen.

14d. Criterion modified per Amendment 3

14d.1. Contraindications, known life threatening allergies, hypersensitivity, or intolerance to cyclophosphamide, fludarabine, lenalidomide, or JNJ-68284528 excipients, including DMSO (refer to Investigator's Brochure).

15d. Hepatitis B infection as defined according to Attachment 10. In the event the infection status is unclear, quantitative levels are necessary to determine the infection status. (Hwang 2015)

16d. Hepatitis C infection defined as (anti-hepatitis C virus [HCV] antibody positive or HCV-RNA positive) or known to have a history of hepatitis C. For subjects with known history of HCV infection, confirmation of sustained virologic response [SVR] is required for study eligibility, defined as ≥24 weeks after completion of antiviral therapy.

17d. Criterion modified per Amendment 2

17d.1. Serious underlying medical condition, such as:

- Evidence of active viral or bacterial infection requiring systemic antimicrobial therapy, or uncontrolled systemic fungal infection
- Active autoimmune disease or a history of autoimmune disease within 3 years
- Overt clinical evidence of dementia or altered mental status
- Any history of Parkinson's disease or other neurodegenerative disorder

18d. Any issue that would impair the ability of the subject to receive or tolerate the planned treatment at the investigational site, to understand informed consent or any condition for which, in the opinion of the investigator, participation would not be in the best interest of the subject (eg, compromise the well-being) or that could prevent, limit, or confound the protocol-specified assessments.

19d Pregnant or breast-feeding, or planning to become pregnant while enrolled in this study and until 1 year after receiving a JNJ-68284528 infusion or for 4 weeks following discontinuation of lenalidomide (whichever is later).

20d. Plans to father a child while enrolled in this study until 1 year after receiving a JNJ-68284528 infusion or for 4 weeks following discontinuation of lenalidomide (whichever is later).

21d. Major surgery within 2 weeks prior to apheresis, or has surgery planned during the study or within 2 weeks after JNJ-68284528. (Note: subjects with planned surgical procedures to be conducted under local anesthesia may participate)

4.5. Cohort E Eligibility Criteria

4.5.1. Cohort E Inclusion Criteria

Each potential subject must satisfy all of the following criteria to be enrolled in Cohort E of the study:

1e. Criterion Modified per Amendment 4

1.e.1. Criterion Modified per Amendment 5

1e.2. Have newly diagnosed multiple myeloma without prior therapy (one cycle of prior therapy before enrollment is acceptable) and classified as high risk defined as:

- International Staging System (ISS) stage III criteria, Beta 2 microglobulin (β2M) ≥ 5.5 mg/L [via local or central laboratory assessment, see section 9.1.2 for more details] (Attachment 19, Greipp 2005); or
- High-risk by any of the following cytogenetics feature such as del(17/17p), t (14;16), t(14;20), and gain of at least 4 total copies of (1q) in at least 20% of the total plasma cell population (Bisht 2021).

2e. Not considered candidate for high-dose chemotherapy with stem cell transplantation due to:

- Being age ≥65 years; or
- Age 18-65 years with presence of comorbid condition(s) likely to have a negative impact on tolerability of high-dose chemotherapy with SCT; or
- Refusal of high-dose chemotherapy with SCT as initial treatment.

3e. Documented diagnosis of multiple myeloma according to IMWG diagnostic criteria (Attachment 5).

4e. Criterion Modified per Amendment 5

4.e.1. Criterion Modified per Amendment 6

4e.2. Measurable disease at Screening as defined by any of the following:

- Serum monoclonal paraprotein (M-protein) level ≥1.0 g/dL or urine M-protein level ≥200 mg/24 hours; or
- Light chain multiple myeloma in whom only measurable disease is by serum FLC levels in the serum: Serum immunoglobulin free light chain ≥10 mg/dL and abnormal serum immunoglobulin kappa lambda free light chain ratio.

Note:

- For subjects that have received 1 cycle of anti-myeloma therapy prior to enrollment (as allowed by Exclusion Criterion 2e.1) measurable disease must be assessed by local laboratory on the most recent evaluation prior to the start of the anti-myeloma therapy.
- Note: Local laboratory assessments may be used to establish measurable disease at Screening, with local laboratory result ≥125% of requirements (eg, M-protein ≥1.25 g/dL if using local labs).

5e. ECOG Performance Status grade of 0 or 1 (Attachment 7).

6e. Clinical laboratory values meeting the following criteria during the Screening Phase:

Hematology	
Hemoglobin	≥8.0 g/dL (≥5 mmol/L) (without prior red blood cell [RBC] transfusion within 7 days before the laboratory test; recombinant human erythropoietin use is permitted)*
Platelets	≥75 x 10^9/L (must be without transfusion support in the 7 days prior to the laboratory test)
Absolute Lymphocyte Count (ALC)	≥0.3 x 10^9/L
Absolute Neutrophil Count (ANC)	≥1 ×10^9/L (prior growth factor support is permitted but must be without support in the 7 days prior to the laboratory test)
Chemistry	
AST and ALT	≤3.0 × upper limit of normal (ULN)
Estimated Glomerular Filtration Rate	≥40 mL/min/1.73 m^2 based upon Modified Diet in Renal Disease formula calculation (Attachment 8) or a 24-hour urine collection.
Total bilirubin	≤2.0 × ULN; except in subjects with congenital bilirubinemia, such as Gilbert syndrome (in which case direct bilirubin ≤1.5 × ULN is required)
Corrected serum calcium	≤12.5 mg/dL (≤3.1 mmol/L) or free ionized calcium ≤6.5 mg/dL (≤1.6 mmol/L)

* For subjects who meet the inclusion criteria at screening, transfusion of RBCs is permitted after screening as needed to maintain a hemoglobin level ≥8.0 g/dL.

7e. A woman of childbearing potential must have a negative highly sensitive serum pregnancy test (β-human chorionic gonadotropin [β-hCG]) at screening.

8e. Criterion modified per Amendment 4

8e.1. Criterion Modified per Amendment 6

8e.2. When a woman is of childbearing potential (See Attachment 16) the following are required:

- Subject must agree to practice 2 methods of reliable birth control simultaneously from 4 weeks prior to initiating treatment with lenalidomide until 1 year after receiving a JNJ-68284528 infusion or for 4 weeks following discontinuation of lenalidomide or for 3 months after discontinuation of daratumumab (whichever is later). One of the birth control methods should be a highly effective method of contraception (failure rate of <1% per year when used consistently and correctly; see examples below) and one other effective method (ie, male latex or synthetic condom, diaphragm, or cervical cap) and subject must agree to remain on both methods. Examples of highly effective contraceptives include:
  - user-independent methods: 1) implantable progestogen-only hormone contraception associated with inhibition of ovulation; 2) intrauterine device; intrauterine hormone-releasing system; 3) vasectomized partner;
  - user-dependent method: progestogen-only hormone contraception associated with inhibition of ovulation (oral or injectable). Estrogen-containing hormonal contraception is contraindicated due to increase risk of thromboembolic events with lenalidomide.
  - women of childbearing potential must follow the contraception criteria outlined in the global REVLIMID/lenalidomide pregnancy prevention program or equivalent local REMS, whichever is more stringent, as applicable in their region.

In addition to the highly effective method of contraception, a man:

- Must always use a condom during any sexual contact with a woman of childbearing potential, even if they have undergone a successful vasectomy, from the time of signing the ICF until 1 year after receiving a JNJ-68284528 infusion or for 4 weeks after discontinuing lenalidomide, or until 3 months after daratumumab (whichever is later).
- Who is sexually active with a woman who is pregnant must use a condom.
- Should agree to practice contraception according to and for the time frame specified in the global REVLIMID/lenalidomide pregnancy prevention program or equivalent local REVLIMID/lenalidomide pregnancy prevention program, whichever is more stringent.

Women and men must agree not to donate eggs (ova, oocytes) or sperm, respectively, during the study and for 1 year after receiving a JNJ-68284528 infusion or for 4 weeks after discontinuing lenalidomide, or until 3 months after daratumumab (whichever is later).

Note: Hormonal contraception may be susceptible to interaction with the study treatment, which may reduce the efficacy of the contraceptive method.

9e. Subject must sign an ICF indicating that he or she understands the purpose of and procedures required for the study and is willing to participate in the study. Consent is to be obtained prior to the initiation of any study-related tests or procedures that are not part of standard-of-care for the subject's disease.

10e. Willing and able to adhere to the prohibitions and restrictions specified in this protocol.

11e. Criterion added in Amendment 5

≥18 years of age.

4.5.2. Cohort E Exclusion Criteria

Any potential subject who meets any of the following criteria will be excluded from participating in Cohort E of the study:

1e. Active malignancies (ie, progressing or requiring treatment change in the last 24 months) other than the disease being treated under study. The only allowed exceptions are:

- non-muscle invasive bladder cancer (NMIBC) treated within the last 24 months that is considered completely cured.
- skin cancer (non-melanoma or melanoma) treated within the last 24 months that is considered completely cured.
- non-invasive cervical cancer treated within the last 24 months that is considered completely cured.
- localized prostate cancer (N0M0):
  - with a Gleason score of ≤6, treated within the last 24 months or untreated and under surveillance,
  - with a Gleason score of 3+4 that has been treated more than 6 months prior to full study screening and considered to have a very low risk of recurrence, or
  - history of localized prostate cancer and receiving androgen deprivation therapy and considered to have a very low risk of recurrence.
- breast cancer: adequately treated lobular carcinoma in situ or ductal carcinoma in situ, or history of localized breast cancer and receiving antihormonal agents and considered to have a very low risk of recurrence.
- malignancy that is considered cured with minimal risk of recurrence.

2e. Criterion modified per Amendment 4

2e.1. Criterion Modified per Amendment 6

2e.2. Prior therapy for plasma cell disorder-multiple myeloma with the exception of one cycle of anti-myeloma therapy any time before enrollment.

3e. Frailty index of ≥2 according to Myeloma Geriatric Assessment score (Palumbo 2015; Attachment 21)

4e. Peripheral neuropathy or neuropathic pain Grade 2 or higher, as defined by the National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE) Version 5.

5e. The following cardiac conditions:

- New York Heart Association (NYHA) stage III or IV congestive heart failure
- Myocardial infarction or coronary artery bypass graft (CABG) ≤6 months prior to enrollment
- History of clinically significant ventricular arrhythmia or unexplained syncope, not believed to be vasovagal in nature or due to dehydration
- History of severe non-ischemic cardiomyopathy
- Impaired cardiac function (left ventricular ejection fraction [LVEF] <45%) as assessed by echocardiogram or multiple-gated acquisition (MUGA) scan (performed ≤8 weeks of apheresis)
- Screening 12-lead ECG showing a baseline QTcF interval >470 msec

6e. Received a strong CYP3A4 inducer within 5 half-lives prior to induction therapy

7e. Known active, or prior history of central nervous system (CNS) involvement or exhibits clinical signs of meningeal involvement of multiple myeloma.

8e. Stroke or seizure within 6 months of signing ICF.

9e. Plasma cell leukemia at the time of screening (>2.0 x 10^9/L plasma cells by standard differential), Waldenström's macroglobulinemia, POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, and skin changes), or primary amyloid light-chain (AL) amyloidosis.

10e. Seropositive for human immunodeficiency virus (HIV).

11e. Vaccinated with live, attenuated vaccine within 4 weeks prior to apheresis.

12e. Hepatitis B infection as defined according to Attachment 10. In the event the infection status is unclear, quantitative levels are necessary to determine the infection status. (Hwang 2015)

13e. Hepatitis C infection defined as (anti-hepatitis C virus [HCV] antibody positive or HCV-RNA positive) or known to have a history of hepatitis C. For subjects with known history of HCV infection, confirmation of sustained virologic response [SVR] is required for study eligibility, defined as ≥24 weeks after completion of antiviral therapy.

14e. Subject must not require continuous supplemental oxygen.

15e. The following pulmonary conditions

- Chronic obstructive pulmonary disease (COPD) with a Forced Expiratory Volume in 1 second (FEV1) <50% of predicted normal (for subjects ≥65 years old FEV1 <50% or DLCO <50%).
- Moderate or severe persistent asthma within the past 2 years (see Attachment 24), or currently has uncontrolled asthma of any classification. (Note that subjects who currently have controlled intermittent asthma or controlled mild persistent asthma are allowed in the study).

16e. Contraindications, known life threatening allergies, hypersensitivity, or intolerance to boron or mannitol, hyaluronidase, sorbitol, corticosteroids, monoclonal antibodies or human proteins, cyclophosphamide, fludarabine, lenalidomide, daratumumab, bortezomib, dexamethasone, or JNJ-68284528 excipients, including DMSO (refer to Investigator's Brochure).

17e. Criterion modified per Amendment 4

17e.1 Serious underlying medical condition, such as:

- Evidence of active viral or bacterial infection requiring systemic antimicrobial therapy, or uncontrolled systemic fungal infection
- Active autoimmune disease or a history of autoimmune disease within 3 years
- Overt clinical evidence of dementia or altered mental status
- Any history of Parkinson's disease or other neurodegenerative disorder

18e. Any issue that would impair the ability of the subject to receive or tolerate the planned treatment at the investigational site, to understand informed consent or any condition for which, in the opinion of the investigator, participation would not be in the best interest of the subject (eg, compromise the well-being) or that could prevent, limit, or confound the protocol-specified assessments.

19e. Pregnant or breast-feeding or planning to become pregnant while enrolled in this study and until 1 year after receiving a JNJ-68284528 infusion, or for 4 weeks following discontinuation of lenalidomide, or until 3 months after daratumumab (whichever is later).

20e. Plans to father a child while enrolled in this study until 1 year after receiving a JNJ-68284528 infusion, or for 4 weeks following discontinuation of lenalidomide, or until 3 months after daratumumab (whichever is later).

21e. Major surgery within 2 weeks prior to study start, or has surgery planned during the study or within 2 weeks after study treatment administration. (Note: subjects with planned surgical procedures to be conducted under local anesthesia may participate.)

22e. Criterion deleted in Amendment 5

4.6. Cohort F Eligibility Criteria

4.6.1. Cohort F Inclusion Criteria

Each potential subject must satisfy all of the following criteria to be enrolled in Cohort F of the study:

1f. Documented new diagnosis of multiple myeloma according to IMWG diagnostic criteria (Attachment 5).

2f. Multiple myeloma classified as standard risk per International Staging System (ISS) stage I or II disease criteria, defined as:

- Stage I: β2 microglobulin (β2M) < 3.5 mg/L and serum albumin ≥ 3.5 g/dL or
- Stage II: serum β2-microglobulin <3.5 mg/L but serum albumin <3.5 g/dL; or serum β2-microglobulin 3.5 to <5.5 mg/L irrespective of the serum albumin level (Attachment 19, Greipp 2005).

3f. Criterion Modified per Amendment 5

3.f.1. Criterion Modified per Amendment 6

3f.2. Received initial therapy as specified below. The dose/schedule of cycles administered will be as per standard of care. It is acceptable for up to 1 cycle of the protocol-specified regimens to be missing one of the listed agents (eg, held due to toxicity). Acceptable combinations include:

- At least 5 to 8 cycles of initial therapy with daratumumab, bortezomib, lenalidomide and dexamethasone (D-VRd). The dose/schedule of cycles administered will be as per standard of care. or
- At least 4 to 8 cycles of initial therapy with daratumumab, lenalidomide and dexamethasone (D-Rd) or

- At least 4 to 8 cycles of initial therapy with a carfilzomib-based triplet or quadruplet regimen

4f. Patient must have a documented efficacy response of VGPR or better, without Progressive Disease prior to enrollment, as assessed per IMWG 2016 criteria.

5f. ECOG Performance Status grade of 0 or 1 (Attachment 7).

6f. Clinical laboratory values meeting the following criteria during the Screening Phase:

Hematology	
Hemoglobin	≥8.0 g/dL (≥5 mmol/L) (without prior red blood cell [RBC] transfusion within 7 days before the laboratory test; recombinant human erythropoietin use is permitted)*
Platelets	≥50 x 10^9/L (must be without transfusion support in the 7 days prior to the laboratory test)
Absolute Lymphocyte Count (ALC)	≥0.3 x 10^9/L
Absolute Neutrophil Count (ANC)	≥0.75×10^9/L (prior growth factor support is permitted but must be without support in the 7 days prior to the laboratory test)
Chemistry	
AST and ALT	≤3.0 × upper limit of normal (ULN)
Estimated Glomerular Filtration Rate	≥40 mL/min/1.73 m^2 based upon Modified Diet in Renal Disease formula calculation (Attachment 8) or a 24-hour urine collection.
Total bilirubin	≤2.0 × ULN; except in subjects with congenital bilirubinemia, such as Gilbert syndrome (in which case direct bilirubin ≤1.5 × ULN is required)
Corrected serum calcium	≤12.5 mg/dL (≤3.1 mmol/L) or free ionized calcium ≤6.5 mg/dL (≤1.6 mmol/L)

* For subjects who meet the inclusion criteria at screening, transfusion of RBCs is permitted after screening as needed to maintain a hemoglobin level ≥8.0 g/dL.

7f. A woman of childbearing potential must have a negative highly sensitive serum pregnancy test (β-human chorionic gonadotropin [β-hCG]) at screening.

8f. When a woman is of childbearing potential (See Attachment 16) the following are required:

- Subject must agree to practice a highly effective method of contraception (failure rate of <1% per year when used consistently and correctly) and agree to remain on a highly effective method of contraception from the time of signing the informed consent form (ICF) until 1 year after receiving a cilta-cel infusion. Examples of highly effective contraceptives include:
  - user-independent methods: 1) implantable progestogen-only hormone contraception associated with inhibition of ovulation; 2) intrauterine device; intrauterine hormone-releasing system; 3) vasectomized partner;

  - user-dependent methods: 1) combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation: oral or intravaginal or transdermal; 2) progestogen-only hormone contraception associated with inhibition of ovulation (oral or injectable)

- In addition to the highly effective method of contraception a man:
  - Who is sexually active with a woman of childbearing potential must agree to use a barrier method of contraception (eg, condom with spermicidal foam/gel/film/cream/suppository) from the time of signing the ICF until 1 year after receiving cilta-cel infusion.
  - Who is sexually active with a woman who is pregnant must use a condom.
- Women and men must agree not to donate eggs (ova, oocytes) or sperm, respectively, during the study and for 1 year after cilta-cel infusion.

Note: Hormonal contraception may be susceptible to interaction with the study treatment, which may reduce the efficacy of the contraceptive method.

9f. Subject must sign an ICF indicating that he or she understands the purpose of, and procedures required for the study and is willing to participate in the study. Consent is to be obtained prior to the initiation of any study-related tests or procedures that are not part of standard-of-care for the subject's disease.

10f. Willing and able to adhere to the prohibitions and restrictions specified in this protocol.

11f. Criterion Added in Amendment 5

≥18 years of age

12f. Criterion Added in Amendment 5

12f. Criterion Modified in Amendment 6

12f.1 Subject may receive up to 1 cycle of alternative anti-myeloma therapy prior to the protocol-specified initial therapy regimens.

4.6.2. Cohort F Exclusion Criteria

Any potential subject who meets any of the following criteria will be excluded from participating in Cohort F of the study:

1f. Active malignancies (ie, progressing or requiring treatment change in the last 24 months) other than the disease being treated under study. The only allowed exceptions are:

- non-muscle invasive bladder cancer (NMIBC) treated within the last 24 months that is considered completely cured.

- skin cancer (non-melanoma or melanoma) treated within the last 24 months that is considered completely cured.
- non-invasive cervical cancer treated within the last 24 months that is considered completely cured.
- localized prostate cancer (N0M0):
- with a Gleason score of ≤6, treated within the last 24 months or untreated and under surveillance,
- with a Gleason score of 3+4 that has been treated more than 6 months prior to full study screening and considered to have a very low risk of recurrence, or
- history of localized prostate cancer and receiving androgen deprivation therapy and considered to have a very low risk of recurrence.

- breast cancer: adequately treated lobular carcinoma in situ or ductal carcinoma in situ, or history of localized breast cancer and receiving antihormonal agents and considered to have a very low risk of recurrence.

  a malignancy that is considered cured with minimal risk of recurrence.

2f. Prior therapy as follows, prior to apheresis:

- Prior treatment with any other CAR-T therapy.
- Any therapy that is targeted to BCMA.
- Received an autologous or allogeneic stem cell transplant.
- Targeted therapy, epigenetic therapy, treatment with an investigational drug, investigational intervention (including investigational vaccines) or used an invasive investigational medical device within 14 days or at least 5 half-lives, whichever is less, or currently enrolled in an investigational study.
- Monoclonal antibody treatment for multiple myeloma within 21 days.
- Cytotoxic therapy within 14 days.
- Proteasome inhibitor therapy within 14 days.
- Immunomodulatory agent therapy within 7 days.
- Radiotherapy within 14 days. However, if the radiation portal covered ≤5% of the bone marrow reserve, the subject is eligible irrespective of the end date of radiotherapy.

3f. Received a cumulative dose of corticosteroids equivalent to ≥70 mg of prednisone within the 7 days prior to apheresis

4f. Ongoing toxicity from previous anticancer therapy must have resolved to baseline levels or to Grade 1 or less except for alopecia or peripheral neuropathy.

5f. Major surgery within 2 weeks prior to apheresis, or surgery planned after apheresis up to 2 weeks after cilta-cel administration. (Note: subjects with planned surgical procedures to be conducted under local anesthesia may participate.)

6f. The following cardiac conditions:

- NYHA stage III or IV congestive heart failure
- Myocardial infarction or CABG ≤6 months prior to enrollment
- History of clinically significant ventricular arrhythmia or unexplained syncope, not believed to be vasovagal in nature or due to dehydration
- History of severe non-ischemic cardiomyopathy
- Impaired cardiac function (LVEF <45%) as assessed by echocardiogram or MUGA scan (performed ≤8 weeks of apheresis)

7f. Known active, or prior history of CNS involvement or exhibits clinical signs of meningeal involvement of multiple myeloma.

8f. Stroke or seizure within 6 months of signing ICF.

9f. Plasma cell leukemia at the time of screening (>2.0 x 10^9/L plasma cells by standard differential), Waldenström's macroglobulinemia, POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, and skin changes), or primary AL amyloidosis.

10f. Seropositive for HIV.

11f. Vaccinated with live, attenuated vaccine within 4 weeks prior to apheresis.

12f. Hepatitis B infection as defined according to Attachment 10. In the event the infection status is unclear, quantitative levels are necessary to determine the infection status. (Hwang 2015)

13f. Hepatitis C infection defined as (anti hepatitis C virus [HCV] antibody positive or HCV-RNA positive) or known to have a history of hepatitis C. For subjects with known history of HCV infection, confirmation of sustained virologic response [SVR] is required for study eligibility, defined as ≥24 weeks after completion of antiviral therapy.

14f. Subjects requiring continuous supplemental oxygen.

15f. Contraindications, known life threatening allergies, hypersensitivity, or intolerance to cyclophosphamide, fludarabine, or cilta-cel excipients, including DMSO (refer to Investigator's Brochure).

16f. Serious underlying medical condition, such as:

- Evidence of active viral or bacterial infection requiring systemic antimicrobial therapy, or uncontrolled systemic fungal infection
- Active autoimmune disease or a history of autoimmune disease within 3 years
- Overt clinical evidence of dementia or altered mental status
- Any history of Parkinson's disease or other neurodegenerative disorder

17f. Any issue that would impair the ability of the subject to receive or tolerate the planned treatment at the investigational site, to understand informed consent or any condition for which, in the opinion of the investigator, participation would not be in the best interest of the subject (eg, compromise the well-being) or that could prevent, limit, or confound the protocol-specified assessments.

18f. Pregnant or breast feeding or planning to become pregnant while enrolled in this study or within 1 year after receiving cilta-cel infusion.

19f. Plans to father a child while enrolled in this study or within 1 year after receiving cilta-cel infusion.

4.7. Prohibitions and Restrictions

Potential subjects must be willing and able to adhere to the following prohibitions and restrictions during the course of the study to be eligible for participation:

1. Refer to Section 8 (Pre-study and Concomitant Therapy) for details regarding prohibited and restricted therapy during the study.
2. Agree to follow all requirements that must be met during the study as noted in the Inclusion and Exclusion Criteria (eg, contraceptive requirements).

5. TREATMENT ALLOCATION AND BLINDING

Randomization will not be used in this study. Subjects will be enrolled into a cohort based on inclusion/exclusion criteria defined for each cohort.

Subjects eligible for both Cohorts G and H, must be enrolled in Cohort B.

As these are single arm study cohorts, blinding procedures are not applicable.

6. DOSAGE AND ADMINISTRATION

For this study, study treatment refers to the cyclophosphamide/fludarabine conditioning regimen and JNJ-68284528 for all cohorts. In addition, for Cohort D lenalidomide given post JNJ-68284528 is also considered a study treatment. For Cohort E daratumumab, bortezomib, lenalidomide, and dexamethasone are also considered study treatments. All dosing information must be recorded in the Dosage Administration page of the electronic case report form (eCRF).

6.1. Study Treatment Administration

The individual medicinal products that are used in the study, as well as their designations and authorization status in the EU/EEA, are listed in Table 10.

Table 10: Designations and EU/EEA Authorization Status of Medicinal Products Used in the Study

Product	Designation	Authorization Status in the EU/EEA
Ciltacabtagene autoleucel	IMP	Authorized
Daratumumab	IMP	Authorized
Bortezomib	IMP	Authorized
Lenalidomide	IMP	Authorized
Dexamethasone	IMP	Authorized
Cyclophosphamide	AxMP	Authorized
Fludarabine	AxMP	Authorized

AxMP=auxiliary medicinal product; EEA=European Economic Area; EU=European Union; IMP=investigational medicinal product.

6.1.1. Criteria for Apheresis (all Cohorts Unless Otherwise Specified)

The investigator should contact the sponsor if evidence of rapid disease progression or suspected CNS involvement is observed between screening and apheresis. Subjects must meet the following criteria to proceed with apheresis:

- hemoglobin ≥8 g/dL (PRBC transfusion is permitted)
- platelet count ≥50×10^9/L (platelet transfusion is permitted)
- Negative pregnancy test for women of childbearing potential up to 72 hours prior to apheresis
- No supplemental oxygen use to maintain adequate oxygenation
- ECOG performance status grade of 0 or 1
- No investigational agents and anti-myeloma therapy within the timeframe as detailed in the exclusion criteria. For Cohort E, apheresis should occur after 1 or 2 cycles of D-VRd induction treatment and at least 21 days after the last dose of D-VRd in a cycle
- No focal radiotherapy as specified in the exclusion criteria, except palliative radiotherapy for symptomatic management of bone disease
- No evidence of serious active viral, bacterial, or uncontrolled systemic fungal infection. Subjects on anti-infective agents within 7 days prior to apheresis must receive approval to proceed from sponsor
- No major surgery as specified in the exclusion criteria
- No new arrhythmia or other cardiac adverse events unless controlled with medical management and approved by the medical monitor

For subjects who require a repeat apheresis, the following assessments should be collected before the second apheresis: weight, hematology laboratory assessments, chemistry laboratory assessments, pharmacokinetics, biomarker, and echocardiogram or MUGA (if clinically indicated).

If the second apheresis falls outside of the 28-day screening window, all screening assessments (except bone marrow collection) must be repeated (not applicable to Cohort E). Subjects in Cohort E may have a second apheresis after the screening period, as subjects in this cohort will begin induction treatment prior to apheresis. If a second apheresis results in a prolonged treatment-free interval between the 4th cycle of induction therapy and initiation of the conditioning regimen, a 5th cycle may be given with sponsor approval.

6.1.2. Administration of Conditioning Regimen (Cyclophosphamide and Fludarabine) (All Cohorts)

The site will be notified in writing by the Janssen team that manufacture of JNJ-68284528 has been completed. Each subject will receive a conditioning regimen of intravenous (IV) cyclophosphamide 300 mg/m^2 and fludarabine 30 mg/m^2 daily for 3 doses; sponsor approval must be obtained to modify the conditioning regimen schedule or dose. The dose of fludarabine should be reduced to 24 mg/m^2 for subjects with an eGFR of 30 to 70 mL/min/1.73m^2. JNJ-68284528 will be administered as a single infusion 5 to 7 days after the start of the conditioning regimen (the first day of conditioning is Day -7 to Day -5, and the day of JNJ-68284528 infusion is Day 1). Cyclophosphamide and fludarabine should be administered using administration procedures and supportive care according to the site's standard of care. JNJ-68284528 should be administered as described in the cell therapy product procedures manual (CTPPM) and investigational product preparation instructions (IPPI).

6.1.2.1. Criteria for Conditioning Regimen (Cyclophosphamide and Fludarabine Dosing) (All Cohorts)

The investigator should contact the sponsor if evidence of rapid disease progression or significant change in the subject's clinical status is observed before the start of the conditioning regimen. In addition, subjects must meet the following criteria to proceed with cyclophosphamide and fludarabine dosing:

- Transfusion support is permitted to maintain a hemoglobin of ≥8.0 g/dL as needed and platelets of ≥50 x 10^9/L until 3 days before the hematology laboratory test, preceding the start of the conditioning regimen.
- Myeloid growth factors are permitted at the investigator's discretion up to 1 day prior to the start of the conditioning regimen. Pegylated myeloid growth factors (ie, pegfilgrastim) are prohibited.
- eGFR ≥30 mL/min per 1.73 m^2. The dose of fludarabine should be reduced according to the guidance in Section 6.1.2.
- The investigator must contact the sponsor if the subject has any sign of a reduction in kidney function, which may be manifested by a clinically significant increase in serum creatinine, clinically significant decrease in eGFR, and/or a clinically significant decrease in urine output compared to baseline.
- ECOG performance status grade of 0 or 1.
- Aspartate aminotransferase (AST) ≤3 × upper limit of normal (ULN).

- Alanine aminotransferase (ALT) ≤3 × ULN.
- Total bilirubin ≤2.0 × ULN; except in subjects with congenital bilirubinemia, such as Gilbert syndrome (in which case direct bilirubin ≤1.5 × ULN is required).
- Negative pregnancy test for women of childbearing potential up to 72 hours prior to the first dose of the conditioning regimen.
- Subjects must not have received any antitumor therapy prior to conditioning in the time period outlined in the Exclusion Criteria.
- No active non-hematologic Grade 3 toxicity secondary to bridging therapy.
- No signs of infection. For subjects requiring systemic antimicrobial treatment or with temperature >38.0°C/100.4°F within 7 days prior to the first dose of conditioning regimen, he investigator must receive approval from the sponsor.
- No cumulative dose of corticosteroids equivalent to ≥70 mg prednisone within the 7 days prior to conditioning regimen dosing. The sponsor should be called for approval if a subject receives corticosteroids at a dose equivalent to >10 mg prednisone per day in the week prior to the start of the conditioning regimen.
- No live, attenuated vaccines within 6 weeks prior to conditioning regimen dosing.
- No supplemental oxygen use to maintain adequate oxygenation.
- No new arrhythmia or other cardiac adverse events unless controlled with medical management and approved by the medical monitor.
- Echocardiogram or MUGA scan for subjects who receive bridging therapy that includes agents with known cardiac toxicity, including but not limited to anthracyclines and carfilzomib (per prescribing information), verification of non-impaired cardiac function (LVEF ≥45%) should be performed after completion of bridging therapy and prior to the first dose of the conditioning regimen.

6.1.3. JNJ-68284528 Administration (All Cohorts)

JNJ-68284528 will be administered as summarized in Table 11.

Table 11: JNJ-68284528 Administration

Dose	JNJ-68284528 will be administered in one infusion. The target dose will be the RP2D, of 0.75 x 10^6 CAR-positive viable T cells/kg (range: 0.5-1.0 x 10^6 CAR-positive viable T cells/kg) as described in Section 3.3. The maximum total dose of cells to be administered to any subject is 1.0 x 10^8 CAR-positive viable T cells (ie, the maximum weight adjusted dose calculated for a 100-kg subject). Product will be manufactured based on weight at apheresis. If after apheresis and CAR-T cell preparation the quantity of JNJ-68284528 manufactured is not sufficient for dosing at the lower end of the dosing range, dosing for that subject may proceed, provided that a measurable quantity of JNJ-68284528 CAR-positive viable T cells that pass quality testing are generated.
Route/Regimen	JNJ-68284528 IV infusion is to be administered under the supervision of site staff. Refer to the IPPI for JNJ-68284528 infusion instructions.
Dosing Instructions	The actual dose for study treatment administration will be based on the subject's weight (kg) at apheresis.

Table 11: JNJ-68284528 Administration

Schedule of Administration	One intravenous infusion
Hospitalization Requirements	Dependent on the subject's status, medical history, concurrent comorbidities, adequate social support (full-time company of a competent adult) or potential risk factors for developing CAR-T toxicities, including CRS and neurotoxicity, it will be at the Investigator's discretion, patient's willingness, and Sponsor approval whether the subject: • will be admitted for inpatient monitoring from the day of infusion (Day 1) through Day 14 post JNJ-68284528 infusion (with potential discharge on Day 10 if there are no CRS, neurotoxicity or other clinically significant events), OR • will receive JNJ-68284528 infusion as an outpatient in close proximity (within 30 min) to the hospital, be monitored for outpatient follow-up and then be admitted for the required inpatient monitoring from Day 5 to Day 14 after JNJ-68284528 infusion (with potential discharge on Day 10 if there are no CRS, neurotoxicity or other clinically significant events) (Attachment 14) This evaluation should occur at the time of apheresis, prior to administration of the conditioning regimen and again prior to JNJ-68284528 infusion, and in consultation with approval from the sponsor to determine whether outpatient administration and follow-up after JNJ-68284528 infusion is suitable for a given subject and site. The patient must be clinically evaluated after JNJ-68284528 infusion for at least 6 hours before being discharged from the outpatient facility Subject to institutional guidance, local regulations, investigator discretion and sponsor approval, if outpatient JNJ-68284528 administration is being considered, please refer to Attachment 14 (JNJ-68284528 Outpatient Administration Guidelines) and Time and Events Schedule Table 1, Table 3, Table 5, and Table 6). For countries or specific hospitals which require hospitalization for all patients treated with cellular therapy, the more stringent requirements for hospitalization will prevail Subjects will be asked to remain within a 1-hour travel time of the hospital and in the company of a competent adult at all times for 1 additional week after hospital discharge, or until study Day 21, whichever is sooner. At the first sign of CRS (such as fever), subjects should be immediately hospitalized for evaluation. Further details regarding management of CRS are described in Table 23. Hospitalization is required for Grade 2, 3, or 4 CAR-T cell-related neurotoxicity (eg, ICANS) temporally associated to CRS. Further details regarding management of CAR-T cell related neurotoxicity are described in Table 24. Hospitalization for neurotoxicity that is not temporally associated with CRS, or any other neurologic adverse events, is at the discretion of the investigator
Vital Sign and Clinical Safety Monitoring	Monitor vital signs as indicated in the Time and Events Schedule (Table 1, Table 3, Table 5, and Table 6).

6.1.3.1. Exceptional Release Criteria

In the event a JNJ-68284528 product is manufactured that does not meet pre-specified product release criteria or protocol-defined maximum total cell dose, the sponsor will evaluate the risk/benefit for administration of the affected product and determine if the supply of the product to the treating physician could be considered. In the event the supply of the affected product is deemed appropriate by the Sponsor and requested by the investigator, the investigator will discuss with the subject the potential risks and benefits of receiving the affected product and treatment alternatives. If required, approval from the relevant local health authorities for use of the product will be obtained in compliance with local regulations regarding notification and approval. Products provided through this exceptional release or similar process that exceed the protocol maximum dose will not qualify for overdose reporting.

6.1.3.2. Evaluation Prior to Administration of JNJ-68284528 (All Cohorts)

JNJ-68284528 Dosing Delays:

Subjects will be evaluated for safety on the day of JNJ-68284528 infusion. If a significant health status change (eg, clinical deterioration, rapidly progressing disease, etc.) occurs following the start of the conditioning regimen (see Section 6.1.2), the investigator must contact the sponsor prior to dosing.

Infusion of JNJ-68284528 must be delayed if any of the following events occur:

- Signs of active infection. Do not administer JNJ-68284528 to patients with active infection. For subjects requiring systemic anti-microbial treatment, or with temperature ≥38.0°C/100.4°F Celsius within 48 hours before JNJ-68284528 infusion, investigator must consult with the sponsor prior to dosing.
- Grade ≥3 non-hematologic toxicities of cyclophosphamide and fludarabine conditioning (except for Grade 3 nausea, vomiting, diarrhea, or constipation). Investigator must consult with the sponsor prior to dosing.

If resolution of these events to Grade ≤1 takes more than 14 days, the conditioning regimen should be re-administered (cyclophosphamide 300 mg/m^2 and fludarabine 30 mg/m^2 daily for 3 days) after a minimum of 21 days following the first dose of the first conditioning regimen (cyclophosphamide and fludarabine).

6.1.3.3. Pre-JNJ-68284528 Infusion Supportive Therapy (All Cohorts)

Prior to JNJ-68284528 infusion, subjects should receive premedication as noted below (Table 12). Corticosteroids should not be used during pre-infusion.

Table 12: Pre-infusion Medications

Medication	Dose	Administration
Antihistamine	diphenhydramine (25 -50 mg IV or PO) or equivalent	Oral – administer 1 hour (±15 minutes) prior to JNJ-68284528 infusion Or IV– start infusion 30 minutes (±15 minutes) prior to JNJ-68284528 infusion
Antipyretic	acetaminophen (650 mg to 1,000 mg) or equivalent	Oral or IV - administer 30 minutes (±15 minutes) prior to JNJ-68284528 infusion

6.1.4. Lenalidomide (Cohort D)

Starting with the 6th subject enrolled in Cohort D (based on DMC recommendation), lenalidomide will be self-administered at a starting dose based on hematologic parameters (Table 13) orally each day on Days 1 through 28 (continuously) of each 28-day cycle until confirmed PD, unacceptable toxicity, or 2 years after initiating lenalidomide treatment (post JNJ-68284528 infusion), whichever occurs first. The first 5 subjects receiving lenalidomide post-JNJ-68284528 will be staggered similarly as the first 5 subjects without lenalidomide, ie, an observation period of at least 4 weeks will be applied between administration of JNJ-68284528 to the 6th through 10th subject to allow for subject 28-day safety review prior to next subject dosing. After these 5 subjects receive at least 1 cycle of lenalidomide post-JNJ-68284528, the DMC will reconvene to review safety and any other relevant data. Based on recommendation of the DMC, subsequent subjects in Cohort D may be permitted to enroll and receive JNJ-68284528 followed by lenalidomide without a staggered approach. Women of childbearing potential are required to practice 2 methods of reliable birth control simultaneously beginning 4 weeks prior to receiving lenalidomide.

- After apheresis and prior to administration of cyclophosphamide and fludarabine (conditioning regimen prior to JNJ-68284528 infusion) subjects will receive 1 cycle of lenalidomide at a dose of 10 mg per day upon adequate hematologic recovery from ASCT (absolute neutrophil count [ANC] $\geq$ 1 x 10^9/L and platelet count $\geq$ 75 x 10^9/L). Additional cycles of lenalidomide may be given, with sponsor approval, if timing to infusion of JNJ-68284528 is delayed. Alternative bridging therapy in addition, or instead of lenalidomide, is also permitted per sponsor approval. Additionally, if an alternative bridging therapy is used, assessments to address lenalidomide toxicity will not be required in Table 3 (footnote v). The purpose of the bridging therapy is to reduce the myeloma disease burden prior to lymphodepletion chemotherapy and JNJ-68284528 administration.
- After infusion of JNJ-68284528: Applicable subjects (after the first 5 subjects who will receive JNJ-68284528 alone) will initiate lenalidomide a minimum of 21 days post JNJ-68284528 after resolution of cytokine release syndrome (CRS) or neurologic toxicities. The initial dose of lenalidomide will depend on the level of hematologic recovery. Additionally, initiation of lenalidomide treatment is dependent on no additional safety concerns by investigator or sponsor.

– Criteria for lenalidomide administration after JNJ-68284528 infusion are summarized in Table 13.

Table 13: Criteria for Lenalidomide Administration after JNJ-68284528 Infusion – Cohort D

Hematologic Parameter			
ANC		**Platelet Count**	**Starting Dose of Lenalidomide**
≥1.0 x 10^9/L	AND	≥75 x 10^9/L	10 mg daily
0.75 x 10^9/L to <1.0 x 10^9/L	AND	≥50 x 10^9/L	Start 5 mg daily, increase to 10 mg per day when ANC is ≥1.0 x 10^9/L and the platelet count is ≥75 x 10^9/L
≥0.75 x 10^9/L	AND	50 x 10^9/L to <75 x 10^9/L	
<0.75 x 10^9/L	OR	<50 x 10^9/L	Lenalidomide must be held if either one of these criteria are present

Starting dose of lenalidomide for subjects with renal impairment is provided in Table 16.

Continuation of lenalidomide treatment is dependent on no additional safety concerns by investigator or sponsor.

- If well tolerated after 3 cycles of lenalidomide treatment at 10 mg, the dose of lenalidomide may be increased to 15 mg per day at the discretion of the investigator.
- For subjects with an eGFR <60 mL/min/1.73m^2, the lenalidomide dose should be reduced to 5 mg per day. Other dose adjustments should be performed based on local prescribing information and in alignment with the guidance provided in Table 16.

Lenalidomide should be taken orally at about the same time each day, either with or without food. Lenalidomide capsules should be swallowed whole with water. The capsules should not be opened, broken, or chewed. Lenalidomide pill counts should be performed every cycle (ie, every 28 days).

Management guidelines for potential risks of lenalidomide, including dose adjustment, are provided in Table 14 (dose modification guidelines), Table 15 (dose reduction steps) and Table 16 (dosing for subjects with renal impairment).

Table 14: Dose Modification Guidelines for Lenalidomide

Toxicity	Lenalidomide Dose Modification
Neutropenia[a] (any of the following): ANC <0.5 x 10^9/L Return to ANC ≥0.5 x 109/L when neutropenia is the only observed toxicity	Interrupt lenalidomide treatment. Resume lenalidomide at 1 dose level lower once daily.
For each subsequent drop below <0.5 x 10^9/L Return to ANC ≥0.5 x 10^9/L	Interrupt lenalidomide treatment. Resume lenalidomide at next lower dose level once daily
Thrombocytopenia Platelet count <30 x 10^9/L Platelet count return to ≥30 x 10^9/L	Interrupt lenalidomide treatment. Resume lenalidomide at 1 dose level lower once daily.
For each subsequent drop below 30 x 10^9/L Platelet count return to ≥30 x 10^9/L	Interrupt lenalidomide treatment. Resume lenalidomide at next lower dose level once daily
Grade 2 or 3 skin rash	Lenalidomide interruption or discontinuation should be considered at the investigator's discretion
Angioedema, Grade 4 rash, exfoliative or bullous rash, or if Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN) or Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) is suspected or confirmed Progressive Multifocal Leukoencephalopathy (PML)	Permanently discontinue lenalidomide.
Other Grade 3 or 4 toxicities judged to be related to lenalidomide[b]	Interrupt lenalidomide treatment and restart at next lower dose level when toxicity has resolved to ≤ Grade 2 at the investigator's discretion. OR Consider modification of dosing schedule to 3 weeks of lenalidomide therapy followed by one week rest for each 28 day cycle.

[a] If neutropenia is the only toxicity at any dose level, add G-CSF and maintain the dose level of lenalidomide, at the investigator's discretion.

[b] Adjustments based on other grade 1-2 toxicities (non-hematologic) may be made at investigator's discretion based on standard of care.

Table 15: Lenalidomide Dose Reduction Steps

	Starting dose (5 mg)	Starting dose (10 mg)	If dose increased (15 mg)
Dose level -1	5 mg (Days 1-21 every 28 day cycle)	5 mg (Days 1-28)	10 mg (Days 1-28)
Dose level -2	Not applicable	5 mg (Days 1-21 every 28-day cycle)	5 mg (Days 1-28)
Dose level -3	Not applicable	Not applicable	5 mg (Days 1-21 every 28-day cycle)

Table 16: Lenalidomide Starting Dose After JNJ-68284528 Infusion for Subjects with Renal Impairment

Renal function (eGFR) / MDRD	Starting Dose[a]
> 60 mL/min/1.73m^2	10 mg once daily
30 ≤ eGFR ≤ 60 mL/min/1.73m^2	5 mg once daily
eGFR < 30 mL/min/1.73m^2, not requiring dialysis	2.5 mg once daily
eGFR < 30 mL/min/1.73m^2, *requiring dialysis*	2.5 mg once daily. On dialysis days, the dose should be administered following dialysis

[a] Subsequent dose increase or decrease based on individual patient tolerance.

Management guidelines for potential risks of lenalidomide, including dose adjustment, are provided in the product labeling (REVLIMID/lenalidomide USPI and SmPC).

6.1.5. Cohort E: Induction and Post JNJ-68284528 Therapy

Subjects in Cohort E will receive D-VRd induction therapy prior to the conditioning therapy and JNJ-68284528 infusion. Subjects will receive lenalidomide consolidation treatment for 2 years post-JNJ-68284528 infusion or until confirmed PD or unacceptable toxicity, whichever occurs first.

Subjects who prematurely discontinue the D-VRd induction treatment (for toxicity or any other reason) may still proceed to receive lymphodepletion and CAR-T therapy after agreement with the sponsor. Subjects receiving lenalidomide consolidation treatment may discontinue if required due to development of toxicities related lenalidomide.

6.1.5.1. Cohort E: D-VRd Induction Treatment

For subjects participating in Cohort E, details pertaining to D-VRd induction therapy are included in Table 17. Sponsor approval is required for any modification to dosing of the D-VRd induction regimen. Additional cycles of D-VRd may be given with sponsor approval if an unanticipated delay in JNJ-68284528 occurs.

Table 17: D-VRd Induction Therapy

	D-VRd Induction therapy (4 Cycles, 21 days per cycle)
Dexamethasone[a] 20 mg PO or IV	On Days 1, 2, 4, 5, 8, 9, 11,12
Bortezomib 1.3 mg/m^2 SC	On Days 1, 4, 8, and 11 of each cycle
Lenalidomide[b] 25 mg PO	On Days 1-14 of 21-day cycle
Daratumumab[c] 1800 mg SC	On Days 1, 8, 15 for Cycles 1-2 [weekly] then Day 1 of Cycles 3-4

IV=intravenous; PO=oral; SC=subcutaneous

[a] Dispense on Induction Day 1 for self-administration (on daratumumab dosing days, dexamethasone pre-medication for daratumumab injection will replace the daily dose of dexamethasone).

[b] Dispense on Induction Day 1 of each cycle for self-administration

[c] Refer to SIPPM or approved prescribing information for drug preparation and administration recommendations

6.1.5.1.1. Daratumumab

Daratumumab-IV infusion requires a large volume (500 mL to 1000 mL) of infusate, resulting in a median infusion time for the first infusion of 7 hours. Subsequent infusions are approximately 3 to 4 hours. To shorten the infusion time and decrease the risk of infusion-related reactions (IRRs), a technology based on a recombinant human hyaluronidase PH20 (rHuPH20) was developed to facilitate subcutaneous (SC) administration of protein therapeutics. rHuPH20 is the active ingredient of the commercial product Hylenex® recombinant (hyaluronidase human injection), which was approved for use in the US in December 2005. Daratumumab has been administered in combination with rHuPH20 in a Phase 1 study (54767414MMY1004; NCT02519452). In some regions, rHuPH20 is also approved in combination with protein therapeutics for SC administration, such as HyQvia (Immune globulin infusion 10% [human] with recombinant human hyaluronidase), as well as anticancer medications such as Herceptin® SC (trastuzumab) and MabThera® SC (rituximab). Only daratumumab SC will be used in this cohort. Daratumumab SC (trade name, DARZALEX FAST-PRO) was approved by the US FDA in May 2020 and the European Commission in June 2020.

6.1.5.1.1.1. Daratumumab Subcutaneous Preparation

Dara-SC will be provided as a fixed-dosed (1800 mg), combination drug product containing rHuPH20 drug substance (2000 U/mL) and daratumumab drug substance (120 mg/mL) in a single vial. Manuals with detailed descriptions for preparation and administration of daratumumab will be supplied to each pharmacy and site.

6.1.5.1.1.2. Daratumumab Administration

Daratumumab (1800 mg) will be administered by SC injection by manual push over 3-5 minutes in the abdominal subcutaneous tissues in left/right locations, alternating between individual doses. The volume of the SC solution will be 15 mL for the 1800 mg dose. Refer to the locally approved label (USPI, SMPC, or equivalent) or IPPI for additional guidance on SC administration of Dara-SC, as applicable. All subjects will be observed for at least 6 hours after the end of the SC injection during Cycle 1 Day 1 and, if deemed necessary by the investigator, after subsequent injections. Reasons for continued observation on subsequent daratumumab injections may include but are not limited to the following: subjects with a higher risk of respiratory complications (eg, subjects with mild asthma or subjects with COPD who have an FEV1 <80% at screening or developed FEV1 <80% during the study without any medical history), subjects with IRR with first injection of study drug, and subject with a decreased condition on day of dosing compared to prior dosing day. The dose of daratumumab will remain constant throughout the study.

Daratumumab will be administered weekly in Cycles 1-2, every 3 weeks in Cycles 3-4. Every effort should be made to keep subjects on the planned dosing schedule see Time and Events Schedules: Cohort E (Table 5 and Table 6) for acceptable window for treatment. Cycles 1-4 are 21 days.

All daratumumab administrations will be in an outpatient setting. Subjects will receive pre-injection medications and post-injection medications as outlined in Section 6.1.5.3.

As noted in the Time and Events Schedule (Table 5), vital signs should be monitored for all cycles before, and after the administration of daratumumab. Additional vital sign assessments should be performed as clinically indicated following administration If the subject experiences any significant medical event, then the investigator should assess whether the subject should stay overnight for observation. If the subject has not experienced a significant medical event but is hospitalized overnight only for observation, then the hospitalization should not be reported as a serious adverse event (Section 12.3.2).

On dosing days where the VRd combination is given with daratumumab they should be administered in the following order: lenalidomide, dexamethasone, daratumumab, and bortezomib. Daratumumab will be manufactured and provided under the responsibility of the sponsor. Refer to the daratumumab locally approved label (USPI, SmPC, or equivalent) or IB (as applicable) for a list of excipients.

Daratumumab must be held if any of the following criteria are met at any time, to allow for recovery from toxicity, regardless of relationship to study drug. Daratumumab administration should only be re-initiated after resolution to Grade 2 or better:

- Grade 4 hematologic toxicity, except for Grade 4 lymphopenia
- Grade 3 or higher thrombocytopenia
- Febrile neutropenia
- Neutropenia with infection, of any grade
- Grade 3 or higher non-hematologic toxicities with the following exceptions:
  - Grade 3 nausea that responds to antiemetic treatment within 7 days
  - Grade 3 vomiting that responds to antiemetic treatment within 7 days
  - Grade 3 diarrhea that responds to antidiarrheal treatment within 7 days
  - Grade 3 fatigue that was present at baseline or that lasts for <7 days after the last administration of daratumumab
  - Grade 3 asthenia that was present at baseline or that lasts for <7 days after the last administration of daratumumab

Any adverse event deemed to be related to daratumumab that requires a dose hold of more than 28 days will result in permanent discontinuation of daratumumab unless, upon consultation with the sponsor and the review of safety and efficacy, continuation is agreed upon.

A daratumumab dose held for more than 3 days from the per-protocol administration date for any reason other than toxicities suspected to be related to daratumumab should be brought to the attention of the sponsor at the earliest possible time. Patients missing ≥3 consecutive planned doses of study drug for reasons other than toxicity should be withdrawn from treatment, unless, upon consultation with the sponsor and the review of safety and efficacy, continuation is agreed upon.

6.1.5.1.2. Bortezomib

The amount (in mg) of bortezomib to be administered will be determined by body surface area, calculated per a standard nomogram, there is no maximum dose (Mosteller 1987). The calculated dose of bortezomib may be rounded to the nearest tenth of a mg (or as per institutional practice).

Subjects will receive 1.3 mg/m^2 bortezomib as a subcutaneous injection twice weekly on Days 1, 4, 8, and 11 of each 21-day cycle for Cycles 1-4. For subjects who experience injection-site reactions at the subcutaneous administration site, bortezomib may be administered by IV injection (see local prescribing information). Subjects will not receive bortezomib after the first 4 cycles of treatment. On treatment days when both bortezomib and daratumumab are administered, bortezomib must be administered after the daratumumab administration. If a subject's weight changes by more than 10% from baseline, the dose of bortezomib will be re-calculated. Bortezomib dosing may be delayed up to 48 hours, however subsequent doses must be adjusted to account for the delay. Note that there should be approximately 3 days between doses of bortezomib. Skipped doses of bortezomib will not be made up later in the cycle. For subjects with unacceptable toxicity at the local injection-site despite dose modifications or change in injection concentration, bortezomib can be administered intravenously as a 3 to 5 sec bolus injection. Refer to local prescribing information for further details on either SC or IV administration.

6.1.5.1.3. Lenalidomide

In Cycles 1 through 4, lenalidomide will be self-administered at a dose of 25 mg orally each day on Days 1 through 14 of each 21-day cycle for subjects with CrCl ≥60 mL/min. Lenalidomide will be continued until disease progression or unacceptable toxicity whichever occurs first. See Table 18, Renal Impairment for lenalidomide dose adjustments in subjects with renal impairment. On daratumumab administration days, it is recommended that lenalidomide should be administered either prior to or at the same time (preferred) as pre-injection medication. Lenalidomide should be taken as a single dose at the same time daily. If a daily lenalidomide dose is missed, it may be taken if <12 hours have elapsed since the time that it should have been taken. Otherwise, the missed lenalidomide dose should be skipped and not be made up for. Lenalidomide can be taken with or without food. Breaking or dividing the lenalidomide capsule is strongly discouraged.

6.1.5.1.4. Dexamethasone

Dexamethasone (or steroid equivalent in accordance with local standards; see Attachment 12 for conversion table) will be self-administered orally, 20 mg on Days 1, 2, 4, 5, 8, 9, 11, 12 of each 21-day cycle for Cycles 1-4. For subjects older than 75 years or underweight (BMI <18.5), the dexamethasone dose may be administered at a dose of 20 mg on days 1, 4, 8, and 11.

6.1.5.1.5. Dose Modification Guidelines for Bortezomib, Lenalidomide, and Dexamethasone

Dose modification guidelines for bortezomib, lenalidomide, and dexamethasone are provided in Table 18.

Note that the dose modifications in Table 18 are suggested, but physician discretion and clinical judgment should prevail.

Sponsor approval is required for any modification to dosing of the D-VRd induction regimen.

Table 18: Dose Modification Guidelines for Bortezomib, Lenalidomide, and Dexamethasone

Body System	NCI-CTC Adverse Event and or Symptom and Category	Bortezomib[g]	Lenalidomide[h]	Dexamethasone[i]
Allergic reactions	Allergic reaction or hypersensitivity Grade 2 OR 3	Hold all therapy. If the toxicity resolves to ≤ Grade 1, restart VRd. Reduce by 1 dose-level the suspected medication(s) AND implement appropriate anti-allergic prophylaxis therapy. If the reaction was anaphylactic in nature, do not resume VRd. NOTE: If the reaction was cutaneous in nature, refer to the cutaneous category below.		
	Allergic reaction or hypersensitivity Grade 4	Discontinue VRd.		
Cardiovascular	Fluid Retention (ie, edema) >Grade 3 (limiting function and unresponsive to therapy or anasarca)			Administer diuretics as needed and decrease dexamethasone dose by 1 dose-level; if edema persists despite above measures, decrease dose another dose-level. Permanently discontinue dexamethasone if symptoms persist despite second dose reduction.
Constitutional	Fatigue[a] ≥ Grade 3 (ie, severe fatigue interfering with activities of daily living)	Hold the dose until resolved to Grade ≤2. Consider reduction of lenalidomide or bortezomib by 1 dose-level or change to bortezomib dosing once per week[j].		
Cutaneous	Non-blistering rash Grade 2	Hold bortezomib therapy. Begin treatment with antihistamines and/or low-dose steroids as per institutional practice. If the toxicity resolves to ≤ Grade 1, reduce dose by 1 level and restart bortezomib. Restart with lower concentration formulation. If recurrent consider IV bortezomib.	Consider holding lenalidomide.	

Table 18: Dose Modification Guidelines for Bortezomib, Lenalidomide, and Dexamethasone

Body System	NCI-CTC Adverse Event and or Symptom and Category	Bortezomib[g]	Lenalidomide[h]	Dexamethasone[i]
	Non-blistering rash ≥ Grade 3 or 4	Hold bortezomib and lenalidomide therapies. Begin treatment with antihistamines and/or low-dose steroids as per institutional practice. If the toxicity resolves to ≤ Grade 1, reduce dose by 1 level and restart bortezomib and lenalidomide and continue antihistamines and/or low-dose steroids as per institutional practice. Restart with lower concentration formulation. If recurrent consider IV bortezomib. For Grade 4 toxicity discontinue bortezomib and lenalidomide permanently.		
	Desquamating (blistering) rash- any grade or erythema multiform ≥ Grade 3	Discontinue bortezomib and lenalidomide permanently. Hold other therapies. Begin treatment with antihistamines and/or low-dose steroids as per institutional practice. If the toxicity resolves to ≤ Grade 1, restart other medications.		
Gastrointestinal	Constipation[b] ≥ Grade 3	Hold bortezomib therapy. Upon recovery to ≤ Grade 1, restart bortezomib at 1 dose-reduced level.		
	Diarrhea[c] ≥ Grade 3	Hold bortezomib and consider loperamide therapy. Upon recovery to ≤ Grade 1, restart bortezomib at 1 dose-reduced level.		
	Dyspepsia, gastric or duodenal ulcer, gastritis Grade 1-2 (requiring medical management)			Treat with histamine-2 blockers, sucralfate, or proton pump inhibitor. If symptoms persist despite above measures, decrease dexamethasone dose by 1 dose-level.

Table 18: Dose Modification Guidelines for Bortezomib, Lenalidomide, and Dexamethasone

Body System	NCI-CTC Adverse Event and or Symptom and Category	Bortezomib[g]	Lenalidomide[h]	Dexamethasone[i]
	Dyspepsia, gastric or duodenal ulcer, gastritis ≥ Grade 3 (requiring hospitalization or surgery)			Hold dexamethasone and consider treatment with histamine-2 blockers, sucralfate, or proton pump inhibitor. Restart and reduce dexamethasone by 1 dose level if symptoms are adequately controlled. If symptoms persist despite above measures, permanently discontinue dexamethasone.
	Acute Pancreatitis			Permanently discontinue dexamethasone.
Hematological	Neutropenia Grade 3 (without complications)	No dose reduction required of bortezomib. Consider treatment with G-CSF.	Hold therapy with lenalidomide until recovery to baseline OR ≤ Grade 2. Consider G-CSF support. Upon recovery if isolated neutropenia, maintain lenalidomide at current dose level. If other hematologic toxicities present reduce lenalidomide by 1 dose level. Maintain bortezomib at current dose. If recurrent episode, reduce lenalidomide by 1 dose-level.	

Table 18: Dose Modification Guidelines for Bortezomib, Lenalidomide, and Dexamethasone

Body System	NCI-CTC Adverse Event and or Symptom and Category	Bortezomib[g]	Lenalidomide[h]	Dexamethasone[i]
	Neutropenia associated with fever (≥38.5ºC): Grade 3 or neutropenia Grade 4	Hold therapy with all drugs until recovery to baseline OR ≤ Grade 2. Consider G-CSF support. Upon recovery if isolated neutropenia, maintain lenalidomide at current dose level. If other hematologic toxicities present reduce lenalidomide by 1 dose level. Maintain bortezomib at current dose. If recurrent episode, reduce lenalidomide and bortezomib by 1 dose-level.		
	Thrombocytopenia Grade 3 (without complications)	No dose reduction required for bortezomib.	Reduce lenalidomide by 1 dose-level for the remainder of the cycle.	
	Platelet count ≤30 x 10^9/L or ANC ≤0.75 x 10^9/L on a bortezomib dosing day	Hold bortezomib dose.		
	Platelet count <25,000/μL (ie, Grade 4) or Grade 3 thrombocytopenia with bleeding	Hold therapy with all drugs until recovery to baseline OR ≤Grade 2. Upon recovery, reduce bortezomib 1 dose level, hold lenalidomide for remainder of the cycle and decrease by 1 dose level at start of next cycle.		
Infection	Herpes Zoster[d] activation or reactivation ANY grade	Hold ALL therapies until lesions are dry. If not already underway, begin antiviral treatment. Once the infection is resolved all medications can be restarted without a dose reduction; however, continued antiviral prophylaxis is required.		
Musculoskeletal	Muscle weakness >Grade 2 (symptomatic and interfering with function +/- interfering with activities of daily living)			Decrease dexamethasone dose by 1 dose-level. If weakness persists despite above measures, decrease dose by 1 *further* dose-level. If symptoms *still* persist, permanently discontinue dexamethasone.
Metabolic	Hyperglycemia ≥ Grade 3			Treatment with insulin or oral hypoglycemics. If uncontrolled despite above measures, decrease dose by 1 dose-level until levels are satisfactory.

Table 18: Dose Modification Guidelines for Bortezomib, Lenalidomide, and Dexamethasone

Body System	NCI-CTC Adverse Event and or Symptom and Category		Bortezomib[g]	Lenalidomide[h]	Dexamethasone[i]
Neurological[e]	Peripheral Neuropathy (Sensory or Motor) and/or Neuropathic Pain	Grade 1 (paresthesias and/or loss of reflexes) without pain or loss of function	No action required, however, changing frequency to weekly[j] may be considered based on clinical judgement and/or institutional practice.		
		Grade 1 with pain or Grade 2 (interfering with function but not with activities of daily living)	Change schedule to once per week[j] or reduce bortezomib by 1 dose-level (maximum dose of 1.0 mg/m^2)		
		Grade 2 with pain or Grade 3 (interfering with activities of daily living)	Hold bortezomib until toxicity resolves to <Grade 2. When toxicity resolves, reinitiate with a reduction by 1 dose-level (maximum dose of 0.7 mg/m^2 once weekly[j]).		
		Grade 4 (permanent sensory loss that interferes with function) and/or severe autonomic neuropathy	Discontinue bortezomib permanently.		
Neuro-psychological	Confusion or mood alteration >Grade 2 (interfering with function ± interfering with activities of daily living)				Hold dexamethasone until symptoms resolve. Restart with 1 dose-level reduction. If symptoms persist despite above measures, permanently discontinue dexamethasone.
Thromboembolic	Venous and /or pulmonary thrombo-embolism ≥ Grade 3 [Deep vein thrombosis or cardiac thrombosis intervention indicate; eg: anticoagulation, lysis, filter, invasive procedure.]			Stop until toxicity resolves and, if not already given, start anticoagulation therapy. Restart lenalidomide and dexamethasone at full dose after adequate anticoagulation.	

Table 18: Dose Modification Guidelines for Bortezomib, Lenalidomide, and Dexamethasone

Body System	NCI-CTC Adverse Event and or Symptom and Category	Bortezomib[g]	Lenalidomide[h]	Dexamethasone[i]
Renal Impairment	Moderate renal impairment-CrCl[f] 30-59 mL/min		Lenalidomide should be given at a dose of 10 mg daily	
	Severe renal impairment-CrCl[f] <30 mL/min (not requiring dialysis)		Lenalidomide should be given at a dose of 15 mg every 48 hrs	
	End-stage renal disease-CrCl[f] <30 mL/min (requiring dialysis)		Lenalidomide should be given at a dose of 5 mg daily. Administer dose after dialysis.	
Other toxicities	Any reported ≥ Grade 3	Determine drug attribution of the toxicity and hold the therapy(ies) as appropriate. If toxicity resolves to ≤Grade 1, resume therapy with 1 level of dose reduction for suspect drug.		

Abbreviations: ANC=absolute neutrophil count; CrCl=creatinine clearance; IV=intravenous; NCI-CTCAE=National Cancer Institute Common Terminology Criteria for Adverse Events; G-CSF=Granulocyte colony stimulating factor; VRd=VELCADE, lenalidomide, and dexamethasone

[a] Determine if fatigue is possibly not medication-related but due to an underlying cause (eg, infection, progression of disease, diarrhea, anemia, depression) and treat these symptoms/causes as appropriate.

[b] Prior to dose reduction of medications, consider/eliminate other possible causes of constipation.

[c] Prior to dose reduction of medications, consider/eliminate other possible causes (ie, bacterial or viral infections) of diarrhea.

[d] In the event that a subject is already receiving antiviral treatment at the time of the Herpes Zoster activation, consider switching to or adding another antiviral agent.

[e] The neurotoxicity-directed questionnaire is a useful tool for determining the presence and intensity of neuropathic pain and/or peripheral neuropathy from the subject's perspective. Neuropathic symptoms are more prominent than abnormalities on the clinical examination. After the subject completes the neurotoxicity-directed questionnaire, the questionnaire should be reviewed to assist with the evaluation of the onset and intensity of peripheral neuropathy and other neurotoxicities that may require intervention or dose modification.

[f] CrCl = creatinine clearance. Estimated by creatinine clearance as calculated by the Cockcroft-Gault formula and adjusted for body weight in subjects with a body mass index >30 kg/m^2. The eGFR (MDRD) or CKD-epi formulas can also be utilized to assess renal function.

[g] See Table 19 for dose levels

[h] See Table 20 for dose levels

[i] See Table 21 for dose levels

[j] Weekly dosing, eg on Days 1, 8, and 15.

Table 19: Dose Modifications for Bortezomib

Starting Dose	First Dose Reduction	Second Dose Reduction	Third Dose Reduction
Bortezomib 1.3 mg/m^2	Bortezomib 1.0 mg/m^2	Bortezomib 0.7 mg/m^2	Discontinue bortezomib

Table 20: Dose Modifications for Lenalidomide

Starting Dose	First Dose Reduction	Second Dose Reduction	Third Dose Reduction	Fourth Dose Reduction	Fifth Dose reduction
Lenalidomide 25 mg	Lenalidomide 20 mg	Lenalidomide 15 mg	Lenalidomide 10 mg	Lenalidomide 5 mg	Discontinue Lenalidomide

Table 21: Dose Modifications for Dexamethasone

First Dose Reduction	Second Dose Reduction	Third Dose Reduction
Reduce dexamethasone by 50% from starting dose	Skip dexamethasone on days when daratumumab is not given	Discontinue dexamethasone

6.1.5.2. Cohort E: Lenalidomide Consolidation Treatment

After infusion of JNJ-68284528, all subjects in Cohort E will initiate lenalidomide a minimum of 21 days post JNJ-68284528 after resolution of CRS or neurologic toxicities associated with JNJ-68284528. Initiation of lenalidomide treatment is dependent on no additional safety concerns by investigator or sponsor. The initial dose of lenalidomide will depend on the level of hematologic recovery.

- Criteria for lenalidomide administration after JNJ-68284528 infusion are summarized in Table 22.

Table 22: Criteria for Lenalidomide Administration after JNJ-68284528 Infusion – Cohort E

Hematologic Parameter			
ANC		Platelet Count	Starting Dose of Lenalidomide
≥1.0 x 10^9/L	AND	≥75 x 10^9/L	10 mg daily
0.75 x 10^9/L to <1.0 x 10^9/L	AND	≥50 x 10^9/L	Start 5 mg daily, increase to 10 mg per day when ANC is ≥1.0 x 10^9/L and the platelet count is ≥75 x 10^9/L
≥0.75 x 10^9/L	AND	50 x 10^9/L to <75 x 10^9/L	
<0.75 x 10^9/L	OR	<50 x 10^9/L	Lenalidomide must be held if either one of these criteria are present

ANC=absolute neutrophil count

- For subjects with an eGFR <60 mL/min/1.73m^2, the lenalidomide dose should be reduced to 5 mg per day. Other dose adjustments should be performed based on local prescribing information consistent with the protocol guidance provided in Table 16.
- Continuation of lenalidomide treatment is dependent on no additional safety concerns by investigator or sponsor.
  - If well tolerated after 3 cycles of lenalidomide treatment, the dose of lenalidomide may be increased to 15 mg per day at the discretion of the investigator.
  - further titration at investigator discretion, by 5 mg increments may proceed after 6 cycles until a maximum dose of 25 mg daily (eg, lenalidomide Cycle 1: 10 mg, Cycle 2: 10 mg, Cycle 3: 10 mg, Cycle 4: 15 mg, Cycle 5: 15 mg, Cycle 6: 15 mg, Cycle 7: 20 mg, Cycle 8: 25 mg).

Lenalidomide will be self-administered orally each day on Days 1 through 21 (21 days on, 7 days off) of each 28-day cycle until confirmed PD, unacceptable toxicity, or 2 years after JNJ-68284528 infusion, whichever occurs first. Lenalidomide will be dispensed on Day 1 of each cycle for self-administration.

The initial dose of lenalidomide will depend on the level of hematologic recovery. The criteria for lenalidomide administration after JNJ-68284528 infusion and the management guidelines for potential risks of lenalidomide, including dose adjustment, are described in Table 14 (dose

modification guidelines), Table 20 (dose reduction steps) and Table 16 (dosing for subjects with renal impairment).

6.1.5.3. Cohort E: Medications Related to Daratumumab Dosing

To decrease the risk of infusion-related reactions, all subjects will receive the following medications 1 to 3 hours prior to daratumumab administration:

- Paracetamol (acetaminophen) 650-1000 mg IV or orally (PO).
- An antihistamine: diphenhydramine 25-50 mg IV or PO, or equivalent (see Attachment 25 for a list of antihistamines that may be used). Avoid IV promethazine.
- Dexamethasone 20 mg IV or oral
  - The dexamethasone 20 mg oral or IV dose administered as a preinjection medication on daratumumab injection days, replaces the oral dexamethasone dose for that day (if applicable).
  - If adverse events due to steroid during pre-medication for consolidation therapy with daratumumab. A reduction to 10 mg IV or PO dexamethasone will be permitted for preinjection medication. If dexamethasone is contraindicated due to adverse events, the sponsor should be consulted regarding before continuing daratumumab dosing.
- Substitutions for dexamethasone are allowed (refer to Attachment 12).
- Predose administration of a leukotriene inhibitor (montelukast 10 mg PO) is recommended on Cycle 1 Day 1 of induction therapy. The leukotriene inhibitor may be administered up to 24 hours before the daratumumab dose.

If necessary, due to timing constraints, all PO pre-administration medications may be administered outside of the clinic on the day of the injection, provided they are taken 1-3 hours before the daratumumab dose.

Prophylaxis for herpes zoster reactivation is recommended (see Section 8.1).

In addition, for any patients with a history of chronic obstructive pulmonary disease, consider prescribing post-infusion medications such as short and long-acting bronchodilators, and inhaled corticosteroids.

6.2. Management Guidelines for Potential Risks (All Cohorts)

6.2.1. Management of Cytokine Release Syndrome

In the Legend-2 study, CRS was reported in approximately 92% of subjects who received LCAR-B38M CAR-T cells. Most CRS events were Grade 1 or Grade 2. All events of CRS started with fever after the infusion of CAR-T therapy (See Section 1.1.5). Of the subjects who developed CRS, approximately 84% experienced transiently increased aspartate aminotransferase (AST). AST increase was Grade 3 or Grade 4 in 31% and 6% of subjects with CRS, respectively. If CRS is suspected, subjects should be monitored for increased AST, and consumptive coagulopathy, indicated by an increase in D-dimers and a decrease in fibrinogen if CRS is suspected.

Symptoms indicative of CRS may include, but are not limited to, fever (with or without rigors), arthralgia, nausea, vomiting, tachypnea, hypoxia, tachycardia, hypotension, headache, confusion, tremor, delirium, dyspnea, pulmonary edema, and capillary leak (Lee 2014). Potentially life-threatening complications of CRS may include cardiac dysfunction, adult respiratory distress syndrome, neurologic toxicity, renal failure, hepatic failure, and disseminated intravascular coagulation.

Laboratory testing to monitor for disseminated intravascular coagulation, a manifestation of CRS, should be carried out in addition to daily monitoring of chemistry and hematology assessments (including ferritin and CRP) when fever or other signs of potential CRS are present (see Table 1 Table 3, Table 6, and Table 7). In addition, pulmonary, renal and hepatic function will be monitored closely (see Table 1 and Table 3). Cytokine release syndrome will be captured as an adverse event of special interest (see Section 12.3.3).

Rarely, severe CRS can evolve into a presentation consistent with hemophagocytic lymphohistiocytosis/macrophage activation syndrome (HLH/MAS) that may require additional therapy. In these cases, laboratory testing may reveal high serum levels of ferritin, lactate dehydrogenase, soluble CD25, and cytokines (such as IFNγ and IL-6), and low serum levels of fibrinogen (Neelapu 2018). Severe thrombocytopenia, low fibrinogen, and often DIC may be features of HLH, all of which combined may increase the risk of severe bleeding in these subjects. If HLH is suspected, anticoagulation should be avoided or modified based on institutional guidelines depending on platelet count and renal function. Subjects with HLH should have their platelet count and coagulation parameters very closely monitored and maximal support should be provided to avoid major bleeding complications. For example, consider platelet transfusion if platelets are less than 50×10^9/L. Under these circumstances, investigators should consider treating the subject in the ICU, so that maximal monitoring and support can be carried out during this period.

Trained clinical personnel should be prepared to intervene in the event of CRS. Resources necessary for resuscitation (ie, agents such as epinephrine and aerosolized bronchodilator; medical equipment such as oxygen, tracheostomy equipment, and a defibrillator) should be readily available. Tocilizumab must be available prior to administration of JNJ-68284528. Vital signs and laboratory parameters must be monitored at regular intervals until normal. Additional specimens for pharmacokinetic and pharmacodynamic testing should be collected as per the schedule outlined in the Time and Events schedules (Table 2, Table 4, Table 7, and Table 8).

Infection and CRS may have a similar presentation. Therefore, investigators are strongly encouraged to evaluate for an infection at the first signs or symptoms of CRS. Cultures and imaging should be obtained: the clinical signs and symptoms should determine which tests are appropriate.

Recommendations for the clinical management of CRS are provided in Table 23. At the first sign of CRS (such as fever), subjects should be immediately hospitalized for evaluation. The use of myeloid growth factors, particularly granulocyte colony-stimulating factor (G-CSF), should be avoided during CRS. Tocilizumab intervention may be considered with presenting symptom of fever per investigator discretion in the absence of clear infectious etiology and early tocilizumab

should be considered in subjects at high risk of severe CRS (for example, high baseline tumor burden, early fever onset, or persistent fever after 24 hours of symptomatic treatment). Other cytokine-targeting therapies (for example, IL1 and/or anti-TNFα) may be used based on institutional practice, especially for cases of neurotoxicity which does not respond to tocilizumab and corticosteroids. Therapy directed at reduction or elimination of CAR-T cells, including chemotherapy, may be considered in consultation with the sponsor for subjects who develop high grade CRS with laboratory findings overlapping with HLH/MAS (including hyperferritinemia) that remains severe or life-threatening following prior therapies, including tocilizumab and corticosteroids.

Table 23: Guidelines for the Management of Cytokine Release Syndrome

<table>
<tr><th>CRS Grade[a]</th><th>Tocilizumab[b]</th><th>Corticosteroids[f]</th></tr>
<tr><td>Grade 1
Temperature ≥38°C[c]</td><td>Tocilizumab 8 mg/kg i.v. over 1 hour (not to exceed 800 mg) may be considered</td><td>NA</td></tr>
<tr><td rowspan="2">Grade 2
Symptoms require and respond to moderate intervention.

Temperature ≥38°C[c] with:

Hypotension not requiring vasopressors,

and/or,

Hypoxia requiring oxygen via canula[e] or blow-by,

or,

Grade 2 organ toxicity.</td><td>Administer tocilizumab 8 mg/kg i.v. over 1 hour (not to exceed 800 mg).

Repeat tocilizumab every 8 hours as needed if not responsive to i.v. fluids up to 1 liter or increasing supplemental oxygen.</td><td>Consider methylprednisolone 1 mg/kg i.v. twice daily or equivalent dexamethasone (eg, 10 mg i.v. every 6 hours).</td></tr>
<tr><td colspan="2">If no improvement within 24 hours or rapid progression, repeat tocilizumab and escalate dose and frequency of dexamethasone (20 mg i.v. every 6 to 12 hours).

After 2 doses of tocilizumab, consider alternative anticytokine agents.[d]

Do not exceed 3 doses of tocilizumab in 24 hours, or 4 doses in total.</td></tr>
<tr><td rowspan="2">Grade 3
Symptoms require and respond to aggressive intervention.

Temperature ≥38°C[c] with:

Hypotension requiring 1 vasopressor with or without vasopressin,

and/or,

Hypoxia requiring oxygen via high-flow nasal canula[e], facemask, nonrebreather mask, or Venturi mask,

or,

Grade 3 organ toxicity or Grade 4 transaminitis.</td><td>Per Grade 2</td><td>Administer methylprednisolone 1 mg/kg i.v. twice daily or equivalent dexamethasone (eg, 10 mg i.v. every 6 hours).</td></tr>
<tr><td colspan="2">If no improvement within 24 hours or rapid progression, repeat tocilizumab and escalate dose and frequency of dexamethasone (20 mg i.v. every 6 to 12 hours).

If no improvement within 24 hours or continued rapid progression, switch to methylprednisolone 2 mg/kg i.v. every 12 hours.

After 2 doses of tocilizumab, consider alternative anticytokine agents.[d]

Do not exceed 3 doses of tocilizumab in 24 hours, or 4 doses in total.</td></tr>
</table>

Table 23: Guidelines for the Management of Cytokine Release Syndrome

CRS Grade[a]	Tocilizumab[b]	Corticosteroids[f]
Grade 4 Life-threatening symptoms. Requirements for ventilator support, CVVHD. Temperature ≥38°C[c] with: Hypotension requiring multiple vasopressors (excluding vasopressin), and/or, Hypoxia requiring positive pressure (eg, CPAP, BiPAP, intubation, and mechanical ventilation), or, Grade 4 organ toxicity (excluding transaminitis).	Per Grade 2 After 2 doses of tocilizumab, consider alternative anticytokine agents.[d] Do not exceed 3 doses of tocilizumab in 24 hours, or 4 doses in total. If no improvement within 24 hours, consider methylprednisolone (1-2 g i.v., repeat every 24 hours if needed; taper as clinically indicated) or other immunosuppressants (eg, other anti-T-cell therapies).	Administer dexamethasone 20 mg i.v. every 6 hours.

ASTCT=American Society for Transplantation and Cellular Therapy; BiPAP=bilevel positive airway pressure; CPAP=continuous positive airway pressure; CVVHD=continuous veno-venous hemodialysis; i.v.=intravenous(ly); NA=not applicable.

a. Based on ASTCT consensus grading (Lee 2019), modified to include organ toxicity.
b. Refer to tocilizumab prescribing information for details.
c. Attributed to CRS. Fever may not always be present concurrently with hypotension or hypoxia, as it may be masked by interventions such as antipyretics or anticytokine therapy (eg, tocilizumab or steroids). Absence of fever does not impact CRS management decision. In this case, CRS management is driven by hypotension and/or hypoxia and by the more severe symptom not attributable to any other cause.
d. Monoclonal antibodies targeting cytokines may be considered based on institutional practice for unresponsive CRS.
e. Low-flow nasal cannula is ≤6 L/min; high-flow nasal cannula is >6 L/min.
f. Continue corticosteroids use until the event is ≤Grade 1; taper steroids if total corticosteroid exposure is greater than 3 days.

Supportive care for CRS (including but not limited to anti-pyretic agents, IV fluid support, vasopressors, supplemental oxygen, etc.) should be administered according to the clinical manifestations of the subject's illness. Similarly, ancillary testing such as B-type natriuretic peptide (BNP) assessment, echocardiograms, arterial blood gas, assessments of coagulation laboratory tests, etc. should be performed if clinically indicated.

6.2.2. Neurologic Toxicities

Based on the specific mode-of-action of JNJ-68284528, severe or serious neurologic toxicities (including ICANS [Immune Effector Cell-Associated Neurotoxicity Syndrome]) and other neurotoxicities may occur (Section 6.2.2.1). Additionally, subjects should be monitored for neurotoxicity until the end of study (Section 6.2.2.2).

6.2.2.1. CAR-T Cell-related Neurotoxicity (Immune Effector Cell-Associated Neurotoxicity Syndrome [ICANS])

Subjects should have the Immune Effector Cell-associated Encephalopathy (ICE) Assessment Tool (ICE-Tool; Attachment 3) performed at baseline (within 24 hours prior to infusion of JNJ-68284528 infusion) and daily after the first symptoms of CAR-T cell related neurotoxicity (eg, ICANS) are suspected and until resolution. Consider performing ICE-Tool more frequently until neurotoxicity symptoms resolve. Consider performing neuroimaging (eg, magnetic resonance

imaging [MRI]) at screening and/or neurology consultation if pre-existing disease is suspected; see Section 9.7, Safety Evaluations.

Subjects should be monitored for neurologic toxicities including, but not restricted to: speech disorders, aphasia, convulsions, disturbances in consciousness, confusion, disorientation, or coordination and balance disorders. If these or other neurologic toxicities are observed, regardless of causality, then the sponsor's medical monitor must be consulted. Hospitalization is required for Grade 2, 3, or 4 CAR-T cell-related neurotoxicity (ie, ICANS) temporally associated to CRS.

At the first sign of neurotoxicity, neurology consultation and evaluation should be considered to rule out alternative etiologies including viral origin (ie, human herpesvirus [HHV] HHV-6, HHV-7). Subjects who have a lumbar puncture as part of their neurologic work up should have a sample of cerebral spinal fluid also sent to the sponsor for additional testing. For signs of seizures or raised intracranial pressure (ICP)/cerebral edema, consider neuroimaging (CT/MRI), transfer the subject to the intensive care unit (ICU) and treat according to institutional guidelines or practices.

General management for CAR-T cell-related neurotoxicity (ie, ICANS) with or without concurrent CRS is summarized in Table 24. Neurologic toxicities, including ICANS, will be captured as an adverse event of special interest (see Section 12.3.3).

If concurrent CRS is suspected during the neurologic toxicity event, administer:

- Corticosteroids according to the more aggressive intervention based on the CRS and neurologic toxicity grades in Table 23 and Table 24
- Tocilizumab according to CRS grade in Table 23
- Antiseizure medication according to neurologic toxicity in Table 24

Table 24: Guidelines for the Management of Immune Effector Cell-Associated Neurotoxicity Syndrome

ICANS Grade[0]	Corticosteroids
Grade 1 ICE score 7-9[0] or depressed level of consciousness: awakens spontaneously.	Consider dexamethasone[0] 10 mg i.v. every 6 to 12 hours for 2 to 3 days Consider nonsedating, antiseizure medicines (eg, levetiracetam) for seizure prophylaxis.
Grade 2 ICE score-3-6[0] or depressed level of consciousness: awakens to voice	Administer dexamethasone[0] 10 mg i.v. every 6 hours for 2 to 3 days, or longer for persistent symptoms. Consider steroid taper if total corticosteroid exposure is greater than 3 days. Consider nonsedating, antiseizure medicines (eg, levetiracetam) for seizure prophylaxis.

Table 24: Guidelines for the Management of Immune Effector Cell-Associated Neurotoxicity Syndrome

ICANS Grade[0]	Corticosteroids
Grade 3 ICE score-0-2[0] (If ICE score is 0, but subject is arousable (eg, awake with global aphasia) and able to perform assessment) or depressed level of consciousness: awakens only to tactile stimulus, or seizures, either: any clinical seizure, focal or generalized, that resolves rapidly, or nonconvulsive seizures on EEG that resolve with intervention, or raised ICP: focal/local edema on neuroimaging.[0]	Administer dexamethasone[0] 10 mg to 20 mg i.v. every 6 hours. If no improvement after 48 hours or worsening of neurologic toxicity, escalate dexamethasone[0] dose to at least 20 mg i.v. every 6 hours; taper within 7 days, or escalate to high-dose methylprednisolone (1g/day, repeat every 24 hours if needed; taper as clinically indicated). Consider nonsedating, antiseizure medicines (eg, levetiracetam) for seizure prophylaxis.
Grade 4 ICE score-0[0] (subject is unarousable and unable to perform ICE assessment), or depressed level of consciousness, either: subject is unarousable or requires vigorous or repetitive tactile stimuli to arouse, or stupor or coma, or seizures, either: life-threatening prolonged seizure (>5 min), or repetitive clinical or electrical seizures without return to baseline in between, or motor findings[0]: deep focal motor weakness such as hemiparesis or paraparesis, or raised ICP/cerebral edema, with signs/symptoms such as: diffuse cerebral edema on neuroimaging, or decerebrate or decorticate posturing, or cranial nerve VI palsy, or papilledema, or Cushing's triad.	Administer dexamethasone[0] 10 mg to 20 mg i.v. every 6 hours. If no improvement after 24 hours or worsening of neurologic toxicity, escalate to high-dose methylprednisolone (1-2 g/day, repeated every 24 hours if needed; taper as clinically indicated). Consider nonsedating, antiseizure medicines (eg, levetiracetam) for seizure prophylaxis. If raised ICP/cerebral edema is suspected, consider hyperventilation and hyperosmolar therapy. Give high-dose methylprednisolone (1-2 g/day, repeat every 24 hours if needed; taper as clinically indicated), and consider neurology and/or neurosurgery consultation.

ASTCT=American Society for Transplantation and Cellular Therapy; EEG=electroencephalogram; i.v.=intravenous(ly).
Note: ICANS grade and management is determined by the most severe event (ICE score, level of consciousness, seizure, motor findings, raised ICP/cerebral edema), not attributable to any other cause.

a Based on ASTCT consensus grading (Lee 2019).
b If subject is arousable and able to perform ICE assessment, assess: **Orientation** (oriented to year, month, city, hospital =4 points); **Naming** (name 3 objects, eg, point to clock, pen, button =3 points); **Following Commands** (eg, "show me 2 fingers" or "close your eyes and stick out your tongue" =1 point); **Writing** (ability to write a standard sentence =1 point); and **Attention** (count backwards from 100 by 10 =1 point) (see Attachment 3). If subject is unarousable and unable to perform ICE assessment (Grade 4 ICANS) =0 points.
c All references to dexamethasone administration are dexamethasone or equivalent.
d Intracranial hemorrhage with or without associated edema is not considered a neurotoxicity feature and is excluded from ICANS grading. It may be graded according to CTCAE version 5.0.
e Tremors and myoclonus associated with immune effector cell therapies may be graded according to CTCAE version 5.0, but they do not influence ICANS grading.

Table 25: Guidelines for the Management of Raised ICP / Cerebral Edema[a]

- Elevate head of patient's bed to an angle of 30 degrees.
- If patient has Ommaya reservoir, drain CSF to target opening pressure of <20 mmHg.
- Hyperventilation to achieve target partial pressure of arterial carbon dioxide ($PaCO_2$) of 28–30 mmHg, but maintained for no longer than 24 hours.
- Consider neurology and/or neurosurgery consultation.
- Use high-dose corticosteroids with methylprednisolone IV 1 g/day, as recommended above.
- Hyperosmolar therapy with either mannitol (20 g/dL solution) or hypertonic saline (3% or 23.4%, as detailed below):
  - Mannitol: initial dose 0.5–1 g/kg; maintenance at 0.25–1 g/kg every 6 hours while monitoring metabolic profile and serum osmolality every 6 hours, and withhold mannitol if serum osmolality is ≥320 mOsm/kg, or the osmolality gap is ≥40,
  - Hypertonic saline: initial 250 mL of 3% hypertonic saline; maintenance at 50–75 ml/hr while monitoring electrolytes every 4 hours, and withhold infusion if serum Na levels reach ≥155 mEq/L,
  - For patients with imminent herniation: initial 30 mL of 23.4% hypertonic saline; repeat after 15 min, if needed.
- Consider IV anesthetics for burst-suppression pattern on electroencephalography.

[a] In addition to toxicity management guidelines provided in Table 24: Guidelines for the Management of ICANS

6.2.2.2. Other Neurotoxicities

If other neurotoxicities characterized by movement and neurocognitive TEAEs noted below are observed, the medical monitor should be contacted, and the subject should be referred immediately to a neurologist for a full evaluation. Particular attention should be paid to the appearance of any of the following:

- movement impairments (e.g., micrographia or changes in handwriting, tremors, bradykinesia, rigidity, shuffling gait, impaired balance and coordination, difficulty writing, difficulty performing activities of daily living like dressing or feeding oneself),
- cognitive impairments (e.g., memory loss or forgetfulness, disturbances in attention, mental slowness or fogginess, difficulty speaking or slurred speech, difficulty reading or understanding words),
- personality change (e.g., reduced facial expression, flat affect, reduced ability to express emotions, less communicative, disinterest in activities).

Additional monitoring and mitigation strategies include enhanced bridging therapy to reduce baseline tumor burden, early aggressive treatment of CRS and ICANS, handwriting assessments for early detection of neurotoxicity symptoms, and extended monitoring and reporting time for neurotoxicity for the duration of study.

Early detection, workup and intervention, may be important to prevent neurologic toxicity from worsening. The following is a list of potential diagnostics that should be considered in subjects with new neurologic symptoms:

- Positron emission tomography/computerized tomography (PET/CT) of the brain and/or brain MRI with perfusion and an electroencephalogram (EEG).

- Lumbar puncture to rule out infection (in particular John Cunningham virus [JCV], herpes zoster virus [HZV], herpes simplex virus [HSV]-1/2, HHV-6, HHV-7, Epstein-Barr virus [EBV], cytomegalovirus [CMV]).
- Serologic testing for HHV-6 and HHV-7 by PCR for viremia.
- CSF flow cytometry and cytology should be considered to rule out leptomeningeal disease.
- Cerebral spinal fluid (CSF) analysis to rule out paraneoplastic syndromes.
- Thiamine level (consider empiric thiamine replacement while awaiting results) (MD Anderson 2019).

Therapy directed at reduction or elimination of CAR-T cells, including chemotherapy, may be considered in consultation with the sponsor for subjects who develop neurotoxicity that remains unresponsive to other interventions.

Per Section 9.5 of the protocol, if cerebral spinal fluid (CSF) or other relevant biological sample analysis is clinically indicated, a sample of CSF will be requested for additional analysis by the sponsor.

6.2.3. Tumor Lysis Syndrome

Subjects must be monitored closely for symptoms of TLS. Management of TLS, including hyperkalemia, hyperuricemia, hyperphosphatemia, and hypocalcemia, is highly recommended. It is also required that high-risk subjects, ie, those with a high tumor burden (≥60% plasma cell infiltrate on the bone marrow biopsy or aspirate [whichever is higher] or a subject with multiple extramedullary disease sites or plasmacytomas), be treated prophylactically in accordance with local standards (eg, extra hydration; diuretics; allopurinol 300 mg daily and primary or secondary uricosuric agents, as indicated).

6.2.4. Second Primary Malignancy

Second primary malignancy is a possibility due to the risk of viral insertion (DNA integration) of the lentiviral vector. Second primary malignancies should be managed per institutional standards. Second primary malignancies must be reported during the duration of the study, irrespective of when they occur, and subsequently will be collected in a long-term follow-up study yearly until 15 years post dosing of JNJ-68284528. A tumor sample should be collected, and DNA, RNA, or protein analysis may be performed to investigate the presence of lentiviral elements.

6.2.5. Prolonged Cytopenia

Subjects may exhibit cytopenias for several weeks following lymphodepleting chemotherapy and JNJ-68284528 infusion. Prolonged neutropenia may increase the risk of infection. Severe thrombocytopenia may increase the risk of bleeding. Frequent monitoring of hematological parameters and provide supportive care (eg, irradiated blood and thrombocyte concentrates, granulocyte-colony stimulating factor for neutropenia) as outlined by institutional guidelines. Pegylated myeloid growth factors (ie, pegfilgrastim) are prohibited. Blood counts should be monitored after JNJ-68284528 infusion. The use of myeloid growth factors, particularly granulocyte colony-stimulating factor (G-CSF), should be avoided during CRS.

Parvovirus B19 monitoring by PCR should be considered in subjects experiencing prolonged neutropenia or a decline in neutrophil counts following recovery.

For subjects in Cohort D and Cohort E, initiating lenalidomide after JNJ-68284528 may cause significant neutropenia and thrombocytopenia. For subjects in Cohort E, daratumumab may also increase the risk of cytopenia. Monitor complete blood counts (CBC) as specified in the Time and Events Schedule (Table 3 and Table 6). A dose interruption and reduction may be required (refer to local prescription information). Guidance is provided in Table 13, Table 14, and Table 15. Subjects should be monitored frequently for infection and bleeding. Supportive care should be provided per institutional standards.

6.2.6. Hypogammaglobulinemia

Hypogammaglobulinemia may occur in subjects receiving JNJ-68284528. Monitor immunoglobulin levels after treatment as detailed in the Time and Events Schedule (see Table 1, Table 3, and Table 6) and more frequently if clinically indicated for safety and treat according to local guidelines, including administration of immunoglobulin replacement and monitoring for infection. Vaccination with live, attenuated virus vaccines is not permitted for at least 6 weeks prior to the start of the conditioning regimen and for 100 days after infusion of JNJ-68284528.

Subjects with IgG <400 mg/dL or recurrent infections may receive prophylactic IVIG as per institutional guidelines.

6.2.7. Serious Infections

Do not administer JNJ-68284528 to subjects with active infection. Administration of JNJ-68284528 may increase the risk of infection due to cytopenias or hypogammaglobulinemia. Subjects should be monitored frequently for infection and should have blood cultures obtained and empiric antibiotics administered per institutional standards. Immunocompromised patients are at risk for opportunistic infections; prophylactic use of antibiotics, antivirals, or antifungals should be considered. Extended use of anti-microbial therapies for at least 6 month (or longer per institutional guidelines) or consistent with post ASCT consensus guidelines after JNJ-68284528 dosing are recommended (see Attachment 18). Perform screening for hepatitis B virus (HBV), hepatitis B virus (HCV), and human immunodeficiency virus (HIV) and monitor as clinically indicated (see HBV monitoring recommendations in Section 9.7 and Attachment 10), and initiate treatment as appropriate. HBV reactivation, in some cases resulting in fulminant hepatitis, hepatic failure and death, may occur in subjects treated with drugs directed against B cells such as JNJ-68284528. HBV reactivation has occurred in subjects receiving other CAR-T products who appear to have resolved hepatitis B infection. Routinely monitor HBV DNA and AST/ALT for subjects with risk of HBV reactivation (see Attachment 10).

Subjects receiving cilta-cel are possibly at a higher risk of severe/fatal outcomes from COVID-19 infection compared with patients who are receiving standard of care therapy. Subjects should be reminded of the importance of vaccines and other preventative measures. Investigators should consider prophylaxis (eg, Evusheld, if available) and antiviral medications (eg, Paxlovid, if available) for patients diagnosed with COVID-19 infection, as noted in Attachment 20.

6.2.8. Hypersensitivity Reactions

Allergic reactions may occur with the infusion of JNJ-68284528. Serious hypersensitivity reactions including anaphylaxis, may be due to dimethyl sulfoxide (DMSO), dextran 40, or residual kanamycin in JNJ-68284528. Subjects should be treated urgently per institutional standards, avoiding corticosteroid use if possible. Subjects should receive premedication prior to JNJ-68284528 dosing as noted in Section 6.1.3.3.

For subjects in Cohort D and Cohort E please refer to the prescribing information for additional risks associated with lenalidomide.

6.2.9. Cohort E: Management of Infusion-related Reactions and Local Injection-site Reactions of Daratumumab SC

6.2.9.1. Infusion-related Reactions

Infusion-related reactions (IRRs) are systemic reactions related to daratumumab administration. Subjects should be observed carefully during daratumumab administrations. Trained study staff at the clinic should be prepared to intervene in case of any IRRs, and resources necessary for resuscitation (eg, agents such as epinephrine and aerosolized bronchodilator, medical equipment such as oxygen tanks, tracheostomy equipment, and a defibrillator) must be available at the bedside. Attention to staffing should be considered when multiple subjects will be dosed at the same time.

If an IRR develops during daratumumab SC administration, then the administration should be temporarily interrupted. Subjects who experience adverse events during daratumumab-SC administration must be treated for their symptoms. Subjects should be treated with paracetamol (acetaminophen), antihistamine, or corticosteroids, as needed. Intravenous saline may be indicated. For bronchospasm, urticaria, or dyspnea, subjects may require antihistamines, oxygen, corticosteroids, or bronchodilators. For hypotension, subjects may require vasopressors. In the event of a life-threatening IRR (which may include pulmonary or cardiac events) or an anaphylactic reaction, daratumumab-SC should be discontinued.

Infusion-related Reactions of Grade 1 or Grade 2

If the investigator assesses a Grade 1-2 IRR to be related to administration of study intervention, then the daratumumab-SC administration should be interrupted. When the subject's condition is stable, daratumumab-SC administration may be restarted at the investigator's discretion. Refer to the SIPPM for further details regarding continuation of daratumumab-SC administration.

If the subject experiences a Grade 2 or higher event of laryngeal edema, or a Grade 2 or higher event of bronchospasm that does not respond to systemic therapy and does not resolve within 6 hours from onset, then the subject must be permanently discontinued from daratumumab-SC treatment.

Infusion-related Reactions of Grade 3 or Higher

For IRR adverse events (other than laryngeal edema or bronchospasm) that are Grade 3, the daratumumab-SC administration must be stopped, and the subject must be observed carefully until resolution of the adverse event or until the intensity of the event decreases to Grade 1, at which point

the daratumumab-SC administration may be restarted at the investigator's discretion. Refer to the SIPPM for further details regarding continuation of daratumumab-SC administration.

If the intensity of the adverse event returns to Grade 3 after restart of the daratumumab-SC administration, then the subject must be permanently discontinued from daratumumab-SC treatment.

For IRR adverse events that are Grade 4, the daratumumab-SC administration must be stopped, and the subject permanently discontinued from daratumumab-SC treatment.

Recurrent Infusion-related Reactions

If a Grade 3 IRR (or Grade 2 or higher event of laryngeal edema, or a Grade 2 or higher event of bronchospasm) recurs during or within 24 hours after a subsequent daratumumab-SC administration, the subject must be permanently discontinued from daratumumab-SC treatment.

6.2.9.2. Injection-site Reactions

In clinical studies, SC administration of daratumumab was associated with local injection site reactions, such as induration and erythema, in some subjects. The reactions usually resolved within 60 minutes. Local injection-site reactions should be managed per institutional standards.

6.3. Treatment of Overdose

Refer to the local product prescribing information for bortezomib, lenalidomide, or dexamethasone regarding overdose. Cilta-cel will be manufactured, formulated, and provided by sponsor individually. Product received should be administered in a single infusion. In the event the manufactured product exceeds the protocol-defined maximum dose, the product will be evaluated per company exceptional release or similar procedures (see Section 6.1.3.1) prior to shipment to clinical site.

7. TREATMENT COMPLIANCE

Apheresis, administration of the conditioning regimen, and infusion of JNJ-68284528 will be done in the controlled environment of a qualified clinical site, under the direct observation of qualified study-site personnel. Subjects will be asked to return containers of lenalidomide at each study visit. Pill counts will be used to assess compliance. Alternative, site specific methods to ensure compliance with outpatient medication administration is permissible. Additional details are provided in the CTPPM. The details of administration will be recorded in the eCRF (including date, dose of cells, start, and stop times of the IV infusion, and volume infused). Precautions associated with the use of the study treatment and concomitant medications will be reviewed by the sponsor.

Refer to the CTPPM for a description of the chain of identity and chain of custody procedures associated with the apheresis product and JNJ-68284528.

Components of the D-VRd regimen and lenalidomide consolidation will be administered or prescribed by qualified site staff, and the details of each administration will be recorded in the eCRF. Additional details are provided in the Non-JNJ-68284528 SIPPM.

8. PRE-STUDY AND CONCOMITANT THERAPY

Throughout the study, investigators may prescribe concomitant medications or treatments (except for those listed in Section 8.3) deemed necessary to provide adequate supportive care. Medications (including prescription and over-the-counter products, and transfusions of blood products) different from the study treatment must be recorded throughout the study beginning with the signing of the ICF until 100 days after infusion of JNJ-68284528 (Cohorts A, B, C, and F), 30 days after the last dose of lenalidomide (Cohort D and Cohort E) or until the start of subsequent systemic anticancer treatment, if earlier. Exceptions include medications used to prevent (including vaccines) and treat COVID-19 and HBV reactivation, which should be reported until 1 year after cilta-cel infusion, regardless of severity or causality (Attachment 20). All concomitant medications will be recorded during screening. Thereafter, selected concomitant medications will be reported. Selected concomitant medications consist of any medication given for an adverse event or serious adverse event, therapeutically or prophylactically, including, but not limited to:

- Anti-cytokine or anti-cytokine receptor therapies
- Anti-seizure medications
- Any medication given for prophylaxis or treatment of TLS
- Any medication given for prevention or treatment of thromboembolic events
- Corticosteroids (including prophylactically for blood product administrations, physiologic replacement doses, high or stress doses, etc.)
- Immunosuppressive agents
- Vaccinations
- Vasopressors and cardiac inotropic agents (For dose, record only maximum daily rate)
- Blood products
- Growth factors
- Systemic antimicrobials – given for prophylaxis or treatment
- Chemotherapy (given for any CAR-T cell related toxicity)

Other:

- Bisphosphonates
- Immunoglobulin therapy
- Medications listed as prohibited in the protocol
- Palliative radiation
- Pain medication
- Any treatment given for SPMs
- Any changes in doses from baseline or newly added concomitant medications to treat new or prior known co-morbidities

Recorded information will include a description of the type of the drug, dosing regimen, route of administration, duration of treatment, and its indication. Medications, including details of previous anticancer treatment, should be documented in the appropriate section of the eCRF.

Anti-myeloma therapy is permitted during bridging therapy (see Section 3.1).

The sponsor must be notified in advance (or as soon as possible thereafter) of any instances in which prohibited therapies are administered.

8.1. Prophylaxis for Infections

For subjects at risk for viral reactivation (all cohorts), prophylaxis for herpes zoster reactivation is strongly recommended. Acceptable antiviral therapy includes acyclovir (eg, 400 mg given orally 3 times a day, or 800 mg given orally 2 times a day or per institutional standards), famciclovir (eg, 125 mg given orally, twice a day or per institutional standards), or valacyclovir (eg, 500 mg given orally, twice a day or per institutional standards), initiated within 1 week after the start of study drug (see Attachment 18).

Please refer to Attachment 20 for guidance on prophylaxis (eg, vaccines) and treatment of COVID-19 infection.

8.2. Permitted Medications

The following are examples of supportive therapies that may be used during the study:

- Standard supportive care therapies (antiemetics, antidiarrheals, anticholinergics, antispasmodics, antipyretics, antihistamines, analgesics, antibiotics and other antimicrobials, histamine receptor [H_2] antagonists or proton pump inhibitors, and other medications intended to treat symptoms or signs of disease) and therapies intended to treat CAR-T cell related toxicity (ie, CRS) as clinically indicated, according to institutional standards and as deemed necessary by the investigator.
- Bisphosphonates may be initiated (if not already being administered) unless contraindicated within 1 week prior to the first dose of study treatment and continued until disease progression is established. In the case of severe adverse events such as hypercalcemia, bisphosphonates may be administrated as clinically indicated, according to institutional standards and as deemed necessary by the investigator.
- Hematopoietic growth factor support and transfusions (irradiated blood products) are permitted to treat symptoms or signs of neutropenia, anemia or thrombocytopenia according to local standards of care. Non-pegylated myeloid growth factors are permitted up to 1 day prior to the start of the conditioning regimen (Section 6.1.2). For subjects in Cohort D and Cohort E, refer to the lenalidomide prescribing information for precautionary language for agents that may increase the risk of thrombosis.
- Documented infectious complications should be treated with oral or IV antibiotics or other anti-infective agents as considered appropriate by the treating investigator, according to standard institutional practice.

- Chemotherapy agents used to treat CAR-T cell related toxicity are permitted upon consultation with the sponsor (see Section 6.2).
- For subjects in Cohort D and Cohort E, see prescribing information for lenalidomide for additional supportive therapies, including consideration for thromboembolic prophylaxis depending on the subject's risk factors.

8.3. Prohibited Therapies

The following medications are prohibited during the study in addition to those therapies identified in Section 6.1.1 (prior to apheresis) and in Section 6.1.2.1 (prior to conditioning regimen). The sponsor must be notified in advance (or as soon as possible thereafter) of any instances in which prohibited therapies are (to be) administered:

- Systemic corticosteroid use should be avoided, except for the treatment of CRS or CAR-T cell-related neurotoxicity (eg, ICANS), as described in Table 23 and Table 24. Alternative therapies, if feasible, should be given prior to corticosteroids. No cumulative dose of corticosteroids equivalent to ≥70 mg prednisone should be administered within the 7 days prior to apheresis (Section 4.1.2 [Cohort A], Section 4.2.2 [Cohort B], Section 4.3.2 [Cohort C], Section 4.4.2 [Cohort D] or within the 7 days prior to the conditioning regimen dosing (Section 6.1.2.1 [all Cohorts]).
- Any chemotherapy, anticancer immunotherapy (other than JNJ-68284528) including any BCMA-directed therapy, or experimental therapy not specified by the protocol (ie, except as described in Section 3.1 [bridging therapy] or protocol specific therapies which may be used in conjunction with JNJ-68284528).
- The use of RANK ligand inhibitors such as denosumab is prohibited due to their potential impact on immune function.
- While in follow-up, emergency orthopedic surgery or radiotherapy is generally prohibited, but may be allowed in the absence of disease progression. Cases must be discussed and approved by the sponsor. Such emergency radiotherapy may consist of localized radiotherapy for pain control or for stabilization of an extensive bone lesion at high risk of pathologic fracture or damage to surrounding tissues.
- Nonsteroidal anti-inflammatory agents should be avoided to minimize the risk of exacerbation of potential sub-clinical myeloma-related kidney disease. Based on the investigator's clinical judgement, low-dose aspirin may be continued for thromboprophylaxis (recommended for Cohort D). For subjects in Cohort D and Cohort E, refer to the lenalidomide prescribing information for recommendations for subjects with prior history of thrombosis.
- Other immunosuppressant agents unless used as protocol-specified pre- or post-treatment medications to treat an adverse event (eg, CRS).
- Vaccination is recommended per local guidelines (including influenza and SARS CoV-2 vaccines). Live attenuated vaccines are prohibited for 6 weeks prior to lymphodepletion and for 100 days post CAR-T administration. See Attachment 20 for COVID-19 vaccine guidance. Note that antibody responses to vaccines may be suboptimal during study treatment.

- The use of IV contrast infusions should be avoided to prevent myeloma-related kidney disease. If administration of IV contrast is necessary, then adequate precautions including hydration are indicated.
- Pegylated myeloid growth factors (ie, pegfilgrastim) are prohibited within the first 100 days after infusion of JNJ-68284528. For subjects in Cohort D, refer to the lenalidomide prescribing information for precautions with use of erythropoietic agents.
- Strong inhibitors or inducers of CYP3A4 or MDR1 should be avoided (eg, ritonavir and nirmatrelvir).

8.3.1. Additional Prohibited Therapies for Cohort E

Concomitant administration of strong CYP3A4 inducers is prohibited with the use of bortezomib. Administration of strong CYP3A4 inhibitors (eg, ketoconazole, ritonavir) should be avoided and is not recommended in subjects receiving bortezomib. If a strong CYP3A4 inhibitor must be given in combination with bortezomib, monitor subjects for signs of bortezomib toxicity and consider a bortezomib dose reduction. For an ongoing list of CYP3A inhibitors and inducers, please refer to https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm.

8.4. Subsequent Anticancer Therapy

Subsequent anticancer therapy administered after JNJ-68284528 (all cohorts) and after lenalidomide (Cohort D and Cohort E), should be only administered after sponsor-confirmed PD per IMWG criteria and recorded in the eCRF. The type of high dose chemotherapy (for example, melphalan) should be documented in the eCRF as a subsequent therapy. The start and end date and best response should be documented in the eCRF, if available.

9. STUDY EVALUATIONS

9.1. Study Procedures

9.1.1. Overview

The Time and Events Schedule summarizes the frequency and timing of procedures and assessments applicable to this study (Table 1 to Table 8).

All planned assessments, including laboratory tests, on the day of JNJ-68284528 dosing must be completed and the results reviewed prior to the start of the infusion. Treatment decisions will be based on safety assessments performed at the local laboratory and disease assessments performed at the central laboratory.

If multiple assessments are scheduled for the same timepoint, it is recommended that procedures be performed in the following sequence: PRO questionnaires, electrocardiogram (ECG), vital signs, blood draw. Blood collections for biomarkers and pharmacokinetic assessments should be kept as close to the specified time as possible. Actual date and time of assessments will be recorded in the source documents and the laboratory requisition form. Within 24 hours of study treatment infusion, if the study treatment is infused peripherally, blood samples must be drawn from a vein

contralateral to the arm into which JNJ-68284528 is infused. If the study treatment is infused via a central vein line, blood samples over the subsequent 24 hours must be drawn from a vein in either arm.

If the subject is unable to complete the PRO assessments, the reason for not completing the questionnaires will be documented. Refer to Section 9.6 for details.

The approximate volume of blood drawn from each subject in Cohorts A, B, C and F (up to 2 years' post-JNJ-68284528 treatment) is 1013 mL, for Cohort D is 1152 mL and for Cohort E is 1365.5 ml. In addition, women of child-bearing potential will have serum pregnancy tests prior to starting a new cycle of lenalidomide and within 4 weeks after stopping the treatment. This is an additional blood volume of 50 mL over the course of the 2-year treatment period. Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

9.1.2. Screening Phase

All subjects must sign an ICF prior to the conduct of any study-related procedures. The screening phase begins when the first screening assessment is performed. Screening procedures will be performed up to 28 days before apheresis or start of induction therapy for Cohort E. If an assessment was performed as part of the subject's routine clinical evaluation and not specifically for this study, it does not need to be repeated after signed informed consent has been obtained provided the assessments fulfill the study requirements and are performed within the specified timeframe prior to the first dose of study treatment. Retesting of abnormal screening values that lead to exclusion are allowed only once during the screening phase (to reassess eligibility). The last result obtained prior to apheresis, or start of induction therapy for Cohort E, will be used to determine eligibility. For Cohort E only, local laboratory β-2 microglobulin measurement prior to treatment with anti-myeloma therapy may be used to determine eligibility. Lab values for β-2 microglobulin drawn after the administration of any anti-myeloma therapy will not be used to determine eligibility. Subjects who do not meet all inclusion criteria or who meet an exclusion criterion may, at the discretion of the investigator, be rescreened once upon the sponsor's written approval. Subjects who are to be rescreened must sign a new informed consent before rescreening. Rescreening and subsequent activities must be conducted in accordance with protocol defined time windows.

Subjects in Cohort E will receive induction treatment with D-VRd after screening and prior to apheresis as described in Section 6.1.5.

9.1.3. Apheresis

Prior to apheresis, review of safety assessments should be completed per the Time and Events Schedule (Table 1, Table 3, and Table 5). Apheresis should be performed according to institutional standards. Instructions for processing and shipping apheresis product are provided in the CTPPM.

9.1.4. Cyclophosphamide and Fludarabine Conditioning Regimen

At the completion of manufacture and quality testing of JNJ-68284528, notification will be sent to the clinical site. Prior to dosing with cyclophosphamide and fludarabine, review of eligibility, safety assessments and disease characteristics should be completed per Section 6.1.2.1. The details regarding safety monitoring and study visits during this phase are included in the Time and Events Schedules (Table 1, Table 3, and Table 5).

A conditioning regimen of cyclophosphamide 300 mg/m^2 and fludarabine 30 mg/m^2 daily for 3 days must be administered prior to administration of JNJ-68284528. The dose of fludarabine should be reduced to 24 mg/m^2 for subjects with an eGFR of 30 to 70 mL/min/1.73m^2. Sponsor approval must be obtained to modify the conditioning regimen schedule or dose.

9.1.5. JNJ-68284528 Administration

Administration of JNJ-68284528 is fully described in Table 11.

9.1.6. Post-treatment Phase

The post-treatment phase starts after the completion of JNJ-68284528 infusion and includes the post-infusion period and the post-treatment period.

9.1.6.1. Post-infusion Period

The post-infusion period starts after the completion of JNJ-68284528 infusion on Day 1 and lasts until Day 100. Any subject who receives an infusion of JNJ-68284528 should continue all subsequent post-infusion assessments as per the Time and Events Schedules (Table 1 to Table 11).

Dependent on the subject's status, medical history, concurrent comorbidities, adequate social support or potential risk factors for developing CAR-T toxicities, including CRS and neurotoxicity, it will be at the Investigator's discretion, subject's willingness, and sponsor approval, whether the subject will be admitted for inpatient monitoring or will receive JNJ-68284528 infusion as an outpatient (See Table 11).

Subjects will be asked to remain within 1 hour travel time of the hospital and in the company of a competent adult at all times for 1 additional week after hospital discharge, or until Study Day 21, whichever is sooner. Subjects will be provided a "patient ID card" with pertinent information about the study and be asked to carry this card with them for the duration of the post-infusion and post-treatment period.

9.1.6.2. Post-treatment Period (Cohorts A, B, C, and F)

The post-treatment period starts on Day 101 and lasts until study completion, defined as 2 years after the last subject in each cohort has received his or her initial dose of JNJ-68284528. Assessments are to be performed per the Time and Events Schedules (Table 1 Table 2, Table 9 and Table 11) and include safety and disease assessments every 28 days up to 12 months then every 56 days thereafter.

After disease progression is documented, survival status and subsequent anticancer therapy will be obtained every 16 weeks until the end of study, unless the subject has died, is lost to follow-up, or has withdrawn consent. PRO assessments will continue to be collected in the post-treatment period even after disease progression is documented or subsequent anticancer therapy is initiated. If the information is obtained via telephone contact, written documentation of the communication must be available for review in the source documents. Survival status will also be collected within 4 weeks prior to the cut off of any planned efficacy analysis, in case a routine survival status collection does not occur within 4 weeks prior to the corresponding cut off. If the subject has died, the date and cause of death will be collected and documented on the eCRF, if or when available. Where allowed by local law, public records may be used to document death or to obtain survival status.

At the investigator discretion and with sponsor approval, study visits (for all cohorts) in the post-treatment part of the study, may be performed remotely via telemedicine technology that connects study subjects to their research coordinators and investigators. Blood sample collection may be performed at the subject's home by mobile study personnel (ie, nurses and mobile phlebotomist), if not using the sponsor's home health nursing solution, in the post-treatment period, as early as after Day 100 after JNJ-68284528 infusion.

9.1.6.3. Lenalidomide Treatment Period after JNJ-68284528 Infusion (Cohort D)

Once introduced, the lenalidomide treatment period starts as early as Day 22 (if required hematological parameters are met) and lasts until study completion, defined as 2 ½ years after the last subject receives their initial dose of JNJ-68284528. Once the lenalidomide treatment is initiated, subsequent assessment should be adjusted to at the start of each lenalidomide cycle according to Time and Event Schedule. Assessments are to be performed per the Time and Events Schedule (Table 3 and Table 4) and include safety and disease assessments. Safety assessments will be every 28 days for patients receiving lenalidomide. Disease assessments every 28 days for up to 12 months then every 56 days thereafter. Disease evaluations should continue to be performed until confirmed disease progression, death, start of a new anticancer treatment, withdrawal of consent for study participation, or study completion, whichever occurs first. Once disease progression is confirmed, subsequent disease assessment is not required. At the investigator discretion and with sponsor approval, study visits (for all cohorts) in the post-treatment part of the study, may be performed remotely via telemedicine technology that connects study subjects to their research coordinators and investigators. Blood sample collection may be performed at the subject's home by mobile study personnel (ie, nurses and mobile phlebotomist), if not using the sponsor's home health nursing solution, in the post-treatment period, as early as after Day 100 after JNJ-68284528 infusion.

After disease progression is documented, survival status and subsequent anticancer therapy will be obtained every 16 weeks until the end of study, unless the subject has died, is lost to follow-up, or has withdrawn consent. PRO assessments will continue to be collected in the post-treatment period even after disease progression is documented or subsequent anticancer therapy is initiated. If the information is obtained via telephone contact, written documentation of the communication

must be available for review in the source documents. Survival status will also be collected prior to any planned efficacy analysis, in case a routine survival status collection does not occur within 4 weeks prior to the corresponding cut off. If the subject has died, the date and cause of death will be collected and documented on the eCRF, if or when available. Where allowed by local law, public records may be used to document death or to obtain survival status.

9.1.6.4. Lenalidomide Consolidation Treatment Period after JNJ-68284528 Infusion (Cohort E)

After infusion of JNJ-68284528, subjects in Cohort E will initiate lenalidomide consolidation treatment (Section 6.1.5.2).

The lenalidomide treatment can be initiated a minimum of 21 days post JNJ-68284528 after resolution of cytokine release syndrome (CRS) or neurological toxicities.

Once lenalidomide treatment is initiated, subsequent safety, efficacy, biomarker, bioanalysis and PRO assessments should be adjusted to the start of the first lenalidomide cycle according to Time and Event Schedule. When possible, initiation of lenalidomide should start on a protocol required visit day to mitigate the need to adjust for subsequent assessments and increased visits at site. Safety assessments will occur every 28 days, at the beginning of each cycle, for subjects receiving lenalidomide. Disease assessments will be performed every 28 days and should continue to be performed until confirmed disease progression, death, start of a new anticancer treatment, withdrawal of consent for study participation, or study completion, whichever occurs first.

At the investigator discretion and with sponsor approval, study visits (for all cohorts) in the post-treatment part of the study, may be performed remotely via telemedicine technology that connects study subjects to their research coordinators and investigators. Blood sample collection may be performed at the subject's home by mobile study personnel (ie, nurses and mobile phlebotomist), if not using the sponsor's home health nursing solution, in the post-treatment period, as early as after Day 100 after JNJ-68284528 infusion.

After disease progression is documented, survival status and subsequent anticancer therapy will be obtained every 16 weeks until the end of study, unless the subject has died, is lost to follow-up, or has withdrawn consent. PRO assessments will continue to be collected in the post-treatment period even after disease progression is documented or subsequent anticancer therapy is initiated. If the information is obtained via telephone contact, written documentation of the communication must be available for review in the source documents. Survival status will also be collected prior to any planned efficacy analysis, in case a routine survival status collection does not occur within 4 weeks prior to the corresponding cut off. If the subject has died, the date and cause of death will be collected and documented on the eCRF, if or when available. Where allowed by local law, public records may be used to document death or to obtain survival status.

9.1.6.5. Long-term Follow-up

Assessment of other delayed AEs including second primary malignancies (SPM) and assessment for replication competent lentivirus (RCL) will be collected for the duration of the study and will continue to be collected yearly for up to 15 years after the last dose of JNJ-68284528 administered in a separate long-term follow-up study (Study 68284528MMY4002). In addition, subjects who received retreatment with JNJ-68284528 and are in follow-up at the end of the study will be monitored in this long-term follow-up study. A tumor sample should be collected, and DNA, RNA, or protein analysis may be performed to investigate the presence of lentiviral elements.

If a subject has died, the date and cause of death will be collected and documented in the eCRF, if or when available. If the information is obtained via telephone contact, written documentation of the communication must be available for review in the source documents. Where allowed by local law, public records may be used to document death or to obtain survival status.

9.2. Efficacy Evaluations

Disease evaluations must be performed as specified in the Time and Events Schedule. Disease evaluations will be performed by a central laboratory (additional samples may be collected for analysis by the local laboratory) until disease progression, death, start of a new anticancer treatment, withdrawal of consent for study participation, or end of the study, whichever occurs first. If central laboratory data is not available for a particular timepoint, local efficacy data may be substituted. In these situations, the source laboratory data should be interpreted by the study investigator and retained in the site's records. Data will be entered in the eCRF (see Section 9.2.7). However, if a subject receives retreatment with JNJ-68284528 after a confirmed disease progression (see Section 3.1), then disease evaluations will continue according to the Time and Events schedule. This study will use the IMWG-based response criteria (Rajkumar 2011). If it is determined that the study treatment interferes with the immunofixation assay, CR will be defined as the disappearance of the original M-protein associated with multiple myeloma on immunofixation, and the determination of CR will not be affected by unrelated M-proteins secondary to the study treatment (Durie 2015).

For quantitative immunoglobulin (QIg) at baseline, M-protein, immunofixation, and free-light chain (FLC) measurements in serum and 24-hour urine, the investigator will use results provided by the central laboratory. Disease progression must be consistently documented across clinical study sites using the criteria in Attachment 1. The sponsor will use a validated computer algorithm to analyze response to treatment.

Subjects in Cohorts A, B, and C who did not meet the definition of measurable disease per inclusion criterion and were enrolled in the study based on disease that is followed by PET/CT or whole body MRI must also follow the efficacy assessments for all other disease compartments (ie, serum, urine, bone marrow, skeletal [bone] lesions) as described in the Time and Events Schedule.

9.2.1. Bone Marrow Examination for MRD Assessment

MRD will be monitored in subjects using next generation sequencing (NGS) or next generation flow (NGF) on bone marrow aspirate DNA by central laboratory. MRD will be assessed via NGF only in Cohort F. Baseline bone marrow aspirates will be used to define the myeloma clones, and post-treatment samples will be used to evaluate MRD negativity at predetermined intervals. Timepoints for the MRD assessment are reflected in the Time and Events schedule (Table 1, Table 3, Table 5 and Table 6). For subjects who have achieved sustained CR or sCR and who continue in yearly follow up, a ± 3 month window is allowable for these assessments. In case the myeloma clone is not identified successfully from the baseline fresh bone marrow aspirate, the sponsor will ask for non-decalcified diagnostic tissue, such as non-decalcified slides (bone marrow aspirate or clot selection) or formalin-fixed, paraffin-embedded block (clot section only, no bone marrow biopsy) or perform MRD assessment using NGF.

9.2.2. Myeloma Protein Measurements in Serum and Urine

Blood and 24-hour urine samples for M-protein measurements will be sent to and analyzed by a central laboratory. Only one serum and one 24-hour urine sample per time point are required by the central laboratory to perform the following tests. Assessments will be performed as specified in the Time and Events Schedule (Table 1, Table 3, Table 5, Table 6, and Table 9).

- Serum quantitative Ig
- Serum protein electrophoresis (SPEP)
- Serum immunofixation electrophoresis
- Serum FLC assay (for subject in suspected CR/sCR and every disease assessment for subjects with serum FLC only disease)
- 24-hour urine M-protein quantitation by electrophoresis (UPEP)
- Urine immunofixation electrophoresis
- Serum β2-microglobulin. For subjects in Cohort F only, serum β2-microglobulin will also be required from local laboratory assessment prior to initiation of any anti-myeloma therapy.

Blood and 24-hour urine samples will be collected as specified in the Time and Events Schedule (Table 1, Table 3, Table 5, Table 6, and Table 9) until the development of confirmed disease progression. Disease progression based on one of the laboratory tests alone must be confirmed by at least 1 repeat investigation. Disease evaluations will continue beyond relapse from CR until disease progression is confirmed. Serum and urine immunofixation and serum free light chain assays will be performed at screening, prior to the start of the conditioning regimen, and thereafter when a CR is suspected (when serum or 24-hour urine M-protein electrophoresis [by SPEP or UPEP] are 0 or non-quantifiable). For subjects with light chain multiple myeloma, serum and urine immunofixation tests will be performed routinely as per the Time and Events Schedule (Table 1, Table 3, Table 5, Table 6, and Table 9).

9.2.3. Serum Calcium Corrected for Albumin

Blood samples for calculating serum calcium corrected for albumin will be collected and analyzed centrally until the development of confirmed disease progression. Development of hypercalcemia (corrected serum calcium >11.5 mg/dL [>2.9 mmol/L]) may indicate disease progression or relapse if it is not attributable to any other cause (see disease response criteria in Attachment 1). Calcium binds to albumin and only the unbound (free) calcium is biologically active; therefore, the serum calcium level must be adjusted for abnormal albumin levels ("corrected serum calcium"). The formula for adjustment is presented in Attachment 9.

9.2.4. Bone Marrow Examination

Bone marrow aspirate or biopsy (acceptable if aspirate is not possible) will be performed for clinical assessments and biomarker evaluations, as indicated in the Time and Events schedule. Clinical staging (morphology, cytogenetics, and immunohistochemistry or immunofluorescence or flow cytometry) should be done by a local laboratory. A portion of the bone marrow aspirate will be sent to the central laboratory for immunophenotyping and to monitor BCMA, checkpoint ligand expression in CD138-positive multiple myeloma cells, and checkpoint expression on T cells. If feasible, bone marrow aspirate also will be performed to confirm CR and sCR and at disease progression. In addition, MRD will be evaluated as specified in Section 9.2.1 and the Time and Events schedules.

9.2.5. Skeletal Survey

A skeletal survey (including skull, entire vertebral column, pelvis, chest, humeri, femora, and any other bones for which the investigator suspects involvement by disease) is to be performed during the screening phase and evaluated by the local laboratory by either roentgenography or low-dose computed tomography (CT) scans without the use of IV contrast. If a CT scan is used it must be of diagnostic quality. Following JNJ-68284528 infusion, and before disease progression is confirmed, X-rays or CT scans should be performed locally, whenever clinically indicated based on symptoms, to document response or progression. Magnetic resonance imaging (MRI) is an acceptable method for evaluation of bone disease and may be included at the discretion of the investigator; however, it does not replace the skeletal survey (see the disease response criteria in Attachment 1). If a radionuclide bone scan is used at screening, in addition to the complete skeletal survey, then both methods must be used to document disease status. These tests must be performed at the same time. Note: a radionuclide bone scan does not replace a complete skeletal survey.

If a subject present with disease progression manifested by symptoms of pain due to bone changes, then disease progression may be documented by skeletal survey or other radiographs, depending on the symptoms that the subject experiences. If the diagnosis of disease progression is obvious by radiographic investigations, then no repeat confirmatory X-rays are necessary. If changes are equivocal, then a repeat X-ray is needed in 1 to 3 weeks after initial x-ray.

9.2.6. Documentation of Extramedullary Disease/ Extramedullary Plasmacytomas

Sites of known extramedullary plasmacytomas must be documented ≤14 days prior to the first dose of the conditioning regimen (Cohorts A, B, C, and F) or at screening (Cohort D and Cohort E). Clinical examination or MRI may be used to document extramedullary sites of disease. CT scan evaluations are an acceptable alternative if there is no contraindication to the use of IV contrast. Positron emission tomography scan or ultrasound tests are not acceptable to document the size of extramedullary plasmacytomas. However, PET/CT fusion scans can be used to document extramedullary plasmacytomas if the CT component of the PET/CT fusion scan is of sufficient diagnostic quality.

Extramedullary plasmacytomas should be assessed for all subjects with a history of plasmacytomas or if clinically indicated at screening, by clinical examination or radiologic imaging. Assessment of measurable sites of extramedullary disease will be performed, measured, and evaluated locally every 4 weeks (for physical examination) for subjects with a history of plasmacytomas or as clinically indicated during treatment for other subjects until development of confirmed CR or confirmed disease progression. If assessment can only be performed radiologically, then evaluation of extramedullary plasmacytomas may be done on Day 78, Day 156, and then every 12 weeks. The methodology used for evaluation of each disease site should be consistent across all visits. Irradiated or excised lesions will be considered not measurable and will be monitored only for disease progression.

To qualify for VGPR, PR, or MR, the sum of products of the perpendicular diameters of the existing extramedullary plasmacytomas must have decreased by over 90% or at least 50%, respectively, and new plasmacytomas must not have developed (see the disease response criteria in Attachment 1). To qualify for disease progression, either the sum of products of the perpendicular diameters of the existing extramedullary plasmacytomas must have increased by at least 50%, or the longest diameter of previous lesion >1cm in short axis must have increased at least 50%, or a new plasmacytoma must have developed. When not all existing extramedullary plasmacytomas are reported, but the sum of products of the perpendicular diameters of the reported plasmacytomas have increased by at least 50%, then the criterion for disease progression is met.

These response criteria are applicable only to patients screened with measurable disease in serum or urine. For subjects in Cohorts A, B, C, and F without measurable disease in serum or urine, who screened via PET/CT or whole body MRI refer to Attachment 22 for response characterization.

9.2.7. Local Laboratory Assessments

All efforts should be made to collect efficacy data centrally. However, local laboratory data may be collected if central laboratory data are not available at a particular timepoint; this does not include screening assessments, with exception of B-2 microglobulin in Cohort E only. If local and central laboratory data are collected on the same day, the central laboratory results will take precedence. Documentation of the local laboratory data should be sent to the Principal Investigator and filed in the medical record. It is the Principal Investigator's responsibility to ascertain that these results are reviewed and entered into the subject's medical record and the eCRF.

9.3. Pharmacokinetics and Immunogenicity

Serum and whole blood samples will be used to evaluate the pharmacokinetics of JNJ-68284528, and the pharmacokinetics of daratumumab as well as the immunogenicity of anti-JNJ-68284528 and anti-daratumumab antibodies. Serum collected for pharmacokinetic and immunogenicity analyses may additionally be used to evaluate safety or efficacy aspects that address concerns arising during or after the study period. Genetic analyses will not be performed on these serum samples. Subject confidentiality will be maintained.

9.3.1. Evaluations

Blood and serum samples will be collected for JNJ-68284528 pharmacokinetics, and immunogenicity (antibodies to JNJ-68284528) assessment as specified in the Time and Events Schedule (Table 2, Table 4, Table 7, Table 8, and Table 11). Also, pharmacokinetic and immunogenicity samples will be collected at the time of onset of suspected CRS or CAR-T cell related neurotoxicity (eg, ICANS) regardless of causality (specified in Table 2). The exact dates and times of blood sampling must be recorded on the laboratory requisition form. Refer to the Laboratory Manual for sample collection requirements. Collected samples must be stored under specified controlled conditions for the temperatures indicated in the Laboratory Manual.

Venous blood samples will be collected for measurement of CAR-T positive cellular concentration and transgene levels of JNJ-68284528. Bone marrow samples will be collected for measurement of transgene levels and cellular concentrations of JNJ-68284528 (see Time and Events schedule).

Blood samples will be collected for exploratory evaluations of soluble circulating BCMA (sBCMA). This data may be used for mechanistic pharmacokinetic/pharmacodynamic modeling. Subject confidentiality will be maintained. Additional information about the collection, handling, and shipment of biological samples can be found in the Laboratory Manual.

Samples to assess both the serum concentration (PK) of daratumumab and the generation of anti-daratumumab antibodies (immunogenicity) will be evaluated from subjects in Cohort E according to the Time and Events Schedule (Table 7). Refer to the Laboratory Manual for sample collection requirements. Collected samples must be stored under specified controlled conditions for the temperatures indicated in the Laboratory Manual. Samples collected for determining serum concentrations/immunogenicity of daratumumab in this study may be retained to address questions about drug characteristics.

9.3.2. Analytical Procedures

Pharmacokinetics

Blood and bone marrow samples will be analyzed to determine CAR-T positive cellular concentration and transgene levels of JNJ-68284528 using specific and sensitive assay methods that are validated by or under the supervision of the sponsor.

Serum samples will be analyzed to determine (PK) of daratumumab and the generation of anti-daratumumab antibodies (immunogenicity) using specific and sensitive assay methods that are validated or appropriately qualified by or under the supervision of the sponsor.

Immunogenicity

The detection and characterization of antibodies to JNJ-68284528 will be performed using a validated or appropriately qualified assay method by or under the supervision of the sponsor. Other analyses may be performed to characterize immunogenicity.

Serum samples for subjects in Cohort E will be analyzed to determine the generation of anti-daratumumab antibodies (immunogenicity) using specific and sensitive assay methods that are validated or appropriately qualified by or under the supervision of the sponsor. For the daratumumab immunogenicity assessments, serum samples will be screened for antibodies binding to daratumumab and serum titer will also be determined from confirmed positive samples. Other immunogenicity analyses (eg, assessment of neutralizing capabilities) may be performed to further characterize the immune responses that are generated.

9.3.3. Pharmacokinetic Parameters

Blood and bone marrow samples will be collected for the measurement of JNJ-68284528 cellular concentrations and transgene levels for pharmacokinetic analyses (Time and Events Schedule). Pharmacokinetic parameters will be estimated for individuals, and descriptive statistics will be calculated for each cohort. Correlation of C_{max} and AUC with dose may also be explored. Pharmacokinetic parameters include, but are not limited to, AUC_{inf}, $AUC_{(0-t)}$, AUC_{tau}, C_{max}, half-life, and T_{max} parameters will be calculated if sufficient data are available for estimation.

Pharmacokinetic samples to determine serum concentration of daratumumab will be obtained from subjects in Cohort E. The descriptive statistics of daratumumab serum concentrations at each sampling timepoint will be reported.

9.3.4. Immunogenicity Assessments/Antibodies to JNJ-68284528

Anti-JNJ-68284528 antibodies will be evaluated in serum samples collected from all subjects according to the Time and Events Schedule. Additionally, serum samples should also be collected at the final visit from subjects who discontinued treatment or were withdrawn from the study. These samples will be tested by the sponsor or sponsor's designee.

Serum samples will be screened for antibodies binding to JNJ-68284528 and the titer of confirmed positive samples will be reported. Other analyses may be performed to verify the stability of antibodies to JNJ-68284528 or further characterize the immunogenicity of JNJ-68284528.

Anti-daratumumab antibodies will be evaluated in serum samples collected from subjects in Cohort E according to the Time and Events Schedule (Table 7).

Serum samples will be screened for antibodies binding to daratumumab and the titer of confirmed positive samples will be reported. Other analyses may be performed to verify the stability of antibodies to daratumumab or further characterize the immunogenicity of daratumumab.

9.4. Pharmacokinetic/Pharmacodynamic Evaluations

Pharmacokinetic/pharmacodynamic modeling for JNJ-68284528 will be explored to understand and characterize the dose-response relationship.

9.5. Biomarkers Evaluations

Biomarker assessments will focus on several objectives: 1) evaluate apheresis and infused CAR-T cell subsets and activation markers including, but not limited to CD4+, CD8+, CD25+, central memory, effector memory cells; 2) serum or plasma proteomic profiling of cytokines (such as IL-6, IL-15, and IL-10) and other immune related proteins; 3) immunophenotyping of biomarkers of response/resistance on myeloma cells (such as BCMA and PD-L1); 4) determine the clinical benefit (ORR, DOR, TTR, PFS, and OS) of JNJ-68284528 in subjects with cytogenetic modifications (del17p, t(4;14), t(14;16), or other high-risk molecular subtypes) in all cohorts; and 5) immunophenotyping of immune cells subsets such as CD4+ and CD8+ T cells, regulatory T cells, B and NK cells. Additional biomarker samples may be collected to help understand an unexplained adverse event including but not limited to serum or PBMCs from whole blood. Additional sample(s) for cytokines will be collected as clinically indicated (Table 2).

To monitor if RCL is generated from JNJ-68284528, whole blood from subjects will be evaluated using a qPCR assay against the lentiviral vesicular stomatitis virus-G gene yearly for up to 15 years in a separate long-term follow-up study. If all samples are negative for RCL during the first year after treatment, no additional samples will be collected and RCL assessments will be terminated. Yearly review of medical history will generally be sufficient for the subject. If any post-treatment samples are positive, further analysis of the RCL, and more extensive patient follow-up should be undertaken. Additional event triggered testing for RCL may be conducted as clinically indicated as specified in Time and Events Schedule (T&E).

Peripheral blood mononuclear cells (PBMCs) will be retained for exploratory analysis of the immune system which may include retroviral insertion analysis, T cell receptor (TCR) analysis (both clonality or diversity of TCR), functional in vitro assays, or other. Biomarker analyses are dependent upon the availability of appropriate biomarker assays and clinical response rates. Biomarker analysis may be deferred or not performed, if during or at the end of the study, it becomes clear that the analysis will not have sufficient scientific value for biomarker evaluation, or if there are not enough samples or responders to allow for adequate biomarker evaluation. In the event the study is terminated early or shows poor clinical efficacy, completion of biomarker assessments is based on justification and intended utility of the data.

Based on emerging scientific evidence, the sponsor may request additional material from, including but not limited to, previously collected bone marrow samples, whole blood, bone marrow aspirate or biopsy, or cerebral spinal fluid, or other tissue sample during or after study completion for a retrospective analysis. For subjects diagnosed with a SPM, a tumor sample should be collected (See Section 6.2.4). Additionally, the sponsor will receive a sample of plasmacytoma if patient relapse is suspected. Subjects who have a lumbar puncture as part of their neurologic work up should have cerebral spinal fluid sent for additional tests by the sponsor. In all cases, such analyses would be specific to research related to the study treatment(s) or diseases being

investigated. If a subject die and an autopsy is performed, specimens may be requested by the sponsor for analysis.

9.5.1. Pharmacodynamic/Predictive Markers

The baseline of the JNJ-68284528 subsets and dynamic changes/persistence and activation of CAR-positive viable T cells may be associated with the depth and durability of response. An evaluation of these cell populations may be performed by flow cytometry or cytometry by time of flight (CyTOF) or both and correlated with response. Additional immunophenotyping may be performed on bone marrow aspirate and whole blood samples to evaluate expression of biomarkers on myeloma cells (such as BCMA and PD-L1) and immune cell populations (such as $CD4^+$ and $CD8^+$ T cells) by flow cytometry or CyTOF. TCR sequencing may be performed to study T cell clonality that may affect drug response. Samples may be characterized by gene expression profiling and somatic mutation analysis by next generation sequencing (whole exome and RNA sequencing) to evaluate potential biomarkers that may correlate with response. Samples may be evaluated by other similar technologies to evaluate protein or RNA expression or for somatic DNA analysis.

Circulating serum biomarkers present following chemotherapy conditioning and following infusion of CAR-T cells have been associated with response to some CAR-T cell-based therapies. Evaluation of cytokines (such as IL-6 and IFN-γ) and other circulating proteins (such as granzymes or perforin) will be analyzed to identify potential pharmacodynamic and predictive biomarkers of response or resistance.

An data review by the DMC will be conducted after the first 5 subjects are treated with JNJ-68284528 in Cohort E to determine if there are any potential pharmacodynamic interactions between D-VRd induction treatment and JNJ-68284528 (see Section 3.1.5).

9.6. Patient-Reported Outcome Assessments

The subjects' HRQoL (disease-related symptoms, functioning, and general well-being) will be captured using PRO measures. These measures will be administered according to the Time and Events Schedule (Table 1, Table 3, Table 5, Table 6, and Table 9) for all cohorts; to be completed by the subjects before any clinical tests, procedures, or other consultations that would influence subject's perceptions of their current health state. The PRO measures will be provided in paper format, in the local language, with the site materials. If a subject requires assistance completing the PRO measures, a study coordinator may assist but should not prompt the subject in selecting their response or provide any interpretation of the questions or response options. The PRO measures can be interviewer-administered, read verbatim, by telephone during the post-treatment period or completed during the home health visit by the mobile study nurse. When a subject completes the PRO measures, the study coordinator should check that the questionnaires are completed in full, or document why they are missing. Full training documentation will be provided to site coordinators before the start of data collection.

Samples of the PRO measures are provided in Attachment 11:

- EORTC QLQ-C30
- MySIm-Q
- PGIS
- PGIC
- PRO-CTCAE

The EORTC-QLQ-C30 version 3 includes 30 items in 5 functional scales (physical, role, emotional, cognitive, and social), 1 global health status scale, 3 symptom scales (pain, fatigue, nausea/vomiting), and 6 single symptom items (dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties). The recall period is 1 week ("past week") and responses are reported using a verbal rating scale. The item and scale scores are transformed to a 0 to 100 scale. A higher score represents greater HRQoL, better functioning, and more (worse) symptoms. The EORTC QLQ-C30 has been widely used among patients with multiple myeloma. Reliability, validity, and clinically meaningful change have been demonstrated (Wisloff 1996; Wisloff 1997).

The Multiple Myeloma Symptom and Impact Questionnaire (MySIm-Q) is a disease-specific PRO measure developed to assess symptoms and impacts important to patients with multiple myeloma. It includes 17 items resulting in a total symptom score and a total impacts score. The recall period is the "past 7 days" and responses are reported on a 5-point verbal rating scale. The MySIm-Q is an optional assessment in this study.

The Patient Global Impression of Severity (PGIS) is a single item to assess severity of pain. Subjects are asked to rate the severity of their current pain on a 5-point verbal rating scale.

The Patient Global Impression of Change (PGIC) is a single item to assess the subject's perception in change of their overall health status using a 7-point verbal rating scale. The PGIC is only administered post-infusion.

The National Cancer Institute's Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE) is an item library of common adverse events experienced by people with cancer that are appropriate for self-reporting and is an optional assessment in this study. Each symptom selected for inclusion can be rated by up to three attributes characterizing the presence/frequency, severity, and/or interference of the adverse event (Trask 2018; PRO-CTCAE 2019). For subjects with multiple myeloma the following items were selected for inclusion: nausea, vomiting, diarrhea, shortness of breath, rash, dizziness, headache, and fatigue/tiredness/lack of energy. A 5-point verbal rating scale is used for subjects to select their experience based on the last 7 days. Responses to the PRO-CTCAE will be kept separate from CTCAE data and sites will confirm that the questions are completed but will not have access to the subject's responses for real time review. Additionally, adverse event reporting will not be derived from the PRO data and safety analysis will not be performed using PRO data.

9.7. Safety Evaluations

Safety will be measured by adverse events, laboratory test results, vital sign measurements, physical examination findings (including neurologic examination), assessment of ICE-Tool scores, handwriting assessments, assessments of cardiac function, and assessment of ECOG performance status grade. Clinically relevant changes occurring during the study must be recorded on the adverse event section of the eCRF. Any clinically significant abnormalities persisting at the end of the study/early withdrawal will be followed by the investigator until resolution or until a clinically stable condition is reached. Safety monitoring assessments may be performed more frequently, if clinically indicated.

The study will include the following evaluations of safety and tolerability according to the time points provided in the Time and Events Schedule:

9.7.1. Adverse Events

All adverse events (with the exception of delayed AEs [see below], HBV reactivation, and COVID-19 infection) and special reporting situations will be reported by the subject (or, when appropriate, by a caregiver, surrogate, or the subject's legally acceptable representative) from the time a signed and dated informed consent is obtained until 100 days after infusion of JNJ-68284528 (Cohorts A, B, C, and F) regardless if PD occurs prior to Day 100 or subsequent anti-myeloma therapy is started prior to Day 100, and 100 days after infusion of JNJ-68284528, or 30 days after last dose of lenalidomide, whichever is later (Cohort D and Cohort E), whichever is later (Cohort E). Beyond the adverse event reporting period, only SAEs regardless of causality and non-serious AEs that are considered related to a study drug need to be reported until the end of the study except as defined for delayed AEs (see Section 9.7.3 and Section 12.3.4). In addition, events of HBV reactivation and COVID-19 infection will be reported during the first-year post-infusion of JNJ-68284528.

See Attachment 26 for additional guidance on adverse event reporting.

All AEs and special reporting situations, whether serious or non-serious, will be collected for subjects who are enrolled and unable to be apheresed or receive bridging therapy, conditioning regimen until PD or until the start of anti-myeloma therapy, whichever is earlier.

All AEs, regardless of seriousness, severity, or presumed relationship to study treatment, must be recorded using medical terminology in the source document and the eCRF. Whenever possible, diagnoses should be given when signs and symptoms are due to a common etiology (eg, cough, runny noses, sneezing, sore throat, and head congestion should be reported as “upper respiratory infection”) with the exception of CRS and CAR-T cell-related neurotoxicity (see below).

Adverse events will be followed by the investigator as specified in Section 12, Adverse Event Reporting and graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE Version 5.0), with the exception of CRS and ICANS. CRS should be evaluated according to the American Society for Blood and Bone Marrow Transplantation (ASBMT) consensus grading (Lee 2019) (Attachment 2). ICANS should be

graded using the ASBMT (American Society for Transplantation and Cellular Therapy [ASTCT]) consensus grading (Attachment 4). In addition to capturing ICANS and CRS adverse events (graded by ASTCT consensus grading), all individual symptoms of CRS (eg, fever, hypotension) and CAR-T cell-related neurotoxicity (eg, depressed level of consciousness, seizures) must be captured as individual adverse events and graded by CTCAE criteria. Neurotoxicity that is not temporally associated with CRS, or any other neurologic adverse events that do not qualify as ICANS, will be graded by CTCAE criteria. Events of neurotoxicity or exacerbation of existing neurologic adverse events will be reported for duration of the study post infusion of JNJ-68284528.

Changes in handwriting (ie, micrographia, dysgraphia, or agraphia) should be graded using the criteria outlined in Attachment 17 and reported as an adverse event in the eCRF. Should a subject experience a serious CAR-T associated neurotoxicity (either ICANS or other neurotoxicity), then a copy of the handwriting assessment log should be submitted with the serious adverse event report.

Subjects with Grade 3 or higher toxicity or unresolved adverse events that lead to treatment discontinuation will continue to be assessed until recovery to Grade ≤1 or baseline, the event is deemed irreversible, the end of the study, or a maximum of 6 months, whichever comes first.

9.7.2. Adverse Events of Special Interest

Adverse events of special interest (AESI) are described in Section 12.3.3.

9.7.3. Delayed Adverse Events

Delayed adverse events are described in Section 12.3.4.

9.7.4. Serious Adverse Events

Serious adverse events are described in Section 12.3.2.

9.7.5. Clinical Laboratory Tests

Blood samples for serum chemistry and hematology will be collected as shown in the Time and Events Schedule (Table 1, Table 3, Table 5, and Table 6). Disease-related laboratory evaluations are detailed in Section 9.2.

The investigator must review the laboratory results, document this review, and record any clinically relevant changes occurring during the study in the adverse event section of the CRF. Grade 3 or higher laboratory abnormalities should continue to be assessed until recovery to Grade ≤1 or baseline, the event is deemed irreversible, the end of study, or a maximum of 6 months, whichever comes first. Laboratory certificates or accreditation and normal ranges of the laboratory facility at the site must be submitted to the sponsor before the enrollment of any subject at the site. If the subject has the laboratory assessments conducted at a laboratory facility other than the one associated with the investigational site, the investigator must submit to the sponsor laboratory certificates or accreditation and normal ranges for that facility as well. The laboratory reports must be filed with the source documents.

The following tests will be performed by the local laboratory except for the calcium and albumin-adjusted calcium, which will be performed at the central laboratory:

Hematology	
Hemoglobin	Absolute lymphocyte count
White blood cell count	Platelet count
Absolute neutrophil count	Absolute number and % CD4
	Absolute number and % CD8
	CD4/CD8 ratio[f]
Coagulation	
Prothrombin time / International normalized ratio	Activated partial thromboplastin time
Fibrinogen	D-dimer
Chemistry	
Sodium	Total bilirubin[a]
Potassium	Alkaline phosphatase
Lactic acid dehydrogenase	Uric acid
Blood urea nitrogen or Urea	Calcium and albumin-adjusted calcium[b]
Creatinine	Phosphate
Glucose	Albumin
AST	Total protein
ALT	Magnesium
Gamma-glutamyl transpeptidase	Creatine phosphokinase (CPK)
Ferritin	C-reactive protein
eGFR[e]	Thyroid Function testing (Cohort D only)[d]
Triglycerides[g]	β2 microglobulin/albumin (Cohort F only)
Pregnancy Test	
Pregnancy Test: serum (<5 IU/mL) β-hCG	
Infectious Disease Testing	
- **Hepatitis B[c]:** HBsAg, anti-HBc, anti-HBs, HBV DNA quantification (for subjects who are anti-HBs positive without a history of vaccination or for subjects who are anti-HBc positive with or without anti-HBs positive) (Attachment 10) - **Hepatitis C:** Hepatitis C virus [HCV] infection is defined as: o positive anti-HCV antibody or o detectable HCV-RNA (for subjects who are anti-HCV positive) or o history of HCV NOTE: Subjects with positive anti-HCV antibody due to prior resolved disease can be enrolled only if a confirmatory HCV-RNA test is undetectable. For subjects with history of HCV infection, confirmation of sustained virologic response is required for study eligibility, defined as undetectable HCV-RNA ≥24 weeks after completion of antiviral therapy. - **HIV** - **CMV and EBV:** serology/PCR testing as indicated in the Time and Events Schedule - **HTLV and other infectious diseases:** as applicable per local regulations	
COVID-19 Antibody Titer (optional)	
As applicable per institutional standards, up to 1 year post cilta-cel infusion	

Abbreviations: ALT=alanine aminotransferase; AST=aspartate aminotransferase; β-hCG=β-human chorionic gonadotropin; HBsAg=hepatitis B surface antigen; anti-HBc=anti-hepatitis B core antibody, anti-HBs=anti-hepatitis B surface antibody; HBV=hepatitis B virus; HCV=hepatitis C virus, HIV=human immunodeficiency virus; HTLV=human T-cell lymphotropic virus.

[a] Direct bilirubin if Gilbert's disease.

[b] Performed by central laboratory.

[c] See Attachment 10 to determine eligibility for enrollment in the study and additional safety monitoring recommendations.

[d] Thyroid assessment: TSH only, if TSH is <LLN or >ULN need free T3 and free T4 testing

[e] Calculated using MDRD formula (Attachment 8)
[f] CD4/CD8 panel will be done for newly enrolled subjects and is optional as locally available.
[g] Triglycerides is at baseline and it would be repeated as clinically indicated thereafter.

9.7.6. Electrocardiogram (ECG)

12-lead ECGs will be performed as specified in the Time and Events Schedule (Table 1, Table 3, Table 5, Table 6, and Table 9). ECGs should be obtained prior to any other study procedures planned for the same day.

During the collection of ECGs, subjects should be in a quiet setting without distractions (eg, television, cell phones). Subjects should rest in a supine position for at least 5 minutes before ECG collection and should refrain from talking or moving arms or legs. If blood sampling or vital sign measurement is scheduled for the same time point as ECG recording, the procedures should be performed in the following order: ECG(s), vital signs, blood draw.

Additional cardiovascular assessments should be performed as clinically appropriate to ensure subject safety. The clinical investigator will review the results, including ECG morphology, for immediate management. Abnormalities noted at screening should be included in the medical history.

9.7.7. Echocardiogram or MUGA scan

Assessment of cardiac function is required at screening using either echocardiogram or MUGA scan (results obtained ≤8 weeks before apheresis [All Cohorts] or Day 1 of D-VRd (Cohort E) are acceptable for determining eligibility). At a minimum, this will include assessment of left ventricular ejection fraction (LVEF) reported as a percentage. This value should be recorded in the eCRF. In addition, subjects who receive medications known to cause cardiotoxicity (per locally available prescribing information) in the bridging therapy should have a repeat assessment of cardiac function within 7 days prior to the start of the conditioning regimen.

9.7.8. Vital Signs

Temperature, pulse/heart rate, respiratory rate, blood pressure and oxygen saturation monitoring will be performed as specified in the Time and Events Schedule (Table 1, Table 3, Table 5, Table 6, and Table 9). Blood pressure and pulse/heart rate measurements should be preceded by at least 5 minutes of rest in a quiet setting without distractions (eg, television, cell phones). Blood pressure and pulse/heart rate measurements will be with a completely automated device, when available.

9.7.9. Physical Examination

The screening physical examination will include, at a minimum, subject's height, general appearance, examination of the skin, ears, nose, throat, lungs, heart, abdomen, extremities, musculoskeletal system, nervous system, and lymphatic system. Thereafter, a symptom-directed physical examination will be conducted as clinically indicated at subsequent timepoints. Abnormalities will be recorded in the appropriate section of the eCRF. Body weight will be measured prior to infusion of JNJ-68284528 (see the Time and Events Schedule [Table 1, Table 3,

Table 5, Table 6, and Table 9]). Clinically significant post-baseline abnormalities should be recorded as adverse events. Refer to Attachment 27 for the schedule of neurologic examinations specific to France.

9.7.10. ECOG Performance Status

The ECOG performance status scale will be used to grade changes in the subject's daily living activities (Attachment 7) and will be assessed as noted in the Time and Events Schedule (Table 1, Table 3, Table 5, and Table 6).

9.7.11. Neurologic Examination

Magnetic resonance imaging (MRI) at screening or neurology consultation should be considered if pre-existing disease is suspected. For subjects with prior pertinent neurologic disease (eg, stroke, encephalitis) consider baseline MRI of brain and an EEG. At the first sign of neurotoxicity, neurology consultation and evaluation should be considered. ICANS should be graded using ASBMT (ASTCT) consensus grading. Other neurologic adverse events not associated with ICANs should be graded based on CTCAE version 5.0. Findings from neurologic testing that support CAR-T cell-related neurotoxicity (eg, ICANS) should be reported in the CRF. Submission of neuroimaging scans may also be requested for sponsor review. Refer to Attachment 27 for the schedule of neurologic examinations specific to France.

9.7.12. Immune-effector Cell-associated Encephalopathy (ICE) Tool Scores

The ICE test was developed to provide objectivity for the grading of multiple overlapping encephalopathy terms currently included on the approved CAR-T products (Lee 2019) (Attachment 3). The ICE tool will be collected as noted in the Time and Events Schedule (Table 1, Table 3, Table 5, Table 6, and Table 9) to guide management throughout both phases of the study. It will also be used to grade the severity of ICANS (Attachment 4). All ICE scores must be reported in the eCRF.

9.7.13. Handwriting Assessment

Qualitative changes in handwriting since baseline are being explored by the sponsor as a potential early clinical predictive marker for neurotoxicity. Currently no standardized CTCAE toxicity gradings are available in the NCI-CTCAE v5.0. for these type of changes in handwriting. Therefore, the sponsor has developed a handwriting assessment criterion to assess subjects for occurrence of the following types of changes in handwriting: micrographia, dysgraphia, or agraphia, as potential early indicators for neurotoxicity (See Attachment 17).

Handwriting assessments will be collected on a writing log according to the Time and Events Schedules and as instructed by the sponsor. Subjects unable to write at baseline are excused from this assessment during study. The sponsor's medical monitor should immediately be notified when changes in handwriting are detected. This will prompt discussion about additional assessments to further evaluate for other neurotoxicity symptoms, further workup, as well as the potential initiation of interventions. All cases of handwriting abnormalities (ie, micrographia, dysgraphia, or agraphia) must be reported as an adverse event in the eCRF. Should a subject experience a

serious CAR-T associated neurotoxicity (either ICANS or other neurotoxicity), then a copy of the handwriting assessment log should be submitted with the serious adverse event report. For visits post Day 100 that are completed remotely via Telemedicine, the handwriting assessment may be administered by the mobile study personnel. Refer to Attachment 27 for the schedule of handwriting sample collection specific to France.

9.7.14. Ocular Examination

The ocular examination, for subjects in Cohort C who have received prior ADC, is to include best - corrected visual acuity (BCVA), slit lamp examination (with special focus on cornea), intraocular pressure, and dilated fundoscopic examination.

9.7.15. Indirect Antiglobulin Test (IAT) (Cohort E)

Blood Type, Rh, and Indirect Antiglobulin Test (IAT) should be done before the first dose of daratumumab. Subject RBC phenotyping (standard or extended) is an alternative option to the IAT test, if locally required. Either method must be completed prior to first daratumumab administration.

Daratumumab interferes with the IAT, which is a routine pre-transfusion test performed to identify a patient's antibodies to minor antigens so that suitable donor blood can be given for transfusion. Daratumumab does not interfere with ABO/RhD typing. CD38 is expressed at very low-levels on erythrocytes. Daratumumab binds to the CD38 on erythrocytes, which results in a positive IAT (Indirect Coombs Test). This positive result masks the detection of antibodies to minor antigens and may prevent or delay blood banks from issuing donor blood for transfusion. This effect occurs during daratumumab treatment and for up to 6 months after treatment ends. Subjects will receive a patient identification wallet (study) card for the study that includes the blood profile (ABO, Rh, and IAT or phenotyping) determined before the first injection of daratumumab along with information on the IAT interference for healthcare providers/blood banks. Subjects will be instructed to carry this card throughout the treatment period and for at least 2 years after JNJ-68284528 infusion.

Blood banks can eliminate the daratumumab interference with IAT by treating reagent RBCs with dithiothreitol (DTT) (Chapuy 2015; Chapuy 2016).

Possible methods for blood banks to provide safe RBCs for transfusion to subjects receiving daratumumab include:

a) Providing ABO/RhD compatible, phenotypically (standard or extended phenotyping) or genotypically matched units

b) Providing ABO/RhD compatible, K-negative units after ruling out or identifying alloantibodies using DTT-treated reagent RBCs

Uncrossmatched, ABO/RhD compatible RBC units should be administered if transfusion is needed emergently as per local blood bank practice.

Despite daratumumab binding to CD38 on erythrocytes, no indication of clinically significant hemolysis has been observed in daratumumab studies. For additional details, refer to the Daratumumab IB.

9.8. Sample Collection and Handling

The actual dates and times of sample collection must be recorded in the CRF or laboratory requisition form. Refer to the Time and Events Schedule (Table 1 to Table 11) for the timing and frequency of all sample collections.

Instructions for the collection, handling, storage, and shipment of samples are found in the laboratory manual that will be provided. Collection, handling, storage, and shipment of samples must be under the specified, and where applicable, controlled temperature conditions as indicated in the laboratory manual.

9.9. Medical Resource Utilization

Health economics data such as medical resource utilization data, associated with medical encounters, will be collected in the CRF by the investigator and study-site personnel for all subjects throughout the study. Protocol-mandated procedures, tests, and encounters are excluded. Per the Time and Events Schedules (Table 1, Table 3, Table 5, Table 6, and Table 9), all medical care encounters since the previous collection will be collected for all subjects. Medical resource evaluation data will be collected until Day 180 (± 7 days). Health economics data such as costs associated with the medical encounters will be collected separately from the eCRF. All health economic data will be used only in a de-identified manner.

The data collected may be used to conduct exploratory economic analyses and will include:

- Number and duration of medical care encounters, including surgeries, and other selected procedures (inpatient and outpatient)
- Duration of hospitalization (total days length of stay, including duration by wards; eg, intensive care unit)
- Number and character of diagnostic and therapeutic tests and procedures
- Outpatient medical encounters and treatments (including physician or emergency room visits, tests and procedures, and medications)

10. SUBJECT COMPLETION/DISCONTINUATION OF STUDY TREATMENT/ WITHDRAWAL FROM THE STUDY

10.1. Completion

A subject will be considered to have completed the study if he or she dies before the end of the specific study cohort, has not been lost to follow-up or has not withdrawn consent for study participation before the end of the corresponding study cohort.

10.2. Discontinuation of Study Treatment

A subject should not receive JNJ-68284528, or must be discontinued from lenalidomide treatment (Cohort D), or D-VRd and lenalidomide treatment (Cohort E) if:

- The investigator believes that for safety reasons or tolerability reasons (eg, adverse event) it is in the best interest of the subject to discontinue study treatment
- Grade ≥3 nonhematologic toxicity related to cyclophosphamide and fludarabine occurs, and precludes retreatment with cyclophosphamide and fludarabine prior to JNJ-68284528 infusion per Section 6.1
- The subject received concurrent (non-protocol) anticancer treatment (with exception of sponsor-approved bridging therapy) prior to initial infusion of JNJ-68284528
- Confirmed disease progression per IMWG criteria (Attachment 1) either between the time of conditioning therapy and infusion of JNJ-68284528, or during the post-JNJ-68284528 infusion treatment phase of Cohort D and Cohort E with lenalidomide (as applicable). For subjects in Cohorts A, B, and C without measurable disease in serum or urine at screening, progression on either PET/CT scan or Whole Body MRI (see Attachment 22 for imaging response criteria) will be used
- Subject refuses further study treatment
- Noncompliance with study treatment or procedure requirements
- The subject becomes pregnant prior to infusion, or during the post-JNJ-68284528 infusion lenalidomide treatment phase of Cohort D and Cohort E

The primary reason for treatment discontinuation will be documented in the eCRF and source documents, and the subject should be followed per standard of care until recovery from bridging therapy or cyclophosphamide and fludarabine conditioning regimen. If a subject's study treatment is discontinued for any reason, this will not result in automatic withdrawal of the subject from the study.

10.3. Withdrawal from the Study

A subject will be withdrawn from the study for any of the following reasons:

- Lost to follow-up
- Withdrawal of consent
- Failure to manufacture JNJ-68284528 after 2 apheresis attempts*
- The sponsor discontinues the study

* A 3rd apheresis attempt may be permitted if an immediately rectifiable cause is identified (eg, product shipped improperly) and with sponsor approval.

The reason(s) for subject withdrawal will be recorded on the eCRF and source documents. If a subject is lost to follow-up, every reasonable effort must be made by the study site personnel to contact the subject and determine the reason for discontinuation/withdrawal. The measures taken to follow up must be documented.

When a subject withdraws following dosing with JNJ-68284528, the reason for withdrawal is to be documented in the CRF and in the source document. Study assessments for the last visit in the post-infusion period (Time and Events Schedule: Day 100) should be completed prior to withdrawal, if feasible. If the reason for withdrawal from the study is withdrawal of consent, then no additional assessments are allowed.

10.4. Withdrawal from the Use of Research Samples

Withdrawal from the Use of Samples in Future Research

The subject may withdraw consent for use of samples for research (refer to Section 16.2.5, Long-Term Retention of Samples for Additional Future Research). In such a case, samples will be destroyed after they are no longer needed for the clinical study. Details of the sample retention for research are presented in the main ICF.

11. STATISTICAL METHODS

Statistical analysis will be done by the sponsor or under the authority of the sponsor. A general description of the statistical methods to be used to analyze the efficacy and safety data is outlined below. Specific details will be provided in the Statistical Analysis Plan.

Statistical analysis will be performed for each cohort separately.

Continuous variables will be summarized using the number of observations, mean, standard deviation, coefficient of variation, median, and range as appropriate. Categorical values will be summarized using the number of observations and percentages as appropriate.

11.1. Subject Information

The analysis populations for this study are defined as follows:

- **Modified Intent-To-Treat (mITT) Analysis Set:**
  - For Cohorts A, B, C, D, and F: This set consists of subjects who received a JNJ-68284528 infusion at the target dose and will be considered as the primary analysis set for all efficacy summaries.
  - For Cohort E: This set consists of subjects who received at least a dose of D-VRd induction therapy and received a JNJ-68284528 infusion at the target dose, and will be considered as the primary analysis set for all efficacy summaries.
- **All Treated Analysis Set:** This set consists of subjects who received JNJ-68284528 infusion and will be considered as the primary analysis set for safety summaries.
- **Pharmacokinetic Analysis Set:** This set consists of all subjects who received JNJ-68284528 infusion and have at least 1 post-dose pharmacokinetic sample. Pharmacokinetic data of subjects who received daratumumab administration in Cohort E and have at least 1 post-dose pharmacokinetic sample may be included in the set.

- **Immunogenicity Analysis Set:** This set consists of all subjects who received JNJ-68284528 infusion and have at least 1 post-dose immunogenicity sample. Immunogenicity data of daratumumab of subjects who received daratumumab administration in Cohort E and have at least 1 post-dos sample may be included in the set.

11.2. Sample Size Determination

No formal statistical hypothesis testing will be performed. The sample size of each cohort is selected to collect necessary data on preliminary efficacy and safety.

11.3. Efficacy Analyses

Endpoint Definitions:

- Minimal residual disease (MRD) negative rate is defined as the proportion of subjects who have negative MRD by bone marrow aspirate at any time point
  - For Cohorts A, B, and C: after initial dose of JNJ-68284528 and before disease progression or starting subsequent therapy including retreatment of JNJ-68284528.
  - For Cohorts D and F: after infusion of JNJ-68284528 and before disease progression or starting subsequent therapy.
  - For Cohort E: after the first dose date of D-VRd and before disease progression or starting subsequent therapy

MRD negative is defined as less than 1 in 10^5 residual tumor cells detected in the bone marrow.

- MRD negative rate at 12 months for subjects who achieved a complete response (CR MRD neg 12 month) is defined as the proportion of subjects who are MRD negative by bone marrow aspirate and meet the IMWG criteria for complete response at 12 months (+/- 3 months) or for subjects without measurable disease in Cohorts A, B, C, and F complete response via imaging criteria (Attachment 22) at 12 months (+/- 3 months)
  - For Cohorts A, B, and C: after initial dose of JNJ-68284528 and before disease progression or starting subsequent therapy including retreatment of JNJ-68284528.
  - For Cohorts D and F: after infusion of JNJ-68284528 and before disease progression or starting subsequent therapy.
  - For Cohort E: after the first dose date of D-VRd and before disease progression or starting subsequent therapy.
- Time to MRD negativity will be calculated among subjects who are MRD negative by bone marrow aspirate
  - For Cohorts A, B, C, D, and F: from the date of the initial infusion of JNJ-68284528 to the initial date of reaching the MRD negative status.
  - For Cohort E: from the first dose date of D-VRd to the initial date of reaching the MRD negative status.

Duration of MRD negativity will be calculated among subjects who are MRD negative by bone marrow aspirate from the date of initial MRD negativity to the date when minimal residual disease is detected at the same threshold.

Overall response rate (ORR) is defined as the proportion of subjects who achieve a PR or better according to the IMWG criteria (Durie 2006; Durie 2015; Rajkumar 2011; Kumar 2016). For subjects with neither serum nor urine measurable disease and using PET/CT or whole body MRI to satisfy the measurable disease criteria (Cohorts A, B, C, and F), see Attachment 22 for adjudication of response criteria and Attachment 23 for reporting considerations. Response to treatment will be analyzed by a validated computerized algorithm (Dimopoulos 2016; Palumbo 2016).

VGPR or better response rate (sCR+CR+VGPR) is defined as the proportion of subjects who achieve a VGPR or better response according to the IMWG criteria (Durie 2006; Durie 2015; Rajkumar 2011; Kumar 2016).

Duration of response (DOR) will be calculated among responders (with a PR or better response) from the date of initial documentation of a response (PR or better) to the date of first documented evidence of progressive disease, as defined in the IMWG criteria. Relapse from CR by positive immunofixation or trace amount of M-protein is not considered as disease progression. Disease evaluations will continue beyond relapse from CR until disease progression is confirmed. For subjects who have not progressed, data will be censored at the last disease evaluation before the start of any subsequent anti-myeloma therapy.

- Time to response (TTR) is defined as
  - For Cohorts A, B, C, D, and F: from the date of the initial infusion of JNJ-68284528 and the first efficacy evaluation that the subject has met all criteria for PR or better.
  - For Cohort E: from the first dose date of D-VRd to the first efficacy evaluation that the subject has met all criteria for PR or better.

Progression-free survival (PFS) is defined as the time from the date of the initial infusion of JNJ-68284528 for Cohorts A, B, C, D, and F or the date of first dose of D-VRd for Cohort E to the date of first documented disease progression, as defined in the IMWG criteria, or death due to any cause, whichever occurs first. For subjects in Cohorts A, B, and C without measurable disease in serum or urine at screening, PFS is defined as the time from the date of the initial infusion of JNJ-68284528 to the date of disease progression as identified by imaging response criteria in Attachment 22 or death due to any cause, whichever occurs first. For subjects who have not progressed and are alive, data will be censored at the last disease evaluation before the start of any subsequent anti-myeloma therapy.

Overall survival (OS) is measured from the date of the initial infusion of JNJ-68284528 for Cohorts A, B, C, D, and F or the date of first dose of D-VRd for Cohort E to the date of the subject's death. If the subject is alive or the vital status is unknown, then the subject's data will be censored at the date the subject was last known to be alive.

The primary analysis for the primary endpoint, the overall MRD negative rate, will be conducted approximately at 1 year after the last subject for each individual cohort has received his or her initial dose of JNJ-68284528, and will be based on the mITT analysis set. For Cohort A, primary analysis of the initial subjects (prior to Cohort A expansion) will occur approximately 1 year after the last the subject is dosed. A primary analysis for subjects in the expanded cohort will occur approximately 1 year after the last subject is dosed in the expanded cohort. The analysis will be performed separately for each cohort. The MRD negative rate and its 2-sided 95% Clopper-Pearson exact CI will be presented. A sensitivity analysis of overall MRD negative rate will be performed based on the subjects in the mITT analysis set who received the JNJ-68284528 product that met all of the pre-specified release criteria.

The efficacy analyses will be provided for each cohort separately.

For time-to-event endpoints, such as DOR, PFS, and OS, the distributions will be provided using Kaplan-Meier estimates. Detailed analysis methods will be provided in the Statistical Analysis Plan.

11.4. Pharmacokinetic Analyses

All concentrations below the lowest quantifiable concentration or missing data will be labeled as such in the concentration database. Concentrations below the lowest quantifiable concentration will be treated as zero in the summary statistics. Descriptive statistics will be used to summarize CAR-T positive cell count and transgene level at each sampling timepoint. By dose level, individual pharmacokinetic parameters, including descriptive statistics (C_{max}, t_{max}, t_{last}, AUC_{last}, AUC_{∞}, λ_z, $t_{1/2}$) will be summarized in tables and listings. Descriptive statistics will be used to summarize daratumumab serum concentrations at each sampling timepoint.

If sufficient data are available, then other pharmacokinetic/pharmacodynamic modeling may be performed, including exploring the relationship between JNJ-68284528 cellular concentrations, transgene levels, pharmacodynamic markers (eg, sBCMA, M-protein) and endpoints of clinical efficacy and safety. If performed, details and results of the analysis will be presented in a separate report.

11.5. Immunogenicity Analyses

The incidence of anti-JNJ-68284528 antibodies will be summarized for all subjects who receive JNJ-68284528 and have appropriate samples for detection of antibodies to JNJ-68284528 (ie, subjects with at least 1 sample obtained after infusion of JNJ-68284528). The results will be summarized by cohort for subjects with appropriate samples for the detection of antibodies to JNJ-68284528.

The incidence of anti-daratumumab antibodies will be summarized for all subjects who receive daratumumab in Cohort E have appropriate samples for detection of antibodies to daratumumab (ie. Subjects with at least 1 sample obtained after first dose of daratumumab).

Immunogenicity analyses will be descriptive in nature and will include the number and percentage of subjects who developed anti-drug antibodies. The effect of anti-drug antibodies on pharmacokinetics, safety, and efficacy may also be evaluated.

11.6. Pharmacokinetic/Pharmacodynamic Analyses

If sufficient data are available, then other pharmacokinetic/pharmacodynamic modeling may be performed, including exploring the relationship between JNJ-68284528 cellular concentrations, transgene levels, pharmacodynamic markers (eg, sBCMA, M-protein) and endpoints of clinical efficacy and safety. If performed, details and results of the analysis will be presented in a separate report.

11.7. Safety Analyses

All safety analyses are to be performed on data from all treated analysis set. The baseline value for safety assessment is defined as the value collected at the time closest to, but prior to, the start of JNJ-68284528 infusion for Cohorts A, B, C, D, and F or the first dose of D-VRd for Cohort E. The safety parameters to be evaluated are the incidence, severity, and type of adverse events, clinically significant changes in the subject's physical examination findings, vital signs measurements, and clinical laboratory results. Exposure to investigational product and reasons for discontinuation of study treatment will be tabulated. Adverse events will be summarized by system organ class, preferred term, worst grade experienced by the subject, and by cohort.

Adverse Events

The verbatim terms used in the CRF by investigators to identify adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Treatment-emergent adverse events are adverse events with onset after JNJ-68284528 infusion for Cohorts A, B, C, D, and F or after the first dose of D-VRd for Cohort E or that are a consequence of a pre-existing condition that has worsened since baseline. All reported treatment-emergent adverse events will be included in the analysis. For each adverse event, the percentage of subjects who experience at least 1 occurrence of the given event will be summarized by cohort. In addition, comparisons between cohorts will be provided if appropriate.

Summaries, listings, datasets, or subject narratives may be provided, as appropriate, for those subjects who die, who experience an adverse event of special interest, who discontinue study treatment due to an adverse event, or who experience a severe or a serious adverse event.

Adverse events that occur after administration of the conditioning regimen and before JNJ-68284528 infusion will be summarized and listed separately.

Parameters with predefined NCI-CTCAE toxicity grades will be summarized except for CRS and ICANS. Cytokine release syndrome grading will be evaluated and summarized according to the ASTCT consensus grading (Attachment 2; Lee 2019). ICANS will be graded and summarized using the ASTCT consensus grading (Attachment 4). In addition, all individual symptoms of CRS (eg, fever, hypotension) and ICANS (eg, depressed level of consciousness, seizures) captured as individual AEs and graded by CTCAE criteria will be also summarized. Neurotoxicity that is not

temporally associated with CRS, or any other neurologic AEs that do not qualify as ICANS, will be graded and summarized by CTCAE criteria. Change from baseline to the worst AE grade experienced by the subject during the study will be provided as shift tables.

Clinical Laboratory Tests

Laboratory data will be summarized by type of laboratory test. Descriptive statistics will be calculated for each laboratory analyte at baseline and for observed values and changes from baseline at each scheduled time point. Worst toxicity grade during treatment will be presented according to NCI-CTCAE Version 5.0. Change from baseline to the worst toxicity grade experienced by the subject during the study will be provided as shift tables.

Electrocardiogram (ECG)

The interpretation of the ECGs as determined by a qualified physician (investigator or qualified designee) will be summarized at scheduled time points.

Vital Signs

Descriptive statistics of temperature, pulse/heart rate, respiratory rate, and blood pressure (systolic and diastolic) values and changes from baseline will be summarized at each scheduled time point. The percentage of subjects with values beyond clinically important limits will be summarized.

11.8. Patient-reported Outcome Assessments

The EORTC QLQ-C30, MySIm-Q, PGIC, and PGIS will be descriptively summarized at each time point. The proportion of subjects exceeding meaningful change thresholds will be evaluated to assess individual change from baseline (EORTC Quality of Life 2018). Frequency distributions of the PRO-CTCAE items by visit will be reported.

12. ADVERSE EVENT REPORTING

Timely, accurate, and complete reporting and analysis of safety information from clinical studies are crucial for the protection of subjects, investigators, and the sponsor, and are mandated by regulatory agencies worldwide. The sponsor has established Standard Operating Procedures in conformity with regulatory requirements worldwide to ensure appropriate reporting of safety information; all clinical studies conducted by the sponsor or its affiliates will be conducted in accordance with those procedures.

12.1. Definitions

12.1.1. Adverse Event Definitions and Classifications

Adverse Event

An adverse event is any untoward medical occurrence in a clinical study subject administered a medicinal (investigational or non-investigational) product. An adverse event does not necessarily have a causal relationship with the treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal finding), symptom, or disease temporally associated with the use of a medicinal (investigational or non-investigational) product, whether or not related

to that medicinal (investigational or non-investigational) product. (Definition per International Conference on Harmonisation [ICH])

This includes any occurrence that is new in onset or aggravated in severity or frequency from the baseline condition, or abnormal results of diagnostic procedures, including laboratory test abnormalities.

Note: The sponsor collects adverse events starting with the signing of the ICF (refer to Section 12.3.1, All Adverse Events, for time of last adverse event recording).

Serious Adverse Event

A serious adverse event based on ICH and EU Guidelines on Pharmacovigilance for Medicinal Products for Human Use is any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening

  (The subject was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe.)
- Requires inpatient hospitalization that was not required by the protocol or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Is a suspected transmission of any infectious agent via a medicinal product
- Is Medically Important*

*Medical and scientific judgment should be exercised in deciding whether expedited reporting is also appropriate in other situations, such as important medical events that may not be immediately life threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent one of the other outcomes listed in the definition above. These should usually be considered serious.

If a serious and unexpected adverse event occurs for which there is evidence suggesting a causal relationship between the study treatment and the event (eg, death from anaphylaxis), the event must be reported as a serious and unexpected suspected adverse reaction even if it is a component of the study endpoint (eg, all-cause mortality).

Unlisted (Unexpected) Adverse Event/Reference Safety Information

An adverse event is considered unlisted if the nature or severity is not consistent with the applicable product reference safety information. For JNJ-68284528 and daratumumab the expectedness of an adverse event will be determined by whether or not it is listed in the Investigator's Brochure. For dexamethasone, bortezomib, and lenalidomide, with a marketing authorization, the expectedness of an adverse event will be determined by whether or not it is listed in the respective USPI or SmPC.

Adverse Event Associated with the Use of the Drug

An adverse event is considered associated with the use of the drug if the attribution is related by the definitions listed in Section 12.1.2, Attribution Definitions.

12.1.2. Attribution Definitions

Not Related

An adverse event that is not related to the use of the drug.

Related

An adverse event that might be due to the use of the drug.

12.1.3. Severity Criteria

An assessment of severity grade will be made by the investigator according to the NCI CTCAE Version 5.0, with the exception of CRS and ICANS. CRS should be evaluated according to the ASTCT consensus grading (Lee 2019) (Attachment 2). ICANS should be graded using the ASTCT consensus grading (Attachment 4). In addition to capturing ICANS and CRS adverse events (graded by ASTCT consensus grading), all individual symptoms of CRS (eg, fever, hypotension) and CAR-T cell-related neurotoxicity (eg, depressed level of consciousness, seizures) must be captured as individual adverse events and graded by CTCAE criteria. Changes in handwriting (ie, micrographia, dysgraphia, or agraphia) should be graded using the criteria outlined in the Attachment 17. Other neurotoxicities will be graded by CTCAE criteria. Any adverse event or serious adverse event not listed in the NCI CTCAE Version 5.0 will be graded according to investigator clinical judgment by using the standard grades as follows:

Grade 1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
Grade 2	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living.*
Grade 3	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living.**
Grade 4	Life-threatening consequences; urgent intervention indicated.
Grade 5	Death related to adverse event.

Activities of Daily Living (ADL)

* Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

** Self-care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

12.2. Special Reporting Situations

Safety events of interest on a sponsor study treatment that may require expedited reporting or safety evaluation include, but are not limited to:

- Overdose of a sponsor study treatment
- Suspected abuse/misuse of a sponsor study treatment
- Accidental or occupational exposure to a sponsor study treatment
- Medication error involving a sponsor product (with or without subject/patient exposure to the sponsor study treatment, eg, name confusion)
- Exposure to a sponsor study treatment from breastfeeding

In the event of a special reporting situation, the investigator or treating physician should contact the Sponsor and closely monitor for adverse events. Special reporting situations should be recorded in the eCRF. Any special reporting situation that meets the criteria of an adverse event should be recorded on the adverse event page of the eCRF. Serious adverse events should also follow the SAE reporting process to the Sponsor.

Since JNJ-68284528 will be individually manufactured and provided by the sponsor for complete administration in a single infusion, overdose with JNJ-68284528 is not applicable for this study.

12.3. Procedures

12.3.1. All Adverse Events

All adverse events (with the exception of delayed AEs [see below] and HBV reactivation and COVID-19 infection) and special reporting situations will be reported by the subject (or, when appropriate, by a caregiver, surrogate, or the subject's legally acceptable representative) from the time a signed and dated informed consent is obtained until 100 days after infusion of JNJ-68284528 (Cohorts A, B, C, and F) regardless if PD occurs prior to Day 100 or subsequent anti-myeloma therapy is started prior to Day 100, and 100 days after infusion of JNJ-68284528, or 30 days after last dose of lenalidomide, whichever is later (Cohort D and Cohort E). Beyond the adverse event reporting period, only SAEs regardless of causality and non-serious AEs that are considered related to a study drug need to be reported until the end of the study except as defined for delayed AEs below. In addition, events of HBV reactivation and COVID-19 infection will be reported during the first-year post infusion of JNJ-68284528.

Adverse events and special reporting situations, whether serious or non-serious, will be collected for 30-days after the last study procedure for subjects who are enrolled and unable to be apheresed or receive bridging therapy, conditioning regimen, or JNJ-68284528; these subjects will continue to be followed for survival and subsequent anti-myeloma therapies until the end of the study.

All adverse events, regardless of seriousness, severity, or presumed relationship to study treatment, must be recorded using medical terminology in the source document and the CRF. Whenever possible, diagnoses should be given when signs and symptoms are due to a common etiology (eg, cough, runny nose, sneezing, sore throat, and head congestion should be reported as "upper respiratory infection"). The exceptions are CRS and JNJ-68284528 CAR-T cell-related neurotoxicity; all symptoms associated with these events will be collected in the eCRF. Investigators must record in the CRF their opinion concerning the relationship of the adverse event

to study therapy. All measures required for adverse event management must be recorded in the source document and reported according to sponsor instructions.

Exceptions:

- Progression of disease should not be considered nor should be reported as an adverse event (or serious adverse event). However, signs and symptoms of disease progression or of clinical sequelae resulting from disease progression/lack of efficacy that are determined by the investigator to be of clinical significance should be reported per the usual reporting requirements (Section 12.1).

All deaths not related to disease progression occurring at any time of the study after receiving JNJ-68284528, should be reported to the sponsor following expedited reporting procedures (i.e. within 24 hours of awareness of the event).

The sponsor assumes responsibility for appropriate reporting of adverse events to the regulatory authorities. The sponsor will also report to the investigator (and the head of the investigational institute where required) all suspected unexpected serious adverse reactions (SUSARs). Testing for RCL will be conducted by the sponsor. The sponsor assumes responsibility for appropriate reporting of RCL positive test results to regulatory authorities. The sponsor will notify the investigator of positive RCL test results in a timely manner. These RCL positive test results will not be collected as an adverse event in the eCRF.

The investigator (or sponsor where required) must report SUSARs to the appropriate Independent Ethics Committee/Institutional Review Board (IEC/IRB) that approved the protocol unless otherwise required and documented by the IEC/IRB.

For all studies with an outpatient phase, including open-label studies, the subject must be provided with a "patient ID card" and instructed to carry this card with them for at least 2 years after JNJ-68284528 infusion indicating the following:

- Study number
- Statement, in the local language(s), that the subject is participating in a clinical study
- Investigator's name and 24-hour contact telephone number
- Local sponsor's name and 24-hour contact telephone number (for medical staff only)
- Site number
- Subject number

12.3.2. Serious Adverse Events

All SAEs, as well as PQC, occurring during the study must be reported to the appropriate sponsor contact person by study site personnel within 24 hours of their knowledge of the event.

Serious AEs (regardless of causality) must be reported for the duration of the study post-infusion of JNJ-68284528 and subsequently will be collected yearly in a long-term follow-up study for up to 15 years post-infusion of JNJ-68284528.

Events that require an escalation of care when the subject is already hospitalized should be recorded as an SAE. Examples of such events include movement from routine care in the hospital to the intensive care unit or if that event resulted in a prolongation of the existing planned hospitalization.

Information regarding SAEs will be transmitted to the sponsor using the Serious Adverse Event Form and Safety Report Form of the CRF, which must be completed and reviewed by a physician from the study site and transmitted to the sponsor within 24 hours. The initial and follow-up reports of an SAE should be transmitted electronically or by facsimile (fax). Telephone reporting should be the exception and the reporter should be asked to complete the appropriate form(s) first.

All serious adverse events that have not resolved by the end of the study, or that have not resolved upon discontinuation of the subject's participation in the study, must be followed until any of the following occurs:

- The event resolves
- The event stabilizes
- The event returns to baseline, if a baseline value/status is available
- The event can be attributed to agents other than the study treatment or to factors unrelated to study conduct
- It becomes unlikely that any additional information can be obtained (subject or health care practitioner refusal to provide additional information, lost to follow-up after demonstration of due diligence with follow-up efforts)

Suspected transmission of an infectious agent by a medicinal product will be reported as a serious adverse event. Any event requiring hospitalization (or prolongation of hospitalization) that occurs during the course of a subject's participation in a study must be reported as a serious adverse event, except hospitalizations for the following:

- Routine monitoring hospitalizations post-infusion required per protocol.
- Hospitalizations not intended to treat an acute illness or adverse event (eg, social reasons such as pending placement in long-term care facility).
- Surgery or procedure planned before entry into the study (must be documented in the CRF). Note: Hospitalizations that were planned before the signing of the ICF, and where the underlying condition for which the hospitalization was planned has not worsened, will not be considered serious adverse events. Any adverse event that results in a prolongation of the originally planned hospitalization is to be reported as a new serious adverse event.
- The administration of blood or platelet transfusions. Hospitalization or prolonged hospitalization for a complication of such transfusion remains a reportable serious adverse event.

- The investigator may choose to hospitalize the subject as per institutional standards for CAR-T therapy and in accordance to the criteria provided in Attachment 14.

For subjects in Cohort E, following treatment with daratumumab, if a subject is hospitalized overnight for observation but has not experienced a significant medical event, that hospitalization should not be reported as a serious adverse event.

12.3.3. Adverse Events of Special Interest

Second primary malignancies are AEs of special interest and will be followed as part of standard safety monitoring activities by the sponsor, regardless of severity or causality from the time of JNJ-68284528 dosing to the end of study. For the purpose of reporting, this includes both new primary malignancies and recurrence of pre-existing malignancies with the exception of multiple myeloma (which should be reported as PD). In addition, CRS and CAR-T cell-related neurotoxicity including ICANS and other neurotoxicities, are also AEs of special interest and will be followed as part of standard safety monitoring activities by the sponsor, regardless of severity or causality. These events will require enhanced data collection in the eCRF, be reported to the sponsor in a timely manner irrespective of seriousness and followed until recovery or until there is no further improvements.

In addition, the following must be reported to the sponsor following the Serious Adverse Event reporting process within 24 hours of awareness of the event beginning from Day 1 of JNJ-68284528 infusion and for the duration of the study, irrespective of seriousness (eg, serious or nonserious AEs) or causality:

- ≥Grade 3 CRS
- ≥Grade 3 neurotoxicity
- Any grade movement and neurocognitive toxicity (ie, parkinsonism)
- any grade SPMs (including recurrence of pre-existing malignancies)

Adverse events of special interest meeting the above criteria that are considered to be nonserious by the investigator are to be indicated as such on the SAE form and in the eDC tool. All AEs of special interest of any grade should be followed until recovery or until there is no further improvement.

12.3.4. Delayed Adverse Events

The following delayed AEs will be collected from the time of JNJ-68284528 administration and for the duration of study regardless of causality and subsequently will be collected yearly in a long-term follow-up study for up to 15 years post-infusion of JNJ-68284528:

- New primary malignancies or recurrence of pre-existing malignancy (all grades), with the exception of multiple myeloma (which should be reported as PD), must be reported to the sponsor within 24 hours of awareness of the event for the duration of the study, irrespective of seriousness or causality. In the event of malignancy, a tumor sample should be collected, and vector integration site analysis may be performed for possible insertional mutagenesis.

- New incidence or exacerbation of a pre-existing neurologic disorder (all grades). Grade 3 or higher neurotoxicity and any grade movement and neurocognitive toxicity (ie, parkinsonism) must be reported to the sponsor within 24 hours of awareness of the event for the duration of the study, irrespective of seriousness or causality.
- New incidence or exacerbation of a pre-existing rheumatologic or other autoimmune disorder (all grades).
- New incidence of Grade ≥3 hematologic disorder.
- New incidence of Grade ≥3 infection.

12.3.5. Pregnancy

All initial reports of pregnancy in subjects or partners of male subjects must be reported to the sponsor by the study-site personnel within 24 hours of their knowledge of the event using the appropriate pregnancy notification form. Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered serious adverse events and must be reported using the Serious Adverse Event Form. Any subject who becomes pregnant during the study must discontinue further study treatment. Because the effect of the study treatment on sperm is unknown, pregnancies in partners of male subjects included in the study will be reported as noted above. Follow-up information regarding the outcome of the pregnancy and any postnatal sequelae in the infant will be required.

For subjects in Cohort D and Cohort E: lenalidomide is a thalidomide analogue and is contraindicated for use during pregnancy. Birth defects have been observed in preclinical studies of lenalidomide similar to thalidomide in humans. Therefore, strict monitoring for pregnancy must be conducted during Screening and throughout the Treatment Phase, as specified in the Time and Events Schedule. Investigators should comply with the lenalidomide Global Pregnancy Prevention Plan or with the respective country specific REVLIMID/lenalidomide Risk Minimization Program (ie, Pregnancy prevention program), whichever is more stringent, as implemented in the post-marketing setting and ensure that all subjects adhere to these programs. When no REVLIMID/lenalidomide Risk Minimization Program exists, subjects must adhere to the lenalidomide Global Pregnancy Prevention Plan. If pregnancy does occur, then study treatment should be discontinued immediately, and the subject should be referred to an obstetrician experienced in reproductive toxicity for further evaluation and counseling.

12.4. Contacting Sponsor Regarding Safety

The names (and corresponding telephone numbers) of the individuals who should be contacted regarding safety issues or questions regarding the study are listed in the Contact Information page(s), which will be provided as a separate document.

13. PRODUCT QUALITY COMPLAINT HANDLING

A product quality complaint (PQC) is defined as any suspicion of a product defect related to manufacturing, labeling, or packaging, ie, any dissatisfaction relative to the identity, quality, durability, or reliability of a product, including its labeling or package integrity. A PQC may have an impact on the safety and efficacy of the product. Timely, accurate, and complete reporting and

analysis of PQC information from studies are crucial for the protection of subjects, investigators, and the sponsor, and are mandated by regulatory agencies worldwide. The sponsor has established procedures in conformity with regulatory requirements worldwide to ensure appropriate reporting of PQC information; all studies conducted by the sponsor or its affiliates will be conducted in accordance with those procedures.

13.1. Procedures

All initial PQCs must be reported to the sponsor by the study-site personnel within 24 hours after being made aware of the event.

If the defect is combined with a serious adverse event, the study-site personnel must report the PQC to the sponsor according to the serious adverse event reporting timelines (refer to Section 12.3.2, Serious Adverse Events). A sample of the suspected product should be maintained for further investigation if requested by the sponsor.

13.2. Contacting Sponsor Regarding Product Quality

The names (and corresponding telephone numbers) of the individuals who should be contacted regarding product quality issues are listed in the Contact Information page(s), which will be provided as a separate document.

14. STUDY TREATMENT INFORMATION

14.1. Physical Description of Study Treatment

JNJ-68284528 therapy is a BCMA-directed genetically modified autologous T cell immunotherapy that involves reprogramming a subject's T cells with a transgene encoding a chimeric antigen receptor (CAR) to identify and eliminate BCMA-expressing malignant and normal cells. Upon binding to BCMA-expressing cells, the CAR transmits a signal to promote T cell expansion, activation, target cell elimination, and persistence of the JNJ-68284528.

14.2. Packaging

JNJ-68284528 will be provided in an infusion bag with specific subject identifiers, this will include subject number and subject apheresis identification number or donor identification number (DIN), subject name and subject date of birth, as allowed by local regulations.

14.3. Labeling

Study treatment labels will contain information to meet the applicable regulatory requirements.

14.4. Preparation, Handling, and Storage

JNJ-68284528 is provided in a single-dose unit containing CAR-positive viable T cells based on the subject weight reported at the time of apheresis.

JNJ-68284528 therapy contains human cells genetically modified with a lentiviral vector. Follow local biosafety guidelines applicable for handling and disposal of such products. The product is prepared from autologous blood collected by apheresis. JNJ-68284528 may carry a risk of

transmitting infectious viruses to healthcare professionals handling the product. Accordingly, healthcare professionals should employ universal precautions to avoid potential transmission of infectious diseases when handling the product.

Detailed instructions for storage conditions and handling will accompany clinical drug supplies to the clinical study sites. The storage conditions and expiry dates are indicated on the label. Refer to the IPPI for additional guidance on study treatment preparation, handling, and storage.

14.5. Drug Accountability

Information in this section relates to study treatment that is supplied to investigational sites from the study sponsor.

The investigator is responsible for ensuring that all sponsor-provided study treatment received at the site is inventoried and accounted for throughout the study. The study treatment administered to the subject must be documented on the treatment accountability form. All study treatment will be stored and disposed of according to the sponsor's instructions. Study-site personnel must not combine contents of the study treatment containers.

Study treatment must be handled in strict accordance with the protocol and the container label and must be stored at the study site in a limited-access area or in a locked cabinet under appropriate environmental conditions. Unused study treatment must be available for verification by the sponsor's study site monitor during on-site monitoring visits. The return to the sponsor of unused study treatment will be documented on the treatment return form.

Potentially hazardous materials such as used ampules, needles, syringes and vials containing hazardous liquids, should be disposed of immediately in a safe manner and therefore will not be retained for treatment accountability purposes.

Study treatment should be dispensed under the supervision of the investigator or a qualified member of the study-site personnel, or by a hospital/clinic pharmacist. Study treatment will be supplied only to subjects participating in the study. The investigator agrees neither to dispense the study treatment from, nor store it at, any site other than the study sites agreed upon with the sponsor.

15. STUDY-SPECIFIC MATERIALS

The investigator will be provided with the following supplies:

- Study protocol
- Investigator's Brochure (JNJ-68284528)
- IPPI/ CTPPM (includes apheresis and cell processing instructions)
- Laboratory manual
- Interactive web response system manual
- Printed PRO questionnaires and PRO Completion Guidelines/Training Materials

- Electronic data capture (eDC) Manual
- Sample ICF
- Subject diaries and instructions/educational materials
- Thermal printer and barcode scanner

16. ETHICAL ASPECTS

16.1. Study-specific Design Considerations

Potential subjects will be fully informed of the risks and requirements of the study and, during the study, subjects will be given any new information that may affect their decision to continue participation. They will be told that their consent to participate in the study is voluntary and may be withdrawn at any time with no reason given and without penalty or loss of benefits to which they would otherwise be entitled. Only subjects who are fully able to understand the risks, benefits, and potential adverse events of the study, and provide their consent voluntarily will be enrolled.

Despite significant progress in the treatment of patients with multiple myeloma, it still remains uncured, indicating the need for new therapeutic strategies for these patients. As discussed in Section 1.1.5, 74 subjects with relapsed or refractory multiple myeloma have received treatment with LCAR-B38M CAR-T cells in a clinical study setting. An analysis of safety data for these subjects demonstrated a manageable safety profile consistent with its known mechanism of action. In view of the Legend-2 study results and the prognosis for the subject population being considered for this study, a positive risk-benefit profile is anticipated. Subjects will be closely monitored throughout the study, as discussed throughout this protocol, for both safety and clinical benefit.

Apheresis risks may include hypotension, faintness, blurry vision, dizziness, coldness, sweating, infection, abnormal blood clotting, allergic reaction, bleeding, seizures, abdominal cramps, and tingling in the limbs. Subjects will be closely monitored during the procedure and will be evaluated for hospitalization in the case of CRS. All subjects (inpatient and outpatient, Table 11) will be hospitalized from Day 5 to Day 14 after JNJ-68284528 infusion (with potential discharge on Day 10 if there are no CRS, neurotoxicity or other clinically significant events).

The blood sample collection scheme was designed to collect the minimum number of blood samples that accurately and completely describe the pharmacokinetic/pharmacodynamic characteristics of the study treatment. This minimizes the number of venipunctures and the total volume of blood collected from each subject during the study. The volume of blood to be drawn is considered to be customary and acceptable for subjects participating in a cancer clinical study and is deemed reasonable over the timeframe of the study, based upon the standard of the American Red Cross.

16.2. Regulatory Ethics Compliance

16.2.1. Investigator Responsibilities

The investigator is responsible for ensuring that the study is performed in accordance with the protocol, current ICH guidelines on Good Clinical Practice (GCP), and applicable regulatory and country-specific requirements.

Good Clinical Practice is an international ethical and scientific quality standard for designing, conducting, recording, and reporting studies that involve the participation of human subjects. Compliance with this standard provides public assurance that the rights, safety, and well-being of study subjects are protected, consistent with the principles that originated in the Declaration of Helsinki, and that the study data are credible.

16.2.2. Independent Ethics Committee or Institutional Review Board

Before the start of the study, the investigator (or sponsor where required) will provide the IEC/IRB with current and complete copies of the following documents (as required by local regulations):

- Final protocol and, if applicable, amendments
- Sponsor-approved ICF (and any other written materials to be provided to the subjects)
- Investigator's Brochure (or equivalent information) and amendments/addenda
- Sponsor-approved subject recruiting materials
- Information on compensation for study-related injuries or payment to subjects for participation in the study, if applicable
- Investigator's curriculum vitae or equivalent information (unless not required, as documented by the IEC/IRB)
- Information regarding funding, name of the sponsor, institutional affiliations, other potential conflicts of interest, and incentives for subjects
- Any other documents that the IEC/IRB requests to fulfill its obligation

This study will be undertaken only after the IEC/IRB has given full approval of the final protocol, amendments (if any, excluding the ones that are purely administrative, with no consequences for subjects, data or study conduct, unless required locally), the ICF, applicable recruiting materials, and subject compensation programs, and the sponsor has received a copy of this approval. This approval letter must be dated and must clearly identify the IEC/IRB and the documents being approved.

During the study the investigator (or sponsor where required) will send the following documents and updates to the IEC/IRB for their review and approval, where appropriate:

- Protocol amendments (excluding the ones that are purely administrative, with no consequences for subjects, data or study conduct)
- Revision(s) to ICF and any other written materials to be provided to subjects

- If applicable, new or revised subject recruiting materials approved by the sponsor
- Revisions to compensation for study-related injuries or payment to subjects for participation in the study, if applicable
- New edition(s) of the Investigator's Brochure and amendments/addenda
- Summaries of the status of the study at intervals stipulated in guidelines of the IEC/IRB (at least annually)
- Reports of adverse events that are serious, unlisted/unexpected, and associated with the study treatment
- New information that may adversely affect the safety of the subjects or the conduct of the study
- Deviations from or changes to the protocol to eliminate immediate hazards to the subjects
- Report of deaths of subjects under the investigator's care
- Notification if a new investigator is responsible for the study at the site
- Development Safety Update Report and Line Listings, where applicable
- Any other requirements of the IEC/IRB

For all protocol amendments (excluding the ones that are purely administrative, with no consequences for subjects, data or study conduct), the amendment and applicable ICF revisions must be submitted promptly to the IEC/IRB for review and approval before implementation of the change(s).

At least once a year, the IEC/IRB will be asked to review and reapprove this study, where required.

At the end of the study, the investigator (or sponsor where required) will notify the IEC/IRB about the study completion (if applicable, the notification will be submitted through the head of investigational institution).

16.2.3. Informed Consent

Each subject (or a legally acceptable representative) must give written consent according to local requirements after the nature of the study has been fully explained. The ICF(s) must be signed before performance of any study-related activity. The ICF(s) that is/are used must be approved by both the sponsor and by the reviewing IEC/IRB and be in a language that the subject can read and understand. The informed consent should be in accordance with principles that originated in the Declaration of Helsinki, current ICH and GCP guidelines, applicable regulatory requirements, and sponsor policy.

Before enrollment in the study, the investigator or an authorized member of the study-site personnel must explain to potential subjects or their legally acceptable representatives the aims, methods, reasonably anticipated benefits, and potential hazards of the study, and any discomfort participation in the study may entail. Subjects will be informed that their participation is voluntary and that they may withdraw consent to participate at any time. They will be informed that choosing not to participate will not affect the care the subject will receive for the treatment of his or her

disease. Subjects will be told that alternative treatments are available if they refuse to take part and that such refusal will not prejudice future treatment. Finally, they will be told that the investigator will maintain a subject identification register for the purposes of long-term follow up if needed and that their records may be accessed by health authorities and authorized sponsor personnel without violating the confidentiality of the subject, to the extent permitted by the applicable law(s) or regulations. By signing the ICF the subject or legally acceptable representative is authorizing such access, which includes permission to obtain information about his or her survival status. It also denotes that the subject agrees to allow his or her study physician to recontact the subject for the purpose of obtaining consent for additional safety evaluations, and subsequent disease-related treatments, if needed. The physician may also recontact the subject for the purpose of obtaining consent to collect information about his or her survival status.

The subject or legally acceptable representative will be given sufficient time to read the ICF and the opportunity to ask questions. After this explanation and before entry into the study, consent should be appropriately recorded by means of either the subject's or his or her legally acceptable representative's personally dated signature. After having obtained the consent, a copy of the ICF must be given to the subject.

If the subject or legally acceptable representative is unable to read or write, an impartial witness should be present for the entire informed consent process (which includes reading and explaining all written information) and should personally date and sign the ICF after the oral consent of the subject or legally acceptable representative is obtained.

When prior consent of the subject is not possible and the subject's legally acceptable representative is not available, enrollment procedures should be described in the protocol with documented approval/favorable opinion by the IEC/IRB to protect the rights, safety, and well-being of the subject and to ensure compliance with applicable regulatory requirements. The subject or legally acceptable representative must be informed about the study as soon as possible and give consent to continue.

16.2.4. Privacy of Personal Data

The collection and processing of personal data from subjects enrolled in this study will be limited to those data that are necessary to fulfill the objectives of the study.

These data must be collected and processed with adequate precautions to ensure confidentiality and compliance with applicable data privacy protection laws and regulations. Appropriate technical and organizational measures to protect the personal data against unauthorized disclosures or access, accidental or unlawful destruction, or accidental loss or alteration must be put in place. For tracking and traceability of the apheresis material and investigational product, subject name and date of birth, as allowed by local regulations, will be collected to ensure chain of identity of the investigational product for the subject. Sponsor personnel whose responsibilities require access to personal data agree to keep the identity of subjects confidential.

The informed consent obtained from the subject (or his or her legally acceptable representative) includes explicit consent for the processing of personal data and for the investigator/institution to allow direct access to his or her original medical records (source data/documents) for study-related monitoring, audit, IEC/IRB review, and regulatory inspection. This consent also addresses the transfer of the data to other entities and to other countries.

The subject has the right to request through the investigator access to his or her personal data and the right to request rectification of any data that are not correct or complete. Reasonable steps will be taken to respond to such a request, taking into consideration the nature of the request, the conditions of the study, and the applicable laws and regulations.

Exploratory biomarker, pharmacokinetic and immunogenicity research is not conducted under standards appropriate for the return of data to subjects. In addition, the sponsor cannot make decisions as to the significance of any findings resulting from exploratory research. Therefore, exploratory research data will not be returned to subjects or investigators, unless required by law or local regulations. Privacy and confidentiality of data generated in the future on stored samples will be protected by the same standards applicable to all other clinical data.

16.2.5. Long-term Retention of Samples for Additional Future Research

Samples, including apheresis product, collected in this study and JNJ-68284528 that was manufactured but not administered to a subject may be stored for up to 15 years (or according to local regulations) for additional research. Samples will only be used to understand JNJ-68284528, to understand multiple myeloma, to understand differential intervention responders, and to develop tests/assays related to JNJ-68284528. The research may begin at any time during the study or the post-study storage period.

Stored samples will be coded throughout the sample storage and analysis process and will not be labeled with personal identifiers. Subjects may withdraw their consent for their samples to be stored for research (refer to Section 10.4, Withdrawal from the Use of Samples in Future Research).

16.2.6. Country Selection

This study will only be conducted in those countries where the intent is to launch or otherwise help ensure access to the developed product if the need for the product persists, unless explicitly addressed as a specific ethical consideration in Section 16.1, Study-Specific Design Considerations.

17. ADMINISTRATIVE REQUIREMENTS

17.1. Protocol Amendments

Neither the investigator nor the sponsor will modify this protocol without a formal amendment by the sponsor. All protocol amendments must be issued by the sponsor and signed and dated by the investigator. Protocol amendments must not be implemented without prior IEC/IRB approval, or when the relevant competent authority has raised any grounds for non-acceptance, except when

necessary to eliminate immediate hazards to the subjects, in which case the amendment must be promptly submitted to the IEC/IRB and relevant competent authority. Documentation of amendment approval by the investigator and IEC/IRB must be provided to the sponsor. When the change(s) involves only logistic or administrative aspects of the study, the IEC/IRB (where required) only needs to be notified.

During the course of the study, in situations where a departure from the protocol is unavoidable, the investigator or other physician in attendance will contact the appropriate sponsor representative listed in the Contact Information page(s), which will be provided as a separate document. Except in emergency situations, this contact should be made before implementing any departure from the protocol. In all cases, contact with the sponsor must be made as soon as possible to discuss the situation and agree on an appropriate course of action. The data recorded in the CRF and source documents will reflect any departure from the protocol, and the source documents will describe this departure and the circumstances requiring it.

17.2. Recruitment Strategy

The first subject screened is considered the first act of recruitment and it becomes the study start date.

17.3. Regulatory Documentation

17.3.1. Regulatory Approval/Notification

This protocol and any amendment(s) must be submitted to the appropriate regulatory authorities in each respective country, if applicable. A study may not be initiated until all local regulatory requirements are met.

17.3.2. Required Prestudy Documentation

The following documents must be provided to the sponsor before shipment of study treatment to the study site:

- Protocol and amendment(s), if any, signed and dated by the principal investigator
- A copy of the dated and signed (or sealed, where appropriate per local regulations), written IEC/IRB approval of the protocol, amendments, ICF, any recruiting materials, and if applicable, subject compensation programs. This approval must clearly identify the specific protocol by title and number and must be signed (or sealed, where appropriate per local regulations) by the chairman or authorized designee.
- Name and address of the IEC/IRB, including a current list of the IEC/IRB members and their function, with a statement that it is organized and operates according to GCP and the applicable laws and regulations. If accompanied by a letter of explanation, or equivalent, from the IEC/IRB, a general statement may be substituted for this list. If an investigator or a member of the study-site personnel is a member of the IEC/IRB, documentation must be obtained to state that this person did not participate in the deliberations or in the vote/opinion of the study.
- Regulatory authority approval or notification, if applicable

- Signed and dated statement of investigator (eg, Form FDA 1572), if applicable
- Documentation of investigator qualifications (eg, curriculum vitae)
- Completed investigator financial disclosure form from the principal investigator, where required
- Signed and dated clinical trial agreement, which includes the financial agreement
- Any other documentation required by local regulations

The following documents must be provided to the sponsor before enrollment of the first subject:

- Completed investigator financial disclosure forms from all subinvestigators
- Documentation of subinvestigator qualifications (eg, curriculum vitae)
- Name and address of any local laboratory conducting tests for the study, and a dated copy of current laboratory normal ranges for these tests, if applicable
- Local laboratory documentation demonstrating competence and test reliability (eg, accreditation/license), if applicable

17.4. Subject Identification, Enrollment, and Screening Logs

The investigator agrees to complete a subject identification and enrollment log to permit easy identification of each subject during and after the study. This document will be reviewed by the sponsor study-site contact for completeness.

The subject identification and enrollment log will be treated as confidential and will be filed by the investigator in the study file. To ensure subject confidentiality, no copy will be made. All reports and communications relating to the study will identify subjects by subject identification and date of birth (as allowed by local regulations). In cases where the subject is not enrolled into the study, the date seen and date of birth (as allowed by local regulations) will be used.

For tracking and traceability of the apheresis material and investigational product, subject name and date of birth, as allowed by local regulations, will be collected to ensure chain of identity of the investigational product for the subject.

The investigator must also complete a subject screening log, which reports on all subjects who were seen to determine eligibility for inclusion in the study.

17.5. Source Documentation

At a minimum, source documents consistent in the type and level of detail with that commonly recorded at the study site as a basis for standard medical care must be available for the following: subject identification, eligibility, and study identification; study discussion and date of signed informed consent; dates of visits; results of safety and efficacy parameters as required by the protocol; record of all adverse events and follow-up of adverse events; concomitant medication; treatment receipt/dispensing/return records; study treatment administration information; and date of study completion and reason for early discontinuation of study treatment or withdrawal from the study, if applicable.

The author of an entry in the source documents should be identifiable.

Specific details required as source data for the study and source data collection methods will be reviewed with the investigator before the study and will be described in the monitoring guidelines (or other equivalent document).

The minimum source documentation requirements for Section 4, Inclusion Criteria and Exclusion Criteria that specify a need for documented medical history are as follows:

- Referral letter from treating physician or
- Complete history of medical notes at the site
- Discharge summaries

Inclusion and exclusion criteria not requiring documented medical history must be verified at a minimum by subject interview or other protocol required assessment (eg, physical examination, laboratory assessment) and documented in the source documents.

An electronic source system may be utilized, which contains data traditionally maintained in a hospital or clinic record to document medical care (eg, electronic source documents) as well as the clinical study-specific data fields as determined by the protocol. This data is electronically extracted for use by the sponsor. If the electronic source system is utilized, references made to the CRF in the protocol include the electronic source system but information collected through the electronic source system may not be limited to that found in the CRF. Data in this system may be considered source documentation.

17.6. Case Report Form Completion

Case report forms are prepared and provided by the sponsor for each subject in electronic format. All CRF entries, corrections, and alterations must be made by the investigator or authorized study-site personnel. The investigator must verify that all data entries in the CRF are accurate and correct.

The study data will be transcribed by study-site personnel from the source documents onto an electronic CRF, if applicable. Study-specific data will be transmitted in a secure manner to the sponsor.

Worksheets may be used for the capture of some data to facilitate completion of the CRF. Any such worksheets will become part of the subject's source documents. Data must be entered into CRF in English. The CRF must be completed as soon as possible after a subject visit and the forms should be available for review at the next scheduled monitoring visit.

If necessary, queries will be generated in the eDC tool. If corrections to a CRF are needed after the initial entry into the CRF, this can be done in either of the following ways:

- Investigator and study-site personnel can make corrections in the eDC tool at their own initiative or as a response to an auto query (generated by the eDC tool).

- Sponsor or sponsor delegate can generate a query for resolution by the investigator and study-site personnel.

17.7. Data Quality Assurance/Quality Control

Steps to be taken to ensure the accuracy and reliability of data include the selection of qualified investigators and appropriate study sites, review of protocol procedures with the investigator and study-site personnel before the study, periodic monitoring visits by the sponsor, and where applicable direct transmission of clinical laboratory data from a central laboratory into the sponsor's data base. Written instructions will be provided for collection, handling, storage, and shipment of samples.

Guidelines for CRF completion will be provided and reviewed with study-site personnel before the start of the study. The sponsor will review CRF for accuracy and completeness during on-site monitoring visits and after transmission to the sponsor; any discrepancies will be resolved with the investigator or designee, as appropriate. After upload of the data into the study database they will be verified for accuracy and consistency with the data sources.

17.8. Record Retention

In compliance with the ICH/GCP guidelines, the investigator/institution will maintain all CRF and all source documents that support the data collected from each subject, as well as all study documents as specified in ICH/GCP Section 8, Essential Documents for the Conduct of a Clinical Trial, and all study documents as specified by the applicable regulatory requirement(s). The investigator/institution will take measures to prevent accidental or premature destruction of these documents.

Essential documents must be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents will be retained for a longer period if required by the applicable regulatory requirements or by an agreement with the sponsor. It is the responsibility of the sponsor to inform the investigator/institution as to when these documents no longer need to be retained.

If the responsible investigator retires, relocates, or for other reasons withdraws from the responsibility of keeping the study records, custody must be transferred to a person who will accept the responsibility. The sponsor must be notified in writing of the name and address of the new custodian. Under no circumstance shall the investigator relocate or dispose of any study documents before having obtained written approval from the sponsor.

If it becomes necessary for the sponsor or the appropriate regulatory authority to review any documentation relating to this study, the investigator/institution must permit access to such reports.

17.9. Monitoring

The sponsor will use a combination of monitoring techniques (central, remote, or on-site monitoring) to monitor this study.

The sponsor will perform on-site monitoring visits as frequently as necessary. The monitor will record dates of the visits in a study site visit log that will be kept at the study site. The first post-initiation visit will be made as soon as possible after enrollment has begun. At these visits, the monitor will compare the data entered into the CRF with the source documents (eg, hospital/clinic/physician's office medical records). The nature and location of all source documents will be identified to ensure that all sources of original data required to complete the CRF are known to the sponsor and study-site personnel and are accessible for verification by the sponsor study-site contact. If electronic records are maintained at the study site, the method of verification must be discussed with the study-site personnel.

Direct access to source documents (medical records) must be allowed for the purpose of verifying that the recorded data are consistent with the original source data. Findings from this review will be discussed with the study-site personnel. The sponsor expects that, during monitoring visits, the relevant study-site personnel will be available, the source documents will be accessible, and a suitable environment will be provided for review of study-related documents. The monitor will meet with the investigator on a regular basis during the study to provide feedback on the study conduct.

In addition to on-site monitoring visits, remote contacts can occur. It is expected that during these remote contacts, study-site personnel will be available to provide an update on the progress of the study at the site.

17.10. Study Completion/Termination

17.10.1. Study Completion/End of Cohort

Cohorts A, B, C, and F will each be considered complete after the last subject has had two years of follow-up after the initial dose of JNJ-68284528. Cohort D and Cohort E will be considered complete 2 ½ years after the last subject receives their initial dose of JNJ-68284528. All subjects who received JNJ-68284528 will be asked to consent to the long-term follow-up study. The sponsor will continue to monitor consented subjects in the long-term follow-up study at least once per year for 15 years. An appropriate transition will be arranged between this study and the long-term follow-up study to ensure continuity in subject monitoring.

The final data from the study site will be sent to the sponsor (or designee) after completion of the final subject assessment at that study site, in the time frame specified in the Clinical Trial Agreement.

17.10.2. Study Termination

The sponsor reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. Study sites will be closed upon study completion.

A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the sponsor or investigator may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IEC/IRB or local health authorities, the sponsor's procedures, or GCP guidelines
- Inadequate recruitment of subjects by the investigator
- Discontinuation of further study treatment development

17.11. On-site Audits

Representatives of the sponsor's clinical quality assurance department may visit the study site at any time during or after completion of the study to conduct an audit of the study in compliance with regulatory guidelines and company policy. These audits will require access to all study records, including source documents, for inspection. Subject privacy must, however, be respected. The investigator and study-site personnel are responsible for being present and available for consultation during routinely scheduled study-site audit visits conducted by the sponsor or its designees.

Similar auditing procedures may also be conducted by agents of any regulatory body, either as part of a national GCP compliance program or to review the results of this study in support of a regulatory submission. The investigator should immediately notify the sponsor if he or she has been contacted by a regulatory agency concerning an upcoming inspection.

17.12. Use of Information and Publication

All information, including but not limited to information regarding JNJ-68284528 or the sponsor's operations (eg, patent application, formulas, manufacturing processes, basic scientific data, prior clinical data, formulation information) supplied by the sponsor to the investigator and not previously published, and any data, including exploratory biomarker research data, generated as a result of this study, are considered confidential and remain the sole property of the sponsor. The investigator agrees to maintain this information in confidence and use this information only to accomplish this study and will not use it for other purposes without the sponsor's prior written consent.

The investigator understands that the information developed in the study will be used by the sponsor in connection with the continued development of JNJ-68284528, and thus may be disclosed as required to other clinical investigators or regulatory agencies. To permit the information derived from the clinical studies to be used, the investigator is obligated to provide the sponsor with all data obtained in the study.

The results of the study will be reported in a Clinical Study Report generated by the sponsor and will contain data from all study sites that participated in the study as per protocol. Recruitment performance or specific expertise related to the nature and the key assessment parameters of the study will be used to determine a coordinating investigator for the study. Results of exploratory biomarker analyses performed after the Clinical Study Report has been issued will be reported in a separate report and will not require a revision of the Clinical Study Report. Study subject identifiers will not be used in publication of results. Any work created in connection with performance of the study and contained in the data that can benefit from copyright protection (except any publication by the investigator as provided for below) shall be the property of the sponsor as author and owner of copyright in such work.

Consistent with Good Publication Practices and International Committee of Medical Journal Editors guidelines, the sponsor shall have the right to publish such primary (multicenter) data and information without approval from the investigator. The investigator has the right to publish study site-specific data after the primary data are published. If an investigator wishes to publish information from the study, a copy of the manuscript must be provided to the sponsor for review at least 60 days before submission for publication or presentation. Expedited reviews will be arranged for abstracts, poster presentations, or other materials. If requested by the sponsor in writing, the investigator will withhold such publication for up to an additional 60 days to allow for filing of a patent application. In the event that issues arise regarding scientific integrity or regulatory compliance, the sponsor will review these issues with the investigator. The sponsor will not mandate modifications to scientific content and does not have the right to suppress information. For multicenter study designs and substudy approaches, secondary results generally should not be published before the primary endpoints of a study have been published. Similarly, investigators will recognize the integrity of a multicenter study by not submitting for publication data derived from the individual study site until the combined results from the completed study have been submitted for publication, within 18 months after study end date, or the sponsor confirms there will be no multicenter study publication. Authorship of publications resulting from this study will be based on the guidelines on authorship, such as those described in the ICMJE Recommendations for the Conduct, Reporting, Editing and Publication of Scholarly Work in Medical Journals, which state that the named authors must have made a significant contribution to the conception or design of the work; or the acquisition, analysis, or interpretation of the data for the work; and drafted the work or revised it critically for important intellectual content; and given final approval of the version to be published; and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Registration of Clinical Studies and Disclosure of Results

The sponsor will register and disclose the existence of and the results of clinical studies as required by law.

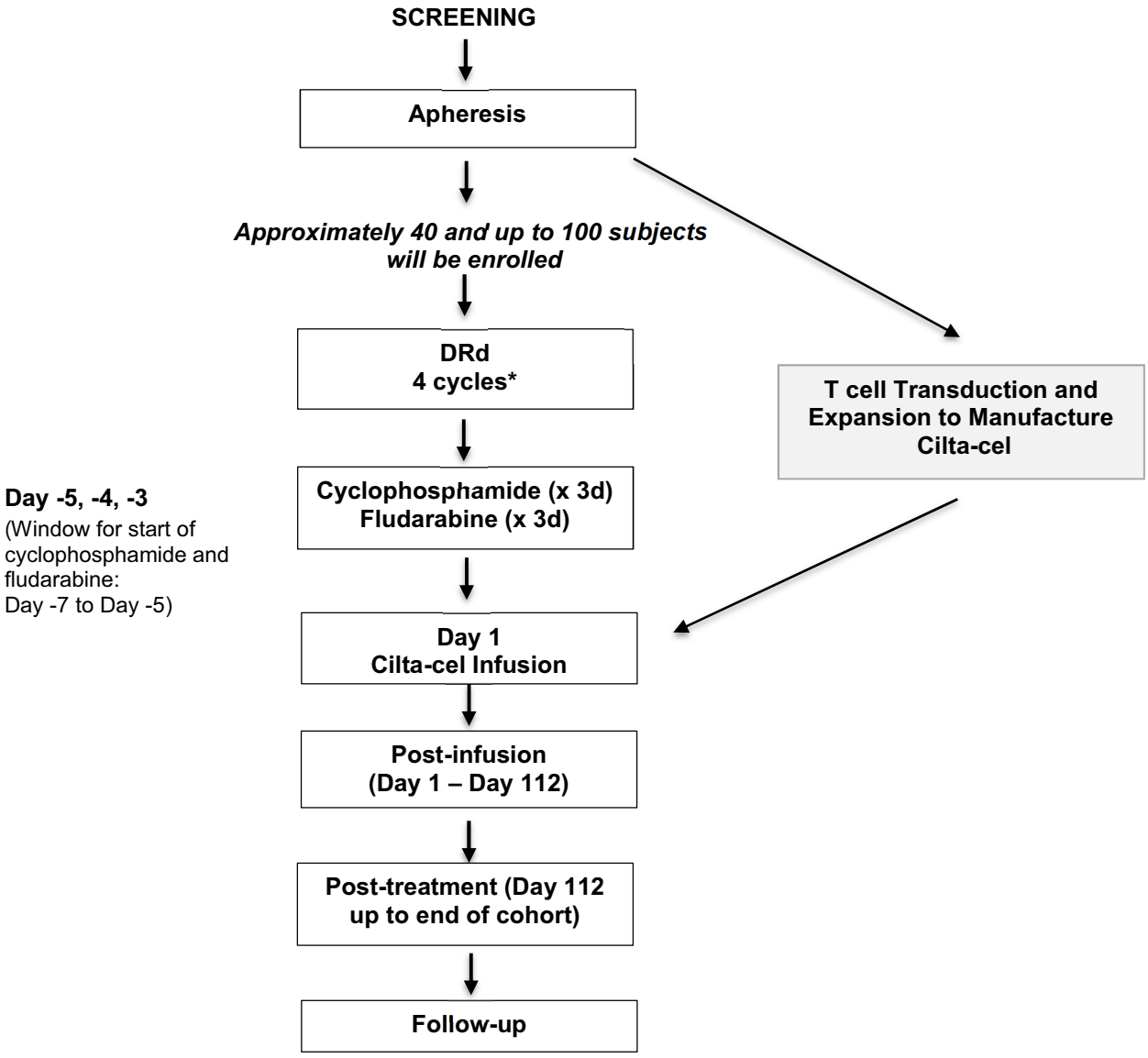
18. PART B

INFORMATION SPECIFIC TO PART B

Part B was added in view of addition of two new cohorts (Cohort G and Cohort H) to the existing study. Only sites in the United States will be enrolling in Cohorts G and H. This section provides information specific to Part B. The conduct and timing of the cohorts G and H will be independent of each other. If a section contains general information that is applicable to all parts, a link is provided back to the text in the main body of the protocol.

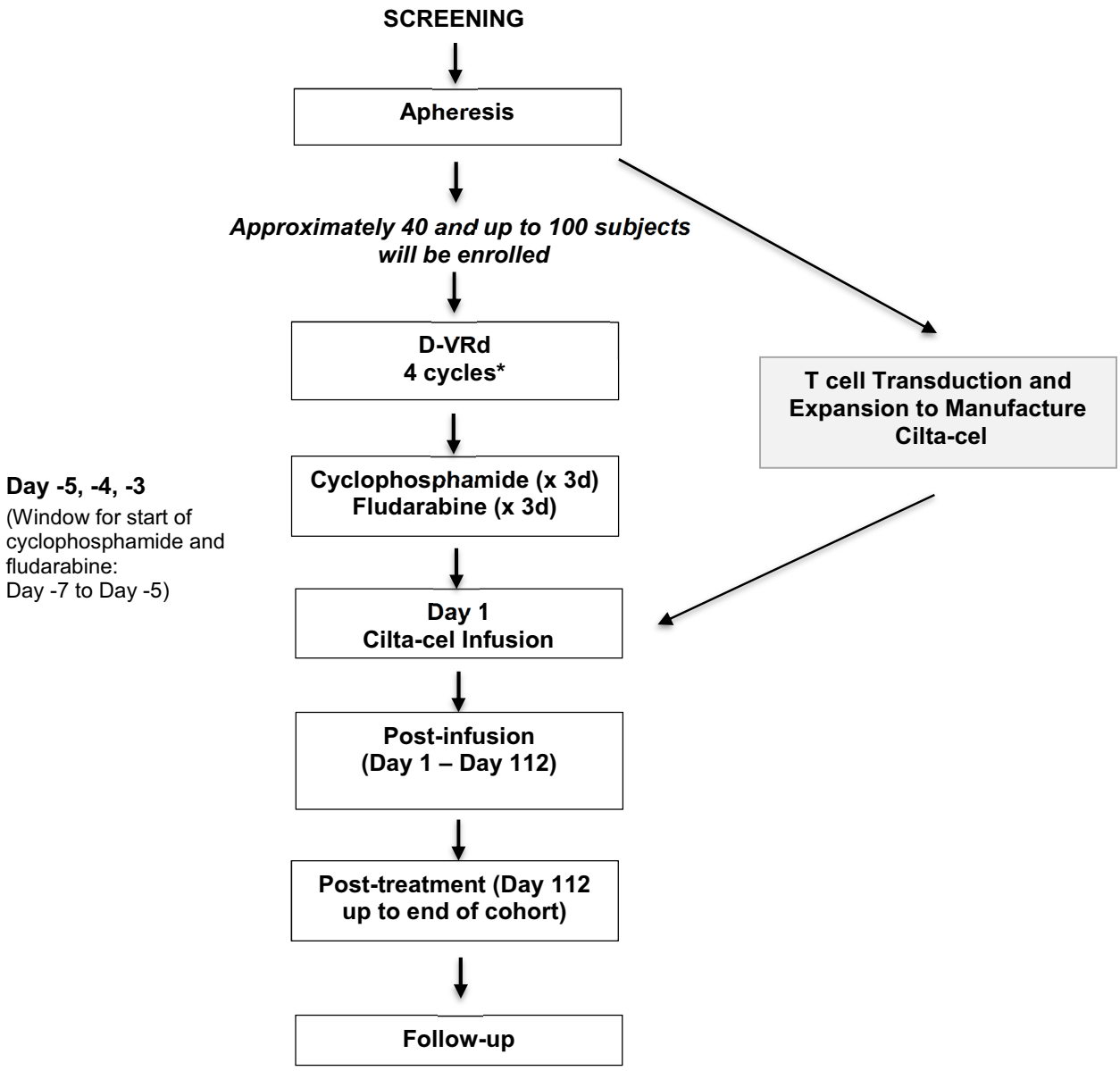
1.1. Schema

Figure 9: Schematic Overview of Cohort G



* Additional cycle(s) permitted with sponsor approval if an unanticipated delay in cilta-cel manufacturing occurs

Figure 10: Schematic Overview of Cohort H



* Additional cycle(s) permitted with sponsor approval if an unanticipated delay in cilta-cel manufacturing occurs

1.2. Time and Event Schedules

1.2.1. Time and Event Schedule for Screening for Cohort G and Cohort H

Screening: All procedures are required unless they are marked optional (≤28 days before enrollment unless specified otherwise)	
STUDY PROCEDURES	**Notes**
Informed consent	Before the 1st study-related procedure
Eligibility criteria	
Demographic, medical & neurologic history	
Disease characteristics/cytogenetics	To be performed locally by FISH to determine the presence or absence of del17, t(4:14), t(14;16) and amp 1q
Physical examination, incl. ECOG performance status	Complete physical examination including neurologic examination. Neurologic exam can be performed by investigator; however, it is strongly recommended to be performed by a neurologist
Transthoracic echocardiogram (TTE) or Multigated Acquisition (MUGA) Scan	Including left ventricular ejection fraction (EF), acceptable if done ≤8 weeks before enrollment
Spirometry test (ie, FEV1)	FEV1 testing is required for subjects who are suspected of having COPD. Acceptable for Screening if performed as part of SOC ≤60 days prior to enrollment.
12-lead electrocardiogram (ECG)	
Vital signs	Including oxygen saturation, height and weight
Frailty index, Attachment B 3	
Blood group and type and indirect antiglobulin test (IAT) results	Record ABO, Rh, and IAT results on subject's identification wallet card
Complete blood count with differential	See Attachment B 2, Clinical Laboratory Tests
Full metabolic panel	See Attachment B 2, Clinical Laboratory Tests
Coagulation	PT/INR, aPTT, fibrinogen, D-dimer
Serology	Serology performed as standard of care within 28 days prior to enrollment is acceptable. Hepatitis B: HBsAg, anti-HBc, anti-HBs, HBV DNA quantification (for subjects who are anti-HBs positive without history of vaccination or for subjects who are anti-HBc positive with or without anti-HBs positive); Hepatitis C: HCV antibody, HCV-RNA (for subjects who are HCV antibody positive); HIV serology.
Infectious disease testing	HIV, hepatitis B, hepatitis C, HTLV, and other infectious disease testing (eg, CMV, EBV, HSV, HHV, VZV) as needed before apheresis per local regulations (whichever is more stringent) (≤60 days prior to apheresis)
Serum or urine pregnancy test	For subjects of childbearing potential with regular or irregular menstrual cycles. Pregnancy tests must have a minimum sensitivity of 25 mIU/mL. Please follow the US REMS program for lenalidomide, for timing of pregnancy testing prior to lenalidomide prescription.
DISEASE EVALUATIONS (SERUM AND URINE): SEE SECTION 1.30 FOR EFFICACY ASSESSMENTS. TO BE PERFORMED LOCALLY	
Serum beta-2 microglobulin / Albumin	Local laboratory
Quantitative immunoglobulins	Includes IgG, IgA, IgM, IgD and IgE. Local laboratory.
SPEP and SIFE	Local laboratory
UPEP (24-hour urine) and UIFE	Local laboratory
Serum FLC	Local laboratory
OTHER DISEASE EVALUATIONS	
Bone marrow aspirate and core biopsy	Disease characterization (morphology and either immunohistochemistry or flow cytometry performed locally). If a biopsy was done within 42 days before start of induction, no need to repeat for morphology. Local laboratory – cytogenetic evaluation for high-risk features (at minimum): del(17p), t(4;14), t(14;16), amp(1q).

Screening: All procedures are required unless they are marked optional (≤28 days before enrollment unless specified otherwise)	
STUDY PROCEDURES	**Notes**
MRD (Bone marrow aspirate)	A BM aspirate must be available for MRD clone identification. NGS (Adaptive) will be the preferred method of MRD monitoring. If a clone was identified by NGS (Adaptive) at the time of diagnosis, then, a repeat aspirate sample for clone identification is not needed. However, if a clone has not been identified at the time of diagnosis, then a repeat BM sample is needed for NGF (if possible, locally done, otherwise centrally done). MRD samples should be prioritized and from first aspiration to ensure clone identification (See Section 1.30.5.1).
Imaging: Assessment of lytic lesions	Whole-body MRI, low-dose whole-body CT, or PET/CT with diagnostic CT component. Acceptable for screening if performed as part of SOC within 42 days before induction.
Assessment of plasmacytomas	Whole-body MRI, low-dose whole-body CT, or PET/CT with diagnostic CT component. Acceptable for screening if performed as part of SOC within 42 days before start of induction.
MRD assessment by PET/CT imaging (optional)	See Section 1.30.5
BIOMARKER SAMPLING	
WES (buccal swab)	See Section 1.35.1

1.2.2. Time and Event Schedule for Cohort G: Treatment Phase

	Notes	Treatment Phase (28-day cycles)						
		Apheresis	Induction Treatment (Cycles 1 to 4)				Conditioning regimen Cyclophosphamide and fludarabine	Cilta-cel
		Upon Enrollment	Day 1	Day 8 (±2 day)	Day 15 (±2 day)	Day 22 (±2 day)	CAR-T Day -5, -4, -3[a]	CAR-T Day 1
Study Procedures								
Physical examination	Complete physical exam including neurologic exam on CAR-T Day 1; symptom-directed exam during induction		Symptom-directed physical examination (including Neurologic Assessment) as clinically indicated					X (prior to cilta-cel infusion)
ECOG			C3D1				X (prior to 1st dose only)	X
Transthoracic echocardiogram or Multigated Acquisition scan			As clinically indicated. Monitor subjects for clinical signs or symptoms of cardiac failure or cardiac ischemia. Evaluate promptly if cardiac toxicity is suspected.					
12-lead ECG			As clinically indicated					
ICE neurologic test	≤24 hrs prior to cilta-cel infusion on CAR-T Day 1							X
Handwriting sample	≤24 hrs prior to cilta-cel infusion on CAR-T Day 1							X
Weight	At apheresis for cilta-cel dose calculation	X	X				X (prior to 1st dose only)	X
Vital signs	Including oxygen saturation	X	X	X (C1-C2 only)	X	X (C1-C2 only)	X	X (multiple times)[b]
Vital signs monitoring via wearable devices (as applicable)	Includes SpO_2, RR, PR, movement, skin temperature, and blood pressure						X	X
Temperature	Measure and record at least twice daily from CAR-T Day 1 to Day 28							X
LABORATORY ASSESSMENTS – TO BE PERFORMED LOCALLY								
CBC with differential	See Attachment B 2 for details	X Prior to apheresis (same day)	X	X (C1-C2 only)	X	X (C1-C2 only)	X Prior to 1st dose only	X (≤24 hours prior to infusion)
CD4/CD8 Lymphocyte panel	See Attachment B 2 for details	X Prior to apheresis (same day)					X Prior to 1st dose only	X (≤24 hours prior to infusion)

	Notes	Treatment Phase (28-day cycles)						
		Apheresis	**Induction Treatment (Cycles 1 to 4)**				**Conditioning regimen Cyclophosphamide and fludarabine**	**Cilta-cel**
		Upon Enrollment	**Day 1**	**Day 8 (±2 day)**	**Day 15 (±2 day)**	**Day 22 (±2 day)**	**CAR-T Day -5, -4, -3[a]**	**CAR-T Day 1**
Full metabolic panel	See Attachment B 2 for details		X		X (C1-C2 only)			
CAR-T chemistry panel	See Attachment B 2 for details	X (≤72 hours window)					X Prior to 1st dose only	X (≤24 hours prior to infusion)
HBV-DNA	Including AST/ALT. For subjects with serologic evidence of resolved HBV infection (ie, positive Anti-HBs or positive Anti-HBc) at Screening, HBV DNA testing by PCR must be performed locally. See Attachment B 2 for details.		C4D1	Every 12 weeks for subjects at risk for HBV activation monitor HBV DNA and AST/ALT (±7 days) until 6 months after the last dose of study treatment or until 1year post-cilta-cel infusion, whichever is later.				
Coagulation	PT/INR, aPTT, fibrinogen						X Prior to 1st dose only	As clinically indicated, ie, for subjects who have fever or other signs of potential CRS
Serum or urine pregnancy test [c]		X (≤72 hour window)	X[c]				Prior to 1st dose only (≤72 hour window)	
Infectious Disease Testing [d]	HIV, hepatitis B, hepatis C, HTLV, and other infectious disease testing as needed for apheresis in countries as required per local regulations	X						
Assessments Prior to Apheresis and Conditioning Regimen								
Criteria for Apheresis	See Section 1.17.2.1.1	X ≤72 hours prior to apheresis						
Criteria for Conditioning Regimen	See Section 1.17.2.2						≤ 72 hours prior to 1st dose only	
Criteria for cilta-cel administration	See Section 1.17.2.3							X (pre-dose)

	Notes	Treatment Phase (28-day cycles)						
		Apheresis	Induction Treatment (Cycles 1 to 4)				Conditioning regimen Cyclophosphamide and fludarabine	Cilta-cel
		Upon Enrollment	Day 1	Day 8 (±2 day)	Day 15 (±2 day)	Day 22 (±2 day)	CAR-T Day -5, -4, -3[a]	CAR-T Day 1
Outpatient Administration: in consultation with and approval of the sponsor.								
Evaluation for outpatient suitability	See Attachment 14 and Attachment 15 for details						≤ 72 hours prior to 1st dose only	X
Study Intervention and Administration								
Cyclophosphamide 300 mg/m^2 IV	Upon recovery from Cycle 4 Induction therapy						X (daily)	
Fludarabine 30 mg/m^2 IV	Upon recovery from Cycle 4 Induction therapy; dose reductions permitted, see 1.17.1.1.						X (daily)	
Pre- and post-injection medications for daratumumab	PO or IV: see Section 1.25.1for full dosing details		X	X (C1-C2 only)	X	X (C1-C2 only)		
Daratumumab 1,800 mg SC	Refer to USPI for recommendations on daratumumab administration rate; see Section 1.17.1 for full dosing details		X	X (C1-C2 only)	X	X (C1-C2 only)		
Lenalidomide 25 mg PO	Dispense on Day 1 for self-administration; see Section 1.17.1 for full dosing details		On Days 1-21 of each cycle for Cycles 1 to 4					
Dexamethasone 40 mg [e]	see Section 1.17.1 for full dosing details.		On Days 1, 8, 15, 22 of 28-day cycles for Cycle 1 to 4					
ACCOUNTABILITY/EXPOSURE CHECK								
Review of medication card	For lenalidomide and dexamethasone		On Day 1 of each cycle for Cycles 2 to 4 only				X (Cycle 4 accountability performed before conditioning)	
DISEASE EVALUATIONS (SERUM AND URINE): SEE SECTION 1.30. FOR EFFICACY ASSESSMENTS. BLOOD AND 24-HOUR URINE. EVERY EFFORT SHOULD BE MADE TO CONDUCT DISEASE EVALUATIONS AS PER SCHEDULE (WINDOW ≤7 DAYS) (CONDUCTED LOCALLY)								
Quantitative Immunoglobulins [f]	Includes IgG, IgA, IgM. Testing for IgD and IgE for subjects with IgD- or IgE-type myeloma only Local laboratory		X ≤7 days				X (prior to first dose [≤7 days]	
SPEP/SIFE	Local laboratory		X ≤7 days				X (prior to first dose [≤7 days]	
UPEP (24-hour urine)/UIFE	Local laboratory		X ≤7 days				X (prior to first dose [≤7 days]	

	Notes	Treatment Phase (28-day cycles)						
		Apheresis	Induction Treatment (Cycles 1 to 4)				Conditioning regimen Cyclophosphamide and fludarabine	Cilta-cel
		Upon Enrollment	Day 1	Day 8 (±2 day)	Day 15 (±2 day)	Day 22 (±2 day)	CAR-T Day -5, -4, -3[a]	CAR-T Day 1
Serum FLC	Local laboratory		X ≤7 days	For subjects with measurable disease only by light chain criteria, serum FLC and SIFE/UIFE will be performed at C1D1 and with every disease evaluation. For subjects with measurable disease by serum and/or urine M spike: serum FLC and SIFE/UIFE will be performed at C1D1 and when CR is suspected or maintained				
DSIFE [g]	See Section 1.30.1 for details.		To confirm a VGPR or better in subjects with IgG kappa myeloma when daratumumab interference is suspected based on SPEP and SIFE results.					
Other Disease Evaluations								
MRD (Bone marrow aspirate)	Central laboratory		Sample should be collected for MRD by NGS: At time of suspected CR or sCR [h] If a clone was not identified, NGF may be used for MRD detection [i]					
Bone marrow aspirate and core biopsy	Disease characterization (morphology and either immunohistochemistry or flow cytometry) performed locally.		• To confirm CR (including sCR) (bone marrow biopsy and aspirate) [h] • In case of a bone marrow is being performed for suspected SPM, sample should be collected for central laboratory.					
Imaging: Assessment of lytic lesions: whole-body MRI or low-dose whole body CT or PET/CT with diagnostic CT component	Refer to Section 1.30.2		Performed as clinically indicated to document PD					
Assessment of plasmacytomas (both extramedullary and bone based)	By clinical examination or by radiologic assessment with MRI, CT, or PET/CT with diagnostic CT component.		For subjects with a history of plasmacytoma: • For assessment by clinical examination (if applicable), every 4 weeks (±7 days) until confirmed CR or PD. • For assessment by radiology, every 12 weeks (±4 weeks) until confirmed CR or PD As clinically indicated for other subjects					
Biopsy of extramedullary or bone-based plasmacytoma	If biopsy of EM or bone-based plasmacytoma is clinically indicated, a sample should be sent to the central lab	The sponsor should receive a sample of plasmacytoma if a plasmacytoma biopsy is performed for any reason.						
MRD assessment by PET/CT imaging (optional)	See Section 1.30.5		At time of BM MRD-negative CR and every 12 months thereafter in BM MRD-negative subjects.					
Biomarker Sampling								
Immuno-phenotyping and flow PK CAR+ T cells (whole blood)		X (≤72 hours window)						Pre-dose (≤4 hour window)
Immune and Omic profiling (whole blood)		X (≤72 hours window)						Pre-dose (≤4 hour window)

	Notes	Treatment Phase (28-day cycles)						
		Apheresis	Induction Treatment (Cycles 1 to 4)				Conditioning regimen Cyclophosphamide and fludarabine	Cilta-cel
		Upon Enrollment	Day 1	Day 8 (±2 day)	Day 15 (±2 day)	Day 22 (±2 day)	CAR-T Day -5, -4, -3[a]	CAR-T Day 1
Cytokine profiling (serum)								Pre-dose (≤4 hour window)
Replication Competent Lentivirus (RCL) (whole blood)							X (prior to first dose [≤7d])	
Ongoing Subject Review								
Adverse Event			Continuous from the time of signing ICF until 30 days after the last dose of study medications, or until CAR-T Day 112 (whichever is later); thereafter, continue to report all SAEs regardless of causality, and any nonserious AEs considered related to study treatment until EOS. Events of HBV reactivations and Covid-19 infection should be reported during the first years post-dosing of cilta-cel. For subjects who progress before CAR-T Day 112, AEs/SAEs should still be reported until CAR-T Day 112 or until resolution, whichever is later.					
Delayed Adverse Events	See Section 12		Continuous from Day 1 of CAR-T infusion until EOS (with the exception of second primary malignancy, which is collected from the time of enrollment until EOS)					
Concomitant therapy	See Section 1.25		Continuous reporting of selected concomitant therapy from the time of signing ICF until at least CAR-T Day 112; thereafter, continue to report concomitant therapy given for any reported AEs until EOS. Medications for the prevention and treatment of COVID-19 (including vaccines) and HBV reactivation should be reported until 1 year after cilta-cel infusion (Attachment 20) Subjects who progress before CAR-T Day 112, selected concomitant therapy should still be reported until CAR-T Day 112.					
Survival			Continuous from first dose of study treatment until end of study.					

a. Assessments may be conducted ≤72 hours predose. Window for the start of the conditioning regimen is Day -7 to Day -5.
b. Vital signs immediately before the start of infusion, at the end of infusion, and 0.5 hours (±5 min), 1 hours (±10 min), and 2 hours (±10 min) after end of infusion. Monitor until normalized after a CRS event.
c. For subjects of childbearing potential with regular or irregular menstrual cycles. Pregnancy tests must have a minimum sensitivity of 25 mIU/mL. Please follow the US REMS program for lenalidomide for timing of pregnancy testing. Additional pregnancy testing may be done as clinically indicated. Please refer to Section 1.31.9 for details.
d. HIV, hepatitis B, hepatitis C, HTLV, and other infectious diseases as applicable per local regulations.
e. On daratumumab dosing days, dexamethasone pre-medication for daratumumab injection will replace the daily dose of dexamethasone. For underweight subjects (BMI <18.5 kg/m^2) and for subjects ≥75 years of age dexamethasone may be administered at a dose of 20 mg on Days 1, 8, 15, and 22 of each cycle.
f. All subjects will be evaluated for IgG, IgA, IgM. Testing for IgD and IgE will only be performed for subjects with IgD and IgE-type myeloma.
g. DSIFE test can be considered if investigator has suspicion for daratumumab interfering with the SIFE test results. Performed centrally, or locally if clinically indicated or available locally.
h. If MRD-negative CR/sCR is not confirmed, repeat BM every 3-6 months until MRD-negative CR/sCR is confirmed or PD.
i. If local NGF is not available, NGF will be performed centrally.

1.2.3. Time and Event Schedule for Cohort H: Treatment Phase

	Notes	Treatment Phase (28-day cycles)						
		Apheresis	Induction Treatment (Cycles 1 to 4)				Conditioning regimen Cyclophosphamide and fludarabine	Cilta-cel
		Upon Enrollment	Day 1	Day 8 (±2 day)	Day 15 (±2 day)	Day 22 (±2 day)	CAR-T Day -5, -4, -3 [a]	CAR-T Day 1
Study Procedures								
Physical examination	Complete physical exam including neurologic exam on CAR-T Day 1; symptom-directed exam during induction		Symptom-directed physical examination (including Neurologic Assessment) as clinically indicated					X (prior to cilta-cel infusion)
ECOG			C3D1				X (prior to 1st dose only)	X
Transthoracic echocardiogram or Multigated Acquisition scan			As clinically indicated. Monitor subjects for clinical signs or symptoms of cardiac failure or cardiac ischemia. Evaluate promptly if cardiac toxicity is suspected.					
12-lead electrocardiogram (ECG)			As clinically indicated					
ICE neurologic test	≤24 hrs prior to cilta-cel infusion on CAR-T Day 1							X
Handwriting sample	≤24 hrs prior to cilta-cel infusion on CAR-T Day 1							X
Weight		X (for cilta-cel dose calculation)	X				X (prior to 1st dose only)	X
Vital signs	Including oxygen saturation	X	X	X	X	X (C1-C2 only)	X	X (multiple times) [b]
Vital signs monitoring via wearable devices (as applicable)	Includes SpO2, RR, PR, skin temperature, and blood pressure						X	X
Temperature	Measure and record temperature at least twice every day from CAR-T Day 1 to Day 28							X

	Notes	Treatment Phase (28-day cycles)						
		Apheresis	Induction Treatment (Cycles 1 to 4)				Conditioning regimen Cyclophosphamide and fludarabine	Cilta-cel
		Upon Enrollment	Day 1	Day 8 (±2 day)	Day 15 (±2 day)	Day 22 (±2 day)	CAR-T Day -5, -4, -3 [a]	CAR-T Day 1
LABORATORY ASSESSMENTS – TO BE PERFORMED LOCALLY								
CBC with differential	See Attachment B 2 for details	X Prior to apheresis (same day)	X	X	X	X (C1-C2 only)	X Prior to 1st dose only	X (≤24 hours prior to infusion)
CD4/CD8 Lymphocyte panel	See Attachment B 2 for details	X Prior to apheresis (same day)					X Prior to 1st dose only	X (≤24 hours prior to infusion)
Full metabolic panel	See Attachment B 2 for details		X		X (C1-C2 only)			
CAR-T chemistry panel	See Attachment B 2 for details	X (≤72 hours window)					X Prior to 1st dose only	X (≤24 hours prior to infusion)
HBV-DNA	Including AST/ALT. For subjects with serologic evidence of resolved HBV infection (ie, positive Anti-HBs or positive Anti-HBc) at Screening, HBV DNA testing by PCR must be performed locally. Refer to Attachment B 2 for details.		C3D1	For subjects at risk for HBV activation monitor HBV DNA and AST/ALT every 12 weeks (±7 days) until 6 months after the last dose of study treatment or until 1-year post-dose of cilta-cel, whichever is later.				
Coagulation	PT/INR, aPTT, fibrinogen,						X (prior to 1st dose only)	As clinically indicated, ie, for subjects who have fever or other signs of potential CRS
Serum or urine pregnancy test [c]		X (≤72 hour window)	X [c]				Prior to 1st dose only (≤72 hour window)	
Infectious Disease Testing [d]	HIV, hepatitis B, hepatis C, HTLV, and other infectious disease testing as needed for apheresis in countries as required per local regulations	X						

	Notes	Treatment Phase (28-day cycles)						
		Apheresis	Induction Treatment (Cycles 1 to 4)				Conditioning regimen Cyclophosphamide and fludarabine	Cilta-cel
		Upon Enrollment	Day 1	Day 8 (±2 day)	Day 15 (±2 day)	Day 22 (±2 day)	CAR-T Day -5, -4, -3 [a]	CAR-T Day 1
Assessments Prior to Apheresis and Conditioning Regimen								
Criteria for Apheresis	See Section 1.17.2.1.1	X ≤72 hours prior to apheresis						
Criteria for Conditioning Regimen	See Section 1.17.2.2						≤ 72 hours prior to 1st dose only	
Criteria for cilta-cel administration	See Section 1.17.2.3							X (pre-dose)
Outpatient Administration: in consultation with and approval of the sponsor								
Evaluation for outpatient suitability	See Attachment 14 and Attachment 15 for details						≤ 72 hours prior to 1st dose only	X
Study Intervention and Administration								
Cyclophosphamide 300 mg/m^2 IV	Upon recovery from Cycle 4 Induction therapy						X (daily)	
Fludarabine 30 mg/m^2 IV	Upon recovery from Cycle 4 Induction therapy; dose reductions permitted, see 1.17.1.1 for details						X (daily)	
Pre- and post-injection medications for daratumumab	PO or IV: see Section 1.17.1.2.1 and Section 1.17.1.2.2 for full dosing details		X	X (C1-C2 only)	X	X (C1-C2 only)		
Daratumumab 1,800 mg SC	Refer to USPI for recommendations on daratumumab administration rate; see Section 1.17.1 for full dosing details		X	X (C1-C2 only)	X	X (C1-C2 only)		
Bortezomib 1.3 mg/m^2 SC	Administer by SC injection. Recalculate the dose if weight has changed ±10% from baseline; see Section 1.17.1 for full dosing details.		On Days 1, 8, 15 of each cycle for Cycles 1 to 4					
Lenalidomide 25 mg PO	Dispense on Day 1 for self-administration; see Section 1.17.1 for full dosing details.		On Days 1-21 of each cycle for Cycles 1 to 4					
Dexamethasone 40 mg [e]	see Section 1.17.1 for full dosing details.		On Days 1, 8, 15, 22 of each cycle for Cycles 1 to 4					
ACCOUNTABILITY/EXPOSURE CHECK								
Review of medication card	For lenalidomide and dexamethasone		On Day 1 of each cycle for Cycles 2 to 4 only				X (Cycle 4 accountability performed before conditioning)	

	Notes	Treatment Phase (28-day cycles)						
		Apheresis	Induction Treatment (Cycles 1 to 4)				Conditioning regimen Cyclophosphamide and fludarabine	Cilta-cel
		Upon Enrollment	Day 1	Day 8 (±2 day)	Day 15 (±2 day)	Day 22 (±2 day)	CAR-T Day -5, -4, -3 [a]	CAR-T Day 1
DISEASE EVALUATIONS (SERUM AND URINE): SEE SECTION 1.30 FOR EFFICACY ASSESSMENTS. BLOOD AND 24-HOUR URINE. EVERY EFFORT SHOULD BE MADE TO CONDUCT DISEASE EVALUATIONS AS PER SCHEDULE (WINDOW ≤7 DAYS) (CONDUCTED LOCALLY)								
Quantitative Immunoglobulins [f]	Includes IgG, IgA, IgM. Testing for IgD and IgE for subjects with IgD- or IgE-type myeloma only. Local laboratory		X [≤7 days]				X (prior to first dose [≤7 days]	
SPEP/SIFE	Local laboratory		X ≤7 days				X (prior to first dose) [≤7 days]	
UPEP (24-hour urine)/UIFE	Local laboratory		X ≤7 days				X (prior to first dose) [≤7 days]	
Serum FLC	Local laboratory		X ≤7 days	For subjects with measurable disease only by light chain criteria, serum FLC and SIFE/UIFE will be performed at C1D1 and with every disease evaluation. For subjects with measurable disease by serum and/or urine M spike: serum FLC and SIFE/UIFE will be performed at C1D1 and when CR is suspected or maintained				
DSIFE [g]	See Section 1.30.1		To confirm a VGPR or better in subjects with IgG kappa myeloma when daratumumab interference is suspected based on SPEP and SIFE results.					
Other Disease Evaluations								
MRD (Bone marrow aspirate)	Central laboratory		Sample should be collected for MRD by NGS: At time of suspected CR or sCR [h] If a clone was not identified, NGF may be used for MRD detection [i]					
Bone marrow aspirate and core biopsy	Disease characterization (morphology and either immunohistochemistry or flow cytometry) performed locally.		• To confirm CR (including sCR) (bone marrow biopsy and aspirate) [h] • In case of a bone marrow is being performed for suspected SPM, sample should be collected for central laboratory.					
Imaging: Assessment of lytic lesions: whole-body MRI or low-dose whole body CT or PET/CT with diagnostic CT component	Refer to Section 1.30.2 and Section 1.31.8		Performed as clinically indicated to document PD					

	Notes	Treatment Phase (28-day cycles)						
		Apheresis	**Induction Treatment (Cycles 1 to 4)**				**Conditioning regimen Cyclophosphamide and fludarabine**	**Cilta-cel**
		Upon Enrollment	**Day 1**	**Day 8 (±2 day)**	**Day 15 (±2 day)**	**Day 22 (±2 day)**	**CAR-T Day -5, -4, -3 [a]**	**CAR-T Day 1**
Assessment of plasmacytomas (both extramedullary and bone based)	By clinical examination or by radiologic assessment with MRI, CT, or PET/CT with diagnostic CT component.		For subjects with a history of plasmacytoma: • For assessment by clinical examination (if applicable), every 4 weeks (±7 days) until confirmed CR or PD • For assessment by radiology, every 12 weeks (±4 weeks) until confirmed CR or PD • As clinically indicated for other subjects					
Biopsy of extramedullary or bone-based plasmacytoma	If biopsy of EM or bone-based plasmacytoma is clinically indicated, a sample should be sent to the central lab	The sponsor should receive a sample of plasmacytoma if a plasmacytoma biopsy is performed for any reason.						
MRD assessment by PET/CT imaging (optional)	See Section 1.30.5		At time of BM MRD-negative CR and every 12 months in BM MRD-negative subjects.					
Biomarker Sampling								
Immuno-phenotyping and flow PK CAR+ T cells (whole blood)		X (≤72 hours window)						Pre-dose (≤4 hour window)
Immune and Omic profiling (whole blood)		X (≤72 hours window)						Pre-dose (≤4 hour window)
Cytokine profiling (serum)								Pre-dose (≤4 hour window)
Replication Competent Lentivirus (RCL) (whole blood)							X (prior to first dose [≤7d])	
Ongoing Subject Review								
Adverse Event			Continuous from the time of signing ICF until 30 days after the last dose of study medications, or until CAR-T Day 112 (whichever is later); thereafter, continue to report all SAEs regardless of causality, and any nonserious AEs considered related to study treatment until EOS. Events of HBV reactivations should be reported during the first-year post-dosing of cilta-cel. For subjects who progress before CAR-T Day 112, AEs/SAEs should still be reported until CAR-T Day 112 or until resolution, whichever is later.					
Delayed Adverse Events	See Section 12		Continuous from Day 1 of CAR-T infusion until EOS (with the exception of second primary malignancy, which is collected from the time of enrollment until EOS)					

	Notes	Treatment Phase (28-day cycles)						
		Apheresis	**Induction Treatment (Cycles 1 to 4)**				**Conditioning regimen Cyclophosphamide and fludarabine**	**Cilta-cel**
		Upon Enrollment	**Day 1**	**Day 8 (±2 day)**	**Day 15 (±2 day)**	**Day 22 (±2 day)**	**CAR-T Day -5, -4, -3 [a]**	**CAR-T Day 1**
Concomitant therapy	See Section 1.25		Continuous reporting of selected concomitant therapy from the time of signing ICF until at least CAR-T Day 112; thereafter, continue to report concomitant therapy given for any reported AEs until EOS. Medications for the prevention and treatment of COVID-19 (including vaccines) and HBV reactivation should be reported until. Subjects who progress before CAR-T Day 112, selected concomitant therapy should still be reported until CAR-T Day 112.					
Survival			Continuous from first dose of study treatment until end of study.					

a. Assessments may be conducted ≤72 hours predose. Window for the start of the conditioning regimen is Day -7 to Day -5.
b. Vital signs immediately before the start of infusion, at the end of infusion, and 0.5 hours (±5 min), 1 hours (±10 min), and 2 hours (±10 min) after end of infusion. Monitor until normalized after a CRS event.
c. For subjects of childbearing potential with regular or irregular menstrual cycles. Pregnancy tests must have a minimum sensitivity of 25 mIU/mL. Please follow the US REMS program for lenalidomide for timing of pregnancy testing. Additional pregnancy testing may be done as clinically indicated. Please refer to Section 1.31.9 for details.
d. HIV, hepatitis B, hepatitis C, HTLV, and other infectious diseases as applicable per local regulations.
e. On daratumumab dosing days, dexamethasone pre-medication for daratumumab injection will replace the daily dose of dexamethasone. For underweight subjects (BMI <18.5 kg/m^2) and for subjects ≥75 years of age dexamethasone may be administered at a dose of 20 mg on Days 1, 8, 15, and 22 of each cycle.
f. All subjects will be evaluated for IgG, IgA, IgM. Testing for IgD and IgE will only be performed for subjects with IgD and IgE-type myeloma.
g. DSIFE test can be considered if investigator has suspicion for daratumumab interfering with the SIFE test results. Performed centrally, or locally if clinically indicated or available locally.
h. If MRD-negative CR/sCR is not confirmed, repeat BM every 3-6 months until MRD-negative CR/sCR is confirmed or PD.
i. If local NGF is not available, NGF will be performed centrally.

1.2.4. Time and Event Schedule for Procedures During Post-Infusion and Post-treatment Follow-up Phase (Cohort G and Cohort H)

	Post -Infusion and Post-Treatment Follow-up Phase															
	CAR-T Day 3	CAR-T Day 7	CAR-T Day 10	CAR-T Day 14	CAR-T Day 21	CAR-T Day 28	CAR-T Day 42	CAR-T Day 56	CAR-T Day 84	CAR-T Day 112	CAR-T Day 140	CAR-T Day168	CAR-T Day 196/ Beyond CAR-T Day 196, Follow up every 28 days [e]	CAR-T Day 365	At PD or at EOS Visit	Post-PD Follow-up every 16 weeks via televisit or a phone call
Window	±1d	±1d	±1d	±1d	±1d	±2d	±2d	±2d	±7d	±7d	±7d	±7d	±7d	±14d	±14d	±14d
	PROCEDURES															
ECOG						X				CAR-T Day 112, then every 12 wks for 2 subsequent assessments, then every 24 wks (±7d) until PD (+-7 days)				X		
Physical Exam	Symptom Directed Physical examination as clinically indicated. Complete physical exam including neurologic exam at least annually.													X	X	
12-lead ECG	As clinically indicated															
Transthoracic echocardiogram or Multigated Acquisition scan	As clinically indicated. Monitor subjects for clinical signs or symptoms of cardiac failure or cardiac ischemia. Evaluate promptly if cardiac toxicity is suspected.															
CBC with differential (conducted locally) [a]	X	X	To be performed daily between Day 10 and Day 14		X	X		X	X	X	Every 4 weeks (±7 days) until 2 years after enrollment, thereafter every 8 weeks, until PD			X	X	
CD4/CD8 Lymphocyte panel		X	X	X	X	X		X								
CAR-T chemistry panel		X	X	X	X	X										
Full metabolic panel [a]								X	X	X		X	At least once yearly	X	X	
HBV-DNA	For subjects at risk for HBV activation monitor HBV DNA and AST/ALT every 12 weeks (±7 days) until 6 months after the last dose of study treatment or until 1 year post-dose of cilta-cel, whichever is later.															
Coagulation PT, PTT, fibrinogen	As clinically indicated for subjects who have fever or other signs of potential CRS															
Serum or urine pregnancy test	As clinically indicated or as mandated by local regulations, whichever is more stringent.															
Vital Signs (including oxygen saturation) [a]	X	X	X	X	X	X		X	X	X	Every 12 weeks			X	X	
Temperature	Measure and record temperature at least twice every day															
ICE neurologic test	ICE test must be repeated at any incidence of suspected CAR-T cell related neurotoxicity (eg, ICANS). Perform at least daily until ICANS is resolved.															

Vital signs monitoring via wearable devices (as applicable)	X (day -7 to day 14)															
Usability questionnaire on wearable devices (only required if participating in the wearable device; See Section 1.31.2.1)				X												
Handwriting Sample	X	X	X	X	X	X	X	Perform monthly up to and including Day 196								
DISEASE EVALUATIONS (SERUM AND URINE): SEE SECTION 1.30 FOR EFFICACY ASSESSMENTS. BLOOD AND 24-HOUR URINE. EVERY EFFORT SHOULD BE MADE TO CONDUCT DISEASE EVALUATIONS AS PER SCHEDULE (WINDOW ±7 DAYS) (CONDUCTED LOCALLY)																
Quantitative Immunoglobulins [b]	On Day 28 (+/- 2 days) and then starting from day 56 after cilta-cel, every 4 weeks (±7 days) until 2 years after enrollment, thereafter every 8 weeks, until PD													X		
SPEP/SIFE	On Day 28 (+/- 2 days) and then starting from Day 56 after cilta-cel, every 4 weeks (±7 days) until 2 years after enrollment, thereafter every 8 weeks, until PD													X		
UPEP (24-hour urine)/UIFE	On Day 28 (+/- 2 days) and then starting from Day 56 after cilta-cel every 4 weeks (±7 days) until 2 years after enrollment, thereafter every 8 weeks, until PD													X		
Serum FLC	For subjects with measurable disease only by light chain criteria, serum FLC and SIFE/UIFE will be performed at C1D1 and with every disease evaluation. For subjects with measurable disease by serum and/or urine M spike: serum FLC and SIFE/UIFE will be performed at C1D1 and when CR is suspected or maintained															
DSIFE [c]	To confirm a VGPR or better in subjects with IgG kappa myeloma when daratumumab interference is suspected based on SPEP and SIFE results.													X		
Other Disease Evaluations																
MRD (Bone marrow aspirate)	Sample should be collected for MRD by NGS (to be done centrally): • Post cilta-cel infusion, bone marrow should not be performed earlier than CAR-T Day 56. • Once MRD negative CR/sCR is confirmed, subsequent MRD assessment to be done yearly, until PD. • If MRD negative CR or sCR is not confirmed, repeat BM every 3-6 months.															
Bone marrow aspirate and core biopsy	• To confirm CR (including sCR) (bone marrow biopsy and aspirate) to be done locally • In case of a bone marrow performed for suspected SPM a sample should be collected for central laboratory.															
Imaging: Assessment of lytic lesions:	Performed as clinically indicated to document PD															
Assessment of plasmacytomas (both extramedullary and bone based)	For subjects with soft tissue plasmacytoma at baseline: • For assessment by clinical examination (if applicable), every 4 weeks (±7 days). • For assessment by radiology, every 12 weeks (±4 weeks) • At Day 365[d] • As clinically indicated for other subjects												X	X		
Biopsy of extramedullary or bone-based plasmacytoma	The sponsor should receive a sample of plasmacytoma if a plasmacytoma biopsy is performed for any reason.															

MRD assessment by PET/CT imaging (optional)	At time of BM MRD-negative CR and every 12 months in BM MRD-negative subjects.				
Ongoing Subject Review					
Adverse Event	Continuous from the time of signing ICF until 30 days after the last dose of study medications, or until CAR-T Day 112 (whichever is later); thereafter, continue to report all SAEs regardless of causality, and any nonserious AEs considered related to study treatment until EOS. Events of HBV reactivations should be reported during the first year post-dosing of cilta-cel. For subjects who progress before CAR-T Day 112, AEs/SAEs should still be reported until CAR-T Day 112 or until resolution, whichever is later.				
Delayed Adverse Events	Continuous from Day 1 of CAR-T infusion until EOS (with the exception of second primary malignancy, which is collected from the time of enrollment until EOS)				
Concomitant therapy	Continuous reporting of selected concomitant therapy from the time of signing ICF until at least CAR-T Day 112; thereafter, continue to report concomitant therapy given for any reported AEs until EOS. Subjects who progress before CAR-T Day 112, selected concomitant therapy should still be reported until CAR-T Day 112				
Subsequent anti-myeloma therapy					X
Survival					X

a. For subjects who are hospitalized, hematology and chemistry laboratory evaluations, vital signs, and oxygen saturation should be performed at least daily or more often as clinically indicated.
b. All subjects will be evaluated for IGG, IGA, IGM testing. For IGD and IGE will only be performed for subjects with IGD and IGE-type myeloma.
c. DSIFE test can be considered if investigator has suspicion for daratumumab interfering with the SIFE test results. Performed centrally, or locally if clinically indicated or available locally.
d. Not needed if plasmacytoma already resolved based on prior imaging or if most recent imaging for plasmacytoma was within the past 3 month.
e. After CAR-T Day 196, subjects may be followed via telehealth visit every 28 days (±7 days) in conjunctions with local laboratories.

1.2.5. Time and Events Schedule for Pharmacokinetic and Biomarker Sampling (from Cilta-cel Infusion to Disease Progression or Study Completion)

	Cilta-cel Infusion			**Post Cilta-cel Infusion and Post-treatment Follow-up Phase [a]**									**At Study Completion for subjects without PD**
	Day 1 (Infusion)	**Day 7**	**Day 10**	**Day 11**	**Day 14**	**Day 21**	**Day 28**	**Day 56**	**Day 84**	**Day 112**	**Day 168**	**Day 365**	
Window	± 1d	± 1d	± 1d	± 1d	± 1d	**± 2**	**± 2**	**± 2**	**± 7**	±7d	±7d	±14d	
PK CAR transgene levels (whole blood) [b]	X Pre-dose (≤4 hr window)		X	X	X	X	X	X				X	

	Cilta-cel Infusion			Post Cilta-cel Infusion and Post-treatment Follow-up Phase [a]									At Study Completion for subjects without PD
	Day 1 (Infusion)	**Day 7**	**Day 10**	**Day 11**	**Day 14**	**Day 21**	**Day 28**	**Day 56**	**Day 84**	**Day 112**	**Day 168**	**Day 365**	
Window	± 1d	± 1d	± 1d	± 1d	± 1d	**± 2**	**± 2**	**± 2**	**± 7**	±7d	±7d	±14d	
ADA sample (serum) [c]	X Pre-dose (<4 hr window)						X	X		X		X	X
Immuno-phenotyping and flow PK CAR+ T cells (whole blood)	X Pre-dose (≤4 hour window)		X	X	X	X	X	X					
Immune and Omic profiling (whole blood)	X Pre-dose (≤4 hour window)												
Cytokine profiling (serum)	X Pre-dose (≤4 hour window)												
Replication Competent Lentivirus (RCL) (whole blood) [d]									X		X	X	

a. For subjects who discontinue the study before Day 112, the Day 112 assessments should be performed if feasible.
b. After 1 year, PK CAR transgene levels greater than LLOQ will continue to be evaluated in patients after rolled over to LTFU.
c. ADA sample should be collected if a subject withdraws from the study after cilta-cel administration but prior to disease progression or study completion.
d. Additional samples may be collected triggered by events which may be relevant, but not limited, to RCL per clinical assessment (see Section 1.35).

1.2.6. Time and Events Schedule for Pharmacokinetic and Biomarker Sampling (in Case of CRS, ICANS, MNTs or Other CAR-T Cell-Related Neurotoxicity)

	CRS or ICANS or any grade other MNT	Post Cilta-cel Infusion until EOS
PK CAR transgene levels (whole blood)	X	Collect additional samples when any of the following are suspected or reported: 1. In case of CRS and/or ICANS - event Grade ≥2; at onset of the event, at time of worsening and at resolution of the event, and as clinically indicated. 2. In case of MNT - any grade event; at onset of the event, at time of worsening and at resolution of the event, and as clinically indicated. If CAR-T directed therapy is given, collect a sample within 24h prior to giving the therapy and discuss with the medical monitor for additional sampling. 3. In case of other neurotoxicity - any grade event; at onset of the event and at time of worsening of the event, and as clinically indicated. If toxicity resolves within 4 weeks, collect samples at resolution of the event. Otherwise, collect samples every 4 weeks and discuss with medical the monitor for additional sampling.
ADA sample (serum)	X	
Immuno-phenotyping and flow PK CAR+ T cells (whole blood)	X	
Cytokine profiling (whole blood)	X	
Immune and Omic profiling (whole blood)	X	
Lumbar puncture to collect CSF for CAR-T analysis	X	If sample collected during ICANS, MNTs and/or other neurotoxicity.

1.3. Rationale For cohorts G and H

The treatment of NDMM patients is evolving and choices of therapy vary with age, comorbidity, aggressiveness of the disease, and related prognostic factors (Palumbo 2011). For transplant eligible NDMM patients, the recommended frontline treatment includes triplet or quadruplet induction therapy, high-dose melphalan, and ASCT, followed by maintenance therapy until PD or toxicity (Dimopoulos 2020, NCCN 2023). For certain patients, high-dose therapy with ASCT is not feasible, mainly due to advanced age, co-morbidities, or patient frailty. For these patients, triplet therapy as induction followed by maintenance therapy until progression with one or more agents is the standard of care. Despite improved outcomes in newly diagnosed multiple myeloma, most patients eventually relapse, and therefore there is an unmet need for more effective and durable regimens. In addition, current treatment algorithms for patients with newly diagnosed myeloma include treatment until disease progression. There is a need to develop effective regimens, which may include finite duration of treatment and allow patients to enjoy a long, treatment-free interval.

Experience with cilta-cel in MMY2001 showed for the first time that mPFS of 34.9 months in a heavily pretreated population can be achieved. Results of the MMY3002 study in subjects with relapsed and lenalidomide-refractory multiple myeloma who received 1 to 3 prior lines of therapy showed a 74% reduction in the risk of an event (death or progression) for the primary endpoint of PFS for cilta-cel (n=208) as compared with standard therapy (PVd or DPd; n=211) (HR=0.26 [95% CI: 0.18, 0.38], p-value<0.0001). As benefit of CAR-T therapy is dependent on a patient's immune response, cilta-cel could have potentially meaningful increase in efficacy and durability of response when administered in the frontline setting to patients with multiple myeloma who have

had less exposure to immunomodulatory and cytotoxic therapy. The prevalence of an early memory T-cell phenotype (CD27+ CD45RO- CD8+) in patients with chronic lymphocytic leukemia treated with CD19 CAR-T cell therapy was shown to be predictive of a clinical response independent of other factors (Fraietta 2018). The same finding has also been demonstrated with BCMA directed CAR-T. Furthermore, the same group has also shown that the early memory T-cell phenotype was significantly higher in newly diagnosed subjects post-induction chemotherapy as compared to relapsed-refractory subjects (Cohen 2018, Dancy 2018). In addition, cumulative chemotherapy has been shown to deplete the naïve T cells and earlier memory T cells, which may result in CAR-T cell therapies being manufactured from less fit T-cells with reduced capacity for in vivo expansion and efficacy potential (Das 2019). Therefore, investigations of CAR-T cell therapy in early lines of treatment are warranted to determine the ability to enhance efficacy and increase depth of response. Further rationale for the population and treatment regimens for Cohorts G and H are provided in Section 1.9.

Two global Phase 3 studies are ongoing or planned (CARTITUDE-5 and CARTITUDE-6 studies, registered as NCT04923893 and NCT05257083, respectively) studying cilta-cel in the newly diagnosed setting in transplant not planned, and transplant-eligible subjects, respectively. Cohorts G and H aim to generate additional evidence of potential activity of cilta-cel in a racially representative population in the US using different induction regimens and schedules and administering cilta-cel as a definitive treatment without the use of maintenance therapy.

1.4. Background

1.4.1. Multiple Myeloma

Multiple myeloma is a plasma cell malignancy characterized by the production of monoclonal Ig proteins or protein fragments (M-proteins) that have lost their function (Kyle 2009; Palumbo 2011). The proliferation of multiple myeloma cells leads to subsequent displacement of normal bone marrow hematopoietic precursors and overproduction of M-proteins. Hallmarks of multiple myeloma include osteolytic lesions, anemia, increased susceptibility to infections, hypercalcemia, renal insufficiency or failure, and neurologic complications (Kyle 2009; Palumbo 2011).

Treatment for multiple myeloma has substantially improved over time and varies depending on the aggressiveness of the disease, underlying prognostic factors, physical condition of the patient, and existing comorbidities. The main therapeutic options include agents such as PIs, IMiDs, monoclonal antibodies, and, for selected patients, ASCT followed by maintenance therapy until PD. Despite recent therapeutic advancements, there is a continued need for novel therapeutic approaches, especially for therapies which offer a finite duration of treatment.

1.4.1.1. Treatment Options for Newly Diagnosed Multiple Myeloma Patients in Whom Transplant is Not Planned

For certain patients, high-dose therapy with autologous stem cell transplant (ASCT) is not always feasible, mainly due to advanced age, co-morbidities, or patient frailty. Thanks to the effectiveness of novel agents and novel triplet and quadruplet therapies, more treatment options are becoming

available for these patients. In addition, some patients choose to defer initial ASCT even if eligible, due to patient preference and the desire to avoid the lengthy inpatient hospital stay and risk of long-term toxicity of high-dose therapy, including secondary myelodysplastic syndrome, acute leukemia, and other secondary malignancies. This strategy is supported by the results of the IFM2009 study (Attal 2017) which showed no overall survival (OS) benefit for subjects who were randomized to VRd + early ASCT compared to subjects who received VRd + deferred ASCT until after first relapse.

The triplet combination of DRd is a standard of care induction regimen for patients with NDMM per NCCN treatment guidelines (NCCN 2023). The superiority of the DRd regimen has been established by the results of the Phase 3 MAIA study, which demonstrated both increased PFS and OS in the DRd arm compared with Rd alone (Facon 2019; Weisel 2023). In this study, the median PFS was 61.9 months in the D-Rd arm as compared to 34.4 months in the Rd arm, with a hazard ration of 0.55 (95% CI 0.45 -0.67). This study resulted in FDA approval for daratumumab in multiple myeloma in combination with lenalidomide and dexamethasone in newly diagnosed patients who are ineligible for autologous stem cell transplant (DARZALEX PI).

1.4.1.2. Treatment Options for Transplant Eligible Newly Diagnosed Multiple Myeloma

Patients with NDMM typically receive induction therapy followed by high-dose chemotherapy and ASCT, then followed by consolidation and/or maintenance treatment until disease progression or intolerance. The addition of daratumumab to multiple standard-of-care regimens has been shown to improve response rates compared with standard of care alone in transplant-eligible patients with NDMM prior to ASCT. Data from the daratumumab Phase 3 Study 54767414MMY3006 (CASSIOPEIA) showed that in transplant-eligible subjects with NDMM, the addition of daratumumab (16/kg intravenously) to VTd before and after ASCT improved depth of response (sCR) as well as PFS compared with VTd (Moreau 2019). As lenalidomide has better tolerability than thalidomide (Gay 2010; Zou 2013), the addition of daratumumab to VRd was investigated in the GRIFFIN study. Daratumumab plus VRd (D-VRd) has been shown to improve response rates and depth of response in patients with transplant-eligible NDMM compared with VRd without additional safety concerns (Voorhees 2020), resulting in the addition of this quadruplet regimen to the NCCN treatment guidelines as an option for patients with transplant-eligible NDMM.

Data from the Phase 2 PLEIADES Study (54767414MMY2040) testing SC daratumumab plus standard treatment regimens, included a cohort for transplant eligible subjects with NDMM receiving daratumumab plus VRd (N=67) (Chari 2021). This study demonstrated response rates that were nearly identical to those for the GRIFFIN study. No new safety concerns were identified, and the rate of IRRs was notably lower than that reported for the daratumumab IV regimen. Given the initial safety and efficacy observed in the PLEIADES study, safety and efficacy of SC daratumumab plus VRd vs VRd is being evaluated in the ongoing Phase 3 PERSEUS study (NCT03710603), designed to demonstrate improved outcomes in patients with NDMM who are transplant eligible (Sonneveld 2019). For NDMM patients who are transplant eligible. D-VRd is recommended by the NCCN guidelines (NCCN 2023)

While ASCT can extend survival in some cases, it is not considered a cure for multiple myeloma, as almost all patients will relapse or progress post-transplant.

1.4.2. B-cell Maturation Antigen

B-cell maturation antigen (also known as CD269 and TNFRSF17) is a 20 kD, type III membrane protein, which is part of the tumor necrosis receptor family (Tai 2015). B-cell maturation antigen is predominantly expressed in B-lineage cells and is selectively induced during plasma cell differentiation associated with the loss of B-cell activating factor receptor (Avery 2003; Carpenter 2013; Darce 2007; Maus 2013). In multiple myeloma cell lines and subjects' samples, BCMA is more stably expressed, specifically on the B-cell lineage, compared with the key plasma cell marker CD138, which is also expressed on normal fibroblasts and epithelial cells (Palaiologou 2014). Taken together, these expression characteristics make BCMA an ideal therapeutic target for the treatment of MM (Darce 2007; Tai 2015).

1.5. Benefit-risk Assessment

The potential benefits of cilta-cel in patients with MM are described in Section 1.3. The potential risks of cilta-cel are identified from the following: 1) mechanism of action; and 2) previous clinical experience with cilta-cel and LCAR-B38M CAR-T cells. Longer follow-up and treatment of additional subjects, particularly subjects who have received fewer prior therapies than subjects in the Legend-2 and 68284528MMY2001 studies, may reveal additional risks.

By stimulating an inflammatory cascade, there is potential for toxicity in other tissues or organs by non-specific immune cell activation. Therefore, special attention should be given to both immunological and immunogenicity-related toxicities as well as overlapping hematologic toxicities between DRd/D-VRd and cilta-cel. Safety risks and mitigation strategies are outlined in Table 26.

Table 26: Risks Associated with Cilta-cel and Mitigation Strategies

Risk	Mitigation Strategies
Cytokine release syndrome (CRS) *	Monitor closely for CRS and follow guidance for management in Section 1.17.2.4.1. Body temperature should be monitored twice daily for 28 days post infusion. At the first sign of CRS (such as fever) subjects should be immediately hospitalized for evaluation. Potentially life-threatening complications of CRS may include cardiac dysfunction, adult respiratory distress syndrome, neurologic toxicity, renal failure, hepatic failure, and disseminated intravascular coagulation. Rarely, severe CRS can evolve into a presentation consistent with hemophagocytic lymphohistiocytosis/macrophage activation syndrome (HLH/MAS) that may require additional therapy. Severe thrombocytopenia, low fibrinogen, and often disseminated intravascular coagulation (DIC) may be features of HLH, all of which combined may increase the risk of severe bleeding in these subjects. Section 1.17.2.4.1. describes measures to be taken if HLH is suspected. The use of myeloid growth factors, particularly granulocyte colony-stimulating factor (G-CSF), should be avoided during CRS. Tocilizumab intervention may be considered with presenting symptom of fever in the absence of clear infectious etiology. Early tocilizumab should be considered in subjects at high risk of severe CRS. Section 1.17.2.4.1. provides management guidelines for CRS. Notify the sponsor if subject is experiencing Grade 2 or higher CRS.

Risk	Mitigation Strategies
Neurologic toxicities *	Immune effector cell-associated neurotoxicity syndrome (ICANS): Monitor closely for neurologic AEs, including CAR-T cell-related neurotoxicity (eg, ICANS) and raised intracranial pressure/cerebral edema; follow guidance for management in protocol. Subjects should be advised to seek medical evaluation if they notice new onset of headache, convulsions, speech disorders, visual disorders, disturbances in consciousness, confusion and disorientation, and coordination and balance disorders, or mental status changes. Notify the sponsor if subject is experiencing any grade ICANS. At the first sign of neurotoxicity, neurology consultation and evaluation should be considered. The immune effector cell-associated encephalopathy (ICE) Assessment Tool (ICE-Tool) should be performed at baseline and daily after the first symptoms of neurotoxicity are suspected and until resolution. Hospitalization is required for ≥ Grade 2 CAR-T cell-related neurotoxicity (eg, ICANS). Section 1.17.2.4.2 provides management guidelines for neurotoxicity. Consider non-sedating, anti-seizure medicines (eg, levetiracetam) for seizure prophylaxis for any Grade 1 or higher neurologic toxicities. Other cytokine-targeting therapies (for example, IL-1) may be used based on institutional practice, especially for cases of neurotoxicity which does not respond to tocilizumab or corticosteroids. Therapy directed at reduction or elimination of CAR-T cells, including chemotherapy, may be considered in consultation with the sponsor for subjects who develop neurotoxicity that remains severe or life-threatening following prior therapies, including tocilizumab and corticosteroids.
	Movement and Neurocognitive Toxicity (ie, Parkinsonism): A cluster of symptoms with variable onset spanning more than one symptom domain was observed, including: changes in movement (eg, micrographia or changes in handwriting, tremors, bradykinesia, rigidity, shuffling gait, impaired balance and coordination, difficulty writing, difficulty performing activities of daily living like dressing or feeding oneself), cognitive impairments (eg, memory loss or forgetfulness, disturbance in attention, mental slowness or fogginess, difficulty speaking or slurred speech, difficulty reading or understanding words), and personality changes (eg, reduced facial expression, flat affect, reduced ability to express emotion, less communicative, disinterest in activities). A cluster of movement and neurocognitive TEAEs were observed at a higher frequency in subjects with high burden of disease and in subjects experiencing higher grade CRS (Grade 2 and above) and any grade ICANS. This may be indicative that ≥Grade 2 CRS or any grade ICANS are early indicators for the development of other neurotoxicity after a period of recovery from CRS and/or ICANS. Therefore, ≥Grade 2 CRS or any grade ICANS may represent an opportunity for early intervention and more aggressive supportive care (including steroids), especially in patients treated with a high tumor burden, that may mitigate the risk for developing late, other neurotoxicity. Infection and sepsis were seen concurrently in many of these patients.

Risk	Mitigation Strategies
	Mitigation strategies for other neurotoxicity include enhanced bridging therapy to reduce baseline tumor burden, early aggressive treatment of CRS and ICANS, handwriting assessments for early detection of neurotoxicity symptoms, and extended monitoring and reporting time for neurotoxicity for the duration of the study. Monitor closely for other neurotoxicities with clinical presentation for the duration the study after infusion. If those neurologic or psychiatric symptoms are noted, contact the medical monitor, and refer the subject immediately to a neurologist for a full evaluation. Section 1.17.2.4.2.2 provides further details for management guidelines for neurotoxicity. Cranial Nerve Palsies: Monitor patients for signs and symptoms of cranial nerve palsies (eg, facial paralysis, facial numbness). Consider management with short-course systemic corticosteroids, depending on the severity and progression of signs and symptoms. Peripheral Neuropathy: Monitor patients for signs and symptoms of peripheral neuropathies (eg, sensory, motor, or sensorimotor neuropathies). Consider management with short-course systemic corticosteroids, depending on the severity and progression of signs and symptoms. Guillain-Barré Syndrome: Monitor for signs and symptoms of GBS after cilta-cel infusion. Symptoms reported include those consistent with Miller-Fisher variant of GBS (encephalopathy, motor weakness, speech disturbances, and polyradiculoneuritis). Consider treatment with IVIG and escalate to plasmapheresis, depending on toxicity severity.
Second primary malignancies (SPMs) *	Second primary malignancies may occur in subjects receiving JNJ-68284528. SPMs should be managed per institutional standards. Second primary malignancies must be reported during the duration of the study, irrespective of when they occur, and subsequently will be collected in a long-term follow-up study yearly until 15 years post dosing of JNJ-68284528. A tumor sample should be collected, and DNA, RNA, or protein analysis may be performed to investigate the presence of lentiviral elements if an SPM develops. Section 1.17.2.4.5 provides management guidelines for SPMs.
Prolonged Cytopenia	Frequent monitoring of hematological parameters and provide supportive care (eg, radiated blood and thrombocyte concentrates, granulocyte-colony stimulating factor for neutropenia) as outlined by institutional guidelines. Pegylated myeloid growth factors (ie, pegfilgrastim) are prohibited. Prolonged neutropenia may increase the risk of infection. Severe thrombocytopenia may increase the risk of bleeding. Initiating lenalidomide after JNJ-68284528 might cause significant neutropenia and thrombocytopenia. Monitor complete blood counts (CBC) weekly for first 2 cycles, biweekly for cycle 3 and every 28 days thereafter. Subjects should be monitored frequently for infection and bleeding. Supportive care should be provided per institutional standards. Section 6.2.5 provides management guidelines for cytopenia. Parvovirus B19 monitoring by PCR should be considered in subjects experiencing prolonged neutropenia or a decline in neutrophil counts following recovery.
Hypogammaglobulinemia	Monitor immunoglobulin levels after treatment and treat according to local guidelines, including administration of immunoglobulin replacement and monitoring for infection. Additional assessments of immunoglobulin levels may be done as per local standards of care. Section 6.2.6 provides management guidelines for hypogammaglobulinemia. Subjects with IgG < 400 mg/dL or recurrent infections (including HBV reactivation) should be considered for prophylactic IV or subcutaneous IgG as per institutional guidelines.
Serious Infections	Do not administer JNJ-68284528 to patients with active infection. Frequent monitoring for the presence of infections, with cultures or implementation of

Risk	Mitigation Strategies
	empiric antibiotic therapy as appropriate, based on clinical judgment and institutional standards. Extended use of anti-microbial therapies for at least 6 month (or longer as per institutional guidelines) or consistent with post ASCT consensus guidelines after JNJ-68284528 dosing is recommended (See Attachment 18). Perform screening for hepatitis B virus (HBV), hepatitis C virus (HCV), and human immunodeficiency virus (HIV) and monitor as clinically indicated, and initiate treatment as appropriate. Perform CMV and EBV serology (at baseline only) and PCR at baseline and according to the Time and Events Schedules (Section 1.2) and as clinically indicated per institutional guidance. HBV reactivation, in some cases resulting in fulminant hepatitis, hepatic failure and death, may occur in subjects treated with drugs directed against B cells such as JNJ-68284528. HBV reactivation has occurred in subjects who appear to have resolved hepatitis B infection. Prophylaxis for herpes zoster reactivation is recommended during study treatment as clinically indicated. Routinely monitor HBV DNA and AST/ALT for subjects with risk of HBV reactivation (Attachment 10). Subjects receiving cilta-cel are possibly at a higher risk of severe/fatal outcomes from COVID-19 infection compared with patients who are receiving standard of care therapy. Subjects should be reminded of the importance of vaccines and other preventative measures. Investigators should consider prophylaxis (eg, Evusheld, if available) and antiviral medications (eg, Paxlovid, if available) for patients diagnosed with COVID-19 infection, as noted in (Attachment 20).
Hypersensitivity reactions	Allergic reactions may occur with the infusion of cilta-cel. Serious hypersensitivity reactions including anaphylaxis, may be due to dimethyl sulfoxide (DMSO), dextran 40, or residual ampicillin or kanamycin in cilta-cel. Subjects should be treated urgently per institutional standards, avoiding corticosteroid use if possible. Subjects should receive premedication prior to cilta-cel dosing as noted in Section 6.1.3.3.
Tumor lysis syndrome	Monitor closely for TLS with frequent monitoring of chemistry parameters and follow guidance for management in protocol. Subjects with high tumor burden or multiple extramedullary disease sites or plasmacytomas should be treated prophylactically in accordance with local standards (eg, extra hydration; diuretics; allopurinol; and primary or secondary uricosuric agents, as indicated).

* Adverse event of special interest (see Section 12.3.3)

More detailed information about the known and expected benefits and risks of JNJ-68284528 may be found in the IB.

Taking into account the measures taken to minimize risk to subjects of this study, the potential risks identified in association with cilta-cel are justified by the anticipated benefits that may be afforded to subjects with NDMM.

1.6. Objectives and Endpoints

Objectives	Endpoints
Primary	
• Cohort G: To evaluate the efficacy of DRd followed by cilta-cel in subjects for whom transplant is not planned • Cohort H: To evaluate the efficacy of D-VRd followed by cilta-cel in subjects who are transplant eligible	• Sustained MRD-negative CR, defined as MRD-negative CR for a minimum 12 months duration, with MRD status determined by NGS or NGF with a sensitivity of at least 10^{-5}

Objectives	Endpoints
Secondary	
• Cohort G: To further evaluate the efficacy of DRd followed by cilta-cel in subjects for whom transplant is not planned • Cohort H: To further evaluate the efficacy of D-VRd followed by cilta-cel in subjects who are transplant-eligible	• Overall response status (PR or better), CR or better status, duration of response, time to response • Overall MRD-negative CR status with a sensitivity of at least 10^{-5} • PFS • OS • Time to subsequent anti-myeloma therapy • PFS on next-line therapy (PFS2)
To characterize the safety of cilta-cel after DRd (Cohort G) or D-VRd (Cohort H) induction therapy	Incidence and severity of AEs, laboratory results and other safety parameters
To determine whether replication competent lentivirus is present in subjects that receive cilta-cel	Presence of replication competent lentivirus.
Exploratory	
To assess the immunogenicity of cilta-cel	Presence of anti-cilta-cel antibodies
To explore imaging plus MRD-negative rate	Imaging plus MRD-negative CR rate by PET/CT, as locally performed
To explore whether the infused CAR-positive T cell subsets impact pharmacodynamics, safety, and clinical activity of cilta-cel	CAR+ central memory, effector memory T cells and expression of activation and/or exhaustion markers including, but not limited to, CD25 and PD-1
To further characterize the safety of cilta-cel after DRd (Cohort G) or DVRd (Cohort H) induction therapy	Pharmacokinetic and pharmacodynamic markers by protein, DNA, and/or RNA analyses, including but not limited to changes in systemic inflammatory cytokine concentrations, markers of T cell activation, exhaustion or memory phenotypes, or genomic or transcriptomic changes
To characterize the pharmacokinetics and pharmacodynamics of cilta-cel	Pharmacokinetic and pharmacodynamic markers, by protein, DNA, or RNA analyses, including but not limited to changes in markers of CAR-T cell expansion (proliferation) and persistence via monitoring CAR-T positive cells and CAR transgene levels.

Refer to Section 1.28, Study Assessments and Procedures for evaluations related to endpoints.

HYPOTHESIS

No statistical hypothesis testing in this study. The clinical hypothesis is that cilta-cel will induce a deep and durable response, measured by sustained MRD negative CR in the clinical settings investigated.

1.7. Overall Design

Part B consists of 2 new cohorts (G and H), added to Study 68284528MMY2003, that will evaluate subjects with newly diagnosed multiple myeloma in the United States. Subjects will be enrolled into 1 of the following cohorts:

- Cohort G (DRd induction followed by cilta-cel): Subjects with NDMM for whom transplant is not planned
- Cohort H (D-VRd induction followed by cilta-cel): Subjects with NDMM who are transplant-eligible

All enrolled subjects will be evaluated for eligibility in one of the 2 cohorts (Section 1.12 and Section 1.13), as mentioned above.

Cilta-cel will be generated from the subjects' T cells selected from the apheresis product. Approximately 40 and up to 100 subjects will be enrolled in each cohort. The conduct and timing of the cohorts G and H will be independent of each other. Enrollment is defined either as apheresis or first day of study treatment, whichever occurs first. Cilta-cel will be generated from the subjects' T cells selected from the apheresis product. Approximately 40 and up to 100 subjects will be enrolled in each cohort.

1.7.1. Study Periods and Their Sequence

The following is the sequence and the duration of the study periods. For more information on the study assessments and procedures during these periods, refer to Time and Events Schedules (Section 1.2), Section 1.7.2 below, and Section 1.28.

Phase/Period	Duration	Notes
Screening	Within 28 days before enrollment	
Apheresis		Before start of DRd (Cohort G) or D-VRd (Cohort H) induction therapy
Induction therapy	4 cycles lasting 28-day each	with DRd (Cohort G) or D-VRd (Cohort H)
Lymphodepleting chemotherapy	After the 4th Cycle of induction therapy	Lymphodepleting chemotherapy start when subject has recovered from the 4th cycle of induction therapy and is followed by cilta-cel infusion.
Post Cilta-cel Infusion	112 days starting from cilta-cel infusion	
Post-treatment Follow-up Phase	Day 113 until end of study/cohort	

1.7.2. Study Treatment Overview

1.7.2.1. Conditioning, Cilta-cel Infusion, And Follow-Up (Cohort G and H)

After completion of 4 cycles of induction therapy (DRd or D-VRd), and after cilta-cel production and product release are completed, all subjects who meet criteria for conditioning (see Section 1.17.2.2) will receive a conditioning regimen of IV cyclophosphamide (300 mg/m^2) and fludarabine (30 mg/m^2) daily for 3 days. The dose of fludarabine should be reduced to 24 mg/m^2 for subjects with an eGFR of 30 to 70 mL/min/1.73m^2. Cilta-cel (at the dose of 0.75 x 10^6 CAR-positive viable T cells/kg; range 0.5-1.0) will be administered 5 to 7 days after the start of the conditioning regimen. The conditioning regimen will lead to lymphodepletion and help to promote CAR-T cell expansion in the subject. After the infusion of cilta-cel, subjects will remain in follow-up until disease progression.

Additional cycles of induction therapy prior to conditioning may be considered based on the subject's clinical status and timing of availability of cilta-cel. This approach may be used in exceptional circumstances and the investigator must contact the sponsor for approval.

No maintenance therapy after cilta-cel will be given on Cohorts G and H.

Following cilta-cel infusion, subjects will enter post-infusion phase. Subjects must continue to have disease evaluations according to the Time and Events schedule until confirmed PD, death, withdrawal of consent, lost to follow-up, or the end of the study. After disease progression is documented, subsequent anticancer treatment, PFS2 (per investigator judgment), second primary malignancies, and survival will also be recorded.

Subjects who progress during induction therapy may receive conditioning therapy followed by cilta-cel as subsequent therapy if they meet criteria for conditioning therapy and after approval from the Sponsor. It is strongly recommended that subjects who progress on DRd or D-VRd induction receive additional salvage therapy, prior to proceeding to conditioning therapy.

All subjects who receive cilta-cel will continue to be monitored for long-term safety under a separate study (68284528MMY4002) for up to 15 years after cilta-cel administration.

Disease status will be evaluated for response and disease progression according to the IMWG consensus criteria for multiple myeloma (see Attachment 1. Efficacy evaluations will include measurements of myeloma protein, imaging of lytic lesions, assessment of extramedullary and bone-based plasmacytomas, bone marrow examinations, and MRD evaluations. MRD will be monitored using NGS on bone marrow aspirate DNA and PET/CT if locally available. MRD will be monitored centrally using NGS and should commence upon suspicion of CR/sCR. Once MRD negative CR/sCR is documented, repeat bone marrow to document sustained MRD negative CR is required yearly until PD. In subjects where a clone identification for MRD detection by NGS was not successful, MRD will be monitored using NGF (Euroflow or equivalent). In these subjects, NGF may be performed locally if available or centrally. The primary endpoint and response-related secondary endpoints will be determined using a validated computer algorithm (Palumbo 2016).

Safety evaluations will include a review of AEs, laboratory test results, vital sign measurements, physical examination findings (including neurologic examination), assessment of cardiac function and assessment of ECOG performance status grade. Subjects will also receive an ICE assessment. Blood samples will be drawn for assessment of pharmacokinetic, pharmacodynamic, and immunogenicity parameters. All study evaluations will be conducted according to the Time and Events Schedules (Section 1.2). Additional blood or tissue samples may be collected for safety work-up of AEs.

The sponsor will establish a data cutoff date for clinical study report (CSR) analyses. For both Cohorts G and H, the primary analysis will be conducted approximately at 1.5 year after the last subject in that cohort started their study treatment. The final analysis will be conducted at cohort completion, which is defined as approximately 2.5 years after the last subject in that cohort has

started their study treatment (Section 1.10). In addition, for Cohort G only, a first analysis may be conducted at approximately 6 to 12 months after the last subject in that cohort started their study treatment. If the first analysis is performed, it may become the primary analysis.

Diagrams of the study design is provided in Section 1.1.

1.8. Scientific Rationale for Cohorts G and H

Rationale for Study Cohorts

Despite improved outcomes in newly diagnosed multiple myeloma, most patients eventually relapse. Experience with cilta-cel in MMY2001 showed for the first time that mPFS of 34.9 months in a heavily pretreated population can be achieved. Results of the MMY3002 study in subjects with relapsed and lenalidomide-refractory multiple myeloma who received 1 to 3 prior lines of therapy showed a 74% reduction in the risk of an event (death or progression) for the primary endpoint of PFS for cilta-cel (n=208) as compared with standard therapy (PVd or DPd; n=211) (HR=0.26 [95% CI: 0.18, 0.38], p-value<0.0001). Given that benefit of CAR-T therapy is dependent on a patient's immune response, cilta-cel could have potential meaningful efficacy and durability when administered in the frontline setting to patients with multiple myeloma who have had less exposure to immunomodulatory and cytotoxic therapy. Therefore, investigations of CAR-T cell therapy in early lines of treatment are warranted to determine the ability to enhance efficacy and increase depth of response. Further rationale for the population and treatment regiments for Cohorts G and H are provided in Section 1.3.

The global ongoing Phase 3 68284528MMY3004 Study is evaluating VRd induction followed by cilta-cel versus VRd induction followed by lenalidomide maintenance, in newly diagnosed MM where ASCT is not intended as part of the initial therapy. In this current study, we seek to evaluate DRd induction followed by cilta-cel infusion. DRd is an alternative, highly efficacious regimen that is increasingly being used in the United States for initial therapy in subjects in whom ASCT is not intended.

The global Phase 3 68284528MMY3005 study will evaluate the efficacy of cilta-cel and maintenance therapy against ASCT and maintenance therapy.

In this current study, we seek to evaluate the efficacy of D-VRd induction followed by cilta-cel infusion without subsequent maintenance therapy. We hypothesize that given the deep and durable responses to cilta-cel seen in the relapsed subject population, the use of cilta-cel after effective induction therapy, may lead to sustained MRD negative responses in most subjects without the added toxicity of ongoing maintenance therapy.

Rationale for Sustained MRD-negative CR Rate as Primary Endpoint

The advent of new treatment strategies for multiple myeloma using a combination of novel agents, in triplet and quadruplet regimens, and ASCT, has led to significant improvement in response rates and long-term outcomes. With this improvement in outcomes and achievement of prolonged PFS

and OS, which is now measured in years, surrogate or early endpoints are critical to ensure that new therapies are made available to subjects as quickly as possible.

The assessment of sustained MRD-negative CR aligns with the IMWG consensus criteria from 2016 (Kumar 2016) that introduced sustained MRD negative as the highest response criterion. The achievement of MRD negativity has been correlated with improvement of PFS and OS in recent meta-analyses (Landgren 2016; Munshi 2017; Munshi 2020) and one combined analysis (Lahuerta 2017). Another meta-analysis further demonstrated a strong correlation between the treatment effect on the odds ratio for achieving MRD negativity and the hazard ratio for PFS (Avet-Loiseau 2020). More recently, published studies have evaluated the importance of achieving a durable MRD negative status. In a pooled analysis of the MAIA and ALCYONE studies in a population with NDMM patients that were transplant ineligible, patients who achieved an MRD-negative status had a longer PFS compared with patients who remained MRD-positive, and the greatest PFS benefit was observed in those patients who reached an MRD durability of at least 6 or 12 months (San-Miguel 2022). Similar outcomes were observed in the FORTE study of patients with NDMM who were transplant eligible (Oliva 2020). This latter study also suggested that the PFS of patients with a sustained MRD negativity was independent of treatment.

These literature references collectively suggest that sustained MRD negative could be a promising early endpoint likely to predict PFS in NDMM.

Rationale for Pharmacokinetic and Immunogenicity Assessments

Blood samples will be obtained from all subjects in Cohorts G and H for pharmacokinetic assessments. This will provide information about the pharmacokinetics of cilta-cel in subjects with NDMM. Data may also be used for a population pharmacokinetic analysis to estimate pharmacokinetic parameters and provide information about the determinants of inter-subject variability in this population.

Immunogenicity to cilta-cel is possible. Therefore, the presence of anti-cilta-cel antibodies will be determined from anti-drug antibody samples collected from each subject in Cohorts G and H.

Rationale for Biomarker Assessments

Samples will be collected to evaluate biomarker endpoints, including but not limited to, the PK properties of cilta-cel-positive T-cells, the depth and durability of clinical response through assessment of MRD via NGS using the clonoSEQ® assay (Adaptive Biotechnologies, Seattle, WA), and the presence of RCL. Additional biomarker analyses may be performed to further characterize the safety of cilta-cel after induction therapy, including but not limited to, exploration of immune cell subsets and fitness by phenotypic and functional markers, cytokines, and potential proteomic, genomic, transcriptomic and/or single cell profiling.

1.8.1. Ethical Design Considerations

While the treatment of NDMM patients continues to improve, the disease remains largely incurable. This study is designed to evaluate the efficacy and safety of cilta-cel for the treatment of subjects with NDMM for whom ASCT is not planned as initial therapy, either due to patient preference or transplant ineligibility (Cohort G), and for the treatment of subjects with NDMM who are transplant eligible (Cohort H). Based on the data from completed and ongoing clinical studies, treatment with cilta-cel is anticipated to provide benefit to subjects in this study. Potential safety risks and mitigation strategies are outlined in Section 1.5. Subjects will be closely monitored.

Potential subjects will be fully informed of the risks and requirements of the study, and, during the study, subjects will be given any new information that may affect their decision to continue participation. They will be told that their consent to participate in the study is voluntary and may be withdrawn at any time with no reason given and without penalty or loss of benefits to which they would otherwise be entitled. Only subjects who are fully able to understand the risks, benefits, and potential AEs of the study, and provide their consent voluntarily will be enrolled.

Subjects enrolled in Cohort G will have received 4 cycles of DRd prior to the cilta-cel administration, and subjects enrolled in Cohort H will have received 4 cycles of D-VRd prior to the cilta-cel administration. In both cases, induction therapy is intended to reduce the tumor burden prior to cilta-cel infusion which is expected to reduce the risk of tumor lysis, CRS, and neurotoxicity following cilta-cel administration. Prior to receiving conditioning regimen and cilta-cel, subjects in both cohorts will be required to meet the criteria specified in Section 1.17.2.2.1 and Section 1.17.2.3.1, respectively.

Subjects in Cohorts G and H will not be able to receive ASCT in the frontline setting. Frontline ASCT has been the standard for treating NDMM in young, fit subjects and selected elderly subjects. Nonetheless, with the advent of present novel therapies, the notion that ASCT should be administered early after diagnosis has been challenged (Kazandjian 2020). Several prospective and retrospective studies failed to demonstrate an OS benefit when comparing early ASCT with late ASCT (Attal 2017; Fermand 1998). In addition, ASCT can improve outcomes whether performed as first line or as rescue treatment in later lines of therapy (Harousseau 2009). Although subjects enrolled in Cohort G and H will not receive ASCT in the front line setting, they will still be able to harvest their stem cells while on study, and can benefit from salvage ASCT after PD is identified and confirmed by the medical monitor.

The total blood volume to be collected is considered to be an acceptable amount of blood to be collected over this time period from the population in this study based upon the standard by the American Red Cross (American Red Cross 2020).

Experience with JNJ-68284528 in Study 68284528MMY2001 and LCAR-B38M CAR-T cells in the Legend-2 study, demonstrates substantial response rates, MRD negative rates, and acceptable toxicity in a heavily pre-treated population of subjects. Use of cilta-cel is hypothesized to result in greater depth and duration of response rates and duration of response when used in earlier lines of

therapy due to improved immune function potentially resulting in a superior CAR-T product (Garfall 2019). Therefore, there is interest in assessing the impact of cilta-cel in a "one and done" dosing for patients with standard risk myeloma to determine whether these patients will have a long disease-free survival without the need for chronic therapy until disease progression – as this is the current standard of care.

1.9. Justification for Dose

1.9.1. Daratumumab, Lenalidomide, and Dexamethasone (DRd) – Cohort G

The DRd regimen is FDA approved for the treatment of multiple myeloma in newly diagnosed subjects who are ineligible for autologous stem cell transplant (DARZALEX FASPRO USPI). The dose and schedule of DRd was selected based on the dose and schedule used in the pivotal MAIA study which resulted in FDA approval in this setting.

1.9.2. Daratumumab, Bortezomib, Lenalidomide, Dexamethasone (D-VRd) – Cohort H

The dose and schedule of the DVRd regimen were selected based on the daratumumab Phase 3 CASSIOPEIA, Phase 3 PERSEUS, and the Phase 2 GRIFFIN studies. Of note, these studies utilized twice weekly bortezomib, while in the current study weekly bortezomib dosing is planned. A Phase 3 study comparing VMPT to VMP was amended and subjects in both arms received weekly bortezomib. 372 subjects received one weekly bortezomib and 139 received twice weekly bortezomib. There was no statistically significant difference in the 3 year PFS and OS rates. There was significant difference in the rates of severe peripheral neuropathy (8% vs 28% for weekly vs. twice weekly bortezomib, respectively) (Bringhen 2010).

RWE suggests that bortezomib is more commonly used weekly in US practice. One study retrospective analyzed 555 NDMM subjects treated at the Mayo Clinic with upfront VRd from 30 June 2008 to 31 December 2018, for variations of bortezomib administration. Bortezomib was administered twice weekly every 21 days in 43%, once weekly every 21 days in 41% and once weekly every 28 days in 16%. 74% of patients proceeded to an autologous stem cell transplant. At a median follow up of 37 months (IQR 22–56), there found no difference in PFS or OS among the groups. Significantly higher rates of peripheral neuropathy were observed in the biweekly bortezomib group (Cook 2021). Further, RWE reported on 296 patients treated at 15 centers in the UK with DVd at first relapse: 99 patients received biweekly bortezomib for at least 3 cycles initially, 197 patients were treated with weekly bortezomib from the onset. There was no significant difference in ORR or PFS between patients treated weekly or with the biweekly to weekly groups. Median OS not reached for either group (McMillan 2023).

1.9.3. Cilta-cel

The conditioning regimen of cyclophosphamide and fludarabine will lead to lymphodepletion and help promote CAR-T cell expansion in the subjects. Cyclophosphamide and fludarabine before cilta-cel infusion (Day 1) are consistent with the conditioning regimens used the cilta-cel package insert (CARVYKTI PI) and in other marketed CAR-T products (Breyanzi PI 2022; Kymriah PI 2022; Tecartus PI 2021; Yescarta PI 2022; Abecma USPI 2021).

Cilta-cel will be administered at FDA-approved targeted infused dose of 0.75 x 10^6 CAR-positive viable T cells/kg (range: 0.5-1.0 x 10^6 CAR-positive viable T-cells/kg, maximum dose: 1.0 x 10^8 CAR-positive viable T cells). This dose was established in the Phase 1b part of Study 68284528MMY2001. Data from Study 68284528MMY2001 showed that a dose of 0.75 x 10^6 cells/kg of cilta-cel CAR-T cell is highly efficacious with an acceptable safety profile in a subject population who had no alternative treatment options. Further discussion of the cilta-cel dose selection is provided in the cilta-cel IB.

In the event the manufactured drug product exceeds the protocol-defined maximum dose, it will be evaluated per company exceptional release criteria or similar process (see Section 1.17.2.3.4) prior to shipment to the study site. Drug products provided through this exceptional release or similar process that exceed the protocol maximum dose will not qualify for overdose reporting.

1.9.4. Emergency treatment prior to enrollment

MM patients can present with hypercalcemia, impending end organ damage or bone damage, at the time of diagnosis and may need emergency measures such as high dose corticosteroids, chemotherapeutic options or local radiation, prior to starting definitive induction treatment. If such a patient is considered for the cohort G and H, then the individual case should be discussed with the sponsor prior to enrollment in the trial. However, it is important to note that the diagnosis of plasma cell leukemia is an exclusion criterion.

1.10. End of Study Definition

End of Cohort Definition

Cohorts G and H will each be considered completed after the last subject has had 2.5 years of follow-up after they started their study treatment. All subjects who received cilta-cel will be asked to consent to the long-term follow-up study 68284528MMY4002 at the end of their study cohort. The sponsor will continue to monitor consented subjects in the long-term follow-up study at least once per year for 15 years. An appropriate transition will be arranged between this study and the long-term follow-up study to ensure continuity in subject monitoring.

End of Study Definition

End of study is defined as approximately 2.5 years after the last subject started their study treatment. An appropriate transition will be arranged between MMY2003 Part B and the long-term follow-up trial MMY4002/CARTINUE as to ensure continuity in subject monitoring.

The final data from the study site will be sent to the sponsor (or designee) after completion of the final subject assessment at that study site, in the time frame specified in the Clinical Trial Agreement.

Subject Study Completion Definition

A subject will be considered to have completed the study if he or she has completed all protocol-specified procedures before the end of the study, has not been lost to follow-up, has not

withdrawn consent for study participation before the end of the study or when the study is terminated by the sponsor.

1.11. STUDY POPULATION

Screening for eligible subjects will be performed within 28 days before enrollment.

Refer to Section 1.15, Screen Failures for conditions under which the repeat of any screening procedures are allowed.

The inclusion and exclusion criteria for enrolling subjects in this study are described below. If there is a question about these criteria, the investigator must consult with the appropriate sponsor representative and resolve any issues before enrolling a subject in the study. Waivers are not allowed.

1.12. Cohort G Eligibility Criteria

1.12.1. Cohort G Inclusion Criteria

Each potential subject must satisfy all of the following criteria to be enrolled in Cohort G of the study:

Age

1g. Be ≥18 years of age at the time of informed consent.

Type of Subject and Disease Characteristics

2g. Documented diagnosis of multiple myeloma according to IMWG diagnostic criteria (Rajkumar 2014, Attachment 5).

3g. Not considered for high-dose chemotherapy with ASCT due to:

a. Ineligibility due to advanced age; or

b. Ineligibility due to presence of comorbid condition(s) likely to have a negative impact on tolerability of high-dose chemotherapy with ASCT; or

c. Subject refusal of high-dose chemotherapy with ASCT as initial treatment.

4g. Measurable disease at Screening as defined by any of the following*:

a. Serum monoclonal paraprotein (M-protein) level ≥1.0 g/dL or urine M-protein level ≥200 mg/24 hours; or

b. Light chain multiple myeloma in subjects in whom the only measurable disease is by serum FLC levels in the serum: Serum immunoglobulin free light chain ≥10 mg/dL and abnormal serum immunoglobulin kappa lambda free light chain ratio.

* For subjects who received 1-2 cycles of DRd prior to enrollment, measurable disease criteria must have been met prior to the start of induction.

5g. Eastern Cooperative Oncology Group Performance Status Grade of 0 or 1 (Attachment 7).

6g. Clinical laboratory values meeting the following criteria during the Screening Phase:

Hematology	
Hemoglobin	≥7.0 g/dL (≥4 mmol/L) (without prior red blood cell [RBC] transfusion within 7 days before the laboratory test; recombinant human erythropoietin use is permitted)[a]
Platelets	≥75 x 10^9/L (must be without transfusion support in the 7 days prior to the laboratory test)
Absolute Lymphocyte Count (ALC)	≥0.3 x 10^9/L
Absolute Neutrophil Count (ANC)	≥1 ×10^9/L (prior growth factor support is permitted but must be without support in the 7 days prior to the laboratory test)
Chemistry	
AST and ALT	≤3.0 × upper limit of normal (ULN)
Estimated Glomerular Filtration Rate	≥40 mL/min/1.73 m^2 based upon Modified Diet in Renal Disease formula calculation or a 24-hour urine collection. See Attachment 8.
Total bilirubin	≤2.0 × ULN; except in subjects with congenital bilirubinemia, such as Gilbert syndrome (in which case direct bilirubin ≤2.0 × ULN is required)

a. For subjects who meet the inclusion criteria at screening, transfusion of RBCs is permitted after screening as needed to maintain a hemoglobin level ≥7.0 g/dL.

Contraceptive/Barrier Requirements (BROAD)

7g. A subject of childbearing potential must have a negative serum pregnancy test, with a minimum sensitivity of 25 mIU/mL for FCBP

8g. Subject must agree to practice 2 methods of reliable birth control simultaneously from 4 weeks prior to initiating treatment with lenalidomide until 1 year after receiving a cilta-cel infusion or for 4 weeks following discontinuation of lenalidomide or for 3 months after discontinuation of daratumumab (whichever is later). One of the birth control methods should be a highly effective method of contraception (failure rate of <1% per year when used consistently and correctly; see examples below) and one other effective method (ie, male latex or synthetic condom, diaphragm, or cervical cap) and subject must agree to remain on both methods. Examples of highly effective contraceptives include:

- user-independent methods: 1) implantable progestogen-only hormone contraception associated with inhibition of ovulation; 2) intrauterine device; intrauterine hormone-releasing system; 3) vasectomized partner.
- user-dependent method: progestogen-only hormone contraception associated with inhibition of ovulation (oral or injectable). Estrogen-containing hormonal contraception is contraindicated due to increased risk of thromboembolic events with lenalidomide.

- subjects of childbearing potential must follow the contraception criteria outlined in the global REVLIMID® pregnancy prevention program or equivalent local REMS, whichever is more stringent, as applicable in their region.

In addition to the highly effective method of contraception, a man:

- Must always use a condom during any sexual contact with a person of childbearing potential, even if they have undergone a successful vasectomy, from the time of signing the ICF until 1 year after receiving a cilta-cel infusion or for 4 weeks after discontinuing lenalidomide (whichever is later).
- Who is sexually active with a person who is pregnant must use a condom.
- Should agree to practice contraception according to and for the time frame specified in the global lenalidomide pregnancy prevention program or equivalent local lenalidomide pregnancy prevention program, whichever is more stringent.

Note: Hormonal contraception may be susceptible to interaction with the study treatment, which may reduce the efficacy of the contraceptive method.

9g. Subjects must agree not to donate eggs (ova, oocytes) or sperm, respectively, during the study and for 1 year after receiving a cilta-cel infusion or for 4 weeks after discontinuing lenalidomide (whichever is later).

Informed Consent

10g. Must sign an ICF indicating that the subject understands the purpose of, and procedures required for, the study and is willing to participate in the study. Consent is to be obtained prior to the initiation of any study-related tests or procedures that are not part of standard of care for the subject's disease.

11g. Willing and able to adhere to the prohibitions and restrictions specified in this protocol.

1.12.2. Cohort G Exclusion Criteria

Any potential subject who meets any of the following criteria will be excluded from participating in Cohort G of the study:

Medical Conditions

1g. Active malignancies (ie, progressing or requiring treatment change in the last 24 months) other than the disease being treated under study. The only allowed exceptions are:

a. non-muscle invasive bladder cancer treated within the last 24 months that is considered completely cured.

b. skin cancer (non-melanoma or melanoma) treated within the last 24 months that is considered completely cured.

c. non-invasive cervical cancer treated within the last 24 months that is considered completely cured.

d. localized prostate cancer (N0M0):

- with a Gleason score of ≥6, treated within the last 24 months or untreated and under surveillance,
- with a Gleason score of 3+4 that has been treated more than 6 months prior to full study screening and considered to have a very low risk of recurrence, or
- history of localized prostate cancer and receiving androgen deprivation therapy and considered to have a very low risk of recurrence.

e. breast cancer: adequately treated lobular carcinoma in situ or ductal carcinoma in situ, or history of localized breast cancer and receiving antihormonal agents and considered to have a very low risk of recurrence.

f. malignancy that is considered cured with minimal risk of recurrence.

2g. Frailty index of ≥ 2 according to Myeloma Geriatric Assessment score (Palumbo 2015, Attachment B 3).

3g. The following cardiac conditions:

a. New York Heart Association stage III or IV congestive heart failure (see Attachment B 4)

b. Myocardial infarction or coronary artery bypass graft ≤6 months prior to enrollment.

c. History of clinically significant ventricular arrhythmia or unexplained syncope, not believed to be vasovagal in nature or due to dehydration

d. History of severe non-ischemic cardiomyopathy.

e. Impaired cardiac function (left ventricular ejection fraction <45%) as assessed by echocardiogram or multiple-gated acquisition scan (performed ≤8 weeks of enrollment)

4g. Known active, or prior history of central nervous system involvement or exhibits clinical signs of meningeal involvement of multiple myeloma

5g. Stroke or seizure within 6 months of signing ICF.

6g. Plasma cell leukemia at the time of screening (>2.0 x 10^9/L plasma cells by standard differential), Waldenström's macroglobulinemia, POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, and skin changes), or primary amyloid light-chain amyloidosis.

7g. Seropositive for HIV.

8g. The following pulmonary conditions:

a. Chronic obstructive pulmonary disease with a FEV1 <50% of predicted normal (for subjects ≥65 years old FEV1 <50%)

b. Moderate or severe persistent asthma within the past 2 years, or currently has uncontrolled asthma of any classification. (Note that subjects who currently have controlled intermittent asthma or controlled mild persistent asthma are allowed in the study).

c. Subject requires continuous supplemental oxygen.

9g. Serious underlying medical condition, such as:

a. Evidence of active viral or bacterial infection requiring systemic antimicrobial therapy, or uncontrolled systemic fungal infection.

b. Active autoimmune disease.

c. Overt clinical evidence of dementia or altered mental status.

10g. Contraindications, known life-threatening allergies, hypersensitivity, or intolerance to any of the study treatments or any of their excipients.

11g. Gastrointestinal disease that may significantly alter the absorption of oral drug.

12g. Any history of Parkinson's disease or other neurodegenerative disorder

Viral Hepatitis Assessments

14g. Hepatitis B infection as defined according to Attachment 10. In the event the infection status is unclear, quantitative levels are necessary to determine the infection status (Hwang 2015)

15g. Hepatitis C infection defined as (anti-HCV antibody positive or HCV-RNA positive) or known to have a history of hepatitis C. For subjects with known history of HCV infection, confirmation of sustained virologic response is required for study eligibility, defined as ≥24 weeks after completion of antiviral therapy

Prior/Concomitant Therapy or Clinical Study Experience

16g. Prior therapy for multiple myeloma or smoldering myeloma with the exception of:

a. short course of corticosteroids (not to exceed 40 mg of dexamethasone, or equivalent per day for a maximum of 4 days, total of 160 mg dexamethasone or equivalent), or

b. 1-2 cycles of DRd

17g. Prior treatment with CAR-T therapy directed at any target.

18g. Prior treatment with any therapy that is targeted to BCMA

19g. Received an investigational intervention (including investigational vaccines) or used an invasive investigational medical device within 15 days before the planned first dose of study intervention or is currently enrolled in an investigational study.

20g. Vaccinated with live, attenuated vaccine within 4 weeks prior to enrollment.

21g. Major surgery within 2 weeks prior to enrollment, or has surgery planned during the study or within 2 weeks after study treatment administration (note: subjects with planned surgical procedures to be conducted under local anesthesia may participate).

22g. Radiation therapy for treatment of plasmacytoma within 14 days of enrollment (palliative radiation for pain control secondary to lytic lesion is allowed within 14 days of enrollment). If the radiation portal covered ≤5% of the bone marrow reserve (Section 1.17.2.1.1), the subject is eligible irrespective of the end date of radiation therapy.

Other Exclusions

23g. Any issue that would impair the ability of the subject to receive or tolerate the planned treatment at the investigational site, to understand informed consent or any condition for which, in the opinion of the investigator, participation would not be in the best interest of the subject (eg, compromise the well-being) or that could prevent, limit, or confound the protocol-specified assessments.

24g. Pregnant or breast-feeding, or planning to become pregnant while enrolled in this study or within 4 weeks after the last dose of lenalidomide, 3 months after the last dose of daratumumab or bortezomib, 1 year after receiving the conditioning regimen (cyclophosphamide and fludarabine) or 1 year after receiving cilta-cel infusion (whichever is later).

25g. Plans to impregnate a person via their semen while enrolled in this study or within 4 weeks after the last dose of lenalidomide, 3 months after the last dose of daratumumab or bortezomib, 1 year after receiving the conditioning regimen (cyclophosphamide and fludarabine) or 1 year after receiving cilta-cel infusion (whichever is later).

26g. Unable or unwilling to undergo antithrombotic prophylactic treatment.

NOTE: Investigators must ensure that all study enrollment criteria have been met at screening. If a subject's clinical status changes (including any available laboratory results or receipt of additional medical records) after screening but before the first dose of study treatment is given such that the subject no longer meets all eligibility criteria, then the subject must be excluded from participation in the study. Section 1.15, Screen Failures, describes options for retesting. The required source documentation to support meeting the enrollment criteria are noted in Section 17.5.

1.13. Cohort H Eligibility Criteria

1.13.1. Cohort H Inclusion Criteria

Each potential subject must satisfy all of the following criteria to be enrolled in Cohort H of the study:

Age

1h. Be ≥18 years of age at the time of informed consent.

Type of Subject and Disease Characteristics

2h. Documented diagnosis of multiple myeloma according to IMWG diagnostic criteria (Rajkumar 2014, Attachment 5).

3h. Considered a candidate for high-dose chemotherapy with ASCT as initial treatment:

4h. Measurable disease at Screening as defined by any of the following*:

a. Serum monoclonal paraprotein (M-protein) level ≥1.0 g/dL or urine M-protein level ≥200 mg/24 hours; or

b. Light chain multiple myeloma in whom the only measurable disease is by serum FLC levels in the serum: Serum immunoglobulin free light chain ≥10 mg/dL and abnormal serum immunoglobulin kappa lambda free light chain ratio.

* For subjects who received 1-2 cycles of DRd prior to enrollment, measurable disease criteria must have been met prior to the start of induction.

5h. Eastern Cooperative Oncology Group Performance Status grade of 0 or 1 (Attachment 7).

6h. Clinical laboratory values meeting the following criteria during the Screening Phase:

Hematology	
Hemoglobin	≥7.0 g/dL (≥4 mmol/L) (without prior red blood cell [RBC] transfusion within 7 days before the laboratory test; recombinant human erythropoietin use is permitted)[a]
Platelets	≥75 x 10^9/L (must be without transfusion support in the 7 days prior to the laboratory test)
Absolute Lymphocyte Count (ALC)	≥0.3 x 10^9/L
Absolute Neutrophil Count (ANC)	≥1 ×10^9/L (prior growth factor support is permitted but must be without support in the 7 days prior to the laboratory test)
Chemistry	
AST and ALT	≤3.0 × upper limit of normal (ULN)
Estimated Glomerular Filtration Rate	≥40 mL/min/1.73 m^2 based upon Modified Diet in Renal Disease formula calculation or a 24-hour urine collection. See Attachment 8.
Total bilirubin	≤2.0 × ULN; except in subjects with congenital bilirubinemia, such as Gilbert syndrome (in which case direct bilirubin ≤2.0 × ULN is required)

[a] For subjects who meet the inclusion criteria at screening, transfusion of RBCs is permitted after screening as needed to maintain a hemoglobin level ≥7.0 g/dL.

Contraceptive/Barrier Requirements (BROAD)

7h. A subject of childbearing potential must have a negative serum pregnancy test, with a minimum sensitivity of 25 mIU/mL for FCBP.

8h. Subject must agree to practice 2 methods of reliable birth control simultaneously from 4 weeks prior to initiating treatment with lenalidomide until 1 year after receiving a cilta-cel infusion or for 4 weeks following discontinuation of lenalidomide or for 3 months after discontinuation of daratumumab (whichever is later). One of the birth control methods should be a highly effective method of contraception (failure rate of <1% per year when used consistently and correctly; see examples below) and one other effective method (ie, male latex or synthetic condom, diaphragm, or cervical cap) and subject must agree to remain on both methods. Examples of highly effective contraceptives include:

- user-independent methods: 1) implantable progestogen-only hormone contraception associated with inhibition of ovulation; 2) intrauterine device; intrauterine hormone-releasing system; 3) vasectomized partner.
- user-dependent method: progestogen-only hormone contraception associated with inhibition of ovulation (oral or injectable). Estrogen-containing hormonal contraception is contraindicated due to increased risk of thromboembolic events with lenalidomide.

- subjects of childbearing potential must follow the contraception criteria outlined in the global lenalidomide pregnancy prevention program or equivalent local REMS, whichever is more stringent, as applicable in their region.

In addition to the highly effective method of contraception, a man:

- Must always use a condom during any sexual contact with a person of childbearing potential, even if they have undergone a successful vasectomy, from the time of signing the ICF until 1 year after receiving a cilta-cel infusion or for 4 weeks after discontinuing lenalidomide (whichever is later).
- Who is sexually active with a woman who is pregnant must use a condom.
- Should agree to practice contraception according to and for the time frame specified in the global lenalidomide pregnancy prevention program or equivalent local lenalidomide pregnancy prevention program, whichever is more stringent.

Note: Hormonal contraception may be susceptible to interaction with the study treatment, which may reduce the efficacy of the contraceptive method.

9h. Subjects must agree not to donate eggs (ova, oocytes) or sperm, respectively, during the study and for 1 year after receiving a cilta-cel infusion or for 4 weeks after discontinuing lenalidomide (whichever is later).

Informed Consent

10h. Must sign an ICF indicating that the subject understands the purpose of, and procedures required for, the study and is willing to participate in the study. Consent is to be obtained prior to the initiation of any study-related tests or procedures that are not part of standard of care for the subject's disease.

11h. Willing and able to adhere to the prohibitions and restrictions specified in this protocol.

1.13.2. Cohort H Exclusion Criteria

Any potential subject who meets any of the following criteria will be excluded from participating in Cohort H of the study:

Medical Conditions

1h. Active malignancies (ie, progressing or requiring treatment change in the last 24 months) other than the disease being treated under study. The only allowed exceptions are:

a. non-muscle invasive bladder cancer treated within the last 24 months that is considered completely cured.

b. skin cancer (non-melanoma or melanoma) treated within the last 24 months that is considered completely cured.

c. non-invasive cervical cancer treated within the last 24 months that is considered completely cured.

d. localized prostate cancer (N0M0):

- with a Gleason score of ≥6, treated within the last 24 months or untreated and under surveillance,
- with a Gleason score of 3+4 that has been treated more than 6 months prior to full study screening and considered to have a very low risk of recurrence, or
- history of localized prostate cancer and receiving androgen deprivation therapy and considered to have a very low risk of recurrence.

e. breast cancer: adequately treated lobular carcinoma in situ or ductal carcinoma in situ, or history of localized breast cancer and receiving antihormonal agents and considered to have a very low risk of recurrence.

f. malignancy that is considered cured with minimal risk of recurrence.

2h. Frailty index of ≥ 2 according to Myeloma Geriatric Assessment score (Palumbo 2015, Attachment B 3).

3h. The following cardiac conditions:

a. New York Heart Association stage III or IV congestive heart failure (Attachment B 4).

b. Myocardial infarction or coronary artery bypass graft ≤6 months prior to enrollment.

c. History of clinically significant ventricular arrhythmia or unexplained syncope, not believed to be vasovagal in nature or due to dehydration

d. History of severe non-ischemic cardiomyopathy.

e. Impaired cardiac function (left ventricular ejection fraction <45%) as assessed by echocardiogram or multiple-gated acquisition scan (performed ≤8 weeks of enrollment)

f. Screening 12-lead ECG showing a baseline QTcF interval >470 msec, except in subjects with a pacemaker.

4h. Known active, or prior history of central nervous system involvement or exhibits clinical signs of meningeal involvement of multiple myeloma.

5h. Stroke or seizure within 6 months of signing ICF.

6h. Plasma cell leukemia at the time of screening (>2.0 x 10^9/L plasma cells by standard differential), Waldenström's macroglobulinemia, POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, and skin changes), or primary amyloid light-chain amyloidosis.

7h. Seropositive for HIV.

8h. The following pulmonary conditions:

a. Chronic obstructive pulmonary disease with a FEV1 <50% of predicted normal (for subjects ≥65 years old FEV1 <50%)

b. Moderate or severe persistent asthma within the past 2 years, or currently has uncontrolled asthma of any classification. (Note that subjects who currently have controlled intermittent asthma or controlled mild persistent asthma are allowed in the study).

c. Subject requires continuous supplemental oxygen.

9h. Serious underlying medical condition, such as:

a. Evidence of active viral or bacterial infection requiring systemic antimicrobial therapy, or uncontrolled systemic fungal infection.

b. Active autoimmune disease.

c. Overt clinical evidence of dementia or altered mental status.

10h. Contraindications, known life-threatening allergies, hypersensitivity, or intolerance to any of the study treatments or any of their excipients.

11h. Gastrointestinal disease that may significantly alter the absorption of oral drug.

12h. Any history of Parkinson's disease or other neurodegenerative disorder

13h. Peripheral neuropathy or neuropathic pain of ≥Grade 2, as defined by National Cancer Institute (NCI)-Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.

Viral Hepatitis Assessments

14h. Hepatitis B infection as defined according to Attachment 10. In the event the infection status is unclear, quantitative levels are necessary to determine the infection status (Hwang 2015).

15h. Hepatitis C infection defined as (anti-HCV antibody positive or HCV-RNA positive) or known to have a history of hepatitis C. For subjects with known history of HCV infection, confirmation of sustained virologic response is required for study eligibility, defined as ≥24 weeks after completion of antiviral therapy.

Prior/Concomitant Therapy or Clinical Study Experience

16h. Prior therapy for multiple myeloma or smoldering myeloma with the exception of:

a. short course of corticosteroids (not to exceed 40 mg of dexamethasone, or equivalent per day for a maximum of 4 days, total of 160 mg dexamethasone or equivalent), or

b. or 1-2 cycles of D-VRd

17h. Prior treatment with CAR-T therapy directed at any target.

18h. Prior treatment with any therapy that is targeted to BCMA.

19h. Received an investigational intervention (including investigational vaccines) or used an invasive investigational medical device within 15 days before the planned first dose of study intervention or is currently enrolled in an investigational study.

20h. Vaccinated with live, attenuated vaccine within 4 weeks prior to enrollment.

21h. Major surgery within 2 weeks prior to enrollment, or has surgery planned during the study or within 2 weeks after study treatment administration (note: subjects with planned surgical procedures to be conducted under local anesthesia may participate).

22h. Radiation therapy for treatment of plasmacytoma within 14 days of enrollment (palliative radiation for pain control secondary to lytic lesion is allowed within 14 days of enrollment). If the radiation portal covered ≤5% of the bone marrow reserve (see (Section 1.17.2.1.1), the subject is eligible irrespective of the end date of radiation therapy.

Other Exclusions

23h. Any issue that would impair the ability of the subject to receive or tolerate the planned treatment at the investigational site, to understand informed consent or any condition for which, in the opinion of the investigator, participation would not be in the best interest of the subject (eg, compromise the well-being) or that could prevent, limit, or confound the protocol-specified assessments.

24h. Pregnant or breast-feeding, or planning to become pregnant while enrolled in this study or within 4 weeks after the last dose of lenalidomide, 3 months after the last dose of daratumumab or bortezomib, 1 year after receiving the conditioning regimen (cyclophosphamide and fludarabine) or 1 year after receiving cilta-cel infusion (whichever is later).

25h. Plans to impregnate a person via their semen while enrolled in this study or within 4 weeks after the last dose of lenalidomide, 3 months after the last dose of daratumumab or bortezomib, 1 year after receiving the conditioning regimen (cyclophosphamide and fludarabine) or 1 year after receiving cilta-cel infusion (whichever is later).

26h. Unable or unwilling to undergo antithrombotic prophylactic treatment.

NOTE: Investigators must ensure that all study enrollment criteria have been met at screening. If a subject's clinical status changes (including any available laboratory results or receipt of additional medical records) after screening but before the first dose of study treatment is given such that the subject no longer meets all eligibility criteria, then the subject must be excluded from participation in the study. Section 1.15, Screen Failures, describes options for retesting. The required source documentation to support meeting the enrollment criteria are noted in Section 17.5.

1.14. Lifestyle Considerations

Potential subjects must be willing and able to adhere to the following lifestyle restrictions during the study to be eligible for participation:

1. Refer to Section 1.25, Concomitant Therapy for details regarding prohibited and restricted therapy during the study.
2. Agree to follow all requirements that must be met during the study as noted in the Inclusion and Exclusion Criteria.

1.15. Screen Failures

Subject Identification, Enrollment, and Screening Logs

The investigator agrees to complete a subject identification and enrollment log to permit easy identification of each subject during and after the study. This document will be reviewed by the sponsor study site contact for completeness. This study will use IWRS. The investigator will generate screening and enrollment logs directly from IWRS.

The subject identification and enrollment log will be treated as confidential and will be filed by the investigator in the study file. To ensure subject confidentiality, no copy will be made. All reports and communications relating to the study will identify subjects by subject identification and age at initial informed consent. In cases where the subject is not enrolled into the study, the date seen and age at initial informed consent will be used.

Individuals who do not meet the criteria for participation in this study (screen failure) may, at the discretion of the investigator, be rescreened upon medical monitor’s written approval. Subjects who will be rescreened must sign a new ICF and will be assigned a new subject number.

1.16. Criteria for Temporarily Delaying Administration of Study Treatment

Criteria for temporarily delaying cilta-cel infusion are specified in Section 1.17.2.3.1.

1.17. STUDY TREATMENT AND CONCOMITANT THERAPY

1.17.1. Study Treatments Administered

The term "study treatment" throughout the protocol refers to the cyclophosphamide/fludarabine conditioning regimen and cilta-cel for both cohorts, as well as to the DRd regimen in Cohort G and to the D-VRd regimen in Cohort H. Study treatment administration must be captured in the source documents and the eCRF.

Cilta-cel will be manufactured and provided under the responsibility of the sponsor. Refer to the IB for a list of excipients.

1.17.1.1. Induction Regimens

Daratumumab, Lenalidomide, and Dexamethasone – Cohort G

Subjects enrolled in Cohort G will receive 4 cycles of DRd prior to cilta-cel infusion (Table 27). If a subject has already received 1 to 2 cycles of DRd before apheresis they should receive additional cycles for a total of 4 cycles of DRd. Subjects should aim to start induction (or resume induction if 1-2 cycles were already received) within 7 days of apheresis.

Sponsor approval should be obtained for:

- Additional cycles of treatment are needed prior to apheresis.
- Additional cycles of DRd are needed due to an unanticipated delay in cilta-cel manufacturing
- Subjects who prematurely discontinue the DRd induction treatment to be considered for conditioning and cilta-cel administration

After completion of 4 cycles of DRd, all subjects will receive a conditioning regimen of cyclophosphamide and fludarabine, followed by cilta-cel infusion. Thereafter, subjects will be in observation (no treatment) until confirmed PD.

Additional cycles of DRd may be considered based on the subject's clinical status and timing of availability of cilta-cel. This approach may be used in exceptional circumstances and the investigator must contact the sponsor for approval of additional DRd bridging therapy.

Table 27: Description of DRd Induction Regimen for Cohort G

Study Treatment	Dose/Route of Administration	Schedule
Daratumumab	1,800 mg SC	Weekly (Days 1, 8, 15, 22) for Cycles 1 to 2 Every 2 weeks (Days 1 and 15) for Cycles 3 to 4
Lenalidomide (dose and regimen can be adjusted as described in Section 1.22.1.3)	25 mg PO[a]	Days 1 to 21 of each 28-day cycle from Cycles 1 to 4
Dexamethasone (dose and regimen can be adjusted as described in Section 1.22.1.4.)	40 mg PO[b,c]	Days 1, 8, 15, and 22 of each 28-day cycle from Cycles 1 to 4

DRd=daratumumab, lenalidomide, and dexamethasone; PO=oral

a. Lenalidomide should be dosed based on renal function and dose should be re-evaluated (and increased) in case of improved renal function for subsequent cycles.

b. The dexamethasone dose of 40 mg may be split over 2 days (20 mg/day x 2 days), if necessary.

c. For underweight subjects (BMI <18.5 kg/m^2) and subjects ≥75 years of age, dexamethasone may be administered at a dose of 20 mg on Days 1, 8, 15, and 22. Dexamethasone may be split over 2 days: Day 1, 2, 8, 9, 15, 16, 22 and 23, as clinically indicated.

Daratumumab, Bortezomib, Lenalidomide, Dexamethasone – Cohort H

Subjects enrolled in Cohort H will receive 4 cycles of D-VRd prior to cilta-cel infusion (Table 28). If a subject has already received 1 to 2 cycles of D-VRd before apheresis they should receive additional cycles for a total of 4 cycles of D-VRd. Subjects should aim to start induction (or resume induction if 1-2 cycles were already received) within 7 days of apheresis.

Sponsor approval should be obtained for:

- Additional cycles of treatment are needed prior to apheresis.
- Additional cycles of D-VRd are needed due to an unanticipated delay in cilta-cel manufacturing
- Subjects who prematurely discontinue the D-VRd induction treatment to be considered for conditioning and cilta-cel administration

After completion of 4 cycles of D-VRd, all subjects will receive a conditioning regimen of cyclophosphamide and fludarabine, followed by cilta-cel infusion. Thereafter, subjects will be in observation (no treatment) until confirmed PD.

Table 28: Description of D-VRd Induction Regimen for Cohort H

Study Treatment	Dose/Route of Administration	Dosing Regimen
Daratumumab	1,800 mg SC	Weekly (Days 1, 8, 15, 22) for Cycles 1 to 2 Every 2 weeks (Days 1 and 15) for Cycles 3 to 4
Bortezomib (dose and regimen can be adjusted as described in Section 1.22.1.2.)	1.3 mg/m^2 SC	Days 1, 8 and 15 of each 28-day cycle from Cycles 1 to 4
Lenalidomide **(**dose and regimen can be adjusted as described in Section 1.22.1.3)	25 mg PO[a]	Days 1 to 21 of each 28-day cycle from Cycles 1 to 4
Dexamethasone **(**dose and regimen can be adjusted as described in Section 1.22.1.4.)	40 mg PO [b,c]	Days 1, 8, 15, and 22 of each 28-day cycle from Cycles 1 to 4

D-VRd=daratumumab, bortezomib, lenalidomide, and dexamethasone; PO=oral.

a. Lenalidomide should be dosed based on renal function and dose should be re-evaluated (and increased) in case of improved renal function for subsequent cycles.
b. The dexamethasone dose of 40 mg may be split over 2 days (20 mg/day x 2 days), if necessary.
c. For underweight subjects (BMI <18.5 kg/m^2) and subjects ≥75 years of age, dexamethasone may be administered at a dose of 20 mg on Days 1, 8, 15, and 22. Subjects receiving 20 mg weekly dexamethasone, should receive the entire weekly dose (20 mg) of dexamethasone on Days 1, 8, 15, and 22. Dexamethasone may be split over 2 days: Day 1, 2, 8, 9, 15, 16, 22 and 23, as clinically indicated.

NOTE APPLICABLE TO BOTH COHORTS

Stem cell harvest for ASCT can be performed in subjects who may need ASCT at a later time, following mobilization with G-CSF or plerixafor or cyclophosphamide or as per the institutional standard. Collection and storage of stem cells will be considered as an off-protocol procedure.

In both cohorts, subjects for whom apheresis or cilta-cel manufacturing fails, may be allowed additional attempts at apheresis or cilta-cel manufacturing, after approval from the medical monitor. The investigator must contact the medical monitor to discuss the timing of such repeat apheresis prior to or during D-VRd/DRd therapy.

Subjects in both treatment arms who discontinue any component of D-VRd/DRd treatment (daratumumab, bortezomib, lenalidomide, or dexamethasone) should continue to receive treatment with the other components of D-VRd/DRd treatment. The reason for discontinuing any individual component should be in line with the product's USPI.

1.17.1.2. Daratumumab

Subcutaneous daratumumab will be provided as a fixed-dosed (1,800 mg) combination drug product containing rHuPH20 drug substance (2,000 U/mL) and daratumumab drug substance (120 mg/mL) in a single vial, per the schedule in Table 28.

Daratumumab (1,800 mg) will be administered to subjects enrolled in Cohort G and H by manual injection over approximately 3 to 5 minutes in the abdominal SC tissue. The volume of the SC solution for injection will be 15 mL for the 1800 mg dose. Refer to the investigational product preparation instructions (IPPI) for additional guidance on SC administration of daratumumab. It is advised to monitor all subjects for sARRs, especially following the first and second

administrations. Reasons for continued observation after subsequent daratumumab administration may include, but are not limited to:

- subjects with a higher risk of respiratory complications (eg, subjects with mild asthma or subjects with COPD who have an FEV1 <80% at screening or developed FEV1 <80% during the study without any medical history),
- subjects with sARRs at first daratumumab administration, and
- subjects with a decreased general condition on the day of dosing compared to the day before dosing.

The dose of daratumumab will remain constant throughout the study. All daratumumab administrations are intended to happen in an outpatient setting. Subjects will receive pre- and post-administration medications as outlined in Section 1.17.1.2.1 and Section 1.17.1.2.2, respectively.

Vital signs should be monitored extensively on Cycle 1 Day 1 before and after the first administration of daratumumab. For all other administrations, vital signs should be measured before the start of injection and at the end of the injection. If the subject experiences any significant medical event, the investigator should assess whether the subject should stay overnight for observation. If the subject has not experienced a significant medical event but is hospitalized overnight only for observation, then the hospitalization should not be reported as an SAE.

1.17.1.2.1. Pre-administration Medication

To decrease the risk of sARRs, all subjects will receive the following medications 1 to 3 hours before each daratumumab administration:

- an antipyretic: paracetamol (acetaminophen) 650 to 1,000 mg intravenously or orally.
- an antihistamine: diphenhydramine 25 to 50 mg intravenously or orally, or equivalent. Avoid intravenous promethazine (see Section 1.25.2 for a list of antihistamines that may be used).
- dexamethasone intravenously or orally. Backbone therapy (given as part of DRd or DVRd) substitutes for the preadministration dexamethasone. Accordingly, 40 mg or 20 mg dexamethasone will be administered intravenously or orally prior to daratumumab in Cycles 1 to 4). Please see Tables 9 and 10 for dexamethasone dosing schedules.

In addition, a leukotriene inhibitor (montelukast 10 mg orally) is recommended on Cycle 1 Day 1, up to 24 hours before daratumumab administration. Use before other daratumumab administrations is optional.

If necessary, due to timing constraints, all oral pre-administration medications may be taken outside of the clinic on the day of daratumumab administration, provided they are taken within 3 hours before the administration.

1.17.1.2.2. Post-administration Medication

Post-administration medication should be used to reduce the risk of delayed sARRs. For subjects with a higher risk of respiratory complications (eg, subjects with mild asthma or subjects with COPD who have an FEV1 <80% at screening or developed FEV1 <80% during the study without any medical history), the following post-administration medications should be considered:

- an antihistamine (diphenhydramine or equivalent)
- a leukotriene inhibitor (montelukast)
- a short-acting β2 adrenergic receptor agonist, eg, salbutamol (albuterol)
- control medications for lung disease (eg, inhaled corticosteroids ±long-acting β2 adrenergic receptor agonists for subjects with asthma; long-acting bronchodilators, eg, tiotropium or salmeterol ±inhaled corticosteroids for subjects with COPD)

In addition, subjects at risk for respiratory complications may be hospitalized for monitoring for up to 2 nights after daratumumab administration. If subjects are hospitalized, an improvement in FEV1 should be performed and documented prior to discharge. If subjects are not hospitalized, a follow-up telephone call should be made to monitor their condition within 48 hours after the first 4 daratumumab administrations or longer if clinically indicated. If the subject has not experienced a significant medical event, but is hospitalized overnight for observation only, then the hospitalization should not be reported as an SAE. Investigators may prescribe bronchodilators, antihistamines, and corticosteroids if deemed necessary to provide adequate supportive care in the event bronchospasm occurs after a subject is released from the hospital/clinic.

1.17.1.2.3. Management Guidelines for Daratumumab

1.17.1.2.3.1. Systemic Administration-related Reactions

Subjects should be observed carefully during daratumumab SC administrations. Trained study staff at the clinic should be prepared to intervene in case of any sARRs, and resources necessary for resuscitation (eg, agents such as epinephrine and aerosolized bronchodilator, also medical equipment eg, oxygen tanks, tracheostomy equipment, and a defibrillator) must be available at the bedside. Attention to staffing should be considered when multiple subjects will be dosed at the same time. See Section 1.17.1.2.1 and Section 1.17.1.2.2 for pre- and post-administration medications for subjects receiving daratumumab.

If an sARR develops during daratumumab SC administration, the administration should be temporarily interrupted or slowed down. Subjects who experience AEs during daratumumab administration must be treated for their symptoms. Subjects should be treated with paracetamol (acetaminophen), antihistamine, or corticosteroids, as needed. Intravenous saline may be indicated. For bronchospasm, urticaria, or dyspnea, subjects may require antihistamines, oxygen, corticosteroids, or bronchodilators. For hypotension, subjects may require vasopressors. In the event of a life-threatening sARR (which may include pulmonary or cardiac events) or an anaphylactic reaction, daratumumab should be permanently discontinued.

Systemic Administration-related Reactions of Grade 1 or Grade 2 for Daratumumab SC

If the investigator assesses a Grade 1 or 2 sARR to be related to administration of study treatment, daratumumab administration should be interrupted. When the subject's condition is stable, daratumumab administration may be restarted at the investigator's discretion. Refer to the study site investigational product and procedures manual for further details regarding continuation of daratumumab administration.

If the subject experiences a ≥Grade 2 event of laryngeal edema, or a ≥Grade 2 event of bronchospasm that does not respond to systemic therapy and does not resolve within 6 hours from onset, the subject must be permanently discontinued from daratumumab treatment.

Systemic Administration-related Reactions of Grade 3 or Higher for Daratumumab SC

For Grade 3 sARR AEs (other than laryngeal edema or bronchospasm), the daratumumab administration must be stopped and the subject must be observed carefully until resolution of the AE or until the intensity of the event decreases to Grade 1, at which point the daratumumab SC administration may be restarted at the investigator's discretion. Refer to the SIPPM for further details regarding continuation of daratumumab administration.

If the intensity of the AE returns to Grade 3 after restart of the daratumumab administration, the subject must be permanently discontinued from daratumumab treatment.

For Grade 4 sARR AEs, the daratumumab administration must be stopped and the subject permanently discontinued from daratumumab treatment.

Recurrent Systemic Administration-related Reactions for Daratumumab SC

If a Grade 3 sARR (or a ≥Grade 2 event of laryngeal edema or bronchospasm) recurs during or within 24 hours after a subsequent daratumumab administration, the subject must be permanently discontinued from daratumumab treatment.

Injection-site Reactions for Daratumumab SC

Skin reactions at or near the injection site (local), including injection-site reactions, can happen with daratumumab. Symptoms at the site of injection may include itching, swelling, bruising, pain, rash, bleeding, or redness of the skin. These reactions sometimes happen more than 24 hours after an injection of daratumumab. Monitor for local reactions and consider symptomatic management.

1.17.1.2.3.2. Infections

Administration of daratumumab may increase the risk of infection. Subjects should be monitored frequently for infection and should have blood cultures obtained and empiric antibiotics administered per institutional standards. For subjects with evidence of positive HBV serology, monitor for clinical and laboratory signs of HBV reactivation during and for at least 6 months following the end of study treatment. Manage subjects according to current clinical guidelines. Consider consulting a hepatitis disease expert as clinically indicated.

In subjects who develop reactivation of HBV while on study treatment, suspend study treatment and any concomitant steroids, chemotherapy, and institute appropriate treatment. Resumption of study treatment in subjects whose HBV reactivation is adequately controlled should be discussed with physicians with expertise in managing HBV.

1.17.1.3. Bortezomib (Cohort H only)

The amount (in mg) of bortezomib to be administered will be determined by body surface area, calculated per a standard nomogram (see Attachment B 5). There is no maximum dose. The calculated dose of bortezomib may be rounded to the nearest tenth of a mg (or per institutional practice).

Subjects in Cohort H will receive 1.3 mg/m^2 bortezomib as an SC injection, per the schedule in Table 28. On treatment days when both bortezomib and daratumumab are administered, bortezomib must be administered after the daratumumab administration.

If a subject's weight changes by more than 10% from baseline, the bortezomib dose will be recalculated. Bortezomib administration may be delayed up to 48 hours. In case of a delay, the timing of subsequent doses must be adjusted to account for the delay. Note that there must be at least 72 hours between doses of bortezomib. Skipped doses of bortezomib will not be made up later in a cycle.

For subjects with unacceptable toxicity at the local injection site despite dose modifications or change in injection concentration, bortezomib can be administered intravenously as a 3- to 5-seconds intravenous bolus injection. Refer to local prescribing information for further details on either SC or intravenous bortezomib administration.

For subjects with renal impairment requiring dialysis, bortezomib should be administered after the dialysis procedure.

1.17.1.4. Lenalidomide

For subjects in both Cohort G and Cohort H, lenalidomide will be self-administered at a dose of 25 mg orally each day on Days 1 through 21 of each 28-day cycle (Cycles 1 to 4). For subjects with a CrCl <60 mL/min, dose adjustments should be performed based on local product prescribing information and in alignment with the guidance provided in Table 37. For subjects in both Cohort G and Cohort H, on daratumumab administration days, it is recommended that lenalidomide should be administered either prior to or at the same time (preferred) as the pre-administration medication.

Lenalidomide should be available to subjects to start simultaneously with other study treatment medications on Day 1 of each cycle.

Lenalidomide should be taken as a single dose at the same time daily, either with or without food. Lenalidomide capsules should be swallowed whole with water. Breaking or dividing the lenalidomide capsule is strongly discouraged.

1.17.1.5. Dexamethasone

For subjects in both Cohort G and Cohort H, dexamethasone will be self-administered at a dose of 40 mg orally weekly (Days 1, 8, 15, and 22). The dexamethasone dose of 40 mg may be split over 2 days (20 mg/day x 2 days), if necessary. For underweight subjects (BMI <18.5 kg/m2) and subjects ≥75 years of age, dexamethasone may be administered at a dose of 20 mg on Days 1, 8, 15, and 22 of each cycle. Subjects receiving 20 mg weekly dexamethasone, should receive the entire weekly dose (20 mg) of dexamethasone on Days 1, 8, 15, and 22. Dexamethasone may be split over 2 days: Day 1, 2, 8, 9, 15, 16, 22 and 23, as clinically indicated.

Dexamethasone should be available to subjects to start simultaneously with other study treatment medications on Day 1 of Cycles 1 to 4. On daratumumab administration days, dexamethasone backbone therapy substitutes for the pre-administration dexamethasone (see Section 1.17.1.2.1). Accordingly, 40 mg dexamethasone will be administered intravenously or orally 1 to 3 hours before the daratumumab administration (or 20 mg before daratumumab administration and 20 mg on the day after). On days when daratumumab is not administered, dexamethasone will be administered orally.

If a weekly dexamethasone dose is missed, it may be taken if <4 days have elapsed since the time that it should have been taken. If the next dose is scheduled to be taken within 3 days, the missed dexamethasone dose should be skipped.

Dexamethasone tablets are to be taken with or immediately after a meal or snack, preferably in the morning.

1.17.2. Cilta-cel

1.17.2.1. Apheresis

All enrolled subjects will undergo apheresis before start of DRd (Cohort G) or D-VRd induction therapy (Cohort H).

Apheresis should be performed according to institutional standards, with the collection target and instructions for processing and shipping apheresis product provided in the cell therapy product procedures manual.

1.17.2.1.1. Criteria for Apheresis

The investigator should contact the medical monitor if evidence of rapid PD or suspected CNS involvement is observed between screening and apheresis.

Subjects must meet the following criteria to proceed with apheresis:

- Subjects may not have received the following antitumor therapy prior to apheresis
  - Daratumumab within 21 days
  - Bortezomib within 14 days

  - Lenalidomide within 7 days
  - A cumulative dose of corticosteroids equivalent to ≥70 mg of prednisone within the 7 days prior to apheresis

- Subjects may not have received investigational agents or antimyeloma therapy within the timeframe as detailed in the exclusion criteria (Section 1.12.2 and Section 1.13.2)
- Subjects may not have received radiation therapy as specified in the exclusion criteria (Section 1.12.2 and Section 1.13.2), except palliative radiation for pain control secondary to lytic lesion. If the radiation portal covered ≤5% of the bone marrow reserve, the subject can proceed
- Hemoglobin ≥8 g/dL (packed red blood cell transfusion is permitted)
- Platelet count ≥50 × 10^9/L (platelet transfusion is permitted)
- Negative pregnancy test for subjects of childbearing potential up to 72 hours prior to apheresis
- Subject must not require continuous supplemental oxygen
- Eastern Cooperative Oncology Group performance status grade of 0 or 1
- No evidence of serious active viral, bacterial, or uncontrolled systemic fungal infection. Subjects on anti-infective agents within 7 days prior to apheresis must receive approval to proceed from sponsor
- No major surgery as specified in the exclusion criteria (Section 1.12.2 and Section 1.13.2)
- No new arrhythmia or other cardiac AEs unless controlled with medical management and approved by the medical monitor

For subjects who require a repeat apheresis, the following assessments should be performed before the repeat apheresis: weight, laboratory assessments (hematology and chemistry), echocardiogram or MUGA scan (if clinically indicated), and biomarker assessments. The investigator must contact the medical monitor to discuss the timing of such repeat apheresis. A third apheresis attempt may be permitted if an immediately rectifiable cause is identified (eg, product shipped improperly) and with approval from the medical monitor.

1.17.2.2. Conditioning Regimen (Cyclophosphamide and Fludarabine)

The study site will be notified in writing by the sponsor that manufacture of cilta-cel has been completed. It is recommended that the site does not initiate conditioning until the cilta-cel is received. Thereafter, each subject will receive a conditioning regimen of intravenous cyclophosphamide 300 mg/m^2 and fludarabine 30 mg/m^2 daily for 3 days. Approval from the medical monitor must be obtained to modify the conditioning regimen schedule or dose. For subjects with severe renal impairment, signs and symptoms of cyclophosphamide toxicity, including hemorrhagic cystitis, pyelitis, urethritis, and hematuria, should be monitored closely.

The dose of fludarabine should be reduced to 24 mg/m^2 for subjects with an eGFR of 30 to 70 mL/min/1.73 m^2.

Cyclophosphamide and fludarabine should be administered using procedures and supportive care according to the study site's standard of care. Cilta-cel should be administered as described in the CTPPM and IPPI.

Cilta-cel will be administered as a single infusion 5 to 7 days after the start of the conditioning regimen (the first day of conditioning is Day -7 to Day -5, the day of cilta-cel infusion is Day 1).

1.17.2.2.1. Criteria for Conditioning Regimen

The investigator should contact the medical monitor if evidence of rapid PD or a significant change in the subject's clinical status is observed before the start of the conditioning regimen.

Subjects must meet below criteria to proceed with cyclophosphamide and fludarabine dosing. If one of these criteria is not met, the investigator must contact the medical monitor to discuss whether a subject can proceed with conditioning.

1. Subjects may not have received the following prior to the start of the conditioning regimen:
   a. Daratumumab within 21 days
   b. Bortezomib within 14 days
   c. Lenalidomide within 7 days
   d. Dexamethasone within 7 days
2. Transfusion support is permitted to maintain a hemoglobin of ≥8.0 g/dL as needed and platelets of $\geq 50 \times 10^9$/L until 3 days before the hematology laboratory test, preceding the start of the conditioning regimen.
3. Myeloid growth factors are permitted at the investigator's discretion up to 1 day prior to the start of the conditioning regimen. Pegylated myeloid growth factors (ie, pegfilgrastim) are prohibited.
4. eGFR ≥30 mL/min/1.73 m^2. The dose of fludarabine should be reduced according to the guidance in Section 1.17.2.2.
5. The investigator must contact the medical monitor if the subject has any sign of a reduction in kidney function, which may be manifested by a clinically significant increase in serum creatinine, clinically significant decrease in eGFR, and/or a clinically significant decrease in urine output compared to baseline.
6. ECOG performance status of grade 0 or 1.
7. AST ≤3x ULN.
8. ALT ≤3x ULN.
9. Total bilirubin ≤2x ULN, except in subjects with congenital nonhemolytic hyperbilirubinemia, such as Gilbert syndrome (in which case direct bilirubin ≤2x ULN is required).
10. Negative pregnancy test for subjects of childbearing potential up to 72 hours prior to the first dose of the conditioning regimen.

11. No signs of active infection. For subjects requiring systemic antimicrobial treatment or with temperature >38.0°C/100.4°F within 7 days prior to the first dose of the conditioning regimen, the investigator must receive approval from the medical monitor.
12. No investigational or live, attenuated vaccines within 6 weeks prior to the first dose of the conditioning regimen.
13. No use of supplemental oxygen to maintain adequate oxygen saturation.
14. No new arrhythmia or other cardiac AEs unless controlled with medical management and approved by the medical monitor.

1.17.2.3. Cilta-cel Administration

1.17.2.3.1. Criteria for Administration of Cilta-cel and its Temporary Delay

Subjects will be evaluated for safety on the day of cilta-cel infusion. If a significant health status change (eg, clinical deterioration, rapidly progressing disease) occurs following the start of the conditioning regimen (see Section 1.17.2.2), the investigator must contact the medical monitor prior to cilta-cel infusion.

Cilta-cel infusion must be delayed if any of the following events occur:

- Signs of active infection: cilta-cel should not be administered to subjects with active infection. For subjects requiring systemic antimicrobial treatment, or with temperature ≥38.0°C/100.4°F within 48 hours before cilta-cel infusion, the investigator must consult with the medical monitor prior to cilta-cel infusion.
- ≥Grade 3 nonhematologic toxicities of cyclophosphamide and fludarabine conditioning (except for Grade 3 nausea, vomiting, diarrhea, or constipation). Investigator must consult with the medical monitor prior to cilta-cel infusion.

If resolution of these events to ≤Grade 1 takes more than 14 days, the conditioning regimen should be readministered (cyclophosphamide 300 mg/m^2 and fludarabine 30 mg/m^2 daily for 3 days) after a minimum of 21 days following the first dose of the first conditioning regimen.

Subjects from both cohorts who have confirmed PD after induction therapy will be permitted to be infused with cilta-cel if requested by the investigator and discussed with the medical monitor. The investigator will discuss with the subject the potential risks and benefits of receiving the product and treatment alternatives. If the subject wishes to proceed with cilta-cel infusion and the investigator determines this is appropriate, the subject may receive cilta-cel. If investigator deems it appropriate, subjects may receive subsequent (salvage) therapy, prior to receiving conditioning and cilta-cel. Once these subjects have received cilta-cel, they will undergo continuous safety assessments, efficacy assessments (locally, per institutional standards), and all other assessments according to the Time and Event Schedules (Section 1.2).

1.17.2.3.2. Pre-cilta-cel Infusion Supportive Therapy

Prior to cilta-cel infusion, subjects should receive pre-infusion medication as outlined in Table 29. Corticosteroids should not be used as pre-infusion medication.

Table 29: Pre-infusion Medications

Medication	Dose	Administration
Antihistimatine	diphenhydramine (25-50 mg PO or IV) or equivalent	PO: administer 1 hour (±15 minutes) prior to cilta-cel infusion OR IV: start infusion 30 minutes (±15 minutes) prior to cilta-cel infusion
Antipyretic	acetaminophen (650-1,000 mg PO or IV) or equivalent	PO or IV: administer 30 minutes (±15 minutes) prior to cilta-cel infusion

IV=intravenously; PO=orally.

1.17.2.3.3. Cilta-cel Administration

Please refer to Section 6.1.3, Table 11.

1.17.2.3.4. Exceptional Release Criteria

Please refer to Section 6.1.3.1.

1.17.2.4. Management Guidelines for Potential Risks of Cilta-cel

1.17.2.4.1. Cytokine Release Syndrome

As of January 2022, CRS TEAEs were reported for 92 of 97 subjects (94.8%) in Study 68284528MMY2001. CRS TEAEs with a maximum severity of Grade 3 were reported for 3 subjects (3.1%), Grade 4 for 1 subject (1.0%), and 1 subject (1.0%) experienced a Grade 5 TEAE. The remaining 87 subjects (89.7%) experienced CRS TEAEs with a maximum severity of Grade 1 or 2. As of November 2022, 134 of the 176 subjects (76.1%) who received cilta-cel as study treatment in Study 68284528MMY3002 experienced CRS TEAEs, generally of Grade 1 (93 subjects [52.8%]) or Grade 2 (39 subjects [22.2%]) severity. Two subjects (1.1%) had Grade 3 CRS. No subjects experienced Grade 4 or 5 CRS TEAEs (refer to the IB for cilta-cel).

Clinical symptoms indicative of CRS may include, but are not limited to, fever (with or without rigors), arthralgia, nausea, vomiting, tachycardia, hypotension, headache, confusion, tremor, delirium, dyspnea, pulmonary edema, and capillary leak (Lee 2019). Potentially life-threatening complications of CRS may include cardiac dysfunction, adult respiratory distress syndrome, neurologic toxicity, renal failure, hepatic failure, and disseminated intravascular coagulation.

Laboratory testing to monitor for disseminated intravascular coagulation, a manifestation of CRS, should be performed in addition to daily monitoring of chemistry and hematology assessments (including ferritin and C-reactive protein) when fever or other signs of potential CRS are present. In addition, pulmonary, renal and hepatic function will be monitored closely (Table 30).

Rarely, severe CRS can evolve into a presentation consistent with HLH/MAS that may require additional therapy. In these cases, laboratory testing may reveal high serum levels of ferritin, LDH, triglycerides, soluble CD25 (also known as soluble IL-2 receptor alpha), and cytokines (eg, IFNγ and IL-6), and low serum levels of fibrinogen (Neelapu 2018). Severe thrombocytopenia, low fibrinogen, and often DIC may be features of HLH, all of which combined may increase the risk of severe bleeding in these subjects. If HLH is suspected, anticoagulation should be avoided or

modified based on institutional guidelines depending on platelet count and renal function. Subjects with HLH should have their platelet count and coagulation parameters very closely monitored and maximal support should be provided to avoid major bleeding complications. For example, consider platelet transfusion if platelets are less than 50×10^9/L. Under these circumstances, investigators should consider treating the subject in the ICU, so that maximal monitoring and support can be carried out during this period. ASTCT has published recommendations for treatment of HLH following CAR-T which may be referenced for further patient management recommendations (Heins 2023). The new ASTCT guidance recommends early treatment with anakinra in conjunction with corticosteroids for mild to moderate manifestations, Jakafi (ruxolitinib) for moderate to severe and low-dose etoposide or emapalumab for severe and life-threatening cases of HLH.

Trained clinical personnel should be prepared to intervene in the event of CRS. Resources necessary for resuscitation (ie, agents such as epinephrine and aerosolized bronchodilator, medical equipment such as oxygen, tracheostomy equipment, and a defibrillator) should be readily available. Tocilizumab must be available on site prior to cilta-cel infusion. Vital signs and laboratory parameters must be monitored at regular intervals until normal. Additional specimens for PK and pharmacodynamic testing should be collected according to the Time and Events Schedules (Section 1.2).

Infection and CRS may have a similar presentation. Therefore, investigators are strongly encouraged to evaluate for an infection at the first signs or symptoms of CRS. Blood cultures and imaging should be obtained: the clinical signs and symptoms should determine which tests are appropriate.

Recommendations for the clinical management of CRS are provided in Table 30. At the first sign of CRS (such as fever), subjects should be immediately hospitalized for evaluation. The use of myeloid growth factors, particularly G-CSF, should be avoided during CRS. Tocilizumab intervention may be considered with presenting symptom of fever per investigator discretion when other sources of fever have been eliminated and early tocilizumab should be considered in subjects at high risk of severe CRS (including high baseline tumor burden, early fever onset, or persistent fever after 24 hours of symptomatic treatment). Other cytokine-targeting therapies (eg, IL-1, TNFα) may be used based on institutional practice, especially for cases of CRS which do not respond to tocilizumab and corticosteroids. Therapy directed at reduction or elimination of CAR-T cells, including chemotherapy, may be considered in consultation with the medical monitor for subjects who develop high-grade CRS with laboratory findings overlapping with HLH/MAS (including hyperferritinemia) that remains severe or life-threatening following prior therapies, including tocilizumab and corticosteroids.

Cytokine release syndrome will be captured as an AE of special interest (see Attachment B 6).

Table 30: Cytokine Release Syndrome Grading and Management Guidelines

CRS Grade[a]	Tocilizumab[b]	Corticosteroids[f]
Grade 1 Temperature ≥38°C[c]	Tocilizumab 8 mg/kg i.v. over 1 hour (not to exceed 800 mg) may be considered	NA
Grade 2 Symptoms require and respond to moderate intervention. Temperature ≥38°C[c] with: Hypotension not requiring vasopressors, and/or, Hypoxia requiring oxygen via canula[e] or blow-by,	Administer tocilizumab 8 mg/kg i.v. over 1 hour (not to exceed 800 mg). Repeat tocilizumab every 8 hours as needed if not responsive to i.v. fluids up to 1 liter or increasing supplemental oxygen.	Consider methylprednisolone 1 mg/kg i.v. twice daily or equivalent dexamethasone (eg, 10 mg i.v. every 6 hours).
	If no improvement within 24 hours or rapid progression, repeat tocilizumab and escalate dose and frequency of dexamethasone (20 mg i.v. every 6 to 12 hours). After 2 doses of tocilizumab, consider alternative anticytokine agents.[d] Do not exceed 3 doses of tocilizumab in 24 hours, or 4 doses in total.	
Grade 3 Symptoms require and respond to aggressive intervention. Temperature ≥38°C[c] with: Hypotension requiring 1 vasopressor with or without vasopressin, and/or, Hypoxia requiring oxygen via high-flow nasal canula[e], facemask, nonrebreather mask, or Venturi mask	Per Grade 2	Administer methylprednisolone 1 mg/kg i.v. twice daily or equivalent dexamethasone (eg, 10 mg i.v. every 6 hours).
	If no improvement within 24 hours or rapid progression, repeat tocilizumab and escalate dose and frequency of dexamethasone (20 mg i.v. every 6 to 12 hours). If no improvement within 24 hours or continued rapid progression, switch to methylprednisolone 2 mg/kg i.v. every 12 hours. After 2 doses of tocilizumab, consider alternative anticytokine agents.[d] Do not exceed 3 doses of tocilizumab in 24 hours, or 4 doses in total.	
Grade 4 Life-threatening symptoms. Requirements for ventilator support, CVVHD. Temperature ≥38°C[c] with: Hypotension requiring multiple vasopressors (excluding vasopressin), and/or, Hypoxia requiring positive pressure (eg, CPAP, BiPAP, intubation, and mechanical ventilation)	Per Grade 2	Administer dexamethasone 20 mg i.v. every 6 hours.
	After 2 doses of tocilizumab, consider alternative anticytokine agents.[d] Do not exceed 3 doses of tocilizumab in 24 hours, or 4 doses in total. If no improvement within 24 hours, consider methylprednisolone (1-2 g i.v., repeat every 24 hours if needed; taper as clinically indicated) or other immunosuppressants (eg, other anti-T-cell therapies).	

ASTCT=American Society for Transplantation and Cellular Therapy; BiPAP=bilevel positive airway pressure; CPAP=continuous positive airway pressure; CVVHD=continuous veno-venous hemodialysis; i.v.=intravenous(ly); NA=not applicable.

a. Based on ASTCT consensus grading (Lee 2019). Even though organ toxicity is not part of CRS grading per ASTCT, if the subject is experiencing concurrent organ toxicity while having CRS, please continue to treat CRS according to the toxicity management table and consider other differential causes for the organ toxicity (and treat any underlying cause accordingly).

b. Refer to tocilizumab prescribing information for details.

c. Attributed to CRS. Fever may not always be present concurrently with hypotension or hypoxia, as it may be masked by interventions such as antipyretics or anticytokine therapy (eg, tocilizumab or steroids). Absence of fever does not impact CRS management decision. In this case, CRS management is driven by hypotension and/or hypoxia and by the more severe symptom not attributable to any other cause.

d. Monoclonal antibodies targeting cytokines may be considered based on institutional practice for unresponsive CRS.

e. Low-flow nasal cannula is ≤6 L/min; high-flow nasal cannula is >6 L/min.

f. Continue corticosteroids use until the event is ≤Grade 1; taper steroids if total corticosteroid exposure is greater than 3 days.

Supportive care for CRS (including but not limited to, antipyretic agents, intravenous fluid support, vasopressors, supplemental oxygen) should be administered according to the clinical manifestations of the subject's illness. Similarly, ancillary testing, eg, B-type natriuretic peptide assessment, echocardiograms, arterial blood gas, assessments of coagulation laboratory tests, and liver and renal function should be performed if clinically indicated.

1.17.2.4.2. Neurologic Toxicities

Based on the specific mode of action of cilta-cel, severe or serious neurologic toxicities, including CAR-T cell neurotoxicity, ie, ICANS and other neurotoxicities, may occur (Section 1.17.2.4.2.1 and Section 1.17.2.4.2.2). Subjects should be monitored for neurotoxicity until end of study.

All neurologic AEs, including CAR-T cell neurotoxicity (eg, ICANS), will be captured as AESIs (see Section 12.3.3).

1.17.2.4.2.1. Immune Effector Cell-associated Neurotoxicity Syndrome

Subjects should have the ICE assessment tool (see Section 1.31.8) performed within 24 hours prior to cilta-cel infusion and daily after the first symptoms of neurotoxicity are suspected and until resolution. Consider performing the ICE Tool more frequently until neurotoxicity symptoms resolve. Consider performing neuroimaging (eg, MRI) at screening and/or neurology consultation if pre-existing disease is suspected (see Section 1.31.8).

Subjects should be monitored for neurologic toxicities, including but not limited to, headache, convulsions, speech disorders, visual disorders, disturbances in consciousness, confusion, disorientation, and coordination and balance disorders, or mental status changes. If these or other neurologic toxicities are observed, regardless of causality, the medical monitor must be consulted. Hospitalization is required for Grade 2, 3, or 4 CAR-T cell neurotoxicity (eg, ICANS) temporarily associated with CRS.

At the first sign of neurotoxicity, neurology consultation and evaluation should be considered. Rule out alternative etiologies including infectious etiologies (eg, viral origin such as HHV-6, HHV-7) if clinically indicated. For signs of seizures or raised ICP/cerebral edema, transfer the subject to the intensive care unit and treat according to institutional guidelines or practices.

General management for ICANS is summarized in Table 31. Guidelines for the management of raised ICP/cerebral edema are summarized in Table 32.

If concurrent CRS is suspected during the neurologic toxicity event, administer:

- Corticosteroids according to the more aggressive intervention based on the CRS and neurologic toxicity grades in Table 30 and Table 31
- Tocilizumab according to CRS Grade in Table 30
- Antiseizure medication according to neurologic toxicity in Table 31

Table 31: Guidelines for the Management of Immune Effector Cell-associated Neurotoxicity Syndrome

ICANS Grade[a]	Corticosteroids
Grade 1 ICE score 7-9[b] or depressed level of consciousness: awakens spontaneously.	Consider dexamethasonec 10 mg i.v. every 6 to 12 hours for 2 to 3 days Consider nonsedating, antiseizure medicines (eg, levetiracetam) for seizure prophylaxis.
Grade 2 ICE score-3-6[b] or depressed level of consciousness: awakens to voice	Administer dexamethasone[c] 10 mg i.v. every 6 hours for 2 to 3 days, or longer for persistent symptoms. Consider steroid taper if total corticosteroid exposure is greater than 3 days. Consider nonsedating, antiseizure medicines (eg, levetiracetam) for seizure prophylaxis.
Grade 3 ICE score-0-2[b] (If ICE score is 0, but subject is arousable (eg, awake with global aphasia) and able to perform assessment) or depressed level of consciousness: awakens only to tactile stimulus, or seizures, either: a) any clinical seizure, focal or generalized, that resolves rapidly, or b) nonconvulsive seizures on EEG that resolve with intervention, or raised ICP: focal/local edema on neuroimaging.[d]	Administer dexamethasone[c] 10 mg to 20 mg i.v. every 6 hours. If no improvement after 48 hours or worsening of neurologic toxicity, escalate dexamethasone[c] dose to at least 20 mg i.v. every 6 hours; taper within 7 days, or escalate to high-dose methylprednisolone (1g/day, repeat every 24 hours if needed; taper as clinically indicated). Consider nonsedating, antiseizure medicines (eg, levetiracetam) for seizure prophylaxis.
Grade 4 ICE score-0[b] (subject is unarousable and unable to perform ICE assessment), or depressed level of consciousness, either: i. subject is unarousable or requires vigorous or repetitive tactile stimuli to arouse, or i. stupor or coma, or seizures, either: i. life-threatening prolonged seizure (>5 min), or v. repetitive clinical or electrical seizures without return to baseline in between, or motor findings[e]: v. deep focal motor weakness such as hemiparesis or paraparesis, or raised ICP/cerebral edema, with signs/symptoms such as: i. diffuse cerebral edema on neuroimaging, or i. decerebrate or decorticate posturing, or i. cranial nerve VI palsy, or x. papilledema, or x. Cushing's triad.	Administer dexamethasone[c] 10 mg to 20 mg i.v. every 6 hours. If no improvement after 24 hours or worsening of neurologic toxicity, escalate to high-dose methylprednisolone (1-2 g/day, repeated every 24 hours if needed; taper as clinically indicated). Consider nonsedating, antiseizure medicines (eg, levetiracetam) for seizure prophylaxis. If raised ICP/cerebral edema is suspected, consider hyperventilation and hyperosmolar therapy. Give high-dose methylprednisolone (1-2 g/day, repeat every 24 hours if needed; taper as clinically indicated), and consider neurology and/or neurosurgery consultation.

Table 31: Guidelines for the Management of Immune Effector Cell-associated Neurotoxicity Syndrome

ICANS Grade[a]	Corticosteroids

ASTCT=American Society for Transplantation and Cellular Therapy; EEG=electroencephalogram; i.v.=intravenous(ly).
Note: ICANS grade and management is determined by the most severe event (ICE score, level of consciousness, seizure, motor findings, raised ICP/cerebral edema), not attributable to any other cause.

a. Based on ASTCT consensus grading (Lee 2019).
b. If subject is arousable and able to perform ICE assessment, assess: Orientation (oriented to year, month, city, hospital =4 points); Naming (name 3 objects, eg, point to clock, pen, button =3 points); Following Commands (eg, "show me 2 fingers" or "close your eyes and stick out your tongue" =1 point); Writing (ability to write a standard sentence =1 point); and Attention (count backwards from 100 by 10 =1 point) (see Attachment 3). If subject is unarousable and unable to perform ICE assessment (Grade 4 ICANS) =0 points.
c. All references to dexamethasone administration are dexamethasone or equivalent.
d. Intracranial hemorrhage with or without associated edema is not considered a neurotoxicity feature and is excluded from ICANS grading. It may be graded according to CTCAE version 5.0.
e. Tremors and myoclonus associated with immune effector cell therapies may be graded according to CTCAE version 5.0, but they do not influence ICANS grading.

Table 32: Guidelines for the Management of Raised Intracranial Pressure/Cerebral Edema*

- Elevate head of subject's bed to an angle of 30 degrees.
- If subject has ommaya reservoir, drain CSF to target opening pressure of <20 mm Hg.
- Hyperventilation to achieve target partial pressure of arterial carbon dioxide ($PaCO_2$) of 28 to 30 mm Hg, but maintained for no longer than 24 hours.
- Consider neurology and/or neurosurgery consultation.
- Use high-dose corticosteroids with methylprednisolone i.v. 1,000 mg/day, as recommended above.
- Hyperosmolar therapy with either mannitol (20 g/dL solution) or hypertonic saline (3% or 23.4%, as detailed below):
  - Mannitol: initial dose 0.5 to 1 g/kg; maintenance at 0.25 to 1 g/kg every 6 hours while monitoring metabolic profile and serum osmolality every 6 hours, and withhold mannitol if serum osmolality is ≥320 mOsm/kg, or the osmolality gap is ≥40,
  - Hypertonic saline: initial 250 mL of 3% hypertonic saline; maintenance at 50 to 75 mL/hour while monitoring electrolytes every 4 hours, and withhold infusion if serum Natrium levels reach ≥155 mEq/L,
  - For subjects with imminent herniation: initial 30 mL of 23.4% hypertonic saline; repeat after 15 minutes, if needed.
- Consider i.v. anesthetics for burst-suppression pattern on EEG.

CSF=cerebrospinal fluid; EEG=electroencephalogram; i.v.=intravenous(ly).
* In addition to toxicity management guidelines provided in Table 31.

1.17.2.4.2.2. Other Neurotoxicities

If any neurologic or psychiatric symptoms are noted (see below), the medical monitor should be contacted, and the subject should be referred immediately to a neurologist for a full evaluation.

Movement and Neurocognitive TEAEs (ie, Parkinsonism)

Subjects are considered to have movement and neurocognitive TEAEs if they meet at least 2 of the below categories (see Section 12.3.3, Section 12.3.4, Table 26, and Attachment B 7 for a more details):

- movement impairments
- cognitive impairments
- personality change

Additional monitoring and mitigation strategies include enhanced bridging therapy to reduce baseline tumor burden (in subjects with NDMM induction (rather than bridging therapy is given), early aggressive treatment of CRS and ICANS, handwriting assessments for early detection of neurotoxicity symptoms, and extended monitoring and reporting time for neurotoxicity until end of study.

Early detection, work-up, and intervention may be important to prevent neurologic toxicity from worsening. The following is a list of potential diagnostics that should be considered in subjects with new neurologic symptoms:

- PET/CT of the brain and/or brain MRI with perfusion and an EEG
- Lumbar puncture to rule out infection (in particular John Cunningham virus, HZV, herpes simplex virus-1/2, HHV-6, HHV-7, EBV, CMV)
- Serologic or PCR testing for HHV-6 and HHV-7 for viremia
- CSF flow cytometry and cytology to rule out leptomeningeal disease
- CSF analysis to rule out paraneoplastic syndromes
- Thiamine level (consider empiric thiamine replacement while awaiting results) (MD Anderson Cancer Center 2020)

Other cytokine-targeting therapies (eg, IL-1, TNFα) may be used based on institutional practice, especially for cases of neurotoxicity which do not respond to tocilizumab or corticosteroids. Therapy directed at reduction or elimination of CAR-T cells, including chemotherapy, may be considered in consultation with the medical monitor for subjects who develop neurotoxicity that remains unresponsive to other interventions.

If CSF or other relevant biological sample analysis is clinically indicated, a sample of CSF must be sent for additional analysis by the sponsor (Section 1.35).

Cranial Nerve Palsies

Monitor subjects for signs and symptoms of cranial nerve palsies (ie, facial numbness, facial paralysis). Consider management with short-course systemic corticosteroids, depending on the severity and progression of signs and symptoms.

Peripheral Neuropathy

Monitor subjects for signs and symptoms of peripheral neuropathies (ie, sensory, motor, or sensorimotor neuropathies). Consider management with short-course systemic corticosteroids, depending on the severity and progression of signs and symptoms.

Guillain-Barré Syndrome

Monitor for signs and symptoms of Guillain-Barré Syndrome (GBS) after cilta-cel infusion (eg, encephalopathy, motor weakness, speech disturbances, and polyradiculoneuritis). Consider treatment with IVIG and escalate to plasmapheresis, depending on toxicity severity.

1.17.2.4.3. Prolonged Cytopenia

Subjects may exhibit prolonged or recurrent cytopenias for several weeks following lymphodepleting chemotherapy and cilta-cel infusion. Prolonged or recurrent neutropenia may increase the risk of infection. Severe thrombocytopenia may increase the risk of bleeding. Blood counts (evaluation of hematological parameters) should be frequently monitored after cilta-cel infusion and supportive care (eg, irradiated blood products, G-CSF for neutropenia) should be provided as outlined by institutional guidelines. Pegylated myeloid growth factors (ie, pegfilgrastim) are prohibited within the first 112 days after cilta-cel infusion. Parvovirus B19 monitoring by PCR should be considered in subjects experiencing prolonged or recurrent neutropenia or a decline in neutrophil counts following count recovery.

1.17.2.4.4. Serious Infections

Do not administer cilta-cel to subjects with active infection. Administration of cilta-cel may increase the risk of infection due to cytopenias or hypogammaglobulinemia. Subjects should be monitored frequently for infection and should have blood cultures obtained, serum inflammatory markers (C-reactive protein) monitored, and/or empiric antibiotics administered per institutional standards. Immunocompromised subjects are at risk for opportunistic infections. Prophylactic use of antibiotics, antivirals, and antifungals should be considered for high-risk subjects. Extended use of antimicrobial therapies for at least 6 months (or longer per institutional guidelines), or consistent with post-ASCT consensus guidelines, after cilta-cel infusion is recommended. Prophylaxis for HZV, CMV, or other HHV reactivation is recommended during study treatment as clinically indicated.

Perform screening for HBV, HCV, and HIV and monitor as clinically indicated (see HBV monitoring recommendations in Attachment 10 and the Time and Events Schedules (Section 1.2), and initiate treatment as appropriate. Consider CMV serology at baseline, monitor with PCR testing as clinically indicated per institutional guidelines.

HBV reactivation, in some cases resulting in fulminant hepatitis, hepatic failure, and death, may occur in subjects treated with drugs directed against B-cells such as cilta-cel. HBV reactivation has occurred in subjects receiving other CAR-T products who appear to have resolved HBV infection. Routinely monitor HBV DNA and AST/ALT for subjects with risk of HBV reactivation (Attachment 10 and Time and Events Schedule, Section 1.2).

Prophylaxis for subjects at high risk of HBV reactivation is recommended per institutional guidelines.

Subjects receiving cilta-cel are possibly at a higher risk of severe/fatal outcomes from COVID-19 infection. Subjects should be reminded of the importance of vaccines and other preventative measures. Investigators should consider prophylaxis (if applicable) and antiviral medications (eg, Paxlovid, if available) for subjects diagnosed with COVID-19 infection, as noted in Attachment 20.

1.17.2.4.5. Second Primary Malignancy

Second primary malignancy is a possibility due to the use of high-dose alkylating therapy, prolonged use of lenalidomide, and the possibility of viral insertion (DNA integration) of the LV vector used to make cilta-cel. Second primary malignancies should be managed per institutional standards and must be reported for the duration of the study, irrespective of when they occur. SPMs will continue to be collected for up to 15 years after cilta-cel infusion in the present study (until end of study) or in a long-term follow-up study (68284528MMY4002). If a bone marrow is planned for suspected SPM, a sample should be collected for central laboratory. Contact sponsor prior to the bone marrow collection for instructions. For subjects diagnosed with an SPM, a tumor sample must be collected, and DNA, RNA, or protein analysis will be performed to investigate the presence of LV elements. Additional samples (including but not limited to blood, tissue, tumor, etc.) may be requested as clinically indicated.

Second primary malignancy will be captured as an AESI (see Section 6.2.4).

1.17.2.4.6. Tumor Lysis Syndrome

Please refer to Section 6.2.3 for the information about TLS.

1.17.2.4.7. Hypogammaglobulinemia

Hypogammaglobulinemia may occur in subjects receiving cilta-cel. Monitor Ig levels after treatment as detailed in the Time and Events Schedule (Section 1.2), and more frequently if clinically indicated, and treat according to local guidelines, including administration of Ig replacement and monitoring for infection. Subjects with IgG <400 mg/dL or recurrent infections (including HBV reactivation) should be considered for prophylactic intravenous or SC IgG per institutional guidelines. Vaccination with investigational or live, attenuated vaccines is prohibited within 4 weeks prior to apheresis and before Day 112 after cilta-cel infusion.

1.17.2.4.8. Hypersensitivity Reactions

Allergic reactions may occur with the infusion of cilta-cel. Serious hypersensitivity reactions including anaphylaxis, may be due to dimethyl sulfoxide, dextran 40, residual kanamycin in cilta-cel. Subjects should be treated urgently per institutional standards, avoiding corticosteroid use if possible. Subjects in both cohorts should receive pre-infusion medication prior to cilta-cel infusion as noted in Section 1.17.2.3.2.

1.18. Preparation/Handling/Storage/Accountability

Preparation/Handling/Storage

Daratumumab, Bortezomib, Lenalidomide, Dexamethasone

Refer to the SIPPM for additional guidance on preparation, handling, and storage for daratumumab. Please refer to package inserts for additional guidance on preparation, handling, and storage for, bortezomib, lenalidomide, and dexamethasone.

Cilta-cel

Please refer to Section 14.4 for the preparation, handling, and storage of cilta-cel.

Accountability

Please refer to Section 14.5 for the drug accountability.

1.19. Assignment to Study Treatment

Please refer to Section 5 for the assignment to study treatment.

1.20. Blinding, Masking

Please refer to Section 5 for blinding and masking.

1.21. Study Treatment Compliance

Compliance with Daratumumab and Bortezomib

Daratumumab and bortezomib administration will be performed in the controlled environment of a qualified study site, under the direct observation of qualified study site personnel. Additional details are provided in the package insert.

Compliance with Lenalidomide and Dexamethasone

Medication cards to account for oral medication use, will be used to assess compliance. Additional details are provided in the Package Insert.

Compliance with Apheresis, Conditioning Regimen, and Cilta-cel

Please refer to Section 7 for this information.

1.22. Dose Modification

For subjects in both cohorts, any dose/dosage adjustment should be overseen by medically qualified study site personnel (principal or sub investigator unless an immediate safety risk appears to be present).

1.22.1. Cycle Delays

For subjects in both cohorts, Day 1 of an induction cycle (DRd or D-VRd) should never be skipped, instead it should be considered a cycle delay. On the first day of each new treatment cycle and before each dose, subjects will be evaluated by the treating physician for possible toxicities that may have occurred after the previous dose(s).

Dose modifications or delays will be made based on the toxicity experienced during the previous cycle of therapy or newly encountered on Day 1 of a cycle (see also Table 34). For any neurological deficits that develop, it is strongly recommended that these be evaluated by the same physician, preferably a neurologist, who performed the neurological assessment at baseline.

The retreatment criteria in Table 33 should be met on the first day of a new cycle (ie, representing baseline inclusion criteria levels).

Table 33: Retreatment Criteria Before the Start of Each DRd (Cohort G) or D-VRd (Cohort H) Induction Cycle

Laboratory Parameter	Requirements Before Each Study Agent Administration
Absolute neutrophil count	$\geq 1.0 \times 10^9$/L
Platelet count	$\geq 50 \times 10^9$/L
Hemoglobin	≥7.5 g/dL (≥4.96 mmol/L)

If the above parameters are not met, the start of the next cycle will be held until recovery to the specified levels. Supportive care medications, including transfusions, should be administered at the investigator discretion.

If there is a delay in the start of a new cycle (ie, none of the study treatments are given during this period) due to insufficient recovery from toxicity for more than 28 days, re-initiation, continuation, or discontinuation of any study treatment(s) will need to be approved by the medical monitor.

1.22.1.1. Daratumumab

Individual dose modification for daratumumab is not permitted. Dose delay is recommended as the only method for managing daratumumab-related toxicities.

Refer to Section 1.17.1.2.3.1 for details on prevention and management of sARRs. If any of the following criteria are met and the toxicity is more than expected for the backbone therapy or underlying multiple myeloma, daratumumab administration must be held to allow for recovery from toxicity as noted below.

The criteria for a dose delay are:

- Grade 4 hematologic toxicity, except for Grade 4 lymphopenia
- Grade 3 thrombocytopenia with bleeding
- Febrile neutropenia of any grade
- Neutropenia with infection, of any grade
- Grade 3 or higher nonhematologic toxicities with the following exceptions:
  - Grade 3 nausea that responds to antiemetic treatment within 7 days
  - Grade 3 vomiting that responds to antiemetic treatment within 7 days
  - Grade 3 diarrhea that responds to antidiarrheal treatment within 7 days
  - Grade 3 fatigue or asthenia that was present at baseline and lasts for <7 days after the last administration of daratumumab

Administration of daratumumab may be restarted upon recovery from toxicity to Grade 2 or baseline, with the exception that Grade 2 laryngeal edema or Grade 2 bronchospasm must be fully recovered.

Other than on Day 1 of a cycle, if any within-cycle daratumumab administration does not commence within the prespecified window (Table 34) of the scheduled administration date, the dose will be considered a missed dose. Administration may restart at the next planned dosing date. A missed dose will not be made up.

Table 34: Daratumumab-related Toxicity Management

Cycles (Cohorts G and H)	Frequency	Missed Dose	Dosing Resumption
1-2	Weekly	>3 days	Next planned weekly dosing date
3-4	Every 2 weeks	>7 days	Next planned every 2 weeks dosing date

SC daratumumab must be permanently discontinued if treatment is interrupted for >28 days due to any toxicity related to daratumumab, unless, upon consultation with the medical monitor and the review of safety and efficacy, continuation is agreed upon.

Delay of Day 1 dosing in any given cycle should not result in a skipped dose but should lead to a delay of the entire cycle instead. A minimum of 4 days between daratumumab doses must be observed.

Daratumumab Interruption or Missed Doses

A daratumumab dose that is held longer than the permitted time (Table 34) from the per-protocol administration date for any reason other than toxicities deemed related to daratumumab should be brought to the attention of the medical monitor at the earliest possible time. Subjects missing ≥3 consecutive planned doses for reasons other than toxicity should be withdrawn from study treatment, unless, upon consultation with the medical monitor and the review of safety and efficacy, continuation is agreed upon.

1.22.1.2. Bortezomib

Dose modifications should be based on the highest grade of toxicity that is ascribed to bortezomib. Bortezomib treatment should be withheld at the onset of any Grade 3 or Grade 4 nonhematological or Grade 4 hematological toxicities, excluding neuropathy, as outlined in Table 35. Once the symptoms of the toxicity have resolved, bortezomib treatment may be reinitiated at a 25% reduced dose per approved labeling, as outlined in Table 35.

Table 35: Dose Modification for Bortezomib

Starting Dose	First Dose Reduction	Second Dose Reduction	Third Dose Reduction
1.3 mg/m^2	1.0 mg/m^2	0.7 mg/m^2	Discontinue bortezomib

Bortezomib doses may be delayed up to 48 hours. All bortezomib doses must be at least 72 hours apart. Doses that are delayed >48 hours or need to be withheld, will be skipped and will not be made up later in the cycle. Dose modifications for toxicity should be followed, as outlined in Table 35.

1.22.1.3. Lenalidomide

Dose modifications should be based on the highest grade of toxicity that is ascribed to lenalidomide, as outlined in Table 36. Dose modifications for lenalidomide during DVRd induction per approved labeling, are outlined in Table 36.

Table 36: Dose Modification for Lenalidomide

	Cycles 1-4 (Cohorts G and H)
Starting Dose	25 mg once daily, Days 1-21
First Dose Reduction	20 mg once daily, Days 1-21
Second Dose Reduction	15 mg once daily, Days 1-21
Third Dose Reduction	10 mg once daily, Days 1-21
Fourth Dose Reduction	5 mg once daily, Days 1-21
Fifth Dose Reduction	Discontinue lenalidomide permanently

If a daily lenalidomide dose is missed, it may be taken if <12 hours have elapsed since the time that it should have been taken. Otherwise, the missed lenalidomide dose should be skipped.

1.22.1.3.1. Renal Impairment

Modification of the lenalidomide dose is recommended to provide appropriate drug exposure in subjects with moderate or severe renal impairment, because lenalidomide is primarily excreted unchanged by the kidney. Lenalidomide dose modification should be instituted for subjects with a CrCl <60 mL/min, as outlined in Table 37. To be enrolled in the study, subjects must have an eGFR ≥40 mL/min/1.73 m^2. If a subject's renal status changes during study treatment, the dose should be modified, as outlined in Table 37.

Table 37: Lenalidomide Dose Modification for Subjects with Renal Impairment

Renal function (Cockcroft-Gault)	**Cycles 1-4 (Cohorts G and H)**
CrCl 30 to 60 mL/min	10 mg once daily, Days 1-21
CrCl <30 mL/min (not requiring dialysis)	15 mg every other day, Days 1-21
CrCl <30 mL/min (requiring dialysis)	5 mg once daily, Days 1-21 On dialysis days, the dose should be administered following dialysis

1.22.1.4. Dexamethasone

The dexamethasone dose may be reduced, if necessary, according to Table 38. For Grade 3 or Grade 4 nonhematologic and nonrenal toxicities, judged by the investigator to be related to dexamethasone alone, dexamethasone treatment should be withheld. Once the toxicity has resolved to ≤Grade 2, dexamethasone treatment may be reinitiated at the next lower dose level. For complete details on dexamethasone, refer to the most current local product prescribing information.

Table 38: Dose Modification for Dexamethasone

Starting Dose	**First Dose Reduction**	**Second Dose Reduction**	**Third Dose Reduction**
40 mg[a]	20 mg[a]	10 mg	Discontinue dexamethasone

[a] The prescribed dose of dexamethasone may be split over two consecutive days.

If a weekly dexamethasone dose is missed, it may be taken if <4 days have elapsed since the time that it should have been taken. If the next dose is scheduled to be taken within 3 days, the missed dexamethasone dose should be skipped.

1.22.1.5. Dose Modification Guidelines

Dose modification guidelines for bortezomib, lenalidomide, and dexamethasone are outlined in Table 39.

Guidelines for dose modifications are listed below (Table 39). However, dose modifications decisions for pomalidomide, bortezomib, daratumumab and dexamethasone will be at the investigator's discretion per the full prescribing information and labeling in the respective current US prescribing. Investigators should follow the local label for the management of interactions with other medical products.

Table 39: Dose Modification Guidelines for Bortezomib, Lenalidomide, and Dexamethasone

Body System	CTCAE and/or Symptom and Category	Bortezomib	Lenalidomide	Dexamethasone
Allergic reaction	Allergic reaction or hypersensitivity Grade 2 or 3	Hold DRd (Cohort G) or D-VRd (Cohort H). If the toxicity resolves to ≤Grade 1, restart DRd (Cohort G) or D-VRd (Cohort H). Reduce by 1 dose level the suspected medication(s) AND implement appropriate antiallergic prophylaxis treatment. If the reaction was anaphylactic in nature, do not restart DRd (Cohort G) or D-VRd (Cohort H). Note: If the reaction was cutaneous in nature, refer to the cutaneous category below.		
	Allergic reaction or hypersensitivity Grade 4	Discontinue DRd (Cohort G) or D-VRd (Cohort H).		
Cardiovascular	Fluid retention (ie, edema) >Grade 3 (limiting function and unresponsive to therapy or anasarca)			Administer diuretics as needed and reduce dexamethasone dose by 1 dose level. If edema persists despite above measures, reduce dose by 1 further dose level. Permanently discontinue dexamethasone if symptoms persist despite second dose reduction.
Constitutional	Fatigue ≥Grade 3 (ie, severe fatigue interfering with activities of daily living) *Note: Determine if fatigue is possibly not treatment-related, but due to an underlying cause (eg, infection, PD, diarrhea, anemia, depression) and treat these symptoms/causes as appropriate.*	Hold bortezomib and lenalidomide treatment until resolved to ≤Grade 2. Consider reduction of lenalidomide or bortezomib dose by 1 dose level		

Table 39: Dose Modification Guidelines for Bortezomib, Lenalidomide, and Dexamethasone

Body System	CTCAE and/or Symptom and Category	Bortezomib	Lenalidomide	Dexamethasone
Cutaneous	Nonblistering rash Grade 2	Hold bortezomib treatment. Start treatment with antihistamines and/or low-dose steroids per institutional practice. If the toxicity resolves to ≤Grade 1, reduce dose by 1 dose level and restart bortezomib. Restart with lower concentration formulation. If recurrent, consider i.v. bortezomib.	Consider holding lenalidomide treatment.	
	Nonblistering rash ≥Grade 3 or 4	Hold bortezomib and lenalidomide treatment. Start treatment with antihistamines and/or low-dose steroids per institutional practice. If the toxicity resolves to ≤Grade 1, reduce dose of suspected agent(s) by 1 dose level and continue antihistamines and/or low-dose steroids per institutional practice. In case of Grade 4 toxicity, permanently discontinue bortezomib and lenalidomide.		
	Desquamating (blistering) rash any grade or Erythema multiform ≥Grade 3	Permanently discontinue bortezomib and lenalidomide. Hold other treatments. Start treatment with antihistamines and/or low-dose steroids per institutional practice. If the toxicity resolves to ≤Grade 1, restart other treatments.		
Gastrointestinal	Constipation ≥Grade 3 *Note: Prior to dose reduction, consider/eliminate other possible causes of constipation and maximize supportive care*	Hold bortezomib treatment. If the toxicity resolves to ≤Grade 1, reduce dose by 1 dose level and restart bortezomib.		
	Diarrhea ≥Grade 3 *Note: Prior to dose reduction, consider/eliminate other possible causes (ie, bacterial or viral infections) of diarrhea*	Hold bortezomib and consider loperamide treatment. If the toxicity resolves to ≤Grade 1, reduce dose by 1 dose level and restart bortezomib.		

Table 39: Dose Modification Guidelines for Bortezomib, Lenalidomide, and Dexamethasone

Body System	CTCAE and/or Symptom and Category	Bortezomib	Lenalidomide	Dexamethasone
	Dyspepsia, gastric or duodenal ulcer, gastritis Grade 1-2 (requiring medical management)			Start treatment with histamine-2 blockers, sucralfate, or PPI. If symptoms persist despite above measures, reduce dexamethasone dose by 1 dose level.
	Dyspepsia, gastric or duodenal ulcer, gastritis ≥Grade 3 (requiring hospitalization or surgery)			Hold dexamethasone and consider treatment with histamine-2 blockers, sucralfate, or PPI. Reduce dose by 1 dose level and restart dexamethasone if symptoms are adequately controlled. If symptoms persist despite above measures, permanently discontinue dexamethasone.
	Acute pancreatitis			Permanently discontinue dexamethasone.
Hematological	Neutropenia Grade 3 (without complications)	No dose reduction required of bortezomib. Consider treatment with G-CSF. Hold treatment with bortezomib and lenalidomide until recovery to baseline or ≤Grade 2. Consider G-CSF support. Upon recovery if isolated neutropenia, maintain lenalidomide at current dose level. If other hematologic toxicities present reduce lenalidomide dose by 1 dose level. If recurrent episode, reduce both lenalidomide and bortezomib doses by 1 dose level.		
	Neutropenia associated with fever (≥38.5ºC) Grade 3 or Neutropenia Grade 4	Hold bortezomib and lenalidomide treatment until recovery to baseline or ≤Grade 2. Consider G-CSF support. Upon recovery if isolated neutropenia, maintain lenalidomide dose at current dose level. If other hematologic toxicities present, reduce lenalidomide dose by 1 dose level. Maintain bortezomib at current dose level. If recurrent episode, reduce both lenalidomide and bortezomib doses by 1 dose level.		
	Thrombocytopenia Grade 3 (without complications)	No bortezomib dose reduction required.	Reduce lenalidomide dose by 1 dose level for the remainder of the cycle if feasible. Otherwise hold lenalidomide until Thrombocytopenia	

Table 39: Dose Modification Guidelines for Bortezomib, Lenalidomide, and Dexamethasone

Body System	CTCAE and/or Symptom and Category		Bortezomib	Lenalidomide	Dexamethasone
	Platelet count $\leq 30 \times 10^9$/L or ANC $\leq 0.75 \times 10^9$/L on a bortezomib dosing day		Hold bortezomib treatment.		
	Platelet count <25,000/μL (ie, Grade 4) or Grade 3 thrombocytopenia with bleeding		Hold bortezomib and lenalidomide treatment until recovery to baseline or ≤Grade 2. Upon recovery, reduce dose 1 dose level and restart bortezomib, hold lenalidomide treatment for remainder of the cycle and reduce dose by 1 dose level at start of next cycle.		
Infection	HZV activation or reactivation any grade		Hold DRd (Cohort G) or D-VRd (Cohort H). until lesions are dry. If not already underway, start antiviral treatment. Once the infection is resolved all treatments can be restarted without a dose reduction; however, continued antiviral prophylaxis is required. *Note: If a subject is already receiving antiviral treatment at the time of the HZV activation, consider switching to or adding another antiviral agent.*		
Metabolic	Hyperglycemia ≥Grade 3				Start treatment with insulin or oral hypoglycemics. If uncontrolled despite above measures, reduce dexamethasone dose by 1 dose level until levels are satisfactory.
Musculoskeletal	Muscle weakness >Grade 2 (symptomatic and interfering with function +/- interfering with activities of daily living)				Reduce dexamethasone dose by 1 dose level. If weakness persists despite above measures, reduce dose by 1 further dose level. If symptoms persist, permanently discontinue dexamethasone.
Neurological*	Peripheral Neuropathy (Sensory or Motor) and/or Neuropathic Pain	Grade 1 (paresthesias and/or loss of reflexes) without pain or loss of function	No action required; however, dose reduction may be considered based on clinical judgement and/or institutional practice.		
		Grade 1 with pain or Grade 2 (interfering with function but not with activities of daily living)	reduce bortezomib dose by 1 dose level (maximum dose of 1.0 mg/m^2).		

Table 39: Dose Modification Guidelines for Bortezomib, Lenalidomide, and Dexamethasone

Body System	CTCAE and/or Symptom and Category		Bortezomib	Lenalidomide	Dexamethasone
		Grade 2 with pain or Grade 3 (interfering with activities of daily living)	Hold bortezomib treatment until recovery to <Grade 2. When toxicity resolves to ≤Grade 1, reduce dose by 1 dose level (maximum dose of 0.7 mg/m^2 once weekly).		
		Grade 4 (permanent sensory loss that interferes with function) and/or severe autonomic neuropathy	Permanently discontinue bortezomib.		
Neuropsychological	Confusion or mood alteration >Grade 2 (interfering with function ±interfering with activities of daily living)				Hold dexamethasone treatment until symptoms resolve. Reduce dose by 1 dose level and restart dexamethasone. If symptoms persist despite above measures, permanently discontinue dexamethasone.
Other toxicities	Any reported toxicity ≥Grade 3		Determine drug attribution of the toxicity and hold treatment(s) as appropriate. If toxicity resolves to ≤Grade 1, reduce dose of suspected drug by 1 dose level and restart treatment.		
Thromboembolic	Venous and/or pulmonary thrombo-embolism ≥Grade 3 (deep vein thrombosis or cardiac thrombosis intervention indicated; e. g, anticoagulation, lysis, filter, invasive procedure.)			Hold lenalidomide and dexamethasone treatment until toxicity resolves and, if not already given, start anticoagulation treatment. Restart lenalidomide and dexamethasone at full dose after adequate anticoagulation.	

i.v.=intravenous(ly); PPI=proton pump inhibitor.

* The neurotoxicity-directed questionnaire is a useful tool for determining the presence and intensity of neuropathic pain and/or peripheral neuropathy from the subject's perspective. Neuropathic symptoms are more prominent than abnormalities on the clinical examination. After the subject completes the neurotoxicity-directed questionnaire, the questionnaire should be reviewed to assist with the evaluation of the onset and intensity of peripheral neuropathy and other neurotoxicities that may require intervention or dose modification. Bortezomib dose modifications due to peripheral neuropathy that are outside those outlined may be allowed based on investigator's clinical judgment.

1.23. Continued Access to Study Treatment After the End of the Study

Subjects will be instructed that study treatment will not be made available to them after they have completed/discontinued study treatment and that they should return to their primary oncologist to determine standard of care.

1.24. Treatment of Overdose

Refer to the local product prescribing information for daratumumab, bortezomib, lenalidomide, or dexamethasone regarding overdose.

Cilta-cel will be manufactured, formulated, and provided under the responsibility of the manufacturer and the sponsor for each subject individually. Drug product received should be administered in a single infusion. In the event the manufactured drug product exceeds the protocol-defined maximum dose, the drug product will be evaluated per company exceptional release or similar procedures (see Section 1.17.2.3.4) prior to shipment to the study site. There is no risk for overdose of JNJ-68284528.

1.25. Concomitant Therapy

Throughout the study, investigators may prescribe concomitant medications or treatments (except for those listed in Section 1.25.3) deemed necessary to provide adequate supportive care. All concomitant medications will be recorded during screening. Thereafter, concomitant medications given for any AE (including delayed AE) or SAE, therapeutically or prophylactically, will be reported. In addition, concomitant medications given for signs or symptoms of PD will be reported in the context of collecting data on symptomatic PD.

The concomitant medications to be reported include, but are not limited to:

- Anticytokine or anticytokine receptor therapies
- Antiseizure medications
- Any medication given for prophylaxis or treatment of TLS
- Any medication given for prevention or treatment of thromboembolic events
- Medication for prevention or treatment of daratumumab sARRs
- Corticosteroids (including prophylactically for blood product administrations, physiologic replacement doses, high or stress doses)
- Immunosuppressive agents
- Vaccinations
- Vasopressors and cardiac inotropic agents (for dose, record only maximum daily rate)
- Blood products
- Growth factors
- Systemic antimicrobials given for prophylaxis or treatment
- Chemotherapy given for CAR-T cell toxicity

Other:

- Bisphosphonates
- Ig therapy

- Medications listed as prohibited in the protocol
- Palliative Radiation
- Pain medication
- Any treatment given for SPMs
- Any changes in doses from baseline or newly added concomitant medications to treat new or prior known comorbidities

For both cohorts, the recording period is from the signing of the ICF until 30 days after the last dose of the last study treatment or Day 112 after cilta-cel infusion, whichever occurs later, and regardless if PD occurs before Day 112 or subsequent antimyeloma therapy is started before Day 112.

Beyond this reporting period, concomitant therapy given for any SAE regardless of causality, any nonserious AE considered related to study treatment, or any delayed AE will be recorded until end of study. Exceptions include medications used to prevent (including vaccines) and treat COVID-19 and HBV reactivation, which should be reported until 1 year after cilta-cel infusion, regardless of severity or causality (Section 1.25).

Recorded information will include a description of the type of therapy, duration of use, dosing regimen, route of administration, and indication. Medications, including details of previous anticancer treatment, should be documented in the eCRF.

The medical monitor must be notified in advance (or as soon as possible thereafter) of any instances in which prohibited therapies are administered.

1.25.1. Recommended Medications

Refer to Section 1.17.1.2.1 and Section 1.17.1.2.2 for pre- and post-administration medications for daratumumab, and to Section 1.17.2.3.2 for medications subjects in both cohorts should receive prior to cilta-cel infusion.

1.25.1.1. Prophylaxis for Thromboembolism

Lenalidomide has been associated with an increased incidence of deep vein thrombosis and pulmonary embolism. Therefore, thromboprophylaxis is strongly recommended for all subjects receiving lenalidomide.

Subjects already on therapeutic anticoagulation may continue their prior anticoagulation regimen. All subjects should have their anticoagulation held according to institutional guidelines when subjects would be at risk of bleeding due to the combination of significant thrombocytopenia and anticoagulation. Once platelet count recovers to an acceptable level per institutional guidelines, anticoagulation should be resumed.

Refer to the lenalidomide prescribing information for recommendations for subjects with prior history of thrombosis.

1.25.1.2. Proton Pump Inhibitor

Prophylactic use of a proton pump inhibitor (PPI) is recommended for all subjects receiving dexamethasone. If a contraindication to PPI exists or the subject is intolerant to PPIs, a histamine receptor (H2) blocker may be substituted for the PPI.

1.25.1.3. Prophylaxis for Infections

Antibacterial prophylaxis for bacterial pneumonia should be considered, as per institutional guidelines, especially in subjects with a history of respiratory disorders. At the start of cilta-cel infusion, prophylaxis with antibacterial (eg, levofloxacin) and antifungal medication (eg, fluconazole) is recommended until ANC returns to ≥0.5x109/L. Prophylaxis for HZV reactivation is recommended during study. Initiate antiviral prophylaxis to prevent HZV reactivation from the study treatment until at least 12 months after cilta-cel infusion. Acceptable antiviral therapy includes acyclovir, famciclovir, or valacyclovir (per institutional standards). Antiviral prophylaxis to prevent HBV reactivation is recommended per institutional guidelines and consultation of a liver disease specialist as clinically indicated. Pneumocystis carinii prophylaxis may be considered per institutional guidelines (see Attachment 18). Subjects with IgG <400 mg/dL or recurrent infections (including HBV reactivation) should be considered for prophylactic intravenous or SC IgG per institutional guidelines. Please refer to Attachment 20 for guidance on prophylaxis (eg, vaccines) and treatment of COVID-19 infection.

1.25.1.4. Prophylaxis for Tumor Lysis Syndrome

It is also recommended that subjects at high risk of TLS, ie, those with a high tumor burden (≥60% plasma cell infiltrate on the bone marrow biopsy or aspirate [whichever is higher] or a subject with multiple extramedullary disease sites or plasmacytomas) or high LDH be treated prophylactically for TLS in accordance with local standards (eg, hydration, diuretics, allopurinol, and primary or secondary uricosuric agents, as indicated).

1.25.2. Permitted Medications

The following are examples of supportive therapies that may be used during the study for subjects enrolled in either Cohort G or Cohort H unless otherwise stated:

- Standard supportive care therapies (antiemetics, antidiarrheals, anticholinergics, antispasmodics, antipyretics, antihistamines, analgesics, antibiotics and other antimicrobials, H2 antagonists or PPIs, and other medications intended to treat symptoms or signs of disease) and therapies intended to treat CAR-T cell toxicity, including CRS and CAR-T cell neurotoxicity, as clinically indicated, according to institutional standards and as deemed necessary by the investigator.
- Bisphosphonates may be administrated as clinically indicated, according to institutional standards. The medical monitor must be notified promptly in cases where bisphosphonates are given for the management of hypercalcemia.

- Hematopoietic growth factor support, and transfusions (irradiated blood products) are permitted to treat symptoms or signs of neutropenia, anemia, or thrombocytopenia according to local standards of care. Nonpegylated myeloid growth factors are permitted up to 1 day prior to the start of the conditioning regimen (Section 1.17.2.2).
- Documented infectious complications should be treated with oral or intravenous antibiotics or other anti-infective agents as considered appropriate by the treating investigator, per standard institutional practice.
- Chemotherapy agents used to treat CAR-T cell toxicity are permitted upon consultation with the medical monitor (Section 1.17.2.4).

Nonlive vaccines approved or authorized for emergency use (eg, COVID-19) by local health authorities are allowed (see Attachment 20).

1.25.3. Prohibited Therapies

Medications that are prohibited during the study for subjects enrolled in either Cohort G or Cohort H are indicated below. The medical monitor must be notified in advance (or as soon as possible thereafter) of any instances in which prohibited therapies are being considered for administration (or were administered).

- Any chemotherapy, anticancer immunotherapy (other than cilta-cel), or experimental therapy, except for the protocol-specified therapies. Chemotherapy agents used to treat CAR-T cell toxicity are permitted upon consultation with the medical monitor (Section 1.17.2.4).
- Other immunosuppressant agents, except for the protocol-specified pre- or post-treatment medications to treat an AE (eg, CRS).
- Orthopedic surgery or radiotherapy is generally prohibited, but may be allowed in the absence of PD. Prior notification of and approval from the medical monitor is required. If necessary, an emergency intervention may proceed without prior approval from the medical monitor. In these cases, the medical monitor should be notified as soon as possible. Such emergency radiotherapy may consist of localized radiotherapy for pain control or for stabilization of an extensive bone lesion at high risk of pathologic fracture or damage to surrounding tissues.
- Corticosteroid use, beyond the required dexamethasone in the DRd regimen (Cohort G) or DVRd regimen (Cohort H) and the preadministration medication for daratumumab, should be avoided, except for the treatment of CRS or ICANS, as described in Table 30 and Table 31. Alternative therapies, if feasible, should be given prior to corticosteroids.
- Concomitant administration of strong CYP3A4 inducers is prohibited with the use of bortezomib (Cohort H; see https://www.fda.gov/drugs/drug-interactions-labeling/drug-developmentand-drug-interactions-table-substrates-inhibitors-and-inducers).
- Vaccination is recommended per local guidelines (including influenza and SARS-CoV-2 vaccines). Live, attenuated vaccines are prohibited for 4 weeks prior to apheresis and before Day 112 after cilta-cel infusion. Refer to Attachment 20 for COVID-19 vaccine guidance. Note that antibody responses to vaccines may be suboptimal during study treatment.
- The use of receptor activator of nuclear factor kappa-B (RANK) ligand inhibitors, eg, denosumab is prohibited due to their potential impact on immune function.

- Pegylated myeloid growth factors (ie, pegfilgrastim) are prohibited from enrollment until the first 112 days after cilta-cel infusion.

Therapies to be avoided

- Nonsteroidal anti-inflammatory agents should be avoided to minimize the risk of exacerbation of potential subclinical myeloma-related kidney disease. Based on the investigator's clinical judgment, low-dose aspirin may be continued for thromboprophylaxis.
- The use of intravenous contrast infusions should be avoided to prevent myeloma-related kidney disease. If administration of intravenous contrast is necessary, then adequate precautions including hydration are indicated.
- Caution should be exercised when bortezomib (Cohort H) is combined with CYP3A4 or CYP2C19 substrates (see https://www.fda.gov/drugs/drug-interactions-labeling/drug-development-anddrug-interactions-table-substrates-inhibitors-and-inducers). Subjects should be closely monitored when given bortezomib in combination with potent CYP3A4 inhibitors.

1.25.4. Subsequent Antimyeloma Therapy

Subsequent antimyeloma therapy administered after study treatment can only be used after PD per IMWG response criteria (see Attachment 5) has been confirmed by the medical monitor and recorded in the eCRF. The start and end date, best response, and date of PD to subsequent therapy should be documented in the eCRF if available.

1.26. DISCONTINUATION OF STUDY TREATMENT AND SUBJECT DISCONTINUATION/WITHDRAWAL

1.26.1. Discontinuation of Study Treatment

A subject's study treatment must be discontinued if:

- The investigator believes that for safety reasons or tolerability reasons (eg, adverse event) it is in the best interest of the subject to discontinue study treatment
- Grade ≥3 nonhematologic toxicity related to cyclophosphamide and fludarabine occurs, and precludes retreatment with cyclophosphamide and fludarabine prior to cilta-cel infusion
- The subject received concurrent (non-protocol) anticancer treatment prior to infusion of cilta-cel
- Subject refuses further study treatment
- Noncompliance with study treatment or procedure requirements
- The subject becomes pregnant prior to cilta-cel infusion (refer to Section 12.3.5).

The primary reason for treatment discontinuation will be documented in the eCRF and source documents. If a subject's study treatment is discontinued for any reason, this will not result in automatic withdrawal of the subject from the study. However, if a subject discontinues study treatment without the cilta-cel infusion, the EOS visit procedures will be performed.

1.26.2. Subject Discontinuation/Withdrawal From the Study

A subject will be withdrawn from the study for any of the following reasons:

- Lost to follow-up
- Withdrawal of consent
- Discontinuation of induction therapy without proceeding to cilta-cel infusion
- The sponsor discontinues the study
- Failure to manufacture cilta-cel after 2 apheresis attempts*

* A 3rd apheresis attempt may be permitted if an immediately rectifiable cause is identified (eg, product shipped improperly) and with sponsor approval.

When a subject withdraws the consent, the EOS visit procedures will be performed.

Withdrawal of Consent

A subject declining to return for scheduled visits does not necessarily constitute withdrawal of consent. Alternate follow-up mechanisms that the subject agreed to when signing the consent form apply (eg, consult with family members, contacting the subject's other physicians, medical records, database searches, use of locator agencies at study completion,) as local regulations permit.

1.26.3. Withdrawal From the Use of Compatible Research

The subject may withdraw consent for use of samples for research (refer to Long-Term Retention of Samples for Scientific Research in Section 16.2.5). In such a case, samples will be destroyed after they are no longer needed for the clinical study. Details of the sample retention for research are presented in the main ICF.

1.27. Lost to Follow up

To reduce the chances of a subject being deemed lost to follow up, prior to enrollment attempts should be made to obtain contact information from each subject, eg, home, work, and mobile telephone numbers and email addresses for both the subject as well as appropriate family members.

A subject will be considered lost to follow up if the subject repeatedly fails to return for scheduled visits and is unable to be contacted by the study site. A subject cannot be deemed lost to follow-up until all reasonable efforts made by the study site personnel to contact the subject are deemed futile. The following actions must be taken if a subject fails to return to the study site for a required study visit:

- The study site personnel must attempt to contact the subject to reschedule the missed visit as soon as possible, to counsel the subject on the importance of maintaining the assigned visit schedule, to ascertain whether the subject wishes to or should continue in the study.

- Before a subject is deemed lost to follow up, the investigator or designee must make every reasonable effort to regain contact with the subject (where possible, 3 telephone calls, emails, fax, and, if necessary, a certified letter to the subject's last known mailing address, or local equivalent methods. Locator agencies may also be used as local regulations permit. These contact attempts should be documented in the subject's medical records.
- Should the subject continue to be unreachable, they will be considered to have withdrawn from the study.
- Site personnel, or an independent third party, will attempt to collect the vital status of the subject within legal and ethical boundaries for all subjects randomized, including those who did not get study treatment. Public sources may be searched for vital status information. If vital status is determined as deceased, this will be documented, and the subject will not be considered lost to follow-up. Sponsor personnel will not be involved in any attempts to collect vital status information.

Should a study site close, eg, for operational, financial, or other reasons, and the investigator cannot reach the subject to inform them, their contact information will be transferred to another study site.

1.28. STUDY ASSESSMENTS AND PROCEDURES

Screening Phase (within 28 Days)

All screening activities for both cohorts (G and H) will be performed according to the Time and Event Schedules (Section 1.2) Screening procedures and within 28 days before enrollment. All subjects must sign an ICF prior to the initiation of any study-related tests or procedures that are not part of standard of care for the subject's disease. The screening phase begins when the first screening assessment is performed. If an assessment was performed as part of the subject's routine clinical evaluation and not specifically for this study, it does not need to be repeated after signed ICF has been obtained provided the assessments fulfill the study requirements and are performed within the specified timeframe prior enrollment. The last result obtained prior to enrollment will be used to determine eligibility. Individuals who do not meet the criteria for participation in this study (screen failure) may, at the discretion of the investigator, be rescreened once upon the medical monitor's written approval (Section 1.15).

Treatment Phase (Cohort G and Cohort H)

Subjects will receive study treatment as it is outlined in Section 1.17.1 and described in more detail in Section 1.7.2. All assessments will be performed according to the Time and Event Schedule (Section 1.2.2 and Section 1.2.3).

For subjects with highly aggressive MM requiring immediate treatment, the investigator will need to discuss the timing of apheresis with the medical monitor.

Prior to apheresis, review of safety assessments and disease characteristics should be completed according to the Time and Event Schedules (Section 1.2) and Section 1.17.2.1.1. Apheresis should be performed according to institutional standards, with the collection target and instructions for processing and shipping apheresis product provided in the CTPPM.

Induction therapy with DRd (Cohort G) or D-VRd (Cohort H) will consist of 4 cycles, 28 days each.

When the manufacturing and quality testing of cilta-cel is complete, a notification will be sent to the study site. Prior to dosing with the conditioning regimen, review of safety assessments and disease characteristics should be completed according to Section 1.17.2.2. Subject must fulfill all criteria for Conditioning prior to administration of cyclophosphamide and fludarabine.

Prior to cilta-cel administration, review of safety assessments and disease characteristics should be completed according to Section 1.17.2.3.1. Subject must fulfill all criteria for Cilta-cel administration, prior to dosing with cilta-cel. Administration of cilta-cel is described in detail in Section 1.17.2.3.

Post-infusion Follow-up Phase (Cohort G and Cohort H)

The Post-treatment Follow-up Phase will last 112 days starting from cilta-cel infusion. Any subject who receives a cilta-cel infusion should undergo all post-infusion assessments during the Post-infusion Follow-up Phase according to the Time and Event Schedule (Section 1.2.4). The Post-infusion Follow-up Phase starts after completion of cilta-cel infusion on Day 1 and lasts until Day 112 post-infusion. During this phase, subjects will be monitored intensively for safety and disease characteristics. Subjects will be asked to check their temperature at least twice daily during the first 28 days after infusion and will be instructed to report any fever (≥38°C or ≥100.4°F) to the investigator immediately to initiate monitoring for development of CRS.

Post-treatment Follow-up Phase (Cohort G and Cohort H)

The post-treatment period will start on Day 113 and lasts until end of study/cohort completion. Onsite visits are also required at 1 year post cilta-cel and subsequently at least annually. See Section 1.2.4 for schedule of assessments. RCL testing will also be required at 1 year post cilta-cel.

Subsequent antimyeloma therapy can only be used after PD was confirmed by the medical monitor. If a subject starts new antimyeloma therapy prior to PD, every attempt should be made to perform disease evaluations until documented PD.

After confirmed PD, subjects will be followed for related AEs/SAEs, delayed AEs, subsequent antimyeloma therapies, response to subsequent antimyeloma therapies including the date of subsequent progression (PFS2) (per investigator judgment), SPMs, and survival status until death or end of study. Refer to the Time and Events Schedule for details (Section 1.2).

The Post-treatment Follow-up Phase will last until death, withdrawal of consent, lost to follow-up, or end of cohort, whichever occurs first.

1.29. Administrative Procedures

Overview

The Time and Events Schedules (Section 1.2) summarizes the frequency and timing of efficacy, PK, immunogenicity, PD, biomarker, benefit-risk, safety and other measurements applicable to this study.

All assessments, including laboratory tests, planned to be performed before the start of study treatment and must be completed with the results reviewed before administration of study treatment. Treatment decisions will be based on safety assessments and disease assessments performed at the local laboratory.

If multiple assessments are scheduled for the same timepoint, it is recommended that procedures be performed in the following sequence ECG, vital signs, blood draw, imaging, bone marrow/other assessments. Blood collections for PK and PD assessments should be kept as close to the specified time as possible. Other measurements may be done earlier than specified timepoints if needed. Actual dates and times of assessments will be recorded in the source documentation and/or the CRF.

The total blood volume to be collected from each subject will be approximately 967.5 mL /year.

Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

Home Health Care and Telemedicine Visits

Please refer to Section 9.1.6.2 for details.

After CAR-T Day 196, subjects may be followed via telehealth visit every 28 days (±7 days) in conjunctions with local laboratories.

Sample Collection and Handling

The actual dates and times of sample collection must be recorded in the CRF or laboratory requisition form.

Refer to the Time and Events Schedule (Section 1.2) for the timing and frequency of all sample collections.

Instructions for the collection, handling, storage, and shipment of samples are found in laboratory manual that will be provided. Collection, handling, storage, and shipment of samples must be under the specified, and where applicable, controlled temperature conditions as indicated in laboratory manual.

Study-Specific Materials

Please refer to Section 15 for details.

1.30. Efficacy Assessments

Disease evaluations must be performed as specified in the Time and Events Schedules (Section 1.2). Disease evaluations will be performed by a local laboratory until confirmed PD, death, withdrawal of consent, or final PFS analysis, whichever occurs first. Local laboratory data will be a subset of screening assessments as outlined in the Time and Events Schedules (Section 1.2).

Documentation of the local laboratory data should be sent to the principal investigator and filed in the medical record. It is the principal investigator's responsibility to ascertain that these results are reviewed and entered into the subject's medical record.

Response assessments will be based on IMWG response criteria (see Attachment 5).

Disease progression must be confirmed by repeating local laboratory testing at any time before the start of any new therapy. The study sites are requested to notify the medical monitor within 1 working day if a subject has been diagnosed with PD (that is also confirmed with a consecutive assessment if based on M-protein/serum FLC levels) and provide documentation of PD. The medical monitor will review the provided data to confirm that the IMWG response criteria for PD have been met. Study treatment discontinuation and start of subsequent antimyeloma therapy should occur only after confirmation of PD by the medical monitor.

1.30.1. Myeloma Protein Measurements in Serum and Urine

Blood and 24-hour urine samples for M-protein measurements will be sent to and analyzed by a local laboratory until confirmed PD. The following assessments will be performed:

- Serum quantitative Igs
- Serum M-protein electrophoresis (SPEP)
- Serum immunofixation electrophoresis (SIFE)
- Serum FLC assay
- 24-hour urine M-protein electrophoresis (UPEP)
- Urine immunofixation electrophoresis (UIFE)
- Blood samples for β2-microglobulin and albumin are to be collected at Screening and will be analyzed locally.

Disease progression based on 1 of the laboratory tests alone must be confirmed by at least 1 repeat investigation. Disease evaluations will continue beyond relapse from CR until confirmed PD.

For subjects with measurable disease only by light chain criteria, SIFE, UIFE, and serum FLC will be performed at screening, at C1D1, and at every disease evaluation. For subjects with measurable disease by serum and/or urine M spike, SIFE, UIFE, and serum FLC will be performed at screening, at C1D1, and when CR is suspected (ie, when SPEP or UPEP is 0 or nonquantifiable).

Daratumumab-specific Immunofixation Electrophoresis

Daratumumab may be detected on SPEP and SIFE assays used for monitoring M-protein, which can lead to false positive SPEP and SIFE results for subjects with IgG kappa M-protein and affect assessments of responses based on IMWG response criteria.

A daratumumab-specific immunofixation electrophoresis (DSIFE) should be performed to confirm a VGPR or better in subjects with IgG kappa myeloma when daratumumab interference is suspected based on SPEP and SIFE results.

1.30.2. Imaging

Imaging will be performed to assess lytic lesions and will be interpreted locally. Any of the following are acceptable, however, the same modality should be used for the follow-up and as clinically indicated to assess for potential PD:

- Whole-body MRI
- Low-dose whole-body CT
- PET/CT with diagnostic CT component (see Attachment 5) investigations are necessary. If changes are equivocal, a repeat CT is needed in 1 to 3 weeks.

The modality used for imaging must be indicated in the eCRF. If cross-sectional imaging is obtained, images and radiology report must be made available to the medical monitor upon request.

1.30.3. Assessment of Extramedullary and Bone-based Plasmacytomas

Sites of extramedullary or bone-based plasmacytomas with soft tissue component must be documented at screening. Radiologic assessment (MRI or PET/CT with diagnostic CT component) must be used to document extramedullary or bone-based plasmacytomas. CT scan evaluations are an acceptable alternative if there is no contraindication to the use of intravenous contrast. PET scans or ultrasound tests are not acceptable to document the size of extramedullary or bone-based plasmacytomas. However, PET/CT scans can be used if the CT component of the PET/CT scan is of sufficient diagnostic quality. The modality used must allow for reporting of bidimensional measurement of the extramedullary plasmacytoma or the soft tissue component of plasmacytomas arising from the bone. To be considered measurable, both dimensions of the extramedullary plasmacytoma or the soft tissue component (external to the bone) of the bone based plasmacytoma must be at least 0.5 cm.

Extramedullary and bone-based plasmacytomas must be assessed for all subjects by radiologic assessment. Measurable sites of extramedullary disease will be assessed locally every 4 weeks in subjects where plasmacytoma is measurable on physical examination. Assessments will continue until confirmed CR or PD as long as the extramedullary plasmacytoma remains measurable on physical examination. If assessment can only be performed radiologically, then extramedullary and bone-based plasmacytomas will be assessed every 12 weeks until confirmed CR or PD. In addition, assessments will be performed as clinically indicated if PD is suspected.

The methodology used for evaluation of each disease site should be consistent across all visits and must be indicated in the eCRF. Images from cross-sectional imaging and radiology report must be made available to the medical monitor upon request. Irradiated or excised lesions will be considered not measurable and will be monitored only for PD.

To qualify for PD, either the sum of products of the perpendicular diameters of the existing extramedullary and bone-based plasmacytomas must have increased by at least 50%, or the longest diameter of a previous lesion >1 cm in short axis must have increased by at least 50%, or a new plasmacytoma must have developed. When not all existing extramedullary or bone-based plasmacytomas are reported, but the sum of the products of the perpendicular diameters of the reported plasmacytomas have increased by at least 50%, then the criterion for PD is met.

1.30.4. Bone Marrow Examination

Bone marrow aspiration and/or core biopsy (acceptable if aspirate is not possible) will be performed for disease evaluations. Disease characterization (morphology and immunohistochemistry [IHC] or immunofluorescence or flow cytometry) should be done by a local laboratory. Cytogenetics will be done by the local laboratory and should include del(17p), t(4;14), t(14;16), and amp(1q) if available. Local laboratory data will be entered into the eCRF. In the event FISH analysis does not yield diagnostic results (locally), an archived bone marrow aspirate or bone marrow clot sample may be tested for FISH analysis.

Bone marrow aspiration and/or core biopsy will also be performed to confirm CR (including sCR) Additionally, subjects in Cohort G and Cohort H will have bone marrow aspiration and/or core biopsy performed according to the Time and Events Schedules (Section 1.2).

1.30.5. Minimal Residual Disease Evaluations

MRD assessment will be done on bone marrow samples.

1.30.5.1. Minimal Residual Disease Assessment

- Bone marrow aspirates will be collected to identify the MRD clones at screening and to monitor MRD status throughout the study. Minimal residual disease will be evaluated using NGS on bone marrow aspirate DNA by a central laboratory. Once MRD negative CR/sCR is documented, repeat MRD assessment will be done yearly, until PD.
- If the MRD assessment was not done at the time of diagnosis, all attempts should be made to identify and collect non-decalcified diagnostic tissue, eg, non-decalcified slides (bone marrow aspirate or clot) or formalin-fixed, paraffin-embedded block (clot section only, no bone marrow biopsy) for NGS testing. Despite above measures, if diagnostic bone marrow sample is not available, then fresh bone marrow aspirate will be requested at screening.

After all the efforts, if a calibration clone for MRD assessment by NGS cannot be identified, subjects will be followed for MRD by NGF. NGF requires a validated analysis of 10 markers (CD38, CD138, CD45, CD19, CD27, CD56, CD81, CD117, cytoplasmic Igκ, cytoplasmic Igλ). NGF may also be used if central NGS data are not available at a particular timepoint. NGF can be performed locally if central laboratory data are not available at a particular timepoint.

In all cases where local laboratory data is used, data must be entered into the eCRF.

1.30.5.2. Minimal Residual Disease Assessment by Positron Emission Tomography/Computed Tomography Imaging (Optional)

Positron emission tomography/CT imaging is recommended at screening to establish baseline levels of metabolic tumor activity and may be used to monitor MRD status throughout the study, if locally available. The MRD assessments by PET/CT imaging, if locally available, will be done in parallel with the MRD assessments in bone marrow by NGS. Adjudication of MRD status by imaging will be performed locally by the study site. Images and radiology report must be made available to medical monitor upon request.

1.31. Safety Assessments

Adverse events will be reported and followed by the investigator as specified in Section 1.32, Adverse Events, Serious Adverse Events, and Other Safety Reporting, and Section 12.

Any clinically relevant changes occurring during the study must be recorded on the Adverse Event section of the CRF.

Any clinically significant abnormalities persisting at the end of the study cohorts/early withdrawal will be followed by the investigator until resolution or until a clinically stable condition is reached.

The study will include the following evaluations of safety and tolerability according to the time points provided in the Time and Events Schedules (Section 1.2).

1.31.1. Physical Examinations

At screening, a complete physical examination will be performed, including, at a minimum, general appearance, examination of the skin, ears, nose, throat, lungs, heart, abdomen, extremities, musculoskeletal system, neurologic system, and lymphatic system (Time and Events Schedules (Section 1.2). Neurologic exam may be performed by investigator; however it is strongly recommended to be performed by a neurologist. A complete physical examination (including a neurologic examination) will be performed prior to cilta-cel infusion on Day 1, and at least annually thereafter. All other physical examinations will be symptom-directed (including a neurologic examination) as clinically indicated (see Time and Events Schedule in Section 1.2.2, Section 1.2.3, and Section 1.2.4). Abnormalities will be recorded in the appropriate section of the eCRF.

1.31.2. Vital Signs

Temperature, pulse/heart rate, respiratory rate, blood pressure, and oxygen saturation will be assessed.

Blood pressure and pulse/heart rate measurements should be preceded by at least 5 minutes of rest in a quiet setting without distractions (eg, television, cell phones).

Subjects in Cohort G and Cohort H will be asked to check their temperature at least twice daily (entering 2 temperatures, including their maximum daily temperature, in the provided diary) for the first 28 days following cilta-cel infusion. They will be provided with a thermometer and instructed on the use of the thermometer and entering temperature in a diary. The diary will be reviewed at each visit, then collected on Day 28 after cilta-cel infusion and stored with the subject's source documents. Subjects will be instructed to report any fever (≥38°C or ≥100.4°F) to the investigator immediately to initiate monitoring for development of CRS.

1.31.2.1. Vital Signs Monitoring via Wearable Device

A subset of subjects will utilize wearable devices to continuously monitor blood oxygen level, respiratory rate, pulse rate, -, and skin temperature from the lymphodepleting chemotherapy up to Day 14. The data collected from these devices may identify onset of CRS or ICANS. Data from the patient and the site regarding the usability of the devices may be collected.

1.31.3. Electrocardiograms

Twelve-lead ECGs will be performed at screening and thereafter as clinically indicated.

During the collection of ECGs, subjects should be in a quiet setting without distractions (eg, television, cell phones). Subjects should rest in a supine position for at least 5 minutes before ECG collection and should refrain from talking or moving arms or legs. If blood sampling or vital sign measurement is scheduled for the same time point as ECG recording, the procedures should be performed in the following order: ECG(s), vital signs, blood draw.

Additional cardiovascular assessments should be performed as clinically appropriate to ensure subject safety. The clinical investigator will review the results, including ECG morphology, for immediate management. Abnormalities noted at screening should be included in the medical history.

1.31.4. Clinical Safety Laboratory Assessments

Blood samples for serum chemistry including LDH at diagnostic screening, and hematology including CD4/CD8 lymphocyte panel will be collected as noted in the Time and Event Schedule (Section 1.2.1) In addition, blood group (ABO), rhesus factor (Rh), and indirect antiglobulin test (IAT) will be performed at screening. The investigator must review the laboratory results, document this review, and record any clinically relevant changes occurring during the study in the AE section of the CRF. Subjects with Grade 3 or higher toxicity or unresolved AEs will continue to be assessed until recovery to Grade ≤1 or baseline, the event is deemed irreversible, the end of the study, or a maximum of 6 months, whichever occurs first.

Laboratory certificates or accreditation and normal ranges of the laboratory facility at the site must be submitted to the sponsor before the enrollment of any subject at the site. If the subject has the laboratory assessments conducted at a laboratory facility other than the one associated with the investigational site, the investigator must submit to the sponsor laboratory certificates or accreditation and normal ranges for that facility as well.

The laboratory reports must be filed with the source documents.

Disease-related laboratory evaluations are detailed in Section 1.30.

1.31.4.1. Indirect Antiglobulin Test

At screening, ABO and Rh typing and an IAT will be performed. Red blood cell phenotyping (standard or extended) is an alternative option to the IAT, if locally required. Daratumumab interferes with the IAT, which is a routine pre-transfusion test performed to identify a subject's antibodies to minor antigens so that suitable donor blood can be given for transfusion. Daratumumab does not interfere with ABO or Rh typing. Daratumumab binds to CD38, expressed at low levels on red blood cells (RBCs), which results in a positive IAT. This positive result masks the detection of antibodies to minor antigens and may prevent or delay blood banks from issuing donor blood for transfusion.

This effect occurs during daratumumab treatment and for up to 6 months after end of treatment.

Subjects will receive an identification wallet card for the study that includes the blood profile (ABO, Rh, and IAT or phenotyping) determined at screening along with information on the IAT interference for healthcare providers/blood banks. Subjects are to carry this card throughout DVRd induction (Cohort H) therapy and for at least 6 months after end of DVRd treatment. Blood banks can eliminate the daratumumab interference with IAT by treating reagent RBCs with dithiothreitol (DTT) (Chapuy 2015, Chapuy 2016).

Possible methods for blood banks to provide safe RBCs for transfusion to subjects receiving daratumumab include:

- Providing ABO/Rh-compatible, phenotypically (standard or extended phenotyping) or genotypically matched units
- Providing ABO/Rh-compatible, K-negative units after ruling out or identifying alloantibodies using DTT-treated reagent RBCs

Uncross matched, ABO/Rh-compatible RBC units should be administered if transfusion is needed emergently as per local blood bank practice.

Despite daratumumab binding to CD38 on RBCs, no indication of clinically significant hemolysis has been observed in daratumumab studies. For additional details, refer to the IB for daratumumab.

1.31.5. Eastern Cooperative Oncology Group Performance Status

Eastern Cooperative Oncology Group performance status will be used to evaluate the effect of the disease status on the activities of daily living (see Attachment 7).

1.31.6. Transthoracic Echocardiogram or MUGA Scan

Assessment of cardiac function using either transthoracic echocardiogram or MUGA scan is required. At a minimum, this will include assessment of left ventricular ejection fraction reported as a percentage. This value should be recorded in the eCRF.

1.31.7. Pulmonary Function Test

All subjects with known or suspected COPD must have a FEV1 test at screening. Additionally, all subjects ≥65 years of age must have FEV1 assessment at screening for confirmation of eligibility. Refer to Section 1.17.1.1 for details on subjects with higher risk of respiratory complications.

1.31.8. Neurologic Examination

Magnetic resonance imaging at screening or neurology consultation should be considered if pre-existing CNS disease is suspected. For subjects with prior pertinent neurologic disease (eg, stroke, encephalitis), neurology consultation, baseline MRI of the brain, and an EEG is recommended. At the first sign of neurotoxicity, neurology consultation and evaluation should be considered. Immune effector cell-associated neurotoxicity syndrome should be graded using American Society for Transplantation and Cellular Therapy (ASTCT) consensus grading. Other neurological AEs which could not be graded by ASTCT grading should be graded based on NCI-CTCAE version 5.0. Findings from neurological evaluation and testing that support CAR-T cell neurotoxicity (eg, ICANS) should be reported in the eCRF. Submission of neuroimaging scans may also be requested for sponsor review.

1.31.8.1. Immune Effector Cell-associated Encephalopathy Tool Scores

The ICE Tool was developed to provide objectivity for the grading of multiple overlapping encephalopathy terms currently included on the approved CAR-T products (see Attachment 3). The ICE Tool will be used to guide management of ICANS throughout the study and to grade the severity of ICANS (see Attachment 4). All ICE Tool scores must be reported in the eCRF.

1.31.8.2. Handwriting Assessment

Qualitative changes in handwriting from baseline are being explored by the medical monitor as a potential early clinical predictive marker for neurotoxicity. Currently, no standardized toxicity gradings are available in CTCAE version 5.0. for these type of changes in handwriting. Therefore, the sponsor has developed a handwriting assessment criterion to assess subjects for occurrence of the following types of changes in handwriting: micrographia, dysgraphia, or agraphia, as potential early indicators for neurotoxicity (see Attachment 17).

Handwriting assessments will be collected on a writing log as instructed by the sponsor. Subjects unable to write at baseline (≤24h prior to cilta-cel infusion) are excused from this assessment during study. The medical monitor should immediately be notified when changes in handwriting are detected. This will prompt discussion about additional assessments to further evaluate for other neurotoxicity symptoms, further work-up, as well as the potential initiation of interventions.

Changes in handwriting (ie, micrographia, dysgraphia, or agraphia) should be graded using the criteria outlined in Attachment 17 and must be reported as AEs in the eCRF (see Attachment B 1). If a subject experiences a serious CAR-T cell neurotoxicity (including, ICANS and other neurotoxicities), a copy of the handwriting assessment log should be submitted with the SAE report.

1.31.9. Pregnancy Testing

Please refer to Section 12.3.5 for more detail.

1.32. Adverse Events, Serious Adverse Events, and Other Safety Reporting

For all information related to adverse events, serious adverse events, special reporting situations, adverse events of special interests, delayed adverse events, and pregnancy, please refer to Section 12. Additional information that is specific to Cohorts G and H are presented in Section 1.32.1 below.

1.32.1. Cohort G and H Specific Adverse Event Reporting Information

All Adverse Events

In Cohorts G and H, all AEs (with the exception of delayed AEs [see Section 12], HBV reactivation and COVID-19 infection) and special reporting situations, whether serious or non-serious, will be reported as follows:

- From the time a signed and dated ICF is obtained until 30 days after the last dose of study treatment, or until Day 112 post infusion of cilta-cel (whichever is later) and regardless if PD occurs prior to Day 112 or subsequent anti-myeloma therapy is started prior to Day 112. Beyond this AE reporting period, only SAEs regardless of causality and non-serious AEs that are considered related to a study drug need to be reported until the end of the study except as defined for delayed AEs below. In addition, events of HBV reactivation and COVID-19 infection will be reported during the first-year post infusion of cilta-cel. For subjects who are unable to complete D-VRd or DRd induction, to be apheresed, or receive conditioning regimen or cilta-cel infusion, all AEs and special reporting situations, whether serious or nonserious, will be collected until 30 days after the last dose of study treatment or until PD or until the start of subsequent antimyeloma therapy, whichever occurs first.

See Attachment B 1 and Attachment B 6 for further reporting information for Cohorts G and H.

1.33. Pharmacokinetics

Blood collected for pharmacokinetics may additionally be used to evaluate safety or efficacy aspects that address concerns arising during or after the study period. Genetic analyses will not be performed on these serum samples. Subject confidentiality will be maintained.

1.33.1. Evaluations

Venous blood samples will be collected for measurement of cilta-cel-positive cellular concentrations as specified in the Time and Events Schedule. Samples will also be collected at the time of onset of suspected CRS or cilta-cel related neurotoxicity (eg, ICANS) regardless of severity or causality (as specified in the Table and Events Schedules, Section 1.2). Transgene levels of cilta-cel may be analyzed to characterize CAR transgene PK and address efficacy or safety concerns arising during or after the study period.

The exact dates and times of sampling must be recorded on the laboratory requisition form. Refer to the Laboratory Manual for sample collection requirements. Collected samples must be stored under specified controlled conditions at the temperatures indicated in the Laboratory Manual.

1.33.2. Analytical Procedures

Post-cilta-cel infusion blood samples will be analyzed to determine CAR-T positive cellular concentration based on the Time and Events Schedules (Section 1.2) using specific and sensitive assays that are validated by or under the supervision of the sponsor. PK CAR transgene blood samples may be analyzed to determine CAR transgene levels using specific and sensitive assays that are validated by or under the supervision of the sponsor.

1.33.3. Pharmacokinetic Parameters and Evaluations

Sparse cilta-cel pharmacokinetics samples may be analyzed. Individual serum concentrations versus time including descriptive statistics will be summarized if feasible. A population PK model may be applied to characterize the PK of cilta-cel, and the results will be reported separately. The PK analysis will be summarized in the clinical pharmacology analysis plan.

1.34. Genetics

Pharmacogenomics are not evaluated in this study. However, DNA may be isolated and sequenced (WES) from blood and from buccal swab for a normal sample. The normal sample will be taken at screening and used for comparison only. Cytogenetic assessments are described in Section 1.35.2.

1.35. Biomarkers

Biomarker assessments may focus on several objectives: 1) evaluate CAR-T cell subsets and activation markers including, but not limited to, CD4+, CD8+, CD25+, central memory, effector memory cells of apheresis and infused CAR-T drug product; 2) serum or plasma profiling including but not limited to cytokines (such as IL-6, IL-15, and IL-10); 3) immunophenotyping of biomarkers of response, resistance or safety (eg, BCMA and PD-L1); 4) determine the clinical benefit (ORR, duration of response, time to response, PFS, and OS) of cilta-cel in subjects with cytogenetic modifications (del(17p), t(4;14), t(14;16), amp(1q), or other high-risk molecular subtypes); and 5) immunophenotyping of immune cells subsets such as CD4+ and CD8+ T cells, regulatory T cells, B and natural killer cells. Additional biomarker samples may be collected to help understand an unexplained AE. Additional sample(s) for PK, PD and cytokines will be collected as clinically indicated (see Time and Event Schedule in Section 1.2.5).

To monitor if RCL is generated from cilta-cel, whole blood from subjects in Cohort G and Cohort H will be evaluated using a qPCR assay against the LV vesicular stomatitis virus-G gene, at approximately 3 months (Day 84), 6 months (Day 168), and 12 months (Day 364) after cilta-cel infusion (as specified in the Time and Events Schedules; Section 1.2). Yearly review of medical history will generally be sufficient for the subject for up to 15 years after cilta-cel infusion in the present study (until end of study) or a separate long-term follow-up study (68284528MMY4002). If any post-infusion samples are positive, further RCL analysis and more extensive subject follow-

up should be undertaken. Additional samples may be collected triggered by events which may be relevant, but not limited to RCL per clinical assessment, as specified in the Time and Events Schedules (Section 1.2).

Peripheral blood mononuclear cells will be retained for exploratory analysis of the immune system which may include retroviral insertion analysis, T cell receptor analysis (both clonality and/or diversity of the T cell receptor), HLA-typing, single cell DNA and/or RNA sequencing analyses (or similar technologies), functional in vitro assays, or other.

Additional Collections

Based on emerging scientific evidence, the sponsor may request additional material from, including but not limited to, previously collected whole blood, BMA or biopsy samples (including formalin-fixed paraffin embedded bone marrow clot samples, unstained bone marrow samples, non-decalcified bone marrow biopsy touch prep samples), or cerebrospinal fluid, or other tissue sample during or after study completion for retrospective analyses. For subjects diagnosed with an SPM, a tumor sample must be collected also for LV analysis. Additional samples (including but not limited to blood, tissue, tumor, etc.) may be requested as clinically indicated. Additionally, the sponsor will receive a sample of plasmacytoma if a plasmacytoma biopsy is performed for any reason. Subjects who have a lumbar puncture as part of their neurologic work up should have cerebrospinal fluid sent for additional tests by the sponsor. In all cases, such analyses would be specific to research related to the study treatment(s) or diseases being investigated. If a subject dies and an autopsy is performed, specimens may be requested by the sponsor for analysis.

Stopping Analysis

Biomarker analyses are dependent upon the availability of appropriate biomarker assays and may be deferred or not performed, if during or at the end of the study, it becomes clear that the analyses will not have sufficient scientific value for biomarker evaluation, or if there are not enough samples or responders to allow for adequate biomarker evaluation. In the event the study is terminated early or shows poor clinical efficacy, completion of biomarker assessments is based on justification and intended utility of the data.

1.35.1. Pharmacodynamics/Predictive Markers

Baseline characteristics of the cilta-cel cell subsets and dynamic changes/persistence and activation of the CAR-positive viable T cells may be associated with the depth and durability of response, resistance, or safety. An evaluation of these cell populations may be performed by flow cytometry, CyTOF, scRNAseq or similar technologies and be correlated with response, resistance, or safety. Additional immunophenotyping may be performed on whole blood samples or its derivatives, to evaluate expression of biomarkers on myeloma cells (such as BCMA and PD-L1) and immune cell populations (such as CD4+ and CD8+ T cells and T cell subsets within CD4 and CD8) by flow cytometry, CyTOF or next generation sequencing (NGS; WES and (sc)RNA sequencing) or both. T cell receptor sequencing (TCRseq) may be performed to study T cell clonality and diversity that may affect drug response. HLA analyses may be performed to evaluate associations between HLA and potential (autoimmune) neurological diseases. Samples may be characterized by gene expression profiling and somatic mutation analysis by NGS (WES and

(sc)RNA sequencing) to evaluate potential biomarkers that may correlate with response, resistance, or safety. Samples may be evaluated by other similar technologies to evaluate protein or RNA expression or for somatic DNA analysis.

Circulating serum biomarkers present following conditioning therapy and CAR-T cell infusion have been associated with response in other CAR-T cell-based therapies. Cytokines (such as IL-6 and IFNγ) and other circulating proteins (such as granzyme or perforin) may be analyzed to identify potential pharmacodynamic and predictive biomarkers of response, resistance, or safety.

1.35.2. High-risk Classification by Cytogenetics

Bone marrow aspirate samples should be evaluated locally as specified in the Time and Events Schedules (Section 1.2) for translocation/mutation/genomic analysis (DNA/RNA) to assess whether specific high-risk molecular subgroups such as del(17p), t(4;14), t(14;16), and amp(1q) if available are responsive to cilta-cel treatment. Results should be entered on the relevant eCRF page. The clinical benefit (ORR, PFS, and OS) of cilta-cel in subjects with these cytogenetic modifications or other high-risk molecular subtypes may be determined.

1.36. Immunogenicity Assessments

Antibodies to JNJ-68284528 will be evaluated in serum samples collected from all subjects in Cohort G and Cohort H according to the Time and Events Schedules (Section 1.2) Samples will also be collected at the time of onset of suspected CRS or CAR-T cell-related neurotoxicity (eg, ICANS) regardless of causality (see Time and Event Schedule in Section 1.2.5). These samples will be tested by the sponsor or sponsor's designee. The exact dates and times of blood sampling must be recorded on the laboratory requisition form. Refer to the Laboratory Manual for sample collection requirements. Collected samples must be stored under specified controlled conditions at the temperatures indicated in the Laboratory Manual.

Cilta-cel PK will also be determined to aid in the interpretation of immunogenicity data. These samples will be stored and evaluated if deemed necessary.

Serum samples will be screened for antibodies binding to JNJ-68284528 and the titer of confirmed positive samples will be reported. Other analyses may be performed to further characterize the immunogenicity of JNJ-68284528.

Serum samples will be used to evaluate the immunogenicity of anti-JNJ-68284528 antibodies. Samples collected for immunogenicity analyses may additionally be used to evaluate safety or efficacy aspects that address concerns arising during or after the study period. Genetic analyses will not be performed on these serum samples. Subject confidentiality will be maintained.

Analytical Procedures

The detection and characterization of antibodies to JNJ-68284528 will be performed using a validated assay by or under the supervision of the sponsor. Other analyses may be performed to characterize immunogenicity.

1.37. STATISTICAL CONSIDERATIONS

Statistical analysis will be done by the sponsor or under the authority of the sponsor. A general description of the statistical methods to be used to analyze the efficacy and safety data is outlined below. Specific details will be provided in the Statistical Analysis Plan.

1.38. Statistical Hypotheses

No formal statistical hypotheses are planned to be tested in this study.

1.39. Subject Analysis Sets

For purposes of analysis, the following analysis sets are defined.

Analysis Sets	Description
Enrolled	All subjects who sign the ICF and take at least 1 dose of study treatment or undergo apheresis
Full analysis set (FAS)	All subjects who received at least a dose of induction therapy and received a cilta-cel infusion as study treatment
Modified full analysis set	All subjects who received at least a dose of induction therapy and received a cilta-cel infusion as study treatment at the targeted dose (ie, within target dose range)
Safety	All subjects who take at least 1 dose of study treatment.

1.40. Statistical Analyses

The statistical analysis plan will be finalized prior to database lock, and it will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of the most important endpoints including primary and key secondary endpoints.

1.40.1. General Considerations

Statistical analysis will be performed for each cohort independently.

Continuous variables will be summarized using the number of observations, mean, standard deviation, coefficient of variation, median, and range as appropriate. Categorical values will be summarized using the number of observations and percentages as appropriate.

1.40.2. Primary Endpoint(s)/Estimands

The primary endpoint is sustained MRD negative CR status with disease response according to the IMWG criteria (Durie 2006; Durie 2015; Rajkumar 2011) as assessed by the computerized algorithm (Palumbo 2016) and MRD status determined by NGS or NGF with a sensitivity of at least 10^{-5}.

Primary Estimand

The primary estimand, the main clinical quantity of interest to be estimated in the study, is defined by the following 5 components:

- Treatment: Treatment condition of interest is the sequence of induction therapy, conditioning regimen and cilta-cel
- Population:
  - Cohort G (DRd induction followed by cilta-cel): Subjects with NDMM for whom for whom transplant is not planned
  - Cohort H (D-VRd induction followed by cilta-cel): Subjects with NDMM who are transplant eligible
- Variable: Sustained MRD negative CR, with disease response assessed by computerized algorithm according to the IMWG criteria and MRD status determined by NGS or NGF with a sensitivity of at least 10-5
- Intercurrent event (strategy):
  - Subsequent antimyeloma therapy (while on treatment strategy)
  - Treatment discontinuation (treatment policy strategy)
- Population-level summary: Sustained MRD negative CR rate

For both Cohorts G and H, the primary analysis will be conducted approximately at 1.5 year after the last subject in that cohort started their study treatment. The final analysis will be conducted at cohort completion, which is defined as approximately 2.5 years after the last subject in that cohort has started their study treatment. In addition, for Cohort G only, a first analysis may be conducted at approximately 6 to 12 months after the last subject in that cohort started their study treatment. If the first analysis is performed, it may become the primary analysis. The sustained MRD negative CR rate and its 95% exact confidence interval (CI) will be calculated based on binomial distribution and will be based on the modified full analysis set.

1.40.3. Secondary Endpoint(s)/Estimands

The secondary efficacy endpoints are defined as follows:

- CR or better status: achieving a CR or better according to the IMWG criteria.
- Overall response status: achieving a PR or better according to the IMWG criteria.
- Overall MRD-negative CR status: achieving MRD-negative CR according to the IMWG criteria and NGS or NGF with a sensitivity of at least 10^{-5}.
- Duration of response (DOR) will be calculated among responders (with a PR or better response) from the date of initial documentation of a response (PR or better) to the date of first documented evidence of progressive disease, as defined in the IMWG criteria. Relapse from CR by positive immunofixation or trace amount of M-protein is not considered as disease progression. Disease evaluations will continue beyond relapse from CR until disease progression is confirmed. For subjects who have not progressed, data will be censored at the last disease evaluation before the start of any subsequent anti-myeloma therapy.
- Time to response (TTR) is defined as the time between the start of study treatment and the first efficacy evaluation that the subject has met all criteria for PR or better.

- Progression-free survival (PFS) defined as the time from the start of study treatment to the date of first documented disease progression, as defined in the IMWG criteria, or death due to any cause, whichever occurs first. For subjects who have not progressed and are alive, data will be censored at the last disease evaluation before the start of any subsequent anti-myeloma therapy.
- Time to subsequent anti-myeloma treatment is defined as the time from start of study treatment to the start of subsequent anti-myeloma treatment. Death due to PD without the start of any subsequent therapy will be considered as event. Subjects who withdrew consent to study or were lost to follow-up or die due to causes other than PD will be censored at the date of death, or the last date known to be alive.
- PFS on next-line therapy (PFS2) is defined as the time interval between the start of study treatment and date of event, which is defined as death from any cause or PD as assessed by investigator that starts after the next line of therapy, whichever occurs first. Subjects who start next line of subsequent therapy without disease progression on study treatment will be censored at the last disease assessment before starting next line of therapy. For subjects who start next line of therapy after progression on study treatment, are still alive and not yet progress on next line of therapy, they will be censored on the last date of follow-up. Subjects without any post-baseline follow-up will be censored at study treatment start.
- Overall survival (OS) is measured from the start of study treatment to the date of the subject's death. If the subject is alive or the vital status is unknown, then the subject's data will be censored at the date the subject was last known to be alive.

1.40.4. Tertiary/Exploratory/Other Endpoint(s)/Estimand Analysis

The statistical analysis methods for the exploratory efficacy endpoints will be described in the SAP.

1.40.5. Safety Analyses

All safety analyses will be made on the Safety Analysis Set.

Adverse Events

The verbatim terms used in the CRF by investigators to identify AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Any new or worsening AE occurring at or after the initial administration of study treatment through the day of last dose plus 112 (if cilta-cel) or 30 (if non-cilta-cel study treatment) days or prior to the start of subsequent anticancer therapy, whichever is earlier, *or* any follow-up AE (linked to an existing TEAE) with onset date and time beyond 112 (if cilta-cel) or 30 (if non-cilta-cel study treatment) days after the last dose of study treatment but prior to the start of subsequent therapy *or* any AE that is considered treatment-related regardless of the start date of the event, is considered to be treatment-emergent. All reported treatment-emergent AEs will be included in the analysis. For each AE, the percentage of subjects who experience at least 1 occurrence of the given event will be summarized.

Summaries, listings, datasets, or subject narratives may be provided, as appropriate, for those subjects who die, who discontinue treatment due to an AE, or who experience a severe or an SAE.

Parameters with predefined National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) toxicity grades will be summarized except for CRS and ICANS. Cytokine release syndrome grading will be evaluated and summarized according to the ASTCT consensus grading (See Attachment 2; Lee 2019). ICANS will be graded and summarized using the ASTCT consensus grading (Attachment 4). In addition, all individual symptoms of CRS (eg, fever, hypotension) and ICANS (eg, depressed level of consciousness, seizures) captured as individual AEs and graded by CTCAE criteria will be also summarized. Neurotoxicity that is not temporally associated with CRS, or any other neurologic AEs that do not qualify as ICANS, will be graded and summarized by CTCAE criteria. Changes in handwriting will be graded using the criteria in Attachment 17. Change from baseline to the worst AE grade experienced by the subject during the study will be provided as shift tables.

Clinical Laboratory Tests

Laboratory data will be summarized by type of laboratory test. Reference ranges and markedly abnormal results (specified in the Statistical Analysis Plan) will be used in the summary of laboratory data. Descriptive statistics will be calculated for each laboratory analyte at baseline and for observed values and changes from baseline at each scheduled time point. Changes from baseline results will be presented in pre- versus post-treatment cross-tabulations (with classes for below, within, and above normal ranges). A listing of subjects with abnormal laboratory results may be provided as defined in the SAP.

Electrocardiogram

Electrocardiogram data will be summarized by ECG parameter. Descriptive statistics will be calculated at baseline and for observed values and changes from baseline at each scheduled time point. Frequency tabulations of the abnormalities will be made.

Descriptive statistics of QTc intervals and changes from baseline will be summarized at each scheduled time point. The percentage of subjects with QTc interval >450 milliseconds, >480 milliseconds, or >500 milliseconds will be summarized, as will the percentage of subjects with QTc interval increases from baseline >30 milliseconds or >60 milliseconds.

All clinically relevant abnormalities in ECG waveform that are changes from the baseline readings will be reported (eg, changes in T-wave morphology or the occurrence of U-waves).

Vital Signs

Vital signs including temperature, pulse/heart rate, respiratory rate, oxygen saturation, and blood pressure (systolic and diastolic) will be summarized over time, using descriptive statistics and/or graphically. The percentage of subjects with values beyond clinically important limits will be summarized.

1.40.6. Other Analyses

1.40.6.1. Pharmacokinetic Analyses

If feasible, population PK analysis of plasma, serum, whole blood, concentration-time data of JNJ-68284528 may be performed using nonlinear mixed-effects modeling. Data may be combined with those of other selected studies to support a relevant structural model. Available baseline subject characteristics (demographics, laboratory variables, genotypes, race, etc.) will be tested as potential covariates affecting PK parameters. Details will be given in a population PK analysis plan and the results of the population PK analysis will be presented in a separate report.

A snapshot date for PK samples to be analyzed will be defined, if required. Samples collected before this date will be analyzed for JNJ-68284528 and included in the population PK analysis. Samples collected after the snapshot date will be analyzed at a later date and may be included in a population PK re-analysis when they become available after database lock.

All concentrations below the lowest quantifiable concentration or missing data will be labeled as such in the concentration database. All subjects and samples excluded from the analysis will be clearly documented in the study report.

Concentrations below the lower quantifiable concentration will be treated as zero in the summary statistics. All subjects and samples excluded from the analysis will be clearly documented in the Clinical Study Report.

Correlation of maximum peripheral blood concentration (C_{max}) and area under the peripheral blood concentration-time curve (AUC) with dose may also be explored. Pharmacokinetic parameters include, but are not limited to, AUC from time 0 to t (AUC[0-t]), Cmax, half-life, and time to reach maximum peripheral blood concentration (T_{max}) parameters may be calculated if sufficient data are available for estimation.

Descriptive statistics will be used to summarize CAR-T positive cell count and transgene level, if available, at each sampling timepoint.

If sufficient data are available, population PK analysis of peripheral cilta-cel transgene level-time data may be performed. If the population PK- analysis is conducted, details will be given in a population-PK analysis plan and the results of the analysis will be presented in a separate report. Exposure-response analyses may also be performed; if performed, details will be provided in a separate analysis plan and report.

1.40.6.2. Biomarkers Analyses

Descriptive statistics may be calculated for each biomarker at baseline and for observed values and changes from baseline (as applicable) at each scheduled time point. Biomarker association to PK, safety, and/or efficacy may also be evaluated. If conducted, details will be given in the statistical analysis plan or a separate biomarker analysis plan, and results of analyses may be presented in the clinical study report or in a separate biomarker report.

1.40.6.3. Immunogenicity Analyses

The incidence of anti-JNJ-68284528 antibodies will be summarized for all subjects who receive at least 1 dose of JNJ-68284528 and have appropriate samples for detection of antibodies to JNJ-68284528 (ie, subjects with at least 1 sample obtained the infusion of cilta-cel).

Immunogenicity analyses will be descriptive in nature and will include the number and percentage of subjects who developed anti-cilta-cel antibodies. The effect of anti-cilta-cel antibodies on pharmacokinetics, safety, and efficacy may also be evaluated.

1.40.6.4. Pharmacokinetic/Pharmacodynamic Analyses

Pharmacokinetic/pharmacodynamic modeling may be performed, including exploring the relationship between serum concentrations of cilta-cel and endpoints of clinical efficacy or safety. Details and results of any analysis performed will be presented in a separate report.

1.40.6.5. Benefit-risk Analyses

Benefit-risk assessment is the evaluation of the demonstrated benefits and harms of a medicinal product and making a judgment as to whether the expected key benefits outweigh the potential key risks associated with its expected use. Benefit-risk assessment is inherently a comparison between treatment alternatives. Given the absence of a comparator arm in the CARTITUDE-2 study, only exploratory, qualitative benefit-risk analyses on the treatment arm with no treatment alternative will be conducted. The B-R analyses are not intended for hypothesis testing.

Benefit-risk assessment of cilta-cel for subjects with NDMM will be assessed using a structured framework approach. Benefits in the assessment may include the primary and secondary efficacy endpoints. Risks in the assessment may include clinically meaningful, treatment-emergent AEs or adverse drug reactions. Outcomes used in the B-R assessment might be adapted from outcomes used in the primary analyses. Benefit-Risk assessment may evaluate time of first occurrence of key outcomes, incidence proportions, and event rates per subject-years.

The benefit-risk assessment will be evaluated over the same study duration as the primary analysis. Benefit-risk analyses will be conducted separately for Cohort G and Cohort H.

1.41. Interim Analysis

Not applicable.

1.42. Sample Size Determination

No formal statistical hypothesis testing will be performed. Approximately 40 and up to 100 subjects will be enrolled in each cohort. If 40 subjects are enrolled per cohort, the 95% confidence interval (CI) and the width of CI under different observed sustained (≥12 months) MRD negative CR rate scenarios are tabulated below.

Observed Number of Subjects Achieving Sustained MRD Negative CR Status	Observed Sustained MRD Negative CR Rate	95% Exact CI	Width of 95% CI
26	65%	(48%, 79%)	31%
28	70%	(53%, 83%)	30%
30	75%	(59%, 87%)	28%
32	80%	(64%, 91%)	27%
34	85%	(70%, 94%)	24%

Assuming the true underlying sustained (≥12 months) MRD negative CR rate is 65%, the probability of observing a sustained MRD negative CR rate ≥55% is at least 90% with a sample size of 40.

19. ATTACHMENTS SPECIFIC TO PART B

Attachment B 1: Adverse Event Reporting Guidance for Study 68284528MMY2003 Cohorts G and H

Reporting Guidelines for Adverse Events for Cohort G and Cohort H in eCRF:

<table>
<tr><th colspan="5">Duration of Study 2003, Part B</th><th rowspan="2">LTFU Study: Up to 15 Years after Cilta-Cel</th></tr>
<tr><th>Signing of ICF</th><th>Day 1 Cilta-Cel</th><th>Day 112 Post Cilta-Cel</th><th>1 Year Post Cilta-Cel</th><th>End of Study</th></tr>
<tr><td colspan="3">All AEs, regardless of causality</td><td colspan="2">Related AEs, per investigator</td><td></td></tr>
<tr><td colspan="6">All SAEs (regardless of causality)</td></tr>
<tr><td rowspan="6"></td><td colspan="5">SPMs (all grades, regardless of causality or seriousness)[a,b]</td></tr>
<tr><td colspan="3">HBV Reactivation (all grades, regardless of causality or seriousness)</td><td colspan="2">≥Grade 3 HBV Reactivation (regardless of causality or seriousness)</td></tr>
<tr><td colspan="3">COVID-19 Infection, all grades (including asymptomatic COVID-19)</td><td colspan="2">≥Grade 3 COVID-19 Infection (regardless of causality or seriousness)</td></tr>
<tr><td colspan="5">New or Exacerbation of Neurologic Disorder (all grades, regardless of causality or seriousness)</td></tr>
<tr><td colspan="5">New or Exacerbation of Autoimmune Disorder (all grades, regardless of causality or seriousness)</td></tr>
<tr><td colspan="5">≥Grade 3 Hematologic Disorder (regardless of causality or seriousness)</td></tr>
<tr><td colspan="5">≥Grade 3 Infection (regardless of causality or seriousness)</td></tr>
</table>

[a] For reporting purposes, this includes both new primary malignancies and recurrence of pre-existing malignancies with the exception of recurrent multiple myeloma (ie, disease progression).

[b] In the event of malignancy, a tumor sample should be collected and vector integration site analysis may be performed for possible insertional mutagenesis.

Expedited Reporting Guidelines for Cohorts G and H to Sponsor GMS:

Duration of Cohort G and Cohort H		
Signing of ICF	**Day 1 Cilta-Cel**	**End of Study**
Expedited Reporting* of all SAEs (regardless of causality) for duration of study.	Expedited Reporting* of all SAEs, and following AESIs (regardless of causality or seriousness): • ≥Grade 3 CRS • ≥Grade 3 Neurotoxicity • Any grade movement and neurocognitive toxicity (ie, parkinsonism) • SPMs (any grade)	

* Expedited reporting includes reporting to Sponsor Global Medical Safety within 24 hours via SAE Fax Form or other defined SAE reporting process per protocol.

Attachment B 2: Clinical Laboratory Tests

The following tests will be performed according to the Time and Events Schedules by the local laboratory:

The actual date of assessment and, if required, the actual time of the assessment of laboratory samples will be recorded in the source documentation and in the eCRF or laboratory requisition form.

Protocol-Required Laboratory Assessments

Laboratory Assessments	Parameters	
CBC with differential	Hemoglobin White Blood Cell (WBC) Platelet count	Absolute lymphocyte count Absolute neutrophil count
CD4/CD8 Lymphocyte Panel	Absolute number and % CD4 Absolute number and % CD8	CD4/CD8 ratio
Coagulation	Prothrombin time/International normalized ratio Fibrinogen[e]	Activated partial thromboplastin time D-dimer
Full Metabolic Panel	Sodium Potassium Lactic acid dehydrogenase (LDH) Blood urea nitrogen (BUN) or urea Creatinine Glucose Aspartate aminotransferase (AST) Alanine aminotransferase (ALT)	Total bilirubin (+ direct bilirubin[a] for screening) Total protein Alkaline phosphatase Uric acid Albumin Phosphate Calcium eGFR[b]
CAR-T Chemistry	Sodium Potassium LDH BUN or urea Creatinine Glucose AST ALT Total bilirubin (+ direct bilirubin[a] for screening) Total protein Triglycerides	Alkaline phosphatase Uric acid Albumin Phosphate Calcium Gamma-glutamyltransferase (GGT) Ferritin Magnesium Creatine phosphokinase (CPK) C-reactive protein eGFR [c] Fibrinogen[e]
Pregnancy Test	Serum (<25 IU/mL) β-hCG or urine	
Serology	• Hepatitis B[d]: HBsAg, anti-HBc, anti-HBs, HBV-DNA quantification (for subjects who are anti-HBs positive without history of vaccination or for subjects who are anti-HBc positive with or without anti-HBs positive) (Attachment 15) • Hepatitis C: HCV antibody, HCV-RNA (for subjects who are anti-HCV positive) • HIV	
Tests for subjects at risk for HBV reactivation	HBV-DNA, ALT, AST	

Laboratory Assessments	Parameters
Tests within 60 days prior to apheresis	HIV, Hepatitis B, Hepatitis C, HTLV, and other infectious disease (eg, CMV, EBV, HSV, HHV, VZV) as applicable per local regulations
COVID-19 antibody titer (optional)	As applicable per institutional standards, up to 1 year post cilta-cel infusion.

Abbreviations: ALT=alanine aminotransferase; AST=aspartate aminotransferase; β-hCG=β-human chorionic gonadotropin; CAR-T=chimeric antigen receptor T-cell; CBC=complete blood count; CMV=cytomegalovirus; EBV=Epstein Barr virus; eGFR=estimated glomerular filtration rate; HBsAg=hepatitis B surface antigen; anti-HBc=anti-hepatitis B core antibody, anti-HBs=anti-hepatitis B surface antibody; HCV=hepatitis C virus; HHV=human herpes virus; HSV=herpes simplex virus; HTLV= human T-lymphotropic virus; MDRD=Modification of Diet in Renal Disease; VZV=Varicella-zoster virus.

a. Direct bilirubin if Gilbert's disease.
b. Calculated using MDRD formula (see Attachment B 4) only to be included at screening.
c. Calculated using MDRD formula (see Attachment 8) only to be included prior to conditioning regimen.
d. See Attachment 10 to determine eligibility for enrollment in the study and additional safety monitoring recommendations.
e. Fibrinogen only needs to be collected once if both panels (coagulation and CAR-T chemistry) need to be collected (for example, CAR-T Day 1).

Attachment B 3: Myeloma Frailty Score Calculator

MYELOMA FRAILTY SCORE CALCULATOR

Developed by International Myeloma Working Group for the prognosis of elderly myeloma patients.

The score system (range 0-5), based on age, comorbidities, cognitive and physical conditions, developed by Palumbo (2015), identifies 3 groups of patients:

- fit (score=0)
- intermediate-fitness (score=1)
- frail (score≥2)

The 3-year overall survival was 84% in fit patients, 76% in intermediate-fitness patients (HR 1.61, 95% CI 1.02-2.56, p=0.042) and 57% in frail patients (HR 3.57 CI 95% 2.37-5.39, p<0.001). The cumulative incidence of grade ≥3 non-hematologic AEs at 12 months was 22.2% in fit, 26.4% in intermediate-fitness (HR 1.23, 95%CI 0.89-1.71; p 0.217) and 34.0% (HR 1.74, 95%CI 1.28-2.38; p<0.001) in frail patients. The cumulative incidence of treatment discontinuation at 12 months was 16.5% in fit, 20.8% in intermediate-fitness (HR 1.41, 95%CI 1.00-2.01, p=0.052) and 31.2% (HR 2.21, 95%CI 1.57-3.09; p<0.001) in frail patients.

This frailty score predicts mortality and the risk of toxicity in elderly myeloma patients. The International Myeloma Working group proposes this score for the measurement of frailty in the treatment decision-making process and in designing future clinical trials.

The myeloma frailty final score (0, 1, ≥2) developed by Palumbo (2015) is calculated based on age and 3 different assessment scales as presented in table below. The 3 assessment scales are: Katz Index of Independence in Activities of Daily Living (ADL), Lawton-Brody Instrumental Activities of Daily Living Scale (IADL), and Charlson Comorbidity Index (CCI) (see Attachment B 3).

Calculation of the myeloma frailty final score:

	Score
Age, y	
≤75	0
76-80	1
>80	2
ADL	
>4	0
≤4	1
IADL	
>5	0
≤5	1
CCI	
≤1	0
≥2	1

ADL=Activities of Daily Living; CCI=Charlson Comorbidity Index;
IADL=Instrumental Activities of Daily Living Scale

Katz Index of Independence in Activities of Daily Living

Katz Index of Independence in Activities of Daily Living		
Activities Points (1 or 0)	**Independence** (1 Point) **NO** supervision, direction or personal assistance.	**Dependence** (0 Points) **WITH** supervision, direction, personal assistance or total care.
BATHING Points: _____	**(1 POINT)** Bathes self completely or needs help in bathing only a single part of the body such as the back, genital area or disabled extremity.	**(0 POINTS)** Need help with bathing more than one part of the body, getting in or out of the tub or shower. Requires total bathing
DRESSING Points: _____	**(1 POINT)** Get clothes from closets and drawers and puts on clothes and outer garments complete with fasteners. May have help tying shoes.	**(0 POINTS)** Needs help with dressing self or needs to be completely dressed.
TOILETING Points: _____	**(1 POINT)** Goes to toilet, gets on and off, arranges clothes, cleans genital area without help.	**(0 POINTS)** Needs help transferring to the toilet, cleaning self or uses bedpan or commode.
TRANSFERRING Points: _____	**(1 POINT)** Moves in and out of bed or chair unassisted. Mechanical transfer aids are acceptable	**(0 POINTS)** Needs help in moving from bed to chair or requires a complete transfer.
CONTINENCE Points:	**(1 POINT)** Exercises complete self control over urination and defecation.	**(0 POINTS)** Is partially or totally incontinent of bowel or bladder
FEEDING Points: _____	**(1 POINT)** Gets food from plate into mouth without help. Preparation of food may be done by another person.	**(0 POINTS)** Needs partial or total help with feeding or requires parenteral feeding.
TOTAL POINTS: _____	**SCORING:** 6 = High (*patient independent*) 0 = Low (*patient very dependent*	

1. Katz S, Ford AB, Moskowitz RW, et al. Studies of Illness in the Aged. The Index of ADL: A Standardized Measure of Biological and Psychosocial Function. JAMA. 1963;185(12):914-919.

Lawton-Brody Instrumental Activities of Daily Living Scale (IADL)

The Lawton Instrumental Activities of Daily Living Scale

A. Ability to Use Telephone

1. Operates telephone on own initiative; looks up and dials numbers 1
2. Dials a few well-known numbers 1
3. Answers telephone, but does not dial 1
4. Does not use telephone at all 0

B. Shopping

1. Takes care of all shopping needs independently 1
2. Shops independently for small purchases 0
3. Needs to be accompanied on any shopping trip 0
4. Completely unable to shop 0

C. Food Preparation

1. Plans, prepares, and serves adequate meals independently 1
2. Prepares adequate meals if supplied with ingredients 0
3. Heats and serves prepared meals or prepares meals but does not maintain adequate diet 0
4. Needs to have meals prepared and served 0

D. Housekeeping

1. Maintains house alone with occasion assistance (heavy work) 1
2. Performs light daily tasks such as dishwashing, bed making 1
3. Performs light daily tasks, but cannot maintain acceptable level of cleanliness 1
4. Needs help with all home maintenance tasks 1
5. Does not participate in any housekeeping tasks 0

E. Laundry

1. Does personal laundry completely 1
2. Launders small items, rinses socks, stockings, etc. 1
3. All laundry must be done by others 0

F. Mode of Transportation

1. Travels independently on public transportation or drives own car 1
2. Arranges own travel via taxi, but does not otherwise use public transportation 1
3. Travels on public transportation when assisted or accompanied by another 1
4. Travel limited to taxi or automobile with assistance of another 0
5. Does not travel at all 0

G. Responsibility for Own Medications

1. Is responsible for taking medication in correct dosages at correct time 1
2. Takes responsibility if medication is prepared in advance in separate dosages 0
3. Is not capable of dispensing own medication 0

H. Ability to Handle Finances

1. Manages financial matters independently (budgets, writes checks, pays rent and bills, goes to bank); collects and keeps track of income 1
2. Manages day-to-day purchases, but needs help with banking, major purchases, etc 1
3. Incapable of handling money 0

Scoring: For each category, circle the item description that most closely resembles the client's highest functional level (either 0 or 1).

Lawton MP, Brody EM. Assessment of older people: self-maintaining and instrumental activities of daily living. Gerontologist. 1969;9(3):179-186.

Charlson Comorbidity Index

Score	Condition
1	Myocardial infarction (history, not ECG changes only)
	Congestive heart failure
	Peripheral vascular disease (includes aortic aneurysm ≥6 cm)
	Cerebrovascular disease: CVA with mild or no residua or TIA
	Dementia
	Chronic pulmonary disease
	Connective tissue disease
	Peptic ulcer disease
	Mild liver disease (without portal hypertension, includes chronic hepatitis)
	Diabetes without end-organ damage (excludes diet-controlled alone)
2	Hemiplegia
	Moderate or severe renal disease
	Diabetes with end-organ damage (retinopathy, neuropathy, nephropathy, or brittle diabetes)
	Tumor without metastases (exclude if >5 y from diagnosis)
	Leukemia (acute or chronic)
	Lymphoma
3	Moderate or severe liver disease
6	Metastatic solid tumor
	AIDS (not just HIV positive)

Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis. 1987; 40(5):373-383.

Attachment B 4: New York Heart Association Functional Classification

NYHA Class	Symptoms
I	Cardiac disease, but no symptoms and no limitation in ordinary physical activity (eg, shortness of breath when walking or climbing stairs).
II	Mild symptoms (mild shortness of breath or angina) and slight limitation during ordinary activity.
III	Marked limitation in activity due to symptoms, even during less-than-ordinary activity (eg, walking short distances [20–100 m]). Comfortable only at rest.
IV	Severe limitations. Experiences symptoms even while *at rest*. Mostly bedbound patients.

Attachment B 5: Body Surface Area Calculation

BSA should be calculated using the Mosteller Formula (shown below); however, the DuBois Formula can be used as an alternative.

$$\text{BSA} = \sqrt{\frac{Ht(inches) \times Wt(lbs)}{3131}}$$

or

$$\text{BSA} = \sqrt{\frac{Ht(cm) \times Wt(kg)}{3600}}$$

Attachment B 6: Adverse Events, Serious Adverse Events, Product Quality Complaints, and Other Safety Reporting: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

Procedures

All Adverse Events

All AEs, regardless of seriousness, severity, or presumed relationship to study treatment, must be recorded using medical terminology in the source document and the CRF. Whenever possible, diagnoses should be given when signs and symptoms are due to a common etiology (eg, cough, runny nose, sneezing, sore throat, and head congestion should be reported as "upper respiratory infection"). Investigators must record in the CRF their opinion concerning the relationship of the AE to study therapy. All measures required for AE management must be recorded in the source document and reported according to sponsor instructions.

For all studies with an outpatient phase, including open-label studies, the subject must be provided with a "wallet (study) card" and instructed to carry this card with them for the duration of the study indicating the following:

- Study number
- Statement, in the local language(s), that the subject is participating in a clinical study
- Investigator's name and 24-hour contact telephone number
- Local sponsor's name and 24-hour contact telephone number (for medical personnel only)
- Site number
- Subject number
- Any other information that is required to do an emergency breaking of the blind

Serious Adverse Events

All SAEs that have not resolved by the end of the study, or that have not resolved upon the subject's discontinuation from the study, must be followed until any of the following occurs:

- The event resolves
- The event stabilizes
- The event returns to baseline, if a baseline value/status is available
- The event can be attributed to agents other than the study treatment or to factors unrelated to study conduct
- It becomes unlikely that any additional information can be obtained (subject or health care practitioner refusal to provide additional information, lost to follow-up after demonstration of due diligence with follow-up efforts)

Any event requiring hospitalization (or prolongation of hospitalization) that occurs during participation in the study must be reported as an SAE, except hospitalizations for the following:

- Routine monitoring hospitalizations post-infusion required per protocol
- Hospitalizations not intended to treat an acute illness or AE (eg, social reasons such as pending placement in long-term care facility)
- Surgery or procedure planned before entry into the study (must be documented in the CRF). Note: Hospitalizations that were planned before the signing of the ICF, and where the underlying condition for which the hospitalization was planned has not worsened, will not be considered SAEs. Any AE that results in a prolongation of the originally planned hospitalization is to be reported as a new SAE.
- The investigator may choose to hospitalize the subject per institutional standards for CART therapy and in accordance to the criteria provided in Attachment 4.
- The administration of blood or platelet transfusions. Hospitalization or prolonged hospitalization for a complication of such transfusion remains a reportable SAE.
- Following treatment with daratumumab, if a subject is hospitalized overnight for observation, but has not experienced a significant medical event, that hospitalization should not be reported as an SAE.

Expected progression of disease should not be considered an AE (or SAE). However, the clinical signs or symptoms of progression and the possibility that the study treatment is enhancing PD, should be reported per the usual reporting requirements.

All deaths not related to PD occurring at any time of the study after receiving cilta-cel, should be reported to the sponsor following expedited reporting procedures.

Expected progression of disease should not be considered an AE (or SAE). However, if determined by the investigator to be more likely related to the study treatment than the underlying disease, the clinical signs or symptoms of progression and the possibility that the study treatment is enhancing disease progression, should be reported per the usual reporting requirements.

Information regarding SAEs will be transmitted to the sponsor using an SAE reporting form and safety report form of the CRF, which must be completed and reviewed by a physician from the study site and transmitted in a secure manner to the sponsor immediately, but no later than within 24 hours of their knowledge of the event. The initial and follow-up reports of an SAE should be transmitted in a secure manner electronically or by facsimile (fax). Telephone reporting should be the exception and the reporter should be asked to complete the appropriate form(s) first.

Severity Criteria

An assessment of severity grade will be made by the investigator according to the NCI-CTCAE Version 5.0, except for CRS and CAR-T cell-related neurotoxicity (eg, ICANS). Cytokine release syndrome should be evaluated according to the ASTCT consensus grading (Attachment 2). CAR-T cell-related neurotoxicity (eg, ICANS) should be graded using the ASTCT consensus grading (Attachment 3). Changes in handwriting (ie, micrographia, dysgraphia, or agraphia) should be

graded using the criteria outlined in Attachment 17. Other neurotoxicities will be graded by CTCAE criteria. Any AEs or SAEs not listed in the NCI-CTCAE Version 5.0 should be evaluated for severity/intensity by using the standard grades as follows:

Grade 1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
Grade 2	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living.*
Grade 3	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living.**
Grade 4	Life-threatening consequences; urgent intervention indicated.
Grade 5	Death related to AE.

Activities of Daily Living (ADL)

* Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

** Self-care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

All Grade 3 or 4 AEs that have not resolved by the protocol-defined adverse event collection period, or that have not resolved upon discontinuation of the subject's participation in the study, must be followed until any of the following occurs:

- The event resolves
- The event stabilizes
- The event returns to baseline, if a baseline value/status is available
- The event can be attributed to agents other than the study treatment or to factors unrelated to study conduct
- It becomes unlikely that any additional information can be obtained (subject or health care practitioner refusal to provide additional information, lost to follow-up after demonstration of due diligence with follow-up efforts)

The investigator should use clinical judgment in assessing the severity of events not directly experienced by the subject (eg, laboratory abnormalities).

Attachment B 7: Movement and Neurocognitive TEAEs (ie, Parkinsonism)

Subjects are considered to have movement and neurocognitive TEAEs if they met all three of the following criteria: (i) must have reported at least one or more of the preferred terms in at least two of the above categories; (ii) these reported preferred terms must have occurred following the recovery of CRS and/or ICANS; and (iii) symptoms must have been assessed by the investigator as CAR T-cell–related neurotoxicity (but not recognized as ICANS)..

Movement disorder	Cognitive Impairment	Personality changes
Bradykinesia	Depressed level of consciousness*	Flat affect
Cogwheel rigidity	Memory impairment	Personality change
Dysgraphia	Mental state changes	Reduced facial expression
Gait disturbance	Psychomotor retardation	Apathy
Micrographia	Apraxia	Monotone speech
Motor dysfunction, Parkinsonism	Akinetic mutism	Low (volume) speech
Posture abnormal, Stereotypy	Mental status changes	Withdrawn
Tremor*	Wordfinding difficulties	Decreased personal hygiene
Decreased arm swing	Intermittent confusion	
Involuntary movements of head	Confusional state	
Difficulty motor planning	Altered mentation	
Saccadic eye movements	Bradylalia	
Decreased eye blink	Abnormal glabellar reflex	
Tongue fasciculations		
Persistence of tongue protrusion		
Masked facies		

*Symptoms seen both during ICANS and later during Parkinsonism
Source: Carvykti™ Risk Evaluation and Mitigation Strategy (REMS)

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21. ATTACHMENTS

Attachment 1: Criteria for Response to Multiple Myeloma Treatment

Response	Response Criteria
Stringent complete response	• CR as defined below, *plus* • Normal FLC ratio, *and* • Absence of clonal PCs by immunohistochemistry or 2- to 4-color flow cytometry
Complete response[a]	• Negative immunofixation of serum and urine, *and* • Disappearance of any soft tissue plasmacytomas, *and* • <5% PCs in bone marrow • No evidence of initial monoclonal protein isotype(s) on immunofixation of the serum and urine.[b]
Very good partial response[a]	• Serum and urine M-component detectable by immunofixation but not on electrophoresis, *or* • ≥90% reduction in serum M-component plus urine M-component <100 mg/24 hours
Partial response	• ≥50% reduction of serum M-protein and reduction in 24-hour urinary M-protein by ≥90% or to < 200 mg/24 hours • If serum and urine M-protein are not measurable, a decrease ≥50% in the difference between involved and uninvolved FLC levels is require in place of the M-protein criteria • If serum and urine M-protein are not measurable, and serum free light assay is also not measurable, ≥50% reduction in bone marrow PCs is required in place of M-protein, provided baseline percentage was ≥30% • In addition to the above criteria, if present at baseline, ≥50% reduction in the size of soft tissue plasmacytomas is also required.
Minimal response	• ≥25% but ≤49% reduction of serum M-protein and reduction in 24-hour urine M-protein by 50% to 89% • In addition to the above criteria, if present at baseline, ≥50% reduction in the size of soft tissue plasmacytomas is also required
Stable disease	• Not meeting criteria for sCR, CR, VGPR, PR, MR, or progressive disease
Progressive disease[c]	Any one or more of the following criteria: • Increase of 25% from lowest response value in any of the following: – Serum M-component (absolute increase must be ≥0.5 g/dL), *and/or* – Urine M-component (absolute increase must be ≥200 mg/24 hours), *and/or* – Only in subjects without measurable serum and urine M-protein levels: the difference between involved and uninvolved FLC levels (absolute increase must be > 10 mg/dL) – Only in subjects without measurable serum and urine M-protein levels and without measurable disease by FLC levels, bone marrow PC percentage (absolute increase must be ≥10%) • Appearance of a new lesion(s), ≥50% increase from nadir in SPD of >1 lesion, or ≥50% increase in the longest diameter of a previous lesion >1 cm in short axis • Definite development of new bone lesions or definite increase in the size of existing bone lesions • ≥50% increase in circulating plasma cells (minimum of 200 cells per μL) if this is the only measure of disease

Key: CR=complete response; FLC=free light chain; PC=plasma cell; PR=partial response; sCR=stringent complete response; SPD=sum of the products of the maximal perpendicular diameters of measured lesions; VGPR=very good partial response.

[a] Clarifications to the criteria for coding CR and VGPR in subjects in whom the only measurable disease is by serum FLC levels: CR in such subjects indicates a normal FLC ratio of 0.26 to 1.65 (or reference range in testing laboratory) in addition to CR criteria listed above. VGPR in such subjects requires a ≥90% decrease in the difference between involved and uninvolved FLC levels. For patients achieving very good partial response by other criteria, a soft tissue plasmacytoma must decrease by more than 90% in the sum of the maximal perpendicular diameter (SPD) compared with baseline.

[b.] In some cases it is possible that the original M protein light-chain isotype is still detected on immunofixation but the accompanying heavy-chain component has disappeared; this would not be considered as a CR even though the heavy-chain component is not detectable, since it is possible that the clone evolved to one that secreted only light chains. Thus, if a patient has IgA lambda myeloma, then to qualify as CR there should be no IgA detectable on serum or urine immunofixation; if free lambda is detected without IgA, then it must be accompanied by a different heavy chain isotype (IgG, IgM, etc.).

[c.] Clarifications to the criteria for coding progressive disease: bone marrow criteria for progressive disease are to be used only in subjects without measurable disease by M-protein and by FLC levels; "25% increase" refers to M-protein, and FLC, and does not refer to bone lesions, or soft tissue plasmacytomas and the "lowest response value" does not need to be a confirmed value.

Notes: All response categories (CR, sCR, VGPR, PR, MR, and progressive disease) require 2 consecutive assessments made at any time before the institution of any new therapy; CR, sCR, VGPR, PR, MR, and stable disease categories also require no known evidence of progressive or new bone lesions if radiographic studies were performed. VGPR and CR categories require serum and urine studies regardless of whether disease at baseline was measurable on serum, urine, both, or neither.

Radiographic studies are not required to satisfy these response requirements. Bone marrow assessments need not be confirmed. For progressive disease, serum M-component increases of ≥1 g/dL are sufficient to define relapse if lowest M-component is ≥5 g/dL.

Source: Adapted from Durie (2015), Rajkumar (2011), Kumar (2016)

Attachment 2: Cytokine Release Syndrome ASTCT Consensus Grading System

Grade	Toxicity
Grade 1	Fever[a] (Temperature ≥38°)
Grade 2	Fever[a] (Temperature ≥38°) with either: • Hypotension not requiring vasopressors • And/or[c] hypoxia requiring low-flow nasal cannula[b] or blow-by
Grade 3	Fever[a] (Temperature ≥38°) with either: • Hypotension requiring a vasopressor with or without vasopressin. • And/or[c] hypoxia requiring high-flow nasal cannula[b], facemask, nonrebreather mask, or Venturi mask.
Grade 4	Fever[a] (Temperature ≥38°) with either: • Hypotension requiring multiple vasopressors (excluding vasopressin). • And/or[c] hypoxia requiring positive pressure (eg, CPAP, BiPAP, intubation and mechanical ventilation)
Grade 5	Death

[a] Fever not attributable to any other cause. In patients who have CRS then receive antipyretics or anticytokine therapy such as tocilizumab or steroids, fever is no longer required to grade subsequent CRS severity. In this case, CRS grading is driven by hypotension and/or hypoxia.

[b] Low-flow nasal cannula is defined as oxygen delivered at ≤6 L/minute or blow-by oxygen delivery. High-flow nasal cannula is defined as oxygen delivered at >6 L/minute.

[c] CRS grade is determined by the more severe event: hypotension or hypoxia not attributable to any other cause.

Note: Organ toxicities associated with CRS may be graded according to CTCAE v5.0 but they do not influence CRS grading.

Source: Lee (2019)

Attachment 3: Immune Effector Cell-associated Encephalopathy (ICE) Tool

Immune Effector Cell-Associated Encephalopathy (ICE) Tool[a]
Orientation: Orientation to year, month, city, hospital: • **4 points** **Naming**: Name 3 objects (e.g., point to clock, pen, button): • **3 points** **Following commands**: (e.g., Show me 2 fingers or Close your eyes and stick out your tongue): • **1 point** **Writing**: Ability to write a standard sentence (e.g., Our national bird is the bald eagle): • **1 point** **Attention**: Count backwards from 100 by ten: • **1 point**
a: ICE-Tool Scoring: • Score 10: No impairment • Score 7-9: Grade 1 ICANS • Score 3-6: Grade 2 ICANS • Score 0-2: Grade 3 ICANS • Score 0 due to patient unarousable and unable to perform ICE assessment: Grade 4 ICANS

Attachment 4: Immune Effector Cell-associated Neurotoxicity Syndrome (ICANS) ASTCT Consensus Grading System[a,b]

Neurotoxicity Domain	Grade 1	Grade 2	Grade 3	Grade 4
ICE Score	7-9	3-6	0-2	0 (patient is unarousable and unable to perform ICE).
Depressed Level of Consciousness	Awakens spontaneously.	Awakens to voice.	Awakens only to tactile stimulus.	Patient is unarousable or requires vigorous or repetitive tactile stimuli to arouse. Stupor or coma.
Seizure	N/A	N/A	Any clinical seizure, focal or generalized, that resolves rapidly; or Non-convulsive seizures on EEG that resolve with intervention.	Life-threatening prolonged seizure (>5 min); or Repetitive clinical or electrical seizures without return to baseline in between.
Motor Findings	N/A	N/A	N/A	Deep focal motor weakness such as hemiparesis or paraparesis.
Raised Intracranial Pressure / Cerebral Edema	N/A	N/A	Focal/local edema on neuroimaging.	Diffuse cerebral edema on neuroimaging; or Decerebrate or decorticate posturing; or Cranial nerve VI palsy; or Papilledema; or Cushing's triad.

a Toxicity grading according to Lee 2019

b ICANS grade is determined by the most severe event (ICE score, level of consciousness, seizure, motor findings, raised ICP/cerebral edema) not attributable to any other cause.

Note: all other neurologic adverse events (not associated with ICANS) should continue to be graded with CTCAE Version 5.0 during both phases of the study

Attachment 5: International Myeloma Working Group Diagnostic Criteria

Diagnostic criteria for myeloma must be met when the patient was diagnosed. Multiple myeloma is defined as clonal bone marrow plasma cells ≥10% or biopsy-proven bony or extramedullary plasmacytoma[a] and any one or more of the following myeloma defining events:

- Myeloma defining events:
  - Evidence of end organ damage that can be attributed to the underlying plasma cell proliferative disorder, specifically:
    - **C:** Hypercalcemia: serum calcium >0.25 mmol/L (>1 mg/dL) higher than the upper limit of normal or >2.75 mmol/L (>11 mg/dL)
    - **R:** Renal insufficiency: creatinine clearance <40 mL per min[b] or serum creatinine >177 μmol/L (>2 mg/dL)
    - **A:** Anemia: hemoglobin value of >20 g/L below the lower limit of normal, or a hemoglobin value <100 g/L
    - **B:** Bone lesions: one or more osteolytic lesions on skeletal radiography, CT, or PET-CT[c,d]
- Any one or more of the following biomarkers of malignancy:
  - Clonal bone marrow plasma cell percentage[a] ≥60%
  - Involved:uninvolved serum free light chain ratio[e] ≥100
  - >1 focal lesions on MRI studies[f]

[a] Clonality should be established by showing κ/λ-light-chain restriction on flow cytometry, immunohistochemistry, or immunofluorescence. Bone marrow plasma cell percentage should preferably be estimated from a core biopsy specimen; in case of a disparity between the aspirate and core biopsy, the highest value should be used.
[b] Measured or estimated by validated equations.
[c] If bone marrow has less than 10% clonal plasma cells, more than one bone lesion is required to distinguish from solitary plasmacytoma with minimal marrow involvement.
[d] PET-CT=^{18}F-fluorodeoxyglucose PET with CT.
[e] These values are based on the serum Freelite assay (The Binding Site Group, Birmingham, UK). The involved free light chain must be ≥100 mg/L.
[f] Each focal lesion must be 5 mm or more in size.

Source: Rajkumar (2011)

Attachment 6: Prior Cancer Therapy for Multiple Myeloma

A line of therapy is defined as one or more cycles of a planned treatment program. This may consist of one or more planned cycles of single-agent therapy or combination therapy, as well as a sequence of treatments administered in a planned manner. For example, a planned treatment approach of induction therapy followed by autologous stem cell transplantation, followed by maintenance is considered one line of therapy. A new line of therapy starts when a planned course of therapy is modified to include other treatment agents (alone or in combination) as a result of disease progression, relapse, or toxicity. A new line of therapy also starts when a planned period of observation off therapy is interrupted by a need for additional treatment for the disease.

Source: Rajkumar (2011)

Attachment 7: Eastern Cooperative Oncology Group Performance Status Grade

Grade	Eastern Cooperative Oncology Group Performance Status
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, eg, light house work, office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead

Source: Eastern Cooperative Oncology Group, Robert Comis M.D., Group Chair (Oken 1982).

Attachment 8: Formulas for Estimating Glomerular Filtration Rate

Modified Diet in Renal Disease (MDRD) Formula

For serum creatinine in **mg/dL**, the estimated glomerular filtration rate (eGFR) for the MDRD formula is:

eGFR (MDRD) mL/min per $1.73m^2$= 175 x [serum creatinine (mg/dL)]$^{-1.154}$ x [age]$^{-0.203}$ x [1.212 if black] x [0.742 if female]

For serum creatinine in **µmol/L**, the eGFR for the MDRD formula is:

eGFR (MDRD) mL/min per $1.73m^2$= 175 x [serum creatinine (µmol/L)/88.4]$^{-1.154}$ x [age]$^{-0.203}$ x [1.212 if black] x [0.742 if female]

Source: Levey (2006)

Attachment 9: Serum Calcium Corrected for Albumin

If calcium is expressed in mg/dL and albumin is expressed in g/dL:
Corrected calcium (mg/dL) =
Serum calcium (mg/dL) + 0.8 × (4 - serum albumin [g/dL])

If calcium is expressed in mmol/L and albumin is expressed in g/L:
Corrected calcium (mmol/L) =
Serum calcium (mmol/L) + 0.02 × (40 - serum albumin [g/L])

Source: Burtis (1998)

Attachment 10: Hepatitis B Virus Screening

The following hepatitis B virus screening guide is to be used to determine subject eligibility for the study:

Eligibility based on hepatitis B virus test results			
	Hepatitis B test result		
Action	Hepatitis B surface antigen (HBsAg)	Hepatitis B surface antibody (anti-HBs)	Hepatitis B core antibody (anti-HBc)
Exclude	+	— *or* +	— *or* +
Include	—	—	—
	—	+*#	+#
	—	—	+#
	—	+*	—

* Subjects who are anti-HBs positive and without history of vaccination, should have HBV-DNA quantification test. Subjects with positive HBV-DNA should be excluded. Subjects with negative HBV-DNA can be enrolled. If required by local country guidelines on HBV prevention, HBV-DNA and AST/ALT laboratories should be performed every 3 months for the first 12 months after JNJ-68284528 administration. If there is evidence of HBV reactivation initiate treatment as appropriate per institutional guidance. For Cohort E only: HBV-DNA and AST/ALT laboratories should also be performed every 3 months during induction therapy and prior to 1st dose of lymphodepletion therapy (≤72 hour). If there is evidence of HBV reactivation initiate treatment as appropriate per institutional guidance. If HBV reactivation is documented (≤72 hour) of 1st dose of lymphodepletion, the sponsor must be notified and lymphodepletion delayed.

Subjects with positive anti-HBc and either positive or negative anti-HBs should have HBV-DNA quantification test. Subjects with positive HBV-DNA should be excluded. Subjects with negative HBV-DNA can be enrolled; however, HBV-DNA and AST/ALT laboratories should be performed every 3 months for the first 12 months after JNJ-68284528 administration. If there is evidence of HBV reactivation initiate treatment as appropriate per institutional guidance. For Cohort E only: HBV-DNA and AST/ALT laboratories should also be performed every 3 months during induction therapy and prior to 1st dose of lymphodepletion therapy (≤72 hour). If HBV reactivation is documented (≤72 hour) of 1st dose of lymphodepletion, the sponsor must be notified and lymphodepletion delayed.

NOTE: The post-treatment follow-up visit (every 28 days [± 7 days] post Day 100) can be coordinated with the HBV-DNA and AST/ALT assessment every 12 weeks to minimize the subject's visits to the clinic.

Attachment 11: Patient Reported Outcomes (PRO) Measures

EORTC QLQ-C30

EORTC QLQ-C30 (version 3)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Please fill in your initials: ____

Your birthdate (Day, Month, Year): ____

Today's date (Day, Month, Year): 31 ____

	Not at All	A Little	Quite a Bit	Very Much
1. Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2. Do you have any trouble taking a long walk?	1	2	3	4
3. Do you have any trouble taking a short walk outside of the house?	1	2	3	4
4. Do you need to stay in bed or a chair during the day?	1	2	3	4
5. Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4

During the past week:	Not at All	A Little	Quite a Bit	Very Much
6. Were you limited in doing either your work or other daily activities?	1	2	3	4
7. Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8. Were you short of breath?	1	2	3	4
9. Have you had pain?	1	2	3	4
10. Did you need to rest?	1	2	3	4
11. Have you had trouble sleeping?	1	2	3	4
12. Have you felt weak?	1	2	3	4
13. Have you lacked appetite?	1	2	3	4
14. Have you felt nauseated?	1	2	3	4
15. Have you vomited?	1	2	3	4
16. Have you been constipated?	1	2	3	4

Please go on to the next page

During the past week:	**Not at All**	**A Little**	**Quite a Bit**	**Very Much**
17. Have you had diarrhea?	1	2	3	4
18. Were you tired?	1	2	3	4
19. Did pain interfere with your daily activities?	1	2	3	4
20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21. Did you feel tense?	1	2	3	4
22. Did you worry?	1	2	3	4
23. Did you feel irritable?	1	2	3	4
24. Did you feel depressed?	1	2	3	4
25. Have you had difficulty remembering things?	1	2	3	4
26. Has your physical condition or medical treatment interfered with your family life?	1	2	3	4
27. Has your physical condition or medical treatment interfered with your social activities?	1	2	3	4
28. Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

For the following questions please circle the number between 1 and 7 that best applies to you

29. How would you rate your overall health during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

30. How would you rate your overall quality of life during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

MULTIPLE MYELOMA SYMPTOM AND IMPACT QUESTIONNAIRE

Instructions: The purpose of this questionnaire is to collect information about your experience with multiple myeloma. Please only consider your experiences related to your multiple myeloma when answering the following questions.

People often experience changes in the severity of their symptoms from day to day or within a single day. When answering the next 4 questions, please only think about the time within the past 7 days when each symptom was at its worst.

1. How would you rate the worst **pain in your back** within the past 7 days?

   ☐ No pain
   ☐ A little pain
   ☐ Moderate pain
   ☐ Quite a bit of pain
   ☐ Severe pain

2. How would you rate the worst **pain in your legs** within the past 7 days?

   ☐ No pain
   ☐ A little pain
   ☐ Moderate pain
   ☐ Quite a bit of pain
   ☐ Severe pain

3. How would you rate the worst **pain in areas other than your back or legs** within the past 7 days?

☐ No pain
☐ A little pain
☐ Moderate pain
☐ Quite a bit of pain
☐ Severe pain

4. How would you rate the worst **numbness or tingling in your hands or feet** within the past 7 days?

☐ No numbness or tingling
☐ A little numbness or tingling
☐ Moderate numbness or tingling
☐ Quite a bit of numbness or tingling
☐ Severe numbness or tingling

For each question, select only 1 answer that best describes how often you experienced each issue within the past 7 days.

5. How much did your **pain interfere** with your usual or daily activities within the past 7 days?

☐ Not at all
☐ A little bit
☐ Moderately
☐ Quite a bit
☐ Very much

6. How often did you have **low energy** within the past 7 days?

☐ Never
☐ Rarely
☐ Some of the time
☐ Most of the time
☐ Always

7. How often did you **tire easily** (for example, needing to rest during activities) within the past 7 days?

☐ Never
☐ Rarely
☐ Some of the time
☐ Most of the time
☐ Always

8. How often did you experience **muscle weakness** within the past 7 days?

☐ Never
☐ Rarely
☐ Some of the time
☐ Most of the time
☐ Always

9. How often did you have trouble with your sleep (for example, difficulty falling asleep or staying sleep) within the past 7 days?

- ☐ Never
- ☐ Rarely
- ☐ Some of the time
- ☐ Most of the time
- ☐ Always

10. How often did you have a poor appetite within the past 7 days?

- ☐ Never
- ☐ Rarely
- ☐ Some of the time
- ☐ Most of the time
- ☐ Always

11. How often did you have difficulty with your memory within the past 7 days?

- ☐ Never
- ☐ Rarely
- ☐ Some of the time
- ☐ Most of the time
- ☐ Always

12. How often did you have **difficulty concentrating** on things (for example, reading a book or following a conversation) within the past 7 days?

☐ Never
☐ Rarely
☐ Some of the time
☐ Most of the time
☐ Always

13. How often were you **limited in doing your daily activities** within the past 7 days (for example, struggling or needing help with work or house chores)?

☐ Never
☐ Rarely
☐ Some of the time
☐ Most of the time
☐ Always

14. How often did you have **difficulty walking** within the past 7 days?

☐ Never
☐ Rarely
☐ Some of the time
☐ Most of the time
☐ Always

15. How often were you **limited in your social life** (for example, activities with your friends or family) within the past 7 days?

☐ Never
☐ Rarely
☐ Some of the time
☐ Most of the time
☐ Always

For each question, select only 1 answer that best describes how you felt within the past 7 days.

16. How often have you felt **depressed about your multiple myeloma** within the past 7 days?

☐ Never
☐ Rarely
☐ Some of the time
☐ Most of the time
☐ Always

17. How often did you **worry that your multiple myeloma could get worse** within the past 7 days?

☐ Never
☐ Rarely
☐ Some of the time
☐ Most of the time
☐ Always

Patient Global Impression of Severity (PGIS)

Patient's Global Impression of Severity (PGIS)
Pain

Overall, how would you rate the severity of your pain currently? (Please select one response)

- ☐ 1. None
- ☐ 2. Mild
- ☐ 3. Moderate
- ☐ 4. Severe
- ☐ 5. Very Severe

Patient Global Impression of Change (PGIC)

Patient's Global Impression of Change (PGIC)
of Overall Health

Compared to before you received the CAR-T infusion in this study, how has your overall health changed? (Please select one response)

- ☐ 1. A lot better now
- ☐ 2. Moderately better now
- ☐ 3. A little better now
- ☐ 4. Neither better, nor worse (no change)
- ☐ 5. A little worse now
- ☐ 6. Moderately worse now
- ☐ 7. A lot worse now

NCI PRO-CTCAE Items

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As individuals go through treatment for their cancer they sometimes experience different symptoms and side effects. For each question, please check or mark an ☒ in the one box that best describes your experiences over the past 7 days...

1.	**In the last 7 days, how OFTEN did you have NAUSEA?**				
	o Never	**o Rarely**	**o Occasionally**	**o Frequently**	**o Almost constantly**
	In the last 7 days, what was the SEVERITY of your NAUSEA at its WORST?				
	o None	**o Mild**	**o Moderate**	**o Severe**	**o Very severe**

2.	**In the last 7 days, how OFTEN did you have VOMITING?**				
	o Never	**o Rarely**	**o Occasionally**	**o Frequently**	**o Almost constantly**
	In the last 7 days, what was the SEVERITY of your VOMITING at its WORST?				
	o None	**o Mild**	**o Moderate**	**o Severe**	**o Very severe**

3.	**In the last 7 days, how OFTEN did you have LOOSE OR WATERY STOOLS (DIARRHEA/DIARRHOEA)?**				
	○ Never	○ Rarely	○ Occasionally	○ Frequently	○ Almost constantly

4.	In the last 7 days, what was the SEVERITY of your SHORTNESS OF BREATH at its WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe
	In the last 7 days, how much did your SHORTNESS OF BREATH INTERFERE with your usual or daily activities?				
	○ Not at all	○ A little bit	○ Somewhat	○ Quite a bit	○ Very much

5.	In the last 7 days, did you have any RASH?	
	○ Yes	○ No

6.	In the last 7 days, what was the SEVERITY of your DIZZINESS at its WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe
	In the last 7 days, how much did DIZZINESS INTERFERE with your usual or daily activities?				
	○ Not at all	○ A little bit	○ Somewhat	○ Quite a bit	○ Very much

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7.	In the last 7 days, how OFTEN did you have a HEADACHE?				
	o Never	o Rarely	o Occasionally	o Frequently	o Almost constantly
	In the last 7 days, what was the SEVERITY of your HEADACHE at its WORST?				
	o None	o Mild	o Moderate	o Severe	o Very severe
	In the last 7 days, how much did your HEADACHE INTERFERE with your usual or daily activities?				
	o Not at all	o A little bit	o Somewhat	o Quite a bit	o Very much

8.	In the last 7 days, what was the SEVERITY of your FATIGUE, TIREDNESS, OR LACK OF ENERGY at its WORST?				
	o None	o Mild	o Moderate	o Severe	o Very severe
	In the last 7 days, how much did FATIGUE, TIREDNESS, OR LACK OF ENERGY INTERFERE with your usual or daily activities?				
	o Not at all	o A little bit	o Somewhat	o Quite a bit	o Very much

Attachment 12: Conversion Table for Glucocorticosteroid Dose

Glucocorticoid	Approximate Equivalent Dose (mg)	Half-life (Biologic) hours
Intermediate-Acting		
Methylprednisolone	4	18-36
Prednisolone	5	18-36
Prednisone	5	18-36
Triamcinolone	4	18-36
Long-Acting		
Betamethasone	0.6 – 0.75	36-54
Dexamethasone	0.75	36-54

Attachment 13: Anticipated Adverse Events

Attachment deleted per Amendment 3

Attachment 14: JNJ-68284528 Outpatient Administration Guidelines

When evaluating the suitability for outpatient administration, if allowed by local regulations and institutional guidance among other considerations, investigators should assess the subject's clinical status and the health care facility capability to safely manage outpatient logistics. General recommendations for each of these considerations are provided below; sponsor approval is required:

3. Clinical consideration

General guidance for clinical considerations for a subject that is suitable for outpatient administration and follow-up includes the following:

- Not requiring packed red blood cell or platelet transfusions more frequently than every 2 days
- No presence of an indwelling central line (with the exception of a PICC line) given risk of infection in the setting of cytopenia
- No fever or active infection (bacterial, fungal, viral) since study enrollment
- No Grade 3 or higher non-hematologic toxicities of cyclophosphamide and fludarabine including nausea, vomiting, and diarrhea
- No clinically significant coagulopathy that would increase the risk of bleeding in the setting of cytopenia
- No high tumor burden defined as at least 60% plasma cell infiltration of the marrow and/or the presence of extramedullary disease
- No risk factors for developing clinically significant tumor lysis syndrome and requiring management with increased hydration, allopurinol, or rasburicase. Patients who are receiving prophylactic treatment for TLS are eligible for outpatient infusion, if deemed stable by the investigator
- No rapidly progressing disease
- No deterioration in neurologic status, including mental status changes such as confusion or increased somnolence. The only exception is confusion or somnolence that has resolved and must be attributed to diphenhydramine premedication for JNJ-68284528.
- The following laboratory parameters:
  - Estimated glomerular filtration rate of ≥40 mL/min/1.73 m^2
  - AST and ALT≤3 times the upper limit of normal

4. Logistical consideration for qualified healthcare facility

Outpatient administration and post-JNJ-68284528 infusion follow-up must take place at a qualified healthcare facility.

The following should be considered for outpatient administration and follow-up until Day 4 prior to inpatient admission from Day 5 to Day 14 of JNJ-68284528 infusion:

- Site must discuss with subjects about how to recognize the presenting signs and symptoms of CAR-T associated toxicities (including but not limited to CRS, neurotoxicities, infections, etc.) as presented in the patient wallet card
- Site must provide patients with educational material including but not limited to emergency contact information

- Subject will receive daily phone call follow-ups from the hospital site staff (as required by the Time and Events Schedule and Attachment 15) during typical business hours
- Subject is required to stay within 30 minutes of transportation to the hospital and remain in the company of a competent adult at all times until the time of readmission on Day 5 after JNJ -68284528 infusion
- Subject must comply with all the protocol requirement procedures, including measuring and recording of body temperature twice per day, and coming to the site for safety assessments according to the Time and Events Schedule (Table 1, Table 3, Table 5, and Table 6).
- Admission to the hospital is required at any time in the event of any presenting signs and symptoms of CRS and/or neurotoxicity even if these occur before Day 5. Even without symptoms of CRS or neurotoxicity, subject will be admitted for inpatient monitoring from Day 5 to Day 14 of JNJ-68284528 infusion
- If a subject does not develop symptoms of CRS or neurotoxicity or other clinically significant adverse event until Day 10 post JNJ-68284528 infusion, subject may be discharged with daily outpatient phone call follow-ups during business hours through study Day 14. Upon discharge from the hospital, the subject must stay locally within 1 hour of transportation to the hospital and remain in the company of a competent adult at all times for 1 additional week, or up to study Day 21, whichever is sooner
- Subjects that experience CRS or neurotoxicity, can be discharged from the hospital when they are afebrile for 24 hours and signs and symptoms of CRS and/or neurotoxicity or other clinically significant adverse event have resolved

Attachment 15: Monitoring for Subjects Receiving JNJ-68284528 as Outpatient

Subjects eligible to receive JNJ-68284528 as an outpatient (see recommendations in Attachment 14) in consultation with and approval of the sponsor

Day 1	JNJ-68284528 infusion
Day 1 to 4	• Subject is required to stay within 30 minutes of transportation to the hospital and remain in the company of a competent adult at all times • Subject will receive daily phone call follow-ups from hospital staff during typical business hours • Admission to the hospital is required at any time in the event of any presenting signs and symptoms of CRS and/or neurotoxicity
Day 5 to 14	• Required inpatient admission • Potential discharge on Day 10 for subjects who do not develop symptoms of CRS, neurotoxicity, or other significant adverse events – Subjects discharged on Day 10 will receive daily phone call follow-ups from the hospital staff during typical business hours through Day 14

Attachment 16: Contraceptive and Barrier Guidance and Collection of Pregnancy Information

Woman of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile (see below).

Woman Not of Childbearing Potential

Premenarchal

A premenarchal state is one in which menarche has not yet occurred.

Postmenopausal

A postmenopausal state is defined as no menses for 24 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level (>40 IU/L or mIU/mL) in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT), however in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient. If there is a question about menopausal status in women on HRT, the woman will be required to use one of the non-estrogen-containing hormonal highly effective contraceptive methods if she wishes to continue HRT during the study.

Permanently sterile

Permanent sterilization methods include hysterectomy, bilateral salpingectomy, bilateral tubal occlusion/ligation procedures, and bilateral oophorectomy.

Note: If the childbearing potential changes after start of the study (eg, a premenarchal woman experiences menarche) or the risk of pregnancy changes (eg, a woman who is not heterosexually active becomes active), a woman must begin a highly effective method of contraception, as described throughout the inclusion criteria.

If reproductive status is questionable, additional evaluation should be considered.

Contraceptive (birth control) use by men or women should be consistent with local regulations regarding the acceptable methods of contraception for those participating in clinical studies.

Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for subjects in clinical studies.

Because of the embryo-fetal risk of lenalidomide, all subjects treated with D-VRd or lenalidomide consolidation must be enrolled in the lenalidomide pregnancy prevention program applicable in their region. Investigators should comply with the lenalidomide Global Pregnancy Prevention Plan or with the respective country-specific REVLIMID® / Lenalidomide Risk Minimization Program (ie, Pregnancy prevention program), whichever is more stringent, as implemented in the post-marketing setting and ensure that all subjects adhere to these programs. When no REVLIMID® /

Lenalidomide Risk Minimization Program exists, subjects must adhere to the Global lenalidomide Pregnancy Prevention Plan.

Examples of Contraceptives

EXAMPLES OF CONTRACEPTIVES[a] ALLOWED DURING THE STUDY INCLUDE:
USER INDEPENDENT
Highly Effective Methods That Are User Independent *Failure rate of <1% per year when used consistently and correctly.*

- Implantable progestogen-only hormone contraception associated with inhibition of ovulation[b]
- Intrauterine device (IUD)
- Intrauterine hormone-releasing system (IUS)
- Bilateral tubal occlusion
- Vasectomized partner
  (Vasectomized partner is a highly effective contraceptive method provided that the partner is the sole sexual partner of the woman of childbearing potential and the absence of sperm has been confirmed. If not, additional highly effective method of contraception should be used. Spermatogenesis cycle is approximately 74 days.)

USER DEPENDENT
Highly Effective Methods That Are User Dependent *Failure rate of <1% per year when used consistently and correctly.*

- Progestogen-only hormone contraception associated with inhibition of ovulation[b]
  - oral
  - injectable
- Sexual abstinence
  (Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the subject.)

NOT ALLOWED AS SOLE METHOD OF CONTRACEPTION DURING THE STUDY (not considered to be highly effective - failure rate of ≥1% per year)

- Progestogen-only oral hormonal contraception where inhibition of ovulation is not the primary mode of action.
- Male or female condom with or without spermicide[c]
- Cap, diaphragm, or sponge with spermicide
- A combination of male condom with either cap, diaphragm, or sponge with spermicide (double-barrier methods)[c]
- Periodic abstinence (calendar, symptothermal, post-ovulation methods)
- Withdrawal (coitus-interruptus)
- Spermicides alone
- Lactational amenorrhea method (LAM)

a) Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for subjects in clinical studies.
b) Hormonal contraception may be susceptible to interaction with the study intervention, which may reduce the efficacy of the contraceptive method. In addition, consider if the hormonal contraception may interact with the study intervention.
c) Male condom and female condom should not be used together (due to risk of failure with friction).

Pregnancy During the Study

All initial reports of pregnancy in subjects or partners of male subjects must be reported to the sponsor by the study-site personnel within 24 hours of their knowledge of the event using appropriate pregnancy notification form. Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, and ectopic pregnancy) are considered serious adverse events and must be reported using the Serious Adverse Event Form. Any subject who becomes pregnant during the study must discontinue further study treatment. Because the effect of the study treatment on sperm is unknown, pregnancies in partners of male subjects included in the study will be reported as noted above. Follow-up information regarding the outcome of the pregnancy and any postnatal sequelae in the infant will be required.

Attachment 17: Handwriting Adverse Event Toxicity Grading Criteria

Adverse Event Term	Grade 1	Grade 2
Micrographia: abnormally small or cramped handwriting	Mildly smaller letters or reduced spacing (eg, <50% decrease from baseline)	Moderate to severely smaller letters or reduced spacing (eg, >=50% decrease from baseline)
Dysgraphia: illegible writing or writing that takes an unusually long time or great effort	Mildly slower writing, impaired straightness of line, difficulty in completing task from baseline; most words are legible	Moderate to severely slower writing, impaired straightness of line, difficulty in completing task from baseline; most words are illegible
Agraphia: pathologic loss of the ability to write	Able to write part of a sentence (3 or more words); noted change from baseline	Able to write just 1 to 2 words, or unable to write any words; noted change from baseline

Attachment 18: Anti-microbial Prophylaxis Recommendations

Subjects should receive antimicrobial prophylaxis as per recommendations below or per institutional standards.

Prophylaxis	Therapy	Start	Stop
Anti-Bacterial	Fluoroquinolones (Levofloxacin - 500 mg PO or IV daily, or equivalent) *Suggested Alternative for subjects with allergy to quinolones*: Cefpodoxime - 200 mg PO twice a day	At neutropenia onset (ANC < 500/μL) Or by Day -1	At Neutropenia resolution (for example, ANC ≥ 500/μL)
Anti-Fungal	Fluconazole - 400 mg daily (or equivalent) *Alternatives*: Caspofungin or Micafungin Prolonged neutropenia – Consider switching to Posaconazole, *or* as per institutional guidelines	At neutropenia onset (ANC < 500/μL) Or by Day -1	At Neutropenia resolution (for example, ANC ≥ 500/μL)
Anti-Viral	Acyclovir – 400 - 800 mg PO twice a day (dose to be adjusted as per institutional guidelines) *Alternative*: Valacyclovir - 500 mg PO twice a day	By Day -1 of infusion	Suggested for at least 12 months post infusion
***Pneumocystis* Pneumonia (PCP)**	Pentamidine (as per institutional guidelines) followed by Trimethoprim-sulfamethoxazole – 1 DS tablet PO daily or 1 SS tablet PO daily *Alternatives*: Pentamidine (as per institutional guidelines), *or* Dapsone – 100 mg PO daily or 50 mg PO BID, *or* Atovaquone – 1500 mg PO daily	By Day -1 of infusion Pentamidine (or alternative) Day 28 (or when cytopenia recovers) Trimethoprim-sulfamethoxazole – 1 DS tablet PO daily or 1 SS tablet PO daily	Suggested duration: 6 months post-infusion OR until CD4 count ≥ 200 cells/μL, (whichever is longer)

Attachment 19: International Staging System (ISS)

Stage	Criteria
I	Serum β2-microglobulin <3.5 mg/L Serum albumin ≥3.5 g/dL
II	Not stage I or III*
III	Serum β2-microglobulin ≥5.5 mg/L

* There are 2 categories for stage II: serum β2-microglobulin <3.5 mg/L but serum albumin <3.5 g/dL; or serum β2-microglobulin 3.5 to <5.5 mg/L irrespective of the serum albumin level.

Source: Adapted from Greipp (2005)

Attachment 20: COVID-19 Guidance on Study Conduct and Vaccine Timing

GUIDANCE ON STUDY CONDUCT DURING THE COVID-19 PANDEMIC

It is recognized that the Coronavirus Disease 2019 (COVID-19) pandemic may have an impact on the conduct of this clinical study due to, for example, self-isolation/quarantine by subjects and study-site personnel; travel restrictions/limited access to public places, including hospitals; study site personnel being reassigned to critical tasks.

In alignment with recent health authority guidance, the sponsor is providing options for study related subject management in the event of disruption to the conduct of the study. This guidance does not supersede any local or government requirements or the clinical judgement of the investigator to protect the health and well-being of subjects and site staff.

Scheduled visits that cannot be conducted in person at the study site will be performed to the extent possible remotely/virtually or delayed until such time that on-site visits can be resumed. At each contact, subjects will be interviewed to collect safety data. Key efficacy endpoint assessments should be performed if required and as feasible. Subjects will also be questioned regarding general health status to fulfill any physical examination requirement.

Every effort should be made to adhere to protocol-specified assessments for subjects on study intervention, including follow up. Modifications to protocol-required assessments may be permitted via COVID-19 Appendix after consultation with the subject, investigator, and the sponsor. Missed assessments/visits will be captured in the clinical trial management system for protocol deviations. Discontinuations of study interventions and withdrawal from the study should be documented with the prefix “COVID-19-related” in the case report form (CRF).

The sponsor will continue to monitor the conduct and progress of the clinical study, and any changes will be communicated to the sites and to the health authorities according to local guidance. Modifications made to the study conduct as a result of the COVID-19 pandemic should be summarized in the clinical study report.

Testing for COVID-19 should be performed according to local guidance. If a subject has tested positive for COVID-19, the following should be reported in the EDC tool:

- all cases of COVID-19, regardless of severity or causality (including asymptomatic COVID19) up to 1 year after cilta-cel infusion
- all medications given to prevent (including vaccines) or treat COVID-19 up to 1 year after cilta-cel infusion

GUIDANCE SPECIFIC TO THIS PROTOCOL:

These emergency provisions are meant to ensure subject safety on study while site capabilities are compromised by COVID-19-related restrictions. As restrictions are lifted and the acute phase of the COVID-19 pandemic resolves, sites should revert to original protocol conduct as soon as feasible.

Study Visits and Assessments

- At the discretion of the investigator and with sponsor approval, study visits may be performed remotely via telemedicine technology that connects study subjects to their research coordinators and investigators. Blood sample collection may be performed at the subject's home by mobile study personnel (ie, nurses and mobile phlebotomist), if not using the sponsor's home health nursing solution. Home health nursing can be done via site contract with a visiting nurse service independent of the sponsor, if not using the sponsor's home health nursing solution. Patient reported outcome questionnaires can be completed by telephone or during the home health visit.
- For subjects who are unable to come to the site for scheduled visits and/or if site capabilities are compromised by COVID-19 related restrictions, contact (eg, telephone, videoconference, or other channels) with the subject should be made in advance, to collect information on the subject's current health status and any new or ongoing adverse events and concomitant medications. Normal study procedures should be followed for the applicable visits as closely as possible even if lab assessments and physical exams are performed locally. Where local laboratories are used, it is important to ensure appropriate documentation of laboratory reference ranges. The remote contact with the subject (as allowable per local regulations), the local laboratory results, and the sponsor discussion should be documented in the subject source record. Similarly, at a minimum, a comment must be entered in the Comments eCRF clearly designating as "COVID-19-related" and acknowledging the discussion between the investigator and the sponsor.
- For subjects eligible to receive retreatment, original protocol conduct must be followed until Day 100 after the CAR-T re-administration.
- All deviations from protocol-required assessments should be documented in detail within the subject's source record and should be clearly designated as "COVID-19-related". It must be documented if a visit is conducted remotely. Source documentation should detail how each assessment was collected (eg, remote vs. on-site, central vs. local laboratory, vital signs taken at home by caretaker vs. delegated in-home nursing).
- Consenting and re-consenting of subjects will be performed as applicable for the measures taken (including also remote consenting by phone or video consultation) and according to local guidance for informed consent applicable during the COVID-19 pandemic.

The above measures are recommended for consideration on a temporary basis during the COVID-19 pandemic to ensure that subject assessments continue as outlined in the protocol without imposing health risk to subjects, their families, and site staff. Every effort should be made to complete all protocol-required assessments.

GUIDANCE ON COVID-19 VACCINE TIMING, AND COVID-19 PREVENTION AND TREATMENT FOR CILTA-CEL RECIPIENTS

It is recommended that subjects receive prophylactic COVID-19 vaccination when locally available, at the discretion of investigator judgement or institutional practice, and in compliance with the cilta-cel study protocol and local labels for the vaccine. Below is general guidance for consideration.

Many vaccines against COVID-19 are being developed with different technologies and platforms and may have safety and efficacy profiles that are not fully characterized even after preliminary health authority approval. However, the benefit-risk ratio of receiving a COVID-19 vaccine among patients with multiple myeloma participating in cilta-cel studies is considered to be positive and should be considered for administration while in compliance with the cilta-cel study protocol and when not otherwise contraindicated for use in the vaccine label.

Per protocol, live attenuated vaccines must be completed at least 6 weeks prior to lymphodepletion therapy or initiated at least 100 days after cilta-cel infusion. There are no specific timing restrictions for inactivated vaccines, which include vaccines which use alternative technology like mRNA or replication-incompetent viral vectors, per protocol. Enrollment into an interventional clinical trial for an experimental vaccine is prohibited during study. Any vaccination, including COVID-19 vaccinations, must be recorded on the Concomitant Medication page of the eCRF.

No data is currently available to suggest that COVID-19 vaccines pose specific or additional safety risk beyond other vaccines for cancer patients undergoing treatment. Theoretically, a diminished immune response may occur in immunocompromised patients, and therefore these patients may have reduced vaccine effectiveness.

While not specifically required per protocol, it is encouraged to complete the COVID-19 vaccine series at least 2 weeks prior to lymphodepletion, and to delay vaccination for at least 3 months after cilta-cel infusion, to maximize immune response.

Several organizations and journals have published recommendations for COVID-19 vaccine administration in cancer patients, including:

- European Society for Blood and Marrow Transplantation (EBMT)

  https://www.ebmt.org/covid-19-and-bmt

- American Society for Transplantation and Cellular Therapy (ASTCT)

  https://www.hematology.org/covid-19/ash-astct-covid-19-vaccination-for-hct-and-car-t-cell-recipients

- National Comprehensive Cancer Network (NCCN)

  https://www.nccn.org/covid-19/pdf/COVID-19_Vaccination_Guidance_V2.0.pdf

- Centers for Disease Control and Prevention (CDC)

  https://www.cdc.gov/vaccines/covid-19/info-by-product/clinical-considerations.html

- Nature Reviews Clinical Oncology: COVID-19 vaccine guidance for patients with cancer participating in oncology clinical trials. Desai A, Gainor JF, Hegde A, et al. (March 15, 2021). DOI: 10.1038/s41571-021-00487-z

- https://www.nature.com/articles/s41571-021-00487-z

Investigators should inform patients that emerging data show that patients receiving cilta-cel are possibly at higher risk of severe/fatal outcomes from COVID-19 infection compared with patients receiving standard of care therapy (see Section 6.2.7).

Based on guidance from the organizations listed above, the following measures should be implemented to minimize subjects' risk of severe COVID-19 infection:

- Subjects, particularly those who are less than 6 to 9 months from cilta-cel infusion, should be reminded that the ongoing pandemic is still putting them at risk of contracting COVID-19. Investigators should ask subjects to continue to limit their risk of exposure to infected individuals as much as possible and strictly adhere to prevention measures such as proper masking, hand hygiene, social distancing, and avoiding travel and public transportation to the extent possible.
- Investigators should discuss with subjects the importance of COVID-19 vaccines in the prevention of severe illness, hospitalization, and death from COVID-19. Subjects should assume that any vaccination administered prior to lymphodepletion and cilta-cel infusion no longer provides protection. For this reason, it is strongly recommended that all subjects receive a full COVID-19 vaccination series (eg, a primary series of 3 vaccines and a 4th booster dose for mRNA vaccines; note: mRNA vaccines are recommended), no sooner than 3 months after cilta-cel infusion, regardless of vaccination status prior to cilta-cel. In addition, if not already vaccinated, caregivers, family, and household contacts should be advised to receive COVID19 vaccination as well.
- Investigators should consider prophylaxis (eg, Evusheld, if available in the region) to reduce subjects' risk of severe/fatal COVID-19 during the first 6 to 9 months after cilta-cel. It is critical that subjects understand that multiple myeloma patients (even those who have not received CAR-T therapy) may not seroconvert until after the 3rd vaccine dose and as a result they may remain at a very high risk of severe COVID-19 for at least 2 to 3 months after starting vaccination (Aleman 2022).
- Investigators should instruct subjects to notify them or study site staff immediately if they are diagnosed with COVID-19, even if they are asymptomatic, so that appropriate treatment measures can be determined.
- If available in the region, antivirals (eg, Paxlovid or other available agents) should be considered early after COVID-19 diagnosis. Subjects may remain asymptomatic or have minimal symptoms for a period of time prior to deteriorating. Investigators should make subjects aware that these drugs may potentially significantly lower their risk of severe COVID-19.

Attachment 21: Myeloma Frailty Score Calculator

MYELOMA FRAILTY SCORE CALCULATOR

Developed by International Myeloma Working Group for the prognosis of elderly myeloma patients.

The score system (range 0-5), based on age, comorbidities, cognitive and physical conditions, developed by Palumbo A. et al[1], identifies 3 groups of patients:

- fit (score=0)
- intermediate-fitness (score=1)
- frail (score≥2)

The 3-year overall survival was 84% in fit patients, 76% in intermediate-fitness patients (HR 1.61, 95%CI 1.02-2.56, p=0.042) and 57% in frail patients (HR 3.57 CI 95% 2.37-5.39, p<0.001). The cumulative incidence of grade ≥3 non-hematologic adverse events at 12 months was 22.2% in fit, 26.4% in intermediate-fitness (HR 1.23, 95%CI 0.89-1.71; p 0.217) and 34.0% (HR 1.74, 95%CI 1.28-2.38; p<0.001) in frail patients. The cumulative incidence of treatment discontinuation at 12 months was 16.5% in fit, 20.8% in intermediate-fitness (HR 1.41, 95%CI 1.00-2.01, p=0.052) and 31.2% (HR 2.21, 95%CI 1.57-3.09; p<0.001) in frail patients.

This frailty score predicts mortality and the risk of toxicity in elderly myeloma patients. The International Myeloma Working group proposes this score for the measurement of frailty in the treatment decision-making process and in designing future clinical trials.

[1]Palumbo A, Bringhen S, Mateos MV, et al. Geriatric assessment predicts survival and toxicities in elderly myeloma patients: an International Myeloma Working Group report. Blood. 2015 Mar 26;125(13):2068-7

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Attachment 22: Characterization of Imaging Response

via PET/CT

complete response:	normalization of abnormal metabolic activity due to multiple myeloma disease activity
partial response:	>/= 50% decrease in sum of products of the longest perpendicular dimensions of dominant lesions
stable disease:	not meeting criteria for partial response or progressive disease
progressive disease:	>/= 50% increase in product of longest perpendicular diameters of dominant lesions and/or new lesions

via Whole Body MRI

complete response:	bone marrow highly likely to be responding and/or for soft-tissue disease, RECIST version 1.1 criteria for CR
partial response:	bone marrow likely to be responding and/or for soft-tissue disease, RECIST version 1.1 criteria meeting requirements for PR
stable disease:	not meeting criteria for partial response or progressive disease
progressive disease:	bone marrow highly likely to be progressing and/or soft-tissue disease, RECIST version 1.1 criteria meeting requirements for PD

References:

Cavo 2017
Cheson 2007
Eisenhauer 2009
Messiou 2019

Attachment 23: Recommendations for the Reporting of Imaging Results

At Baseline

A radiological report on whole-body imaging in patients with monoclonal plasma cell disorders should include:

A. Infiltration and bone destruction pattern:
   a. Minimal (normal appearing)
   b. Focal lesions
   c. Diffuse infiltration and bone destruction
   d. Mixed (focal lesions on diffuse background)

B. Absolute number of focal lesions:
   a. For whole body MRI: 0, 1, 2–7, or >7
   b. For PET/CT: 0, 1–3, or >3

C. Number of fractures (new vs old, location, and likelihood of malignant vs benign cause)

D. Extramedullary disease

E. Soft tissue masses growing out of the bone marrow into the surrounding tissue

F. Infiltration of the long bones

G. Evidence of surgical procedures at the skeletal system

H. Incidental findings

In Remission

Differentiate these findings with regards to response to therapy in imaging (guidelines papers for PET/CT and whole body MRI):

A. Response
   a. Normalization of bone marrow signal in previously affected areas
   b. Decrease in the number and size of focal lesions
   c. Resolution of severely infiltrated bone marrow infiltrate into focal lesions
   d. Decrease in the of number and size of soft tissue tumors (paramedullary and extramedullary)

B. No change

C. Progression
   a. Worsening of diffuse bone marrow signal or new appearance of infiltration in previously unaffected areas
   b. Increase in the number and size of focal lesions
   c. Merging of focal lesions into severely infiltrated bone marrow
   d. Increase in the size or number of soft tissue tumors (paramedullary and extramedullary)

D. Cystic or liquid transformation of focal lesions after therapy (for Whole Body MRI only)

Source: Hillengass 2019

Attachment 24: Asthma Guidelines

Components of Severity		Classification of Asthma Severity											
		Intermittent			Persistent								
					Mild			Moderate			Severe		
		0-4 yrs	5-11 yrs	12 + yrs	0-4 yrs	5-11 yrs	12 + yrs	0-4 yrs	5-11 yrs	12 + yrs	0-4 yrs	5-11 yrs	12 + yrs
Impairment Normal FEV_1/FVC : 8-19 yr 85% 20-39 yr 80% 40-59 yr 75% 60-80 yr 70%	Symptoms	≤ 2 days/week			more than 2 days/week but not daily			Daily			Throughout the day		
	Nighttime awakenings	0	≤ 2x/month		1-2x/ month	3-4x/month		3-4x/ month	> 1x/week but not nightly		> 1x/ month	Often 7x/week	
	SABA use for symptom control (not prevention of EIB)	≤ 2 days/week			≤ 2 days/week but not daily		>2 days/ week but not daily, and not more than 1x on any day	Daily			Several time per day		
	Interference with normal activity	None			Minor limitation			Some limitation			Extremely limited		
	Lung function FEV1 FEV1/FVC	N/A	Normal FEV1 between exacerbations >80% >85%	Normal FEV1 between exacerbations >80% Normal	N/A	>80% >80%	>80% Normal	N/A	60-80% 75-80%	60-80% Reduced 5%	N/A	<60% <75%	<60% Reduced 5%

Components of Severity		Classification of Asthma Severity											
		Intermittent			Persistent								
					Mild			Moderate			Severe		
		0-4 yrs	5-11 yrs	12 + yrs	0-4 yrs	5-11 yrs	12 + yrs	0-4 yrs	5-11 yrs	12 + yrs	0-4 yrs	5-11 yrs	12 + yrs
Risk	Exacerbations requiring oral systemic corticosteroids	0-1/year			≥ 2 exacerbations in 6 months requiring oral steroids or >4 wheezing episodes/1-year lasting >1 day and risk factors for persistent asthma	≥2/year Relative annual risk may be related to FEV1.	≥2/year Relative annual risk may be related to FEV1.	≥ 2 exacerbations in 6 months requiring oral steroids or >4 wheezing episodes/1-year lasting >1 day and risk factors for persistent asthma	≥ 2/year Relative annual risk may be related to FEV1.	≥ 2/year Relative annual risk may be related to FEV1.	≥ 2 exacerbations in 6 months requiring oral steroids or >4 wheezing episodes/ 1-year lasting >1 day and risk factors for persistent asthma	≥2/year Relative annual risk may be related to FEV1.	≥2/year Relative annual risk may be related to FEV1.
		Consider severity and interval since last exacerbation. Frequency and severity may fluctuate over time for subjects in any severity category.											
Recommended Step for Initiating Treatment		Step 1			Step 2			Step 3 and consider short course of oral steroids	Step 3: medium dose ICS and consider short course of oral steroids	Step 3 and consider short course of oral steroids	Step 3 and consider short course of oral steroids	Step 3: medium dose ICS OR Step 4 and consider short course of oral steroids	Step 4 or 5 and consider short course of oral steroids
		In 2-6 weeks, evaluate level of asthma control that is achieved. 0-4 years: If no clear benefit is observed in 4-6 weeks, stop treatment and consider alternate diagnosis or adjusting therapy. 5-11 and 12+ years: adjust therapy accordingly.											

Components of Control		Classification of Asthma Control								
		Well Controlled			Not Well Controlled			Very Poorly Controlled		
		0-4 yrs	5-11 yrs	12 + yrs	0-4 yrs	5-11 yrs	12 + yrs	0-4 yrs	5-11 yrs	12 + yrs
	Symptoms	≤ 2 days/week but not more than once on each day		≤ 2 days/ week	> 2 days/week or multiple times on ≤2 days/week		> 2 days/ week	Throughout the day		
Impairment	Nighttime awakenings	≤ 1x/month		≤ 2x/month	> 1x/month	≥ 2x/month	1-3x/week	> 1x/week	≥ 2x/week	≥ 4x/week
	Interference with normal activity	None			Some limitation			Extremely limited		
	SABA use for symptom control (not prevention of EIB)	≤ 2 days/week			> 2 days/week			Several times per day		
	Lung function FEV1 or peak flow FEV1/FVC	N/A	> 80% > 80%	> 80%	N/A	60-80% 75-80%	60-80%	N/A	< 60% < 75%	< 60%
	Validated questionnaires ATAQ ACQ ACT			0 ≤ 0.75 ≥ 20			1-2 ≥ 1.5 16-19			3-4 N/A ≤ 15
Risk	Exacerbations requiring oral systemic corticosteroids	0-1/year			≥ 2/year					
		Consider severity and interval since last exacerbation								
	Reduction in lung growth/ Progressive loss of lung function	Evaluation requires long-term follow-up								
		• Maintain current step • Regular follow-up every 1-6 months			Step up 1 step	Step up at least 1 step	• Step up 1 step • Reevaluate	• Consider short course of oral steroids • Step up 1-2 steps		• Consider short course of oral steroids

Components of Control	Classification of Asthma Control								
	Well Controlled			Not Well Controlled			Very Poorly Controlled		
	0-4 yrs	5-11 yrs	12 + yrs	0-4 yrs	5-11 yrs	12 + yrs	0-4 yrs	5-11 yrs	12 + yrs
Recommended Action for Treatment	• Consider step down if well controlled for at least 3 months			• **Before step up**: Review adherence to medication, inhaler technique, and environmental control. If alternative treatment was used, discontinue it and use preferred treatment for that step. • **Reevaluate the level of asthma control in 2-6 weeks to achieve control**. 0-4 years: If no clear benefit is observed in 4-6 weeks, consider alternative diagnoses or adjusting therapy. 5-11 years: Adjust therapy accordingly. • **For side effects**, consider alternative treatment options.		in 2-6 weeks • For side effects, consider alternative treatment options	• **Before step up**: Review adherence to medication, inhaler technique, and environmental control. If alternative treatment was used, discontinue it and use preferred treatment for that step. • **Reevaluate the level of asthma control in 2-6 weeks to achieve control**. 0-4 years: If no clear benefit is observed in 4-6 weeks, consider alternative diagnoses or adjusting therapy. 5-11 years: Adjust therapy accordingly. • **For side effects**, consider alternative treatment options.		• Step up 1-2 steps • Reevaluate in 2 weeks • For side effects, consider alternative treatment options

Attachment 25: Antihistamines That May Be Used Predose

The following antihistamines may be used predose, before Dara-SC injection (including, but not limited to):

- Diphenhydramine
- Cetirizine
- Fexofenadine
- Loratadine
- Clemastine
- Dexchlorpheniramine
- Promethazine*

* The IV use of promethazine should be avoided.

Attachment 26: Adverse Event Reporting Guidance for Study 68284528MMY2003

Reporting Guidelines for Adverse Events for Cohorts A-F in eCRF:

<table>
<tr><th colspan="5">Duration of Study</th><th rowspan="2">LTFU Study[d]</th></tr>
<tr><th>Signing of ICF</th><th>Day 1 Cilta-Cel</th><th>Day 100 Post Cilta-Cel[a]</th><th>1 Year Post Cilta-Cel</th><th>End of Study</th></tr>
<tr><td colspan="3">All AEs, regardless of causality</td><td colspan="2">Related AEs, per investigator</td><td></td></tr>
<tr><td colspan="6">All SAEs (regardless of causality)</td></tr>
<tr><td rowspan="7"></td><td colspan="5">SPMs (all grades, regardless of causality or seriousness)[b, c]</td></tr>
<tr><td colspan="3">HBV Reactivation (all grades, regardless of causality or seriousness)</td><td colspan="2">≥Grade 3 HBV Reactivation (regardless of causality or seriousness)</td></tr>
<tr><td colspan="3">COVID-19 Infection, all grades (including asymptomatic COVID-19)</td><td colspan="2">≥Grade 3 COVID-19 Infection (regardless of causality or seriousness)</td></tr>
<tr><td colspan="5">New or Exacerbation of Neurologic Disorder (all grades, regardless of causality or seriousness)</td></tr>
<tr><td colspan="5">New or Exacerbation of Rheumatologic or Other Autoimmune Disorder (all grades, regardless of causality or seriousness)</td></tr>
<tr><td colspan="5">≥Grade 3 Hematologic Disorder (regardless of causality or seriousness)</td></tr>
<tr><td colspan="5">≥Grade 3 Infection (regardless of causality or seriousness)</td></tr>
</table>

[a] Or 30 days after last dose of lenalidomide, whichever is later, for Cohort D and Cohort E.
[b] For reporting purposes, this includes both new primary malignancies and recurrence of pre-existing malignancies with the exception of recurrent multiple myeloma (ie, disease progression).
[c] In the event of malignancy, a tumor sample should be collected and vector integration site analysis may be performed for possible insertional mutagenesis.
[d] Refer to the Study 68284528MMY4002 for specific details.

Note: Adverse events and special reporting situations, whether serious or non-serious, will be collected for 30-days after the last study procedure for subjects who are enrolled (cohort-specific) and unable to undergo apheresis or receive bridging therapy, conditioning regimen, or JNJ-68284528; these subjects will continue to be followed for survival and subsequent anti-myeloma therapies until the end of the study.

Expedited Reporting Guidelines for Cohorts A-F to Sponsor GMS:

<table>
<tr><th colspan="3">Duration of Study</th></tr>
<tr><th>Signing of ICF</th><th>Day 1 Cilta-Cel</th><th>End of Study</th></tr>
<tr><td>Expedited Reporting[a] of all SAEs (regardless of causality) for duration of study.</td><td colspan="2">Expedited Reporting[a] of all SAEs, and following AESIs (regardless of causality or seriousness):
• ≥Grade 3 CRS
• ≥Grade 3 Neurotoxicity
• Any grade movement and neurocognitive toxicity (ie, parkinsonism)
• SPMs (any grade)</td></tr>
</table>

[a] Expedited reporting includes reporting to Sponsor Global Medical Safety within 24 hours via SAE Fax Form or other defined SAE reporting process per protocol.

Attachment 27: Country/Territory-specific Requirements

Requirements for France

Section	Requirement	Amendment No.
Table 1, Cohort G, Cohort H, Cohort C, and Cohort F: Time and Events Schedule for Study Procedures/ Assessments; Table 3, Cohort D: Time and Events Schedule for Study Procedures/ Assessments; Table 5, Cohort E: Time and Events Schedule for Study Procedures/Assessments (Screening to Conditioning Regimen); Table 6, Cohort E: Time and Events Schedule for Study Procedures/ Assessments (JNJ-68284528 Infusion to Post-treatment)	Routine neurologic examination was added to Time and Events Schedules in response to French health authority request. • For Table 1, Table 3, and Table 6, a 'neurologic examination' row has been added, with assessments planned for the following timepoints: Day 1; as clinically indicated and before hospital discharge; Day 28; Day 56; Day 78; Day 100; Day 128; Day 156; Day 184; and every 6 months (±1 month) until 3 years post-dose of JNJ-68284528 or End of Cohort, whichever occurs first. Timeframe for collection of handwriting samples was extended in response to French health authority request. • For Table 1, Table 3, and Table 6, in the Post-treatment Period (Lenalidomide Treatment Period for Cohort D; Lenalidomide Consolidation Treatment Period for Cohort E), the timeframe in which handwriting assessments will be performed has been extended, from 'Perform monthly up to Day 184' to 'Perform monthly until 1 year post JNJ-68284528 infusion'.	1

Table 1: Cohort G, Cohort H, Cohort C, and Cohort F: Time and Events Schedule for Study Procedures/Assessments

	Screening Phase	**Apheresis**	**Cyclophosphamide and fludarabine conditioning regimen**	**JNJ-68284528 Infusion**	**Post Infusion (Day 1 to Day 100) (any subject who received an infusion of JNJ-68284528 should continue all subsequent assessments)**										**Post-treatment (Day 101 and up to End of Cohort)**
	≤28 days prior to apheresis	**Upon enrollment**	**Day -5,* -4, -3 *Window of Day -7 to Day -5**	**Day 1 (Infusion)**	**Day 3**	**Day 7 (± 1 day)**	**Day 10 (± 1 day)**	**Day 14 (± 1 day)**	**Day 21 (± 1 day)**	**Day 28 (± 2 days)**	**Day 35 (± 2 days)**	**Day 42 (± 2 days)**	**Day 56 (± 2 days)**	**Day 78 (± 2 days)**	**Day 100 (± 2 days)**	**(every 28 days up to Day 352 then every 56 days)(± 7 days)**
Screening Assessments															
Neurologic Examination				X (prior to JNJ-68284528 infusion)	Perform as clinically indicated and before hospital discharge (see Table 11 for hospitalization requirements)					X			X	X	X	Days 128, 156, 184 (±7 days). Then every 6 months (±1 month) until 3 years post-dose of JNJ-68284528 or End of Cohort, whichever occurs first
Handwriting sample				X (≤24 hours prior to infusion)	X	X	X	X	X	X	X	X	X	X	X	Perform monthly until 1 year post JNJ-68284528 infusion

Table 3: Cohort D: Time and Events Schedule for Study Procedures/Assessments

	Screening Phase	**Apheresis**	**Lenalidomide (upon adequate hematologic recovery from ASCT)**	**Cyclophosph-amide and fludarabine conditioning regimen**	**JNJ-68284528 Infusion**	**Post Infusion (Day 1 to Day 100) (any subject who received an infusion of JNJ-68284528 should continue all subsequent assessments)**										**Lenalidomide Treatment Period (As early as Day 22 and up to End of Cohort)**
	≤28 days prior to apheresis	**Upon enrollment**	**Cycle 1 (Additional Cycles permitted with Sponsor approval)**	**Day -5,* -4, -3 *Window of Day -7 to Day -5**	**Day 1 (Infusion)**	**Day 3**	**Day 7 (± 1 day)**	**Day 10 (± 1 day)**	**Day 14 (± 1 day)**	**Day 21 (± 1 day)**	**Day 28 (± 2 days)**	**Day 35 (± 2 days)**	**Day 42 (± 2 days)**	**Day 56 (± 2 days)**	**Day 78 (± 2 days)**	**Day 100 (± 2 days)**	**(every 28 days up to Day 352 then every 56 days) (± 7 days)**
Screening Assessments																	
Neurologic Examination					X (prior to JNJ-68284528 infusion)	Perform as clinically indicated and before hospital discharge (see Table 11 for hospitalization requirements)					X			X	X	X	Days 128, 156, 184 (±7 days). Then every 6 months (±1 month) until 3 years post-dose of JNJ-68284528 or End of Cohort, whichever occurs first
Handwriting sample					X (≤24 hours prior to infusion)	X	X	X	X	X	X	X	X	X	X	X	Perform monthly until 1 year post JNJ-68284528 infusion

Table 6: Cohort E: Time and Events Schedule for Study Procedures/Assessments (JNJ-68284528 Infusion to Post-treatment)

	JNJ-68284528 Infusion	**Post Infusion (Day 1 to Day 100) (any subject who received an infusion of JNJ-68284528 should continue all subsequent assessments)**										**Consolidation Lenalidomide Treatment (As early as day 21 and up to End of Cohort)**
	Day 1 (Infusion)	**Day 3**	**Day 7 (± 1 day)**	**Day 10 (± 1 day)**	**Day 14 (± 1 day)**	**Day 21 (± 1 day)**	**Day 28 (± 2 days)**	**Day 35 (± 2 days)**	**Day 42 (± 2 days)**	**Day 56 (± 2 days)**	**Day 78 (± 2 days)**	**Day 100 (± 2 days)**	**(every 28 days) (± 7 days)**
Screening Assessments													
Neurologic Examination	X (prior to JNJ-68284528 infusion)	Perform as clinically indicated and before hospital discharge (see Table 11 for hospitalization requirements)					X			X	X	X	Days 128, 156, 184 (±7 days). Then every 6 months (±1 month) until 3 years post-dose of JNJ-68284528 or End of Cohort, whichever occurs first
Handwriting sample	X (≤24 hours prior to infusion)	X	X	X	X	X	X	X	X	X	X	X	Perform monthly until 1 year post JNJ-68284528 infusion

- For Table 5, a 'neurologic examination' row has been added, with assessments planned for the following timepoints: at Screening and as clinically indicated during induction.

Table 5: Cohort E: Time and Events Schedule for Study Procedures/Assessments (Screening to Conditioning Regimen)

	Screening Phase	**Induction Treatment D-VRd** (Cycles 1-4, 21-Day Cycle) Upon enrollment			**Apheresis** *Note: Occurs after Cycle 1 or 2, before Cycle 3* Minimum of 21 days after last dose of D-VRd	Peripheral Stem Cell Mobilization and Harvesting (Optional)[c]	**Cyclophosphamide and fludarabine conditioning regimen** Upon recovery from C4 Induction therapy; Minimum of 21 days after last dose of D-VRd
	≤28 days prior to Induction Treatment	D1	D8 (±2 days)	D15 (±2 days)		After apheresis (Post-Induction Cycle 2, 3 or 4)	**Day -5,* -4, -3 *Window of Day -7 to Day -5**
Screening Assessments							
Neurologic examination	X	As clinically indicated during induction					

9.7.9 Physical Examination; 9.7.11 Neurologic Examination;	In Section 9.7.9 and Section 9.7.11 the following text that is specific to France: 'Neurologic examination will be performed according to the Time and Events Schedules.' has been updated to: 'Refer to Attachment 27 for the schedule of neurologic examinations specific to France.'	1

INVESTIGATOR AGREEMENT

I have read this protocol and agree that, in conjunction with the accompanying protocol, it contains all necessary details for carrying out this study. I will conduct the study as outlined herein and will complete the study within the time designated.

I will provide copies of the protocol and all pertinent information to all individuals responsible to me who assist in the conduct of this study. I will discuss this material with them to ensure that they are fully informed regarding the study intervention, the conduct of the study, and the obligations of confidentiality.

Coordinating Investigator (where required):

Name (typed or printed): _____

Institution and Address: _____

_____

_____

_____

Signature: _____ Date: _____

(Day Month Year)

Principal (Site) Investigator:

Name (typed or printed): _____

Institution and Address: _____

_____

_____

_____

Telephone Number: _____

Signature: _____ Date: _____

(Day Month Year)

Sponsor's Responsible Medical Officer:

Name (typed or printed): Nikoletta Lendvai, MD

Institution: Clinical Research and Development
US Clinical Oncology

Signature: electronic signature appended at the end of the protocol Date: 23 October 2023

(Day Month Year)

Note: If the address or telephone number of the investigator changes during the study, written notification will be provided by the investigator to the sponsor, and a protocol amendment will not be required

Signature

User	Date	Reason
Lendvai Nikoletta 1071465	23-Oct-2023 19:11:16 (GMT)	Document Approval