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 1

JNJ-68284528

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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 1	31 October 2019
Original Protocol	7-Jun-2019

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	
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	

Section number and Name	Description of Change	Brief Rationale
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.
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

Section number and Name	Description of Change	Brief Rationale
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.	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	
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	

Section number and Name	Description of Change	Brief Rationale
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
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 A and B; 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	

Section number and Name	Description of Change	Brief Rationale
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.	
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).	

Section number and Name	Description of Change	Brief Rationale
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
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.	

Section number and Name	Description of Change	Brief Rationale
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
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

Section number and Name	Description of Change	Brief Rationale
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
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

JNJ-68284528 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 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 express an identical CAR protein. The JNJ-68284528 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 JNJ-68284528 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.

PRIMARY OBJECTIVE, ENDPOINT

Objective	Endpoint
Primary	
• To evaluate the overall minimal residual disease (MRD) negative rate of subjects who receive JNJ-68284528	• MRD negative rate (10^{-5} threshold) as defined by the International Myeloma Working Group (IMWG) criteria using next generation sequencing (NGS)

STUDY HYPOTHESES

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

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. Multiple patient populations of unmet medical need will be studied. Approximately 20 subjects will be enrolled in each cohort. 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: recently diagnosed 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

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). JNJ-68284528 will be generated from the subject's T cells selected from the apheresis product. After JNJ-68284528 production and product release, subjects will receive a conditioning regimen of cyclophosphamide and fludarabine. JNJ-68284528 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 JNJ-68284528. Cohorts A, B, and C will be considered complete after the last subject has had 2 years of follow-up after the initial dose of JNJ-68284528. Cohort D will be considered complete after the last subject has discontinued lenalidomide for 4 weeks or 2 years after receiving the initial dose of JNJ-68284528, whichever is later.

DOSAGE AND ADMINISTRATION

All 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 $mL/min/1.73m^2$. JNJ-68284528 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).

Subjects in Cohort D will also receive the following:

- After apheresis and prior to administration of cyclophosphamide and fludarabine (conditioning regimen prior to JNJ-68284528 infusion): 1 cycle 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).
- After infusion of JNJ-68284528: All subjects will initiate lenalidomide at a minimum of 21 days post JNJ-68284528 infusion after resolution of cytokine release syndrome (CRS) or neurological toxicities associated with JNJ-68284528. 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 will depend on the level of hematologic recovery.
  - Criteria for lenalidomide administration after JNJ-68284528 infusion are summarized 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 5mg daily, increase to 10mg 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, 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.

EVALUATIONS

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.

Blood and serum samples will be collected for assessment of JNJ-68284528 pharmacokinetics, immunogenicity (antibodies to JNJ-68284528), and predictive biomarkers of response or resistance to JNJ-68284528.

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 neurological examination), assessments of cardiac function, Immune Effector Cell-associated Encephalopathy (ICE) score. Performance status will be assessed with the ECOG scale.

STATISTICAL METHODS

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

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

Table 1: Cohort A, Cohort B, and Cohort C: 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**	**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 42 (± 2 days)**	**Day 56 (± 2 days)**	**Day 78 (± 2 days)**	**Day 100 (± 2 days)**[c]	**(every 28 days up to 12 months 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	X														
Disease Characteristics[e]	X														
ECOG performance status	X		Prior to 1st dose only	X								X		X	
12-lead ECG	X		As clinically indicated												
Physical Examination	X		A symptom-directed physical examination should be performed as clinically indicated												
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 resolved.										
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 (predose)											

Table 1: Cohort A, Cohort B, and Cohort C: 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**	**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 42 (± 2 days)**	**Day 56 (± 2 days)**	**Day 78 (± 2 days)**	**Day 100 (± 2 days)**[c]	**(every 28 days up to 12 months then every 56 days)**[d] **(± 7 days)**
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 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) ≤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 participant's home by mobile study personnel (i.e. nurses and mobile phlebotomist) in the post-treatment period, after the Day 100.															
Hematology	X	X (Prior to apheresis [same day])	Prior to 1st dose only (≤72 hour window)	X (predose) ≤24-hour window	X	X	X	X	X	X	X	X	X	X	
Chemistry	X	X (≤72 hour window)	Prior to 1st dose only (≤72 hour window)	X (predose) ≤24-hour window	X	X	X	X	X	X	X	X	X	X	
Serology [g]	X				For subjects at risk for HBV activation monitor HBV DNA and AST/ALT every 12 weeks (±7 days) for 12 months post JNJ-68284528 dose [g]										
Coagulation (PT/INR, aPTT, fibrinogen, D-dimer)	X			As clinically indicated for subjects who have fever or other signs of potential CRS											

Table 1: Cohort A, Cohort B, and Cohort C: 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**	**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 42 (± 2 days)**	**Day 56 (± 2 days)**	**Day 78 (± 2 days)**	**Day 100 (± 2 days)**[c]	**(every 28 days up to 12 months then every 56 days)**[d] **(± 7 days)**
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											
Infectious Disease Testing[h]		X													
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 SIPPM 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. 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 within the US, blood samples collection may be performed at the participant'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])												

Table 1: Cohort A, Cohort B, and Cohort C: 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	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 42 (± 2 days)	Day 56 (± 2 days)	Day 78 (± 2 days)	Day 100 (± 2 days)[c]	(every 28 days up to 12 months then every 56 days)[d] (± 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 Day 56, at suspected CR and, relative to Day 1, at 6 month, 12 month, 18 month (Day 520), 24 (Day 744) months (± 16 days) and then yearly for subjects that achieve CR/sCR and remain on study up to 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		As clinically indicated to document disease progression or response.												
Assess extramedullary Plasmacytomas [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 (for all subjects with a history of plasmacytomas or as clinically indicated for others) Day 28 to 100 (±2 day window), Day 101 and later (±7 day 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				X				X		X	X	X	X; every 112 days (±7 days)
MySIm-Q (Optional)	X	X				X				X		X	X	X	X; every 112 days (±7 days)

Table 1: Cohort A, Cohort B, and Cohort C: 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	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 42 (± 2 days)	Day 56 (± 2 days)	Day 78 (± 2 days)	Day 100 (± 2 days)[c]	(every 28 days up to 12 months then every 56 days)[d] (± 7 days)
PGIS	X	X				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
Ongoing Subject Review															
Adverse Events	Continuous from the time of signing of ICF until 100 days after last administration of any study treatment. 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 Second primary malignancies should be followed from the time of signing of ICF signing to study completion [p] CRS should be evaluated according to the ASBMT (ASTCT) consensus grading (Lee 2019) (Attachment 2) CAR-T cell-related neurotoxicity (eg, ICANS) should be graded according to the ASBMT (ASTCT)consensus grading (Attachment 4) Events of HBV reactivations should be reported during the first year post-dosing of JNJ-68284528														
Concomitant medication	Continuous from the time of signing of ICF until 100 days after last administration of any study treatment														
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); CR=complete response; sCR=stringent complete response; CRS= cytokine release syndrome; CT=computed tomography; CTCAE=Common Terminology Criteria for Adverse Events; D=Day; 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; 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.

[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. The end of each study cohort will be defined as 2 years after the last subject in that particular cohort received his or her initial dose of JNJ-68284528

[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 should be performed before pre-medication with diphenhydramine

[g] Hepatitis B**:** 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-HBs positive and anti-HBc positive); Only in subjects who are positive for antibodies to hepatitis B core antigen (anti-HBc) and/or antibodies to hepatitis B surface antigen (anti-HBs). Monitor HBV-DNA, AST/ALT every 12 weeks (±7 days) for 12 months post-dose of JNJ-68284528. Subjects with serologic findings suggestive of HBV vaccination (anti-HBs positivity as the only serologic marker) and a known history of prior HBV vaccination do not need to be tested for HBV-DNA by PCR. Hepatitis C**:** HCV antibody, HCV RNA (for subjects who are anti HCV positive); HIV serology. See Attachment 10

[h] HIV, hepatitis B, hepatitis C, HTLV, and other infectious diseases as applicable per local regulations

[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.

[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

[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.

Table 2: Cohort A, Cohort B, and Cohort C: 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 (± 2 days)	Day 28 (± 2 days)	Day 42 (± 2 days)	Day 56 (± 2 days)	Day 78 (± 2 days)	Day 100 (± 2 days)	Day 184 (±7 days)		
Pharmacokinetics																		
PK CAR transgene levels blood sample[b]			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
Biomarker Sampling																		
Immuno-phenotyping (whole blood)[d, f]		X	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[d]

Table 2: Cohort A, Cohort B, and Cohort C: 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 (± 2 days)**	**Day 28 (± 2 days)**	**Day 42 (± 2 days)**	**Day 56 (± 2 days)**	**Day 78 (± 2 days)**	**Day 100 (± 2 days)**	**Day 184 (±7 days)**		
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					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 (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, 6, and 12 months; then yearly for 15 years post infusion												

Table 2: Cohort A, Cohort B, and Cohort C: 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 (± 2 days)**	**Day 28 (± 2 days)**	**Day 42 (± 2 days)**	**Day 56 (± 2 days)**	**Day 78 (± 2 days)**	**Day 100 (± 2 days)**	**Day 184 (±7 days)**		
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; 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

[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] For subjects in the US, 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

[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

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)**	**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 21 and up to End of Cohort)[c]**
	≤28 days prior to apheresis[a]	**Upon enrollment**	**Cycle 1**	**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 42 (± 2 days)**	**Day 56 (± 2 days)**	**Day 78 (± 2 days)**	**Day 100 (± 2 days)[c]**	**(every 28 days up to 12 months 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	X															
Disease Characteristics[e]	X															
ECOG performance status	X			Prior to 1st dose only	X								X		X	
12-lead ECG	X		As clinically indicated													
Physical Examination	X		A symptom-directed physical examination should be performed as clinically indicated													
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 resolved.										

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) [c]										Lenalidomide Treatment Period (As early as Day 21 and up to End of Cohort)[c]
	≤28 days prior to apheresis[a]	Upon enrollment	Cycle 1	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 42 (± 2 days)	Day 56 (± 2 days)	Day 78 (± 2 days)	Day 100 (± 2 days)[c]	(every 28 days up to 12 months then every 56 days)[d, t] (± 7 days)
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								
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)											

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)[c]**										**Lenalidomide Treatment Period (As early as Day 21 and up to End of Cohort)[c]**
	≤28 days prior to apheresis[a]	**Upon enrollment**	**Cycle 1**	**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 42 (± 2 days)**	**Day 56 (± 2 days)**	**Day 78 (± 2 days)**	**Day 100 (± 2 days)[c]**	**(every 28 days up to 12 months then every 56 days)[d, t] (± 7 days)**
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 participant's home by mobile study personnel (i.e. nurses and mobile phlebotomist) in the post-treatment period, after the Day 100.																
Hematology[s]	X	X (Prior to apheresis [same day])	X (as only 1 cycle is given): within 24 hrs of 1st dose)	Prior to 1st dose only (≤72 hour window)	X (predose)	X	X	X	X	X	X	X	X	X	X	X (weekly for the first 2 cycles, twice a month for Cycle 3 then once a month at start of each Len cycle)
Chemistry[s]	X	X (≤72 hour window)	X (as only 1 cycle is given): within 24 hrs of 1st dose)	Prior to 1st dose only (≤72 hour window)	X (predose)	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 activation monitor HBV DNA and AST/ALT every 12 weeks (±7 days) s for 12 months post JNJ-68284528 dose [g]										
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 of 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 and repeated at a maximum of at least every 28 days (or every 14 days for women of child bearing 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										

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)[c]										Lenalidomide Treatment Period (As early as Day 21 and up to End of Cohort)[c]
	≤28 days prior to apheresis[a]	Upon enrollment	Cycle 1	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 42 (± 2 days)	Day 56 (± 2 days)	Day 78 (± 2 days)	Day 100 (± 2 days)[c]	(every 28 days up to 12 months then every 56 days)[d, t] (± 7 days)
Infectious Disease Testing[h]		X														
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														
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 SIPPM and IPPI for administration of JNJ-68284528)					X											
Lenalidomide			Start at 10mg if NC ≥1.0 x 10^9/L and platelets ≥75 x 10^9/L x1 28-day cycle			Initiate lenalidomide a minimum of 21 days post JNJ-68284528 after resolution of associated CRS or neurological toxicities. Refer to Table 8 and Section 6.1.4 for additional dosing considerations Lenalidomide will be taken daily (continuously) in 28-day cycles, until PD										

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)[c]**										**Lenalidomide Treatment Period (As early as Day 21 and up to End of Cohort)[c]**
	≤28 days prior to apheresis[a]	**Upon enrollment**	**Cycle 1**	**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 42 (± 2 days)**	**Day 56 (± 2 days)**	**Day 78 (± 2 days)**	**Day 100 (± 2 days)[c]**	**(every 28 days up to 12 months then every 56 days)[d, t] (± 7 days)**
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. 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 participant'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
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 Day 56, at suspected CR and, relative to Day 1, at 6 month, 12 month, 18 month (Day 520), 24 (Day 744) months (± 16 days) and then yearly for subjects that achieve CR/sCR and remain on study up to disease progression.											

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)[c]**										**Lenalidomide Treatment Period (As early as Day 21 and up to End of Cohort)[c]**
	≤28 days prior to apheresis[a]	**Upon enrollment**	**Cycle 1**	**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 42 (± 2 days)**	**Day 56 (± 2 days)**	**Day 78 (± 2 days)**	**Day 100 (± 2 days)[c]**	**(every 28 days up to 12 months then every 56 days)[d, t] (± 7 days)**
Bone marrow aspirate and core biopsy for disease evaluation	X				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		As clinically indicated to document disease progression or response.													
Assess extramedullary Plasmacytomas [o]	X				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).											
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					X				X		X	X	X	X; every 112 days (±7 days)
MySIm-Q (Optional)	X	X					X				X		X	X	X	X; every 112 days (±7 days)
PGIS	X	X					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

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) [c]										Lenalidomide Treatment Period (As early as Day 21 and up to End of Cohort)[c]
	≤28 days prior to apheresis[a]	Upon enrollment	Cycle 1	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 42 (± 2 days)	Day 56 (± 2 days)	Day 78 (± 2 days)	Day 100 (± 2 days)[c]	(every 28 days up to 12 months then every 56 days)[d, t] (± 7 days)
Ongoing Subject Review																
Adverse Events	Continuous from the time of signing of ICF until 100 days after administration of JNJ-68284528, or 30 days after last dose of lenalidomide, whichever is later. 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 Second primary malignancies should be followed from the time of signing of ICF signing to study completion [p] CRS should be evaluated according to the ASBMT (ASTCT)consensus grading (Lee 2019) (Attachment 2) CAR-T cell-related neurotoxicity (eg, ICANS) should be graded according to the ASBMT (ASTCT) consensus grading (Attachment 4) Events of HBV reactivations should be reported during the first year post-dosing of JNJ-68284528														
Concomitant medication	Continuous from the time of signing of ICF until 100 days after administration of JNJ-68284528, or 30 days after last dose of lenalidomide, whichever is later															
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; CRS= cytokine release syndrome; CT=computed tomography; CTCAE=Common Terminology Criteria for Adverse Events; D=Day; 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.

[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 will be considered complete after the last subject has discontinued lenalidomide for 4 weeks or 2 years after receiving the initial dose of JNJ-68284528, whichever is later.

[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 should be performed before pre-medication with diphenhydramine

[g] Hepatitis B**:** 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-HBs positive and anti-HBc positive); Only in subjects who are positive for antibodies to hepatitis B core antigen (anti-HBc) and/or antibodies to hepatitis B surface antigen (anti-HBs). Monitor HBV-DNA, AST/ALT every 3 months for one year post-dose of JNJ-68284528. Subjects with serologic findings suggestive of HBV vaccination (anti-HBs positivity as the only serologic marker) and a known history of prior HBV vaccination do not need to be tested for HBV-DNA by PCR. Hepatitis C**:** HCV antibody, HCV RNA (for subjects who are anti HCV positive); HIV serology. See Attachment 10

[h] HIV, hepatitis B, hepatitis C, HTLV, and other infectious diseases as applicable per local regulations

[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.

[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

[q] 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.

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

	Screening Phase	Apheresis	Lenalidomide	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	Cycle 1	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 (± 2 days)	Day 28 (± 2 days)	Day 42 (± 2 days)	Day 56 (± 2 days)	Day 78 (± 2 days)	Day 100 (± 2 days)	Day 184 (±7 days)		
Pharmacokinetics																		
PK CAR transgene levels blood sample[b]				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
Biomarker Sampling																		
Immuno-phenotyping (whole blood)[d,f] Includes the flow PK		X		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[e]

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

	Screening Phase	Apheresis	Lenalidomide	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	Cycle 1	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 (± 2 days)	Day 28 (± 2 days)	Day 42 (± 2 days)	Day 56 (± 2 days)	Day 78 (± 2 days)	Day 100 (± 2 days)	Day 184 (±7 days)		
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						X	X	X	X	X		X		X	X	X	X[d, e]
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, 6, and 12 months; then yearly for 15 years post infusion												
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; 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

[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 participant'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

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 Bone Marrow Transplantation
ASCO	American Society of Clinical Oncology
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
β-hCG	β human chorionic gonadotropin
BCMA	B-cell maturation antigen
BiPAP	Bilevel Positive Airway Pressure
BiTE	bispecific T-cell engager
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
CRES	CAR-T cell-related encephalopathy syndrome
CRF	case report form
CRS	cytokine release syndrome
CSR	clinical study report
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CyTOF	cytometry by time of flight
DLT	dose limiting toxicity
DMSO	dimethyl sulfoxide
DOR	duration of response
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
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
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
IEC	independent ethics committee
ICP	intracranial pressure
Ig	immunoglobulins
IL	interleukin
IMiD	immunomodulatory drug
IMWG	International Myeloma Working Group
IPPI	investigational product preparation instructions
IRB	Institutional Review Board
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
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
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 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

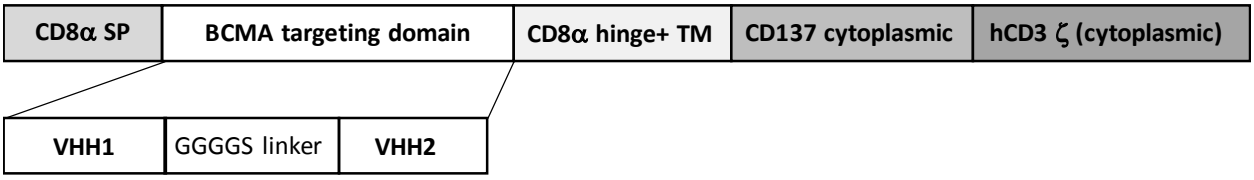
Chimeric antigen receptor T (CAR-T) cell therapy uses modified autologous T cells that are activated in a MHC-independent manner upon binding to their target. This results in lysis of the targeted cells. An ongoing Phase 1 clinical study with bb2121, a BCMA-directed CAR-T immunotherapy, demonstrated 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 682845238MMY2003 (CARTITUDE-2).

1.1.5. Clinical Studies

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. Study enrollment was completed in November 2017; 74 subjects have been treated on this study. The clinical cutoff for the analysis presented here is 06 February 2018 with updated survival, efficacy data, and CRS grading provided as of 31 December 2018. As of the 31 December 2018 update, the median follow-up was 17.41 months (range: 0.4–32.2 months).

All subjects had relapsed or refractory multiple myeloma with a median of 3 (range: 1-9) prior lines of therapy including PI therapy (73%), IMiD (87.8%), and both PI and IMiD (64.9%). Prior autologous stem cell transplant (ASCT) was reported for 24.3% of subjects. The median age at study entry was 54.5 years (range: 27-74 years).

Of the 74 subjects included in the Legend-2 study, 68 (91.9%) subjects had an adverse event of CRS (median time to onset 9 days [range: 1-19 days]). The majority of CRS events were of Grade 1 or Grade 2 severity. Six (8.1%) subjects experienced Grade 3 CRS and 1 (1.4%) subject experienced Grade 5 CRS. The fatal event of CRS occurred in a subject who experienced CRS and tumor lysis syndrome (TLS) and died on Day 13 after receiving the LCAR-B38M CAR-T cell infusion. For most subjects, symptoms of CRS were mild and reversible. Grade 1 neurotoxicity was reported for 1 subject.

In addition to the subject who died from CRS, 1 subject had a fatal adverse event of potential acute pulmonary embolism and potential acute coronary syndrome on Day 22 after infusion of LCAR-B38M CAR-T cells.

As of the 31 December 2018 update, the ORR (complete response [CR] + very good partial response [VGPR] + partial response [PR]) was 87.8%. Complete response was achieved by 54 (73.0%) subjects and 49 (66.2%) subjects were negative for MRD as assessed by bone marrow 8-color flow cytometry assay.

As of the 31 December 2018 update, the Kaplan-Meier estimate of median duration of response was 22.34 months (95% confidence interval [CI]: 11.79-29.14). The median progression-free survival (PFS) for the overall population was 16.2 months (95% CI: 10.61-28.16) and among the 49 subjects achieving MRD-negative CR, the median PFS was 28.16 months.

Study 68284528MMY2001

As of the 24 June 2019 data cutoff, 25 subjects had received an infusion of JNJ-68284528 in Study 68284528MMY2001. The safety profile is consistent with observations from the Legend-2 study.

- Twenty-four of the 25 subjects who received JNJ-68284528 had at least 1 treatment-emergent adverse event (TEAE).
  - The most commonly reported TEAEs (>20% of subjects) were CRS (88.0%), neutropenia (80.0%), anemia (76.0%), thrombocytopenia (72.0%), leukopenia (40.0%), lymphopenia (28.0%), fatigue (24.0%), headache (24.0%), cough (24.0%), and diarrhea (20.0%).
- Grade 3 or 4 TEAEs were reported for all 24 of the 25 subjects.
  - The most commonly reported Grade 3 or 4 TEAEs (>10% of subjects) were neutropenia (76.0%), anemia (48%), thrombocytopenia (60.0%), leukopenia (40.0%), lymphopenia (16%), and CRS (16.0%).
- Serious adverse events were reported for 6 subjects:
  - One subject had serious TEAEs of Grade 3 CAR-T cell-related encephalopathy syndrome (CRES) and Grade 3 CRS.
  - One subject had serious TEAEs of: CRS, with Grade 5 hemophagocytic lymphohistiocytosis (HLH) secondary to CRS, and Grade 4 acute kidney injury.
  - One subject had serious TEAEs of Grade 4 thrombocytopenia and Grade 3 pneumonia
  - One subject had a serious TEAE of Grade 2 influenza A
  - One subject had a serious TEAE of Grade 3 encephalitis
  - One subject had serious TEAEs of Grade 1 CRS and Grade 1 confusional state
- One subject died due to CRS, with Grade 5 hemophagocytic lymphohistiocytosis secondary to CRS.
- Twenty-two of the 25 subjects (88.0%) experienced CRS. Three subjects experienced Grade 3 CRS and 1 subject experienced Grade 5 CRS.
- CAR-T cell-related neurotoxicity was reported in 4 subjects. One subject had Grade 3 CRES, the second subject had Grade 1 neurological adverse events (dysarthria, slow mentation, gait disturbance, and somnolence), the third subject had Grade 1 CRES, and the fourth subject had a Grade 1 immune effector cell-associated neurotoxicity syndrome (ICANS) event (difficulty in finding words). All events occurred in the setting of CRS.

The median duration of follow-up for the 21 subjects who received JNJ-68284528 and had at least 1 post-dose disease evaluation as of 24 June 2019 was 2.99 months (range: 1.3 to 9.9 months). The ORR (sCR + CR + VGPR + PR) for the 21 subjects with at least 1 post-dose disease evaluation as of the 24 June 2019 cutoff was 90.5% (including unconfirmed responses). Thirteen subjects (61.9%) having VGPR or better and 6 subjects (28.6%) having CR or better. A stringent complete response (sCR) was achieved by 4 subjects. Fifteen subjects had post-baseline bone marrow samples available for MRD assessment. All 10 subjects (100%) evaluable at the 10^{-5} sensitivity level were negative for MRD by next generation flow cytometry and/or next generation sequencing (NGS; Adaptive v 2.0). In the remaining 5 subjects, two subjects were indeterminate at 10^{-5} due to insufficient cell counts but were MRD negative at the sensitivity threshold of 10^{-4} by NGS. No clone identification could be performed in 3 subjects by NGS.

Follow-up for response continues, however these preliminary data suggest compelling efficacy in this population of heavily pre-treated subjects.

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 LCAR-B38M CAR-T cells in adult subjects with relapsed or refractory multiple myeloma. Approximately 60 subjects will be enrolled into the study. 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 21 July 2019, 6 subjects were enrolled into the study and 5 subjects received LCAR-B38M CAR-T cells. Subject 3 received an infusion of LCAR-B38M CAR-T cells on 06 May 2019 and died on 12 May 2019. Preliminary information received for this subject are summarized below. Subjects 1, 2, 4, and 5 experienced Grade 3, Grade 2, Grade 3, and Grade 1 CRS, respectively. The events of CRS resolved for all 4 subjects who were subsequently discharged from the hospital.

The Subject 3 expired due to hemorrhage secondary to thrombocytopenia. The investigator attributed the thrombocytopenia, CRS and acute renal failure to LCAR-B38M CAR-T cell therapy.

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 20 subjects will be enrolled in each cohort. 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: Subjects with recently diagnosed 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.

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. Clinical experience with JNJ-68284528 and LCAR-B38M CAR-T cells is limited. Therefore, the 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 5.

Table 5: 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 6 for other hospitalization requirements. Rarely, severe CRS can evolve into a presentation consistent with hemophagocytic lymphohistiocytosis/macrophage activation syndrome (HLH/MAS) that may require additional therapy. 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.
Neurologic adverse events including CAR-T cell-related neurotoxicity (eg, immune effector cell-associated neurotoxicity syndrome [ICANS])[a]	Early recognition of neurologic adverse events is critical to management. 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, balance disorders, or mental status changes. At the first sign of neurotoxicity, neurology consultation and evaluation should be considered. Hospitalization is required for Grade ≥2 CAR-T cell-related neurotoxicity (eg, ICANS). Section 6.2.2 provides management guidelines for neurotoxicity.

Table 5: Risks Associated with JNJ-68284528 and Mitigation Strategies

Risk	Mitigation Strategies
Tumor lysis syndrome (TLS) [a]	Monitor closely for TLS with frequent monitoring of chemistry parameters and follow guidance for management in Section 6.2.3.
Second primary malignancies (SPMs)[a]	Second primary malignancies may occur in subjects receiving JNJ-68284528. SPM 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.
Cytopenias	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 Tables 8, 9, and 10). 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.
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.
Infections	Frequent monitoring for the presence of infections, with cultures or implementation of empiric antibiotic therapy as appropriate, based on clinical judgment and institutional standards. 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. 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. Routinely monitor HBV DNA and AST/ALT for subjects with risk of HBV reactivation (Attachment 10)
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.

[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)

Objectives	Endpoints
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)
• 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	• 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).

Objectives	Endpoints
• 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

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 20 subjects will be enrolled in each cohort. 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 and Section 4.2, 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 will include subjects with recently diagnosed 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.

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, 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, Table 2). For Cohorts A, B, and C, at select sites within the US and at the investigator discretion, study visits in the post-treatment part of the study, after Day 100, 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) in the post-treatment period, after the Day 100.

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, cohort completion will be defined as 4 weeks after the last subject in the cohort has discontinued lenalidomide or 2 years after receiving the initial dose of JNJ-68284528, whichever is later. 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.

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.

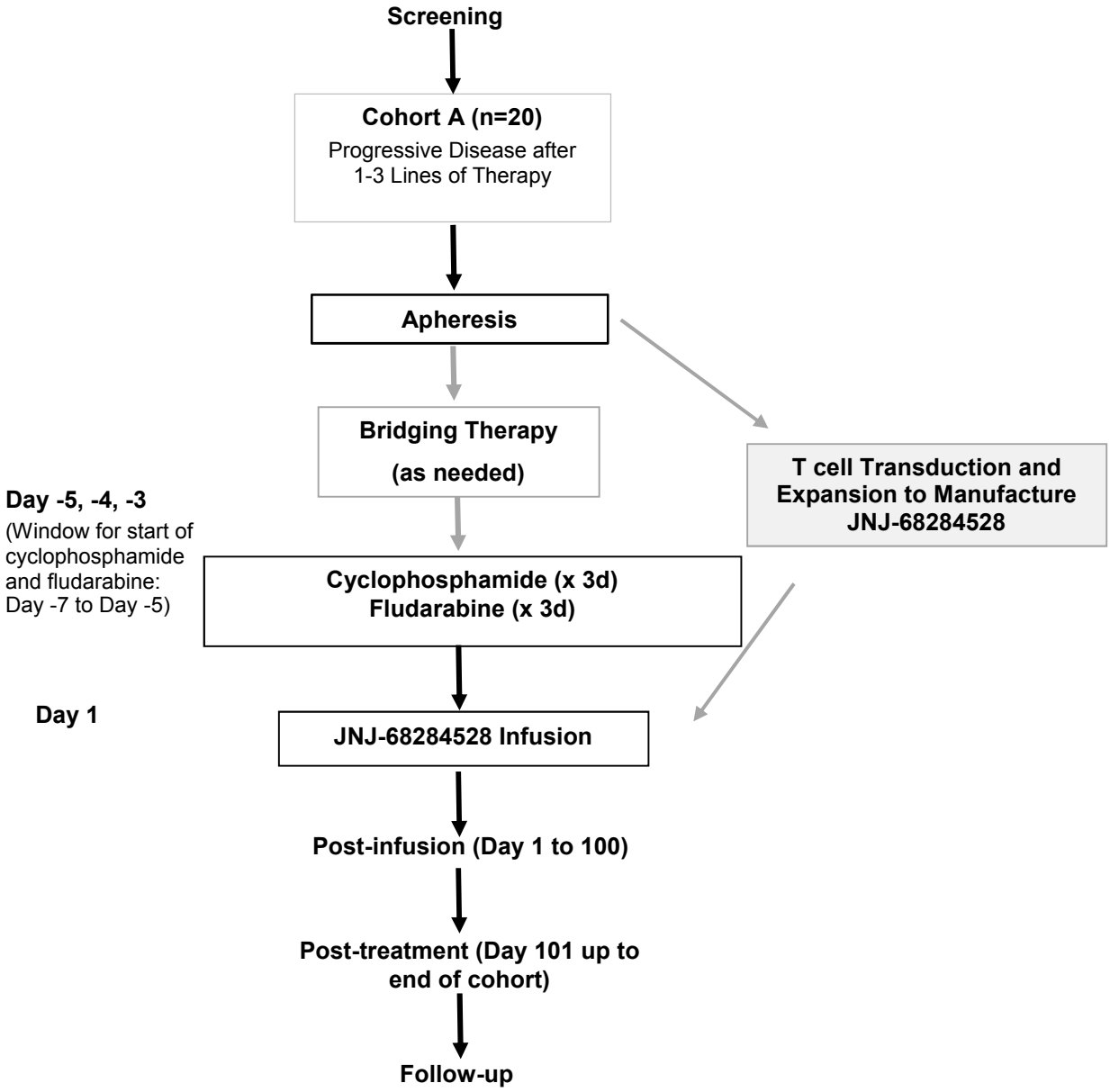
Bridging therapy (anti-plasma cell directed treatment between apheresis and lymphodepletion) will be allowed when clinically indicated (ie, to maintain disease stability while waiting for manufacturing of JNJ-68284528), with the permission of the sponsor. Bridging therapy must be a short-term treatment which previously generated at least a response of stable disease for the subject. The sponsor will not permit subjects who are found to be in 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.

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

Figure 2: Schematic Overview of the Study, Cohort A



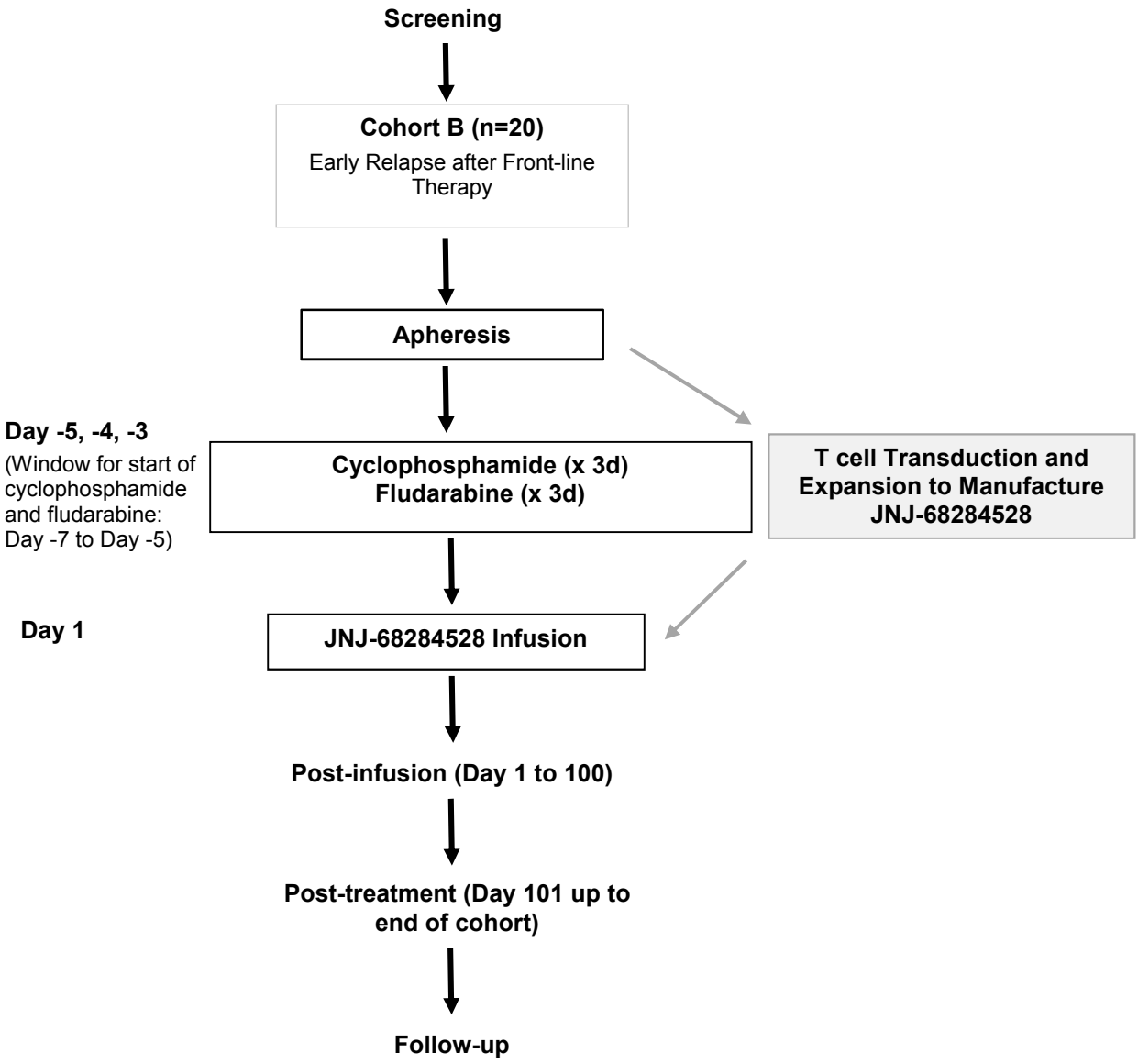
3.1.2. Cohort B Study Design

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 disease stability while waiting for manufacturing of JNJ-68284528), with the permission of the sponsor. Bridging therapy must be a short-term treatment used in the subject's first line of therapy. If disease is refractory to all these agents further discussion will be needed with sponsor to select an adequate therapy. Subjects who are in CR should not receive JNJ-68284528.

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 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 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.

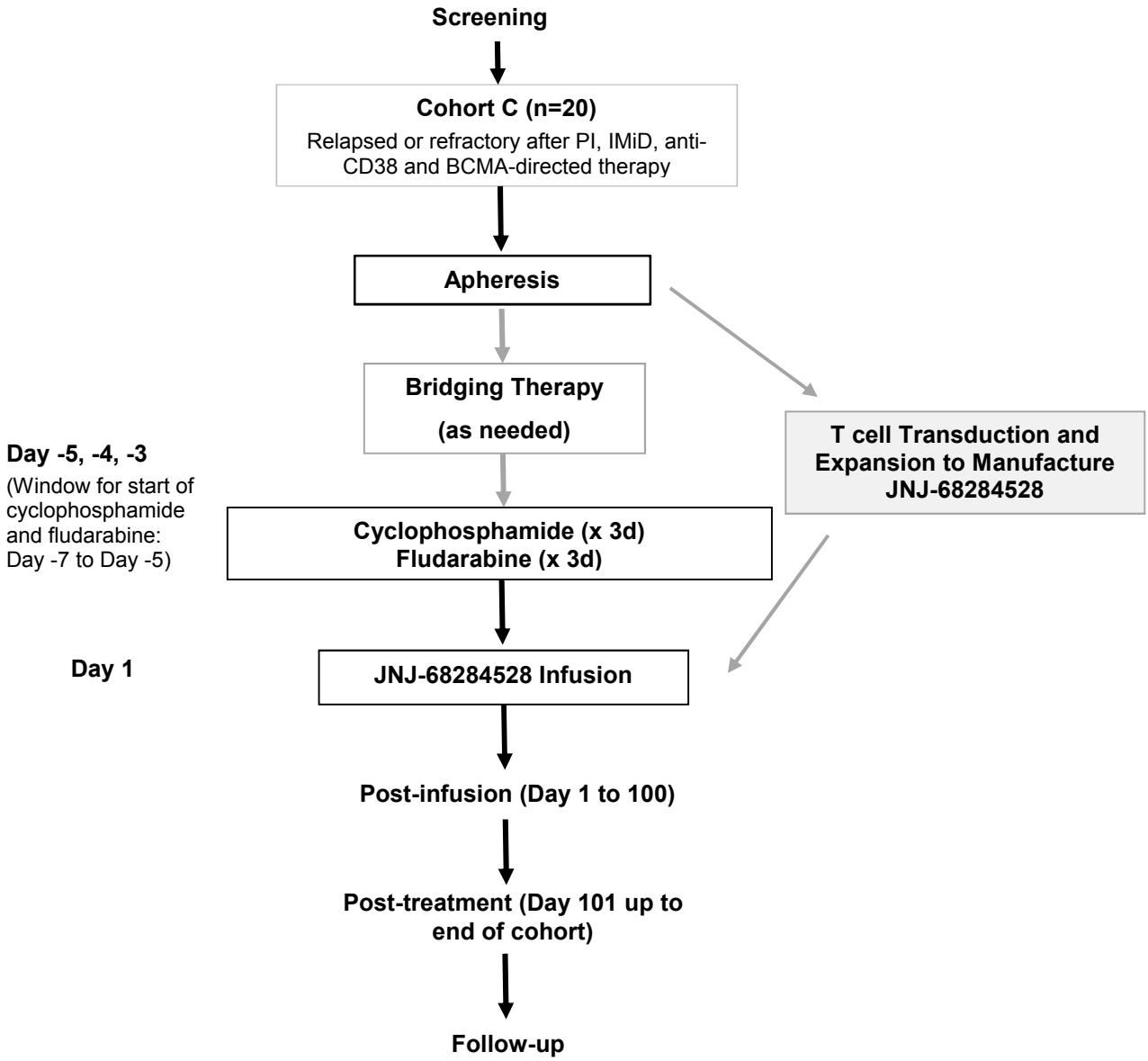
Bridging therapy (anti-plasma cell directed treatment between apheresis and lymphodepletion) will be allowed when clinically indicated (ie, to maintain disease stability while waiting for manufacturing of JNJ-68284528), with the permission of the sponsor. Bridging therapy must be a short-term treatment which previously generated at least a response of stable disease for the subject. 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 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.

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 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) when minimum laboratory requirements are met.

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 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.

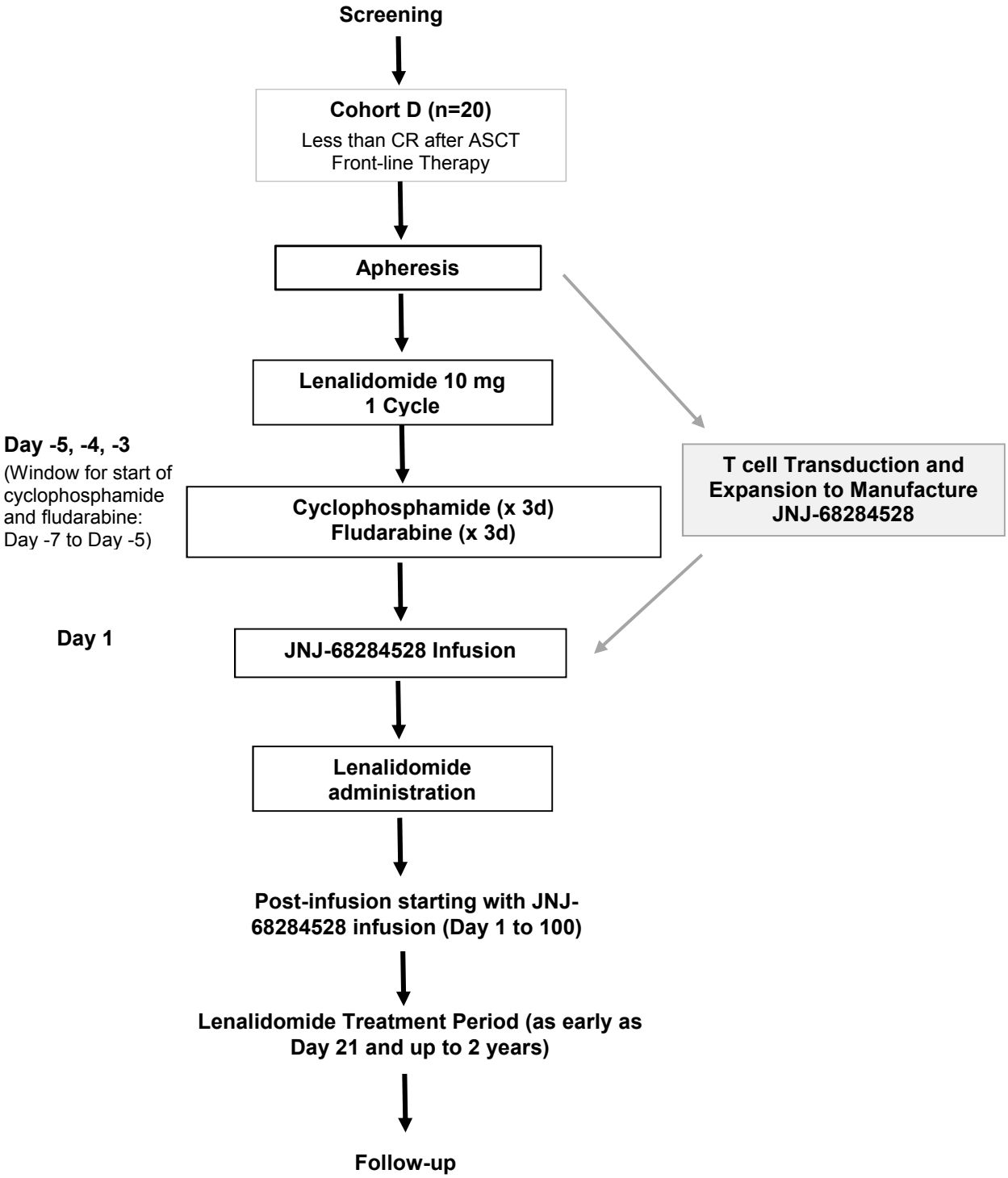
A strategy of staggered dosing with JNJ-68284528 will be applied to Cohort D. There must be an observation period of approximately 1 week between administration of JNJ-68284528 to the first and second subject and the second and third subjects. No observation periods are mandated after the third subject receives an infusion of JNJ-68284528.

A minimum of 21 days after infusion of JNJ-68284528, after resolution of CRS or neurological toxicities associated with JNJ-68284528, 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.

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



3.1.5. Retreatment with JNJ-68284528

Subjects in Cohorts A, B, and C may be considered for retreatment with JNJ-68284528. Subjects in Cohort D 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 exclusion criteria 1 and 2, to be eligible for retreatment. A maximum of 1 retreatment may occur per subject. Bridging therapy will not be allowed for subjects receiving retreatment.

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 9.1.7.3). 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.

As of the 24 June 2019 data cutoff, 25 subjects had received an infusion of JNJ-68284528 in Study 68284528MMY2001. Twenty-one subjects had at least 1 post-baseline disease evaluation. An overall response rate of 90.5% was observed, with 4 stringent complete response (sCR), 2 CRs, 7 very good partial responses (VGPR), and 6 partial responses (PR). The responses occurred rapidly, with most subjects exhibiting ≥50% myeloma protein reduction at the first disease assessment (scheduled at Day 28 after JNJ-68284528 dosing). The responses appear to be continuously deepening for all subjects who are in follow-up and no disease progression has been observed as of data cutoff.

The safety profile was consistent with observations from the Legend-2 study (Section 1.1.5). Data from these 25 subjects were reviewed by the Safety Evaluation Team (SET), which recommended maintaining the dose of 0.75 x 10^6 CAR-positive viable T cells/kg for the Phase 2 portion of Study 68284528MMY2001.

Together, preliminary efficacy and safety 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 in a patient population with no alternative treatment options.

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 and Otahal 2016). The combination of anti-BCMA CAR-T

cells and lenalidomide treatment is currently under study in patients with multiple myeloma (NCT03070327).

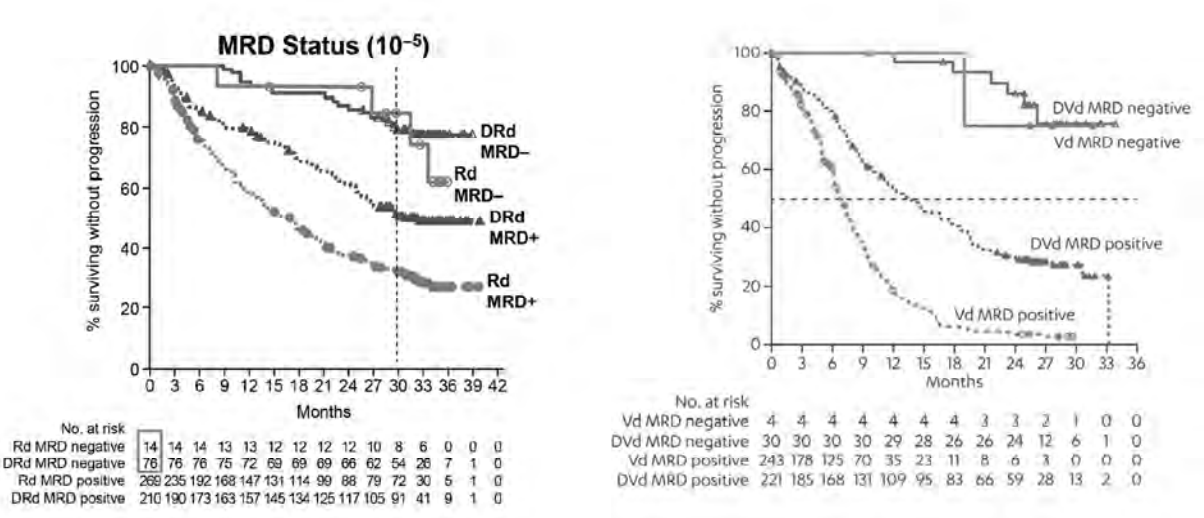
Rationale for MRD as Primary Endpoint

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 6) (Avet 2016). Subjects achieving MRD negative status demonstrated improved PFS (Figure 6). 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 6: 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, and Cohort D in Section 4.4.

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. 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, during treatment or ≤60 days after cessation of treatment. Progression on lenalidomide maintenance 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. 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).

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. 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. Prior antitumor therapy as follows, prior to apheresis:

- 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 less.
- 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. Known life threatening allergies, hypersensitivity, or intolerance to cyclophosphamide, fludarabine, JNJ-68284528 or its excipients, including DMSO (refer to Investigator's Brochure).

17a. Criterion modified per Amendment 1

17a.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

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. 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. 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).

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. 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. Prior antitumor therapy as follows, prior to apheresis:

- 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 less.
- 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. Known life threatening allergies, hypersensitivity, or intolerance to cyclophosphamide, fludarabine, JNJ-68284528 or its excipients, including DMSO (refer to Investigator's Brochure).

17b. Criterion modified per Amendment 1

17b.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

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. 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).

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

7c. 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.

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. 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. Prior antitumor therapy as follows, prior to apheresis:

- 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.
- 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 109/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. Known life threatening allergies, hypersensitivity, or intolerance to cyclophosphamide, fludarabine, JNJ-68284528 or its excipients, including DMSO (refer to Investigator's Brochure).

16c. 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

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. 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 the time of signing the informed consent form (ICF) 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 increase risk of thromboembolic events with lenalidomide.
  - women of childbearing potential must follow the contraception criteria outlined in the local REVLIMID® pregnancy prevention program.

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 local REVLIMID pregnancy prevention program.

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

- Targeted therapy, epigenetic therapy, or treatment with an investigational drug or used as invasive investigational medical device within 14 days or at least 5 half-lives, whichever is less.
- 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. Known life threatening allergies, hypersensitivity, or intolerance to cyclophosphamide, fludarabine, lenalidomide, JNJ-68284528 or its 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. 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

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. 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 (Prestudy 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 A and B, must be enrolled in Cohort B. As this is a single arm study, 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 is also consider a study treatment. All dosing information must be recorded in the Dosage Administration page of the electronic case report form (eCRF).

6.1. Study Treatment Administration

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
- 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, 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.

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 site investigational product procedures manual (SIPPM) 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 >10mg prednisone per day in the week prior to the start of the conditioning regimen.
- No live, attenuated vaccines within 4 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 (Cohorts A and B) 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 6.

Table 6: JNJ-68284528 Administration

Dose	JNJ-68284528 will be administered in one infusion. The target dose will be the RP2D, which is anticipated to be 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). 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.
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 of 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) 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 and Table 3). 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 12. Hospitalization is required for Grade 2, 3, or 4 CAR-T cell-related neurotoxicity (eg, ICANS). Further details regarding management of CAR-T cell related neurotoxicity are described in Table 13.
Vital Sign and Clinical Safety Monitoring	Monitor vital signs as indicated in the Time and Events Schedule (Table 1 and Table 3).

6.1.3.1. Exceptional Release Criteria

In the event a JNJ-68284528 product that did not meet pre-specified release criteria is produced during the manufacturing procedures, 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. If required, approval from the relevant health authorities for use of the product will be obtained in compliance with local regulations regarding notification and approval. In the event the supply of the affected product is deemed appropriate, the investigator will inform the study subject that the product did not meet release specifications prior to administration. The investigator will discuss with the subject the potential risks and benefits of receiving the product, treatment alternatives, including the potential for a second apheresis and discuss alternatives with the patient, including repeat apheresis and alternative therapies.

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 7). Corticosteroids should not be used during pre-infusion.

Table 7: 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)

For subjects in Cohort D, lenalidomide will be self-administered at a dose of 10 mg 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.

- After apheresis and prior to administration of cyclophosphamide and fludarabine (conditioning regimen prior to JNJ-68284528 infusion): 1 cycle of lenalidomide at a dose of 10 mg per day upon adequate hematologic recovery (absolute neutrophil count [ANC] ≥1 x 10^9/L and platelet count ≥ 75 x 10^9/L) when minimum laboratory requirements are met.
- After infusion of JNJ-68284528: All subjects will initiate lenalidomide a minimum of 21 days post JNJ-68284528 after resolution of cytokine release syndrome (CRS) or neurological toxicities associated with JNJ-68284528. 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 8.

Table 8: Criteria for Lenalidomide Administration after JNJ-68284528 Infusion

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 5mg daily, increase to 10mg 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

  - 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.
  - For subjects with an eGFR <60 mL/min/1.73m2, 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 11.

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.

Management guidelines for potential risks of lenalidomide, including dose adjustment, are provided in Table 9 (dose modification guidelines), Table 10 (dose reduction steps) and Table 11 (dosing for subjects with renal impairment).

Table 9: 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 10: Lenalidomide Dose Reduction Steps

	Starting dose (5mg)	Starting dose (10 mg)	If dose increased (15 mg)
Dose level -1	5mg (Days 1- 21)	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 11: 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 (REVLMID® USPI and SmPC).

6.2. Management Guidelines for Potential Risks with JNJ-68284528 (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). In addition, pulmonary, renal and hepatic function will be monitored closely (see Table 1). 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).

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).

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 12. 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 monoclonal antibodies targeting cytokines (for example, anti-IL1 and/or anti-TNFα) may be used based on institutional practice, especially for cases of CRS which does not respond to tocilizumab. 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 12: Guidelines for the Management of Cytokine Release Syndrome

Presenting Symptoms	Tocilizumab[a]	Corticosteroids[b]
Temperature ≥38°C[c]	May be considered	N/A
Temperature ≥38°C[c] with either: Hypotension responsive to fluids and not requiring vasopressors. Or, oxygen requirement of low-flow nasal cannula[d] or blow-by,	Administer tocilizumab[b] 8 mg/kg intravenously over 1 hour (not to exceed 800 mg). Repeat tocilizumab every 8 hours as needed if not responsive to intravenous fluids or increasing supplemental oxygen. Limit to a maximum of 3 doses in a 24-hour period; maximum total of 4 doses.	Manage per guidance below if no improvement within 24 hours of starting tocilizumab.
Temperature ≥38°C[c] with either: Hypotension requiring one vasopressor with or without vasopressin. Or, oxygen requirement of high-flow nasal cannula[d], facemask, non-rebreather mask, or Venturi mask	Administer tocilizumab 8 mg/kg intravenously over 1 hour (not to exceed 800 mg). Repeat tocilizumab every 8 hours as needed if not responsive to intravenous fluids or increasing supplemental oxygen. Limit to a maximum of 3 doses in a 24-hour period; maximum total of 4 doses.	If no improvement, administer methylprednisolone 1 mg/kg intravenously twice daily or equivalent dexamethasone (eg, 10 mg intravenously every 6 hours). Continue corticosteroids use until the event is Grade 1 or less, then taper over 3 days.

Table 12: Guidelines for the Management of Cytokine Release Syndrome

Presenting Symptoms	Tocilizumab[a]	Corticosteroids[b]
Temperature ≥38°C[c] with either: Hypotension requiring multiple vasopressors (excluding vasopressin). Or, oxygen requirement of positive pressure (eg, CPAP, BiPAP, intubation, and mechanical ventilation).	Administer tocilizumab 8 mg/kg intravenously over 1 hour (not to exceed 800 mg). Repeat tocilizumab every 8 hours as needed if not responsive to intravenous fluids or increasing supplemental oxygen. Limit to a maximum of 3 doses in a 24-hour period; maximum total of 4 doses.	As above, or administer methylprednisolone 1000 mg intravenously per day for 3 days per investigator discretion. If no improvement or if condition worsens, consider alternate immunosuppressants.[b]

CPAP=Continuous Positive Airway Pressure; BiPAP=Bilevel Positive Airway Pressure
a: Refer to tocilizumab prescribing information for details [1]
b: Monoclonal antibodies targeting cytokines may be considered based on institutional practice for unresponsive CRS.
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).
d: Low-flow nasal cannula is ≤6 L/min, and high-flow nasal cannula is >6 L/min.
Note: At first sign of CRS (such as fever) subjects should be immediately hospitalized for evaluation.

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 Adverse Events

Based on the specific mode-of-action of JNJ-68284528, severe or serious neurologic toxicities (including CAR-T cell-related neurotoxicity, eg, ICANS [Immune Effector Cell-Associated Neurotoxicity Syndrome]) may occur. 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 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 (eg, ICANS).

At the first sign of neurotoxicity, neurology consultation and evaluation should be considered. 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 (eg, ICANS) with or without concurrent CRS is summarized in Table 13. All neurologic adverse events, including CAR-T cell-related neurotoxicity (eg, ICANS), will be captured as an adverse event of special interest (see Section 12.3.3).

Table 13: Guidelines for the Management of CAR-T Cell-related Neurotoxicity (eg, ICANS)

Presenting Symptoms[a]	Concurrent CRS	No Concurrent CRS
ICE score 7-9[b] or depressed level of consciousness[c]: awakens spontaneously.	Management of CRS as appropriate per Table 12. Monitoring of neurologic symptoms and consider neurology consultation and evaluation, per investigator discretion.	Monitor neurologic symptoms and consider neurology consultation and evaluation,per investigator discretion.
	Consider non-sedating, anti-seizure medicines (eg, levetiracetam) for seizure prophylaxis.	
ICE score-3-6 [b] or depressed level of consciousness[c]: awakens to voice.	Administer tocilizumab per Table 12 for management of CRS. If no improvement after starting tocilizumab, administer dexamethasone[d] 10 mg intravenously every 6 hours if not already taking other corticosteroids. Continue dexamethasone use until the event is Grade 1 or less, then taper.	Administer dexamethasone[d] 10 mg intravenously every 6 hours. Continue dexamethasone use until the event is Grade 1 or less, then taper.
	Consider non-sedating, anti-seizure medicines (eg, levetiracetam) for seizure prophylaxis. Consider neurology consultation and other specialists (ie, intensivists) for further evaluation, as needed.	
ICE score-0-2 [b] or depressed level of consciousness[c]: awakens only to tactile stimulus, or seizures[c], either: • any clinical seizure, focal or generalized, that resolves rapidly, or • non-convulsive seizures on EEG that resolve with intervention, or raised ICP: focal/local edema on neuroimaging[c].	Administer tocilizumab per Table 12 for management of CRS. In addition, administer dexamethasone[d] 10 mg intravenously with the first dose of tocilizumab and repeat dose every 6 hours. Continue dexamethasone use until the event is Grade 1 or less, then taper.	Administer dexamethasone[d] 10 mg intravenously every 6 hours. Continue dexamethasone use until the event is Grade 1 or less, then taper.
	Consider non-sedating, anti-seizure medicines (eg, levetiracetam) for seizure prophylaxis. Consider neurology consultation and other specialists (ie, intensivists) for further evaluation, as needed.	
ICE score-0[b] or depressed level of consciousness[c] either: • subject is unarousable or requires vigorous or repetitive tactile stimuli to arouse, or • stupor or coma, or seizures[c], either: • life-threatening prolonged seizure (>5 min), or • repetitive clinical or electrical seizures without return to baseline in between, or motor findings[c]: • deep focal motor weakness such as hemiparesis or paraparesis,	Administer tocilizumab per Table 12 for management of CRS. As above, or consider administration of methylprednisolone 1000 mg intravenously per day with first dose of tocilizumab and continue methylprednisolone 1000 mg intravenously per day for 2 or more days, per investigator discretion.	As above, or consider administration of methylprednisolone 1000 mg intravenously per day for 3 days; if improves, then manage as above.
	Consider non-sedating, anti-seizure medicines (eg, levetiracetam) for seizure prophylaxis. Consider neurology consultation and other specialists (ie, intensivists) for further evaluation, as needed. In case of raised ICP/cerebral edema, refer to Table 14 for additional management guidelines.	

Table 13: Guidelines for the Management of CAR-T Cell-related Neurotoxicity (eg, ICANS)

Presenting Symptoms[a]	Concurrent CRS	No Concurrent CRS
or raised ICP / cerebral edema[c], 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.		

a Management is determined by the most severe event, not attributable to any other cause
b If subject is arousable and able to perform Mental Status assessment, the following domains should be tested: orientation, naming, following commands, writing, and attention (see Attachment 3; ICE-Tool).
c Attributable to no other cause.
d All references to dexamethasone administration are dexamethasone or equivalent

Table 14: 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 13: Guidelines for the Management of CAR-T Cell-Related Neurotoxicity (ie, ICANS)

6.2.3. Tumor Lysis Syndrome

Although TLS is uncommon in subjects with multiple myeloma, one subject in the Phase 1 Legend-2 Study experienced fatal TLS. 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). TLS will be captured as an adverse event of special interest (see Section 12.3.3).

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. Cytopenia

Subjects may exhibit cytopenias for several weeks following lymphodepleting chemotherapy and JNJ-68284528 infusion. 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. Prolonged neutropenia may increase the risk of infection. Severe thrombocytopenia may increase the risk of bleeding. 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.

For subjects in Cohort D, initiating lenalidomide after JNJ-68284528 may cause significant neutropenia and thrombocytopenia. Monitor complete blood counts (CBC) as specified in the Time and Events Schedule (Table 3). A dose interruption and reduction may be required (refer to local prescription information). Guidance is provided in tables 8, 9, and 10. 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) and more frequently if clinically indicated and treat according to local guidelines, including administration of immunoglobulin replacement and monitoring for infection. Vaccination with live virus vaccines is not permitted for at least 4 weeks prior to the start of the conditioning regimen and for 100 days after infusion of JNJ-68284528.

6.2.7. Infections

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. 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.

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 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.

For subjects in Cohort D, please refer to the prescribing information for additional risks associated with lenalidomide.

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. Additional details are provided in the SIPPM. 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 SIPPM for a description of the chain of identity and chain of custody procedures associated with the apheresis product and JNJ-68284528.

8. PRESTUDY 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, and C), and 30 days after the last dose of lenalidomide (Cohort D) or until the start of subsequent systemic anticancer treatment, if earlier. 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 (including any given for HLH)

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 (medications which the subject has previously received) is permitted during bridging therapy (see Section 3.1) (Attachment 6).

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 Herpes Zoster Reactivation

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.

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, 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.
- For subjects in Cohort D, 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 12 and Table 13. 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 as part of therapy intended to treat CAR-T cell related toxicity [ie, CRS] Section 8.2, and Section 8.4).
- 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, 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 with live, attenuated vaccine after signing consent and in the ≤4 weeks prior to the infusion of JNJ-68284528, and for 100 days after infusion of JNJ-68284528.
- 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.

8.4. Subsequent Anticancer Therapy

Subsequent anticancer therapy administered after JNJ-68284528 (all cohorts) and after lenalidomide (Cohort D only), should be only administered after 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 4).

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, and C (up to 2 years' post-JNJ-68284528 treatment) is 912 mL, and for cohort D is 1010 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. 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 will 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.

9.1.3. Apheresis

Prior to apheresis, review of safety assessments should be completed per the Time and Events Schedule (Table 1 and Table 3). Apheresis should be performed according to institutional standards, with a collection target of 6×10^9 PBMCs (range: 2 to 20×10^9 PBMCs); two apheresis collections may be performed to attain this target. Instructions for processing and shipping apheresis product are provided in the SIPPM.

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 and Table 3).

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 6.

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.

9.1.7. Post-treatment Phase

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 and Table 4).

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 6).

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.

9.1.7.1. Post-treatment Period (Cohorts A, B, and C)

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) 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, study visits 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) in the post-treatment period, after the Day 100. PRO assessments may be captured via smart-phone based application and electronic patient reported outcomes (ePRO) instruments.

9.1.7.2. Lenalidomide Treatment Period after JNJ-68284528 infusion (Cohort D)

The lenalidomide treatment period starts on Day 21 (if required hematological parameters are met) and lasts until study completion, defined as 2 years after the last subject in Cohort D has received his or her 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.

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.

9.1.7.3. Long-term Follow-up

Second primary malignancies will be reported for the duration of the study. Following completion of this study, assessment for replication competent lentivirus (RCL) and secondary primary malignancies will be collected yearly until 15 years after the last dose with JNJ-68284528 on a follow-up study. 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.

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. 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.

9.2.1. Bone Marrow Examination for MRD Assessment

MRD will be monitored in subjects using next generation sequencing (NGS) on bone marrow aspirate DNA by central laboratory. 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. A fresh bone marrow aspirate will be collected prior to the first dose of conditioning regimen (≤7 days). 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). Additional timepoints for the MRD assessment are reflected in the Time and Events schedule (Table 1 and Table 3).

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 and Table 3).

- 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

Blood and 24-hour urine samples will be collected as specified in the Time and Events Schedule (Table 1 and Table 3) 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 and Table 3).

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 presents 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, and C) or at screening (Cohort D). 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 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.

9.3. Pharmacokinetics and Immunogenicity

Serum and whole blood samples will be used to evaluate the pharmacokinetics of JNJ-68284528, as well as the immunogenicity of anti-JNJ-68284528 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). 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.

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.

Immunogenicity

The detection and characterization of antibodies to JNJ-68284528 will be performed using a validated assay method by or under the supervision of the sponsor. Other analyses may be performed to characterize immunogenicity.

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.

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.

9.4. Pharmacokinetic/Pharmacodynamic Evaluations

Pharmacokinetic/pharmacodynamic modeling 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. Additional sample(s) for cytokines will be collected as clinically indicated (Table 2).

The potential presence of RCL will be evaluated from whole blood samples of subjects treated with JNJ-68284528. RCL will be evaluated using a qPCR assay against the lentiviral vesicular stomatitis virus-G gene for 15 years in the follow-up study.

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 during or after study completion for a retrospective analysis. Additionally, the sponsor will receive a sample of plasmacytoma if patient relapse is suspected. In all cases, such analyses would be specific to research related to the study treatment(s) or diseases being investigated.

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.

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 and Table 3) 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. If an in-person visit is not scheduled during the post-treatment period, the PRO measures can be interviewer-administered, read verbatim, by telephone. 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, 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:

Adverse Events

Adverse events (except for second primary malignancy and HBV reactivation) 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, and C), and 100 days after infusion of JNJ-68284528 or 30 days after last dose of lenalidomide, whichever is later (Cohort D) or until the start of subsequent anticancer therapy, if earlier. 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. Second primary malignancies will be reported for the duration of the study and, subsequently, will be collected on a long-term follow-up study yearly until 15 years' post dosing of JNJ-68284528. Events of HBV reactivations will be reported during the first year post-dosing of JNJ-68284528.

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 CAR-T cell-related neurotoxicity (eg, ICANS). CRS should be evaluated according to the American Society for Blood and Bone Marrow Transplantation (ASBMT) consensus grading (Lee 2019) (Attachment 2). CAR-T cell-related neurotoxicity (eg, ICANS) should be graded using the ASBMT (American Society for Transplantation and Cellular Therapy [ASTCT]) consensus grading (Attachment 4). 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.

Clinical Laboratory Tests

Blood samples for serum chemistry and hematology will be collected as shown in the Time and Events Schedule (Table 1 and Table 3). 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	
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]
Pregnancy Test	
Pregnancy Test: serum (<5 IU/mL) β-hCG	
Tests at Screening only	
Serology: - **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-HBs positive and anti-HBc positive) (Attachment 10) - **Hepatitis C:** HCV antibody, HCV RNA (for subjects who are anti HCV positive) - **HIV**	
Tests at Apheresis only[b]	
HIV, Hepatitis B, Hepatitis C, HTLV and other infectious diseases as applicable per local regulations	

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)

Electrocardiogram (ECG)

12-lead ECGs will be performed as specified in the Time and Events Schedule (Table 1 and Table 3). 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.

Echocardiogram or MUGA scan

Assessment of cardiac function is required at screening using either echocardiogram or MUGA scan (results obtained ≤8 weeks of apheresis [All Cohorts] 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.

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 and Table 3). 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.

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 and Table 3]). Clinically significant post-baseline abnormalities should be recorded as adverse events.

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 and Table 3).

Neurologic Examination

Magnetic resonance imaging (MRI) at screening or neurology consultation should be considered if pre-existing disease is suspected. At the first sign of neurotoxicity, neurology consultation and evaluation should be considered. CAR-T cell-related neurotoxicity (eg, 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.

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 and Table 3) 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.

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.

9.8. 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 and Table 3) 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

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 and Table 3), 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).

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) 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)
- Confirmed disease progression per IMWG criteria (Attachment 1) either between the time of conditioning therapy and infusion of JNJ-68284528, or during the lenalidomide treatment (Cohort D).
- Subject refuses further study treatment
- Noncompliance with study treatment or procedure requirements
- The subject becomes pregnant prior to infusion, or during the lenalidomide treatment (Cohort D).

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

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:**
  - 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.
- **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.
- **Immunogenicity Analysis Set:** This set consists of all subjects who received JNJ-68284528 infusion and have at least 1 post-dose immunogenicity sample.

11.2. Sample Size Determination

No formal statistical hypothesis testing will be performed. The sample size 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 after initial dose of JNJ-68284528 and before disease progression or starting subsequent therapy including retreatment of JNJ-68284528.

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) after initial dose of JNJ-68284528 and before disease progression or starting subsequent therapy including retreatment of JNJ-68284528.

Time to MRD negativity will be calculated among subjects who are MRD negative by bone marrow aspirate from the date of the initial infusion of JNJ-68284528 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).

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 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.

Progression-free survival (PFS) is defined as the time from the date of the initial infusion of JNJ-68284528 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.

Overall survival (OS) is measured from the date of the initial infusion of JNJ-68284528 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. 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.

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.

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.

Immunogenicity analyses will be descriptive in nature and will include the number and percentage of subjects who developed anti-JNJ-68284528 antibodies. The effect of anti-JNJ-68284528 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 the 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. 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 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.

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. 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. A listing of subjects with any laboratory results outside the reference ranges will be provided.

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, the expectedness of an adverse event will be determined by whether or not it is listed in the Investigator's Brochure.

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 CAR-T cell-related neurotoxicity (eg, ICANS). CRS should be evaluated according to the ASBMT (ASTCT) consensus grading (Lee 2019) (Attachment 2). CAR-T cell-related neurotoxicity (eg, ICANS) should be graded using the ASBMT consensus grading (Attachment 4). 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

Special reporting situations should be recorded in the CRF. Any special reporting situation that meets the criteria of a serious adverse event should be recorded on the serious adverse event page of the CRF.

12.3. Procedures

12.3.1. All Adverse Events

All adverse events (with the exception of second primary malignancies, see Section 12.3.3, and HBV reactivation) and special reporting situations, whether serious or non-serious, will be reported from the time a signed and dated ICF is obtained until 100 days after infusion of JNJ-68284528 (Cohorts A, B, and C), and 100 days after infusion of JNJ-68284528 or 30 days after last dose of lenalidomide, whichever is later (Cohort D). Events of HBV reactivations will be reported during the first year post-dosing of JNJ-68284528. Beyond the adverse event reporting period, only adverse events that are considered related to study drug need to be reported. Adverse events of special interest are defined in Section 12.3.3.

Serious adverse events, including those spontaneously reported to the investigator within 100 days after infusion of JNJ-68284528 (Cohorts A, B, and C), and 100 days after infusion of JNJ-68284528 or 30 days after last dose of lenalidomide, whichever is later (Cohort D), must be reported using the Serious Adverse Event Form. Beyond the serious adverse event reporting period, only serious adverse event that are considered related to study drug need to be reported. The sponsor will evaluate any safety information that is spontaneously reported by an investigator beyond the time frame specified in the protocol. All events that meet the definition of a serious adverse event will be reported as serious adverse events, regardless of whether they are protocol-specific assessments. Anticipated events will be recorded and reported as described in Attachment 13.

AEs 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-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:

- Expected progression of disease should not be considered an adverse event (or serious adverse event). 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 (see 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.

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). For anticipated events reported as individual serious adverse events the sponsor will make a determination of relatedness in addition to and independent of the investigator’s assessment. The sponsor will periodically evaluate the accumulating data and, when there is sufficient evidence and the sponsor has determined there is a reasonable possibility that the drug caused a serious anticipated event, they will submit a safety report in narrative format to the investigators (and the head of the investigational institute where required).

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 serious adverse events 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.

Information regarding serious adverse events will be transmitted to the sponsor using the Serious Adverse Event Form, which must be completed and signed by a physician from the study site, and transmitted to the sponsor within 24 hours. The initial and follow-up reports of a serious adverse event should be made by facsimile (fax).

Events that require an escalation of care when the subject is already hospitalized should be recorded as a serious adverse event. Examples of such events include movement from routine care in the hospital to the ICU or if that event resulted in a prolongation of the existing planned hospitalization.

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.

12.3.3. Adverse Events of Special Interest

Cytokine release syndrome, neurotoxicity (including CAR-T cell-related neurotoxicity [eg, ICANS]), tumor lysis syndrome, and second primary malignancy of any grade will be followed as part of standard safety monitoring activities by the sponsor, regardless of severity or causality. All events of CRS, neurotoxicity, and TLS (any grade) must be reported until 100 days after infusion of JNJ-68284528 (Cohorts A, B, and C), and 100 days after infusion of JNJ-68284528 or 30 days after last dose of lenalidomide, whichever is later (Cohort D) or until the start of subsequent anticancer therapy, if earlier.

Second primary malignancies must be reported for the duration of the study, irrespective of treatment emergent status, and subsequently will be collected in a long-term follow-up study yearly until 15 years post dosing of JNJ-68284528.

The following events must be reported to the sponsor using the Serious Adverse Event Form within 24 hours of awareness of the event, irrespective of seriousness (eg, serious and nonserious adverse events):

- ≥Grade 3 CRS,
- ≥Grade 3 neurotoxicity,
- ≥Grade 3 tumor lysis syndrome,
- Any second primary malignancies.

Adverse events of special interest that are considered to be non-serious by the investigator are to be included on the serious adverse events form and in the eCRF. Grade 1 or 2 adverse events of special interest would not qualify for expedited reporting unless they meet serious adverse event criteria. All adverse events of special interest of any grade should be followed until recovery or until there is no further improvement.

Because of the embryo-fetal risk of lenalidomide, all subjects must adhere to the lenalidomide pregnancy prevention program applicable in their region. Investigators should comply with the local label for lenalidomide for guidance on subject education and ensure that all subjects adhere to the local Lenalidomide Risk Evaluation Mitigation Strategy (REMS) program. When no local lenalidomide REMS program exists, subjects must adhere to the lenalidomide Global Pregnancy Prevention Plan.

12.3.4. Pregnancy

All initial reports of pregnancy in female 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: 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. 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

The investigator is responsible for ensuring that all 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/SIPPM (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 6) 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. Regulatory Documentation

17.2.1. 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.

17.2.2. 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

17.3. 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.

17.4. 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 Section 4.2, 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.

17.5. 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.

17.6. 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.

17.7. 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.

17.8. 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.

17.9. Study Completion/Termination

17.9.1. Study Completion/End of Cohort

Cohorts A, B, and C will be considered complete after the last subject has had two years of follow-up after the initial dose of JNJ-68284528. Cohort D will be considered complete after the last subject has discontinued lenalidomide for 4 weeks or 2 years after receiving the initial dose of JNJ-68284528, whichever is later.

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.

17.9.2. 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

17.10. 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.

17.11. 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.

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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 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) and Rajkumar (2011), Kumar (2016)

Attachment 2: Cytokine Release Syndrome ASBMT (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) ASBMT (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 et al 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 dosing.

Subjects with positive anti-HBc and positive 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 dosing

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

MySIm Q

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

NCI PRO-CTCAE™ ITEMS

Item Library Version 1.0
English
Form created on 6 September 2018

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?				
	○ Never	○ Rarely	○ Occasionally	○ Frequently	○ Almost constantly
	In the last 7 days, what was the SEVERITY of your NAUSEA at its WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe

2.	In the last 7 days, how OFTEN did you have VOMITING?				
	○ Never	○ Rarely	○ Occasionally	○ Frequently	○ Almost constantly
	In the last 7 days, what was the SEVERITY of your VOMITING at its WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ 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

NCI PRO-CTCAE™ ITEMS

Item Library Version 1.0
English
Form created on 6 September 2018

7.	In the last 7 days, how OFTEN did you have a HEADACHE?				
	○ Never	○ Rarely	○ Occasionally	○ Frequently	○ Almost constantly
	In the last 7 days, what was the SEVERITY of your HEADACHE at its WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe
	In the last 7 days, how much did your HEADACHE INTERFERE with your usual or daily activities?				
	○ Not at all	○ A little bit	○ Somewhat	○ Quite a bit	○ Very much

8.	In the last 7 days, what was the SEVERITY of your FATIGUE, TIREDNESS, OR LACK OF ENERGY at its WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe
	In the last 7 days, how much did FATIGUE, TIREDNESS, OR LACK OF ENERGY INTERFERE with your usual or daily activities?				
	○ Not at all	○ A little bit	○ Somewhat	○ Quite a bit	○ 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

Anticipated Event

An anticipated event is an adverse event that commonly occurs independent of exposure to the drug under investigation.

For the purposes of this study the following serious adverse events will be considered anticipated events:

- Anaemia
- Bleeding
- Bone diseases
- Hypercalcaemia
- Hyperuricemia
- Infection
- Neutropenia
- Renal failure and insufficiency
- Thrombocytopenia

These anticipated events will be periodically analyzed in aggregate by the sponsor during study conduct. The sponsor will prepare a safety report in narrative format if the aggregate analysis indicates that the anticipated event occurs more frequently in the treatment group than in the control group and the sponsor concludes there is a reasonable possibility that the drug under investigation caused the anticipated event.

The plan for monitoring and analyzing the anticipated events is specified in a separate Anticipated Events Safety Monitoring Plan. The assessment of causality will be made by the sponsor's unblinded safety assessment committee.

The sponsor assumes responsibility for appropriate reporting of the listed anticipated events according to the requirements of the countries in which the studies are conducted.

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:

1. 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 $\geq$40 mL/min/1.73 m^2
  - AST and ALT$\leq$3 times the upper limit of normal

2. 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 and Table 3).
- 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: Definition of Woman of Childbearing Potential

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 12 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.

INVESTIGATOR AGREEMENT

JNJ-68284528
Clinical Protocol 68284528MMY2003 Amendment 1

INVESTIGATOR AGREEMENT

I have read this protocol and agree that 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): Jordan Schecter, MD

Institution: Janssen Research & Development

Signature: _____ Date: 01 /Nov /2019
(Day Month Year)

Note: If the address or telephone number of the investigator changes during the course of the study, written notification will be provided by the investigator to the sponsor, and a protocol amendment will not be required.

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Approved, Date: 31 October 2019