CLINICAL RESEARCH PROTOCOL

INVESTIGATIONAL MEDICINAL PRODUCT:	FT576
PROTOCOL NUMBER:	FT576-101
PROTOCOL TITLE:	A Phase I Study of FT576 as Monotherapy and in Combination with Daratumumab in Subjects with Relapsed/Refractory Multiple Myeloma
IND NUMBER:	IND 026941
SPONSOR:	Fate Therapeutics, Inc. 12278 Scripps Summit Drive San Diego, CA 92131
VERSION NUMBER:	4.0

Sponsor Signatory Name and Title	**Digital Signature Date and Time (Version Date)**
John Byon, MD, PhD Vice President, Clinical Development	DocuSigned by: John Byon Signer Name: John Byon Signing Reason: I approve this document Signing Time: 3/23/2022	10:46:45 AM PDT C075D5B6BA5542079B6B49DD10DABABA

This protocol was subject to critical review and has been approved by the Sponsor.

CONFIDENTIALITY STATEMENT

CONFIDENTIALITY AND INVESTIGATOR STATEMENT

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I have read the protocol, including all appendices, and the Investigator's Brochure, and I agree that it contains all of the necessary information for me and my staff to conduct this study as described. I will conduct this study as outlined herein, in accordance with the regulations stated in the Federal Code of Regulations for Good Clinical Practices and International Council for Harmonisation guidelines and will make a reasonable effort to complete the study within the time designated.

I will provide all study personnel under my supervision copies of the protocol and any amendments, and access to all information provided by FATE or its specified designees. I will discuss the material with them to ensure that they are fully informed about FT576 and the study. I will inform them that this is confidential and proprietary information of FATE and that this information may not be disclosed to other third parties, except as described above.

Principal Investigator Name (Printed)	**Signature**

Date (dd-mmm-yyyy)	**Site Number**

PROTOCOL AMENDMENT SUMMARY OF CHANGES

Document History

Document	Date
Amendment Version 4.0	See digital signature date on protocol cover page.
Amendment Version 3.0	08 November 2021
Amendment Version 2.0	27 January 2021
Original Protocol (Version 1.0)	19 November 2020

Protocol FT576-101, Version 4.0

Overall Rationale: In order to support efficient enrollment for Regimens A1 and B1 dose-escalation cohorts to treat patients at potentially clinically relevant dose levels, Protocol FT576-101 has been amended to change dose escalation based on relative dose increases from dose level to dose level. Clarification has been made to explain Regimens A1 and B1 as multidose cycles and to explain that the starting doses of these regimens are at the most recently cleared dose-escalation cohort from Regimen A. These changes will allow higher doses to drive efficacy and to enter dose expansion approximately 4 to 6 months sooner in the multiple-dose level Regimens A1 and B1.

Additional minor modifications have been made to improve clarity and consistency.

A description of the change to the protocol, along with a rationale for the change, follows.

Section Number	Description of Change and Rationale
1.1	The synopsis has been revised to reflect the changes to the protocol.
1.2	The study schema has been updated to replace "fractionated doses" with "multiple doses" for Regimens A1 and B1.
1.3	Schedule of Activities: **Table 1:** • Reference to footnote "b" has been removed from the Day -5 column, as assessments are only performed on 2 consecutive days (Days -4 and -3). Footnote "b" has been updated to reflect this change. • Footnotes "r" and "s" have been revised to clarify that for subjects with disease that is only detectable in the serum, a 24-hour urine protein electrophoresis (UPEP) is only required at screening, for confirmation of CR, as clinically indicated, and at end-of-study visit.

(Continued)

Section Number	Description of Change and Rationale
	(Continued)
	• Footnote "z" has been added to clarify that a full skeletal survey including the skull is required for bone lesion assessment. A single positron emission tomography-computed tomography (PET-CT) scan may be used for detection of myeloma bone disease and extramedullary disease (if suspected/known) at baseline. The CT portion should be of diagnostic quality and, if used at screening, the same modality should be followed during the study period for suspected skeletal progression and/or assessment of extramedullary disease during confirmation of complete response (CR), plateau of response based on laboratory data, or suspected progression. **Table 3:** Footnote "l" has been added to clarify that for subjects with disease that is only detectable in the serum, a 24-hour UPEP is only required at screening, for confirmation of complete remission, as clinically indicated, and at end-of-study visit.
4, 4.6.2	Dose levels have been modified to reflect relative dose increases from cleared dose levels in order to provide greater flexibility to optimize dose and schedule during the dose escalation portion of the study. Dosing for Regimens A1 and B1 (including Figure 4 and Table 6) has been changed from fractionated to multiple dosing based on several Sponsor-supported studies that have demonstrated overall safety and tolerability of engineered NK-cell therapies when administered as multiple doses up to 9×10^8 cells/dose. The trial has robust safety monitoring in place, including a Safety Assessment Committee, to ensure subject safety. The doses for dose level (DL) 4 have been updated, and DL5 has been removed. Text has been revised to clarify that initiation of Regimen A1 and B1 on Days 1 and 15 will begin at the most recently cleared dose level (i.e., meets acceptable safety and tolerability to escalate) of Regimen A. The rationale for multiple (instead of fractionated) FT576 dosing on Day 1 and Day 15 (Regimens A1 and B1) has been updated (Section 4.6.2). The number of subjects and study sites has been decreased from 204 to 180 subjects and from 14-18 to 12-16 sites, respectively, to account for current enrollment projections. In addition, the number of subjects for Regimens A1 and B1 were decreased from 57 to 45 for total enrollment and from 42 to 30 in dose escalation.
5.2	Inclusion criterion #9c has been updated to reference Centers for Disease Control and Prevention (CDC) guidance regarding positive serologic and PCR test results for hepatitis C virus (HCV) infection.
6.1.2.1	Text has been revised to clarify that immediately prior to cyclophosphamide (CY) administration, subjects will receive 300 mL of intravenous (IV) normal saline **or** per institutional standards. Subjects may receive additional IV normal saline following CY administration, **if** based on institutional standards and/**or** investigator discretion following assessment of subject hydration status.
6.1.3	Table 9 has been updated to clarify daratumumab IV versus subcutaneous (SC) administration instructions.

(Continued)

Section Number	Description of Change and Rationale
(Continued)	
8.3.3	The Sample Retention section has been updated to clarify the length of time samples collected during the study will be stored.
Appendix 5	Contraception information has been updated to include guidance for fludarabine in addition to cyclophosphamide.

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1 PROTOCOL SUMMARY

1.1 Synopsis

Sponsor: Fate Therapeutics, Inc. 12278 Scripps Summit Drive San Diego, CA 92131	
Protocol Title: A Phase I Study of FT576 as Monotherapy and in Combination with Daratumumab in Subjects with Relapsed/Refractory Multiple Myeloma	
Protocol Number: FT576-101	**Phase of Development:** I
Investigational Medicinal Product: FT576 FT576 comprises allogeneic natural killer (NK) cells, derived from a clonal, CD38-knockout, human-induced pluripotent stem cell line (iPSC) that expresses anti-B-cell maturation antigen (BCMA) chimeric antigen receptor (CAR), high-affinity, non-cleavable CD16 (hnCD16), and IL-15/IL-15 receptor fusion protein (IL-15RF).	

Study Rationale

Despite advances in treatment, multiple myeloma (MM) remains uncurable and the majority of patients will experience serial cycles of response, relapse, and progression. Therefore, treatment for relapsed/refractory (r/r) disease remains a significant area of unmet medical need. Administration of T cells engineered to express a CAR targeting BCMA has resulted in high response rates, as well as deep responses in patients with r/r MM. Results from a Phase II study (KarMMa; Munshi et al. 2021) in 128 subjects treated with idecabtagene vicleucel, a BCMA-directed CAR T-cell therapy reported an encouraging objective response rate of 73% (complete response or better in 33%). However, the median progression-free survival was 8.8 months, which suggests that the responses were not durable, and many patients still experienced disease relapse and progression as 34% died during the study, with most deaths attributed to disease progression. Moreover, significant barriers to the broad use of idecabtagene vicleucel remain, including serious clinical safety risks as evidenced by approximately 5% reported rate of Grade 3+ cytokine release syndrome including one fatal event and approximately 3% rate of Grade 3+ neurotoxicity in KarMMa. Finally, complex manufacturing processes necessitated bridging therapy in 88% of patients prior to infusion of CAR T-cells and often result in heterogeneous products of limited quantity.

FT576 is an off-the-shelf CAR NK-cell product candidate that is manufactured from a clonal master human-induced pluripotent stem cell (iPSC) line that has the potential to address the shortcomings of current-generation CAR T-cell therapy. The functional attributes of FT576, as described in the protocol, support the rationale for the proposed Phase I study of FT576 as monotherapy and in combination with daratumumab for the treatment of subjects with r/r MM. The purpose of this study is to assess the safety, tolerability, and clinical activity of FT576 in r/r MM.

Objectives and Endpoints

Objectives	Endpoints
Primary	
• To determine the RP2D for FT576 when administered as monotherapy and in combination with daratumumab • To evaluate the safety and tolerability of FT576 when administered as monotherapy and in combination with daratumumab	• Incidence and nature of DLTs within each dose escalation cohort to determine the MTD or MAD for Regimens A, A1, B, and B1. The RP2D will be determined based on the overall safety and anti-tumor activity among the dose-escalation and dose-expansion cohorts. • Incidence, nature, and severity of AEs, with severity determined according to NCI CTCAE, v5.0
Secondary	
• To evaluate the anti-tumor activity of FT576 when administered as monotherapy and in combination with daratumumab • To characterize the PK of FT576 when administered as monotherapy and in combination with daratumumab	• ORR, defined as the proportion of subjects with a best overall response of sCR, CR, VGPR, or PR, as determined by the investigator according to standard IMWG response criteria • DOR, defined as the duration from the first occurrence of a documented objective response until the time of disease progression or relapse, or death due to progressive disease, as determined by the investigator according to standard IMWG response criteria • PFS, defined as the time from first dose of study treatment to disease progression or relapse, or to the day of death from any cause, as determined by the investigator according to standard IMWG response criteria • RFS from CR, defined as the duration from the start of sCR or CR until the time of relapse from sCR or CR, as determined by the investigator according to standard IMWG response criteria • OS, defined as the time from first dose of study treatment to death from any cause • PK of FT576 as assessed by detection of FT576 in peripheral blood following FT576 administration
Exploratory (refer to the protocol)	

AE = Adverse event; CR = Complete response; DLT = Dose-limiting toxicity; DOR = Duration of response; IMWG = International Myeloma Working Group; MAD = Maximum administered dose; MTD = Maximum tolerated dose; NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events; PFS = Progression-free survival; PK = Pharmacokinetics; RP2D = Recommended Phase II dose; ORR = Objective response rate; OS = Overall survival; PR = Partial response; RFS = Relapse-free survival; sCR = Stringent complete response; VGPR = Very good partial response

Overall Study Design

This is a Phase I, open-label, multicenter study to evaluate the safety, pharmacokinetics, and anti-tumor activity of FT576 in subjects with r/r MM in the following regimens:

- **Regimen A:** FT576 monotherapy administered as a single dose on Day 1
- **Regimen A1:** FT576 monotherapy administered as multiple doses on Day 1 and Day 15
- **Regimen B:** FT576 administered as a single dose on Day 1 in combination with daratumumab
- **Regimen B1:** FT576 administered as multiple doses on Day 1 and Day 15 in combination with daratumumab

Subjects will be enrolled in 2 stages: a dose-escalation stage and a dose-expansion stage. After the safety and tolerability have been assessed to define the maximum tolerated dose (MTD; or through the maximum administered dose in the absence of dose-limiting toxicity [DLT] defining the MTD) in the dose-escalation stage, the dose-expansion stage will further evaluate the safety and activity of FT576. Dose-escalation and dose-expansion will be conducted independently for each regimen upon clearance of the first monotherapy cohort in Regimen A.

The study will include an up to 28-day screening period and a treatment period with conditioning followed by FT576 as monotherapy or FT576 in combination with daratumumab. Subjects will return for a treatment completion visit on Day 29. Subjects who discontinue study treatment prematurely will return to the clinic for an early treatment discontinuation visit that includes the activities described for the Day 29 visit. Dose and schedule of study treatments are detailed in the protocol.

Subjects will be followed for DLTs per dose-escalation rules through Day 29, which is also the time at which the first disease response assessment will be performed. Thereafter, study assessments and procedures will be performed as described in the Schedules of Activities (SoAs). Subjects with evidence of clinical benefit may be eligible for additional treatment as described in the protocol.

Subjects will be followed for safety, anti-tumor activity, and survival for up to 15 years.

Study Population

The study is expected to enroll up to approximately 180 subjects at approximately 12 to 16 sites in the United States, as described below.

- **Regimen A:** up to 45 subjects—up to 30 in dose escalation; up to 15 in a single dose-expansion cohort
- **Regimen A1:** up to 45 subjects—up to 30 in dose escalation; up to 15 in a single dose-expansion cohort
- **Regimen B:** up to 45 subjects—up to 30 in dose escalation; up to 15 in a single dose-expansion cohort
- **Regimen B1:** up to 45 subjects—up to 30 in dose escalation; up to 15 in a single dose-expansion cohort

For all regimens, additional dose-specific dose-expansion cohorts of up to 15 subjects/cohort may be enrolled.

The study is expected to enroll over a period of approximately 3 years (approximately 16 to 20 months in dose escalation for each regimen and approximately 6 months in dose expansion for each regimen).

Inclusion Criteria

Subjects are eligible for the study only if all of the following criteria apply:

1. Diagnosis of r/r MM as described below.
   - Regimens A, A1, B, and B1: Measurable disease, defined by at least one of the following:
     - Serum M-protein ≥1.0 g/dL
     - Urine M-protein ≥200 mg/24 hours
     - Involved serum free light chain level ≥10 mg/dL, with an abnormal κ/λ ratio if the serum M-protein <1.0 g/dL and/or urine M-protein <200 mg/24 hours
   - Regimens A and A1 only: MM that has relapsed or progressed after ≥3 prior approved therapies, including:
     - A proteasome inhibitor (e.g., bortezomib, carfilzomib), and
     - An immunomodulatory drug (IMiD; e.g., lenalidomide, pomalidomide), and
     - Anti-CD38 therapy (e.g., daratumumab, isatuximab)

     Planned sequential therapy (e.g., induction therapy followed by hematopoietic stem-cell transplantation [HSCT] and maintenance) is considered one line of therapy.
   - Regimens B and B1 only: MM that has relapsed or progressed after ≥2 prior approved therapies, including:
     - A proteasome inhibitor, and
     - An IMiD

   For all regimens, prior treatment with BCMA CAR T-cell therapy and BCMA-targeted therapy is allowed.
2. Willingness to provide informed consent, which includes compliance with the requirements and restrictions listed in the Informed Consent Form (ICF) and in this protocol
3. Age ≥18 years old at the time of signing the ICF
4. Agreement to comply with study procedures, including providing bone marrow biopsy/ aspirate samples as described in the SoAs
5. Male subjects and female subjects of childbearing potential who engage in heterosexual intercourse must agree to use protocol specified method(s) of contraception as described in the protocol.

Exclusion Criteria

Subjects are excluded from the study if any of the following criteria apply:

1. Females who are pregnant or breastfeeding
2. Eastern Cooperative Oncology Group Performance Status ≥2
3. Evidence of insufficient hematologic function defined by the following:
   a. Absolute neutrophil count <1000/μL without growth factor support ≤7 days prior to the absolute neutrophil count measurement to determine eligibility
   b. Platelet count <75,000/μL without platelet transfusion ≤72 hours prior to the platelet count measurement to determine eligibility

   Subjects who do not meet the criteria for hematologic function because of extensive marrow involvement of disease and/or disease-related cytopenias may be enrolled into the study with approval from the Medical Monitor.
4. Evidence of insufficient organ function defined by any one of the following:
   a. Estimated creatinine clearance <50 mL/minute by Cockcroft-Gault method or other standard institutional method
   b. Total bilirubin >1.5 × upper limit normal (ULN), not applicable for subjects with Gilbert's syndrome
   c. AST >3 × ULN or ALT >3 × ULN, not applicable if determined to be directly due to underlying malignancy

   NOTE: Subjects who have a laboratory blood test value that is exclusionary per exclusion criteria 4a, 4b, or 4c are permitted one repeat test, and if no longer exclusionary, may continue to enroll.

   d. Oxygen saturation <92% on room air
5. Clinically significant cardiovascular disease including any of the following: myocardial infarction within 6 months prior to first study treatment; unstable angina or congestive heart failure of New York Heart Association Grade 2 or higher; or cardiac ejection fraction <40%
6. Subjects with active central nervous system (CNS) involvement, including leptomeningeal disease

   Subjects with prior CNS involvement may be enrolled into the study if effective treatment of their CNS disease was completed at least 3 months prior to Day 1 with no evidence of disease clinically and at least stable findings on relevant CNS imaging.
7. Non-malignant CNS disease such as stroke, epilepsy, CNS vasculitis, or neurodegenerative disease or receipt of medications for these conditions in the 2-year period leading up to study enrollment
8. Currently receiving or likely to require immunosuppressive therapy (e.g., prednisone >5 mg daily) for any reason during the treatment period, with the exception of corticosteroids

9. Clinically significant infections including:
    a. Positive serologic test results for HIV infection
    b. Positive serologic or PCR test results for HBV infection

       HBV infection status that cannot be determined by serologic test results (https://www.cdc.gov/hepatitis/hbv/pdfs/serologicchartv8.pdf) must be negative for HBV by PCR to be eligible for study participation.
    c. Positive serologic and PCR test results for HCV infection

       Subjects who are positive for HCV antibody must be negative for HCV by PCR to be eligible for study participation (https://www.cdc.gov/hepatitis/hcv/pdfs/hcv_graph.pdf).
10. Live vaccine <6 weeks prior to start of conditioning
11. Receipt of an allograft organ transplant
12. Ongoing requirement for systemic graft-versus-host disease therapy
13. Known allergy to the following FT576 components: albumin (human) or dimethyl sulfoxide (DMSO)
14. Presence of any medical or social issues that are likely to interfere with study conduct or may cause increased risk to subject
15. Any medical condition or clinical laboratory abnormality that per investigator or Medical Monitor judgment precludes safe participation in and completion of the study, or that could affect compliance with protocol conduct or interpretation of results

    Subjects who have had prior receipt of a Fate Therapeutics' investigational human iPSC product may be eligible for the study with approval from the Medical Monitor.
16. Plasma cell leukemia defined as a plasma cell count >2000/mm^3
17. Prior malignancy (other than current indication including any antecedent hematologic disorder) within the 2 years prior to enrollment except for the following: basal or squamous cell carcinomas of the skin, carcinoma in situ of the cervix or breast treated with curative intent, or localized prostate cancer treated with curative intent, or malignancy that, in the opinion of the investigator and Sponsor's Medical Monitor, is considered cured with minimal risk of recurrence within 3 years.
18. Washout periods from prior therapies:
    a. For all subjects (Regimens A, A1, B and B1), receipt of the following:

       Chemotherapy, or radiation therapy, except for palliative purposes, within 14 days prior to the first dose of FT576 (Day 1) or five half-lives, whichever is shorter

       Investigational therapy within 30 days prior to the first dose of FT576 (Day 1) or five half-lives, whichever is shorter

       Biologic therapy (except for anti-CD38 monoclonal antibodies in Regimens B and B1 only), including autologous cellular immunotherapy (e.g., CAR-T/CAR-NK),

antibody-drug conjugates or bi-specific immune-cell engaging antibody within 30 days prior to the first dose of FT576 (Day 1) or five half-lives, whichever is shorter

Prior allogeneic HSCT or allogeneic CAR T/CAR NK within 6 months of first dose of FT576 (Day 1)

b. For subjects in Regimens B and B1 only, receipt of the following:

Anti-CD38 therapy alone or in combination within 3 months prior to Day -11

19. Allergy or hypersensitivity to antibodies or antibody-related proteins

Study Treatments

FT576 (all subjects): The investigational medicinal product for this study is FT576. Dosing is based on CAR expression, where ≥80% of administered FT576 viable cells express BCMA-CAR. FT576 will be provided by the Sponsor in a cryopreserved bag and thawed at the site of administration. FT576 must be administered using an IV administration set with an in-line filter.

FT576 will be administered as an IV infusion via gravity at planned dose levels, as described in the table below:

Dose Level	**Regimen A: Single Dose of FT576 Monotherapy/ Regimen B: Single Dose of FT576 with Daratumumab**	**Regimen A1: Multiple Doses of FT576 Monotherapy/ Regimen B1: Multiple Doses of FT576 with Daratumumab**
Day	**Day 1**	**Day 1, Day 15**
DL0[a]	5×10^7	Not applicable
DL1	1×10^8	D1 = 1×10^8, D15 = 1×10^8
DL2	≤ 3 × DL1	D1 = ≤ 3 × DL1, D15 = ≤ 3 × DL1
DL3	≤ 3 × DL2	D1 = ≤ 3 × DL2, D15 = ≤ 3 × DL2
DL4	≤ 3 × DL3	D1 = ≤ 3 × DL3, D15 = ≤ 3 × DL3
DL4A[a]	≤ 3 × DL3	D1 = ≤ 2 × DL3, D15 = ≤ 2 × DL3

NOTE: Dose-escalation increments are approximate, with allowable ± 15% variance.

[a] DL0 and/or DL4A are explored only if DL1 and/or DL4, respectively, are deemed to be unacceptably toxic or a de-escalation decision is made per the mTPI dose-escalation rules.

D = Day; DL = Dose level; DLT = Dose-limiting toxicity; mTPI = modified toxicity probability interval

Refer to the protocol for additional details.

Refer to the FT576 Investigator's Brochure and the Pharmacy Manual for FT576 for additional administration instructions and details on packaging, handling, storage, and stability.

Additional treatments used in this study include cyclophosphamide (CY), fludarabine (FLU), and daratumumab.

Conditioning (All Subjects):

- CY, 300 mg/m^2 IV infusion for 3 consecutive days (Days -5, -4, and -3)
- FLU, 30 mg/m^2 IV infusion for 3 consecutive days (Days -5, -4, and -3)

FT576 infusion must be administered no earlier than the third calendar day after the last dose of conditioning. FT576 may be administered beyond the Day 1 window with Medical Monitor approval; however, depending on the length of the delay, repeat conditioning may be considered.

Daratumumab (Regimens B and B1):

Daratumumab will be administered by IV infusion at a dose of 16 mg/kg actual body weight, or daratumumab + hyaluronidase will be administered subcutaneously at a dose of 1800 mg/30,000 units starting on Day -11, then weekly for a total of 8 doses, then every 2 weeks for a total of 8 doses, then every 4 weeks until disease progression or unacceptable toxicity.

Statistical Methods

In general, clinical data will be summarized by cohort, separately by each regimen, using descriptive statistics (n, mean, standard deviation, standard error, median, first quartile, third quartile, minimum, and maximum for continuous variables, and frequencies and percentages for categorical variables). When categorical data are presented, the percentages will be suppressed when the frequency count is zero. Non-zero percentages will be rounded to one decimal place, except for 100%, which will be displayed without any decimal places. For selected assessments, confidence intervals will be displayed.

Additional summaries may be performed by clinical characteristics, e.g., age, prior therapies, baseline disease status, and/or tumor characteristics, e.g., disease subtypes defined by genetic abnormalities, tumor microenvironment.

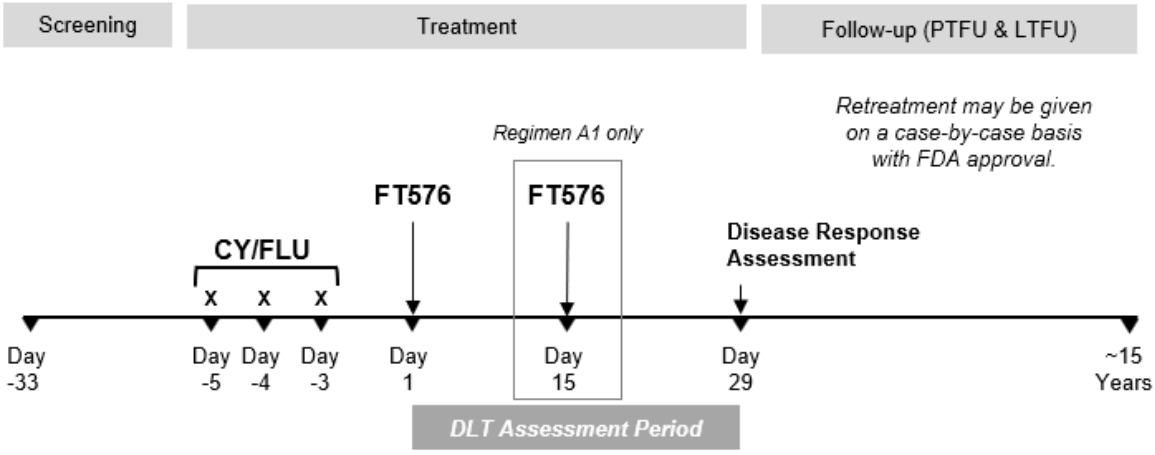
1.2 Schemas

Figure 1. Study Treatment Schemas

There is no Day 0; i.e., days within each cycle progress from Day -5 to Day -1, followed by Day 1.

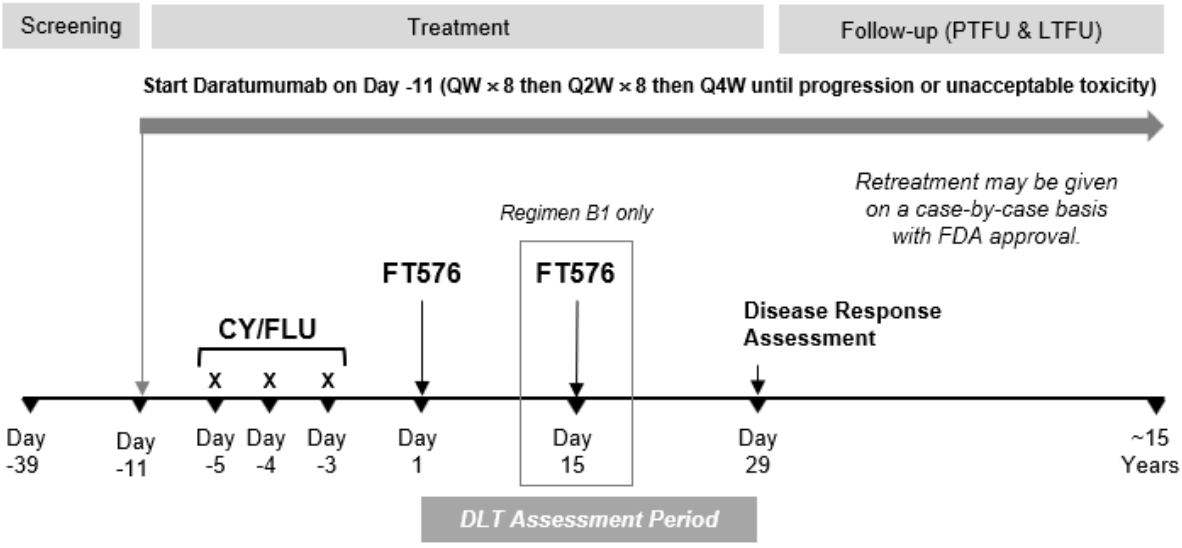
Regimen A: FT576 Monotherapy Administered as a Single Dose on Day 1

Regimen A1: FT576 Monotherapy Administered as Multiple Doses on Days 1 and 15



Regimen B: FT576 Administered as a Single Dose on Day 1 + Daratumumab

Regimen B1: FT576 Administered as Multiple Doses on Days 1 and 15 + Daratumumab



See the Schedule of Activities (Section 1.3) for details on the daratumumab dosing schedule. Refer to Appendix 3 for details for retreatment.

CY = Cyclophosphamide; DLT = Dose-limiting toxicity; FDA = U.S. Food and Drug Administration; FLU = Fludarabine; LTFU = Long-term follow-up; PTFU = Post-treatment follow-up; QW = Every week; Q2W = Every 2 weeks; Q4W = Every 4 weeks; SoA = Schedule of Activities

1.3 Schedules of Activities

Table 1. SoA: Screening and Treatment Phase

	Screening[a]	Treatment													
Visit Days	D -33 to D -6 (A & A1) D -39 to D -12 (B & B1)	D -11 (B & B1 only)	D -5	D -4 & D -3[b]	D1[c]	D2[d]	D4	D8	D11	D15	D18	D22	D25 (B & B1 only)	Early Tx Discont. or Tx Completion (D29)[e]	Pre-Retreatment Monitoring (if applicable)[f]
Visit Window (days)	-	-	-	-	-	-	±1	±1	±1	±1	±1	±1	±1	+3[g]	-
GENERAL PROCEDURES															
Informed consent[h]	X														
Medical and cancer history	X														
Demographics	X														
Inclusion and exclusion review[i]	X														
ECOG PS	X				X									X	X
Full physical examination[j]	X				X										
Targeted physical examination[k]		X	X	X		X	X	X	X	X	X	X		X	X
ICANS (neurotoxicity) monitoring[l]			X			X	X	X	X	X	X	X		X	X[m]
Weight	X	X	X												
Height	X														
Vital signs[n]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medications[o]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse events[p]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

(Continued)

Table 1. SoA: Screening and Treatment Phase

	Screening[a]	**Treatment**													
Visit Days	**D -33 to D -6 (A & A1)** **D -39 to D -12 (B & B1)**	**D -11 (B & B1 only)**	**D -5**	**D -4 & D -3**[b]	**D1**[c]	**D2**[d]	**D4**	**D8**	**D11**	**D15**	**D18**	**D22**	**D25 (B & B1 only)**	**Early Tx Discont. or Tx Completion (D29)**[e]	**Pre-Retreatment Monitoring (if applicable)**[f]
Visit Window (days)	-	-	-	-	-	-	±1	±1	±1	±1	±1	±1	±1	+3[g]	-
(Continued)															
12-lead ECG	X													X	
LVEF (ECHO, MUGA, or cardiac MRI)	X														
DISEASE RESPONSE ASSESSMENTS[q]															
SPEP and IFE	X	X[r]	X[s]											X	
DIRA (Regimens B and B1 only)[t]														X[t]	
sFLC	X	X[r]	X[s]											X	
Immunoglobulins (IgD[u], IgG, IgA, IgM)	X	X[r]	X[s]											X	
24-hour UPEP and UIFE	X	X[r]	X[s]											X	
Bone marrow biopsy with aspirate (refer to Table 11 for additional details)[v]	X					Between D2-D8 (Aspirate only)								X[w]	X[w,x]
Optional tumor biopsy (for subjects with EMD; refer to Section 8.3.4.5 for additional details)[y]	X					Between D2-D8								X	

(Continued)

Table 1. SoA: Screening and Treatment Phase

	Screening[a]	**Treatment**													
Visit Days	**D -33 to D -6 (A & A1)** **D -39 to D -12 (B & B1)**	**D -11 (B & B1 only)**	**D -5**	**D -4 & D -3**[b]	**D1**[c]	**D2**[d]	**D4**	**D8**	**D11**	**D15**	**D18**	**D22**	**D25 (B & B1 only)**	**Early Tx Discont. or Tx Completion (D29)**[e]	**Pre-Retreatment Monitoring (if applicable)**[f]
Visit Window (days)	-	-	-	-	-	-	±1	±1	±1	±1	±1	±1	±1	+3[g]	-
(Continued)															
Skeletal disease (skeletal survey, PET-CT, CT, or MRI)[z]	X				At suspected skeletal disease progression[z]										
Extramedullary disease (PET-CT, CT, or MRI)[aa]	X				If extramedullary disease is present at baseline, perform D29 assessment then every 12 weeks (±7 days) after the D29 assessment until CR or plateau response based on laboratory data, and at suspected disease progression										
LOCAL LABORATORY TESTS															
Pregnancy test[bb]	X	X	X												
Blood type, Rh, and indirect antiglobulin test (Regimens B and B1 only)[cc]	X														
β2 microglobulin	X														
HIV, HBV, and HCV testing[dd]	X														
Hematology[ee]	X	X	X		X	X	X	X	X	X	X	X		X	X
Serum chemistry[ee]	X	X	X		X	X		X		X		X		X	X
Urinalysis[ee]	X				X	As clinically indicated								X	As clinically indicated
CRP and ferritin[ff]					X	For suspected clinical CRS									

(Continued)

Table 1. SoA: Screening and Treatment Phase

	Screening[a]	**Treatment**													
Visit Days	**D -33 to D -6 (A & A1)** **D -39 to D -12 (B & B1)**	**D -11 (B & B1 only)**	**D -5**	**D -4 & D -3**[b]	**D1**[c]	**D2**[d]	**D4**	**D8**	**D11**	**D15**	**D18**	**D22**	**D25 (B & B1 only)**	**Early Tx Discont. or Tx Completion (D29)**[e]	**Pre-Retreatment Monitoring (if applicable)**[f]
Visit Window (days)	-	-	-	-	-	-	±1	±1	±1	±1	±1	±1	±1	+3[g]	-
(Continued)															
CENTRAL LABORATORY TESTS															
See Table 2															
STUDY TREATMENT															
CY/FLU (Regimens A, A1, B, and B1)[gg]			X	X											
FT576 (Regimens A and B)					X										
FT576 (Regimens A1 and B1)					X					X[hh]					
Daratumumab (Regimens B and B1)		Start on Day -11: QW for 8 doses (Days -11, -4, 4, 11, 18, and 25, and 2 doses QW [±1 day] thereafter); then Q2W (±1 day) for 8 doses; then Q4W (±2 days) until disease progression or unacceptable toxicity													

NOTES: For data collection purposes the treatment phase is denoted as Cycle 1. If retreatment is approved and initiated (see Appendix 3), subsequent treatment cycle(s) will be denoted as Cycle 2, Cycle 3, etc.

If scheduled activity, including study treatment administration, coincides with a weekend/holiday that precludes the activity, the activity should be performed on the nearest following date.

On days when peripheral blood sample and/or urine collection occur on the same day as study treatment administration, peripheral blood sample and/or urine collection should be obtained prior to study treatment administration.

An unscheduled visit is a visit that occurs in addition to the predefined protocol-specific schedule of activities. If an unscheduled visit occurs for a given subject in follow up to a safety event, the visit or assessment must be documented on the Unscheduled Visit eCRF, as outlined by the Sponsor in the eCRF Completion Guidelines.

(Continued)

Table 1. SoA: Screening and Treatment Phase

(Continued)

[a] Results of standard-of-care tests or examinations performed prior to obtaining informed consent and within the screening period may be used; these tests do not need to be repeated for screening.

[b] Assessments will be performed on 2 consecutive days: Days -4 and -3, unless otherwise specified.

[c] Start of Day 1 may be delayed if additional time is required between conditioning and the first dose of FT576 administration. All study visits, both preceding and subsequent to Day 1, will be projected from the first dose of FT576 administration. Medical Monitor approval will be required for delays between conditioning and FT576 administration.

[d] There is no visit window for Day 2; Day 2 assessments will be performed 1 day following Day 1 assessments.

[e] Subjects who complete the FT576 treatment cycle will return to the clinic for a visit on Day 29. Subjects who discontinue study treatment prematurely (Section 7.1) will return to the clinic for an early treatment discontinuation visit that includes the activities described for the Day 29 visit and continue to have Post-Treatment Follow-Up assessments as described in Table 3 and/or Long-Term Follow-Up per Table 4. Subjects who discontinue from the study (Section 7.2) should return to the clinic for a discontinuation visit that includes the activities described for the Day 29 visit. (NOTE: The treatment completion/early treatment discontinuation visit may be used as this visit.)

[f] Pre-retreatment monitoring applies only to those subjects being considered for retreatment. Subjects may be eligible for retreatment with subsequent treatment cycle(s) based on evidence of clinical benefit and with approval from the FDA on a case-by-case basis (see Appendix 3). Pre-retreatment monitoring should be performed on subjects being considered for retreatment under one of the following scenarios: **(1) Subjects who complete the treatment cycle through the response assessment on Day 29 and who are considered to directly proceed to receive subsequent treatment cycle(s) pending FDA approval for retreatment:** These subjects will have additional weekly pre-retreatment monitoring visits leading up to the start of the subsequent treatment cycle to ensure adequate recovery from AE(s) from the prior treatment cycle(s). After completion of retreatment, subjects who have not progressed, relapsed, and/or have not started a non-protocol-defined anti-cancer therapy will begin the post-treatment follow-up period (Table 3). **(2) Subjects who complete the treatment cycle through the response assessment on Day 29 without consideration for immediate retreatment, entered the post-treatment follow-up period, and subsequently become eligible to receive retreatment** (see Appendix 3): After FDA approval for retreatment has been obtained, subjects may be required (based on the timing of the last post-treatment follow-up assessment) to complete weekly pre-retreatment monitoring visits leading up to the start of the subsequent treatment cycle to ensure adequate recovery from AE(s) from prior treatment cycle(s). After completion of retreatment, subjects who have not progressed or relapsed and have not started a non-protocol-defined anti-cancer therapy will then re-enter the post-treatment follow-up period starting with the FU 1 visit (Table 3).

[g] The visit window for Cycle 1 Day 29 is +3 days in order to capture assessments through the DLT window. If additional treatment cycle(s) are administered as part of retreatment (see Appendix 3), the visit window for Day 29 in subsequent cycle(s) is ±3 days.

[h] Informed consent may be signed prior to the start of the screening period (Day -33 for Regimens A and A1; Day -39 for Regimens B and B1). All other screening assessments must be done within the screening period.

[i] Subjects with prior CNS involvement with their malignancy must have completed effective treatment of their CNS disease at least 3 months prior to Day 1 with no evidence of disease clinically and at least stable findings on relevant CNS imaging or no evidence of disease based on evaluation of CSF.

[j] A full physical examination will include an evaluation of the head, eyes, ears, nose, and throat; extremities/joints; and the cardiovascular, respiratory, abdominal, musculoskeletal, neurological, lymphatic, and dermatological systems. Urogenital and rectal examinations are not necessary unless clinically indicated. Any clinically significant findings should be recorded on the Adverse Event or Medical History eCRF, as applicable.

(Continued)

Table 1. SoA: Screening and Treatment Phase

(Continued)

[k] A targeted physical examination will be performed at specified timepoints and as clinically indicated based on symptoms reported. Targeted physical examinations should be limited to systems of primary relevance, i.e., cardiovascular, respiratory, those associated with symptoms, and those associated with tumor assessment (lymph nodes, liver, and spleen), if applicable. Any clinically significant findings should be recorded on the Adverse Event or Medical History eCRF, as applicable.

[l] Neurotoxicity will be monitored using ASTCT consensus grading for ICANS using the ICE score. ICANS monitoring will occur just prior to start of conditioning, at specified timepoints, and as needed in Post-Treatment Follow-Up to document complete resolution to baseline status. Unscheduled ICE score assessments should be performed if neurotoxicity is suspected. Refer to Section 9.5.2.3 for details.

[m] Perform if residual neurotoxicity at end of the treatment cycle until resolution to baseline status.

[n] Vital signs include temperature, systolic and diastolic blood pressure, heart rate, and pulse oximetry. On Day -5 through Day -3, the first set of vital signs prior to conducting study-related activities or procedures should be recorded on the eCRF. On the day of FT576 administration, collect as follows: 10 (±5) minutes prior to infusion of FT576, every 15 (±5) minutes during the infusion period as applicable, after the completion of the flush following the last administered bag of FT576 (+5 minutes), and every 15 (±5) minutes thereafter for 1 hour.

[o] For subjects who have disease relapse/progression or initiate new anti-cancer therapy, only concomitant medications for SAEs possibly or probably related to FT576 per investigator assessment will be recorded.

[p] All AEs will be collected and recorded in the subject's medical record and on the Adverse Event eCRF; refer to Section 9.6. Specific conditions potentially related to engineered cellular immunotherapy products such as FT576, including but not limited to, new malignancies, new or worsening neurologic disorders, new or worsening autoimmune or rheumatologic disorders, or new hematologic disorders, should be documented; refer to Section 9.

[q] Disease response assessment will be performed according to IMWG response criteria in MM, including criteria for MRD (Kumar et al. 2016; Appendix 1). Assessments for disease response will be performed by a local laboratory, with the exception of bone marrow aspirate for MRD, which will be performed by a central laboratory. Allocated material from bone marrow biopsy with aspirate samples obtained as part of disease response assessment, as well as the bone marrow biopsy with aspirate obtained at disease relapse or progression, will be used for exploratory analyses (see Section 8.3.4.6). PET-CT based radiologic assessment will be obtained at baseline to evaluate for extramedullary disease. Post-baseline PET-CT based radiologic assessments will be performed in subjects with baseline extramedullary disease as part of disease response assessment; the same imaging modality is to be used throughout the study. Refer to Appendix 1 for additional details regarding methods for disease response assessment and disease response assessment criteria.

[r] SPEP/IFE, sFLC, immunoglobulins, and 24-hour UPEP/UIFE assessments on Day -11 are to be performed for Regimens B and B1 only and must be performed prior to administering daratumumab. These assessments are not required at this visit if the corresponding screening assessments were performed within 1 week prior to Day -11. For subjects with disease that is only detectable in the serum, a 24-hour UPEP is only required at screening, for confirmation of CR, as clinically indicated, and at end-of-study visit.

[s] SPEP/IFE, sFLC, immunoglobulins, and 24-hour UPEP/UIFE assessments on Day -5 are to be performed for Regimens A and A1 only and must be performed prior to initiating conditioning therapy. These assessments are not required at this visit if the corresponding screening assessments were performed within 1 week prior to Day -5. For subjects with disease that is only detectable in the serum, a 24-hour UPEP is only required at screening, for confirmation of CR, as clinically indicated, and at end-of-study visit.

[t] See Appendix 2 for details on DIRA.

[u] IgD will be collected only for subjects with IgD disease. Subjects with IgD myeloma will have IgD levels checked per IMWG response criteria.

(Continued)

Table 1. SoA: Screening and Treatment Phase

(Continued)

[v] The bone marrow biopsy with aspirate screening sample may be obtained after the other screening procedures have been completed and enrollment of the subject is confirmed by the Medical Monitor. Bone marrow aspirate samples will be obtained for exploratory analyses before and after initial FT576 treatment. Exceptions for samples obtained outside of the specified window may be granted with Medical Monitor approval. Where applicable, bone marrow samples for exploratory analyses should be obtained from the same bone marrow biopsy with aspirate procedure at each disease response assessment as detailed in Section 8.3.1. A bone marrow biopsy with aspirate may be required to rule out DLT (Section 4.2.3) and as clinically indicated in cases of prolonged cytopenias beyond the DLT assessment period; bone marrow samples from these procedures may be used for exploratory analyses (Section 8.3.4.6). All subjects being considered for retreatment, regardless of rationale, must undergo a repeat bone marrow biopsy with aspirate (Appendix 3) within 21 days prior to start of the retreatment cycle.

[w] On Day 29+ and to confirm CR/sCR.

[x] See Appendix 1 for details on IMWG response criteria.

[y] For subjects with extramedullary disease, an optional tumor tissue biopsy sample may be obtained from a safely accessible site for exploratory analyses before and after initial FT576 treatment. Biopsies may also be collected after progression/relapse after initial treatment or retreatment. Exceptions for samples obtained outside of the specified window may be considered and must be approved by the Medical Monitor.

[z] A complete skeletal assessment for bone lesions must include the skull. A single PET-CT scan may be used for detection of myeloma bone disease and extramedullary disease (if suspected/known) at baseline. The CT portion should be of diagnostic quality. The same imaging modality used at screening should be used at the time of suspected disease progression due to new or increasing size of bone lesions.

[aa] Only required for patients with suspected or known extramedullary disease. CT should be of diagnostic quality.

[bb] WOCBP must undergo a serum pregnancy test during the screening period, a urine or serum pregnancy test on Day -11, and a urine or serum pregnancy test at the other indicated timepoints. All pregnancy test results must be negative before the start of study treatment administration, i.e., prior to start of the mAb on Day -11, conditioning administration on Day -5, or FT576 administration on Day 1 if conditioning is not administered. A pregnancy test must be performed and confirmed negative prior to the start of any subsequent treatment cycle.

[cc] Serologic testing (blood typing, Rh testing, and indirect antiglobulin test [indirect Coombs test]) should be performed prior to the first dose of daratumumab (Regimens B and B1) on Day -11 only if the subject has not received prior daratumumab.

[dd] Subjects will be tested for HIV, HBV, and HCV by serologic or PCR testing. Subjects whose HBV infection status cannot be determined by serologic test results (https://www.cdc.gov/hepatitis/hbv/pdfs/serologicchartv8.pdf) must be negative for HBV by PCR to be eligible for study participation. Subjects who are positive for HCV antibody must be negative for HCV by PCR to be eligible for study participation. Subjects who have positive serologic results for HIV are not eligible for study participation.

[ee] Refer to Table 12 for hematology, chemistry, and urinalysis laboratory testing details.

[ff] Clinical assessment of CRS will be performed in accordance with ASTCT consensus grading (Lee et al. 2019). Collection of peripheral blood for CRS cytokines (central laboratory testing) and CRP and ferritin (local laboratory testing) will occur on Day 1 prior to FT576 administration. Subsequent laboratory testing for CRS will occur only if clinical CRS is suspected; CRS cytokines (central laboratory testing) and CRP and ferritin (STAT local laboratory testing) will be collected approximately 1 hour, between 4-6 hours, and 24 hours following initial evaluation of CRS. In cases of documented elevations in CRP and ferritin due to CRS, CRS cytokines (central laboratory testing) and CRP and ferritin (local laboratory testing) should continue to be monitored at least every 24 hours until resolution to baseline CRP (Day 1, pre-FT576 infusion), or if no evidence of continued resolution to baseline CRP in the absence of clinical CRS per investigator assessment.

(Continued)

Table 1. SoA: Screening and Treatment Phase

(Continued)

[gg] Conditioning will be given on 3 consecutive days: Days -5, -4, and -3. FT576 infusion must be administered no earlier than the third calendar day after the last dose of conditioning. FT576 may be administered beyond the Day 1 window with Medical Monitor approval. Study retreatment, contingent on FDA approval, is described in Appendix 3. During retreatment, dose modifications to conditioning should be considered based on observed hematologic or non-hematologic toxicity. Exceptions may be granted by the Medical Monitor after discussion with the investigator in clinically appropriate situations. For subjects not receiving CY/FLU during the additional treatment cycle, only the Day -5 assessments are required.

[hh] Day 1 and Day 15 dosing is applicable for FT576 (Regimens A1 and B1) once Regimen A DL1 Day 1 dosing clears DLT assessment.

AE = Adverse event; ASTCT = American Society for Transplantation and Cellular Therapy; CIBMTR = Center for International Blood and Marrow Transplant Research; CNS = Central nervous system; CR = Complete response; CRP = C-reactive protein; CRS = Cytokine release syndrome; CSF = Cerebrospinal fluid; CY = Cyclophosphamide; D = Day; DIRA = Daratumumab interference reflex assay; Discont. = Discontinuation; DL = Dose level; DLT = Dose-limiting toxicity; ECG = Electrocardiogram; ECHO = Echocardiogram; ECOG PS = Eastern Cooperative Oncology Group Performance Status; eCRF = Electronic Case Report Form; EMD = Extramedullary disease; FDA = U.S. Food and Drug Administration; FLU = Fludarabine; GvHD = Graft-versus-host disease; HBV = Hepatitis B virus; HCV = Hepatitis C virus; ICANS = Immune effector cell-associated neurotoxicity syndrome; ICE = Immune Effector Cell-Associated Encephalopathy; ICF = Informed Consent Form; IFE = Immunofixation electrophoresis; IgA, IgD, IgG, IgM = Immunoglobulin A, D, G, M; IMWG = International Myeloma Working Group; LVEF = Left ventricular ejection fraction; mAb = Monoclonal antibody; MM = Multiple myeloma; MRD = Measurable residual disease; MRI = Magnetic resonance imaging; MUGA = Multigated acquisition; NCI CTCAE, v5.0 = National Cancer Institute Common Terminology Criteria for Adverse Events, Version 5.0; PCR = Polymerase chain reaction; PET = Positron emission tomography; QW = Weekly; Q2W = Every 2 weeks; Q4W = Every 4 weeks; r/r = Relapsed or refractory; SAE = Serious adverse event; sFLC = Serum free light chain; SoA = Schedule of Activities; SPEP = Serum protein electrophoresis; Tx = Treatment; UIFE = Urine immunofixation electrophoresis; UPEP = Urine protein electrophoresis; WOCBP = Woman of childbearing potential

Table 2. SoA: Central Laboratory Tests

CENTRAL LABORATORY TESTS														
	Screening	**Treatment**												
Visit Days	**D -33 to D -6 (A & A1)** **D -39 to D -12 (B & B1)**	**D -11 (B & B1 only)**	**D -5**	**D -4**	**D1**	**D2[a]**	**D4**	**D8**	**D11**	**D15**	**D18**	**D22**	**D25 (B & B1 only)**	**Early Tx Discont. or Tx Completion (D29)[b]**
Visit Window (days)	**-**	**-**	**-**	**-**	**-**	**-**	**±1**	**±1**	**±1**	**±1**	**±1**	**±1**	**±1**	**+3[c]**
On days in which samples occur on the same day as study treatment administration, samples should be obtained prior to study treatment administration:														
Baseline sample for cell therapy safety monitoring[d]	X													
Immunogenicity of FT576[e]	X													X
HLA/KIR typing	X													
CRS cytokines[f]					X	For suspected clinical CRS								
Exploratory serum biomarkers[g]	X	X	X[h]		X	X	X	X	X	X	X	X		X
Exploratory immune monitoring[g]	X	X	X[h]		X	X	X	X	X	X	X	X		X
FT576 PK (Regimens A, A1, B, and B1)[i,j]														
0-60 min pre-infusion					X					X[k]				
0-30 min post-infusion					X					X[k]				
24 (±4) h after FT576 infusion						X								
Non-infusion day PK							X	X	X	X[l]	X	X		X

(Continued)

Table 2. SoA: Central Laboratory Tests

CENTRAL LABORATORY TESTS														
	Screening	**Treatment**												
Visit Days	**D -33 to D -6 (A & A1)** **D -39 to D -12 (B & B1)**	**D -11 (B & B1 only)**	**D -5**	**D -4**	**D1**	**D2[a]**	**D4**	**D8**	**D11**	**D15**	**D18**	**D22**	**D25 (B & B1 only)**	**Early Tx Discont. or Tx Completion (D29)[b]**
Visit Window (days)	-	-	-	-	-	-	±1	±1	±1	±1	±1	±1	±1	+3[c]
(Continued)														
Daratumumab PK (Regimens B and B1 only)[i,j]														
0-60 min pre-daratumumab infusion		X		X			X		X		X		X	
0-30 min post-daratumumab infusion		X		X			X		X		X		X	
Before FT576 infusion					X									
24 (±4) h after FT576 infusion						X								
Non-infusion day PK[j]								X		X		X		X

NOTES: If scheduled activity, including study treatment administration, coincides with a weekend/holiday that precludes the activity, the activity should be performed on the nearest following date.

On days when peripheral blood sample occurs on the same day as study treatment administration, peripheral blood sample should be obtained prior to study treatment administration.

An unscheduled visit is a visit that occurs in addition to the predefined protocol-specific schedule of activities. If an unscheduled visit occurs for a given subject in follow up to a safety event, the visit or assessment must be documented on the Unscheduled Visit eCRF, as outlined by the Sponsor in the eCRF Completion Guidelines.

[a] There is no visit window for Day 2; Day 2 assessments will be performed 1 day following Day 1 assessments.

[b] Subjects who complete the FT576 treatment cycle will return to the clinic for a visit on Day 29. Subjects who discontinue study treatment prematurely (Section 7.1) will return to the clinic for an early treatment discontinuation visit that includes the activities described for the Day 29 visit and continue to have Post-Treatment Follow-Up assessments as described in Table 3 and/or Long-Term Follow-Up (Table 4). Subjects who discontinue from the study (Section 7.2) should return to the clinic for a discontinuation visit that includes the activities described for the Day 29 visit. (NOTE: The treatment completion/early treatment discontinuation visit may be used as this visit.)

(Continued)

Table 2. SoA: Central Laboratory Tests

(Continued)

[c] The visit window for Cycle 1 Day 29 is +3 days in order to capture assessments through the DLT window. If additional treatment cycle(s) are administered as part of retreatment (refer to Appendix 3), the visit window for Day 29 in subsequent cycle(s) is ±3 days.

[d] Baseline peripheral blood sample will be obtained for cell therapy safety monitoring (see Section 8.3.4.7).

[e] Peripheral blood samples will be collected for detection of alloimmunization to the FT576 product. Refer to Section 8.3.4.3 for additional details.

[f] Clinical assessment of CRS will be performed in accordance with ASTCT criteria (Lee et al. 2019). Collection of peripheral blood for CRS cytokines (central laboratory testing) and CRP and ferritin (local laboratory testing) will occur on Day 1 prior to FT576 administration. Subsequent laboratory testing for CRS will occur only if clinical CRS is suspected; CRS cytokines (central laboratory testing) and CRP and ferritin (STAT local laboratory testing) will be collected approximately 1 hour, between 4-6 hours, and 24 hours following initial evaluation of CRS. In cases of documented elevations in CRP and ferritin due to CRS, CRS cytokines (central laboratory testing) and CRP and ferritin (local laboratory testing) should continue to be monitored at least every 24 hours until resolution to baseline CRP (Day 1, pre-FT576 infusion), or if no evidence of continued resolution to baseline CRP in the absence of clinical CRS per investigator assessment.

[g] Refer to Section 8.3.4.6 for details on exploratory biomarker assessments.

[h] Collect samples prior to start of conditioning (CY/FLU).

[i] Do not draw blood for PK from the line through which FT576 or daratumumab was infused. Blood draws for PK should be collected from the opposite arm of that where FT576 or daratumumab was infused. For subjects with single-lumen central venous catheters, blood draws for PK should be collected from the opposite arm of that where FT576 or daratumumab was infused. If venipuncture access cannot be obtained on the opposite arm, then the blood draw for PK should be collected by venipuncture distal (below) to the site of the infusion line.

[j] Refer to the FT576-101 Laboratory Manual for additional details.

[k] The Day 15 pre-/post-PK draw should be performed only for subjects enrolled in Regimens A1 and B1, on the day of scheduled Day 15 FT576 dosing.

[l] The non-infusion day PK applies to subjects enrolled into Regimen A and B where FT576 is administered on Day 1 only.

ASTCT = American Society for Transplantation and Cellular Therapy; CRP = C-reactive protein; CRS = Cytokine release syndrome; CY = Cyclophosphamide; D = Day; Discont. = Discontinuation; eCRF = Electronic Case Report Form; FLU = Fludarabine; h = Hour; HLA = Human leukocyte antigen; KIR = Killer-cell immunoglobulin-like receptor; min = Minute; MM = Multiple Myeloma; PK = Pharmacokinetic; r/r = Relapsed or refractory; SoA = Schedule of Activities; Tx = Treatment

Table 3. SoA: Post-Treatment Follow-Up

	Post-Treatment Follow-Up[a]			
Visit	**Every 2 Weeks FU1, FU2**	**Every Month FU3, FU4, FU5, FU6**	**Every 3 Months FU7, FU8, FU9, FU10, FU11**	**FU12**
Post-FT576 Infusion (since Day 1; in months)	**2**	**3-6**	**9, 12, 15, 18, 21**	**24**
Visit Window (days)	**±3**	**±7**	**±14**	**±14**
ECOG PS	X	X	X	X
Targeted physical examination[b]	X	X	X	X
ICANS (neurotoxicity) monitoring[c]	Perform if residual neurotoxicity at end of the treatment cycle until resolution to baseline level			
Concomitant medications[d]	X	X	X	X
Adverse events[e]	X	X	X	X
Cell therapy safety monitoring[f]	Collect blood sample 3 (±1) months, 6 (±2) months, and 12 (±3) months after the last dose of FT576; additional samples may be required depending on results (see Section 8.3.4.7)			
FT576 PK	X	X	X (FU7 & FU8 only)	
Exploratory immune monitoring	X	X	X (FU7 & FU8 only)	
Exploratory serum biomarkers	X	X	X (FU7 & FU8 only)	
Bone marrow aspirate (refer to Table 11 for additional details)[g]		X (FU 6 only)	X (FU 8 only)	
Hematology[h]	X	X	X	X
Serum chemistry[h]	X	X	X	X
Urinalysis[h]	As clinically indicated			

(Continued)

Table 3. SoA: Post-Treatment Follow-Up

		Post-Treatment Follow-Up[a]			
Visit		**Every 2 Weeks FU1, FU2**	**Every Month FU3, FU4, FU5, FU6**	**Every 3 Months FU7, FU8, FU9, FU10, FU11**	**FU12**
Post-FT576 Infusion (since Day 1; in months)		**2**	**3-6**	**9, 12, 15, 18, 21**	**24**
Visit Window (days)		**±3**	**±7**	**±14**	**±14**
(Continued)					
CRP and ferritin[i]		If clinical CRS is suspected			
Continued treatment with daratumumab (Regimens B and B1)		Continue daratumumab treatment per schedule indicated in Table 1 until disease progression or unacceptable toxicity			
Disease Response Assessment[j]	SPEP and IFE	X (FU 2 only)	X	X	X
	sFLC	X (FU 2 only)	X	X	X
	Immunoglobulins (IgD[k], IgG, IgA, IgM)	X (FU 2 only)	X	X	X
	24-hour UPEP and UIFE[l]	X (FU 2 only)	X	X	X
	Bone marrow biopsy with aspirate (refer to Table 11 for additional details)	To confirm CR/sCR and at disease progression			X
	Skeletal disease (skeletal survey, CT, MRI)	At suspected skeletal disease progression			
	PET-CT based imaging	If extramedullary disease present at baseline, every 12 weeks (±7 days) after the D29 assessment until CR or plateau response based on laboratory data, and at suspected disease progression, through 2 years after the last dose of FT576			
Optional tumor biopsy (for subjects with EMD; refer to Section 8.3.4.5 for additional details)[m]		At progression or relapse			

(Continued)

Table 3. SoA: Post-Treatment Follow-Up

(Continued)

NOTES: Post-treatment follow-up begins 2 weeks after the Day 29 visit.

If scheduled activity, including study treatment administration, coincides with a weekend/holiday that precludes the activity, the activity should be performed on the nearest following date.

On days when peripheral blood sample and/or urine collection occur on the same day as study treatment administration, peripheral blood sample and/or urine collection should be obtained prior to study treatment administration.

An unscheduled visit is a visit that occurs in addition to the predefined protocol-specific schedule of activities. If an unscheduled visit occurs for a given subject in follow up to a safety event, the visit or assessment must be documented on the Unscheduled Visit eCRF, as outlined by the Sponsor in the eCRF Completion Guidelines.

[a] Post-treatment follow-up visits will continue until up to 2 years following the completion of the last FT576 treatment cycle **or** until one of the following occurs: disease progression or relapse, initiation of a new anti-cancer therapy, withdrawal of consent, or lost to follow-up, whichever occurs first. Refer to Section 4.4 for additional details. Subjects who remain relapse or progression-free up to 2 years after the last FT576 treatment cycle; experience disease relapse or progression prior to 2 years; begin a new, non-protocol-defined anti-cancer therapy; or withdraw consent from post-treatment follow-up will be followed for up to 15 years, according to the schedule in Table 4.

[b] A targeted physical examination will be performed at specified timepoints or as clinically indicated based on symptoms reported. Any clinically significant findings should be recorded on the Adverse Event or Medical History eCRF, as applicable.

[c] Neurotoxicity will be monitored using the ASTCT guidelines for grading ICANS using the ICE score. ICANS monitoring will occur just prior to start of conditioning, at specified timepoints, and as needed in Post-Treatment Follow-Up to document complete resolution to baseline status. Unscheduled ICE score assessments should be performed if neurotoxicity is suspected. Refer to Section 9.5.2.3 for details.

[d] For subjects who have disease relapse/progression or initiate new anti-cancer therapy, only concomitant medications for SAEs possibly or probably related to FT576 per investigator assessment will be recorded.

[e] All AEs will be collected and recorded in the subject's medical record and on the Adverse Event eCRF; refer to Section 9.6. Specific conditions potentially related to engineered cellular immunotherapy products such as FT576, including but not limited to, new malignancies, new or worsening neurologic disorders, new or worsening autoimmune or rheumatologic disorders, or new hematologic disorders, should be documented; refer to Section 9.

[f] Peripheral blood samples will be obtained for cell therapy safety monitoring per Section 8.3.4.7. Cell therapy safety monitoring that is not collected during Post-Treatment Follow-Up, e.g., due to disease relapse/progression and initiation of subsequent anti-cancer therapy prior to FU12, will be completed as part of Long-Term Follow-Up (Table 4).

[g] Bone marrow aspirate samples will be obtained for exploratory analyses after FT576 treatment to monitor MRD status. FU6 and FU8 samples only apply to subjects in CR/sCR. Where applicable, bone marrow samples for exploratory analyses should be obtained from the same bone marrow biopsy with aspirate procedure at each disease response assessment as detailed in Section 8.3.1.

[h] Refer to Section 8.3.2 for hematology, serum chemistry, and urinalysis laboratory testing details. Hematology, serum chemistry, and/or urinalysis should not be collected after initiation of subsequent anti-cancer therapy.

(Continued)

Table 3. SoA: Post-Treatment Follow-Up

(Continued)

[i] Clinical assessment of CRS will be performed in accordance with ASTCT criteria (Lee et al. 2019). Collection of peripheral blood for CRS cytokines (central laboratory testing) and CRP and ferritin (local laboratory testing) will occur on Day 1 prior to FT576 administration. Subsequent laboratory testing for CRS will occur only if clinical CRS is suspected; CRP and ferritin (STAT local laboratory testing) will be collected approximately 1 hour, between 4-6 hours, and 24 hours following initial evaluation of CRS. In cases of documented elevations in CRP and ferritin due to CRS, CRS cytokines (central laboratory testing) and CRP and ferritin (local laboratory testing) should continue to be monitored at least every 24 hours until resolution to baseline CRP (Day 1, pre-FT576 infusion).

[j] Disease response assessment will be performed according to IMWG response criteria and measurable residual disease assessment (Kumar et al. 2016; Appendix 1) for Regimens A, A1, B, and B1. Allocated material from bone marrow biopsy with aspirate samples obtained as part of disease response assessment, including those documenting disease relapse or progression will also be used for exploratory analyses (refer to Table 11 for details). Post-baseline PET-based radiologic assessments will be performed in subjects with baseline extramedullary disease as part of disease response assessment; the same imaging modality is to be used throughout the study. Refer to Appendix 1 for additional details regarding the method for tumor response assessment and tumor response assessment criteria. For subjects who have disease relapse/progression or initiate new anti-cancer therapy, tumor response assessments will no longer be required. For subjects who remain relapse/progression free at the 2-year timepoint, disease response assessments should be performed only to confirm disease relapse/progression. For subjects who have disease relapse/progression, a bone marrow biopsy and/or aspirate should be obtained for exploratory analyses (see Table 11).

[k] Subjects with IgD myeloma need to have serum IgD levels drawn at every follow-up timepoint per IMWG.

[l] For subjects with disease that is only detectable in the serum, a 24-hour UPEP is only required at screening, for confirmation of CR, as clinically indicated, and at end-of-study visit.

[m] For subjects with extramedullary disease, an optional tumor tissue biopsy sample may be obtained from a safely accessible site for exploratory analyses. Biopsies may be collected after progression/relapse after initial treatment or retreatment. Exceptions for samples obtained outside of the specified window may be considered and must be approved by the Medical Monitor.

AE = Adverse event; AML = Acute myelogenous leukemia; ASTCT = American Society for Transplantation and Cellular Therapy; CIBMTR = Center for International Blood and Marrow Transplant Research; CR = Complete remission (per IMWG response criteria); CRP = C-reactive protein; CRS = Cytokine release syndrome; D = Day; ECOG PS = Eastern Cooperative Oncology Group Performance Status; eCRF = Electronic Case Report Form; FU = Follow-up; GvHD = Graft-versus-host disease; ICANS = Immune effector cell-associated neurotoxicity syndrome; ICE = Immune Effector Cell-Associated Encephalopathy; ICF = Informed Consent Form; IFE = Immunofixation electrophoresis; IgA, IgD, IgG, IgM = Immunoglobulin A, D, G, M; IMWG = International Myeloma Working Group; MM = Multiple myeloma; MRD = Measurable residual disease; MRI = Magnetic resonance imaging; NCI CTCAE, v5.0 = National Cancer Institute Common Terminology Criteria for Adverse Events, Version 5.0; PET = Positron emission tomography; SAE = Serious adverse event; sFLC = serum free light chain; SoA = Schedule of Activities; SPEP = Serum protein electrophoresis; UIFE = Urine immunofixation electrophoresis; UPEP = Urine protein electrophoresis

Table 4. SoA: Long-Term Follow-Up

	Long-Term Follow-Up[a]		
Post-FT576 Infusion (since Day 1; in years)	**0-1**	**1-2**	**2-15**
Visit Window (days)	**±14**	**±14**	**±30**
Concomitant medications[b]	Every 3 months	Every 6 months	Every 12 months
Adverse events[c]			
Clinical safety assessment			
Cell therapy safety monitoring[d]	Collect blood sample 3 (±1) months, 6 (±2) months, and 12 (±3) months after the last dose of FT576; additional samples may be required depending on results (see Section 8.3.4.7)		
Subsequent anti-cancer therapy[e,f]	X	X	--
Disease response[g]	As clinically indicated		

NOTES: If scheduled activity, including study treatment administration, coincides with a weekend/holiday that precludes the activity, the activity should be performed on the nearest following date.

An unscheduled visit is a visit that occurs in addition to the predefined protocol-specific schedule of activities. If an unscheduled visit occurs for a given subject in follow up to a safety event, the visit or assessment must be documented on the Unscheduled Visit eCRF, as outlined by the Sponsor in the eCRF Completion Guidelines.

[a] Subjects who remain relapse or progression-free up to 2 years after the last FT576 treatment cycle, experience disease relapse or progression prior to 2 years, begin a new, non-protocol-defined anti-cancer therapy, or withdraw consent from Post-Treatment Follow-Up will enter Long-Term Follow-Up and will be evaluated every 3 months through the first year, every 6 months through Year 2, and then every 12 months until Year 15; refer to Section 4.5.

[b] For subjects who have disease relapse/progression or initiate new anti-cancer therapy, only concomitant medications for SAEs possibly or probably related to FT576 per investigator assessment will be recorded (see Section 6.4).

[c] Relevant SAEs will be collected and recorded in the subject's medical record and on the Adverse Event eCRF; refer to Section 9.6.2. Specific conditions potentially related to engineered cellular immunotherapy products such as FT576, including, but not limited to, new malignancies, new or worsening neurologic disorders, new or worsening autoimmune or rheumatologic disorders, or new hematologic disorders, should be documented; refer to Section 9.

[d] Peripheral blood samples will be obtained for cell therapy safety monitoring per Section 8.3.4.7. Cell therapy safety monitoring that is not collected during Post-Treatment Follow-Up, e.g., due to disease relapse/progression and initiation of subsequent anti-cancer therapy prior to FU12 (Table 3), will be completed as part of Long-Term Follow-Up.

[e] Following initiation of subsequent anti-cancer therapy, Long-Term Follow-Up clinical safety information will be collected at the time of each visit or through telephone calls, subject medical records, and/or e-mail/mail. Subjects will be followed for survival status, new malignancies, selected new or worsening medical conditions, or unexpected illnesses as described in Appendix 4.

(Continued)

Table 4. SoA: Long-Term Follow-Up

(Continued)

[f] Subsequent anti-cancer therapy will be recorded until 2 years after disease progression following FT576 treatment, until the subject withdraws from the study, is considered lost to follow-up, withdraws consent, or dies, whichever occurs first (Section 6.4.4).

[g] Disease response assessments will be performed only to confirm disease relapse/progression, based on IMWG response criteria (Kumar et al. 2016; Appendix 1) in subjects who remain relapse/progression free at the 2-year timepoint.

AE = Adverse event; ASTCT = American Society for Transplantation and Cellular Therapy; CIBMTR = Center for International Blood and Marrow Transplant Research; CRP = C-reactive protein; CRS = Cytokine release syndrome; D = Day; FU = Follow-up; GvHD = Graft-versus-host disease; ICANS = Immune effector cell-associated neurotoxicity syndrome; ICE = Immune Effector Cell-Associated Encephalopathy; ICF = Informed Consent Form; IMWG = International Myeloma Working Group; NCI CTCAE, v5.0 = National Cancer Institute Common Terminology Criteria for Adverse Events, Version 5.0; SAE = Serious adverse event; SoA = Schedule of Activities

2 INTRODUCTION

2.1 Study Rationale

Despite advances in treatment, multiple myeloma (MM) remains uncurable and the majority of patients will experience serial cycles of response, relapse, and progression. Therefore, treatment for relapsed/refractory (r/r) disease remains a significant area of unmet medical need. Administration of T cells engineered to express a chimeric antigen receptor (CAR) targeting B-cell maturation antigen (BCMA) has resulted in high response rates, as well as deep responses in patients with r/r MM. Results from a Phase II study (KarMMa; Munshi et al. 2021) in 128 subjects treated with idecabtagene vicleucel, a BCMA-directed CAR T-cell therapy reported an encouraging objective response rate (ORR) of 73% (complete response [CR] or better in 33%). However, the median progression-free survival (PFS) was 8.8 months, which suggests that the responses were not durable, and many patients still experienced disease relapse and progression as 34% died during the study, with most deaths attributed to disease progression. Moreover, significant barriers to the broad use of idecabtagene vicleucel remain, including serious clinical safety risks as evidenced by approximately 5% reported rate of Grade 3+ cytokine release syndrome (CRS) including one fatal event and approximately 3% rate of Grade 3+ neurotoxicity in KarMMa. Finally, complex manufacturing processes necessitated bridging therapy in 88% of patients prior to infusion of CAR T-cells and often result in heterogeneous products of limited quantity.

FT576 is an off-the-shelf CAR natural killer (NK)-cell product candidate that is manufactured from a clonal master human-induced pluripotent stem cell (iPSC) line that has the potential to address the shortcomings of current-generation CAR T-cell therapy. The functional attributes of FT576, as described in Section 2.2.2, support the rationale for the proposed Phase I study of FT576 as monotherapy and in combination with daratumumab for the treatment of subjects with r/r MM. The purpose of this study is to assess the safety, tolerability, and clinical activity of FT576 in r/r MM. The rationale for specific features of the study design is described in Section 4.6.

2.2 Background

2.2.1 Natural Killer Cells

Cancer immunotherapy is a rapidly evolving field that has transformed the treatment of many tumor types, including advanced hematologic malignancies. Key advancements in this field include the development of monoclonal antibodies (mAbs) that block key inhibitory pathways on T cells, such as those that block programmed cell death receptor-1 (PD-1) and programmed cell death ligand-1 (PD-L1), and the development of adoptive transfer of immune cells as exemplified by CAR T-cell therapy. Both approaches have led to the development of novel therapeutic regimens that have increased survival in patients with a variety of solid and hematopoietic tumors. However, despite these important advances, the majority of patients will either not respond or eventually experience disease relapse. Further understanding of the biology that enables these cells to enter tumors and retain anti-tumor cytotoxic activity is important in order to maximize their clinical benefit for patients.

NK cells are so named for their "natural" ability to kill cancer cells without prior sensitization (Kiessling et al. 1975). NK cells target and kill cancer cells by multiple mechanisms (Figure 2), including direct cytotoxicity, cytokine secretion, and antibody-dependent cellular cytotoxicity (ADCC), which support their clinical investigation in oncologic indications as monotherapy and in combination with mAb therapy as follows:

- Direct cytotoxicity through the targeted release of perforins and granzymes. Importantly, while major histocompatibility complex class I (MHC-I)-deficient cells evade CD8 T-cell recognition, they are preferential targets for NK cells and are highly susceptible to NK-cell-mediated killing (Malmberg et al. 2017).
- Secretion of cytokines, including interferon-gamma (IFNγ) and tumor necrosis factor-alpha (TNFα), promote direct tumor-cell killing (Wang et al. 2012).
- ADCC, which occurs when an antibody binds to a tumor cell and the antibody's Fc region binds to the CD16 receptor on NK cells, triggering a targeted and engaged cytotoxic response toward the tumor cell (Waldhauer and Steinle 2008; Wang et al. 2015).

In addition to direct effects on tumor cells, NK cells can interact with the adaptive immune system to generate and maintain adaptive immune responses against cancer cells as follows:

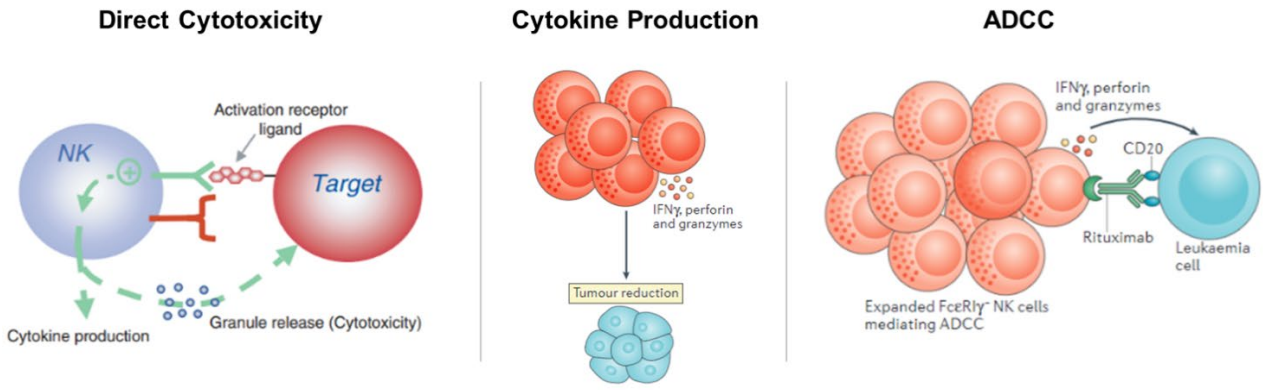
- Killing of tumor cells by NK cells results in the release of tumor antigens for recognition by the adaptive immune system (Dahlberg et al. 2015).
- Upon activation, NK cells secrete cytokines that recruit and activate endogenous T cells. Importantly, activated NK cells are potent producers of chemokines such as CXCL10, CCL4, and CCL5, which are known recruitment factors for T cells. Cytokines secreted by NK cells also induce maturation of dendritic cells, which serve as antigen-presenting cells to mediate adaptive immune responses (Smyth et al. 2002).

Through the aforementioned mechanisms, NK cells have the intrinsic potential to bridge the innate and adaptive immune response and turn a tumor that is immunologically "cold" to one that is "hot," characterized by an increased immune infiltrate that can potentially restore adaptive immune function (Figure 3).

In clinical investigations, allogeneic NK-cell therapies have been well tolerated with documented anti-tumor activity. NK cells expanded from human umbilical cord blood have been infused post- hematopoietic stem-cell transplantation (HSCT) in patients with MM (Shah et al. 2017). None of the 12 participants in this small Phase I study developed graft-vs-host disease (GvHD), CRS, or neurotoxicity. Near CR or better responses were observed in 75% of cases. More than 500 patients across 30 completed clinical studies have received allogeneic NK cells (Veluchamy et al. 2017). Notably, and unlike allogeneic T-cell therapies, allogeneic NK cells have not been associated with GvHD. Furthermore, with the exception of NK cells combined with a potent IL-15 agonist (Cooley et al. 2019), allogeneic NK-cell therapies have not been associated with CRS or neurotoxicity, which are common complications observed with CAR T-cell therapies. Complete remission rates ranging from 21% to 53% have been observed following a single administration of allogeneic NK cells in subjects with r/r acute myelogenous leukemia (AML; Miller et al. 2005;

Bachanova et al. 2014; Romee et al. 2016), and in subjects with poor prognosis refractory non-Hodgkin lymphoma (Bachanova et al. 2018). Clinical responses have also been reported in subjects with solid tumors, including non-small cell lung cancer (Iliopoulou et al. 2010; Tonn et al. 2013), as well as in subjects with platinum-resistant ovarian cancer (Geller et al. 2011), melanoma (Arai et al. 2008), and renal cell carcinoma (Arai et al. 2008).

Figure 2. Mechanisms of Natural Killer-Mediated Tumor Cell Killing

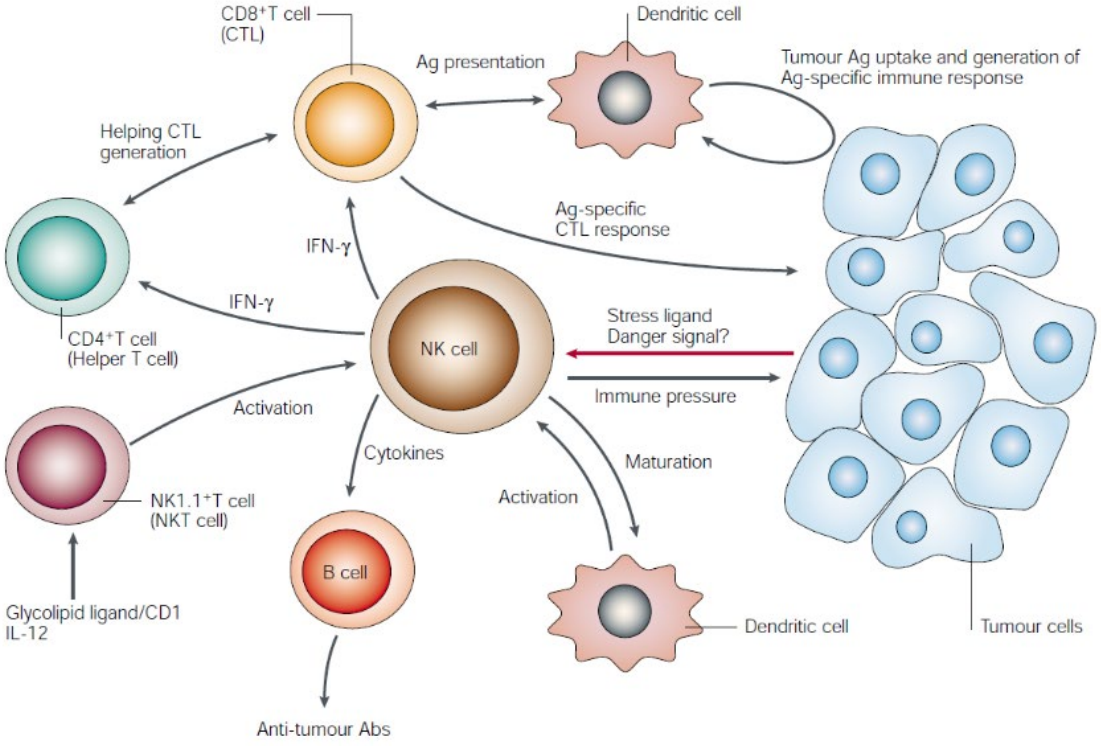


Sources: Direct Cytotoxicity figure, French and Yokoyama 2004; Cytokine Production and ADCC figures, Cerwenka and Lanier 2016.

ADCC = Antibody-dependent cellular cytotoxicity; IFNγ = Interferon-gamma; NK = Natural killer

Figure 3. Natural Killer Cells Bridge the Innate and Adaptive Immune Systems

NK-cell lysis of cancer cells provides tumor Ag for DCs, which induce them to mature and present Ag to CTLs in lymph nodes. Cytokines, such as IFNγ, which are produced by activated NK cells, activate CTL and CD4+ helper T-cell responses and regulate B-cell production of anti-tumor antibodies. This leads to the proliferation of tumor-specific CTLs and the generation of an anti-tumor adaptive immune response.



Source: Smyth et al. 2002.

Ag = Antigen; CTL = Cytotoxic T cell; DC = Dendritic cell; IFNγ = Interferon-gamma; IL = Interleukin; NK = Natural killer

2.2.2 FT576

Despite encouraging clinical observations described in Section 2.2.1, the clinical utility of allogeneic NK-cell therapies has been limited by challenges associated with donor cell sourcing, dose-to-dose variability, and limited opportunities for repeat dosing. FT576 is an allogeneic NK-cell immunotherapy lacking CD38 and expressing anti-BCMA CAR, high-affinity, non-cleavable CD16 (hnCD16), and interleukin (IL)-15/IL-15 receptor fusion protein (IL-15RF) and is produced from a clonal master iPSC line that addresses many of these challenges.

Unlike the manufacturing process for patient- and donor-derived engineered cell therapies, which requires batch-to-batch genetic engineering of large quantities of primary effector cells and produces drug product with genomic variability, the Sponsor (Fate Therapeutics, Inc.):

- Genetically engineers iPSCs;
- Selects and characterizes a single genetically engineered iPSC; and
- Expands such engineered iPSC to generate a clonal master cell bank (MCB) for use as the starting material in the routine manufacture of the FT576 drug product.

In this manner, genetic engineering occurs in a one-time defined event prior to MCB generation and the routine manufacture of FT576 drug product from the MCB does not include any genetic engineering. In many respects, the manufacturing process is analogous to that of mAb therapies, which uses an MCB as the starting material for drug product manufacture. The MCB starting cellular material is intended to directly address many of the limitations associated with current patient- and donor-specific cell therapies. Notably, many doses of FT576 drug product can be uniformly produced in a single manufacturing campaign. These doses of drug product are homogeneous and can be (i) tested to assure compliance with a predefined quality specification, (ii) cryopreserved in an infusion media, and (iii) stored to maintain a sustainable inventory. As such, in the clinical setting, FT576 has off-the-shelf availability for potential use in multi-dose regimens, which may prove critical for driving long-term durable responses in patients with aggressive r/r disease.

The engineered features of FT576 are designed to result in increased activity against target tumor cells as monotherapy and when combined with mAbs (i.e., daratumumab) that can mediate ADCC. Important functional attributes of FT576 include the following:

- FT576 is expected to have superior innate effector function compared to patients' endogenous NK cells, which are typically diminished in number and function due to prior treatment regimens (e.g., chemotherapy) and tumor suppressive mechanisms. FT576 mediates "innate cytotoxicity" that is potent and specific to transformed cells.
- The CD38 gene KO in FT576 is intended to prevent anti-CD38 antibody-mediated NK-cell fratricide and consequently enhance ADCC when FT576 is administered with concurrent anti-CD38 mAb therapy (Bjordahl et al. 2019). In addition, NK cells with CD38 KO have been shown to be more resistant to oxidative stress and exhibit enhanced effector function (Cichocki et al. 2019).

- FT576 expresses an anti-BCMA CAR designed to support NK cell anti-tumor efficacy against BCMA+ cells. Activation of FT576 cells in response to BCMA CAR stimulation is driven by NKG2D transmembrane and 2B4 and CD3ζ co-stimulatory domains, which support potent killing against BCMA+ MM cells. In nonclinical studies, CAR designs consisting of NKG2D transmembrane and 2B4 and CD3ζ co-stimulatory domains outperformed a conventional CAR, consisting of CD28 and 41BB co-stimulatory domains, when expressed in NK cells (Li et al 2018).
- FT576 expresses an hnCD16 Fc receptor. The high-affinity CD16 variant arising from a naturally occurring 158V polymorphism has demonstrated enhanced ADCC when combined with therapeutic mAbs in nonclinical studies. In clinical studies evaluating patients whose endogenous NK cells express the high-affinity CD16 Fc receptor variant, higher objective response rates and increased PFS were observed with treatment with rituximab, cetuximab, and trastuzumab (Cartron et al. 2002; Musolino et al. 2008; Bibeau et al. 2009). In addition, hnCD16 contains the genetic alteration (S179P) that prevents cleavage of CD16 by the metalloproteinase ADAM17 (Lajoie et al. 2014; Jing et al. 2015), a mechanism in the regulation and attenuation of NK-cell activity by the tumor microenvironment (Romee et al. 2013).
- FT576 expresses IL-15RF, designed to provide an endogenous activation and proliferation signal, reducing the dependence on exogenous cytokine administration such as IL-2 and IL-15, both of which have been associated with significant toxicities that may limit clinical usage when incorporated into clinical studies of peripheral blood NK cells (Cooley et al. 2019).

Non-clinical data of FT576 activity was generated with FT576-R, the non-Good Manufacturing Practice (non-GMP), research-use equivalent of FT576, and include the following:

- In vitro, the phenotypic profile of FT576-R cells was consistent with a pure population of activated NK cells engineered for expression of hnCD16, IL-15RF, and BCMA CAR with absence of CD38. FT576-R cells demonstrated the unique ability to continuously target MM.1R cells through several rounds of re-stimulation, either directly through CAR-mediated cytotoxicity or in combination with mAb to elicit ADCC. Data demonstrated that the hnCD16 transgene expressed by FT576-R cells supports uniform surface expression of CD16 and is resistant to activation-induced cleavage, as no reduction in the frequency of hnCD16 surface-expressing cells was observed after activation with various stimuli. The presence of a dose-response between daratumumab concentration and cytotoxicity of peripheral blood NK cells confirms published data describing NK cell fratricide caused by daratumumab binding to CD38 and induction of ADCC among peripheral blood NK cells; the absence of such a response in FT576-R NK cells demonstrates that CD38 gene knockout on FT576-R cells prevents daratumumab-induced NK cell fratricide. Induction of a significant proinflammatory cytokine response by FT576-R cells against myeloma cell lines as a single agent, which is further augmented when FT576-R cells are delivered in combination with a CD38 targeting monoclonal antibody, illustrates both the CAR-directed activity and ADCC function of FT576-R. Additionally, FT576-R cells exhibit preferential targeting of BCMA expressing tumor cells,

consistent with the expression of BCMA-CAR. FT576-R cells also exhibit enhanced cytotoxic activity against BCMA+ MM.1S cells while maintaining tolerance against normal allogeneic peripheral blood mononuclear cells.

- Biodistribution and persistence of FT576-R cells in immunodeficient NSG mice were evaluated following 3 intravenous injections at 3×10^6 cells/mouse or 1.2×10^7 cells/mouse administered on Study Day 1, Day 8, and Day 15. The data demonstrate that FT576-R is detected in all tissues and their persistence generally decreases over time to a level approaching or below the lower limit of detection by Day 71. FT576-R cells were effective at controlling MM progression in an in vivo xenograft model of disseminated MM, where FT576-R cells demonstrated anti-myeloma activity as a monotherapy that was further enhanced when combined with daratumumab.
- FT576 is expected to be uniform in composition, enable multi-dose treatment cycles, prevent anti-CD38 antibody-mediated NK-cell fratricide, support anti-tumor efficacy against BCMA+ cells, and enhance anti-tumor activity when FT576 is combined with an ADCC-competent mAb. Additionally, FT576 is expected to demonstrate improved cellular persistence compared with non-engineered NK-cell therapeutics. These differentiated features provide the rationale for the proposed Phase I study of FT576 alone or in combination with daratumumab in subjects with MM.

Additional information on nonclinical studies with FT576 is provided in the FT576 Investigator's Brochure.

2.3 Benefit/Risk Assessment

To date, there are no clinical data for FT576. The evaluation of potential risks of FT576 in humans is based primarily on data from nonclinical studies with FT576 (refer to the FT576 Investigator's Brochure) and documented risks associated with autologous and allogeneic NK-cell-based therapies.

Characteristics of FT576 cells and its formulation that may potentially confer safety risks are summarized as follows:

- FT576 is formulated in dimethyl sulfoxide (DMSO) to enable cryopreservation. DMSO side effects and symptoms are generally associated with histamine release and include coughing, flushing, rash, chest tightness and wheezing, nausea and vomiting, and cardiovascular instability (AABB 2016).
- FT576 is a cell therapy of human origin, and transmission of infectious disease and/or disease agents by known or unknown agents may occur. The MCB from which FT576 is derived has been extensively tested to minimize the potential risk of disease transmission; however, these measures do not completely eliminate the risk. For some infectious agents, there are no routine tests to predict or prevent disease transmission (AABB 2016).

- FT576 has been engineered to eliminate CD38 expression and to constitutively express BCMA CAR, hnCD16, and IL-15RF. The potential benefits of these engineered features are described in Section 2.1 and Section 2.2. Clinical experience relevant to these individual elements are summarized as follows:
  - There is no clinical experience with cellular products that have been engineered to eliminate CD38 expression.
  - There is no clinical experience with the specific BCMA CAR expressed by FT576. Autologous CAR T-cell therapies utilizing multiple alternative BCMA CAR designs have successfully validated BCMA as a therapeutic CAR target (D'Agostino and Raje 2020).
  - The hnCD16 transgene encodes a naturally occurring polymorphism that is homozygously present in approximately 10% of the population and additionally is engineered to prevent cleavage of the CD16 receptor upon activation. The non-cleavable modification is situated near the membrane and is not anticipated to alter the safety of an allogeneic NK cell. Published data indicate that patients with the naturally occurring high-affinity CD16 variant have improved outcomes with rituximab-, cetuximab-, and trastuzumab-based therapies, without evidence of additional toxicity (Musolino et al. 2008).
  - Cytokine support of NK-cell therapy has been previously studied in clinical trials (Section 2.2). IL-15 is a known homeostatic cytokine in the maintenance of peripheral NK cells (Ranson 2003). Recent clinical experience of haploidentical NK cells given in combination with exogenous IL-15 indicated increased NK-cell activity and proliferation, but also increased CRS and neurotoxicity (Cooley et al. 2019). Data from the current study will allow for an initial assessment of whether the IL-15RF provides evidence for an improved therapeutic index compared to systemically administered cytokine support.

As an allogeneic cell product, FT576 may induce an immune response, which will be monitored during the study. The long-term safety effects of FT576, including time of onset, severity, and duration of treatment-emergent adverse events (TEAEs) are not known.

Based on the clinical experience with autologous and allogeneic NK-cell-based therapies and the clinical evidence supporting the potential clinical benefit of BCMA-targeting therapies in the treatment of r/r MM (see Section 2.2.1; Raje et al. 2019; Shah et al. 2020), further clinical development of FT576 in this patient population is supported.

In addition to treatment with FT576, all subjects will receive cyclophosphamide (CY) and fludarabine (FLU) as conditioning. Subjects enrolled in Regimens B and B1 will also receive daratumumab (see Section 4.1). Known and potential safety risks of FT576, CY, FLU, and daratumumab are described in Section 9.

The eligibility criteria, the study design, and study procedures are considered to be appropriate for the safe conduct of the planned study. To assess the benefit/risk profile, the study will enroll subjects with r/r disease who have no available curative treatment options and who have limited prognosis with currently available therapies, and for which clinical data of BCMA directed therapies (antibody drug conjugate [ADC], bi-specific immune cell engagers, CAR T-cells) exist. The safety profile of FT576 as a monotherapy may differ when given in combination with an anti-CD38 monoclonal antibody such as daratumumab. Consequently, dose-escalation and dose-expansion will be independently conducted for each regimen.

After the safety and tolerability have been assessed to define the maximum tolerated dose (MTD) or maximum assessed dose (MAD) in the dose-escalation stage for each regimen, the dose-expansion stage will further evaluate the safety and activity of FT576 ± daratumumab to determine the recommended Phase II dose (RP2D). Subjects will be closely monitored for safety consistent with standard practices for first-in-human studies and under continuous medical observation during the study.

More detailed information about the potential benefits, risks, and AEs of FT576 can be found in the FT576 Investigator's Brochure.

3 OBJECTIVES AND ENDPOINTS

This study will evaluate the safety, pharmacokinetics (PK), and anti-tumor activity of FT576 as monotherapy and in combination with daratumumab in subjects with r/r MM. Specific objectives and corresponding endpoints for the study are outlined below.

Table 5. Objectives and Endpoints

Objectives	Endpoints
Primary	
• To determine the RP2D for FT576 when administered as monotherapy and in combination with daratumumab • To evaluate the safety and tolerability of FT576 when administered as monotherapy and in combination with daratumumab	• Incidence and nature of DLTs within each dose escalation cohort to determine the MTD or MAD for Regimens A, A1, B, and B1. The RP2D will be determined based on the overall safety and anti-tumor activity among the dose-escalation and dose-expansion cohorts. • Incidence, nature, and severity of AEs, with severity determined according to NCI CTCAE, v5.0
Secondary	
• To evaluate the anti-tumor activity of FT576 when administered as monotherapy and in combination with daratumumab • To characterize the PK of FT576 when administered as monotherapy and in combination with daratumumab	• ORR, defined as the proportion of subjects with a best overall response of sCR, CR, VGPR, or PR, as determined by the investigator according to standard IMWG response criteria (Appendix 1) • DOR, defined as the duration from the first occurrence of a documented objective response until the time of disease progression or relapse, or death due to progressive disease, as determined by the investigator according to standard IMWG response criteria • PFS, defined as the time from first dose of study treatment to disease progression or relapse, or to the day of death from any cause, as determined by the investigator according to standard IMWG response criteria • RFS from CR, defined as the duration from the start of sCR or CR until the time of relapse from sCR or CR, as determined by the investigator according to standard IMWG response criteria • OS, defined as the time from first dose of study treatment to death from any cause • PK of FT576 as assessed by detection of FT576 in peripheral blood following FT576 administration

(Continued)

Table 5. Objectives and Endpoints

Objectives	Endpoints
(Continued)	
Exploratory	
• To evaluate the anti-tumor activity of FT576 in subjects based on IMWG MRD criteria when administered as monotherapy and in combination with daratumumab • To assess the association of PK and pharmacodynamics of FT576 with safety and anti-tumor activity when administered as monotherapy and in combination with daratumumab • To assess the PK of daratumumab when administered in combination with FT576 • To assess the association of clinical and tumor characteristics with safety and anti-tumor activity of FT576 when administered as monotherapy and in combination with daratumumab	• Proportion of sCR/CR subjects with MRD-negative response according to IMWG MRD criteria (Appendix 1) • Proportion of sCR/CR subjects with sustained MRD-negative response for at least 1 year according to IMWG MRD criteria • Proportion of sCR/CR subjects with imaging plus MRD-negative response according to IMWG MRD criteria • Time to MRD-negative response, defined as the time from first dose of study treatment to first MRD-negative response assessment according to IMWG MRD criteria • RFS from MRD-negative, defined as the duration from the start of MRD negativity until the time of relapse from MRD negativity according to IMWG MRD criteria • Detection of FT576 in tumor samples • Pharmacodynamics of FT576, as assessed by peripheral blood cytokines and immunophenotyping • PK of daratumumab, as assessed by serum concentration measurements • Characterization of the tumor and tumor microenvironment in bone marrow samples pre- and post-treatment • Incidence, nature, and severity of AEs, and ORR, DOR, PFS, OS, and MRD status (as applicable) among subject groups defined by baseline clinical characteristics and tumor characteristics (including those based on exploratory analyses as described in Section 8.3.4.6) • Incidence, nature, and severity of AEs, and ORR, DOR, PFS, OS, and MRD status (as applicable) among subject groups defined by FT576 PK and pharmacodynamic characteristics

AE = Adverse event; CR = Complete response; DLT = Dose-limiting toxicity; DOR = Duration of response; IMWG = International Myeloma Working Group; MAD = Maximum administered dose; MTD = Maximum tolerated dose; NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events; PFS = Progression-free survival; PK = Pharmacokinetics; MRD = Measurable residual disease; RP2D = Recommended Phase II dose; ORR = Objective response rate; OS = Overall survival; PR = Partial response; RFS = Relapse-free survival; sCR = Stringent complete response; VGPR = Very good partial response

4 STUDY DESIGN

4.1 Overall Design

This is a Phase I, open-label, multicenter study to evaluate the safety, PK, and anti-tumor activity of FT576 in subjects with r/r MM in the following regimens (Figure 1):

- **Regimen A:** FT576 monotherapy administered as a single dose on Day 1
- **Regimen A1:** FT576 monotherapy administered as multiple doses on Day 1 and Day 15
- **Regimen B:** FT576 administered as a single dose on Day 1 in combination with daratumumab
- **Regimen B1:** FT576 administered as multiple doses on Day 1 and Day 15 in combination with daratumumab

Subjects will be enrolled in 2 stages: a dose-escalation stage (Section 4.2) and a dose-expansion stage (Section 4.3). After the safety and tolerability have been assessed to define the MTD (or through the MAD in the absence of dose-limiting toxicity [DLT] defining the MTD) in the dose-escalation stage, the dose-expansion stage will further evaluate the safety and activity of FT576 (Figure 4). Dose-escalation and dose-expansion will be conducted independently for each regimen upon clearance of the first monotherapy cohort in Regimen A.

The study will include an up to 28-day screening period and a treatment period with conditioning followed by FT576 as monotherapy or FT576 in combination with daratumumab, as shown in Figure 1 (also refer to the Schedules of Activities [SoAs; Section 1.3] for details). Subjects will return for a treatment completion visit on Day 29. Subjects who discontinue study treatment prematurely will return to the clinic for an early treatment discontinuation visit that includes the activities described for the Day 29 visit. Dose and schedule of study treatments are detailed in Section 6.1.

Subjects will be followed for DLTs per dose-escalation rules described in Section 4.2.2 through Day 29, which is also the time at which the first disease response assessment will be performed. Thereafter, study assessments and procedures will be performed as described in the SoAs (Section 1.3). Subjects with evidence of clinical benefit may be eligible for additional treatment as described in Appendix 3.

Subjects will be followed for safety, anti-tumor activity, and survival for up to 15 years as described in Sections 4.4 and 4.5.

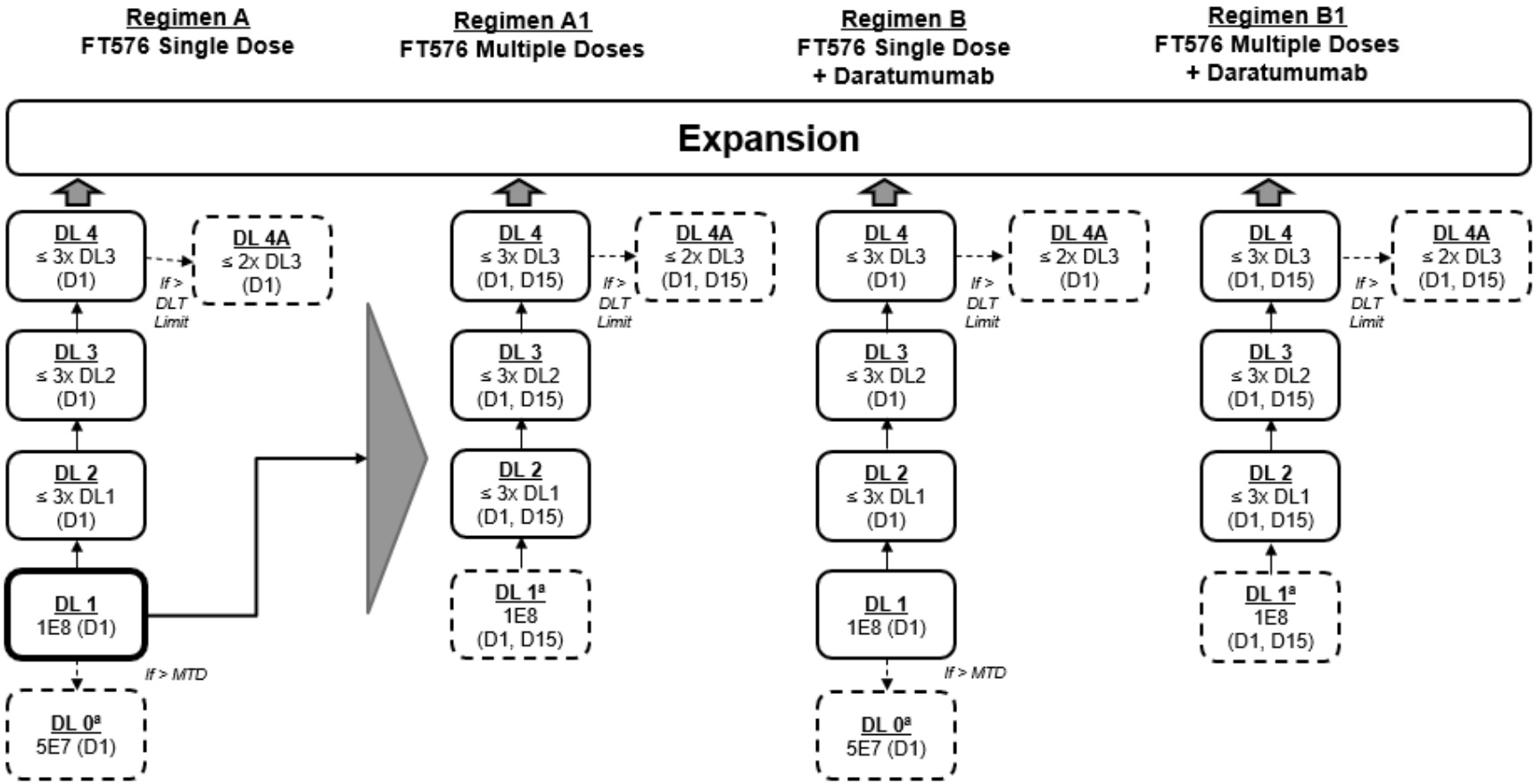
The study is expected to enroll up to approximately 180 subjects at approximately 12 to 16 sites in the United States, as described below.

- **Regimen A:** up to 45 subjects—up to 30 in dose escalation; up to 15 in a single dose-expansion cohort
- **Regimen A1:** up to 45 subjects—up to 30 in dose escalation; up to 15 in a single dose-expansion cohort
- **Regimen B:** up to 45 subjects—up to 30 in dose escalation; up to 15 in a single dose-expansion cohort
- **Regimen B1:** up to 45 subjects—up to 30 in dose escalation; up to 15 in a single dose-expansion cohort

For all regimens, additional dose-specific dose-expansion cohorts of up to 15 subjects/cohort may be enrolled. Refer to Section 4.3 for additional details on subjects enrolled in dose expansion.

The study is expected to enroll over a period of approximately 3 years (approximately 16 to 20 months in dose escalation for each regimen and approximately 6 months in dose expansion for each regimen).

Figure 4. Dose-Escalation Schema



NOTE: Upon clearance of Regimen A DL1, initiation of Regimens A1, B, and B1 may begin. The starting dose level for Regimen B will be 1×10^8 viable cells, while the starting dose level for Regimens A1 and B1 will be based on the most recently cleared dose level in Regimen A.

[a] The dose level is deemed to be unacceptably toxic or a de-escalation decision is made per the mTPI dose-escalation rules.

D = Day; DL = Dose level; mTPI = modified toxicity probability interval; MTD = Maximum tolerated dose

4.2 Dose-Escalation Stage

The objective of the dose-escalation stage is to determine dose levels of FT576 not exceeding the MTD as monotherapy and in combination with daratumumab appropriate for further assessment in dose expansion to determine the RP2D as monotherapy or in combination with daratumumab.

4.2.1 Planned FT576 Dose-Escalation Levels and Cohorts

The dose-escalation schema is illustrated in Figure 4. Dose escalation will be conducted by the Sponsor in consultation with the study investigators using the dose-escalation rules described in Section 4.2.2. Doses of FT576 given outside of the study visit windows will be allowed per Section 9.5.1. DLT-evaluable includes all subjects who receive all anticipated doses per the SoAs within the 29-day treatment window (Table 1). Any delay to Day 15 dosing greater than 7 days will extend the DLT observation window by that number of days. Subjects who do not receive all anticipated FT576 doses for reasons other than a protocol-defined DLT will not be considered DLT-evaluable and will be replaced. Subjects who are not considered DLT-evaluable during dose escalation will be replaced. See Section 4.2.3 for the definition of DLT.

Planned FT576 dose levels in dose escalation are presented in Table 6.

Table 6. Planned FT576 Dose Levels

Dose Level	**Regimen A:** **Single Dose of FT576 Monotherapy/** **Regimen B: Single Dose of FT576 with Daratumumab**	**Regimen A1:** **Multiple Doses of FT576 Monotherapy/** **Regimen B1: Multiple Doses of FT576 with Daratumumab**
Day	**Day 1**	**Day 1, Day 15**
DL0[a]	5×10^7	Not applicable
DL1	1×10^8	D1 = 1×10^8, D15 = 1×10^8
DL2	≤ 3 × DL1	D1 = ≤ 3 × DL1, D15 = ≤ 3 × DL1
DL3	≤ 3 × DL2	D1 = ≤ 3 × DL2, D15 = ≤ 3 × DL2
DL4	≤ 3 × DL3	D1 = ≤ 3 × DL3, D15 = ≤ 3 × DL3
DL4A[a]	≤ 2 × DL3	D1 = ≤ 2 × DL3, D15 = ≤ 2 × DL3

NOTE: Dose-escalation increments are approximate, with a possible ± 15% variance.

[a] DL0 and/or DL4A are explored only if DL1 and/or DL4, respectively, are deemed to be unacceptably toxic or a de-escalation decision is made per the mTPI dose-escalation rules.

D = Day; DL = Dose level; DLT = Dose-limiting toxicity; mTPI = modified toxicity probability interval

Dosing is based on CAR expression, where ≥80% of administered FT576 viable cells express BCMA-CAR.

The planned progression of FT576 dose escalation is as follows:

- For Regimen A, the starting FT576 dose level will be 1×10^8 viable cells (DL1) on Day 1
- Initiation of Regimen B, at the dose level of 1×10^8 viable cells (DL1) on Day 1, will be contingent on clearance of Regimen A DL1
- Initiation of Regimen A1 on Days 1 and 15 will begin at the most recently cleared dose level (i.e., meets acceptable safety and tolerability to escalate) of Regimen A
- Initiation of Regimen B1 on Days 1 and 15 will begin at the most recently cleared dose level (i.e., meets acceptable safety and tolerability to escalate) of Regimen A
- DL0 of 5×10^7 viable cells will be tested in both Regimens A and B independently only if DL1 in each respective regimen is deemed to be unacceptably toxic or a de-escalation decision is made per the modified toxicity probability interval (mTPI) dose-escalation rules
- DL4A for the single dose ($\leq 2 \times$ DL3, Day 1) and for the multiple doses ($\leq 2 \times$ DL3, Days 1 and 15) will be tested independently across all regimens only if DL4 in each respective regimen is deemed too toxic or exceeds the defined DLT limit per dose level
- Dose escalation will proceed independently among Regimens A, A1, B, and B1 in order to identify the MTD/MAD of FT576 as monotherapy and in combination with daratumumab

4.2.2 Dose-Escalation Rules

Dose escalation/de-escalation will be conducted by the Sponsor in consultation with the study investigators following an mTPI algorithm (Ji et al. 2010) with a target DLT rate of 25% and an equivalence interval of (20%, 30%). A minimum of 3 subjects will be enrolled to a dose level and the maximum number of subjects for each dose level will be capped at 12. Additional subjects may be added to explore additional dose levels after the maximum number of subjects has been reached. A dose level will be considered as unacceptably toxic if it has an estimated probability of ≥95% exceeding the target DLT rate of 25% with at least 3 subjects treated at that dose level. The DLT assessment period will be from start of FT576 administration on Day 1 through Day 29.

Subjects will be enrolled in cohorts of 3 subjects per dose level with the following intervals between subjects.

Single dosing:

- The minimum interval between dosing of FT576 for the first and second subject in a dose-escalation cohort will be 28 days.
- For the first dose-escalation cohort, e.g., DL1 (Figure 4), the minimum interval between dosing of FT576 for the second and third subject will be 28 days. If the dose level is decreased to DL0, the minimal interval between dosing of FT576 for the second and third subject would also be 28 days. In the absence of DLTs, the minimum interval between dosing of FT576 for the second and third subject in subsequent dose-escalation cohorts above DL1 may be reduced to 14 days.

Multiple doses:

- The minimum interval between dosing of FT576 for the first and second subject in a dose-escalation cohort will be 28 days.
- For the first dose-escalation cohort, e.g., DL1 (Figure 4), the minimum interval between dosing of FT576 for the second and third subject will be 28 days. In the absence of DLTs, the minimum interval between dosing of FT576 for the second and third subject in subsequent dose-escalation cohorts may be reduced to 14 days.

Start of enrollment in the subsequent dose-escalation cohort will be contingent on all subjects in the previous dose-escalation cohort being assessed through the entirety of the DLT assessment period.

Table 7 provides the dose-escalation and de-escalation guidelines based on the number of subjects treated at a dose level who experience a DLT. Dose escalation may be halted once a dose level with acceptable safety and satisfactory antitumor activity has been selected for evaluation in expansion. The MTD will be determined, based on isotonic regression analysis (Ji et al. 2010) applied to the DLT rates observed during the dose-escalation. However, it is possible that the MTD may not be identified in this study. In the absence of establishing the MTD, the highest-assessed dose level is the MAD.

For a dose level to be considered safe, at least 3 DLT-evaluable subjects must have completed the 28-day DLT-evaluation period and the level estimated to be safe per the mTPI algorithm. When a dose level is cleared by mTPI, additional subjects may be enrolled into the dose level where there is evidence of clinical and/or pharmacodynamic activity with FT576. However, these subjects will not be part of the DLT-evaluable population. The decision to open a new dose level for enrollment will be made by the Sponsor based on results from the mTPI algorithm after consultation with the Principal Investigators at each site as appropriate.

Table 7. Dose-Escalation and De-escalation Guidelines

Number of Subjects with DLTs	Number of Subjects Treated at Current Dose											
	1[a]	2[a]	3	4	5	6	7	8	9	10	11	12
0			E	E	E	E	E	E	E	E	E	E
1			S	S	S	E[b]	E	E	E	E	E	E
2			D	D	S	S	S	S	S	S	S	E[c]
3			DU	DU	DU	D	S	S	S	S	S	E[c]
4				DU	DU	DU	DU	DU	D	S	S	D[c]
5					DU	DU	DU	DU	DU	DU	D	D[c]
6						DU	DU	DU	DU	DU	DU	DU
7							DU	DU	DU	DU	DU	DU
8								DU	DU	DU	DU	DU
9									DU	DU	DU	DU
10										DU	DU	DU
11											DU	DU
12												DU

Source: Modified from Ji et al. 2010.

NOTE: Target toxicity rate = 25% and equivalence interval = (20%, 30%); Sample size cap for each dose level = 12 subjects. When a given dose level is deemed to be DU, enrolment into this dose level or higher will be stopped.

[a] A minimum of 3 subjects will be enrolled at each dose level before a dose escalation decision is made.

[b] The original mTPI algorithm was S for this case and is modified to E as the observed DLT rate is 17%.

[c] The original mTPI algorithm was S for these cases and is modified to either E or D according to whether the observed DLT rate is < or ≥ the target toxicity of 25%, respectively.

D = De-escalate to the next lower dose level; DLT = Dose-limiting toxicity; DU = Current dose is unacceptably toxic; E = Escalate to the next higher dose level; S = Stay at the current dose level

4.2.3 Definition of Dose-Limiting Toxicity

A DLT is defined as any AE that is at least possibly related to FT576 occurring following the first FT576 infusion through the end of the DLT assessment period on Day 29, and with extension of the DLT assessment period beyond Day 29 to allow for AE recovery as defined below, that meets one of the following criteria based on the National Cancer Institute Common Terminology Criteria for Adverse Events, Version 5.0 (NCI CTCAE, v5.0) or the American Society for Transplantation and Cellular Therapy (ASTCT) Consensus Grading Guidelines for Cytokine Release Syndrome and Neurological Toxicity Associated with Immune Effector Cells (Lee et al. 2019). Grading of acute GvHD will be based on the Center for International Blood and Marrow Transplant Research (CIBMTR) acute GvHD scoring scale (Section 9.5.2.4). Grading of laboratory AEs will be assessed relative to baseline laboratory values defined as the last assessment prior to the start of protocol-designated study treatment.

Non-hematologic AEs

- Any non-hematologic AE Grade 4
  - Grade 4 infusion-related reaction will be a DLT.
  - Grade 4 fever associated with CRS that occurs in the context of Grade <3 CRS will not be considered a DLT.
- Grade 3 pulmonary or cardiac AE of any duration
- Grade 3 immune cell associated neurotoxicity syndrome (ICANS) of any duration
- Any non-hematologic AE Grade 3 >72 hours' duration. The following are exceptions, and therefore will NOT be considered DLTs:
  - Grade 3 renal or hepatic AE lasting ≤7 days
  - Grade 3 laboratory abnormality, unless otherwise specified, that is asymptomatic and determined by the treating investigator not to be clinically significant
  - Grade 3 fatigue lasting ≤7 days
  - Grade 3 febrile neutropenia lasting ≤14 days
- Any Grade ≥II acute GvHD requiring systemic steroid administration and without resolution to Grade ≤I within 7 days

Hematologic AEs

- Any Grade ≥3 hematologic AE. The following are exceptions and therefore will not be considered DLTs:
  - Grade 3-4 neutropenia or Grade 4 leukopenia that can be managed with institutional supportive care, e.g., G-CSF, in the absence documented infections, and that improves to Grade ≤2 or to ≥80% of baseline, whichever is lower, within 21 days of the neutrophil count nadir
  - Grade 3-4 anemia that can be managed with institutional supportive care, e.g., red blood cell transfusions, in the absence of clinically significant signs and symptoms, and that improves to Grade ≤2 or to ≥80% of baseline, whichever is lower, within 21 days of the hemoglobin concentration nadir
  - Grade 3-4 thrombocytopenia that can be managed with institutional supportive care, e.g., platelet transfusions, in the absence of Grade ≥2 bleeding, and that improves to Grade ≤2 or to ≥80% of baseline, whichever is lower, within 21 days of the platelet count nadir
  - Grade 3 or 4 lymphopenia of any duration
  - Grade 3 leukopenia of any duration

4.3 Dose-Expansion Stage

The objectives of dose expansion are to further assess safety and tolerability of FT576 as monotherapy and combined with daratumumab in subjects with r/r MM, and to identify clinical activity signals to guide and support future development. Enrollment in dose expansion will occur independently among Regimens A, A1, B, and B1. The schema for dose expansion is illustrated in Figure 4.

The doses of FT576 for dose expansion with Regimens A, A1, B, and B1 will each be determined based on the clinical and available PK and pharmacodynamic data from dose escalation and will not exceed the MTD or the MAD for that regimen.

For each regimen, one or more dose-expansion cohort(s) of up to 15 subjects/cohort may be opened to:

- More fully characterize safety/tolerability at a given dose level, including evaluation of alternate doses and schedules of FT576, provided the dose of FT576 does not exceed the MTD or MAD; and
- More fully characterize the clinical activity of a specific regimen (e.g., Regimens A, A1, B, or B1) in a specific patient population (e.g., International Staging System [ISS]/Revised ISS stage, cytogenetic risk category, presence of extra-medullary disease, etc.).

4.4 Post-Treatment Follow-Up

Post-treatment follow-up visits, as defined in the SoA (Table 3), will continue until up to 2 years following the completion of the last FT576 treatment cycle **or** until one of the following occurs: disease progression or relapse, initiation of a new anti-cancer therapy, withdrawal of consent, or lost to follow-up, whichever occurs first.

Refer to Sections 7.6.1 and 7.6.2 for details on follow-up for subjects who withdraw consent from the study or are lost to follow-up, respectively.

Subjects who are in post-treatment follow-up and subsequently become eligible to receive retreatment may be required, based on the timing of the last post-treatment follow-up assessment, to complete weekly pre-retreatment monitoring visits (as outlined in Table 1) leading up to the start of the subsequent treatment cycle to ensure adequate recovery from AE(s) from prior treatment cycle(s). Refer to Appendix 3 for detailed guidelines for retreatment. After completion of retreatment, subjects who have not progressed, relapsed, and/or have not started a non-protocol-defined anti-cancer therapy will then re-enter the post-treatment follow-up period starting with the FU 1 visit (Table 3).

4.5 Long-Term Follow-Up

Following post-treatment follow-up, subjects who remain relapse- or progression-free up to 2 years after the last FT576 treatment cycle, experience disease relapse or progression prior to 2 years, begin a new, non-protocol-defined anti-cancer therapy, or withdraw consent from post-treatment follow-up will be followed for up to 15 years, according to the schedule in Table 4. Only information related to the following will be collected:

- Subsequent anti-cancer therapies (Section 6.4.4)
- Long-term follow-up safety assessments (Appendix 4)
- Cell therapy safety monitoring (Section 8.3.4.7)
- Relevant serious adverse events (SAEs) (Section 9.6.2) and associated concomitant therapy (Section 6.4).

No other clinical, laboratory, or disease response assessments related to FT576 treatment will be collected.

Refer to Sections 7.6.1 and 7.6.2 for details on follow-up for subjects who withdraw consent from the study or are lost to follow-up, respectively.

4.6 Scientific Rationale for Study Design

4.6.1 Rationale for Study Population

This study will evaluate the clinical activity of FT576 in subjects with r/r MM, which despite improvements in outcomes with evolving therapies remain areas of significant unmet medical need. In particular, patients who are refractory to immunomodulatory drugs (IMiDs) and proteasome inhibitors have a median overall survival (OS) of approximately 13 months (Kumar et al. 2017). Outcomes for patients who are refractory to an anti-CD38 monoclonal antibody in addition to an IMiD and proteasome inhibitor are even worse with an OS of <9 months (Ganhdi et al. 2019).

4.6.2 Rationale for FT576 Treatment Regimens

Monotherapy FT576 Dosing on Day 1 (Regimen A)

BCMA is a validated target in MM (e.g., belantamab mafadotin-blmf United States Package Insert [USPI]) with various modalities being explored (e.g., ADC, bispecific immune cell engager, CAR T cell). Therefore, it is expected that FT576 will likely exhibit monotherapy activity.

Multiple FT576 Dosing on Day 1 and Day 15 (Regimen A1 and Regimen B1)

Many clinical trials have demonstrated acceptable safety and tolerability of CAR T- and NK-cell therapies when administered in multiple doses following a single round of conditioning chemotherapy. For example, multiple doses up to 5×10^9 cells/m^2 per dose of CD33 CAR NK-92 were given to patients with relapsed AML (Fabian and Hodge, 2021). Multiple studies being conducted by the Sponsor of iPSC derived NK cell therapies, which include engineered modalities that have been incorporated into FT576, e.g., hnCD16, IL15R/F, and tumor antigen targeting CAR,

are currently assessing safety and clinical activity when administered in multiple doses following a single round of conditioning chemotherapy (Janakiram et al. 2020; Bachanova et al. 2021; Strati et al. 2021). Available data from Phase I dose escalation of FT516, FT538, and FT596 in hematologic malignancies support the overall safety and tolerability when administered as multiple doses at up to 9×10^8 cells/dose.

Multiple dosing on Days 1 and 15 in Regimens A1 and B1 will investigate whether this dose administration schedule leads to comparable safety and tolerability, improved clinical efficacy, and favorable PK as compared with single dose administration on Day 1 explored in Regimens A and B. One potential advantage with this approach is in the ability to explore giving a second dose of FT576 within the same cycle without the need to administer another round of conditioning chemotherapy which could put patients at risk of prolonged cytopenias. Multiple dosing may be particularly useful in combination with daratumumab (Regimen B1) to maximize ADCC.

Because the safety profile of FT576 when administered in multiple doses per cycle is unknown, the trial will have robust safety monitoring in place that includes staggered subject enrollment during dose escalation, clearly defined stopping rules for safety (Section 7.4) and utilization of mTPI methodology (Section 4.2.2) to more precisely define the MTD/MAD. Additionally, the Safety Assessment Committee (SAC; Section 9.7.2) will review data on a periodic basis and make recommendations as needed to ensure subject safety.

FT576 Combinations with Daratumumab (Regimen B and Regimen B1)

One of the proposed mechanisms of progression or relapse after BCMA CAR T-cell therapy is antigen escape and this has been described by the group at the NCI (Brudno et al. 2018). Dual antigen targeting has been proposed as a method to minimize antigen escape and promote deeper and more durable responses.

The expression of hnCD16 on FT576, which enhances the ADCC of mAbs, such as daratumumab, allows for the opportunity to utilize the combination to achieve dual antigen targeting and test this hypothesis.

Further, the CD38 gene KO in FT576 is intended to mitigate daratumumab mediated NK-cell fratricide and provide additional enhanced ADCC when FT576 is administered with concurrent anti-CD38 mAb therapy (Bjordahl et al. 2019).

The dose and schedule of daratumumab in Regimens B and B1 represent the approved dose and schedule in subjects with r/r MM (Darzalex® USPI; Darzalex Faspro™ USPI). Different daratumumab administration schedules from the approved doses and schedules may be evaluated based on emerging nonclinical efficacy, clinical safety, PK, and/or pharmacodynamic data.

4.6.3 Rationale for Retreatment

Current generation autologous and allogeneic BCMA CAR T-cell therapies are mostly administered as a single infusion. Retreatment with BCMA CAR T-cell therapies remains under investigation. However, there is emerging evidence that retreatment with the CD19 CAR T-cell product at the time of relapse or progressive disease can achieve or regain anti-tumor activity. Examples of this evidence include the following:

- Results from a clinical study of an autologous CD19 CAR T-cell product in which 44 subjects with B-cell malignancies, including B-ALL, CLL/Richter transformation, and BCL, received a second CD19 CAR T-cell infusion following relapse or progression on the first CD19 CAR T-cell infusion. Objective responses (21% CR in B-ALL, 36% ORR in CLL/Richter, and 53% ORR in BCL) were observed following the second CD19 CAR T-cell infusion, with durable PFS observed in a subset of subjects. The safety and tolerability profile following the second CD19 CAR T-cell infusion was similar to that following the initial CD19 CAR T-cell infusion (Bezerra et al. 2019).
- Results from a clinical study of the allogeneic CD19 CAR T-cell product UCART19 for the treatment of pediatric and adult subjects with r/r B-ALL, in which 3 subjects received a second dose of UCART19 for r/r disease following initial UCART19 treatment. Two of the 3 subjects, including 1 subject who was refractory after initial UCART19 treatment, achieved measurable residual disease (MRD)-negative disease status after receiving the second UCART19 dose (Benjamin et al. 2018).

The conditions under which an enrolled subject may receive FT576 retreatment are described in Appendix 3. Proceeding to additional treatment cycle(s) of FT576 will be done on a case-by-case basis in consultation with and approval from the U.S. Food and Drug Administration (FDA). In addition, post-progression/pre-retreatment tumor samples should be obtained to determine BCMA-expression status. BCMA expression should be determined given that downregulation or loss of BCMA is a known resistance mechanism to BCMA CAR T-cell therapy (Brudno et al. 2018; Martin et al. 2020).

4.6.4 Rationale for Conditioning

The purpose of conditioning prior to the administration of FT576 is to create an immune environment amenable to FT576 persistence and expansion. This is accomplished by promoting homeostatic proliferation of FT576 as well as eliminating regulatory immune cells and other competing elements of the immune system that compete for homeostatic cytokines (Klebanoff et al. 2005). Conditioning with CY and FLU has been established with CD19 CAR T-cell therapies (Kymriah USPI; Yescarta USPI) and was shown to improve CAR T expansion and persistence associated with clinical benefit (Turtle et al. 2016). The doses and schedules of CY and FLU conditioning used in this study are identical to those administered as conditioning prior to infusion of BCMA CAR T cells (Raje et al. 2019).

4.6.5 Rationale for Allowing Palliative Radiation Therapy

Subjects who enroll in this study will be allowed to receive palliative radiation therapy (Section 6.4.1). Biologically, radiation therapy may create a more immunogenic microenvironment that would enhance FT576 anti-tumor activity. There exists evidence that radiation therapy administered in conjunction with adoptive cell therapies may potentiate and/or enhance anti-tumor activity. For example, abscopal effects following localized radiation therapy that lead to systemic anti-tumor responses have been observed in different indications (DeSelm et al. 2018; Minn et al. 2019; Smith et al. 2019). Furthermore, radiation therapy as a debulking step prior to CD19 CAR T-cell therapy administration in r/r diffuse large B-cell lymphoma with high tumor burden was associated with lower rates of high-grade CRS and neurotoxicity compared to debulking by high-dose chemotherapy and with similar ORRs (Qu et al. 2020).

4.6.6 Rationale for Exploratory Analyses

The exploratory analyses of potential predictive and prognostic biomarkers associated with the mechanism of action of FT576 and underlying disease immunobiology are described in Section 8.3.4.6. Such biomarkers may correlate with clinical outcomes. These associations may differ by indication and study subject population. Changes in immune-related biomarkers in the peripheral blood and within tumors may provide evidence for the biologic activity of FT576. An exploratory objective of this study is to assess potential pharmacodynamic biomarkers including, but not limited to, serum free light chain (sFLC), serum B-cell maturation antigen (sBCMA), cytokines, PK of FT576, daratumumab, and NK and T-cell numbers and function and any potential associations with dose-dependent safety and anti-tumor activity.

In addition to peripheral blood sampling, bone marrow biopsies and/or aspirates will be obtained from subjects following initial treatment with FT576. In cases where extramedullary disease is present at baseline and accessible, a tumor biopsy may be obtained. Demonstrating the ability of FT576 to infiltrate sites of tumor is of importance, as well as evaluating changes to the tumor microenvironment in understanding potential mechanisms of FT576 resistance. In this regard, effort will be made in this study to obtain tumor biopsies following disease progression and relapse. Information from on-treatment and post-progression biopsies are of potential importance in directing the development of future cell therapies that address these mechanisms of resistance.

4.7 End of Study Definition

The end of the study is defined as the date of the last subject's last assessment (scheduled or unscheduled). Follow-up visits, as defined in the SoAs (Table 3 for post-treatment follow-up and Table 4 for long-term follow-up), may continue until up to 15 years following the completion of the last FT576 treatment cycle or withdrawal of consent, whichever occurs first. The expected duration of the study is approximately 15 years from the time of the last enrolled subject treated with FT576.

The Sponsor may terminate the study at any time (Section 7.3).

5 STUDY POPULATION

5.1 Inclusion Criteria

Subjects are eligible for the study only if all of the following criteria apply:

1. Diagnosis of r/r MM as described below.

   - Regimens A, A1, B, and B1: Measurable disease, defined by at least one of the following:
     - Serum M-protein ≥1.0 g/dL
     - Urine M-protein ≥200 mg/24 hours
     - Involved serum free light chain level ≥10 mg/dL, with an abnormal κ/λ ratio if the serum M-protein <1.0 g/dL and/or urine M-protein <200 mg/24 hours
   - Regimens A and A1 only: MM that has relapsed or progressed after ≥3 prior approved therapies, including:
     - A proteasome inhibitor (e.g., bortezomib, carfilzomib), and
     - An IMiD (e.g., lenalidomide, pomalidomide), and
     - Anti-CD38 therapy (e.g., daratumumab, isatuximab)

     Planned sequential therapy (e.g., induction therapy followed by HSCT and maintenance) is considered one line of therapy.
   - Regimens B and B1 only: MM that has relapsed or progressed after ≥2 prior approved therapies, including:
     - A proteasome inhibitor, and
     - An IMiD

   For all regimens, prior treatment with BCMA CAR T-cell therapy and BCMA-targeted therapy is allowed.

2. Willingness to provide informed consent as described in Appendix 7, which includes compliance with the requirements and restrictions listed in the Informed Consent Form (ICF) and in this protocol

3. Age ≥18 years old at the time of signing the ICF

4. Agreement to comply with study procedures, including providing bone marrow biopsy/ aspirate samples as described in the SoAs

5. Male subjects and female subjects of childbearing potential who engage in heterosexual intercourse must agree to use protocol specified method(s) of contraception as described in Appendix 5.

5.2 Exclusion Criteria

Subjects are excluded from the study if any of the following criteria apply:

1. Females who are pregnant or breastfeeding
2. Eastern Cooperative Oncology Group Performance Status (ECOG PS) ≥2
3. Evidence of insufficient hematologic function defined by the following:
   a. Absolute neutrophil count <1000/μL without growth factor support ≤7 days prior to the absolute neutrophil count measurement to determine eligibility
   b. Platelet count <75,000/μL without platelet transfusion ≤72 hours prior to the platelet count measurement to determine eligibility

   Subjects who do not meet the criteria for hematologic function because of extensive marrow involvement of disease and/or disease-related cytopenias may be enrolled into the study with approval from the Medical Monitor.
4. Evidence of insufficient organ function defined by any one of the following:
   a. Estimated creatinine clearance <50 mL/minute by Cockcroft-Gault method or other standard institutional method
   b. Total bilirubin >1.5 × upper limit normal (ULN), not applicable for subjects with Gilbert's syndrome
   c. AST >3 × ULN or ALT >3 × ULN, not applicable if determined to be directly due to underlying malignancy

   NOTE: Subjects who have a laboratory blood test value that is exclusionary per exclusion criteria 4a, 4b, or 4c are permitted one repeat test, and if no longer exclusionary, may continue to enroll.

   d. Oxygen saturation <92% on room air
5. Clinically significant cardiovascular disease including any of the following: myocardial infarction within 6 months prior to first study treatment; unstable angina or congestive heart failure of New York Heart Association Grade 2 or higher; or cardiac ejection fraction <40%
6. Subjects with active CNS involvement, including leptomeningeal disease

   Subjects with prior CNS involvement may be enrolled into the study if effective treatment of their CNS disease was completed at least 3 months prior to Day 1 with no evidence of disease clinically and at least stable findings on relevant CNS imaging.
7. Non-malignant CNS disease such as stroke, epilepsy, CNS vasculitis, or neurodegenerative disease or receipt of medications for these conditions in the 2-year period leading up to study enrollment

8. Currently receiving or likely to require immunosuppressive therapy (e.g., prednisone >5 mg daily) for any reason during the treatment period, with the exception of corticosteroids, as described in Section 6.4.3

9. Clinically significant infections including:
    a. Positive serologic test results for HIV infection
    b. Positive serologic or PCR test results for HBV infection

       HBV infection status that cannot be determined by serologic test results (https://www.cdc.gov/hepatitis/hbv/pdfs/serologicchartv8.pdf) must be negative for HBV by PCR to be eligible for study participation.
    c. Positive serologic and PCR test results for HCV infection

       Subjects who are positive for HCV antibody must be negative for HCV by PCR to be eligible for study participation (https://www.cdc.gov/hepatitis/hcv/pdfs/hcv_graph.pdf).

10. Live vaccine <6 weeks prior to start of conditioning

11. Receipt of an allograft organ transplant

12. Ongoing requirement for systemic graft-versus-host disease therapy

13. Known allergy to the following FT576 components: albumin (human) or DMSO

14. Presence of any medical or social issues that are likely to interfere with study conduct or may cause increased risk to subject

15. Any medical condition or clinical laboratory abnormality that per investigator or Medical Monitor judgment precludes safe participation in and completion of the study, or that could affect compliance with protocol conduct or interpretation of results

    Subjects who have had prior receipt of a Fate Therapeutics' investigational human iPSC product may be eligible for the study with approval from the Medical Monitor.

16. Plasma cell leukemia defined as a plasma cell count >2000/mm^3

17. Prior malignancy (other than current indication including any antecedent hematologic disorder) within the 2 years prior to enrollment except for the following: basal or squamous cell carcinomas of the skin, carcinoma in situ of the cervix or breast treated with curative intent, or localized prostate cancer treated with curative intent, or malignancy that, in the opinion of the investigator and Sponsor's Medical Monitor, is considered cured with minimal risk of recurrence within 3 years.

18. Washout periods from prior therapies:

    a. For all subjects (Regimens A, A1, B and B1), receipt of the following:

        Chemotherapy, or radiation therapy, except for palliative purposes, within 14 days prior to the first dose of FT576 (Day 1) or five half-lives, whichever is shorter

        Investigational therapy within 30 days prior to the first dose of FT576 (Day 1) or five half-lives, whichever is shorter

        Biologic therapy (except for anti-CD38 mAbs in Regimens B and B1 only), including autologous cellular immunotherapy (e.g., CAR-T/CAR-NK), antibody-drug conjugates or bi-specific immune-cell engaging antibody within 30 days prior to the first dose of FT576 (Day 1) or five half-lives, whichever is shorter

        Prior allogeneic HSCT or allogeneic CAR T/CAR NK within 6 months of first dose of FT576 (Day 1)

    b. For subjects in Regimens B and B1 only, receipt of the following:

        Anti-CD38 therapy alone or in combination within 3 months prior to Day -11

19. Allergy or hypersensitivity to antibodies or antibody-related proteins

5.3 Lifestyle Considerations

No lifestyle restrictions are required for this study.

5.4 Screen Failures

Screen failures are defined as individuals who consent to participate in the clinical trial but do not receive any study treatment. A minimal set of screen-failure information is required, including demography, screen-failure details, relevant eligibility criteria, and any SAE. Individuals who screen fail may not be rescreened unless specifically approved by the Medical Monitor. Subjects who screen fail will be replaced.

6 STUDY TREATMENTS AND OTHER TREATMENTS RELEVANT TO THE STUDY DESIGN

6.1 Study Treatment Administered

The investigational medicinal product (IMP) for this study is FT576.

Additional treatments used in this study include CY, FLU, and daratumumab. In this protocol, "study treatment" refers to the combination of treatments assigned to subjects as part of this study (i.e., FT576, CY, FLU, and, if applicable, daratumumab). Study site staff should refer to the manufacturer's current local prescribing information for additional details on dosing administration, clinical safety, and activity of the individual agents. Administration guidance in this protocol for these agents will be in accordance with the respective current local prescribing information. Changes made to the administration guidance due to the investigator's clinical judgment or institutional standard of care will not be captured as protocol deviations, e.g., mAb infusion times that run slightly shorter or longer than that specified in the protocol.

Study treatment must be administered by a qualified member of the study site staff in a monitored setting where there is immediate access to trained personnel and facilities to manage potentially SAEs. Study site staff are also responsible for accurately completing the subject's study treatment records. The start/stop date and start/stop times of the FT576 administration, along with the additional study treatment administration, including whether the full dose was administered and any dose interruptions were required and their reasons, should be documented in the electronic Case Report Form (eCRF) for each subject.

Refer to Table 8 for an overview of the study treatments. Concomitant therapy is described in Section 6.4.

See Section 9 for risks associated with study treatments, including guidelines for managing AEs.

Table 8. Overview of Study Treatments

Conditioning Therapy
CY: 300 mg/m^2 IV infusion[a]
FLU: 30 mg/m^2 IV infusion[a]
FT576 infusion must be administered no earlier than the third calendar day after the last dose of conditioning. FT576 may be administered beyond the Day 1 window with Medical Monitor approval; however, depending on the length of the delay, repeat conditioning may be considered.
FT576
FT576: administered as an IV infusion via gravity. Planned FT576 dose levels in dose escalation are described in Section 4.2.2. Dosing is based on CAR expression, where ≥80% of administered FT576 viable cells express BCMA-CAR.
Daratumumab
Daratumumab: 16 mg/kg IV infusion starting on Day -11; OR **Daratumumab/hyaluronidase**: 1800 mg/30,000 units SC starting on Day -11: • QW for 8 doses (Days -11, -4, 4, 11, 18, and 25, and 2 doses QW [±1 day] thereafter); then • Q2W (±1 day) for 8 doses; then • Q4W (±2 days) until disease progression or unacceptable toxicity

[a] Repeat administration of CY/FLU is required unless subject has ongoing Grade 3 or higher cytopenias (WBCs, neutrophils, platelets). Medical Monitor approval is required in cases where CY/FLU will be omitted.

CY = Cyclophosphamide; FL = Fludarabine; IV = Intravenous; QW = Once weekly; Q2W = Every 2 weeks; Q4W = Every 4 weeks; SC = Subcutaneous; WBC = White blood cell

6.1.1 FT576

FT576 drug product is an allogeneic NK-cell immunotherapy lacking CD38 and expressing BCMA CAR, hnCD16, and IL-15RF. FT576 cells are suspended in infusion medium containing albumin (human) and DMSO.

Because FT576 is an investigational product, it can only be used and administered under an FDA-approved protocol. Subjects will not be treated with FT576 after study closure.

FT576 will be provided by the Sponsor in a cryopreserved bag and thawed at the site of administration. FT576 must be administered using an IV administration set with an in-line filter.

FT576 will be administered as an IV infusion via gravity at planned dose levels as described in Table 8.

Refer to the FT576 Investigator's Brochure and the Pharmacy Manual for FT576 for additional administration instructions and details on packaging, handling, storage, and stability.

6.1.1.1 FT576 Pre-medications

Subjects should be pre-medicated with acetaminophen 650 mg orally (PO) and diphenhydramine 25-50 mg PO or IV before and 4-6 hours after FT576 administration. Corticosteroids must not be used as pre-medication for FT576.

6.1.2 Conditioning

6.1.2.1 Cyclophosphamide

Subjects should be well hydrated beginning 24 hours prior to CY administration. Immediately prior to CY administration, subjects will receive 300 mL of IV normal saline or per institutional standards. Subjects may receive additional IV normal saline following CY administration, if based on institutional standards and/or investigator discretion following assessment of subject hydration status. Dose adjustments for weight/creatinine may be made per institutional guidelines and do not impact FT576 administration.

CY will be administered as an IV infusion at a dose of 300 mg/m^2 per institutional standard of care for 3 consecutive days on Day -5, Day -4, and Day -3 of the treatment cycle. CY dosing is calculated based on actual body weight (ABW). If ABW is >150% of the ideal body weight (IBW) then the dose should be computed using adjusted body weight as follows, or per institutional standard:
Adjusted body weight = IBW + 0.5(ABW-IBW)

For additional details on the administration of CY, including formulation, packaging, and handling information, refer to the current local prescribing information.

6.1.2.2 Fludarabine

FLU will be administered as an IV infusion at a dose of 30 mg/m^2 per institutional standard of care for 3 consecutive days on Day -5, Day -4, and Day -3 of the treatment cycle. Dose adjustments for weight and/or renal function (e.g., as assessed by creatinine clearance) may be made per institutional guidelines.

For additional details on the administration of FLU, including formulation, packaging, and handling information, refer to the current local prescribing information.

6.1.3 Daratumumab (Regimens B and B1)

Daratumumab will be administered by IV infusion at a dose of 16 mg/kg ABW, or daratumumab + hyaluronidase will be administered subcutaneously (SC) at a dose of 1800 mg/30,000 units starting on Day -11, then weekly (QW) for a total of 8 doses, then every 2 weeks (Q2W) for a total of 8 doses, then every 4 weeks (Q4W) until disease progression or unacceptable toxicity. No dose modification for daratumumab is allowed.

Daratumumab will be administered per the instructions outlined in Table 8. For additional details on the dosage and administration of daratumumab (IV or SC), including formulation, packaging, and handling information, refer to the current local prescribing information.

Prophylaxis for Infusion-Related Reactions

Because infusion-related reactions have been observed with daratumumab, and to minimize the potential impact of corticosteroids on NK-cell function, pre- and post-infusion medications should be given as described in Table 9. Additional modifications to prophylaxis for infusion-related reactions may be made based on evolving clinical data. In all cases, long-acting corticosteroids such as dexamethasone should not be administered.

Table 9. Daratumumab Pre-infusion and Post-infusion Medications

Timepoint	Medication(s)
Pre-infusion (1-3 hours prior to daratumumab infusion)	• Oral acetaminophen 650-1000 mg prior to each daratumumab dose • Oral or IV diphenhydramine 25-50 mg, or equivalent, prior to each daratumumab dose • Intermediate-acting corticosteroid (no long-acting corticosteroids should be administered) – Prior to Day -11: methylprednisolone 100 mg, or equivalent, administered IV[a] – Prior to Day -4: methylprednisolone 60 mg, or equivalent, administered orally or IV – **For daratumumab doses administered between Day 1 and Day 29 of the FT576 treatment cycle:** methylprednisolone should not be administered. If an infusion-related reaction is observed following administration of daratumumab on Day -11 or Day -4, then methylprednisolone 60 mg orally should be administered prior to subsequent daratumumab infusions. – **For daratumumab doses administered outside of the FT576 treatment cycle period:** methylprednisolone 60 mg, or equivalent, administered orally or IV should be administered.
Post-infusion	• **For daratumumab doses administered between Day 1 and Day 29 of the FT576 treatment cycle:** post-infusion methylprednisolone should not be administered. If a delayed-onset infusion-related reaction is observed, then methylprednisolone 20 mg orally should be administered following subsequent infusions. • **For daratumumab doses administered outside of the FT576 treatment cycle period:** administer methylprednisolone 20 mg, or equivalent, on each of the 2 days following daratumumab infusion beginning the day after the infusion
For subjects with a history of chronic obstructive pulmonary disease: • Consider prescribing post-infusion medications such as short- and long-acting bronchodilators, and inhaled corticosteroids. • Following the first 4 IV (not SC) doses, if the subject experiences no major infusion-related reactions, these additional post-infusion medications may be discontinued. For SC daratumumab, post-infusion medications may be discontinued after the first 3 doses if the subject does not experience any major infusion-related reactions.	

[a] Subjects receiving daratumumab + hyaluronidase may receive Day -11 methylprednisolone (100 mg or equivalent) IV or orally.

IV = Intravenous

Prophylaxis for Herpes Zoster Reactivation

Initiate antiviral prophylaxis, per institutional standards, to prevent herpes zoster reactivation within 1 week after starting daratumumab and continue for 3 months after receiving the last dose.

Daratumumab Administration and Monitoring

Administration of daratumumab will be performed in a monitored setting where there is immediate access to trained personnel and adequate equipment and medications to manage potentially serious reactions.

Table 10 provides guidelines for monitoring daratumumab IV for subjects who do not experience an infusion-related reaction with the Day -11 and Day -4 doses, and who do not initially receive steroid pre-medication during the FT576 treatment cycle. These subjects will receive daratumumab IV at a reduced infusion rate as described in Table 14.

For subjects who receive steroid pre-medication during the FT576 treatment cycle, and for all subjects receiving daratumumab IV administration outside of the FT576 treatment cycle, monitoring and administration infusion rates will be in accordance with current local prescribing information.

Table 10. Daratumumab IV Monitoring and Administration Infusion Rates During FT576 Treatment Cycle[a]

Monitoring	Administration Infusion Rates
• Vital signs (heart rate, respiratory rate, blood pressure and temperature) should be recorded within 60 minutes prior to infusion. • Monitor vital signs during daratumumab infusion every 15 (±5) minutes during the first 2 hours of each infusion, every 60 minutes thereafter for the remainder of the infusion, and at the completion of the infusion. • Following the completion of daratumumab infusion, the subject should be monitored for an additional 60 minutes. Monitor vital signs 30 (±10) minutes after the infusion is completed.	Daratumumab will be infused as follows: • Initial rate (first hour): 50 mL/hour • Rate increment: 50 mL/hour every hour • Maximum rate: 100 mL/hour[b]

[a] FT576 treatment cycle corresponds to the period from the first FT576 dose administration on Day 1 through the completion of the post-FT576 administration observation period on Day 29. Daratumumab monitoring and administration infusion rates outside of the FT576 treatment cycle should be conducted in accordance with local prescribing information.

[b] Maximum daratumumab infusion rate corresponds to 50% of the maximum infusion rate specified in the Darzalex United States Prescribing Information.

For daratumumab SC monitoring, sites should follow their institutional guideline/standard operating procedure(s).

Guidelines for the management of infusion-related reactions that occur with daratumumab are provided in Section 9.5.2.1.

6.2 Method of Treatment Assignment

This is a non-randomized, open-label study. Regimen assignment must conform to the required eligibility criteria (Section 5) and dose-escalation rules (Section 4.2.2). The availability of enrollment into each regimen will be monitored by the Sponsor and communicated regularly to sites.

6.3 Study Treatment Accountability

The site monitor will review the records of the protocol-designated IMP(s) held by the investigator (or designee) to ensure accountability and appropriate storage conditions at each monitoring visit.

The investigator must maintain accurate records of all IMP(s) administered per the protocol, including date received, number of units received, and lot number. The investigator must also ensure that the IMP(s) are kept secured and accounted for with access limited to only those individuals authorized by the investigator. The investigator (or designee) must also maintain adequate records of distribution, storage, dispensing, and destruction/return of all IMP(s) to be able to reconcile the IMP records (i.e., accountability or dispensing logs) at the end of the study. All IMP records must be readily available for inspection by the site monitor, auditor, and/or inspector. Unused IMP(s) should be disposed of in accordance with local institutional practice and with written approval from the Sponsor.

6.4 Concomitant Therapy

Concomitant therapy consists of any medication (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by a subject in addition to protocol-mandated treatment from the initiation of any study treatment to initiation of subsequent anti-cancer therapy. All such medications should be reported to the investigator and recorded on the eCRF. For subjects who have disease relapse/progression or initiate new anti-cancer therapy, only concomitant medications for SAEs possibly or probably related to FT576 per investigator assessment will be recorded.

6.4.1 Permitted Therapy

Subjects are permitted to use the following therapies during the study:

- Supportive care
  - Throughout the study, the investigator may prescribe any concomitant medications not otherwise described as cautionary therapy (Section 6.4.2) or prohibited therapy (Section 6.4.3) or treatment deemed necessary to provide adequate supportive care.
  - Supportive care may include antibiotics, analgesics, transfusions, growth factors, etc. Only irradiated blood products should be used to minimize the risk of transfusion-associated GvHD.
- Palliative radiation
  - Subjects may receive palliative radiation therapy at any time and with schedules at the discretion of the investigator provided that the schedule of palliative radiation therapy does not interfere with protocol-specified assessments (Section 4.6.5).

6.4.2 Cautionary Therapy

Systemic corticosteroids should be avoided during the treatment cycle, unless absolutely required, because they may inhibit NK-cell function. Because of their deleterious effect on NK-cell-based therapy, corticosteroids as pre-medication for CY and FLU should be avoided unless considered necessary by the investigator and should not be administered within 24 hours before or after FT576 administration.

Intravenous glucocorticoid as pre-medication for CY, FLU, and daratumumab may be administered per the USPI or institutional guidelines. Methylprednisolone should be used as the preferred glucocorticoid pre-medication given its shorter half-life. Long-acting corticosteroids, such as dexamethasone, should not be used, except when necessary to treat CRS or ICANS.

Glucocorticoids must not be used as pre-medication for FT576.

6.4.3 Prohibited Therapy

Any antineoplastic agent for therapeutic intent other than protocol-designated study treatment(s) is prohibited.

Exceptions include:

- Any prior therapy leading up to the administration of study treatment as described in the inclusion/exclusion criteria (Sections 5.1 and 5.2, respectively)
- Anti-cancer therapy administered for disease progression following completion of FT576 administration (Section 6.4.4)
- Palliative radiotherapy (Sections 4.6.5 and 6.4.1)

6.4.4 Subsequent Anti-cancer Therapy

Subsequent anti-cancer therapy, including non-study specified chemotherapy, immunotherapy, targeted agents, radiation therapy, and stem cell transplant will be recorded until 2 years after disease progression following FT576 treatment, until the subject withdraws from the study, is considered lost to follow-up, withdraws consent, or dies, whichever occurs first.

Specific information to be collected includes the following:

- Description of the therapy, e.g., name and type of therapeutic agent administered
- Best response
- Where applicable, date of disease progression or relapse

7 TREATMENT, SUBJECT, AND STUDY DISCONTINUATION

7.1 Study Treatment Discontinuation

Study treatment may be discontinued at any time upon subject request. Discontinuing study treatment does not mean discontinuation from the study.

Subjects will be permanently discontinued from receiving further study treatment if any of the following are observed:

- Any medical condition, including TEAEs, that the investigator or the Sponsor determines may jeopardize the subject's safety if study treatment is continued
- Discontinuation of study treatment is in the best interest of the subject based on investigator or Sponsor assessment
- Pregnancy
- Use of prohibited anti-cancer therapy per protocol
- Symptomatic deterioration attributed to disease progression

The primary reason for study treatment discontinuation should be documented in the appropriate eCRF.

After study treatment discontinuation, subjects will return to the clinic for an early treatment discontinuation visit that includes the activities described for the Day 29 visit (Table 1) and continue to have post-treatment follow-up assessments as described in Table 3 and/or long-term follow-up assessments as described in Table 4.

Information on survival, subsequent anti-cancer therapies, and long-term follow-up safety monitoring will be collected via telephone calls, subject medical records, email/mail, and/or clinic visits according to the schedule in Table 3 and Table 4 unless the subjects withdraws consent or is lost to follow up, or if the Sponsor terminates the study.

Refer to Sections 7.6.1 and 7.6.2 for details on follow-up for subjects who withdraw consent from the study or are lost to follow-up, respectively.

7.2 Subject Discontinuation from the Study

Subjects are permitted to withdraw from participation in the study at any time upon request. In addition, the investigator has the right to withdraw a subject from the study at any time. Reasons for subject discontinuation from the study may include, but are not limited to, the following:

- Completion of all protocol-mandated activities
- Withdrawal of consent
- Loss to follow-up
- Study termination by the Sponsor

- Subject non-compliance, defined as failure to comply with protocol requirements based on investigator or Sponsor assessment
- Adverse event

A discontinuation visit should be conducted that includes the activities described for the Day 29 visit.

Every effort should be made to obtain a reason for subject discontinuation from the study. The primary reason for discontinuation from the study should be documented in the appropriate eCRF.

Refer to Sections 7.6.1 and 7.6.2 for details on follow-up for subjects who withdraw consent from the study or are lost to follow-up, respectively.

7.3 Study Discontinuation

The Sponsor may terminate this study, after informing investigators, at any time. Investigators will be notified by the Sponsor (or designee) if the study is placed on hold, completed, or closed. Conditions that may warrant termination of the study may include, but are not limited to:

- The discovery of an unexpected, serious, or unacceptable risk to the subjects in the study
- A decision on the part of the Sponsor to suspend or discontinue testing, evaluation, or development of the product
- Insufficient compliance to protocol requirements

The Sponsor also has the right to discontinue the study at a site at any time. Reasons for discontinuing the study at a site may include, but are not limited to:

- Excessively slow recruitment
- Poor protocol adherence
- Inaccurate or incomplete data recording
- Non-compliance with the International Council for Harmonisation (ICH) E6 guideline for Good Clinical Practice (GCP)
- No additional or outstanding required study activities, e.g., all enrolled subjects have completed the study and all obligations have been fulfilled

7.4 Study Stopping Rules

Any of the following will result in a temporary halt to study enrollment:

- Any subject death deemed probably or possibly related to FT576;
- Grade ≥III GvHD;
- Grade 4 hypersensitivity reaction; or

- Occurrence of 2 Grade 4 DLTs, or one Grade 4 neurotoxicity event among the first 5 subjects enrolled and treated with at least one dose of FT576

Safety data will be reviewed by the Fate Therapeutics SAC.
Based on the recommendations of the SAC and in consultation with the study investigator(s) decisions regarding study conduct, including changes to subject enrollment, will be made.

7.5 Subject Replacement

Subjects who receive a study treatment (Section 6.1) or are assigned to a cohort slot but do not receive FT576 will be replaced.

Subjects in the dose-escalation cohorts who receive FT576 and who withdraw prior to Day 29 for reasons other than a protocol-defined DLT will be replaced. Subjects who receive FT576 and withdraw because of a DLT will not be replaced.

7.6 Follow-up for Subjects Who Withdraw Consent or Are Lost to Follow-up

7.6.1 Withdrawal of Consent

If a subject withdraws consent from the study, no new health information will be gathered after the date of withdrawal and the study staff should attempt to verify survival status via public information sources (e.g., county records) annually and in accordance with local laws.

Refer to Section 7.1 for information regarding subjects who request to discontinue study treatment, but have not withdrawn consent from the study.

7.6.2 Lost to Follow-up

The following actions must be taken if a subject fails to return to the clinic for a required study visit:

- The site staff will attempt to contact the subject and reschedule the missed visit and counsel the subject on the importance of maintaining the assigned visit schedule and ascertain if the subject wishes to and/or should continue in the study.
- Before a subject is deemed lost to follow-up, the investigator or designee will make every effort to regain contact with the subject (where possible, 3 telephone calls and, if necessary, a certified letter to the subject's last known mailing address or local equivalent methods). These contact attempts should be documented in the subject's medical record or study file.
- Should the subject continue to be unreachable, he or she will be considered to have withdrawn from the study with a primary reason of being lost to follow-up.

Subjects who are lost to follow-up will continue to have their vital statistics searched at least annually via public information sources (e.g., county records) and in accordance with local laws until subject death is documented.

8 STUDY ASSESSMENTS AND PROCEDURES

Study assessments and procedures and their timing are provided in the SoAs (Section 1.3). Results of standard-of-care tests or examinations performed prior to obtaining informed consent and within the screening period may be used; these tests do not need to be repeated for screening.

8.1 Efficacy Assessments

8.1.1 Disease Response Assessments for r/r MM

Disease response will be assessed according to the International Myeloma Working Group (IMWG) response criteria and MRD assessment (Kumar et al. 2016).

For specific efficacy assessments and procedures related to disease response, refer to Appendix 1 and Section 8.3.

8.2 Safety Assessments

Safety assessments are described below; planned timepoints are provided in the SoA (Section 1.3). Laboratory evaluations and biological samples are described in Section 8.3.

8.2.1 Physical Examination

Full physical examinations will include an evaluation of the head, eyes, ears, nose, and throat; extremities/joints; and the cardiovascular, respiratory, abdominal, musculoskeletal, neurological, lymphatic, and dermatological systems. Urogenital and rectal examinations are not necessary, unless clinically indicated.

A targeted physical exam will be performed at specified timepoints and as clinically indicated based on symptoms reported. Targeted physical examinations should be limited to systems of primary relevance, i.e., cardiovascular, respiratory, those associated with symptoms, and those associated with tumor assessment (lymph nodes, liver, and spleen), if applicable.

Any clinically significant findings should be recorded on the Adverse Event or Medical History eCRF, as applicable.

Height and weight will also be measured and body mass index (BMI) will be calculated (BMI = weight [kg]/height $[m]^2$).

8.2.2 Vital Signs

Vital signs (temperature, systolic and diastolic blood pressure, heart rate, and pulse oximetry) will be collected at specified timepoints. Subjects must be in a seated or supine position for at least 5 minutes before assessing vital signs.

8.2.3 12-Lead Electrocardiogram

Subjects must be in a supine (includes sitting in a recliner chair) position for at least 5 minutes before performing 12-lead electrocardiogram (ECG) tests. Subject position at the time of collection of ECGs should be consistent across study visits. A single 12-lead ECG recording will be obtained. A repeat 12-lead ECG recording may be obtained in order to confirm ECG findings at the discretion of the investigator.

8.2.4 Left-Ventricular Ejection Fraction

Left-ventricular ejection fraction (LVEF) will be assessed by cardiac echocardiogram (ECHO), multigated acquisition (MUGA) scan, or cardiac magnetic resonance imaging (MRI) per institutional practice.

8.2.5 ECOG Performance Status

ECOG PS will be collected to evaluate subject functioning. The ECOG PS scale shown in Appendix 6 will be used to assess subject functioning in terms of their ability to care for themselves, daily activity, and physical ability (walking, working, etc.; Oken et al. 1982).

8.2.6 Medical History and Demographics

Medical history represents event(s) starting before signing the informed consent and includes clinically significant diseases, surgeries, non-MM cancer history (including prior cancer therapies and procedures), and reproductive status. Further, use of alcohol or drugs of abuse, and all medications (e.g., prescription drugs, over-the-counter drugs, herbal or homeopathic remedies, nutritional supplements) used by the subject at the time of the initial screening visit will be collected. "Clinically significant" is defined as an event, diagnosis, or presence of signs or symptoms, or laboratory value that requires either treatment, medical intervention and/or additional monitoring or follow-up.

Multiple myeloma cancer history will include prior systemic therapies including transplants, procedures and an assessment of molecular cytogenetic classification of the disease.

8.3 Laboratory Evaluations and Biological Samples

Data arising from sample analysis, including data on genomic variants, will be subject to the confidentiality standards described in Appendix 7.

For sampling procedures, storage conditions, and shipment instructions, see the FT576-101 Laboratory Manual.

8.3.1 Bone Marrow Biopsy/Aspirate Samples

Bone marrow biopsy/aspirate samples will be collected from subjects with r/r MM according to Table 11 and per instructions in the FT576-101 Laboratory Manual.

Requirements for bone marrow assessments are described in Appendix 1.

Table 11. Bone Marrow Biopsy/Aspirate Samples

Sample Timing (unless otherwise stated, both a biopsy and an aspirate sample will be collected)	**Sample Assessment(s)**	**Notes**
Before Dosing		
Screening Between completion of last prior therapy and initiation of any study treatment (D -5 for Regimens A and A1 and D -11 for Regimens B and B1)	Baseline disease assessment (including sample for central MRD testing)	• Local assessment • Refer to Appendix 1 • Refer to the FT576-101 Laboratory Manual for shipment of samples to central laboratories
	Exploratory analyses (Section 8.3.4.6)	• Refer to the FT576-101 Laboratory Manual for shipment of samples to central laboratories
After Dosing		
Between Days 2-8; Aspirate Only (1-7 days following the first dose of FT576)	Exploratory analyses (Section 8.3.4.6)	• Refer to the FT576-101 Laboratory Manual for shipment of samples to central laboratories
Day 29 (treatment completion) or early treatment discontinuation	Disease response assessment (including sample for central MRD testing)	• Local assessment • Refer to Appendix 1 • Refer to the FT576-101 Laboratory Manual for shipment of samples to central laboratories
	Exploratory analyses (Section 8.3.4.6)	• Refer to the FT576-101 Laboratory Manual for shipment of samples to central laboratories
Post-Day 29 (when applicable)	To confirm CR/sCR (including sample for central MRD monitoring)	• Local assessment • Refer to Appendix 1 • Refer to the FT576-101 Laboratory Manual for shipment of samples to central laboratories
FU6; Aspirate Only (only for subjects who continue to be in CR/sCR)	Central MRD monitoring and exploratory analyses (Section 8.3.4.6)	• Refer to the FT576-101 Laboratory Manual for shipment of samples to central laboratories
FU8; Aspirate Only (only for subjects who continue to be in CR/sCR)	Central MRD monitoring and exploratory analyses (Section 8.3.4.6)	• Refer to the FT576-101 Laboratory Manual for shipment of samples to central laboratories
2 years after the last dose of FT576 **or** at time of disease relapse/ progression, whichever occurs first	To evaluate status at 2 years and at relapse/progression (including sample for central MRD monitoring), if applicable	• Local assessment • Refer to Appendix 1 • Refer to the FT576-101 Laboratory Manual for shipment of samples to central laboratories

(Continued)

Table 11. Bone Marrow Biopsy/Aspirate Samples

Sample Timing (unless otherwise stated, both a biopsy and an aspirate sample will be collected)	**Sample Assessment(s)**	**Notes**
(Continued)		
Retreatment		
Pre-retreatment All subjects being considered for retreatment, regardless of rationale, must undergo a repeat bone marrow biopsy with aspirate (Appendix 3) within 21 days prior to start of the retreatment cycle.	Baseline disease assessment (including sample for central MRD testing)	• Local assessment • Refer to Appendix 1 • Refer to the FT576-101 Laboratory Manual for shipment of samples to central laboratories
	Exploratory analyses (Section 8.3.4.6)	• Refer to the FT576-101 Laboratory Manual for shipment of samples to central laboratories

CR = Complete response; DLT = Dose-limiting toxicity; MRD = Measurable residual disease; sCR = Stringent complete response

8.3.2 Local Laboratory Evaluations

Blood and urine samples will be collected for clinical safety laboratory tests (e.g., hematology, clinical chemistry, urinalysis) and sent to the study site's local laboratory for analyses (Table 12). Samples should be collected prior to administration of any study treatment on the days a study treatment is administered. Any test result that is considered clinically significant after the start of any study treatment may be repeated.

Table 12. Local Laboratory Tests

Hematology	**Clinical Chemistry**	**Urinalysis (Dipstick Permitted)**	**Other**
Hematocrit Hemoglobin Platelet count WBC count with differential[a] Neutrophils Lymphocytes Eosinophils Basophils Monocytes Plasma cells[b]	Albumin ALP ALT AST Bilirubin (total and direct) BUN Calcium Bicarbonate Chloride Creatinine Glucose Lactate dehydrogenase Magnesium Phosphorus Potassium Sodium Total protein	pH Specific gravity Glucose Protein Ketones Blood	Pregnancy test (serum and/or urine) HIV, HBV, and HCV tests DIRA β2 microglobulin **For Regimens B and B1 subjects only:** Blood type, Rh, and indirect antiglobulin test **If clinical CRS is suspected:** CRP and ferritin

[a] Differential will be obtained based on a minimal WBC count in accordance with local laboratory guidelines.
[b] As clinically indicated.

CRP = C-reactive protein; CRS = Cytokine release syndrome; DIRA = Daratumumab interference reflex assay; WBC = White blood cell

8.3.3 Sample Retention

Biological samples will be transferred to the Sponsor or its contracted laboratory for storage.

Samples will be retained for up to 5 years after either marketing approval of FT576 or until completion of the Clinical Study Report, whichever occurs last.

When a subject withdraws from the study, samples collected prior to the date of study withdrawal may be analyzed unless the subject specifically requests that the samples be destroyed, or local laws require their destruction. Results from samples that have been tested prior to subject withdrawal will remain as part of the overall research database.

Collection of any subject samples may be terminated by the Sponsor at any time. The decision to discontinue sample collection will be communicated to sites (Institutional Review Boards [IRBs] and Ethics Committees [ECs]) by means of memoranda and will not require a protocol amendment.

8.3.4 Central Laboratory Evaluations

Blood and tissue samples for the laboratory tests described below will be sent to a central laboratory for analyses, which may include third-party central laboratories contracted by the Sponsor.

8.3.4.1 Pharmacokinetics of FT576

Peripheral blood samples will be collected to characterize the PK of FT576. Samples will be collected before and after FT576 infusion on days when the cells are administered. FT576 quantification may also be performed on tumor samples.

8.3.4.2 CRS Cytokines

Peripheral blood samples will be collected for measurement of CRS cytokines prior to FT576 administration and in the event of clinically suspected CRS. CRS cytokines will be tested at a central laboratory.

In addition to CRS cytokines to be tested at a central laboratory, C-reactive protein (CRP) and ferritin will be tested locally (Table 12).

8.3.4.3 Immunogenicity of FT576

Peripheral blood samples will be collected for detection of alloimmunization to the FT576 product.

8.3.4.4 Measurable Residual Disease Testing

MRD status by DNA sequencing and clone identification or multiparameter flow cytometry will be performed using bone marrow samples from subjects as appropriate.

8.3.4.5 Optional Biopsy of Extramedullary Disease

Patients with extramedullary disease may provide optional tumor biopsies to allow for additional analysis of the tumor microenvironment at the following study visits:

- During the screening period
- Between Days 2 through 8, and on D29 of the study cycle
- After progression or relapse following initial treatment
- After progression or relapse following retreatment

8.3.4.6 Additional Exploratory Analyses

In addition, samples will be stored, and analyses may be performed as described below.

Peripheral blood and/or serum samples will be collected for exploratory biomarker and exploratory immune monitoring analysis that may include, but is not limited to:

- HLA and killer-cell immunoglobulin-like receptor (KIR) typing
- Exploratory serum biomarkers
  - Measurement of peripheral blood cytokine levels
  - Measurement of protein biomarkers of disease progression and/or response to therapy including but not limited to sFLC and sBCMA
- Exploratory immune monitoring
  - PBMC functional characterization and immunophenotyping, e.g., T-cell subset analysis
- PK for daratumumab (Regimens B and B1)

Exploratory biomarker analysis will also be performed on tumor tissue and bone marrow biopsies/aspirate samples or other tissue/aspirate samples obtained while the subject is on study (Sections 8.3.1 and 8.3.2), which may include but is not limited to:

- Tumor somatic mutation profiling, e.g., tumor mutation burden, microsatellite instability, ploidy analysis
- Tumor microenvironment characterization, e.g., tumor infiltrating T-cell characterization, tumor-infiltrating innate immune cell characterization, immune inhibitory molecule expression by tumor cells
- Gene expression profiling to determine baseline and post-treatment effects of FT576 on tumor microenvironment
- Pre-treatment gene polymorphism and expression panels to explore correlation of alterations with outcome

Assays and other exploratory analyses may include, but are not limited to, analysis of lymphocytes, T-cell activation, T-cell receptor repertoire, cytokines associated with inflammation, circulating tumor DNA (ctDNA) or MRD, cell of origin, and genes or gene signatures associated with tumor immunobiology. Exploratory analyses may involve extraction of DNA, cell-free DNA, or RNA; analysis of mutations, single nucleotide polymorphisms, and other genomic variants; and genomic profiling through use of next-generation sequencing of a comprehensive panel of genes; as well additional method development, assay validation, and characterization.

8.3.4.7 Cell Therapy Safety Monitoring

Peripheral blood samples obtained for cell therapy safety monitoring may include, but are not limited to, assessment of replication-competent lentivirus (RCL), banking of peripheral blood samples for testing of FT576 PK, host immune responses to FT576, and tests for autoimmune disease markers. In cases of positive test results, additional sample collection beyond the required collection may be required following agreement between the Sponsor and health authorities.

9 EVALUATION OF SAFETY

To date, there are no clinical data for FT576. The long-term safety risk is not known and may include conditions with delayed onset relative to FT576 administration. The information provided below on potential risks associated with FT576 is extrapolated from other NK-cell products and other cell products in general.

Specific conditions potentially related to engineered cellular immunotherapy products such as FT576 including, but not limited to, new malignancies, new or worsening neurologic disorders, new or worsening autoimmune or rheumatologic disorders, or new hematologic disorders should be documented.

Measures will be taken to ensure the safety of subjects participating in this study. Subjects will undergo safety monitoring during the study, including assessment of the nature, frequency, and severity of AEs. Guidelines for managing AEs are provided in Section 9.5.

9.1 Potential Risks Associated with FT576-Based Combination Therapies

The information provided in this section regarding potential risks associated with FT576 is extrapolated from other NK-cell products and other cell products in general. As FT576 may be combined with a mAb in order to enhance ADCC, there may be contributory risks that are driven by the specific mAb combination partner. The specific risks associated with a given mAb are described in detail in Section 9.3 and additional details are provided in the respective current local prescribing information.

9.1.1 Acute Allergic/Infusion Reaction

Acute allergic/infusion reactions may occur with any treatment, including with the use of CY, FLU, and mAbs. Subjects should be closely monitored for the occurrence of acute allergic/anaphylactoid infusion reactions such as rigors and chills, rash, urticaria, hypotension,

dyspnea, and angioedema during and following completion of the infusion. Clinical assessments, including vital signs, are described in the SoA (Section 1.3).

Acute allergic/infusion reactions may also be a manifestation of FT576 immunogenicity given that FT576 is an allogeneic cell product. Recommended guidelines for management of subjects who develop acute allergic/infusion reactions to FT576 are provided in Table 13.

9.1.2 Immunogenicity Risks

It is possible that FT576 may induce an immune response, which may manifest only through laboratory assessments, or may manifest clinically, e.g., as infusion-related reactions with varying degrees of severity, including serious life-threatening anaphylactic reactions. In addition, FT576 immunogenicity may have an impact on FT576 PK, which in turn may have an impact on FT576 anti-tumor activity. Evidence of FT576 immunogenicity and its clinical impact will be monitored during the study. AEs arising from FT576 immunogenicity will be managed per institutional practice.

9.1.3 DMSO-Related Risks

FT576 is formulated in DMSO to enable cryopreservation. DMSO side effects and symptoms are generally associated with histamine release and include coughing, flushing, rash, chest tightness and wheezing, nausea and vomiting, and cardiovascular instability. Treat by slowing the rate of infusion, medicating with antihistamines, and treating symptoms per institutional practice (AABB 2016).

9.1.4 Infection

FT576 is cell therapy of human origin. During processing, the cells are in contact with reagents of animal origin, and FT576 has a final formulation that contains albumin (human). As with any product of human and/or animal origin, transmission of infectious disease and/or disease agents by known or unknown agents may occur. FT576 has been extensively tested to minimize the potential risk of disease transmission. However, these measures do not completely eliminate the risk. For some infectious agents, there are no routine tests to predict or prevent disease transmission (AABB 2016).

9.1.5 Cytokine Release Syndrome

CRS is defined as a supraphysiologic response following any immune therapy that results in the activation or engagement of endogenous or infused immune effector cells (Lee et al. 2019). Clinical manifestations of CRS include cardiac, gastrointestinal, hepatic, coagulation, renal, respiratory, skin, and constitutional (fever, rigors, headaches, malaise, fatigue, arthralgia, nausea, and vomiting) signs and symptoms. TEAEs that may be attributed at least in part to CRS include fever, febrile neutropenia, hypotension, acute vascular leak syndrome, renal failure, hypoxia, and pleural effusion. Because the signs and symptoms of CRS are not unique to CRS, other causes of fever, hypotension, and/or hypoxia must be excluded. Notably, bacteremia and other severe infections have been reported concurrent with and even mistaken for CRS (Lee et al. 2019).

While CRS is a clearly defined syndrome with CAR T-cell therapy, it has generally not been observed as a toxicity associated with NK-cell therapies unless administered with systemic cytokines that may independently drive the proliferation and activation of CD8+ T cells, e.g., exogenous IL-15 (Cooley et al. 2019).

To consistently characterize its severity, CRS should be defined and graded according to ASTCT CRS consensus grading (Lee et al. 2019; Table 15) and not by NCI CTCAE. Clinical symptoms as noted above that are not considered related to FT576 should not be reported as CRS. In addition to clinical manifestations, if CRS is suspected, CRP and ferritin levels should be assessed locally, and blood samples should be collected for central cytokine analysis per the SoAs (Section 1.3).

Recommended guidelines for management of subjects who develop CRS are provided in Table 16.

9.1.6 Tumor Lysis Syndrome

Tumor lysis syndrome (TLS) is a possible fatal risk associated with anti-tumor therapy in both hematologic and solid tumors, especially with large tumor burden (Mirrakhimov et al. 2014). TLS symptoms include nausea, vomiting, diarrhea, muscle cramps or twitches, weakness, numbness or tingling, fatigue, decreased urination, irregular heart rate, restlessness, irritability, delirium, hallucinations, and seizures. TLS is comprised of abnormal laboratory changes that include hyperuricemia, hyperkalemia, hyperphosphatemia, and hypocalcemia. TLS has been reported to occur within 7 days following chemotherapy across various solid tumor settings, with 10 published reports of TLS cases in patients with gynecological cancer (Mirrakhimov et al. 2014). One case of fatal metabolic syndrome compatible with TLS was reported following NK-cell therapy in a patient with ovarian cancer 5 days after receiving CY (Geller et al. 2011). Prophylaxis for and management of TLS should be done in accordance with standard institutional practice.

Following FT576 administration, subjects should be followed closely for signs and symptoms of TLS, with regular clinical (including telemetry where applicable) and laboratory monitoring as described in the SoA (Section 1.3). Laboratory abnormalities suggestive of TLS should prompt immediate action by the treating clinicians, and TLS should be treated aggressively per institutional practice.

9.1.7 Immune Cell-Associated Neurotoxicity Syndrome (ICANS)

Neurologic toxicities arising as a result of immune therapies has been termed ICANS, defined as a disorder characterized by a pathologic process involving the CNS following any immune therapy that results in the activation or engagement of endogenous or infused immune effector cells (Lee et al. 2019). ICANS has been reported with CAR-T cell therapy and bispecific antibodies such as blinatumomab (Blincyto® USPI; Kochenderfer et al. 2015; Maude et al. 2014). The exact mechanism of toxicity in these settings is not known and may not be responsive to cytokine-directed therapy such as tocilizumab but has generally improved with treatment discontinuations and corticosteroids (Blincyto USPI; Goebeler et al. 2016; Kochenderfer et al. 2015).

While ICANS is a clearly defined syndrome associated with CAR T-cell-based therapies, it is rare and generally not believed to be a toxicity associated with NK-cell therapies. Neurotoxicity

resembling ICANS was reported in one trial of adoptively transferred NK cells given with SC IL-15, but the mechanism of the toxicity was not well defined (Cooley et al. 2019). Central nervous system toxicities following CD19 CAR T-cell therapy is characterized by encephalopathy, confusion, delirium, aphasia, obtundation, and seizures (Kymriah USPI; Yescarta USPI). Cases of cerebral edema have also been reported (Brudno and Kochenderfer 2016).

To consistently characterize its severity, ICANS must be graded using ASTCT consensus guidelines (Lee et al. 2019; Table 17). Recommended guidelines for management of subjects who develop neurologic conditions that are potential manifestations of ICANS are provided in Table 18, Table 19, and Table 20.

Neurotoxicity not considered related to FT576 should not be reported as ICANS. Any neurotoxicity not meeting the criteria for ICANS should be graded according to NCI CTCAE.

9.1.8 Acute Graft-versus-Host Disease

Because FT576 is an allogeneic immune effector cell product, there is a potential risk of GvHD even though allogeneic NK-cell therapies have not been associated with GvHD (Veluchamy et al. 2017).

Acute GvHD assessments will be performed with assignment of the overall severity based on the CIBMTR acute GvHD grading scale (Table 21). Management of GvHD should be done in accordance with local institutional practice.

9.2 Risks Associated with Conditioning

9.2.1 Cyclophosphamide

Warnings and precautions ascribed to CY include:

- Myelosuppression, immunosuppression, bone marrow failure, and infections (Section 9.2.3)
- Urinary tract and renal toxicity including hemorrhagic cystitis, pyelitis, ureteritis, and hematuria
  - Urinary tract obstructions must be corrected prior to receipt of CY.
- Cardiotoxicity including myocarditis, myopericarditis, pericardial effusion, arrythmias, and congestive heart failure, which may be fatal
  - Subjects should be closely monitored, especially those with risk factors for cardiotoxicity or pre-existing cardiac disease.
- Pulmonary toxicity including pneumonitis, pulmonary fibrosis, and pulmonary veno-occlusive disease leading to respiratory failure
- Secondary malignancies
- Veno-occlusive liver disease, which can be fatal
- Embryo-fetal toxicity

Adverse reactions reported most often include neutropenia, febrile neutropenia, fever, alopecia, nausea, vomiting, and diarrhea.

For the complete safety profile of CY, as well as information regarding supportive care and management of associated toxicities, refer to the current local prescribing information. Considerations of dose modifications due to toxicity should be discussed with the Medical Monitor.

9.2.2 Fludarabine

Warnings and precautions ascribed to FLU include:

- Severe bone marrow suppression, notably anemia, thrombocytopenia, and neutropenia (Section 9.2.3)
- Transfusion-associated GvHD
  - Use only irradiated blood products for transfusions.
- Severe CNS toxicity
  - Severe CNS toxicity was observed in patients treated at FLU doses of 96 mg/m^2 for 5-7 days. This toxicity was observed in ≤0.2% of patients treated at FLU doses of 25 mg/m^2.
- Infections
- Renal insufficiency
  - The subject's renal function should be monitored closely.
- TLS (Section 9.1.6)
- Embryo-fetal toxicity

Adverse reactions occurring in >30% of subjects treated with FLU include myelosuppression (neutropenia, thrombocytopenia, and anemia), fever, infection, nausea and vomiting, fatigue, anorexia, cough, and weakness. Also refer to Section 9.2.3 below.

For the complete safety profile of FLU, as well as information regarding supportive care and management of associated toxicities, refer to the current local prescribing information. Considerations of dose modifications due to toxicity should be discussed with the Medical Monitor.

9.2.3 Myelosuppression, Immunosuppression, Bone Marrow Failure, and Infections

Some adoptive cell therapies delivered with supportive medications, such as CY and FLU for conditioning, have been reported to cause myelosuppression (neutropenia and/or thrombocytopenia), leukopenia, anemia, and in some cases, bone marrow failure. Hematologic cytopenias could be further compounded by other factors such as underlying disease, concurrent illnesses, and concomitant medications. Close monitoring of complete blood count (Section 8.3.2) for the development of cytopenias and infections is strongly recommended. Management of cytopenias and infections, including transfusion support, antimicrobial prophylaxis, and use of growth factors, should be done in accordance with standard institutional practice.

9.3 Risks Associated with Daratumumab

Daratumumab is associated with risks such as infusion reactions, interference with laboratory tests (e.g., cross-matching and red blood cell antibody screening, serum protein electrophoresis [SPEP], and immunofixation assay in patients with IgG κ myeloma protein), neutropenia, and thrombocytopenia (Darzalex USPI; Darzalex Faspro USPI).

Safety monitoring should be performed using institutional standard clinical safety and laboratory assessments and study assessments as outlined in the protocol.

For the complete safety profile of daratumumab, refer to the current local prescribing information.

9.4 Drug Interactions

There are no known interactions with FT576 with other therapies. Refer to the current local prescribing information for study-specific therapies for drug interactions with these agents.

In addition to the known and potential risks of FT576, CY, FLU, and other study-specific therapies, additional risks of the combination treatment including, but not limited to, increased frequency and/or severity of risks known to CY, FLU, and study-specific therapies may occur. Additional information on the toxicities of CY, FLU, and study-specific therapies, whose frequency and severity may be affected by combination treatment with FT576, are described in the respective current local prescribing information. The nature, frequency, and severity of these toxicities in the context of FT576 administration is not currently known.

9.5 Management of Adverse Events

9.5.1 Dose and Schedule Modification for FT576

For AE(s) considered not related or unrelated to FT576, dose and schedule modification of FT576 is not required if, in the opinion of the investigator, such AE(s) do not represent a safety risk to the subject.

Dose and schedule modifications of FT576 for TEAE(s) considered related or at least possibly related to FT576 are as follows:

- If a Grade 3 or Grade 4 DLT is observed, then the subsequent FT576 infusions will not be administered.
- If a Grade 3 non-hematologic AE that is not a DLT is observed and recovers to baseline or Grade ≤1 by the subsequent scheduled FT576 infusion, then FT576 will be dose-reduced to at least one lower dose level.
  - Dose reduction will not be required for Grade 3 laboratory abnormalities that are not clinically significant
- If a Grade 3 non-hematologic AE that is not a DLT is observed and ongoing at the time of the subsequent scheduled FT576 infusion, FT576 infusion will be delayed until resolution of the AE to baseline or Grade ≤1, at which time FT576 will be dose-reduced to at least one lower dose level.
  - Dose reduction will not be required for Grade 3 laboratory abnormalities that are not clinically significant
  - For AEs occurring after the first FT576 infusion:

    If recovery to baseline or Grade ≤1 is observed by Day 15, the scheduled Day 15 FT576 infusion may be administered.

    If recovery to baseline or Grade ≤1 is not observed by Day 15, the scheduled Day 15 FT576 infusion will be skipped.
- If a Grade 3 hematologic AE that is not a DLT is observed, then FT576 dosing will continue according to schedule and without dose modification.

Additional modifications to the FT576 dosing schedule, including dosing delays and dose reduction(s), will be based on consultation between the investigator and the Medical Monitor.

Decisions to stop, hold, or restart daratumumab therapy due to toxicity should be discussed with the Medical Monitor.

9.5.2 Recommended Management Guidelines for Specific Adverse Events

Recommended guidelines for the management of specific AEs are outlined below.

For cases in which management guidelines are not covered in the protocol or current local prescribing information, subjects should be managed as deemed appropriate by the investigator according to best medical judgement.

9.5.2.1 Acute Allergic/Infusion Reactions

The recommended management of acute infusion or allergic reactions that occur during FT576 administration is described in Table 13.

Refer to Table 14 for the recommended management of infusion-related reactions that occur during daratumumab administration. Also see Section 6.4.2 for prophylaxis for infusion-related reactions with daratumumab.

Appropriate medical care beyond what is described in the protocol should be instituted as per the respective current local prescribing information or standard institutional practices. Because they may inhibit NK-cell function, systemic corticosteroids should be avoided unless absolutely required the for management of acute allergic/infusion reactions, as determined by the investigator.

Table 13. Recommended Guidelines for the Management of Acute Allergic/Infusion Reaction with FT576 Administration

Grade	Management
Any Grade	• Interrupt FT576 administration. • Manage symptoms, e.g., with antihistamines, antipyretics, and analgesics, according to standard institutional practice standards.
Grade ≤3	• Resume FT576 administration only upon complete resolution of the infusion-related reaction and at the discretion of the investigator. Given that FT576 administration may involve single or multiple bags depending on the total planned dose and accounting for the stability of FT576 post-thaw, FT576 administration may continue following resolution of Grade ≤3 infusion-related reactions as follows: • If single-bag FT576 dosing: – No additional FT576 may be administered. – The volume of FT576 administered prior to the infusion-related reaction must be documented; retain any remaining product and contact the Sponsor for further instruction. – Additional bags may not be administered to make up for FT576 that was not administered from the bag during which the infusion-related reaction occurred. • If multiple-bag FT576 dosing: – The volume of FT576 administered from the bag during which the infusion-related reaction occurred must be documented; retain any remaining product from the bag and contact the Sponsor for further instruction. – If dosing with additional FT576 bags was planned, they may be thawed and administered. – Additional bags beyond what was originally planned may not be administered to make up for FT576 that was not administered from the bag during which the infusion-related reaction occurred. • Refer to the Pharmacy Manual for FT576 for information on administration instructions and stability of the thawed FT576 drug product.
Grade 4	• Stop FT576 administration. Do not restart. – The volume of FT576 administered prior to the infusion-related reaction must be documented; retain any remaining product and contact the Sponsor for further instructions.

Table 14. Recommended Guidelines for the Management of Infusion-Related Reactions with IV Daratumumab Administration

Grade	Management
Any Grade	• Interrupt infusion. • Institute medical management; corticosteroids may be administered as clinically indicated.
Grade 1–2	• Once reaction signs and symptoms resolve, resume the infusion at no more than one-half the rate at which the reaction occurred. • In the absence of further infusion-related reactions signs and symptoms, resume infusion rate escalation at increments and intervals as clinically appropriate up to the original infusion rate. • If the subject experiences Grade ≥2 laryngeal edema or Grade ≥2 bronchospasm that does not respond to systemic therapy and does not resolve within 6 hours, then daratumumab should be discontinued.
Grade 3	• Once reaction signs and symptoms resolve, consider restarting the infusion at no more than one-half the rate at which the reaction occurred. • In the absence of further infusion-related reaction signs and symptoms, re-initiate daratumumab infusion at an initial rate of 50 mL/hour and increase by 50 mL/hour every hour to the target infusion rate. • Repeat interruption and re-initiation in the event of recurrent Grade 3 signs and symptoms. Permanently discontinue daratumumab upon the third occurrence of Grade 3 infusion-related reaction.
Grade 4	• Permanently discontinue daratumumab treatment.

9.5.2.2 Cytokine Release Syndrome or CRS-Like Symptoms

CRS will be graded according to ASTCT consensus grading (Lee et al. 2019; Table 15).

Management of CRS should follow the recommended management algorithm provided in Table 16 (Neelapu et al. 2018) and/or institutional practice.

Table 15. ASTCT Consensus Grading for Cytokine Release Syndrome[a]

CRS Parameter	Grade 1	Grade 2	Grade 3	Grade 4
Fever[b]	Temperature ≥38˚C	Temperature ≥38˚C	Temperature ≥38˚C	Temperature ≥38˚C
With either:				
Hypotension	None	Not requiring vasopressors	Requiring vasopressors with/without vasopressin	Requiring multiple vasopressors (excluding vasopressin)
And/or[c]				
Hypoxia	None	Requiring low-flow nasal cannula [d] or blow-by	Requiring high-flow nasal cannula, facemask, non-rebreather mask, or venturi mask	Requiring positive pressure (e.g., CPAP, BiPAP, intubation and mechanical ventilation)

Source: Lee et al. 2019.

[a] Organ toxicities associated with CRS may be graded according to NCI CTCAE, v5.0, but they do not influence CRS grading.

[b] Fever is defined as temperature ≥38°C not attributable to any other cause. Constitutional symptoms of CRS, such as myalgia, arthralgia, and malaise, are by themselves nonspecific; however, when coincident with fever in the expected timeframe, the etiology of CRS is more likely. In subjects who have CRS then receive antipyretics or anti-cytokine 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.

[c] CRS grade is determined by the more severe event: hypotension or hypoxia not attributable to any other cause. For example, a subject with temperature of 39.5°C, hypotension requiring one vasopressor and hypoxia requiring low flow nasal cannula is classified as having Grade 3 CRS.

[d] Low-flow nasal cannula is defined as oxygen delivered at ≤6 liters/minute. Low flow also includes blow-by oxygen delivery, sometimes used in pediatrics. High-flow nasal cannula is defined as oxygen delivered at >6 liters/minute.

ASTCT = American Society for Transplantation and Cellular Therapy; BiPAP = Bilevel positive airway pressure; CPAP = Continuous positive airway pressure; CRS = Cytokine release syndrome; NCI CTCAE, v5.0 = National Cancer Institute Common Terminology Criteria for Adverse Events, Version 5.0

Table 16. Recommended Guidelines for the Management of Cytokine Release Syndrome

Grade	Sign/Symptom	Management
Grade 1	Fever or organ toxicity	• Acetaminophen and hypothermia blanket for the treatment of fever • Ibuprofen can be used as second treatment option for fever, if not contraindicated • Assess for infection using blood and urine cultures, and chest radiography • Empiric broad-spectrum antibiotics and filgrastim if neutropenic • Maintenance IV fluids for hydration • Symptomatic management of constitutional symptoms and organ toxicities • Consider tocilizumab 8 mg/kg[a] IV or siltuximab 11 mg/kg IV for persistent (lasting >3 days) and refractory fever
Grade 2	Hypotension	• IV fluid bolus of 500-1000 mL of normal saline • Can give a second IV fluid bolus if systolic blood pressure remains <90 mmHg • Tocilizumab 8 mg/kg[a] IV or siltuximab 11 mg/kg IV for the treatment of hypotension that is refractory to fluid boluses; up to 3 additional doses of tocilizumab may be administered, and the interval between consecutive doses should be at least 8 hours • If hypotension persists after 2 fluid boluses and anti-IL-6 therapy, start vasopressors, consider transfer to ICU, obtain echocardiogram, and initiate other methods of hemodynamic monitoring • In subjects at high-risk[b] or if hypotension persists after 1-2 doses of anti-IL-6 therapy, dexamethasone can be used at 10 mg IV every 6 hours • Manage fever and constitutional symptoms as in Grade 1
	Hypoxia	• Supplemental oxygen • Tocilizumab or siltuximab ± corticosteroids and supportive care, as recommended for the management of hypotension
	Organ toxicity	• Symptomatic management of organ toxicities, as per standard guidelines • Tocilizumab or siltuximab ± corticosteroids and supportive care, as indicated for hypotension
Grade 3	Hypotension	• IV fluid boluses as needed, as recommended for the treatment of Grade 2 CRS • Tocilizumab or siltuximab as recommended for Grade 2 CRS, if not administered previously • Vasopressors as needed • Transfer to ICU, obtain echocardiogram, and perform hemodynamic monitoring as in the management of Grade 2 CRS • Dexamethasone 10 mg IV every 6 hours; if refractory, increase to 20 mg IV every 6 hours • Manage fever and constitutional symptoms as indicated for Grade 1 CRS
	Hypoxia	• Supplemental oxygen including high-flow oxygen delivery and non-invasive positive pressure ventilation • Tocilizumab or siltuximab plus corticosteroids and supportive care, as described above
		(Continued)

Table 16. Recommended Guidelines for the Management of Cytokine Release Syndrome

Grade	Sign/Symptom	Management
	(Continued)	
	Organ toxicity	• Symptomatic management of organ toxicities as per standard guidelines • Tocilizumab or siltuximab plus corticosteroids and supportive care, as described above
Grade 4	Hypotension	• IV fluids, anti-IL-6 therapy, vasopressors, and hemodynamic monitoring as defined for the management of Grade 3 CRS • Methylprednisolone 1 g/day IV • Manage fever and constitutional symptoms as in Grade 1 CRS
	Hypoxia	• Mechanical ventilation • Tocilizumab or siltuximab plus corticosteroids and supportive care, as described above
	Organ toxicity	• Symptomatic management of organ toxicities as per standard guidelines • Tocilizumab or siltuximab plus corticosteroids and supportive care, as described above

Source: Neelapu et al. 2018; Actemra® USPI.

NOTE: All doses indicated are for adults.

[a] Maximum amount of tocilizumab per dose is 800 mg.

[b] High-risk subjects include those with bulky disease and those with comorbidities.

CRS = Cytokine release syndrome; ICU = Intensive care unit; IL = Interleukin; IV = Intravenous; USPI = United States Prescribing Information

9.5.2.3 Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS)

ICANS must be monitored at the timepoints specified in the SoA (Section 1.3) using ASTCT consensus grading for ICANS (Lee et al. 2019; Table 17).

The Immune Effector Cell-Associated Encephalopathy (ICE) score is one component of ICANS grading. Determinants of the ICE score are:

- **Orientation:** Orientation to year, month, city, hospital: 1 point each for maximum of 4 points
- **Naming:** Name 3 objects (e.g., point to clock, pen, button): 1 point each for maximum of 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 10: 1 point

Management of clinical manifestations of ICANS, i.e., encephalopathy syndrome, status epilepticus, and raised intracranial pressure, should follow current recommendations for CAR T-cell therapies (Neelapu et al. 2018; Table 18, Table 19, and Table 20) and/or institutional practice.

Table 17. ASTCT ICANS Grading[a]

Neurotoxicity Domain	Grade 1	Grade 2	Grade 3	Grade 4
ICE score[b]	7–9	3–6	0–2	0 (Subject is unarousable and unable to perform ICE.)
Depressed level of consciousness[c]	Awakens spontaneously	Awakens to voice	Awakens only to tactile stimulus	Subject is unarousable or requires vigorous or repetitive tactile stimuli to arouse; stupor or coma
Seizure	NA	NA	Any clinical seizure Focal/generalized that resolves rapidly; or Non-convulsive seizures on EEG that resolve with intervention	Life-threatening prolonged seizure (>5 minutes); or repetitive clinical or electrical seizures without return to baseline in between
Motor findings[d]	NA	NA	NA	Deep focal motor weakness such as hemiparesis or paraparesis
Raised ICP/ cerebral edema	NA	NA	Focal/local edema on neuroimaging[e]	Diffuse cerebral edema on neuroimaging; decerebrate or decorticate posturing; or cranial nerve VI palsy; or papilledema; or Cushing's triad

Source: Lee et al. 2019.

[a] 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. For example, a subject with an ICE score of 3 who has a generalized seizure is classified as having Grade 3 ICANS.

[b] A subject with an ICE score of 0 may be classified as having Grade 3 ICANS if the subject is awake with global aphasia, but a subject with an ICE score of 0 may be classified as having Grade 4 ICANS if the subject is unarousable.

[c] Depressed level of consciousness should be attributable to no other cause (e.g., no sedating medication).

[d] Tremors and myoclonus associated with immune effector cell therapies may be graded according to NCI CTCAE, v5.0, but they do not influence ICANS grading.

[e] Intracranial hemorrhage with or without associated edema is not considered a neurotoxicity feature and is excluded from ICANS grading. It may be graded according to NCI CTCAE, v5.0.

ASTCT = American Society for Transplantation and Cellular Therapy; ICANS = Immune effector cell-associated neurotoxicity syndrome; ICE = Immune Effector Cell-Associated Encephalopathy (score); ICP = Intracranial pressure; EEG = Electroencephalogram; NA = Not applicable; NCI CTCAE, v5.0 = National Cancer Institute Common Terminology Criteria for Adverse Events, Version 5.0

Table 18. Recommended Guidelines for the Management of ICANS

Grade	Management
Grade 1	• Vigilant supportive care; aspiration precautions; IV hydration • Withhold oral intake of food, medicines, and fluids, and assess swallowing • Convert all oral medications and/or nutrition to IV if swallowing is impaired • Avoid medications that cause central nervous system depression • Low doses of lorazepam (0.25–0.5 mg IV every 8 hours) or haloperidol (0.5 mg IV every 6 hours) can be used, with careful monitoring, for agitated subjects • Neurology consultation • Fundoscopic exam to assess for papilledema • MRI of the brain with and without contrast; diagnostic lumbar puncture with measurement of opening pressure; MRI spine if the subject has focal peripheral neurological deficits; CT scan of the brain can be performed if MRI of the brain is not feasible • Daily 30-minute EEG until toxicity symptoms resolve; if no seizures are detected on EEG, continue levetiracetam 750 mg every 12 hours • If EEG shows non-convulsive status epilepticus, treat as per algorithm in Table 19 • Consider anti-IL-6 therapy with tocilizumab 8 mg/kg[a] IV or siltuximab 11 mg/kg IV if encephalopathy is associated with concurrent CRS
Grade 2	• Supportive care and neurological work-up as described for Grade 1 encephalopathy • Tocilizumab 8 mg/kg[a] IV or siltuximab 11 mg/kg IV if associated with concurrent CRS • Dexamethasone 10 mg IV every 6 hours or methylprednisolone 1 mg/kg IV every 12 hours if refractory to anti-IL-6 therapy, or for encephalopathy without concurrent CRS • Consider transferring subject to ICU if encephalopathy associated with Grade ≥2 CRS
Grade 3	• Supportive care and neurological work-up as indicated for Grade 1 encephalopathy • ICU transfer is recommended • Anti-IL-6 therapy if associated with concurrent CRS, as described for Grade 2 encephalopathy and if not administered previously • Corticosteroids as outlined for Grade 2 encephalopathy if symptoms worsen despite anti-IL-6 therapy or for encephalopathy without concurrent CRS; continue corticosteroids until improvement to Grade 1 encephalopathy and then taper • Stage 1 or 2 papilledema with CSF opening pressure <20 mmHg should be treated as per algorithm presented in Table 20 • Consider repeat neuroimaging (CT or MRI) every 2–3 days if subject has persistent Grade ≥3 encephalopathy

(Continued)

Table 18. Recommended Guidelines for the Management of ICANS

Grade	Management
(Continued)	
Grade 4	• Supportive care and neurological work-up as outlined for Grade 1 encephalopathy • ICU monitoring; consider mechanical ventilation for airway protection • Anti-IL-6 therapy and repeat neuroimaging as described for Grade 3 encephalopathy • High-dose corticosteroids continued until improvement to Grade 1 encephalopathy and then taper; for example, methylprednisolone IV 1 g/day for 3 days, followed by rapid taper at 250 mg every 12 hours for 2 days, 125 mg every 12 hours for 2 days, and 60 mg every 12 hours for 2 days • For convulsive status epilepticus, treat as per algorithm in Table 19 • Stage ≥3 papilledema, with a CSF opening pressure ≥20 mmHg or cerebral edema, should be treated as per algorithm in Table 20

Source: Neelapu et al. 2018.
[a] Maximum amount of tocilizumab per dose is 800 mg.

CRS = Cytokine release syndrome; CSF = Cerebrospinal fluid; CT = Computed tomography; EEG = Electroencephalogram; ICU = Intensive care unit; IL = Interleukin; IV = Intravenous; MRI = Magnetic resonance imaging

Table 19. Recommended Guidelines for the Management of Status Epilepticus

Status Epilepticus Type	Management
Non-convulsive status epilepticus	• Assess airway, breathing, and circulation; check blood glucose • Lorazepam[a] 0.5 mg IV, with additional 0.5 mg IV every 5 minutes, as needed, up to a total of 2 mg to control electrographical seizures • Levetiracetam 500 mg IV bolus, as well as maintenance doses • If seizures persist, transfer to ICU and treat with phenobarbital loading dose of 60 mg IV • Maintenance doses after resolution of non-convulsive status epilepticus are as follows: lorazepam 0.5 mg IV every 8 hours for 3 doses; levetiracetam 1000 mg IV every 12 hours; phenobarbital 30 mg IV every 12 hours
Convulsive status epilepticus	• Assess airway, breathing, and circulation; check blood glucose • Transfer to ICU • Lorazepam[a] 2 mg IV, with additional 2 mg IV to a total of 4 mg to control seizures • Levetiracetam 500 mg IV bolus, as well as maintenance doses • If seizures persist, add phenobarbital treatment at a loading dose of 15 mg/kg IV • Maintenance doses after resolution of convulsive status epilepticus are lorazepam 0.5 mg IV every 8 hours for 3 doses; levetiracetam 1000 mg IV every 12 hours; phenobarbital 1–3 mg/kg IV every 12 hours • Continuous electroencephalogram monitoring should be performed if seizures are refractory to treatment

Source: Neelapu et al. 2018.
NOTE: All doses indicated are for adults.
[a] Lorazepam is the recommended benzodiazepine because it is short-acting, compared with diazepam, and has been widely used in the management of seizures.

ICU = Intensive care unit; IV = Intravenous

Table 20. Recommended Guidelines for the Management of Raised Intracranial Pressure (ICP)

Stage	Management
Stage 1 or 2 papilledema[a] with CSF opening pressure of <20 mmHg without cerebral edema	• Acetazolamide 1000 mg IV, followed by 250–1000 mg IV every 12 hours (adjust dose based on renal function and acid-base balance, monitored 1–2 times daily)
Stage 3, 4, or 5 papilledema[a] with any sign of cerebral edema on imaging studies, or a CSF opening pressure of ≥20 mmHg	• Use high-dose corticosteroids with methylprednisolone IV 1 g/day, as recommended for Grade 4 encephalopathy syndrome (Table 18) • Elevate head end of the subject's bed to an angle of 30 degrees • Hyperventilation to achieve target partial pressure of arterial carbon dioxide ($PaCO_2$) of 28–30 mmHg, but maintained for no longer than 24 hours • 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/h while monitoring electrolytes every 4 hours, and withhold infusion if serum Na levels reach ≥155 mEq/L – For subjects with imminent herniation: initial 30 mL of 23.4% hypertonic saline; repeat after 15 minutes, if needed • If subject has ommaya reservoir, drain CSF to target opening pressure of <20 mmHg • Consider neurosurgery consultation and IV anesthetics for burst-suppression pattern on electroencephalography • Metabolic profiling every 6 hours and daily CT scan of head, with adjustments in usage of the aforementioned medications to prevent rebound cerebral edema, renal failure, electrolyte abnormalities, hypovolemia, and hypotension

Source: Neelapu et al. 2018.

NOTE: All doses indicated are for adults.

[a] Papilledema grading should be performed according to the modified Frisén scale.

CSF = Cerebrospinal fluid; CT = Computed tomography; ICP = Intracranial pressure; IV = Intravenous

9.5.2.4 Acute Graft-versus-Host Disease

Acute GvHD will be assessed according to criteria established by the CIBMTR Scale (Table 21). Management of GvHD should be done in accordance with local institutional practice.

Table 21. Acute GvHD Scoring System for Individual Organs: CIBMTR Scale

	Skin	Liver	Gut
Stage			
1	Rash on <25% of skin[a]	Bilirubin 2-3 mg/dL[b]	Diarrhea >500 mL/day[c] or persistent nausea[d]
2	Rash on 25%-50% of skin	Bilirubin 3-6 mg/dL	Diarrhea >1000 mL/day
3	Rash on >50% of skin	Bilirubin 6-15 mg/dL	Diarrhea >1500 mL/day
4	Generalized erythroderma with bullous formation	Bilirubin >15 mg/dL	Severe abdominal pain with or without ileus
Grade[e]			
I	Stage 1-2	None	None
II	Stage 3 or	Stage 1 or	Stage 1
III	—	Stage 2-3 or	Stages 2-4
IV[f]	Stage 4	Stage 4	—

Source: CIBMTR 2020.

[a] Use "Rule of Nines" or burn chart to determine extent of rash.

[b] Range given as total bilirubin. Downgrade one stage if an additional cause of elevated bilirubin has been documented.

[c] Volume of diarrhea applies to adults. For pediatric subjects, the volume of diarrhea should be based on body surface area. Downgrade one stage if an additional cause of diarrhea has been documented.

[d] Persistent nausea with histologic evidence of GvHD in the stomach or duodenum.

[e] Criteria for grading given as minimum degree of organ involvement required to confer that grade.

[f] Grade IV may also include lesser organ involvement with an extreme decrease in Performance Status.

CIBMTR = Center for International Blood and Marrow Transplant Research; GvHD = Graft-versus-host disease

9.6 Adverse Events and Serious Adverse Events

9.6.1 Safety Parameters and Definitions

Safety assessments will consist of monitoring and recording AEs, including SAEs, adverse events of special interest (AESIs), and DLTs, performing protocol-specified safety laboratory assessments, measuring protocol-specified vital signs, and conducting other protocol-specified tests that are deemed critical to the safety evaluation of the study.

9.6.1.1 Adverse Event

An AE is any untoward medical occurrence in a patient or clinical study subject temporally associated with the use of study treatment, whether or not considered related to the study treatment.

NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.

Events Meeting the Definition of Adverse Event

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (i.e., not related to progression of underlying disease). Refer to Section 9.6.6.1 for recording procedures.
- Exacerbation of a chronic or intermittent pre-existing condition, including either an increase in frequency and/or intensity of the condition. Refer to Section 9.6.6.2 for recording procedures.
- New conditions detected or diagnosed after study treatment administration even though it may have been present before the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study treatment(s) or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae. Refer to Section 9.6.12 for additional information on the treatment of overdose.

Events NOT Meeting the Definition of Adverse Event

- The disease/disorder being studied or disease progression as a singular event. Refer to Section 9.6.6.4 for recording procedures.
- Any significant abnormal laboratory findings or other abnormal safety assessments that are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the subject's condition.

- Medical or surgical procedure (e.g., endoscopy, appendectomy); the condition that leads to the procedure is the AE.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

9.6.1.2 Serious Adverse Event (Immediately Reportable to the Sponsor)

SAEs are required to be reported by the investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; refer to Section 9.6.7 for reporting instructions). Additional information will be reported to the Sponsor or its representatives as a follow-up report within 24 hours of receipt. If an event is not an AE per the definition above then it cannot be an SAE even if serious conditions are met (e.g., hospitalization for signs/symptoms of the disease under study, death due to progression of disease; see Section 9.6.6).

An SAE is defined as any untoward medical occurrence that, at any dose:

- Results in death
- Is life-threatening
  - The term "life-threatening" in the definition of "serious" refers to an event in which 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 in-patient hospitalization or prolongation of existing hospitalization. Refer to Section 9.6.6.3 for recording procedures.
- Results in a persistent or significant disability or incapacity
- Is a congenital anomaly/birth defect
- Other: Medically significant/important medical event (not covered by other serious criteria):
  - Medical or scientific judgment should be exercised in deciding whether SAE reporting is 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 medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.
  - Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias, or convulsions that do not result in in-patient hospitalization, or the development of drug dependency or drug abuse.

The terms "severe" and "serious" are not synonymous. Severity refers to the intensity of an AE (e.g., rated as mild, moderate, or severe, or according to NCI CTCAE; see Section 9.6.4); the event itself may be of relatively minor medical significance (such as severe headache without any further findings).

Severity and seriousness need to be independently assessed for each AE recorded on the eCRF.

9.6.1.3 Adverse Event of Special Interest

AESIs for this study are as follows:

- Any grade CRS
- Any grade infusion-related reaction during any FT576 treatment cycle period
- Any grade TLS (Grade ≥3 per NCI CTCAE, v5.0)
- Any grade neurotoxicity, i.e., ICANS, encephalopathy syndrome, status epilepticus, and raised intracranial pressure
- Any grade acute GvHD

AESIs that fulfill criteria of an SAE (refer to Section 9.6.1.2) are required to be reported by the investigator to the Sponsor immediately, within 24 hours after learning of the event, as an SAE. Non-serious AESIs should not be reported as an SAE, but should be reported to the Sponsor within 5 business days. Refer to Section 9.6.7 for complete reporting instructions.

9.6.1.4 Dose-Limiting Toxicity (Immediately Reportable to the Sponsor)

During the DLT assessment window, AEs identified as DLTs, as defined in Section 4.2.3, are required to be reported by the investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event). See Section 9.6.7 for reporting instructions.

9.6.2 Time Period and Frequency for Collecting AE and SAE Information

Investigators will seek information on AEs at each subject contact. All AEs will be collected and recorded in the subject's medical record and on the Adverse Event eCRF as follows:

- From signing of ICF until first dose of any study treatment: All SAEs and only AEs leading to subject/study discontinuation
- From first dose of any study treatment through subject/study discontinuation or initiation of subsequent anti-cancer therapies, whichever occurs first: All AEs and SAEs
- In long-term follow-up, from initiation of subsequent anti-cancer therapies through subject/study discontinuation: SAEs possibly or probably related to FT576 per investigator assessment

See Section 9.6.6 for instructions on recording AEs and SAEs, including abnormal laboratory values, pre-existing medical conditions, hospitalization, and disease progression, relapse, or disease-related death.

For each AE recorded on the Adverse Event eCRF, the investigator will make an assessment of seriousness (Section 9.6.1.2), severity (Section 9.6.4), and causality (Section 9.6.5).

SAEs are required to be reported by the investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event). See Section 9.6.7 for reporting instructions.

Investigators are not obligated to actively seek AE or SAE after conclusion of the study participation. However, if the investigator learns of any SAE, including a death, at any time after a subject has been discharged from the study and he/she considers the event to be reasonably related to the study drug or study participation, the investigator must promptly notify the Sponsor.

9.6.3 Method of Detecting AEs and SAEs

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the subject is the preferred method to inquire about AE occurrences.

9.6.4 Assessment of Severity

The investigator will make an assessment of the severity of each AE using his/her clinical expertise and grade each AE per the NCI CTCAE, v5.0. Table 22 will be used for assessing severity of AEs not listed in the NCI CTCAE, v5.0.

Table 22. Severity Grading Scale for Adverse Events Not Listed in NCI CTCAE

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:** 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:** life-threatening consequences; urgent intervention indicated
Grade 5	**Death:** Death-related adverse event

Exceptions to use of the NCI CTCAE, v5.0, will be for the following:

- Overall grading of CRS and neurotoxicity, in which ASTCT consensus grading will used for the AE reported as the syndrome (Table 15)
- Overall grading of acute GvHD, in which CIBMTR acute GvHD scoring system will be used for the AE reported as the syndrome (Table 21)

The individual signs and symptoms associated with CRS and neurotoxicity and the manifestations for acute GvHD will be collected on separate eCRFs and graded per NCI CTCAE, v5.0, or the Severity Grading Scale for Adverse Events Not Listed in NCI CTCAE (Table 22). In addition, the clinical stage for the target organs of the skin, liver, and gut for acute GvHD will be graded per the CIBMTR scoring system (Table 21).

9.6.5 Assessment of Causality

For all AEs, determination of the causal relationship to all study treatments by the investigator is required. Causality assessment includes assessment of temporal relationships, dechallenge/rechallenge information (if applicable), association (or lack of association) with underlying disease, presence (or absence) of a more likely cause, and physiological plausibility.

For reporting to regulatory agencies, "Not related" and "Unlikely related" will be considered "Not related;" "Possibly related" and "Probably related" will be considered "Related."

- **Not related** (both circumstances must be met)
  - Is due to underlying or concurrent illness, complications, concurrent treatments, or effects of concurrent drugs
  - Is not related to a study treatment, i.e., does not follow a reasonable temporal relationship to the administration of the study treatment or has a much more likely alternative etiology
- **Unlikely related** (either one or both circumstances are met)
  - Has little or no temporal relationship to the study treatment
  - A more likely alternative etiology exists
- **Possibly related** (both circumstances must be met)
  - Follows a reasonable temporal relationship to the administration of the study treatment
  - An alternative etiology is equally or less likely compared to the potential relationship to the study treatment
- **Probably related** (both circumstances must be met)
  - Follows a strong temporal relationship to the administration of study treatment, which may include but is not limited to the following:

    Reappearance of a similar reaction upon re-administration (positive rechallenge)

    Positive results in a drug sensitivity test, e.g., skin test

    Toxic level of the study treatment as evidenced by measurement of the study treatment concentration in the blood or other bodily fluid
  - Another etiology is unlikely or significantly less likely

The investigator should consult the FT576 Investigator's Brochure and/or current local prescribing information for marketed products in his/her assessment.

The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.

9.6.6 Recording of AEs and SAEs

When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (e.g., hospital progress notes, laboratory reports, and diagnostics reports) related to the event.

The investigator is responsible for ensuring all relevant information is recorded on the Adverse Event eCRF and SAE eCRF, as applicable.

The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE. Avoid the use of vague, ambiguous, or colloquial expressions.

To clearly define the timing of AE onset on the day of the first dose of conditioning and the first administration of FT576, the time of onset of AEs will be recorded.

Refer to Section 9.6.1 for definitions of AEs and SAEs.

9.6.6.1 Abnormal Laboratory Values

Laboratory abnormalities without clinical significance are not recorded as AEs or SAEs. However, laboratory abnormalities (e.g., clinical chemistry, hematology, and urinalysis) that require medical or surgical intervention or lead to IMP interruption, modification, or discontinuation must be recorded as an AE, as well as an SAE, if applicable. In addition, laboratory or other abnormal assessments (e.g., ECG, X-rays, vital signs) that are associated with signs and/or symptoms must be recorded as an AE or SAE if they meet the definition of an AE or SAE as described in this section and Section 9.6.1. If the laboratory abnormality is part of a syndrome, record the syndrome or diagnosis (e.g., anemia), not the laboratory result (i.e., decreased hemoglobin).

9.6.6.2 Pre-existing Medical Conditions

Pre-existing medical conditions that are present before the start of study treatment (i.e., conditioning) will not be recorded as AEs but will be documented as part of the subject's medical history. Pre-existing medical conditions that worsen in frequency, severity, duration, or character after initiation of any study treatment will be recorded as AEs. When recording such events on the Adverse Event eCRF, it is important to convey the concept that the pre-existing medical condition has changed by including applicable descriptors, e.g., "more frequent headaches," "worsening of," or "exacerbation of."

9.6.6.3 Hospitalization or Prolonged Hospitalization

Any AE that requires inpatient hospitalization or prolonged hospitalization should be documented and reported as an SAE (per the definition of SAE in Section 9.6.1.2), except as outlined below.

An event that leads to hospitalization under the following circumstances should not be recorded as an SAE:

- An emergency room or observational unit visit without hospital admission unless other serious criteria are met
- Hospitalization for a procedure scheduled or planned before signing of the ICF
- Admission to the hospital for social or situational reasons (e.g., no place to stay, live too far away to come for hospital visits)

9.6.6.4 Disease Progression, Relapse, or Disease-Related Death

The events of disease progression, relapse, or disease-related death as distinct descriptors will not be recorded as AEs but will be assessed as part of the efficacy endpoint of the study and will be recorded in an eCRF separate from the Adverse Event eCRF. New or worsening clinical symptoms and/or laboratory abnormalities attributed to disease progression or relapse will be reported as AEs.

9.6.7 Reporting of SAEs, AESIs, and DLTs

The investigator or designee will notify the Sponsor (see contact information in Table 23) and the IRB, if necessary, immediately and not later than 24 hours after knowledge of the SAE/serious AESI/DLT. The investigator will submit any updated event data to the Sponsor within 24 hours of it being available.

The following is a list of events that the investigator must report to the Sponsor within 24 hours after learning of the event, regardless of relationship to study drug:

- SAEs, including serious AESIs (defined in Section 9.6.1.2)
- DLTs during the DLT assessment window (defined in Section 9.6.1.4)
- Pregnancies (see Section 9.6.10 for details on reporting requirements)

The investigative site personnel will be responsible for submitting the initial and follow-up SAE report(s) to the Sponsor within 24 hours of awareness of the event or information. or notification of the event. The Sponsor will provide 24-hour telephone coverage for reporting of SAEs. The study site will be instructed to de-identify (i.e., black out with permanent marker/china marker) associated medical records of confidential information prior to sending to the Sponsor.

The primary mechanism for reporting an initial and follow-up SAE report to the Sponsor will be through the electronic data capture (EDC) system. The Sponsor safety group will be notified electronically via email. If the study site has a temporary interruption in its internet access or computer access, a paper back-up SAE form will be completed and submitted to the Sponsor safety

group. When the EDC system becomes available, the SAE information must be entered within 24 hours.

Collection of SAEs during the course of the study are described in Section 9.6.2. Any SAE ongoing when the subject completes the study or discontinues from the study will be followed by the investigator until the event has resolved, stabilized, or returned to baseline status.

Non-serious AESIs should be reported to the Sponsor within 5 business days. The primary mechanism for reporting a non-serious AESI to the Sponsor will be through communication with the Medical Monitor. The event should also be entered into the EDC system within 5 business days.

Table 23. Contact Information for Sponsor's Drug Safety Team

Name	Contact Information
FATE Drug Safety Team	Phone: 888-690-0025 Email: PV@fatetherapeutics.com

9.6.8 Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each subject at subsequent visits/contacts. The investigator must continue to follow the subject until satisfactory resolution stabilization, subsequent anti-cancer therapy is initiated, the subject is lost to follow-up, or the subject withdraws consent.

The investigator will submit any updated SAE data to the Sponsor within 24 hours of receipt of the information.

Procedures for follow-up of AEs and SAEs is as follows:

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the Sponsor to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other healthcare professionals.
- If a subject dies during participation in the study or during a recognized follow-up period, the investigator will provide a copy of any post-mortem findings, including but not limited to autopsy report and/or histopathology to the FATE Safety Inbox: PV@fatetherapeutics.com.
- New or updated information will be recorded in the originally completed eCRF.

All pregnancies reported during the study should be followed according to the instructions provided in Section 9.6.10.

9.6.9 Regulatory Reporting Requirements for SAEs

Prompt notification by the investigator to the Sponsor of an SAE is essential so that legal obligations and ethical responsibilities toward the safety of subjects and the safety of a study treatment under clinical investigation are met.

The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study treatment under clinical investigation. The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRBs/ECs, and investigators.

Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR), except those related to protocol-mandated procedures according to local regulatory requirements and Sponsor policy and forwarded to investigators as necessary.

An investigator who receives an investigator safety report describing an SAE or other specific safety information (e.g., summary or listing of SAEs) from the Sponsor will review and then file it along with the Investigator's Brochure and will notify the IRB/EC, if appropriate, according to local requirements.

9.6.10 Reporting Requirements for Pregnancies

If the female subject or the partner of a male subject participating in the study becomes pregnant during the study—which covers the period from signing the ICF at study enrollment, through post-treatment follow-up or part of LTFU and until ICF withdrawal by the subject, or being discontinued from the study by the Primary Investigator—the investigator should report the pregnancy to the designated safety group within 24 hours of being notified. For pregnant subjects, the safety group will then forward the "Exposure in Utero" form to the investigator for completion. For pregnant partners, where permissible and if the pregnant partner consents, the safety group will then forward the "Exposure in Utero" form to the investigator for completion. Where not permissible for the site to complete the "Exposure in Utero" form or interact with the subject, the study site should give the Sponsor's contact information to the male subject for transmission to the pregnant partner to contact the Sponsor. The Sponsor will then consent the pregnant partner and obtain information from her.

The pregnancy itself is not considered an AE, nor is an induced elective abortion to terminate a pregnancy without medical reasons.

Any premature termination of pregnancy (e.g., a spontaneous abortion, an induced therapeutic abortion due to complications or other medical reasons) must be reported within 24 hours as an SAE. The underlying medical reason for this procedure should be recorded as the AE term. A spontaneous abortion is always considered to be an SAE and will be reported as described in Section 9.6.1.2. Furthermore, any SAE occurring as an adverse pregnancy outcome post-study must be reported to Sponsor.

The subject or partner (if consented) should be followed by the investigator until completion of the pregnancy.

If the pregnancy ends for any reason before the anticipated date, the investigator should notify the Sponsor or designee. At the completion of the pregnancy, the investigator will document the outcome of the pregnancy.

9.6.11 Reporting Requirements for Special Situations

Accidental overdose, medication error, reports of AEs associated with product complaints, lactation exposure via breastfeeding, and/or accidental or occupational exposure (hereafter collectively referred to as "special situations") are defined as follows:

- Accidental overdose: accidental administration of a drug in a quantity that is above the maximum single or cumulative recommended dose as per protocol or in the product labeling (as it applies to the daily dose of the subject in question); see Section 9.6.1.2.
- Medication error: any unintentional error in the prescribing, dispensing, or administration of a medicinal product. Medication errors regardless of an associated AE or serious outcome should be reported. Medication errors that were avoided, but had they not been detected would have resulted in a medication error (i.e., near misses), should be reported.
  - Examples of medication errors include the dispensation of incorrect drug bottles, incorrect treatment, wrong protocol drug dispensed, expired drug dispensed, incorrect drug dispensed, wrong dose dispensed, or wrong drug taken.
- Product complaints: complaints arising from potential deviations in the manufacture, packaging, or distribution of the medicinal product. All AE/SAEs as a result of a product complaint must be reported.
- Accidental or occupational exposure: exposure to study treatment(s) as a result of preparation or administration of study treatment(s), i.e., needle stick or eye splash.
- Lactation exposure via breastfeeding: infant exposure via breastfeeding.

Special situations are not AEs but may be associated with AEs. All clinical sequelae in relation to these special situation reports will be reported as AEs or SAEs at the same time using the Adverse Event CRF/eCRF and/or the SAE report form. Details of the symptoms and signs, clinical management, and outcome will be reported, when available.

9.6.12 Treatment of Overdose

An MTD for FT576 has not been established. Therefore, there are no data or guidance for overdose as of the version date for this protocol. For specific information associated with overdose of the other study treatments used in this study, consult the product-specific current local prescribing information.

For the purposes of this protocol, overdose is defined as the subject receiving greater than 130% of a single or cumulative protocol-specified FT576 dose. Any instance of overdose must be reported in the appropriate section of the eCRF. Details of any signs or symptoms and their management should be recorded.

9.7 Safety Oversight

9.7.1 Safety Assessment for Dose Escalation

The Sponsor, in consultation with the study investigators, will determine whether dosing may proceed to the next cohort level in accordance with the dose-escalation rules and DLT criteria described in Section 4.2.

9.7.2 Overall Safety Oversight (Safety Assessment Committee)

Safety oversight will be under the direction of the SAC, which is a multidisciplinary committee whose objective is to provide input, assessment, and risk recommendations related to the following questions:

- Are there any newly identified or potential risks?
- Are there any "unanticipated problems" to be reported to IRBs or regulatory agencies?
- Has the benefit-risk profile of the product changed given any of the aforementioned newly identified or potential risks or "unanticipated problems?"
- Are there any items identified during SAC review that require additional Sponsor review and oversight?

The SAC is composed of cross-functional representatives from FATE. The SAC will also include an independent, unbiased member with medical expertise who is not directly involved with the study team. The SAC activities for this clinical study are outlined in the Sponsor's Standard Operating Procedure on Pharmacovigilance Oversight of Clinical Trials (Fate Therapeutics, on file).

10 STATISTICAL CONSIDERATIONS

10.1 Statistical Hypotheses

No formal hypotheses testing will be conducted.

10.2 Sample Size Determination

A total of approximately 18 subjects will be enrolled in the dose-escalation part of the study for Regimens A and B and 24 subjects for Regimens A1 and B1. A sample size of 15 subjects for each regimen's MTD dose expansion will provide an opportunity to identify early signs of promising clinical activity for subsequent formal Phase II expansion. Table 24 displays the probability of observing at least one response for the true response rate of 10%, 15%, and 20%.

Table 24. Probability of Observing at Least One Response

Dose Expansion Cohort Sample Size	True Response Rate	Probability of Observing at Least One Response
15 subjects	10%	79.4%
	15%	91.3%
	20%	96.5%

10.3 Populations for Analyses

The overall population will include all subjects enrolled into the study (i.e., all subjects giving informed consent), regardless of whether or not they receive FT576. The disposition, demographics, baseline, and disease characteristics will be based on overall population. The corresponding data set is defined as the full analysis set.

The safety population will include all subjects who receive any amount of FT576. The safety population will be used for all safety analyses, as well as determination of the RP2D in conjunction with efficacy analyses in both the dose-escalation and dose-expansion cohorts.

The DLT-evaluable population for the dose-escalation cohorts will include all subjects who complete the observation period for DLTs that allow assessment for DLTs as described in Section 4.2.3. Subjects who do not receive the entire assigned dose of FT576 and all anticipated infusions of mAb (Regimens B and B1 only), or who are not followed for the duration of the DLT assessment period as described in Section 4.2.3 for reasons other than experiencing a protocol-designated DLT, will not be DLT evaluable. The DLT-evaluable population will be used for all primary analyses to determine the MTD or MAD.

The efficacy-evaluable population will include all subjects who receive any amount of FT576 and who have completed a post-treatment tumor assessment or have discontinued due to documented clinical progression. The efficacy-evaluable population will be used for all efficacy analyses.

10.4 Statistical Analyses

10.4.1 General Approach

Detailed methodology for summaries and statistical analyses of the data collected will be documented in a separate Statistical Analysis Plan (SAP) and will be finalized before database lock. Any changes to the methods described in the final SAP will be described and justified as needed in the Clinical Study Report.

Statistical analyses will be primarily descriptive; no formal hypothesis testing will be conducted. Analyses will be performed using SAS® (Version 9.4, or higher).

In general, clinical data will be summarized by cohort, separately by each regimen, using descriptive statistics (n, mean, standard deviation, standard error, median, first quartile [Q1], third quartile [Q3], minimum, and maximum for continuous variables, and frequencies and percentages for categorical variables). When categorical data are presented, the percentages will be suppressed when the frequency count is zero. Non-zero percentages will be rounded to one decimal place, except for 100%, which will be displayed without any decimal places. For selected assessments, confidence intervals (CIs) will be displayed.

Additional summaries may be performed by clinical characteristics (e.g., age, prior therapies, tumor burden) and/or tumor characteristics (e.g., disease subtypes defined by genetic abnormalities, tumor microenvironment).

10.4.2 Efficacy Analyses

The secondary objective of the study is to evaluate anti-tumor activity of FT576 when administered as monotherapy and in combination with daratumumab based on the ORR, duration of response (DOR), PFS, relapse-free survival (RFS), and OS on study in all regimens.

Disease response will be assessed using IMWG response criteria (Appendix 1) and will be classified into the best of the following response categories: stringent complete response (sCR), CR, very good partial response (VGPR), partial response (PR), minimal response (MR), stable disease (SD), or progressive disease (PD). As part of the best overall response, the secondary endpoint of ORR will summarize the proportion of subjects achieving a response of PR or better by regimen and dose cohort. In addition, the exact 95% CI will be determined. For subjects with an sCR or CR response, the proportion of subjects with an MRD-negative response, with a sustained MRD-negative response for at least 1 year, and with an MRD-negative response with imaging based on the IMWG MRD criteria will be summarized descriptively along with the 95% CI by regimen and dose cohort as exploratory endpoints.

The time-to-event endpoints include DOR, PFS, RFS from CR, and OS as secondary endpoints and time to MRD-negative response and RFS from MRD-negative response as exploratory endpoints. Refer to A1-Table 1 in Appendix 1 for the criteria for relapse from CR and relapse from an MRD-negative response. Time-to-event endpoints will be summarized using Kaplan-Meier methods. Kaplan-Meier plots will be presented by treatment regimen. The number of

events and the number of censored subjects will be summarized, along with the quartiles, including the median time-to-event and their respective 95% CIs.

10.4.3 Safety Analyses

The primary endpoint, incidence of subjects with DLTs, will be summarized by dose cohort for the dose-escalation cohorts, and separately for each regimen using the DLT-evaluable population. The RP2D will be determined based on the overall safety and efficacy analyses among the dose-escalation and dose-expansion cohorts.

Safety analyses will be descriptive and presented for the dose-escalation and dose-expansion cohorts by regimen and dose cohort.

Safety and tolerability will be evaluated based on AEs, clinical laboratory assessments, vital signs, ECGs, and ECOG PS. AEs that occur at or after the start of any study treatment, as defined in Section 6.1, will be classified as TEAEs. For Regimens A and A1, study treatment starts on Day -5; for Regimens B and B1, study treatment starts on Day -11. As part of the primary objective, the incidence, severity, and relationship of TEAEs will be summarized by the Medical Dictionary for Regulatory Activities (MedDRA) System Organ Class and Preferred Term. Subject listings will also be provided for any deaths, SAEs, and AEs leading to discontinuation of the study. Signs and symptoms of CRS and neurotoxicity (ICANS) and the manifestations for acute GvHD will also be summarized.

The actual values and changes from baseline at each post-baseline timepoint in clinical laboratory tests, ECGs, and ECOG PS will be summarized by visit and timepoint (where applicable). Baseline will be defined as the last assessment prior to the start of protocol-designated study treatment (Section 6). Select clinical laboratory tests will be graded according to NCI CTCAE, v5.0, and the worst scheduled post-baseline NCI CTCAE grade for each clinical laboratory test will be summarized using a shift table to assess changes from baseline.

10.4.4 FT576 Pharmacokinetics

A secondary objective of the study is to characterize the PK of FT576 as assessed by the detection of FT576 in peripheral blood following FT576 administration as monotherapy and in combination with daratumumab. The summary will be done per PK population, which is defined as subjects in the safety population who provide at least 1 post- FT576 dosing evaluable sample.

10.4.5 Exploratory Analyses

Exploratory analyses will be descriptive and include assessments of potential predictive and prognostic biomarkers (Section 8.3.4.6) in peripheral blood or serum and bone marrow biopsies and/or aspirate samples, as well as changes in the tumor microenvironment, as appropriate. The association of PK and pharmacodynamics of FT576 as monotherapy and in combination with daratumumab with safety and anti-tumor activity will be assessed descriptively. The PK of daratumumab when administered in combination with FT576 will also be assessed descriptively.

The association between baseline clinical and tumor characteristics, safety, and anti-tumor activity of FT576, including MRD status, will also be explored.

10.4.6 Missing Data Handling

Due to the exploratory nature of this study and the lack of statistical testing, missing data will not be imputed.

10.4.7 Planned Interim Analysis

No formal interim analyses are planned. Safety will be reviewed in an ongoing fashion as described in Section 9.

11 APPENDICES

This section includes the following appendices:

- Appendix 1: International Myeloma Working Group Response Criteria in Multiple Myeloma, Including Criteria for Measurable Residual Disease
- Appendix 2: Daratumumab Interference Reflex Assay (DIRA) and Interpretation
- Appendix 3: FT576 Retreatment Guidelines
- Appendix 4: Long-Term Follow-Up Safety Assessment
- Appendix 5: Contraception Guidance
- Appendix 6: Eastern Cooperative Oncology Group Performance Status Scale
- Appendix 7: Regulatory and Ethical Considerations
- Appendix 8: Data Collection and Management
- Appendix 9: Study Documentation, Monitoring, and Administration
- Appendix 10: Abbreviations

Appendix 1. International Myeloma Working Group Response Criteria in Multiple Myeloma, Including Criteria for Measurable Residual Disease

The International Myeloma Working Group (IMWG) response criteria in multiple myeloma, including criteria for measurable residual disease (MRD; adapted from Kumar et al. 2016) are presented below.

1 METHOD OF ASSESSMENT

Assessments of response in multiple myeloma are primarily performed through analysis of peripheral blood and urine for the presence of monoclonal proteins and bone marrow for the presence of malignant plasma cells. A single blood draw can be used for both hematology and disease response assessment if collected within 1 week of bone marrow biopsy with aspirate collection. Radiographic methods should be used to document extramedullary disease (i.e., plasmacytoma).

Categories of response, based on standard IMWG response criteria, are summarized in A1-Table 1. IMWG MRD response criteria are provided for reference only. Bone marrow biopsy and aspirate should be performed as close to the peripheral blood collection that is indicative of stringent complete response (sCR) or complete response (CR) as is feasible (preferably within 1 week). Peripheral blood collection for tumor response assessment may substitute for hematology assessments as part of the follow-up visit in the SoAs (Table 3) if it occurs within 1 week of the scheduled follow-up visit.

MRD will be assessed at a central laboratory designated by the Sponsor.

For subjects with documented extramedullary disease, positron emission tomography (PET)-based imaging methods with ^{18}F-fluorodeoxyglucose (^{18}F-FDG) in combination with anatomic scans: PET-computed tomography (PET-CT) or, where available, PET-MRI scans, should be required. PET-CT scans are preferred; PET-MRI scans should only be performed when clinically appropriate (e.g., subject intolerance/allergy to contrast). Additional assessments may be done at the discretion of the investigator. The same radiographic method used to evaluate extramedullary disease at baseline should be used in subsequent assessments.

A1-Table 1 International Myeloma Working Group Response Criteria in Multiple Myeloma, Including Criteria for Measurable Residual Disease

Response Criteria[a]	
IMWG MRD Criteria (Requires a CR, as Defined Below)	
Sustained MRD-negative	MRD negativity in the marrow (NGF or NGS, or both) and by imaging as defined below, confirmed minimum of 1 year apart. Subsequent evaluations can be used to further specify the duration of negativity (e.g., MRD-negative at 5 years)[b]
Flow MRD-negative	Absence of phenotypically aberrant clonal plasma cells by NGF[c] on bone marrow aspirates using the EuroFlow standard operation procedure for MRD detection in multiple myeloma (or validated equivalent method) with a minimum sensitivity of 1 in 10^5 nucleated cells or higher
Sequencing MRD-negative	Absence of clonal plasma cells by NGS on bone marrow aspirate in which presence of a clone is defined as less than 2 identical sequencing reads obtained after DNA sequencing of bone marrow aspirates using the LymphoSIGHT platform (or validated equivalent method) with a minimum sensitivity of 1 in 10^5 nucleated cells[d] or higher
Imaging plus MRD-negative	MRD negativity as defined by NGF or NGS plus disappearance of every area of increased tracer uptake found at baseline or a preceding PET-CT or decrease to less mediastinal blood pool SUV or decrease to less than that of surrounding normal tissue[e]
Standard IMWG Response Criteria[f]	
sCR	CR as defined below plus normal FLC ratio[g] and absence of clonal cells in bone marrow biopsy by immunohistochemistry (κ/λ ratio ≤4:1 or ≥1:2 for κ and λ patients, respectively, after counting ≥100 plasma cells)[h]
CR	Negative immunofixation on the serum and urine and disappearance of any soft tissue plasmacytomas and <5% plasma cells in bone marrow aspirates
VGPR	Serum and urine M-protein detectable by immunofixation but not on electrophoresis or ≥90% reduction in serum M-protein plus urine M-protein level <100 mg per 24 hours
PR	≥50% reduction of serum M-protein plus reduction in 24-h urinary M-protein by ≥90% or to <200 mg per 24 h; If the serum and urine M-protein are unmeasurable, a ≥50% decrease in the difference between involved and uninvolved FLC levels is required in place of the M-protein criteria; If serum and urine M-protein are unmeasurable, and serum-free light assay is also unmeasurable, ≥50% reduction in plasma cells is required in place of M-protein, provided baseline bone marrow plasma-cell percentage was ≥30%. In addition to these criteria, if present at baseline, a ≥50% reduction in the size (SPD)[i] of soft tissue plasmacytomas is also required.
MR	≥25% but ≤49% reduction of serum M-protein and reduction in 24-h urine M-protein by 50-89%. In addition to the above-listed criteria, if present at baseline, a ≥50% reduction in the size (SPD)[i] of soft tissue plasmacytomas is also required.

(Continued)

A1-Table 1 International Myeloma Working Group Response Criteria in Multiple Myeloma, Including Criteria for Measurable Residual Disease

(Continued)	
SD	Not recommended for use as an indicator of response; stability of disease is best described by providing the time-to-progression estimates. Not meeting criteria for CR, VGPR, PR, MR, or PD.
PD[j,k]	Any one or more of the following criteria: • Increase of 25% from lowest confirmed response value in one or more of the following criteria: – Serum M-protein (absolute increase must be ≥0.5 g/dL); – Serum M-protein increase ≥1 g/dL, if the lowest M-component was ≥5 g/dL; – Urine M-protein (absolute increase must be ≥200 mg/24 h); • In patients without measurable serum and urine M-protein levels, the difference between involved and uninvolved FLC levels (absolute increase must be >10 mg/dL); • In patients without measurable serum and urine M-protein levels and without measurable involved FLC levels, bone marrow plasma-cell percentage irrespective of baseline status (absolute increase must be ≥10%); • Appearance of a new lesion(s), ≥50% increase from nadir in SPD[i] of >1 lesion, or ≥50% increase in the longest diameter of a previous lesion >1 cm in short axis; • ≥50% increase in circulating plasma cells (minimum of 200 cells per μL) if this is the only measure of disease
Clinical relapse	Clinical relapse requires one or more of the following criteria: • Direct indicators of increasing disease and/or end organ dysfunction (CRAB features - calcium elevation, renal failure, anemia, lytic bone lesions) related to the underlying clonal plasma-cell proliferative disorder. It is not used in calculation of time to progression or progression-free survival but is listed as something that can be reported optionally or for use in clinical practice; • Development of new soft tissue plasmacytomas or bone lesions (osteoporotic fractures do not constitute progression); • Definite increase in the size of existing plasmacytomas or bone lesions. A definite increase is defined as a 50% (and ≥1 cm) increase as measured serially by the SPD[i] of the measurable lesion; • Hypercalcemia (>11 mg/dL); • Decrease in hemoglobin of ≥2 g/dL not related to therapy or other non-myeloma-related conditions; • Rise in serum creatinine by 2 mg/dL or more from the start of the therapy and attributable to myeloma; • Hyperviscosity related to serum paraprotein

(Continued)

A1-Table 1 International Myeloma Working Group Response Criteria in Multiple Myeloma, Including Criteria for Measurable Residual Disease

(Continued)	
Relapse from CR (to be used only if the end point is disease-free survival)	Any one or more of the following criteria: • Reappearance of serum or urine M-protein by immunofixation or electrophoresis; • Development of ≥5% plasma cells in the bone marrow; • Appearance of any other sign of progression (i.e., new plasmacytoma, lytic bone lesion, or hypercalcemia see above)
Relapse from MRD-negative (to be used only if the end point is disease-free survival)	Any one or more of the following criteria: • Loss of MRD-negative state (evidence of clonal plasma cells on NGF or NGS, or positive imaging study for recurrence of myeloma); • Reappearance of serum or urine M-protein by immunofixation or electrophoresis; • Development of ≥5% clonal plasma cells in the bone marrow; • Appearance of any other sign of progression (i.e., new plasmacytoma, lytic bone lesion, or hypercalcemia)

Source: Adapted from Kumar et al. 2016.

NOTE: For MRD assessment, the first bone marrow aspirate should be sent to MRD (not for morphology) and this sample should be taken in one draw with a volume of minimally 2 mL (to obtain sufficient cells), but maximally 4-5 mL to avoid hemodilution.

[a] All response categories require 2 consecutive assessments made any time before starting any new therapy; for MRD there is no need for 2 consecutive assessments, but information on MRD after each treatment stage is recommended (e.g., after induction, high-dose therapy/ASCT, consolidation, maintenance). MRD tests should be initiated only at the time of suspected CR. All categories of response and MRD require no known evidence of progressive or new bone lesions if radiographic studies were performed. However, radiographic studies are not required to satisfy these response requirements except for the requirement of ^{18}F-FDG-PET if imaging MRD-negative status is reported.

[b] Sustained MRD negativity when reported should also annotate the method used (e.g., sustained flow MRD-negative, sustained sequencing MRD-negative).

[c] Bone marrow MFC should follow NGF guidelines (Paiva et al. 2012). The reference NGF method is an eight-color, two-tube approach, which has been extensively validated. The two-tube approach improves reliability, consistency, and sensitivity because of the acquisition of a greater number of cells. The eight-color technology is widely available globally, and the NGF method has already been adopted in many flow laboratories worldwide. The complete eight-color method is most efficient using a lyophilized mixture of antibodies, which reduces errors, time, and costs. 5 million cells should be assessed. The flow cytometry method employed should have a sensitivity of detection of at least 1 in 10^5 plasma cells.

[d] DNA sequencing assay on bone marrow aspirate should use a validated assay such as LymphoSIGHT® (Sequenta).

[e] Criteria used by Zamagni and colleagues (2015) and expert panel (IMPetUs; Italian Myeloma criteria for PET Use) (Nanni et al. 2016; Usmani et al. 2013). Baseline positive lesions were identified by presence of focal areas of increased uptake within bones, with or without any underlying lesion identified by CT and present on at least 2 consecutive slices. Alternatively, an SUV_{max} = 2.5 within osteolytic CT areas >1 cm in size or SUV_{max} = 1.5 within osteolytic CT areas ≤1 cm in size were considered positive. Imaging should be performed once MRD negativity is determined by MFC or NGS.

(Continued)

A1-Table 1 International Myeloma Working Group Response Criteria in Multiple Myeloma, Including Criteria for Measurable Residual Disease

(Continued)

[f] Derived from international uniform response criteria for multiple myeloma (Durie 2006). Minor response definition and clarifications derived from Rajkumar and colleagues (2011). When the only method to measure disease is by serum FLC levels: CR can be defined as a normal FLC ratio of 0.26 to 1.65 in addition to the CR criteria listed previously. VGPR in such patients requires a ≥90% decrease in the difference between involved and uninvolved FLC levels. All response categories require 2 consecutive assessments made at any time before the institution of any new therapy; all categories also require no known evidence of progressive or new bone lesions or extramedullary plasmacytomas if radiographic studies were performed. Radiographic studies are not required to satisfy these response requirements. Bone marrow assessments do not need to be confirmed. Each category, except for SD, will be considered unconfirmed until the confirmatory test is performed. The date of the initial test is considered as the date of response for evaluation of time dependent outcomes such as duration of response.

[g] All recommendations regarding clinical uses relating to serum FLC levels or FLC ratio are based on results obtained with the validated Freelite® test (Binding Site, Birmingham, UK).

[h] Presence/absence of clonal cells on immunohistochemistry is based upon the κ/λ/L ratio. An abnormal κ/λ ratio by immunohistochemistry requires a minimum of 100 plasma cells for analysis. An abnormal ratio reflecting presence of an abnormal clone is κ/λ of >4:1 or <1:2. Special attention should be given to the emergence of a different monoclonal protein following treatment, especially in the setting of patients having achieved a conventional CR, often related to oligoclonal reconstitution of the immune system. These bands typically disappear over time and in some studies have been associated with a better outcome. Also, appearance of monoclonal IgG κ in patients receiving monoclonal antibodies should be differentiated from the therapeutic antibody.

[i] Plasmacytoma measurements should be taken from the CT portion of the PET-CT, MRI scans, or dedicated CT scans where applicable. For patients with only skin involvement, skin lesions should be measured with a ruler. Measurement of tumor size will be determined by the SPD.

[j] Positive immunofixation alone in a patient previously classified as achieving a CR will not be considered progression. For purposes of calculating time to progression and progression-free survival, patients who have achieved a CR and are MRD-negative should be evaluated using criteria listed for PD. Criteria for relapse from a CR or relapse from MRD should be used only when calculating disease-free survival.

[k] In the case where a value is felt to be a spurious result per physician discretion (e.g., a possible laboratory error), that value will not be considered when determining the lowest value.

ASCT = Autologous stem-cell transplantation; CR = Complete response; CRAB features = Calcium elevation, renal failure, anemia, lytic bone lesions; CT = Computed tomography; ^{18}F-FDG-PET = ^{18}F-fluorodeoxyglucose-PET; FLC = Free light chain; IMWG = International Myeloma Working Group; M-protein = Myeloma protein; MFC = Multiparameter flow cytometry; MR = Minimal response; MRD = Measurable residual disease; MRI = Magnetic resonance imaging; NGF = Next-generation flow; NGS = Next-generation sequencing; PD = Progressive disease; PET-CT = Positron emission tomography-computed tomography; PR = Partial response; sCR = Stringent complete response; SD = Stable disease; SPD = Sum of the products of the maximal perpendicular diameters of measured lesions; SUV_{max} = Maximum standardized uptake value; VGPR = Very good partial response

Appendix 2. Daratumumab Interference Reflex Assay (DIRA) and Interpretation

Background: International Myeloma Working Group (IMWG) and clinical response assessment in multiple myeloma relies on SPEP and IFE. Because daratumumab is a monoclonal IgG kappa antibody, the SPEP and IFE can interfere with response assessment and be positive for daratumumab at the serum levels anticipated for patients who receive daratumumab in Regimens B and B1 for this protocol.

Implementation: To mitigate this interference, sites will employ the Daratumumab Interference Reflex Assay (DIRA) to distinguish a positive SPEP/IFE due to the presence of daratumumab versus the presence of the underlying (endogenous) M protein (McCudden et al. 2015). The DIRA test will be performed if a subject with IgG kappa multiple myeloma has an SPEP ≤0.2 g/dL on 2 or more consecutive readings. In addition, the DIRA test will be completed if a subject has an SPEP of 0, but persistently positive IFE for IgG kappa on 2 or more occasions.

Interpretation of Results:

The results available to the investigator will be reported as either "positive" or "negative."

Positive: indicates that the sample is still positive for underlying (endogenous) monoclonal myeloma protein. Therefore, this patient is not in a complete response (CR), because the CR response criteria requires a negative SPEP and serum IFE.

Negative: indicates that the sample is negative for underlying (endogenous) monoclonal myeloma protein. This subject may be in a CR if the other criteria for CR (including negative bone marrow biopsy with aspirate) are achieved.

Appendix 3. FT576 Retreatment Guidelines

1 CRITERIA FOR STUDY RETREATMENT

The FT576-101 study is designed initially to test the safety and clinical activity of a single treatment cycle, comprised of conditioning, FT576 and, for Regimens B and B1, daratumumab (Section 6.1). In cases where an individual subject is deriving ongoing clinical benefit from the administration of FT576, additional treatment cycle(s) (conditioning, FT576 and, for Regimens B and B1, daratumumab) may be considered. Additionally, subjects who achieve a confirmed response to initial FT576 administration and then develop disease progression or relapse may also be considered for retreatment.

Considerations for administration of additional treatment cycle(s) of FT576 **prior** to disease progression or relapse include the following:

- To determine whether a confirmed, objective response can be achieved or improved with an additional treatment cycle of FT576 (plus daratumumab, if applicable), which would provide evidence supportive of longer treatment duration. Notably, clinical experience with idecabtagene vicleulcel has demonstrated that deeper responses (i.e., complete response/stringent complete response [CR/sCR]) are more frequent at higher dose levels and deeper responses result in a longer duration of response (Munshi et al. 2021).
- To determine whether patients with clinical benefit and who in the investigator's opinion, would benefit from retreatment sooner and without a confirmed objective response (e.g., subjects with penta-refractory disease, high-risk cytogenetics etc.) are able to achieve a durable response.
- The ethical conduct of a clinical study of cancer treatment requires that subjects have the opportunity to continue study treatment, provided that it is safe and tolerable and demonstrates evidence of anti-tumor activity, and further, provided that subjects continue to comply with protocol requirements.

Considerations for administration of additional treatment cycle(s) of FT576 **after** initially achieving an objective response but has since experienced disease progression or relapse include the following:

- To determine whether a confirmed, objective response can be regained with FT576 (plus daratumumab, if applicable) retreatment, which would provide supportive evidence of longer, initial treatment duration.
- To characterize whether antigen escape is a major resistance mechanism to FT576.

Retreatment will be considered based on, but not limited to, the following:

- The subject did not experience a treatment-emergent adverse event that meets the protocol-defined criteria for dose-limiting toxicity (DLT; Section 4.2.3).
  - A subject who experiences TLS that otherwise fulfill protocol-defined DLT criteria may be eligible for retreatment with approval of the Medical Monitor.

- Resolution of adverse events considered by the investigator to be related to study medications (cyclophosphamide, fludarabine, FT576, and daratumumab) to Grade ≤1 or baseline grade, whichever is higher
- Evidence of ongoing clinical benefit including, but not limited to:
  - Absence of signs and symptoms, including worsening laboratory values, indicating unequivocal disease progression
  - No decline in ECOG PS
  - No clear evidence of PD during the first cycle, based on clinical assessment by the investigator and International Myeloma Working Group (IMWG) criteria

    Exceptions based on consultation between the investigator and the Medical Monitor may be made in cases where pseudoprogression due to the influx of immune cells into tumor sites are suspected, provided absence of signs and symptoms (including worsening of laboratory values) indicating unequivocal clinical disease progression, and an absence of tumor progression at critical anatomical sites where compromised organ function may increase the acute risk of severe and/or irreversible disability or death.
- All subjects being considered for retreatment, regardless of rationale, must undergo a repeat bone marrow biopsy with aspirate within 21 days prior to start of the retreatment cycle.

Additional specific criteria for subjects who demonstrate evidence of ongoing clinical benefit include the following:

- Subjects who have achieved and maintained an IMWG objective response of SD, MR, or PR for ≥6 months with no evidence of PD
- AE resolution to Grade 1 or baseline (exception with cytopenias noted below)
- Conditioning regimen of CY/FLU required unless patient has Grade 3 or higher cytopenias (white blood cells [WBCs], neutrophils, or platelets) 1 week prior with Medical Monitor approval
- Requires overall Medical Monitor approval

Additional specific criteria for subjects who progress or relapse after initial treatment include the following:

- Prior IMWG objective response of PR or better with ≥3 months' duration, with current evidence of confirmed PD or relapse
- Must meet initial study eligibility requirements, other than what is stated below for ongoing cytopenias
- No prior DLT
- No intervening anti-cancer therapy between initial FT576 and retreatment

- Repeat administration of CY/FLU is required unless patient has ongoing Grade 3 or higher cytopenias (WBC, neutrophils, platelets). Medical Monitor approval is required in cases where CY/FLU will be omitted.
- Requires overall Medical Monitor approval

Decisions regarding potential retreatment with additional treatment cycle(s) will be made only following consultation with and approval from the U.S. FDA on a case-by-case basis.

2 STUDY RETREATMENT DOSE AND SCHEDULE

If retreatment is approved by the FDA, then study treatment would be administered following generally the same schedule as Cycle 1 (refer to A3-Table 1 below). The nature of study treatment with respect to the dose/schedule of conditioning and/or dose of FT576 administered will be determined in consultation with and approval from the FDA.

A3-Table 1. Overview of Study Treatments

Conditioning Therapy
CY: 300 mg/m^2 IV infusion[a]
FLU: 30 mg/m^2 IV infusion[a]
FT576 infusion must be administered no earlier than the third calendar day after the last dose of conditioning. FT576 may be administered beyond the Day 1 window with Medical Monitor approval; however, depending on the length of the delay, repeat conditioning may be considered.
FT576
FT576: administered as an IV infusion via gravity. Planned FT576 dose levels in dose escalation are described in Section 4.2.2. Dosing is based on CAR expression, where ≥80% of administered FT576 viable cells express BCMA-CAR.
Daratumumab
Daratumumab: 16 mg/kg IV infusion starting on Day -11; OR **Daratumumab/hyaluronidase**: 1800 mg/30,000 units SC starting on Day -11: • QW for 8 doses (Days -11, -4, 4, 11, 18, and 25, and 2 doses QW [± 1 day] thereafter); then • Q2W (± 1 day) for 8 doses; then • Q4W (± 2 days) until disease progression or unacceptable toxicity

[a] CY/FLU conditioning prior to retreatment may be dose reduced or omitted altogether based on the judgment of the Principal Investigator in discussion with Sponsor's Medical Monitor and subject to FDA approval. Factors that may influence this decision include disease response at the end of Cycle 1, potential toxicities such as prolonged cytopenias experienced by the subject during the initial round of conditioning, and the kinetics of host immune reconstitution.

CAR = Chimeric antigen receptor; CY = Cyclophosphamide; FDA = U.S. Food and Drug Administration; FL = Fludarabine; IV = Intravenous; SC = Subcutaneous; QW = Once weekly; Q2W = Every 2 weeks; Q4W = Every 4 weeks; WBC = White blood cells

3 SCHEDULE OF ACTIVITIES FOR STUDY RETREATMENT

Subjects who are being considered for study retreatment will continue to be monitored weekly (pre-retreatment monitoring). If approval for study retreatment is given, the same SoAs described in Section 1.3 will be followed. All subjects being considered for retreatment, regardless of rationale, must undergo a repeat bone marrow biopsy with aspirate within 21 days prior to start of the retreatment cycle.

If approval for study medication retreatment is not given, subjects will proceed to Post-Treatment Follow-Up or post-relapse/progression follow-up, as appropriate (Table 3).

Appendix 4. Long-Term Follow-Up Safety Assessment

NOTE: The following information should be collected as part of the Long-Term Follow-Up clinical safety assessment (see Long-Term Follow-Up Schedule of Activities; Table 4).

Subject ID: _____

Date of follow-up: _____

Method of follow-up:

Chart review ☐
Contact via phone, email, or letter ☐

If follow-up by contact, was information obtained from the subject, healthcare provider, or legal guardian? _____

Updated subject, healthcare provider, or legal guardian contact information:

_____

SURVIVAL INFORMATION

Is subject alive?

Yes ☐
No ☐
Unknown ☐

If "No," please provide

Date and cause of death: _____

Was autopsy performed?

Yes ☐
No ☐

If autopsy performed, willingness to inquire about consent to access to autopsy report?

Yes ☐
No ☐

NEW CANCERS

Has the subject experienced any new cancers different from the original cancer under study?

Yes ☐
No ☐

If "Yes" please include

Type and Stage of the cancer: _____

Date of diagnosis: _____
Name and contact information of physician making the diagnosis:_____

NEW OR WORSENING MEDICAL CONDITIONS

Has the subject experienced any new or worsening neurologic disorders?

Yes ☐
No ☐

If "Yes" please include
Diagnosis: _____
Date of diagnosis: _____
Name and contact information of physician making the diagnosis:
_____

Has the subject experienced any new or worsening autoimmune or rheumatologic disorders?

Yes ☐
No ☐

If "Yes" please include
Diagnosis: _____
Date of diagnosis: _____
Name and contact information of physician making the diagnosis:
_____

Has the subject experienced any new or worsening hematologic disorders?

Yes ☐
No ☐

If "Yes" please include
Diagnosis: _____
Date of diagnosis: _____
Name and contact information of physician making the diagnosis:
_____

Has the subject experienced any unexpected illnesses?

Yes ☐
No ☐

If "Yes" please include
Diagnosis: _____
Date of diagnosis: _____
Name and contact information of physician making the diagnosis:
_____

Name of person completing the assessment: _____

Signature and Date: _____

Appendix 5. Contraception Guidance

Definition of Women of Childbearing Potential (WOCBP):

A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile (see below).

If fertility is unclear (e.g., amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before first dose of study treatment, additional evaluation should be considered.

Women in the following categories are <u>not</u> considered WOCBP:

1. Premenarchal

2. Premenopausal female with 1 of the following:
   - Documented hysterectomy
   - Documented bilateral salpingectomy
   - Documented bilateral oophorectomy

For individuals with permanent infertility due to an alternate medical cause other than the above, (e.g., mullerian agenesis, androgen insensitivity), investigator discretion should be applied to determining study entry.

NOTE: Documentation can come from the site personnel's: review of the subject's medical records, medical examination, or medical history interview.

3. Postmenopausal female
   - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
   - A high follicle-stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormone-replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, confirmation with more than one FSH measurement is required.
   - Females on HRT and whose menopausal status is in doubt will be required to use one of the non-estrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

Contraception Guidance:

Contraceptive use by women or men should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.

Female patients of childbearing potential, or male partners thereof, must be willing to practice a highly effective approved method of birth control with their partners (see list below); starting at

the time of informed consent and for the durations listed below after the completion of the study treatment regimen.

For the purpose of this guidance, methods that can achieve a failure rate of less than 1% per year when used consistently and correctly are considered as highly effective birth control methods. Such methods include:

a. Approved methods of birth control are as follows:
   - Total abstinence
   - Hormonal contraception (i.e., birth control pills, injection, implant, transdermal patch, vaginal ring)
   - Intrauterine device (IUD)
   - Tubal ligation
   - Vasectomy
   - Implantable or injectable contraceptives
   - Use of a male or female condom with spermicide
   - Cervical cap or contraceptive sponge with spermicide

b. Female subjects: Duration for use of highly effective method of contraceptive starts from the screening visit until at least 12 months after the final dose of cyclophosphamide (CY) and fludarabine (FLU), at least 4 months after the final dose of FT576, and at least 4 months after the final dose of daratumumab, whichever is latest.

c. Male subjects: Males with a female partner of childbearing potential or pregnant female partner must be sterile (biologically or surgically) or use a highly effective method of contraception (any combination of physical and chemical methods) from the screening visit until at least 14 months after the final dose of CY and FLU, at least 6 months after the final dose of FT576, and at least 6 months after the final dose of daratumumab, whichever is latest.

Refer to the current local prescribing information of the respective study treatment for additional details on contraception use for WOCBP and men (as applicable, depending on treatment regimen and schedule).

Reporting of pregnancy information is described in Section 9.6.10.

Appendix 6. Eastern Cooperative Oncology Group Performance Status Scale

A6-Table 1. ECOG PS Scale

Grade	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, e.g., light housework, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities; up and about more than 50% of waking hours
3	Capable of only limited selfcare; confined to bed or chair more than 50% of waking hours
4	Completely disabled; cannot carry on any selfcare; totally confined to bed or chair
5	Dead

ECOG PS = Eastern Cooperative Oncology Group Performance Status

Appendix 7. Regulatory and Ethical Considerations

1 ETHICAL AND SCIENTIFIC CONDUCT OF STUDY

This study will be conducted in accordance with the protocol, the ICH E6 guideline for GCP, and the principles of the Declaration of Helsinki, or the applicable laws and regulations of the country in which the research is conducted. Compliance with these standards provides public assurance that the rights, safety, and wellbeing of study subjects are protected and that the clinical study data are credible.

2 INSTITUTIONAL REVIEW BOARD/INDEPENDENT ETHICS COMMITTEE

Federal regulations and ICH require that approval be obtained from an Institutional Review Board (IRB)/Independent Ethics Committee (IEC) prior to participation of subjects in research studies.

The protocol, the ICFs, any information to be given to the subject, advertisements (if applicable), safety updates, annual progress reports, and relevant supporting information must be submitted to the IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.

No FT576 will be released to the site for dosing until written IRB/IEC authorization has been received by the Sponsor.

The Sponsor or its designee is responsible for obtaining record of approval of the IRB/IEC according to regional, national, and local regulations.

3 INFORMED CONSENT

The Sponsor's master ICF will be provided to each site. Changes made to the master ICF must be agreed to by the Sponsor or Sponsor's designee and the IRB/IEC prior to its use and must be in compliance with all ICH GCP, local regulatory requirements, and legal requirements.

Informed consent is a process that is initiated prior to an individual's agreeing to participate in the study and continues throughout that individual's study participation. The investigator must ensure that each study subject is fully informed about the nature and objectives of the study and possible risks associated with participation and must ensure that the study subject has been informed of his/her rights to privacy as per the Code of Federal Regulations (CFR), ICH, and any other applicable regional, national, and local laws and regulations. The rights and welfare of the subjects will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study. Subjects must be informed that participation is voluntary and that they may withdraw from the study at any time, without prejudice. Subjects will have the opportunity to carefully review the written consent form and ask questions prior to signing. The subjects should have the opportunity to discuss the study with their family or surrogates or think about it prior to agreeing to participate. The investigator will obtain a signed written informed consent from each subject before any study-specific activity is performed and should document in the source documentation that consent was obtained prior to enrollment in the study. The original signed copy of the ICF must be maintained by the investigator and is subject to

inspection by the Sponsor, their representatives, auditors, the IRB/IEC and/or regulatory agencies. A signed copy of the ICF will be given to the subject.

4 SUBJECT CONFIDENTIALITY

The confidentiality of records that could identify subjects must be protected, respecting privacy and confidentiality rules applicable to regulatory requirements and the subjects' signed ICF. Subject medical information obtained by this study is confidential and may be disclosed to third parties only as permitted by the ICF (or separate authorization for use and disclosure of personal health information) signed by the subject, unless permitted or required by law. This confidentiality extends to cover testing of biological samples and genetic tests, including those conducted for research purposes in a third-party laboratory, in addition to the clinical information relating to subjects. No information concerning the study or the data may be released to any unauthorized third party without prior written approval of the Sponsor.

The study subject's contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by local IRB and institutional regulations.

Study subject research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored within the study database. This will not include the subject's contact or identifying information. Rather, individual subjects and their research data will be identified by a unique study identification number. The study data entry and study management systems used by clinical sites and by the Sponsor and the Sponsor's designee(s) will be secured and password protected. At the end of the study, all study databases will be de-identified and archived by the Sponsor.

5 FINANCIAL DISCLOSURE

Investigators are required to provide financial disclosure information to the Sponsor to permit the Sponsor to fulfill its obligations under 21 CFR Part 54, and any other applicable regional, national, and local laws and regulations. In addition, investigators must commit to promptly updating this information if any relevant changes occur during the study and for a period of 1 year after the completion of the study as indicated in the CFR.

6 INSURANCE AND INDEMNITY

In accordance with the relevant national regulations, the Sponsor has obtained subject liability insurance for all subjects who have given their consent to the clinical study. This coverage is intended to cover injuries resulting from the proper performance of the clinical study.

Appendix 8. Data Collection and Management

1 DATA QUALITY ASSURANCE

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site Principal Investigator. The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

The investigator will prepare and maintain adequate and accurate source documents designed to record all observations and other pertinent data for each subject in accordance with the ICH E6 guideline for GCP and as required by the applicable regional, national, and local regulations.

Source documents are defined as original documents and certified copies of original documents, data, and records of the observations and activities of a clinical study necessary for the reconstruction and evaluation of the study. Source documents may include, but are not limited to, signed ICFs, study progress notes, email correspondence, radiographic scans, subject quality-of-life surveys, subject diaries (if applicable), computer printouts, laboratory data, electronically collected data, and recorded data from automated instruments.

Data reported in the electronic Case Report Form (eCRF) derived from source documents should be consistent with the source documents or the discrepancies should be explained and captured in a progress note and maintained in the subject's official electronic study record. Every data point in the eCRF should have a corresponding data point in the source documents, unless otherwise directed in a study-specific plan.

Clinical data (including adverse events [AEs], concomitant medications, and expected adverse reactions data) and clinical laboratory data will be entered into a 21 Code of Federal Regulations (CFR) Part 11-compliant data capture system provided by the Sponsor. The data system includes password protection and internal quality checks, such as automatic checks, to identify data that appear inconsistent, incomplete, or inaccurate. Clinical data will be entered directly from the source.

Data will be recorded at the site on eCRFs and reviewed by the clinical research associate (CRA) during monitoring visits. The CRA(s) will verify data recorded in the electronic data capture (EDC) system with source documents. All corrections or changes made to any study data must be appropriately tracked in an audit trail in the EDC system. An eCRF will be considered complete when all missing, incorrect, and/or inconsistent data has been accounted for and it has been reviewed and signed by the investigator.

1.1 Computer Systems

Data will be processed using a validated computer system conforming to regulatory requirements as per 21 CFR Part 11.

1.2 Data Entry

The investigator will ensure that eCRFs are accurate, legible, and complete in accordance with the eCRF Completion Guidelines. All site personnel must log into the system using their secure

username and password to enter, review, or correct study data. These procedures must comply with 21 CFR Part 11 and other appropriate international regulations. All passwords will be strictly confidential and may not be shared.

1.3 Medical Information Coding

For medical information, the following dictionaries will be used for coding and the software version documented in the Clinical Study Report:

- Medical Dictionary for Regulatory Activities (MedDRA) for medical history and AEs
- World Health Organization Drug Dictionary for prior and concomitant medications

1.4 Data Validation

Validation checks programmed within the EDC system, as well as supplemental validation performed via review of the downloaded data, will be applied to the data to ensure accurate, consistent, and reliable data. Data identified as erroneous, or data that are missing, will be referred to the investigative site for resolution through data queries.

The eCRFs must be reviewed and electronically signed by the investigator.

2 RETENTION OF RECORDS

To enable evaluations and/or audits from regulatory authorities or the Sponsor, the investigator is responsible for maintaining records and documents pertaining to the conduct of the study and the distribution of the investigational drug, including the identity of all participating subjects (sufficient information to link records, e.g., eCRFs and hospital records), all original signed ICFs, copies of all eCRFs, SAE forms, source documents, detailed records of treatment disposition, and all other supporting documentation. The records must be retained by the investigator according to the ICH GCP or for the length of time required by relevant national or local health authorities, whichever is longest. The investigator must obtain written permission from the Sponsor before disposing of any records, even if retention requirements have been met. Prior to transfer or destruction of these records, the Sponsor must be notified in writing and be given the opportunity to further store such records.

If the investigator relocates, retires, or for any reason withdraws from the study, the Sponsor should be prospectively notified. The study records must be transferred to an acceptable designee, such as another investigator, another institution, or to the Sponsor.

Appendix 9. Study Documentation, Monitoring, and Administration

1 STUDY DOCUMENTATION

The investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented, including, but not limited to, the protocol, protocol amendments, Informed Consent Forms (ICFs), source documents, documentation of Institutional Review Board (IRB)/Independent Ethics Committee (IEC) approval, and other Sponsor-critical correspondence pertaining to the study. Refer to Appendix 8 for details on source documents and record retention.

2 PROTOCOL DEVIATIONS

A protocol deviation is generally an unplanned nonconformity with the protocol. The investigator should document and explain any protocol deviations, including those that are discovered during monitoring visits. Protocol deviations must be reviewed and approved by the IRB and the Sponsor prior to implementation, unless the change is necessary to eliminate apparent immediate hazards to the human subjects (21 Code of Federal Regulations [CFR] 312.66) or to protect the life or physical wellbeing of the subject (21 CFR 812.35(a)(2)), and generally communicated to the U.S. FDA and any other applicable health authorities. Situations in which the investigator failed to perform tests or examinations as required by the protocol or failures on the part of study subjects to complete scheduled visits as required by the protocol would be considered protocol deviations (per FDA Compliance Program Guidance Manual, Program 7348.811, Chapter 48 – Bioresearch Monitoring, Clinical Investigators and Sponsor-Investigators, 08 December 2008). The Sponsor will review all protocol deviations and assess whether any represent a serious breach of GCP guidelines and require reporting to health authorities.

One exception to the reporting of protocol deviations is non-compliance with timeframes that are subject to clinical judgment or do not impact subject safety or data integrity. Timeframes indicated throughout this protocol are intended to be targeted timeframes unless “must” or a time window is specified.

3 STUDY MONITORING

Appropriate monitoring procedures will be performed before, during, and after the completion of the study. The designated monitor will aid the investigator and, at the same time, the Sponsor in the maintenance of complete, legible, well organized, and easily retrievable data. Before the enrollment of any subject in this study, the Sponsor or its designee will review with the investigator and site personnel the following documents/processes: protocol, Investigator’s Brochure, electronic Case Report Forms (eCRFs), and procedures for their completion; informed consent process; procedure for receiving, accounting for, disposing of, and administering study treatment(s); and the procedure for reporting serious adverse events.

The investigator will permit the Sponsor or its designee to monitor the study as frequently as deemed necessary to determine that data recording and protocol adherence are satisfactory. During the monitoring visits, information recorded on the eCRFs will be verified against source documents and requests for clarification or correction may be made. After the eCRF data is entered by the site, the CRA will review the data for safety information, completeness, accuracy, and

logical consistency. Computer programs that identify data inconsistencies may be used to help monitor the clinical study. If necessary, requests for clarification or correction will be sent to investigators. The investigator and his/her staff will be expected to cooperate with the monitor and provide any missing information, whenever possible.

All monitoring activities will be reported and archived. In addition, monitoring visits will be documented at the investigational site by signature and date on the study-specific monitoring log.

4 AUDITS AND INSPECTIONS

During and/or after completion of the study, quality assurance auditors acting on behalf of Sponsor or inspectors acting on behalf of a regulatory authority or IRB/IEC may wish to perform on-site audits/inspections (ICH E6 guideline for GCP). The purpose of an audit/inspection, which is independent from routine monitoring, is to evaluate study conduct and compliance with the protocol, Standard Operating Procedures, ICH GCP, and applicable regional, national, and local regulations.

The investigators accept that by endorsing the protocol signature page that the Sponsor, IRB/IEC, or regulatory authorities may conduct an audit/inspection to verify compliance of the study with ICH GCP. Representatives of the Sponsor, IRB/IEC, or regulatory authority should be permitted direct access to source data and documents.

If a regulatory authority or IRB/IEC notifies the investigator of an inspection, the investigator agrees to immediately notify the Sponsor and provide the reason, if any, for the inspection. The investigator agrees to promptly provide the Sponsor with copies of any feedback (e.g., FDA Form 483, Establishment Inspection Report) issued at the end of the inspection.

5 DISCLOSURE OF DATA

Data generated by this study must be available for inspection by the FDA, the Sponsor or its designee, applicable foreign health authorities, and the IRB/IEC, as appropriate. The clinical study site must permit access to such records.

Subjects or their legal representatives may request their medical information be given to their personal physician or other appropriate medical personnel responsible for their welfare.

Subject medical information obtained during the study is confidential and disclosure to third parties other than those noted above is prohibited.

6 PUBLICATION POLICY

Following completion of the study, the data may be considered for publication in a scientific journal or for reporting at a scientific meeting in accordance with the Clinical Study Agreement. Each investigator is obligated to keep data pertaining to the study confidential. The investigator must consult with the Sponsor before any study data are submitted for publication. The Sponsor reserves the right to deny publication rights until mutual agreement on the content, format, interpretation of data in the manuscript, and journal selected for publication are achieved.

7 PROTOCOL AMENDMENTS

Per 21 CFR §312.30, the Sponsor shall submit a protocol amendment describing any change in a Phase I protocol that significantly affects the safety of subjects or any change in a Phase II or III protocol that significantly affects the safety of subjects, the scope of the investigation, or the scientific quality of the study. Examples of changes requiring an amendment include:

- Any increase in drug dosage or duration of exposure of individual subjects to the drug beyond that in the current protocol, or any significant increase in the number of subjects under study
- Any significant change in the design of a protocol (such as the addition or dropping of a control group)
- The addition of a new test or procedure that is intended to improve monitoring for, or reduce the risk of, a side effect or adverse event; or the dropping of a test intended to monitor safety

Any amendments to the study protocol will be communicated to the investigators by the Sponsor or its designee. A protocol amendment may be implemented after it has been approved by the IRB/IEC, unless immediate implementation of the change is necessary for subject safety.

8 STUDY ADMINISTRATIVE INFORMATION

This study will be sponsored and managed by FATE. The Sponsor will provide clinical operations management, data management, and medical monitoring.

A9-Table 1. Study Administrative Contact Information

Contact	**Address**	**Telephone and Facsimile**
Sponsor	Fate Therapeutics, Inc. 12278 Scripps Summit Drive San Diego, CA 92131 USA	Telephone: 858-875-1800 Facsimile: 858-875-1843

Appendix 10. Abbreviations

Abbreviation	Definition
^{18}F-FDG	^{18}F-fluorodeoxyglucose
ABW	Actual body weight
ADC	Antibody drug conjugate
ADCC	Antibody-dependent cellular cytotoxicity
AE	Adverse event
AESI	Adverse event of special interest
AML	Acute myelogenous leukemia
ASTCT	American Society for Transplantation and Cellular Therapy
BCMA	B-cell maturation antigen
BMI	Body mass index
CAR	Chimeric antigen receptor
CFR	Code of Federal Regulations
CI	Confidence interval
CIBMTR	Center for International Blood and Marrow Transplant Research
CNS	Central nervous system
CR	Complete response
CRA	Contract research associate
CRP	C-reactive protein
CRS	Cytokine release syndrome
CT	Computed tomography
CY	Cyclophosphamide
D	Day
DIRA	Daratumumab Interference Reflex Assay
DL	Dose level
DLT	Dose-limiting toxicity
DMSO	Dimethyl sulfoxide
DOR	Duration of response
ECG	Electrocardiogram
ECHO	Echocardiogram
eCRF	Electronic Case Report Form

(Continued)

Abbreviation	Definition
(Continued)	
ECOG PS	Eastern Cooperative Oncology Group Performance Status
EDC	Electronic data capture
FDA	U.S. Food and Drug Administration
FLU	Fludarabine
FSH	Follicle-stimulating hormone
GvHD	Graft-versus-host disease
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HRT	Hormone replacement therapy
HSCT	Hematopoietic stem-cell transplantation
IBW	Ideal body weight
ICANS	Immune Effector Cell-Associated Neurotoxicity Syndrome
ICE	Immune Effector Cell-Associated Encephalopathy (score)
ICF	Informed Consent Form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IFE	Immunofixation electrophoresis
IgA, IgD, IgG, IgM	Immunoglobulin A, D, G, M
IMiD	Immunomodulatory drugs
IMP	Investigational medicinal product
IMWG	International Myeloma Working Group
IRB	Institutional Review Board
ISS	International Staging System
IUD	Intrauterine device
KIR	Killer-cell immunoglobulin-like receptor
LVEF	Left ventricular ejection fraction
mAb	Monoclonal antibody
MAD	Maximum assessed dose
MCB	Master cell bank
MedDRA	Medical Dictionary for Regulatory Activities

(Continued)

Abbreviation	Definition
(Continued)	
MM	Multiple myeloma
MRD	Measurable residual disease
MRI	Magnetic resonance imaging
MTD	Maximum tolerated dose
MUGA	Multigated acquisition (scan)
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NGS	Next-generation sequencing
NK	Natural killer
ORR	Objective response rate
OS	Overall survival
PCR	Polymerase chain reaction
PD	Progressive disease
PD-1	Programmed cell death receptor-1
PD-L1	programmed cell death ligand-1
PET	Positron emission tomography
PFS	Progression-free survival
PK	Pharmacokinetics
PO	Orally
PR	Partial response
QW	Weekly
Q2W	Every 2 weeks
Q4W	Every 4 weeks
r/r	Relapsed or refractory
RCL	Replication-competent lentivirus
RFS	Relapse-free survival
RP2D	Recommended Phase II dose
SAC	Safety Assessment Committee
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SC	Subcutaneous

(Continued)

Abbreviation	Definition
(Continued)	
sCR	Stringent complete response
SD	Stable disease
SoA	Schedule of Activities
sBCMA	Serum B-cell maturation antigen
sFLC	Serum free light chain
SPEP	Serum protein electrophoresis
SUSAR	Suspected unexpected serious adverse reaction
TEAE	Treatment-emergent adverse event
TLS	Tumor lysis syndrome
ULN	Upper limit normal
USPI	United States Prescribing Information
VGPR	Very good partial response
WBC	White blood cell
WOCBP	Woman of childbearing potential

Appendix 11. Protocol Amendment History

Protocol FT576-101, Version 3.0

Overall Rationale: Protocol FT576-101 has been amended to clarify how subjects may proceed from study treatment cycle(s) to post-treatment follow-up and to allow for the retreatment of subjects after entering the post-treatment follow-up period. In addition, revisions have been made to the study schedules and study enrollment numbers as described below.

Additional minor modifications have been made to improve clarity and consistency.

A description of the change to the protocol, along with a rationale for the change, follows.

Section Number	Description of Change and Rationale
Protocol Cover Sheet, 1.1, 11 (Appendix 9)	The Sponsor address has been updated.
Protocol Cover Sheet	The Sponsor signatory for the protocol has been changed from Yu-Waye Chu, MD, Senior Vice President, Clinical Development to John Byon, MD, PhD, Vice President, Clinical Development.
1.1	The synopsis has been revised to reflect the changes to the protocol.
1.2	The study schemas have been revised to reflect the changes to the screening period timing and the removal of the Day -11 visit for Regimens A and A1. Additional minor clarifications have also been made.
1.3	Schedules of Activities **Tables 1 and 2:** • The Day -11 visit has been removed for subjects in the monotherapy arms of the study (Regimens A and A1) because these subjects are not receiving daratumumab, which begins on Day -11 in Regimens B and B1 only. The assessments that were part of the Day -11 visit for Regimens A and A1 will now be performed on Day -5. As a result of this change, the screening period timing has been revised accordingly and additional minor clarifications have been made.

(Continued)

Section Number	Description of Change and Rationale
	(Continued)
1.3	**Table 1:** • An optional tumor biopsy for exploratory and correlative analyses has been added at screening, between Days 2 and 8, and at Day 29 for subjects with extramedullary disease. Footnote "y" has also been added, including a clarification that biopsies may also be collected after progression/relapse after treatment or retreatment. • Footnote "a" has been added to allow for standard-of-care results from tests or examinations performed prior to obtaining informed consent to be used instead of repeating such tests during screening. • Footnote "c" has been added to clarify the timing of Day 1 dosing in relation to conditioning. • Footnote "f" has been revised to allow for retreatment of subjects who have entered post-treatment follow-up without the need to remain in pre-retreatment monitoring while awaiting the decision to retreat. • Footnote "k" has been revised to provide additional details for the physical examination assessment. **Table 2:** • Visit windows have been revised to align with those in Table 1. **Table 3:** • Clarifications have been made for the timing of exploratory samples. • A bone marrow aspirate sample assessment has been added for measurable residual disease (MRD) monitoring; footnote "g" has also been added to further explain this assessment. • Clarifications have been made for the timing of disease response assessments. • An optional tumor biopsy for exploratory and correlative analyses has been added for subjects with extramedullary disease. Footnote "l" has also been added, including a clarification that biopsies may be collected after progression/relapse after treatment or retreatment. • Skeletal disease assessment, at suspected skeletal disease progression, has been added as part of the disease response assessment.
1.3, 8.3.1, 11 (Appendix 3)	A clarification has been made throughout the protocol that all subjects being considered for retreatment, regardless of rationale, must undergo a repeat bone marrow biopsy with aspirate within 21 days prior to start of the retreatment cycle.
2.1	Results from the KarMMa study have been updated according to the recent Munshi et al. 2021 publication.
4.1	The number of subjects and study sites has been increased from 168 to 204 subjects and from 8-12 to 14-18 sites, respectively, to account for current enrollment projections. In addition, the enrollment period timing has been updated. Figure 4 has been updated to clarify the gating of the regimens.
4.2.2	A clarification has been made to the dose-escalation rules such that the "minimum interval between enrollment" has been revised to "minimum interval between dosing of FT576."

(Continued)

Section Number	Description of Change and Rationale
(Continued)	
4.3	Details have been added to the language describing dose-expansion cohorts.
4.4	Language has been added to the post-treatment follow-up section of the protocol to allow for retreatment of subjects who have entered post-treatment follow-up without the need to remain in pre-retreatment monitoring while awaiting the decision to retreat.
4.6.6	Clarifications have been made to the rationale for exploratory analyses based on current exploratory assessments planned for the study.
5.1	Contraception details for inclusion criterion #5 have been moved to Appendix 5.
5.2	Exclusion criterion #6 has been revised to clarify that active central nervous system (CNS) involvement includes leptomeningeal disease. As a result, prior criterion #17 has been removed. Exclusion criterion for prior allogeneic hematopoietic stem-cell transplantation (HSCT) or CAR-T/CAR-NK therapy (prior criterion #12) has been moved and is now included as part of criterion #18 for washout periods from prior therapies. Exclusion criterion #17 has been added to exclude non-multiple myeloma cancers, with exceptions, within the past 2 years prior to enrollment. Clarifications have been made to washout periods from prior therapies (criterion #18).
6.1.1, 9.5.2.1	The Storage, Handling, and Administration Guidance for FT576 has been renamed the Pharmacy Manual for FT576 (Table 13).
7.1	Language has been added to specify collection of information on survival, subsequent anti-cancer therapies, and long-term follow-up safety monitoring.
7.6	A section for withdrawal of consent has been added to provide clarification on collection of survival information if a subject withdraws from the study.
8	Language has been added to allow for standard-of-care results from tests or examinations performed prior to obtaining informed consent to be used instead of repeating such tests during screening.
8.2.1	Additional details have been provided for the physical examination assessment.
8.2.6	Details have been added to the section on medical history and demographics to provide sites clearer direction on what is expected to be obtained for this assessment.
8.3.1	Table 11 has been updated to align with the changes made to the SoA. Sample timing for FU6 and FU8 have been added for subjects who are in CR to allow for monitoring of MRD status.
8.3.4.5	A section describing the optional tumor biopsy, to allow for additional analysis of the tumor microenvironment, has been added.
9.1.5, 9.1.7, 9.5.2.3	Language has been clarified regarding the definition and management of cytokine release syndrome and Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS).

(Continued)

Section Number	Description of Change and Rationale
(Continued)	
9.5.1	Clarification has been made to the section on dose and schedule modification such that it now only applies to TEAEs considered related or possibly related to FT576. Also, additional clarity has been added regarding the severity of AEs leading to delay of FT576 administration.
9.6.1.3, 9.6.7	Timing for the reporting of non-serious adverse event of special interest (AESIs) has been changed from "within 24 hours after learning of the event" to "within 5 business days." AESIs that fulfill the criteria of a serious adverse event (SAE) are still required to be reported by the investigator to the Sponsor immediately, within 24 hours after learning of the event, as an SAE. Applicable reporting instructions have been updated accordingly. Dose-limiting toxicity (DLT) has been removed from the list of AESIs for this study.
9.6.2	Clarifications have been made for the time period and frequency for collection AE and SAE information.
11	Appendix 3, FT576 Retreatment Guidelines: A3-Table 1, footnote "a" has been modified to address CY/FLU conditioning prior to retreatment. Appendix 5, Contraception Guidance: Updates have been made to meet the current guidance for contraception language in clinical trials.

Protocol FT576-101, Version 2.0

Overall Rationale: Protocol FT576-101 has been amended in agreement with the U.S. Food and Drug Administration (FDA). Additional minor modifications have been made to improve clarity and consistency.

A description of the change to the protocol, along with a rationale for the change, follows.

Section Number	Description of Change and Rationale
4.2.2	The staggering period in the single-dose regimen has been revised to include a minimum interval of 28 days between the second and third subject in Dose Level 1. In addition, it has been clarified that in the absence of dose-limiting toxicities, the minimum interval between enrollment of the second and third subject in subsequent dose-escalation cohorts may be reduced to 14 days.
9.6.7	The contact email for the FATE Safety Team has been updated (Table 23).

12 REFERENCES

Actemra® (tocilizumab) injection, for intravenous or subcutaneous use [Prescribing Information]. San Francisco, CA. Genentech, Inc.; 2021

American Association of Blood Banks (AABB). Circular of Information for the Use of Human Blood and Blood Components. 2016. Accessed 8 July 2020. Available at: https://www.aabb.org/tm/coi/Documents/coi1017.pdf

Arai S, Meagher R, Swearingen M, et al. Infusion of the allogeneic cell line NK-92 in patients with advanced renal cell cancer or melanoma: a phase I trial. *Cytotherapy*. 2008;10:625-632.

Bachanova V, Cooley S, Defor TE, et al. Clearance of acute myeloid leukemia by haploidentical natural killer cells is improved using IL-2 diphtheria toxin fusion protein. *Blood*. 2014;123:3855-3863.

Bachanova V, Sarhan D, Defor T, et al. Haploidentical natural killer cells induce remissions in non-Hodgkin lymphoma patients with low levels of immune-suppressor cells. *Cancer Immunol Immunother*. 2018;67:483-494.

Bachanova V, Ghobadi A, Patel K, et al. Safety and efficacy of FT596, a first-in-class, multi-antigen targeted, off-the-shelf, iPSC-derived CD19 CAR NK cell therapy in relapsed/refractory B-cell lymphoma. *Blood*. 2021;138(Suppl 1):823.

Benjamin R, Graham C, Yallop D, et al. Preliminary data on safety, cellular kinetics and anti-leukemic activity of UCART19, an allogenic anti-CD19 CAR T-cell product, in a pool of adult and pediatric patients with high-risk CD19+ relapsed/refractory B-cell acute lymphoblastic leukemia. *Blood*. 2018;132(Suppl 1):896.

Bezerra ED, Gauthier J, Hirayam AV, et al. Factors associated with response, CAR-T cell in vivo expansion, and progression-free survival after repeat infusions of CD19 CAR-T cells. *Blood*. 2019;134(Suppl 1):201.

Bibeau F, Lopez-Crapez E, Di Fiore F, et al. Impact of FcRIIa-FcRIIIa polymorphisms and KRAS mutations on the clinical outcome of patients with metastatic colorectal cancer treated with cetuximab plus irinotecan. *J Clin Oncol*. 2009;27:1122-1129.

Bjordahl R, Gaidarova S, Woan K, et al. Preclinical development of an off-the-shelf adoptive NK cell immunotherapy with targeted disruption of CD38 to prevent anti-CD38 antibody-mediated fratricide and enhance ADCC in multiple myeloma when combined with daratumumab. ASH Annual Meeting, abstract 133. 2019.

Blincyto® (blinatumomab) for injection, for intravenous use [Prescribing Information]. Thousand Oaks, CA. Amgen; 2021.

Brudno J, Kochenderfer J. Toxicities of chimeric antigen receptor T cells: recognition and management. *Blood.* 2016;127:3321-30.

Brudno J, Maric I, Hartman S, et al. T cells genetically modified to express an anti-B-cell maturation antigen chimeric antigen receptor cause remissions of poor-prognosis relapsed multiple myeloma. *J Clin Oncol*. 2018;36(22):2267-80.

Cartron G, Dacheux L, Salles G, et al. Therapeutic activity of humanized anti-CD20 monoclonal antibody and polymorphism in IgG Fc receptor FcRIIIa gene. *Blood*. 2002;99(3):754-758.

Cerwenka A, Lanier LL. Natural killer cell memory in infection, inflammation and cancer. *Nat Rev Immunol.* 2016;16:112-23.

Center for International Blood and Marrow Transplant Research (CIBMTR) Forms Instruction Manual, Q19-44: Graft versus Host Disease (Allogenic Only). Last modified: 07 April 2020. Available at: https://www.cibmtr.org/manuals/fim/1/en/topic/q15-18-graft-versus-host-diseaseallogeneic-only

Cichocki F, Woan W, Wu C-Y, et al. NK cells lacking CD38 are resistant to oxidative stress-induced death. ASH Annual Meeting, abstract 3215. 2019.

Cooley S, He F, Bachanova V, et al. First-in-human trial of rhIL-15 and haploidentical natural killer cell therapy for advanced acute myeloid leukemia. *Blood Adv*. 2019;3:1970-80.

D'Agostino M and Raje N. Ant-BCMA CAR T-cell therapy in multiple myeloma: can we do better? *Leukemia*. 2020;34:21-34.

Dahlberg CIM, Sarhan D, Chrobok M, et al. Natural killer cell-based therapies targeting cancer: possible strategies to gain and sustain anti-tumor activity. *Front Immunol.* 2015;6:605.

Darzalex® (daratumumab) injection, for intravenous use [Prescribing Information]. Horsham, PA. Janssen Biotech, Inc, 2021.

Darzalex Faspro™ (daratumumab and hyaluronidase-fihj) injection, for subcutaneous use [Prescribing Information]. Horsham, PA. Janssen Biotech, Inc, 2021.

DeSelm C, Palomba ML, Yahalom J, et al. Low-dose radiation conditioning enables CAR T cells to mitigate antigen escape. *Mol Ther.* 2018;26:2542-52.

Durie BG, Harousseau JL, Miguel JS, et al, for the International Myeloma Working Group. International uniform response criteria for multiple myeloma. *Leukemia.* 2006;20:1467-73.

Fabian KP, Hodge JW. The merging role of off-the-shelf engineered natural killer cells in targeted cancer immunotherapy. *Mol Ther Oncolytics*. 2021;23:266-76.

French AR, Yokoyama WM. Natural killer cells and autoimmunity. *Arthritis Res Ther.* 2004;6:8-14.

Frey N, Shaw P, Hexner E, et al. Optimizing chimeric antigen receptor T-cell therapy for adults with acute lymphoblastic leukemia. *J Clin Oncol*. 2020;38(5):415-22.

Gandhi UH, Cornell RF, Lakshman A, et al. Outcomes of patients with multiple myeloma refractory to CD38-targeted monoclonal antibody therapy. *Leukemia*. 2019;33(9):2266-75.

Geller MA, Cooley S, Judson PL, et al. A Phase II study of allogeneic natural killer cell therapy to treat patients with recurrent ovarian and breast cancer. *Cytotherapy.* 2011;13:98-107.

Goebeler ME, Knop S, Viardot A, et al. Bispecific T-cell engager (BiTE) antibody construct blinatumomab for the treatment of patients with relapsed/refractory non-Hodgkin lymphoma: final results from a Phase I study. *J Clin Oncol.* 2016;34:1104-11.

Iliopoulou EG, Kountourakis P, Karamouzis MV, et al. A Phase I trial of adoptive transfer of allogeneic natural killer cells in patients with advanced non-small cell lung cancer. *Cancer Immunol Immunother.* 2010;59:1781-9.

Janakiram M, Vij R, Siegel DS, et al. A phase I study of FT538, a first-of-kind, off-the-shelf, multiplexed engineered, iPSC-derived NK cell therapy as monotherapy in relapsed/refractory acute myelogenous leukemia and in combination with daratumumab or elotuzumab in relapsed/refractory multiple myeloma. *Blood.* 2020;136(Suppl 1):3.

Ji Y, Liu P, Li Y, et al. A modified toxicity probability interval method for dose-finding trials. *Clin Trials*. 2010;7:653-663.

Jing Y, Ni Z, Wu J, et al. Identification of an ADAM17 cleavage region in human CD16 (FcgRIII) and the engineering of a non-cleavable version of the receptor in NK cells. *PLOS One.* 2015;10(3):e0121788.

Kiessling R, Klein E, Wigzell H. "Natural" killer cells in the mouse. I. Cytotoxic cells with specificity for mouse Moloney leukemia cells. Specificity and distribution according to genotype. *Eur J Immunol*. 1975;5:112-7.

Klebanoff CA, Khong HT, Antony PA, et al. Sinks, suppressors and antigen presenters: how lymphodepletion enhances T cell-mediated tumor immunotherapy. *Trends Immunol.* 2005; 26:111-7.

Kochenderfer JN, Dudley ME, Kassim SH, et al. Chemotherapy-refractory diffuse large B-cell lymphoma and indolent B-cell malignancies can be effectively treated with autologous T cells expressing an anti-CD19 chimeric antigen receptor. *J Clin Oncol*. 2015;6:540-9.

Kumar S, Paiva B, Anderson KC, et al. International Myeloma Working Group consensus criteria for response and minimal residual disease assessment in multiple myeloma. *Lancet Oncol.* 2016;17:e328-e346.

Kumar SK, Rajkumar V, Kyle RA, et al. Multiple myeloma. *Nat Rev Dis Primers*. 2017;3:17046.

Kymriah® (tisagenlecleucel) suspension for intravenous infusion [Prescribing Information]. East Hanover, NJ. Novartis Pharmaceuticals Corporation; 2021.

Lajoie L, Congy-Jolivet N, Bolzec A, et al. ADAM17-mediated shedding of FcgRIIIA on human NK cells: identification of the cleavage site and relationship with activation. *J Immunol*. 2014;192:741-751.

Lee DW, Santomasso BD, Locke FL, et al. ASTCT consensus grading for cytokine release syndrome and neurological toxicity associated with immune effector cells. *Biol Blood Marrow Transplant*. 2019;25:625-38.

Li Y, Hermanson DL, Moriarity BS, et al. Human iPSC-derived natural killer cells engineered with chimeric antigen receptors enhance anti-tumor activity. *Cell Stem Cell*. 2018;23:181-192.

Malmberg KJ, Carlsten M, Björklund A, et al. Natural Killer cell-mediated immunosurveillance of human cancer. *Semin Immunol.* 2017;31:20-9.

Martin N, Thompson E, Dell'Aringa J, et al. Correlation of tumor BCMA expression with response and acquired resistance to idecabtagene vicleucel in the KARMMA study in relapsed and refractory multiple myeloma. European Hematology Association, abstract EP985. 2020.

Maude SL, Frey N, Shaw PA, et al. Chimeric antigen receptor T cells for sustained remissions in leukemia. *New Engl J Med.* 2014;16:1507-17.

McCudden C, Axel A, Slaets, et al. Monitoring multiple myeloma patients treated with daratumumab: teasing out monoclonal antibody interference. *Clin Chem Lab Med*. 2015;54(6):1095-1104.

Miller JS, Soignier Y, Panoskaltsis-Mortari A, et al. Successful adoptive transfer and in vivo expansion of human haploidentical NK cells in patients with cancer. *Blood.* 2005;105:3051-7.

Minn I, Rowe SP, and Pomper MG. Enhancing CAR T-cell therapy through cellular imaging and radiotherapy. *Lancet Oncol*. 2019;20:e443-51.

Mirrakhimov AE, Ali AM, Khan M, et al. Tumor lysis syndrome in solid tumors: an up to date review of the literature. *Rare Tumors.* 2014;6:5389.

Munshi NC, Anderson, Jr LD, Shah N, et al. Idecabtagene vicleucel in relapsed and refractory multiple myeloma. *N Engl J Med.* 2021;384(8):705-716.

Musolino A, Naldi N, Bortesi B, et al. Immunoglobulin G fragment C receptor polymorphisms and clinical efficacy of trastuzumab-based therapy in patients with HER-2/neu–positive metastatic breast cancer. *J Clin Oncol*. 2008;26:1789-1796.

Nanni C, Zamagni E, Versari A, et al. Image interpretation criteria for FDG PET/CT in multiple myeloma: a new proposal from an Italian expert panel. IMPeTUs (Italian Myeloma criteria for PET USe). *Eur J Nucl Med Mol Imaging*. 2016;43:414-21.

Neelapu SS, Tummala S, Kebriaei P, et al. Chimeric antigen receptor T-cell therapy - assessment and management of toxicities. *Nat Rev Clin Oncol.* 2018;15:47-62.

Oken MM, Creech RH, Tormey DC, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. *Am J Clin Oncol*. 1982;5:649-55.

Qu C, Ping N, Kang L, et al. Radiation priming chimeric antigen receptor T-cell therapy in relapsed/refractory diffuse large B-cell lymphoma with high tumor burden. *J Immunother*. 2020;43:32-37.

Raje N, Berdeja J, Lin Y, et al. Anti-BCMA CAR T-cell therapy bb2121 in relapsed or refractory multiple myeloma. *N Engl J Med*. 2019;380:1726-1737.

Rajkumar SV, Harousseau JL, Durie B, et al, for the International Myeloma Workshop Consensus Panel 1. Consensus recommendations for the uniform reporting of clinical trials: report of the International Myeloma Workshop Consensus Panel 1. *Blood.* 2011;117:4691-95

Ranson T, Vosshenrich CA, Corcuff E, et al. IL-15 is an essential mediator of peripheral NK-cell homeostasis. *Blood*. 2003;101(12):4887-93.

Romee R, Foley B, Lenvik T, et al. NK cell CD16 surface expression and function is regulated by a disintegrin and metalloprotease-17 (ADAM17). *Blood*. 2013;121:3599-3608.

Romee R, Rosario M, Berrien-Elliott MM, et al. Cytokine-induced memory-like natural killer cells exhibit enhanced responses against myeloid leukemia. *Sci Transl Med.* 2016;8:357ra123.

Shah N, Li L, McCarty J, et al. Phase I study of cord blood-derived natural killer cells combined with autologous stem cell transplantation in multiple myeloma. *Brit J of Haematol*. 2017;177(3):457-66.

Shah N, Chari A, Scott E, et al. B-cell maturation antigen (BCMA) in multiple myeloma: rationale for targeting and current therapeutic approaches. *Leukemia*. 2020;34:985-1005.

Smith EL, Mailankody S, Staehr M et al. BCMA-targeted CAR T-cell therapy plus radiotherapy for the treatment of refractory myeloma reveals potential synergy. *Cancer Immunol Res*. 2019; 7:1047-53.

Smyth MJ, Hayakawa Y, Takeda K, et al. New aspects of natural-killer-cell surveillance and therapy of cancer. *Nat Rev Cancer.* 2002;2:850-61.

Strati P, Bachanova V, Goodman A, et al. Preliminary results of a phase I trial of FT516, an off-the-shelf natural killer (NK) cell therapy derived from a clonal master induced pluripotent stem

cell (iPSC) line expressing high-affinity, non-cleavable CD16 (hnCD16), in patients (pts) with relapsed/refractory (R/R) B-cell lymphoma (BCL). *J Clin Oncol*. 2021;39(Suppl 15):7541.

Tonn T, Schwabe D, Klingemann, et al. Treatment of patients with advanced cancer with the natural killer cell line NK-92. *Cytotherapy.* 2013;15:1563-70.

Turtle CJ, Hanafi L-A, Berger C, et al. Immunotherapy of non-Hodgkin's lymphoma with a defined ratio of CD8+ and CD4+ CD19-specific chimeric antigen receptor-modified T-cells. *Science Translational Medicine*: 2016;8:355ra116.

Usmani SZ, Mitchell A, Waheed S, et al. Prognostic implications of serial 18-fluoro-deoxyglucose emission tomography in multiple myeloma treated with total therapy 3. *Blood.* 2013;121:1819-23.

Veluchamy JP, Kok N, van der Vliet HJ, et al. The rise of allogeneic natural killer cells as a platform for cancer immunotherapy: recent innovations and future developments. *Front Immunol.* 2017;8:631.

Waldhauer I, Steinle A. NK cells and cancer immunosurveillance. *Oncogene.* 2008;27:5932-43.

Wang R, Jaw JJ, Stutzman NC, et al. Natural killer cell-produced IFN-g and TNF-a induce target cell cytolysis through up-regulation of ICAM-1. *J Leukoc Biol.* 2012;91:299-309.

Wang W, Erbe A, Hank J, et al. NK cell-mediated antibody-dependent cellular cytotoxicity in cancer immunotherapy. *Front Immunol.* 2015;6:368.

Yescarta® (axicabtagene ciloleucel) suspension for intravenous infusion [Prescribing Information]. Santa Monica, CA. Kite Pharma, Inc.; 2021.