Janssen Scientific Affairs, LLC*

Clinical Protocol

A Safety and Efficacy Study of JNJ-68284528 (ciltacabtagene autoleucel) Out-of-Specification (OOS) for Commercial Release in Patients with Multiple Myeloma

Protocol 68284528MMY2005; Phase 2
AMENDMENT 2

JNJ-68284528 (ciltacabtagene autoleucel)

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

IND: 18080

Status: Approved
Date: 02 September 2022
Prepared by: Janssen Scientific Affairs, LLC;
EDMS number: EDMS-RIM-145877, 4.0

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

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY	
Document	**Date**
Amendment 2	02-Sep-2022
Amendment 1	26-May-2021
Original Protocol	21-Jan-2021

Amendment 2 (02-Sep-2022)

Overall Rationale for the Amendment: The overall reason for this amendment is to integrate an urgent safety measure for this product into the protocol, to align with the USPI for this product, addressing increased risk of COVID-19 for this product, and clarification in alignment with global protocol in order to preclude redundant testing.

The changes made to the clinical protocol 68284528MMY2005 as part of Protocol Amendment 2 are listed below, including the rationale of each change and a list of all applicable sections. Changes made in previous protocol amendments are listed in Section 10.18, Appendix 18: Protocol Amendment History.

Section Number and Name	Description of Change	Brief Rationale
1.3. Schedule of Activities (SoA)	Footnote s was added: "If the time from consent to the start of lymphodepleting (LD) chemotherapy is ≤ 7 days, repeat assessments prior to administration of LD chemotherapy are not required with exception of weight and vitals." Footnotes m and n were updated. In both footnotes, "8 weeks until 1 year" was revised to "12 weeks until 1 year".	To align with the visit schedule . To align with the visit schedule
1.3. Schedule of Activities (SoA)	Footnote b was modified, the text "All participants who received cilta-cel OOS will continue to be monitored under a separate long-term follow-up (LTFU) safety study (68284528MMY4002) for up to 15 years after last dose of cilta-cel OOS" was added. Footnote m was modified, the text " Additional event-triggered testing immunophenotyping may be conducted as clinically indicated." was added. The text containing "Outpatient administration: In consultation with and approval from sponsor Appendix 10.16" was deleted from SoA table.	To comply with FDA mandate to follow all CAR-T patients for 15 years. To evaluate role of CARs in AEs/SAEs. To align with latest USPI.
1.3. Schedule of Activities (SoA), PK and Biomarker assessments	Added "X" at prior to first dose of lymphodepleting chemotherapy at Replication competent Lentivirus assessment.	To compare with the baseline value.
1.3. Schedule of Activities (SoA)	The timing for Screening Phase was revised as "After cilta-cel out of specifications (OOS) is approved for exceptional release"; additional wording was added for Screening Phase to specify "28 days from time of consent" the timing; and footnote a was updated.	To be in line with exceptional release process for OOS products and for more clarity.

Section Number and Name	Description of Change	Brief Rationale
1.3. Schedule of Activities (SoA), Review Protocol Safety criteria	New row of "Review Protocol Safety criteria" was added.	To specifically align the increased risk of COVID-19 infection with use of the drug product.
1.3. Schedule of Activities (SoA), Infectious disease testing	Deleted "Infectious disease testing" parameter from Schedule of Activities table as it seemed duplicate of Serology which covers infectious disease testing mandated by the study and accordingly, footnotes from m to t were updated.	The content was condensed into previous "Serology" section to eliminate duplication.
1.3. Schedule of Activities (SoA), Coagulation	The timing for coagulation test was modified as "As clinically indicated, including participants who have fever (≥38°C) or other signs of potential CRS".	To align coagulation testing with symptoms
1.3. Schedule of Activities (SoA), Flow cytometry	The timing for flow cytometry (bone marrow aspirate-central laboratory) was updated from Day 28 to Day 56. Also the text "~~6 months after cilta-cel OOS in participants who have not had a bone marrow within the last 3 months and~~" was deleted for Day 100, Posttreatment Day 101, and EOS.	Bone marrow at Day 28 is often acellular but sufficiently recover at Day 56, such that these assessments are more feasible
1.3. Schedule of Activities (SoA), Flow cytometry, MRD, 24-hour urine protein electrophoresis sample (SOC)	Day 56 was added as a timepoint and footnote h was revised to reflect "For patients in CR/sCR spot urine protein showing continued CR/sCR is permitted".	Bone marrow at Day 28 is often acellular but sufficiently recover at Day 56, such that these assessments are more feasible
1.3. Schedule of Activities (SoA), ECOG, Bone marrow aspirate and core biopsy	Added 'X' at Day 56 to indicate that Eastern Cooperative Oncology Group (ECOG) assessment is to be performed at Day 56. Added Day 56 to specify that Bone marrow aspirate and core biopsy should be performed at Day 56.	To align with the visit schedule
1.3. Schedule of Activities (SoA), Assess extramedullary Plasmacytomas 8.1.4. Documentation of extramedullary plasmacytomas	Revised the frequency for post Day 100 radiologic assessment from "every 16 weeks" to "every 12 weeks".	To have MD visits lined up with imaging visits
1.3. Schedule of Activities (SoA), Laboratory Assessments	Text regarding calcium and albumin adjusted calcium was added.	For increased accuracy of lab assessments
2.1. Study Rationale 11. References	Text was reworded and revised to add that patient may still benefit from out-of-specifications drug product. Seven new references (ECIS 2020, American Cancer Society 2022, Turesson 2018, Kumar 2020a, Howlader 2021, Marinac 2020, and Orlowski 2013) have been added to the list of references to support Multiple myeloma information and references Kyle 2009, Palumb0	To further clarify the study rationale.

Section Number and Name	Description of Change	Brief Rationale
	2011, and Korde 2011 was deleted as text related to them was deleted.	
2.2.1. Multiple myeloma	Text was replaced and was revised per the updated references.	To update with more recent data.
2.3.1. Risks for Study Participation, Table 2 and Table 3	Texts related to CRS, other neurotoxicities, prolonged or recurrent cytopenia, serious infection were updated in Table 2. Text related to Hypogammaglobulinemia, TLS, and Hypersensitivity reactions was updated in Table 3.	To align with the latest USPI
2.3.3. Benefit-Risk Assessment	Text related to the assumed cilta-cel OOS safety and efficacy was updated.	To clarify risk: benefit of receiving OOS product
4.3. Justification of dose	Text in this section was revised	To align with the latest USPI
4.4. End of Study Definition	The definition of end of study and participant study completion definition were reworded	To better define end of study for patients
6.1. Study Intervention Administered	The text in this section was revised	To align with the latest USPI
6.1.2. Criteria for Lymphodepleting Chemotherapy (Cyclophosphamide and Fludarabine) Administration	Criteria for Lymphodepleting Chemotherapy related to clinical laboratory values, echocardiogram/MUGA scan, Eastern Cooperative Oncology Group (ECOG), Grade 3 toxicity to any bridging therapy, cumulative dose of corticosteroids, major surgery, live attenuated vaccine, supplemental oxygen, new arrhythmia, new medical conditions, washout from bridging therapy, which are not as per the latest USPI were removed. In addition, text related to presence of indwelling catheter to the dose of lymphodepleting chemotherapy and text related to dose modification were deleted.	To align with the latest USPI To align with the latest USPI To align with the latest USPI
6.1.5.Cilta-cel OOS Administration, Table 5 Description of Cilta-cel OOS 6.1.4. Clinical assessment Prior to cita-cel OOS Infusion	Text related to Hospitalization requirements or administration of Cilta cel OOS was revised as per the latest USPI. Signs of active infection or inflammatory disorders, wherein inflammatory disorders was added and some of the redundant text regarding manufacturing and quality testing of cilta-cel OOS was deleted.	To align the text with latest USPI To align the text with latest USPI
6.1.6.1. Management of Cytokine Release Syndrome; 6.1.6.2. Neurologic toxicities	New text and table regarding “CRS Grading and Management Guidance” and CAR-T-cell related neurotoxicity was added/modified.	To align the text with latest USPI
6.1.6.2.2. Other Neurotoxicities	Text regarding Guillain-Barre Syndrome (GBS), Peripheral neuropathy, and Cranial Nerve Palsies was updated.	To align text with latest USPI

Section Number and Name	Description of Change	Brief Rationale
	Text of "movement impairments" was revised to Parkinsonism.	Some points in this section were added from a specificity perspective.
6.8. Concomitant Therapy 6.5. Dose Modification	Text related to bridging therapy was deleted and text related to prevention and treatment of COVID-19 and HBV reactivation was added. Text related to dose modification was updated.	To align text with latest USPI To align text with latest USPI
6.1.6.4. Prolonged or Recurrent Cytopenia; 6.1.6.5. Hypogammaglobulinemia; 6.1.6.6. Serious infection; 6.1.6.7. Hypersensitivity reactions 6.1.6.8. Secondary primary malignancy	Text regarding prolonged cytopenia, hypogammaglobulinemia, Serious infection, hypersensitivity reactions, and secondary primary malignancy was updated.	To align text with latest USPI
Throughout the protocol	Precaution text regarding COVID-19 was added. Consenting phase was revised to "Screening Phase" Cilta-cel was used consistently Randomization was changed to enrollment	Added as new safety signal for CAR-T and COVID-19 meaning that there is an increased risk of death from COVID-19 post cilta-cel infusion. As consent is either acquired or it isn't and study procedures cannot occur until consent is acquired. To maintain consistency throughout the document. There is no randomization as it is a single arm study.
8. Study assessments and Procedures, Post infusion, Post-treatment	The frequency for obtaining survival status and subsequent anticancer therapy after disease progression is documented was changed from "every 12 weeks until the end of study" to "every 16 weeks until the end of study". Also text regarding hospitalization was updated per the institutional guidelines.	To decrease the frequency of follow up once patient is off study (all patients will be in case of progressive disease)
8. Study assessments and Procedures, Overview, Post-treatment, Screening, Lymphodepleting chemotherapy	ECG was replaced with ECOG/MUGA. Text "Rescreening may occur with sponsor approval" was inserted in Screening Phase and overall text regarding all the phases was updated and revised.	To align with the visit schedule. To allow for consideration on individual basis for re-screening for trial

Section Number and Name	Description of Change	Brief Rationale
8.1.2. Bone marrow examination	Text related to bone marrow aspiration or biopsy was updated and revised.	As it was confirmed that bone marrow examination was required only if CR or progressive disease
8.1.3. Minimal Residue Disease evaluation	Text related to fresh bone marrow aspirate was updated from screening to "prior to LD chemotherapy"	To give broader time frame with which BM sample can be collected
8.2.2. Vital Signs	Text related to vital signs was updated.	To give broader time frame with which BM sample can be collected
8.3.1. Time period and Frequency for Collecting adverse event and Serious Adverse event Information	Text related to HBV reactivations and COVID-19 infections, neurocognitive toxicity, AE seriousness was updated. Deaths not related to disease progression was added as a new criterion. Also in AESI second primary malignancy was added along with prolonged and recurrent cytopenias. "Any grade movement and neurocognitive toxicity [ie, Parkinsonism] was added as SAEs to be reported within 24 hours of awareness.	To align with latest USPI To align with latest USPI To align with latest USPI
10.2. Appendix 2 Clinical laboratory tests	Urine drug screen test and "fasting" from glucose (fasting) were deleted. Statement related to testing of calcium and albumin was added.	To remove unnecessary laboratory test To align with addition of those tests in lab section of SoA.
10.6. Appendix 6 Study Conduct During a Natural Disaster/Major Disruption/ Pandemic	Text in this section was updated	To align with the latest template
10.16. Appendix 16 Monitoring for Participants Receiving cilta-cel OOS as Outpatient	Appendix 16 was deleted	To align with latest USPI
10.15. Appendix 15: Cilta-cel OOS Outpatient Administration Guidelines	Text in Logistical consideration for qualified healthcare facility was updated.	To align with the latest USPI
Throughout the protocol	Minor grammatical, formatting, or spelling, and template related changes were made.	Minor errors were noted

TABLE OF CONTENTS

LIST OF IN-TEXT TABLES AND FIGURES

TABLES

FIGURES

1. PROTOCOL SUMMARY

1.1. Synopsis

A Safety and Efficacy Study of JNJ-68284528 (ciltacabtagene autoleucel) Out-of-Specification (OOS) for Commercial Release in Patients with Multiple Myeloma

Insert Short Title: Not Applicable.

JNJ-68284528 (ciltacabtagene autoleucel [cilta-cel]) is an autologous chimeric antigen receptor-T cell (CAR-T) therapy that targets B-cell maturation antigen (BCMA), a molecule expressed on the surface of mature B-lymphocytes and malignant plasma cells. Results from Study 68284528MMY2001 (CARTITUDE-1) indicate that cilta-cel has significant anti-myeloma activity and a safety profile consistent with the known mechanism of action of the product. In this study, participants whose manufactured cilta-cel does not meet the commercial release specifications (cilta-cel out-of-specifications [OOS]) are eligible for inclusion.

OBJECTIVES

Primary objective:

- To evaluate the efficacy of cilta-cel OOS based on overall response of partial response (PR) or better (overall response rate, ORR).

Secondary objectives:

- To assess the safety of cilta-cel OOS.
- To further characterize the efficacy of cilta-cel OOS based on other endpoints.
- To determine whether replication competent lentivirus is present in participants that receive cilta-cel OOS.

Hypothesis

The study hypothesis is that cilta-cel OOS will demonstrate similar safety and efficacy to data from study 68284528MMY2001, as assessed by the primary and secondary endpoints.

OVERALL DESIGN

This is an open-label, single-arm multicenter Phase 2 study to evaluate the safety and efficacy of cilta-cel OOS in adult participants (≥18 years) with multiple myeloma (MM) as described in cilta-cel US prescribing information ([USPI] or locally approved label, respectively), and whose final manufactured cilta-cel does not meet the commercial release specifications.

Upon written notification of the cilta-cel being OOS, the treating physician can request the sponsor to activate an exceptional release process, during which cilta-cel OOS will be assessed individually by the sponsor for the expected benefit/risk profile. If the benefit/risk profile is deemed favorable, the treating physician/principal investigator will initiate eligibility and consenting procedures and can formally request the shipment of the cilta-cel OOS for administration within the study. Exceptional Release of OOS Product Request Form must be completed and signed off by treating physician/principal investigator before releasing cilta-cel OOS to the participant.

The study will be conducted in following 5 phases:

- Screening Phase,
- Lymphodepleting Chemotherapy,

- Cilta-cel OOS Administration,
- Post infusion, and
- Post-treatment

Cilta-cel OOS will not be administered to a participant whose medical condition does not meet the criteria for CAR-T infusion. Non-eligible medical conditions include active uncontrolled infection or condition where ~~an~~ administration of cilta-cel OOS constitutes serious health risk to the participant.

Eligible participants may continue bridging therapy (ie, anti-plasma cell directed treatment between apheresis and the first dose of the lymphodepleting chemotherapy) as clinically indicated. Bridging therapy and lymphodepleting chemotherapy will be considered as part of standard-of-care and are prescribed by the treating physician, if clinically indicated.

Lymphodepleting chemotherapy consists of IV cyclophosphamide 300 mg/m^2 and fludarabine 30 mg/m^2 daily for 3 days per USPI or locally approved label. Cilta-cel OOS will be administered at a total targeted dose of 0.75×10^6 CAR-positive viable T cells/kg (range: 0.5 to 1.0×10^6 CAR-positive viable T cells/kg) or per exceptional release criteria determined alternative dose, 5 to 7 days after start of the lymphodepleting chemotherapy.

Following the infusion of cilta-cel OOS, the participant will be followed for 2 years in this study to assess response, duration of response (DOR), progression-free survival (PFS), overall survival (OS), and safety. All participants who received cilta-cel OOS will continue to be monitored for long-term safety under a separate long-term follow-up (LTFU) study (68284528MMY4002) for up to 15 years after last dose of cilta-cel OOS.

A Data Review Committee (DRC) will be commissioned for this study.

NUMBER OF PARTICIPANTS

No formal enrollment target is planned for this study since the number of potential participants with cilta-cel OOS is unknown at this time. Based on the current manufacturing experience with study 68284528MMY2001, at least 20 participants are anticipated to enroll in the study.

INTERVENTION GROUP AND DURATION

Prior to administration of cilta-cel OOS, all participants will receive a lymphodepleting chemotherapy (standard-of-care) of IV cyclophosphamide 300 mg/m^2 and fludarabine 30 mg/m^2 daily for 3 days per USPI or locally approved label, respectively. The dose of fludarabine may be reduced to 24 mg/m^2 for participants with an estimated glomerular filtration rate (eGFR) of 30 to 70 mL/min/1.73m^2. Cilta-cel OOS (after approval) will be administered 5 to 7 days after the start of the lymphodepleting chemotherapy. The anticipated duration of enrollment of participants in this study is 2 years and duration of study is expected to be 4 years with potential extension.

EFFICACY EVALUATIONS

Efficacy evaluations include myeloma protein measurements and imaging as indicated for enrolled participants to evaluate response and disease progression. Efficacy evaluations will be measured from Screening Phase through end of study by the investigator per International Myeloma Working Group (IMWG) consensus recommendations for MM treatment response criteria. Blood, serum and bone marrow samples will be collected for assessment of cilta-cel OOS pharmacokinetics (PK), minimal residual disease (MRD)-negative rate, and predictive biomarkers of response or resistance to cilta-cel OOS.

SAFETY EVALUATIONS

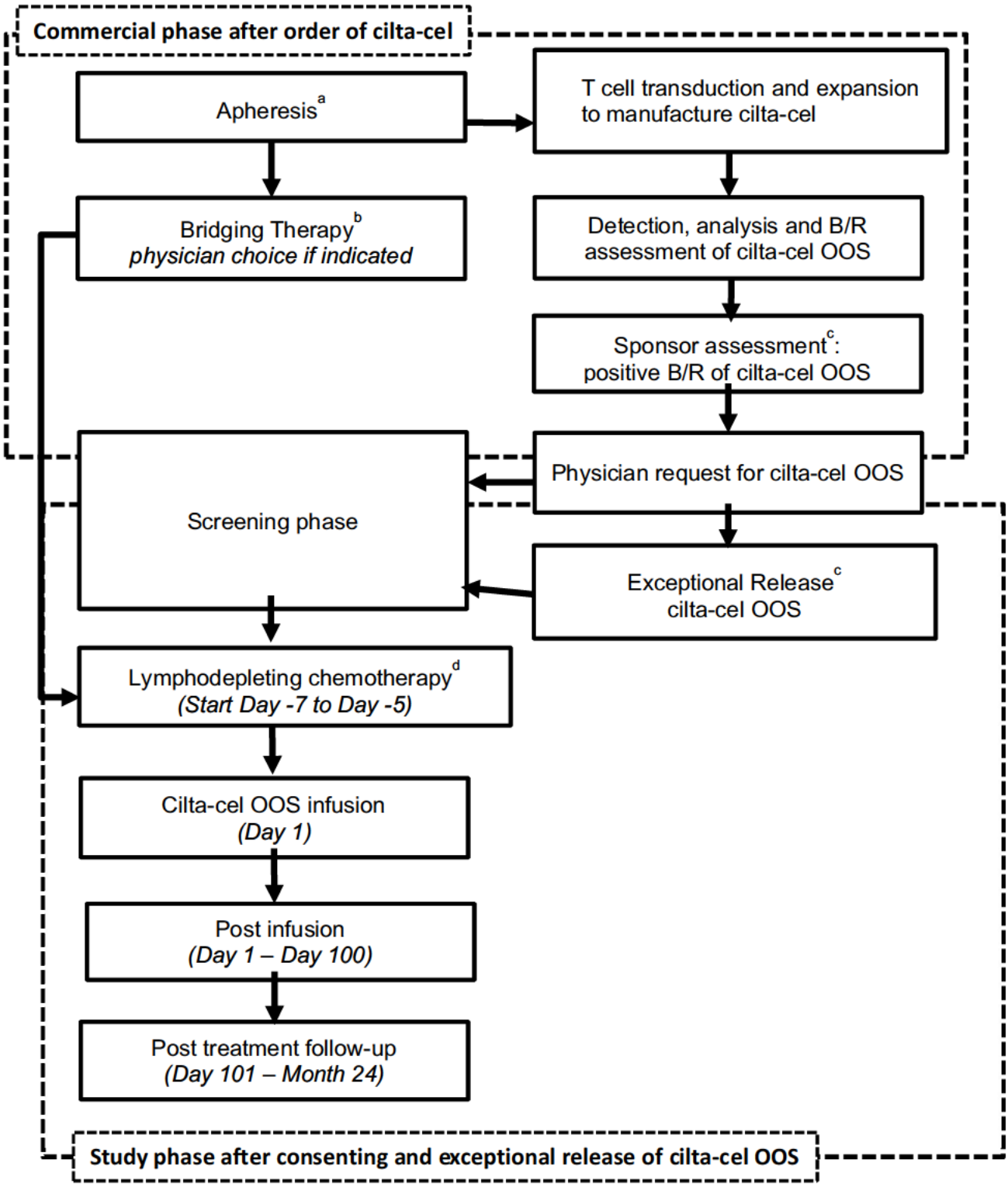
Safety of cilta-cel OOS infusion will be assessed by adverse events, laboratory test results, vital sign measurements, physical examination findings, handwriting assessments, assessment of Immune-Effector Cell-associated Encephalopathy (ICE) Tool scores, and assessment of Eastern Cooperative Oncology Group (ECOG) performance status grade. The continuing safety profile of the enrolled participants will be evaluated at the periodic DRC meetings. Follow-up of participants will continue to include all SAEs and delayed AEs, disease progression, and survival during the Post-treatment Phase.

STATISTICAL METHODS

No formal statistical hypothesis testing will be performed for the study. All participants who received a cilta-cel OOS infusion will be included in the analysis for efficacy and safety summaries. Descriptive statistics and time to event analysis as appropriate will be described in detail in the statistical analysis plan. Initially, data will be reviewed by the DRC after every 10 participants have been treated and followed for at least 3 months to assess efficacy and safety

1.2. Schema

Figure 1: Schematic Overview of Manufacturing Cilta-Cel OOS Drug Product and Study Flow Chart



Abbreviations: IV=intravenous; B/R=benefit/risk; OOS=out-of-specifications.
Footnotes:

a Apheresis is performed to collect peripheral blood mononuclear cells (PBMCs) and is required for manufacturing of cilta-cel.

b Eligible participants may continue bridging therapy (anti-plasma cell directed treatment between apheresis and the first dose of the lymphodepleting chemotherapy) as determined by treating physician based on participant's clinical status and timing of availability of cilta-cel OOS. Therapy must be stopped within 14 days or at least 5 half-lives, whichever is earlier, prior to start of lymphodepleting chemotherapy to complete washout (please refer to detailed guidance for drug classes and radiotherapy to protocol section 6.1.2).

c Exceptional release will be based on release specification criteria and a sponsor medical review process to determine and document the benefit/risk assessment, which will include the potential OOS safety and efficacy impact, participant alternative options/medical need, and assessment of potential immediate risk of not receiving the product. Treating physician then decides whether to request the cilta-cel OOS.

d Lymphodepleting chemotherapy will be prescribed by the site per standard-of-care, as clinically indicated. It consists of IV cyclophosphamide 300 mg/m^2 and fludarabine 30 mg/m^2 daily for 3 days, with the first Day-7 to Day-5 prior to infusion of cilta-cel OOS on Day 1. The dose of fludarabine may be reduced to 24 mg/m^2 for participants with an estimated glomerular filtration rate (eGFR) of 30 to 70 $mL/min/1.73m^2$ (please refer to Section 10.16, Appendix 16 for eGFR calculation).

1.3. Schedule of Activities (SoA)

Table 1: Schedule of Activities for Study Procedures/Assessments

Phase	Screening Phase (28 days from time of consent)	Cyclophosphamide and fludarabine lymphodepleting chemotherapy[s] (SOC)	Cilta-cel OOS infusion	Post Infusion (Day 1 to Day 100) Any participant who received an infusion of cilta-cel OOS should continue all subsequent assessments[b]										Posttreatment Day 101 and up to End of study[b]
Day	**After cilta-cel OOS is approved for exceptional release**	**Day-5* (assessments may be conducted ≤72 hours predose) *Window for start of lymphodepleting chemotherapy: Day-7 to Day-5**	**Day 1 (Infusion)**	**Day 3**	**Day 7 (± 1 day)**	**Day 10 (± 1 day)**	**Day 14 (± 1 day)**	**Day 21 (± 2 days)**	**Day 28 (± 2 days)**	**Day 35 (± 2 days)**	**Day 42 (± 2 days)**	**Day 56 (± 2 days)**	**Day 100 (± 2 days)[b]**	**(every 84 days after Day 100)[c] (± 7 days)**
Screening Assessments														
Informed consent[a]	X Before the first study-related procedure													
Eligibility criteria	X													
Review Protocol Safety Criteria		See Section 6.1.2	See Section 6.1.4											
Demography, Medical History	X													
Disease Characteristics[d]		X (prior to start of lymphodepleting chemotherapy)												
ECOG	X	Prior to first dose only	X									X	X	X
Physical Examination	X		A symptom-directed physical examination should be performed as clinically indicated											
Height	X													
Handwriting Test			X (≤24 hours prior to infusion)[l]	X	X	X	X	X	X	X	X	X	X	Every 84 days until Day 184

Table 1: Schedule of Activities for Study Procedures/Assessments

Phase	**Screening Phase (28 days from time of consent)**	**Cyclophosphamide and fludarabine lymphodepleting chemotherapy[s] (SOC)**	**Cilta-cel OOS infusion**	**Post Infusion (Day 1 to Day 100) Any participant who received an infusion of cilta-cel OOS should continue all subsequent assessments[b]**										**Posttreatment Day 101 and up to End of study[b]**
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ICE neurological test			X (≤24 hours prior to infusion)[l]	ICE test must be repeated at any incidence of suspected CAR-T cell-related neurotoxicity (eg, ICANS). Perform at least daily until resolved.										
Echocardiogram or MUGA scan (optional)		Optional assessment for participants who receive bridging therapy that includes agents with known cardiac toxicity (per prescribing information), verification of non-impaired cardiac function (LVEF≥45%) should be performed in the time interval between completion of bridging therapy and prior to the first dose of the lymphodepleting chemotherapy.												
Safety Criteria (prior to lymphodepleting chemotherapy / prior to infusion of cilta-cel OOS)														
Safety criteria (See respective Sections)		≤72 hours of the first dose only (See Section 6.1.2)	X (See Section 6.1.4)											
Laboratory Assessments (See Section 8.2) To be performed by the local laboratory except for the calcium and albumin-adjusted calcium which will be performed at the central laboratory (local labs may be used to assess eligibility). Blood samples collection may be performed at the participant's home by mobile study personnel (ie, nurses and mobile phlebotomist) per standard-of-care in the post-treatment period.														
Hematology (see Section 10.2 Appendix 2)	X	Prior to first dose only	X (predose)	X	X	X	X	X	X		X	X	X	X
Chemistry (see Section 10.2, Appendix 2)	X	Prior to first dose only	X (predose)	X	X	X	X	X	X		X	X	X	X
Serology[e]	X			As clinically indicated and for participants at risk for HBV reactivation, monitor HBV DNA and AST/ALT (See Section 10.14, Appendix 14)[e]										
Coagulation (PT/international normalized ratio [INR], aPTT, fibrinogen, D-dimer)	X			As clinically indicated, including participants who have fever (≥38°C) or other signs of potential CRS										
Urinalysis	X		As clinically indicated											

Table 1: Schedule of Activities for Study Procedures/Assessments

Phase	**Screening Phase (28 days from time of consent)**	**Cyclophosphamide and fludarabine lymphodepleting chemotherapy[s] (SOC)**	**Cilta-cel OOS infusion**	**Post Infusion (Day 1 to Day 100) Any participant who received an infusion of cilta-cel OOS should continue all subsequent assessments[b]**										**Posttreatment Day 101 and up to End of study[b]**
Day	**After cilta-cel OOS is approved for exceptional release**	**Day-5* (assessments may be conducted ≤72 hours predose) *Window for start of lymphodepleting chemotherapy: Day-7 to Day-5**	**Day 1 (Infusion)**	**Day 3**	**Day 7 (± 1 day)**	**Day 10 (± 1 day)**	**Day 14 (± 1 day)**	**Day 21 (± 2 days)**	**Day 28 (± 2 days)**	**Day 35 (± 2 days)**	**Day 42 (± 2 days)**	**Day 56 (± 2 days)**	**Day 100 (± 2 days)[b]**	**(every 84 days after Day 100)[c] (± 7 days)**
Serum Pregnancy test (in participants with childbearing potential)	X	Prior to first dose only		As clinically indicated										
Study Treatment Administration														
Weight	X	Prior to first dose only	X											
Vital signs, including oxygen saturation	X	X	X[f]	X	X	X	X	X			X		X	
Temperature			Measure at least twice a day[g]											
Cyclophosphamide and fludarabine (SOC) (see Section 6.1.2)		X												
Pre-infusion medication (see Section 6.1.1 for requirements prior to dosing with cilta-cel OOS)			X											
Cilta-cel OOS (USPI or locally approved label)			X											
Serum and Urine Disease Evaluations (See Section 8.1 for efficacy assessments). Blood and 24-hour urine: to be sent to the central laboratory[r]. Disease evaluation should continue to be performed until confirmed disease progression, death, start of a new anticancer treatment, withdrawal of consent for study participation, or end of study, whichever occurs first.														

Table 1: Schedule of Activities for Study Procedures/Assessments

Phase	**Screening Phase (28 days from time of consent)**	**Cyclophosphamide and fludarabine lymphodepleting chemotherapy[s] (SOC)**	**Cilta-cel OOS infusion**	**Post Infusion (Day 1 to Day 100) Any participant who received an infusion of cilta-cel OOS should continue all subsequent assessments[b]**										**Posttreatment Day 101 and up to End of study[b]**
Day	**After cilta-cel OOS is approved for exceptional release**	**Day-5* (assessments may be conducted ≤72 hours predose) *Window for start of lymphodepleting chemotherapy: Day-7 to Day-5**	**Day 1 (Infusion)**	**Day 3**	**Day 7 (± 1 day)**	**Day 10 (± 1 day)**	**Day 14 (± 1 day)**	**Day 21 (± 2 days)**	**Day 28 (± 2 days)**	**Day 35 (± 2 days)**	**Day 42 (± 2 days)**	**Day 56 (± 2 days)**	**Day 100 (± 2 days)[b]**	**(every 84 days after Day 100)[c] (± 7 days)**
Serum M-protein quantitation by electrophoresis (SOC)	X	X (prior to first dose of lymphodepleting chemotherapy [≤7 days])							X			X	X	X
24-hour urine protein electrophoresis sample (SOC)	X[h]	X (prior to first dose of lymphodepleting chemotherapy [≤7 days])							X			X	X	X
Quantitative Immunoglobulins	X[q]	X (prior to first dose of lymphodepleting chemotherapy [≤7 days])							X		X	X	X	X
Serum free-light chain (FLC) and serum/urine immunofixation	X	Serum FLC and serum/urine immunofixation are to be performed prior to the start of lymphodepleting chemotherapy (≤7 days) and when CR is suspected or maintained; for participants with measurable disease only by light-chain criteria serum FLC will also be performed at every assessment when an SPEP is performed												
Other Disease Evaluations														
Bone marrow aspirate and core biopsy[i]		X (prior to first dose of lymphodepleting chemotherapy [≤7 days]). Fluorescence in situ hybridization (FISH) testing		On Day 56 and to confirm CR, sCR, and at disease progression (immunohistochemistry or flow cytometry).										

Table 1: Schedule of Activities for Study Procedures/Assessments

Phase	**Screening Phase (28 days from time of consent)**	**Cyclophosphamide and fludarabine lymphodepleting chemotherapy[s] (SOC)**	**Cilta-cel OOS infusion**	**Post Infusion (Day 1 to Day 100) Any participant who received an infusion of cilta-cel OOS should continue all subsequent assessments[b]**										**Posttreatment Day 101 and up to End of study[b]**
Day	**After cilta-cel OOS is approved for exceptional release**	**Day-5* (assessments may be conducted ≤72 hours predose) *Window for start of lymphodepleting chemotherapy: Day-7 to Day-5**	**Day 1 (Infusion)**	**Day 3**	**Day 7 (± 1 day)**	**Day 10 (± 1 day)**	**Day 14 (± 1 day)**	**Day 21 (± 2 days)**	**Day 28 (± 2 days)**	**Day 35 (± 2 days)**	**Day 42 (± 2 days)**	**Day 56 (± 2 days)**	**Day 100 (± 2 days)[b]**	**(every 84 days after Day 100)[c] (± 7 days)**
		required to be performed at a central laboratory.												
Skeletal Survey[j]	X	As clinically indicated to assess for disease progression												
Assess extramedullary Plasmacytomas [k]		X (≤14 days prior to first dose of lymphodepleting chemotherapy)	Measurable sites Day 28, Day 56, Day 100 then every 12 weeks for physical examination (if applicable) and Day 100 and then every 12 weeks for radiologic assessment (for participants with a history of plasmacytomas or as clinically indicated for others).											
Ongoing Participant Review After disease progression is documented, survival status and subsequent anticancer therapy will be obtained every 16 weeks until end of study														
Adverse Events	Continuous from the time of signing of ICF until 100 days after cilta-cel dosing; thereafter, continue to report all SAEs regardless of causality, and any nonserious adverse events considered related to study treatment until EOS. For participants who progress before Day 100 post cilta-cel, AEs/SAEs should still be reported until 100 days post cilta-cel or until resolution, whichever is later. In addition, the following delayed AEs (regardless of causality) will be collected from the time of cilta-cel infusion and for the duration of the study, and subsequently in a separate long-term follow-up study for up to 15 years after last administration of cilta-cel: new malignancies or recurrence of pre-existing malignancy (all grades)[p], new incidence or exacerbation of pre-existing neurologic AEs (all grades), new incidence or exacerbation of a pre-existing rheumatologic or other autoimmune disorder (all grades), new incidence of Grade ≥ 3 hematologic disorder, and new incidence of Grade ≥3 infections CRS should be evaluated according to the ASTCT consensus grading (Lee 2019) (Section 10.7, Appendix 7). CAR-T cell-related neurotoxicity (eg, ICANS) should be graded according the ASTCT consensus grading (Section 10.8, Appendix 8). Events of HBV reactivations and COVID-19 infection should be reported during the first year post-dosing of cilta-cel.												
Concomitant medication	Continuous from the time of signing of ICF until 100 days cilta-cel OOS infusion. Thereafter, collect concomitant medications for treatment of any reported AEs/SAEs (including delayed AE) and all treatments for multiple myeloma (MM) until EOS and subsequently in a long-term follow-up (LTFU) safety study for up to 15 years after last dose of cilta-cel. Medications for the prevention and treatment of COVID-19 (including vaccines) and HBV reactivation should be reported until 1 year after cilta cel infusion (Appendix 10.29).													
PHARMACOKINETIC (PK) AND BIOMARKER ASSESSMENTS														

Table 1: Schedule of Activities for Study Procedures/Assessments

Phase	**Screening Phase (28 days from time of consent)**	**Cyclophosphamide and fludarabine lymphodepleting chemotherapy[s] (SOC)**	**Cilta-cel OOS infusion**	**Post Infusion (Day 1 to Day 100) Any participant who received an infusion of cilta-cel OOS should continue all subsequent assessments[b]**										**Posttreatment Day 101 and up to End of study[b]**
Day	**After cilta-cel OOS is approved for exceptional release**	**Day-5* (assessments may be conducted ≤72 hours predose) *Window for start of lymphodepleting chemotherapy: Day-7 to Day-5**	**Day 1 (Infusion)**	**Day 3**	**Day 7 (± 1 day)**	**Day 10 (± 1 day)**	**Day 14 (± 1 day)**	**Day 21 (± 2 days)**	**Day 28 (± 2 days)**	**Day 35 (± 2 days)**	**Day 42 (± 2 days)**	**Day 56 (± 2 days)**	**Day 100 (± 2 days)[b]**	**(every 84 days after Day 100)[c] (± 7 days)**
Replication Competent Lentivirus (RCL) (whole blood)		X	Predose	At approximately 3, 6 and 12 months, then yearly until EOS or until the post-treatment assays for an individual participant are negative for RCL during the first year. Additional event-triggered testing for RCL may be conducted as clinically indicated.										
Immunophenotyping (Whole blood)[o]			X		X	X	X	X	X		X	X	X	X[m]
PK CAR transgene levels (whole blood)[o]			Predose		X	X	X	X	X		X	X	X	X[n]
Immunogenicity[o]			Predose				X		X			X	X	X (Day 184)
Flow cytometry (bone marrow aspirate-central laboratory)		X (prior to first dose of lymphodepleting chemotherapy [≤7 days])										X	At suspected CR and at progressive disease (PD) or EOS	

Table 1: Schedule of Activities for Study Procedures/Assessments

Phase	**Screening Phase (28 days from time of consent)**	**Cyclophosphamide and fludarabine lymphodepleting chemotherapy[s] (SOC)**	**Cilta-cel OOS infusion**	**Post Infusion (Day 1 to Day 100) Any participant who received an infusion of cilta-cel OOS should continue all subsequent assessments[b]**										**Posttreatment Day 101 and up to End of study[b]**
Day	**After cilta-cel OOS is approved for exceptional release**	**Day-5* (assessments may be conducted ≤72 hours predose) *Window for start of lymphodepleting chemotherapy: Day-7 to Day-5**	**Day 1 (Infusion)**	**Day 3**	**Day 7 (± 1 day)**	**Day 10 (± 1 day)**	**Day 14 (± 1 day)**	**Day 21 (± 2 days)**	**Day 28 (± 2 days)**	**Day 35 (± 2 days)**	**Day 42 (± 2 days)**	**Day 56 (± 2 days)**	**Day 100 (± 2 days)[b]**	**(every 84 days after Day 100)[c] (± 7 days)**
Cytokine profiling (serum)[o]		X (≤7 days prior to first dose)	Predose 2 hours post-dose (±10 min)	X	X	X	X	X	X		X	X	X	
MRD (bone marrow aspirate) (central laboratory)		X (prior to first dose of lymphodepleting chemotherapy [≤7 days])			On Day 56 and at time of suspected CR and disease progression.									

Abbreviations: AE=adverse event; aPTT=activated partial thromboplastin time; ALT=alanine aminotransferase; AST=aspartate aminotransferase; ASTCT=American Society for Transplantation and Cellular Therapy; BCMA=B-cell maturation antigen; CAR-T=chimeric antigen receptor-T cell; CR=complete response; sCR=stringent complete response; CRS=cytokine release syndrome; CT=computed tomography; D=Day; ECHO=echocardiography; ECOG=Eastern Cooperative Oncology Group; EOS=End of Study; FISH=fluorescence in situ hybridization; FLC=free-light chain; HBV=hepatitis B virus; HCV=hepatitis C virus; HTLV=Human T-cell lymphotropic virus; HBsAg=hepatitis B surface antigen; ICANS=Immune-Effector Cell-associated Neurotoxicity Syndrome; ICE=Immune-Effector Cell-associated Encephalopathy; ICF=informed consent form; Ig=Immunoglobulins; INR=international normalized ratio; LD=lymphodepleting; LLOQ=lower limit of quantitation; LTFU=long-term follow-up; LVEF=left ventricular ejection fraction; OOS=out-of-specifications; PD=progressive disease; PI=prescribing information; PK=pharmacokinetics; PT=prothrombin time; RCL=Replication Competent Lentivirus; SAE=serious adverse event; SOC=standard-of-care; SPEP=serum protein electrophoresis; MM=multiple myeloma; MRD=minimal residual disease; MRI=magnetic resonance imaging; MUGA=multiple-gated acquisition; UPEP=urine protein electrophoresis; US=United States.

Footnotes:

a. ICF must be signed after cilta-cel OOS is approved for exceptional release and before first study related procedures are performed. Evaluations for eligibility determination performed outside the screening window may need to be repeated.

b. For participants who discontinue the study before Day 100, the Day 100 assessments should be performed prior to withdrawal if feasible. Participants who discontinue after Day 100 but before end of study should have urine and serum disease assessments performed prior to withdrawal if feasible at the time of discontinuation, unless performed within 14 days prior to discontinuation. End of Study (EOS) is defined as 2 years after each participant has received his or her initial dose of cilta-cel OOS. All participants who received cilta-cel OOS will continue to be monitored under a separate long-term follow-up (LTFU) safety study (68284528MMY4002) for up to 15 years after last dose of cilta-cel OOS.

c. Post-treatment assessments to be obtained until progressive disease is documented or the start of subsequent anticancer therapy, with the exception of survival status and subsequent anticancer therapy, which are to be collected until end of study. Telephone contact will be made to determine survival status and subsequent anticancer therapy every 84 days for up to EOS, unless the participant has died, is lost to follow-up, or has withdrawn consent.
d. Disease characteristics cytogenetics (full karyotyping or FISH as well as molecular genetics [if applicable]), both of which may originate from prior to or during the screening period within 42 days before, availability of cilta-cel OOS infusion or before the lymphodepleting chemotherapy, as applicable. A pathologist/cytogeneticist should complete the cytogenetics data collection worksheet.
e. Serology results performed as standard-of-care within 28 days prior to written notification for availability of cilta-cel OOS. Hepatitis B: HBsAg, anti-HBc, anti-HBs, HBV DNA quantification (for participants who are-anti-HBs positive without history of vaccination-or-for participants who are anti-HBs positive and anti-HBc positive); For participants at risk for HBV reactivation, monitor HBV DNA, AST/ALT every 12 weeks (±7 days) for one year post-dose of cilta-cel OOS (See Section 10.14, Appendix 14). Hepatitis C: HCV antibody, HCV-RNA (for participants who are anti HCV positive); HIV serology. Human T-cell lymphotropic virus (HTLV), and other infectious diseases as applicable per local regulations.
f. Immediately before the start of infusion, at the end of infusion, and 0.5, 1, 2 hours after end of infusion. Monitor until normalized after a CRS event.
g. Temperature will be checked at least twice a day up to Day 28. Participants will be provided with a thermometer and instructed on the use of the thermometer and entering 2 temperatures including their maximum daily temperature in a diary. Diary will be reviewed at each visit, then collected on Day 28 and stored with participant source documents.
h. UPEP sample collected as part of the standard-of-care and prior to the participant signing ICF may be used for analysis at the central laboratory. For patients in CR/sCR spot urine protein showing continued CR/sCR is permitted.
i. Bone marrow morphology from an aspirate and core biopsy to be assessed locally at all time points. Additionally, FISH testing needs to be done for bone marrow aspirate or biopsy samples collected prior to lymphodepleting chemotherapy at a central laboratory.
j. Results from skeletal survey performed as routine follow-up within 42 days may be used without these tests being repeated. The skeletal survey is to be performed by either roentgenography or low dose computed tomography (CT) scans without the use of IV contrast. If a CT scan is used it must be of diagnostic quality. Additional imaging (X-ray, CT, or magnetic resonance imaging [MRI]) will be performed as clinically indicated (eg, to document response or progression).
k. Extramedullary plasmacytomas should be assessed for all participants with a history of plasmacytomas or if clinically indicated prior to the first dose of the lymphodepleting chemotherapy, by clinical examination or radiologic imaging, including MRI or CT as appropriate, see also Sections 8.1.4 and 2.3.1.
l. Pre-infusion ICE test and handwriting sample should be performed before premedication with diphenhydramine.
m. Immunophenotyping samples should also be collected at suspected CR, every 12 weeks until 1-year and then every 6 months post-1 year. Samples will not be collected if LLOQ is reached after 1-year. Additional event-triggered testing immunophenotyping may be conducted as clinically indicated.
n. Samples for PK CAR transgene levels should also be collected at suspected CR, every 12 weeks until 1-year and then at least annually until EOS. Samples will not be collected if LLOQ is reached after 1-year. Additional event-triggered testing for PK CAR transgene may be conducted as clinically indicated.
o. Collect additional samples when any of the following are observed or reported: 1) CRS or ICANS/neurotoxicity related to CAR-T therapy (Grade ≥3) (at onset of the event, at any increase in grade of the CRS and at time of resolution) or additional event-triggered testing for immunophenotyping and PK CAR transgene levels may be conducted as clinically indicated. If these additional sampling timepoints occur on a day of a regularly scheduled sample collection, only 1 sample collection is required for that day.
p. Yearly monitoring of malignancies will be continued until 15 years after the last administration of cilta-cel OOS on a separate long-term-follow-up study. For participants diagnosed with a new or recurrent malignancy, a tumor sample should be collected, and DNA, RNA, or protein analysis may be performed to investigate the presence of lentiviral elements.
q. All participants will be evaluated for IgG, IgA, IgM. Testing for IgD and IgE will only be performed for participants with IgD and IgE-type myeloma. Additional immunoglobulin samples may be collected as clinically indicated for safety and treated according to institutional guidelines (see Section 6.1.6.5).
r. Local laboratory assessments may be used under specified circumstances (See Section 8.1).
s. If the time from consent to the start of lymphodepleting (LD) chemotherapy is ≤ 7 days, repeat assessments prior to administration of LD chemotherapy are not required with exception of weight and vitals.

2. INTRODUCTION

Cilta-cel (ciltacabtagene autoleucel [cilta-cel]) is a genetically modified autologous T cell immunotherapy that binds to B-cell maturation antigen (BCMA, also known as CD269 and tumor necrosis factor receptor superfamily member 17 [TNFRSF17]). Cilta-cel employs chimeric antigen receptor (CAR) technology to genetically engineer autologous peripheral blood T cells to identify and kill cells that express BCMA, which is primarily expressed on late-stage B cells, plasma cells, and malignant B-lineage cells. Cilta-cel is being developed for the treatment of multiple myeloma.

For the most comprehensive nonclinical and clinical information regarding cilta-cel, refer to the US prescribing information (USPI) (or locally approved label) for cilta-cel and Investigator's Brochure (IB) (IB JNJ-68284528).

The term "study treatment" throughout the protocol, refers to "study intervention-cilta-cel OOS" as defined in Section 6.1, Study Intervention Administered.

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

The term "participant" throughout the protocol refers to the common term "subject" or "patient".

2.1. Study Rationale

Cilta-cel is an autologous BCMA-targeted CAR-T cell therapy that relies on the participant's T cells, collected during apheresis, as starting material for the manufacturing process. There exists a high degree of individual variability of the apheresis material and issues during the manufacturing process that may cause the finished drug product to not meet all pre-specified release criteria. As a personalized therapy, unlike off-the-shelf therapies, such as small molecule or antibody therapies, the drug product cannot be exchanged by another drug product eg, from another readily manufactured batch fully meeting all specifications. The clinical circumstances of a participant may also not allow the additional time required to re-apherese or re-manufacture to produce a drug product that fully meets specifications. Additionally, a patient may still benefit from out-of-specifications (OOS) drug product.

Participants whose final manufactured cilta-cel batches do not meet the commercial release specifications are eligible for inclusion. Upon written notification of the cilta-cel being OOS, the treating physician can request the sponsor to activate an exceptional release process, during which cilta-cel OOS will be assessed individually by the sponsor for the expected benefit/risk profile. If the benefit/risk profile is deemed favorable, the treating physician/principal investigator will initiate eligibility and screening procedures and can formally request the shipment of the cilta-cel OOS for administration within the study. After providing informed consent the participant is enrolled into the study to receive cilta-cel OOS and followed for 2 years in this study to assess the safety and efficacy of cilta-cel OOS. All participants who received cilta-cel OOS will continue to

be monitored under a separate long-term follow-up (LTFU) safety study (68284528MMY4002) for up to 15 years after last dose of cilta-cel OOS.

2.2. Background

Cilta-cel is an autologous CAR-T therapy that targets BCMA, a molecule expressed on the surface of mature B-lymphocytes and malignant plasma cells. Results from study 68284528MMY2001 (CARTITUDE-1) indicate that cilta-cel has significant anti-myeloma activity and a safety profile consistent with the known mechanism of action of the product.

2.2.1. Multiple Myeloma

Multiple myeloma is an incurable, malignant, plasma cell disorder. It is the second most common hematologic malignancy, with 35,842 cases and approximately 23,275 deaths estimated in the EU-27 countries in 2020 (ECIS 2020). The current 5-year relative survival rate in Europe for patients with multiple myeloma is approximately 50%, with the most recent estimate of 51.3% provided by a study from the Swedish Multiple Myeloma Registry for the period 2011-2015 (Turesson 2018). In the US, multiple myeloma accounts for approximately 18% of hematological malignancies and 1.8% of all new cancer cases (Kumar 2020a). For 2022, the American Cancer Society projects about 34,470 new cases of multiple myeloma and 12,640 deaths in the US (American Cancer Society 2022). The 5-year survival rate in the US for patients with multiple myeloma diagnosed from 2011 to 2017 was 55.6% (Howlader 2021). By race and ethnicity, the incidence and death rates are highest in the non-hispanic black population (American Cancer Society 2022; Marinac 2020).

Multiple myeloma is characterized by the proliferation of neoplastic clones of plasma cells derived from B-lymphocytes. These neoplastic clones grow in the bone marrow, frequently invade the adjacent bone, disrupt both bone homeostasis and hematopoiesis, and cause multifocal destructive lesions throughout the skeleton that result in bone pain and fracture (Chung 2017). Common clinical presentations of multiple myeloma are hypercalcemia, renal insufficiency, anemia, bony lesions, bacterial infections, hyperviscosity, and secondary amyloidosis (Orlowski 2013).

Treatment options for multiple myeloma have substantially improved over time and vary depending on the aggressiveness of the disease, underlying prognostic factors, physical condition of the patient, and existing co-morbidities (Chung 2017). Therapeutic options include agents such as proteasome inhibitors, immunomodulatory drugs (IMiDs), monoclonal antibodies, and stem cell transplantation.

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

2.2.2. B-cell Maturation Antigen

B-cell maturation antigen (BCMA, also known as CD269 and TNFRSF17) is a 20 kilodalton, type III membrane protein that is part of the tumor necrosis receptor superfamily. BCMA is predominantly expressed in B-lineage cells and plays a critical role in B-cell maturation and subsequent differentiation into plasma cells (Tai 2015). BCMA binds 2 ligands that induce B-cell

proliferation: a proliferation inducing ligand (APRIL; CD256) and B-cell activating factor (BAFF; CD257) (Avery 2003; Darce 2007; Patel 2004). Upon binding of BCMA monomers to the APRIL trimer, activation and phosphorylation of p38MAPK, ELK, and NF-κB are triggered through intracellular tumor necrosis factor receptor (TNF-R)-associated factor (TRAF) molecules leading to pro-survival gene regulation (Bossen 2006; Hatzoglou 2000; Kimberley 2009).

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

2.2.3. CAR-T Therapy

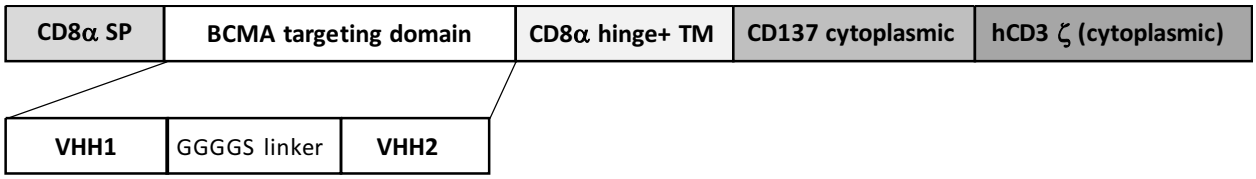
Chimeric antigen receptor-T (CAR-T) cell therapy uses modified autologous T cells that are activated in an MHC-independent manner upon binding to their target. This results in lysis of the targeted cells (Mikkilineni 2020).

2.2.4. Cilta-cel

Cilta-cel consists of autologous CAR-T cells that target BCMA. The novel design features two targeting domains on BCMA, to confer avidity of LCAR-B38M to the BCMA expressing cells.

The LCAR-B38M coding sequence comprises a human CD8 alpha signal peptide (CD8α SP), BCMA targeting domain consisting of 2 different variable fragments of heavy chain antibodies (VHH [single domain antibody, clone VHH1 and VHH2]), human CD8 alpha hinge and transmembrane domain (CD8α hinge+TM), human CD137 cytoplasmic domain (4-1BB costimulatory domain), and a human CD3 zeta cytoplasmic domain (CD3ζ (Figure 2). The expression of LCAR-B38M is driven and controlled by a human elongation factor 1 alpha promoter (hEF1α promoter).

Figure 2: LCAR-B38M Coding Region



Abbreviations: BCMA=B-cell maturation antigen; hCD3ζ=a human CD3 zeta cytoplasmic domain; CD8α SP=CD8 alpha signal peptide; CD8α hinge+TM=CD8 alpha hinge and transmembrane domain; GGGGS=4 glycines and 1 serine; VHH=variable fragments of heavy-chain antibodies (clone A37353 as VHH1 and clone A37917 as VHH2).

2.2.5. Nonclinical Studies

The nonclinical pharmacology program was designed to characterize the biologic activity and mechanism of action of cilta-cel. In vitro mechanistic proof-of-principle studies have assessed target engagement with respect to:

- On-target binding (ie, binding of VHH to BCMA)
- Off-tumor target activity (ie, in human non-myeloma cell lines, including lung, liver, breast, brain, embryonic kidney and kidney expressing hERG)
- On-tumor target activity (ie, in human multiple myeloma cell lines)

Refer to the latest edition of Investigator's Brochure (IB JNJ-68284528) for a complete description of the nonclinical study information.

2.2.6. Clinical Studies

Efficacy and Safety Studies

Study Legend-2

Legend-2 is an ongoing Phase 1, single-arm, open-label, multicenter, first-in-human trial to determine the safety and efficacy of LCAR-B38M CAR-T cells used to treat participants with relapsed multiple myeloma. Enrollment in this investigator-initiated study completed in November 2017; a total of 74 participants with relapsed or refractory multiple myeloma have been treated with LCAR-B38M CAR-T cell therapy (NCT 03090659). Refer to the latest edition of Investigator's Brochure (IB JNJ-68284528) for a complete description of the safety and efficacy outcomes of Legend-2.

Study 68284528MMY2001

A total of 113 participants (Phase 1b: 35; Phase 2: 78) were enrolled (apheresed) between 16 July 2018 and 7 October 2019 across 16 sites in US, out of which 101 participants (Phase 1b: 30; Phase 2: 71) received lymphodepleting chemotherapy and 97 participants (Phase 1b: 29; Phase 2: 68) received cilta-cel infusion and received it at the targeted recommended Phase 2 dose (RP2D). These 97 participants constituted the all treated analysis set, which was the basis for all efficacy and safety analyses presented below. At the clinical data cutoff, 1 September 2020, the median duration of follow-up for the all treated analysis set was 12.4 months. Four participants received lymphodepleting chemotherapy but did not receive cilta-cel infusion. Two of them refused future study treatment, one withdrew due to adverse event and one died.

In the all treated analysis set, the median time since initial diagnosis to enrollment was 5.94 years, and the median number of lines of prior therapy was 6. Participant's median age was 61 years. All participants had received prior treatment with a proteasome inhibitor, IMiD, and anti-CD38 antibody therapy. Ninety-six (99%) participants were refractory to the last line of therapy prior to study entry, and 85 (87.6%) participants were triple-refractory (refractory to an anti-CD38, a

proteasome inhibitor, and a IMiD) and 41 (42.3%) participants penta-refractory (refractory to an anti-CD38, at least 2 PIs, and at least 2 IMiDs), respectively. A total of 87 (89.7%) participants had one or more prior autologous stem cell transplant(s) and 8 (8.2%) participants had a prior allogeneic transplant.

Primary efficacy endpoint:

Response was assessed by an Independent Review Committee (IRC) based on International Myeloma Working Group (IMWG) criteria. The ORR (stringent complete response [sCR]+complete response [CR]+very good partial response [VGPR]+partial response [PR]) was 97.9% (95% confidence interval [CI]: 92.7%, 99.7%), with 92 participants (94.8%) achieving VGPR or better and 78 participants (80.4%) achieving an sCR. The median duration of response (DOR) was 21.8 months (95% CI: 21.8 months, not evaluable [NE]).

Major secondary efficacy endpoints:

- Time to response (TTR): median time to first response (PR or better) and to best response were 0.95 and 2.56 months, respectively
- Fifty-six participants (57.7%) achieved minimal residual disease (MRD) negativity at the 10^{-5} threshold of sensitivity with 42 participants (43.3%) achieving MRD-negative CR/sCR.
- The overall median progression-free survival (PFS) based on the IRC response assessment was 22.8 months (95% CI: 22.8 months, NE) and the 12-month PFS rate was 76.3% (95% CI: 66.5%, 83.6%).

Exposure:

The median (range) of cilta-cel dose formulated and dose administered were 0.693 (0.52, 0.94) and 0.709 (0.51, 0.95) × 10^6 CAR-positive viable T cells/kg, respectively.

- All 97 participants (100%) experienced at least one treatment emergent adverse event (TEAE). The most common (at least 20%) TEAEs were: neutropenia, cytokine release syndrome (CRS), anemia, thrombocytopenia, leukopenia, lymphopenia, fatigue, cough, hypocalcemia, hypophosphatemia, diarrhea, decreased appetite, aspartate aminotransferase increased, nausea, hypoalbuminemia, alanine aminotransferase increased, hyponatremia, constipation, hypokalemia, chills, pyrexia.
- All but one participant had at least one TEAE considered to be related to ~~JNJ-68284528~~ cilta-cel by the investigator.
- All participants experienced at least one Grade 3 or 4 TEAE.
- Fifty-three (54.6%) participants experienced treatment-emergent SAEs, among whom 29 (29.9%) had Grade 3 or 4 and 6 (6.2%) participants had Grade 5 treatment-emergent SAEs.
- Among the 97 participants in the all treated population, 21 deaths (21.6%) were reported, of which 10 were attributed to progressive disease. The 11 remaining deaths were attributed to AEs with 6 related to cilta-cel (3 infections, 1 respiratory failure, 1 CRS/ HLH, and 1 neurotoxicity). None of the deaths occurred within 30 days of the initial cilta-cel infusion. Two deaths (sepsis on Day 45 and CRS/HLH on Day 99) occurred within 100 days of the initial cilta-cel infusion.

- Adverse event of special interest (AESI):
  - CRS: All-grade CRS was reported for 92 (94.8%) participants, with 3, 1, and 1 participants experienced Grades 3, 4, and 5 events, respectively, evaluated by the American Society for Transplantation and Cellular Therapy (ASTCT) consensus grading system. Median time from cilta-cel infusion to CRS onset was 7 days (range: 1 to 12), and the median duration of CRS was 4 days (range: 1 to 14 after excluding one participant with a 97-day duration complicated by HLH). All events of CRS had recovered, with the exception of 1 (1.1%) fatal event from the participant with the 97-day duration with HLH.
  - Neurotoxicity was reported for 20 (20.6%) participants:
    - Immune Effector Cell-Associated Neurotoxicity (ICANS): All grade ICANS was reported for 16 (16.5%) participants. Of these, 2 (2.1%) participants had maximum Grade 3 or 4 events, evaluated by the ASTCT consensus grading system. Median time from cilta-cel infusion to ICANS onset was 8 days (range: 3 to 12), and the median duration of ICANS was 4 days (range: 1 to 12). All events had recovered. Concurrent CRS was noted for 15 out of 16 participants.
    - Other neurotoxicities (not reported as ICANS [ie, onset after a period of recovery from CRS and ICANS]): All-grade other neurotoxicities were reported for 12 (12.4%) participants. Of these, 8 participants had maximum Grade 3 or 4 events and 1 participant had a fatal event. Median time from cilta-cel infusion to first onset of other neurotoxicities was 26.5 days (range: 11 to 108). Events of other neurotoxicities was fatal for 1 participant, did not recover for 5 participants, and recovered for 6 participants. Among those recovered, the median time to recovery was 74.5 days.
  - Tumor lysis syndrome (TLS): 1 participant reported Grade 4 treatment-emergent TLS, accompanied by Grade 3 blood creatinine increased.
  - Ten participants (10.3%) experienced a SPM. Eight participants (8.2%) developed second hematologic malignancies with the most frequently reported being myelodysplastic syndrome in 6 participants (6.2%). Three participants (3.1%) developed acute myeloid leukemia, all of which resulted in death. Cutaneous/noninvasive and noncutaneous/invasive malignancies were reported for 3 (3.1%) and 1 (1.0%) participants, respectively. All SPMs were considered not related to cilta-cel by investigator assessment.
- Other safety observations:
  - Cytopenic TEAEs were reported for all 97 participants (100.0%). Ninety-six participants (99.0%) reported 1 or more Grade 3 or 4 cytopenic TEAEs. No participants experienced Grade 5 cytopenic TEAEs. Three participants (3.1%) experienced serious thrombocytopenia, 1 participant (1.0%) experienced serious neutropenia, and 4

participants (4.1%) experienced serious febrile neutropenia. Eight (8.2%), 10 (10.3%), and 23 (23.7%) participants had their initial Grade 3 or 4 events not recovered to Grade 2 or lower by Day 60 for lymphopenia, neutropenia, and thrombocytopenia, respectively. The most frequently reported (>40% of participants) TEAEs (by Preferred Term) within the Blood and lymphatic system disorders System Organ Class included:

  - anemia: 79 participants (81.4%) (Grade 3 or 4: 66 [68.0%]),
  - thrombocytopenia: 77 participants (79.4%) (Grade 3 or 4: 58 [59.8%]),
  - leukopenia: 60 participants (61.9%) (Grade 3 or 4: 59 [60.8%]), and
  - lymphopenia: 51 participants (52.6%) (Grade 3 or 4: 48 [49.5%]).

- Infections: 56 (57.7%) participants had infection TEAE, of whom 19 (19.6%) participants with Grade 3 or 4 events, and 3 (3.1%) participants with fatal events (sepsis, septic shock, lung abscess).

Conclusion:

Data from study 68284528MMY2001 establishes a positive benefit/risk profile for cilta-cel in the treatment of patients with heavily pretreated, relapsed and highly refractory multiple myeloma. Cilta-cel treatment yielded deep and durable responses with VGPR or better in 94.8% of participants and a median DOR was 21.8 months. The safety profile is generally consistent with the current understanding of CAR-T therapy. CRS was common (94.8%), but most were low grade. Neurotoxicity was reported in 20.6% of participants, including ICANS and other events not defined as ICANS (Grade ≥3 in 9.2% of participants).

Grade 3 or 4 cytopenias were common in the post-infusion period, and the majority of these events recovered by Day 60. Infectious AEs Grade ≥3 were reported for 22.7% of participants. Six participants died due to cilta-cel related AEs, including 1 each of CRS complicated by secondary HLH, neurotoxicity, respiratory failure, and 3 due to infection (NCT03548207).

2.3. Benefit-Risk Assessment

The potential risks of cilta-cel OOS are identified from the following: 1) results of nonclinical studies; 2) mechanism of action; and 3) previous clinical experience with cilta-cel and LCAR-B38M CAR-T cells. Detailed information about the known and expected benefits and risks of cilta-cel may be found in the latest edition of IB (IB JNJ-68284528).

By stimulating an inflammatory cascade, there is potential for toxicity in other tissues or organs by non-specific immune cell activation. Therefore, special attention should be given to both immunological and immunogenicity-related toxicities. Longer post-treatment follow-up and treatment of additional participants, particularly participants who have received fewer prior therapies than participants in the Legend-2 and 68284528MMY2001 studies, may reveal additional risks.

As part of this study, participants will be treated with drug product that did not meet the pre-defined release specifications required for commercial product. While a benefit/risk assessment for each individual study participant will be performed via medical review by the sponsor, there is a risk that cilta-cel OOS has a different safety and efficacy profile compared to cilta-cel meeting all drug product specifications. Main risks regarding potential benefit is to receive a drug product with inferior efficacy compared to historic data from 68284528MMY2001. In terms of safety there may also be risks for higher rates, more severe or new adverse events (AEs) after receipt of cilta-cel OOS compared to data from 68284528MMY2001.

Important identified and potential risks with mitigation strategies associated with cilta-cel and cilta-cel-OOS, respectively, are outlined in Table 2 and other potential risks and mitigation strategies for cilta-cel are presented in Table 3.

2.3.1. Risks for Study Participation

Table 2: Important Identified and Potential Risks with Mitigation Strategies for Study Participants (cilta-cel OOS and cilta-cel)

Risks of Clinical Significance	Risk Characterization and Rationale	Mitigation Strategies
Potential risks associated with cilta-cel OOS		
Lack of efficacy	• Administration of cilta-cel OOS may be less efficacious compared to drug product fully meeting drug product specifications	• Sponsor medical review process will determine and document the benefit/risk assessment for each study participant, which will include the potential OOS safety and efficacy impact, study participant alternative options/medical need, and assessment of potential immediate risk of not receiving the product.
More frequent, more severe, new adverse events	• Cilta-cel OOS may exhibit a different safety profile compared to drug product fully meeting drug product specifications	• Sponsor medical review process will determine and document the benefit/risk assessment for each study participant, which will include the potential OOS safety and efficacy impact, study participant alternative options/medical need, and assessment of potential immediate risk of not receiving the product.
Risks associated with cilta-cel		
It is assumed that all important identified and other potential risks of cilta-cel apply to cilta-cel OOS. Study participants should be closely monitored, and adverse events managed according to current recommendations for cilta-cel as summarized below		
Important Identified Risks associated with cilta-cel		
Risks of Clinical Significance	**Risk Characterization and Rationale**	**Mitigation Strategies**

Table 2: Important Identified and Potential Risks with Mitigation Strategies for Study Participants (cilta-cel OOS and cilta-cel)

Risks of Clinical Significance	Risk Characterization and Rationale	Mitigation Strategies
Cytokine Release Syndrome	• Symptoms indicative of CRS may include, but are not limited to, fever (with or without rigors), arthralgia, nausea, vomiting, tachypnea, hypoxia, tachycardia, hypotension, headache, confusion, tremor, delirium, dyspnea, pulmonary edema, and capillary leak. • Potentially life-threatening complications of CRS may include cardiac dysfunction, adult respiratory distress syndrome, neurologic toxicity, renal failure, hepatic failure, and disseminated intravascular coagulation. • Rarely, severe CRS can evolve into a presentation consistent with hemophagocytic lymphohistiocytosis/macrophage activation syndrome (HLH/MAS) that may require additional therapy. Severe thrombocytopenia, low fibrinogen, and often disseminated intravascular coagulation (DIC) may be features of HLH, all of which combined may increase the risk of severe bleeding in these subjects. Section 6.1.5.1 describes measures to be taken if HLH is suspected. • Fatal HLH occurred in one patient (1%), 99 days after cilta-cel infusion. The HLH event was preceded by prolonged CRS lasting 97 days. The manifestations of HLH/MAS include hypotension, hypoxia with diffuse alveolar damage, coagulopathy, cytopenia and multi-organ dysfunction, including renal dysfunction.	• Monitor closely for CRS and follow guidance for management in protocol. • Laboratory testing to monitor for disseminated intravascular coagulation, a manifestation of CRS, • Daily monitoring of chemistry and hematology assessments (including ferritin and CRP), when fever or other signs of potential CRS are present. Body temperature should be monitored at least twice daily for 28 days post infusion. • Pulmonary, renal and hepatic function to be monitored closely • Resources necessary for resuscitation (ie, agents such as epinephrine and aerosolized bronchodilator; medical equipment such as oxygen, tracheostomy equipment, and a defibrillator) should be readily available. • At the first sign of CRS (such as fever) participants should be immediately hospitalized for evaluation. See Table 5 for hospitalization requirements. • Tocilizumab (at least 2 doses) must be available prior to administration of cilta-cel OOS. Tocilizumab intervention may be considered with presenting symptom of fever in the absence of clear infectious etiology. Early tocilizumab should be considered in participants at high risk of severe CRS. • Vital signs and laboratory parameters must be monitored at regular intervals until normal. • Based on institutional practice guidelines, consider alternate immunosuppressants (eg, other cytokine-targeting therapies) for participants who develop high grade CRS with laboratory findings overlapping with HLH/MAS that remains severe or life-threatening following administration of tocilizumab and corticosteroids.

Table 2: Important Identified and Potential Risks with Mitigation Strategies for Study Participants (cilta-cel OOS and cilta-cel)

Risks of Clinical Significance	Risk Characterization and Rationale	Mitigation Strategies
		• The use of myeloid growth factors, particularly granulocyte colony-stimulating factor (G-CSF), should be avoided during CRS. • Notify the sponsor if participant is experiencing Grade 2 or higher CRS. CRS will be captured as an adverse event of special interest.
Neurotoxicity Immune-Effector Cell-Associated Neurotoxicity Syndrome (ICANS)	• Symptoms indicative of ICANS may include, but are not limited to speech disorders, aphasia, convulsions, disturbances in consciousness, confusion, disorientation, or coordination and balance disorders • Early recognition of neurologic adverse events is critical to management. Participants should be advised to seek medical evaluation if they notice new onset of headache, convulsions, speech disorders, visual disorders, disturbances in consciousness, confusion and disorientation, and coordination, balance disorders, or mental status changes. Notify the sponsor if participant is experiencing any grade ICANS	• Monitor closely for neurologic AEs, including CAR-T cell-related neurotoxicity (eg, ICANS) and raised intracranial pressure / cerebral edema; follow guidance for management in protocol. • Participants should have the Immune-Effector Cell-associated Encephalopathy (ICE) Assessment Tool performed at baseline and daily after the first symptoms of CAR-T cell-related neurotoxicity (eg, ICANS) are suspected and until resolution. • Consider performing neuroimaging (eg, magnetic resonance imaging [MRI]) at screening and/or neurology consultation if pre-existing disease is suspected. • Monitor patients for signs or symptoms of neurologic toxicities for 4 weeks after infusion and treat promptly. At the first sign of neurotoxicity, neurology consultation and evaluation should be considered. • Consider non-sedating, anti-seizure medicines (eg, levetiracetam) for seizure prophylaxis for any Grade 2 or higher neurologic toxicities. • Treatment with tocilizumab should be considered when concurrent with CRS. Other causes of neurologic symptoms should be ruled-out. Guidelines for the management of raised ICP/cerebral edema as per Table 8.

Table 2: Important Identified and Potential Risks with Mitigation Strategies for Study Participants (cilta-cel OOS and cilta-cel)

Risks of Clinical Significance	Risk Characterization and Rationale	Mitigation Strategies
		• Other cytokine-targeting therapies (for example, IL1) may be used based on institutional practice, especially for cases of neurotoxicity which does not respond to tocilizumab or corticosteroids. Therapy directed at reduction or elimination of CAR-T cells, including chemotherapy, may be considered in consultation with the sponsor for participants who develop neurotoxicity that remains severe or life-threatening following prior therapies, including tocilizumab and corticosteroids.
• Other Neurotoxicities	• Other severe or serious neurological toxicities may occur after a period of recovery from CRS and/or initial ICANS. • <u>Movement and Neurocognitive Toxicity (ie, Parkinsonism)</u>: A cluster of symptoms with variable onset spanning more than one symptom domain was observed, including: changes in movement (eg, micrographia or changes in handwriting, tremors, bradykinesia, rigidity, shuffling gait, impaired balance and coordination, difficulty writing, difficulty performing activities of daily living like dressing or feeding oneself), cognitive impairments (eg, memory loss or forgetfulness, disturbance in attention, mental slowness or fogginess, difficulty speaking or slurred speech, difficulty reading or understanding words), and personality changes (eg, reduced facial expression, flat affect, reduced ability to express emotion, less communicative, disinterest in activities). • This delayed onset of movement and neurocognitive toxicity was observed at a higher frequency in participants with high burden of disease and in participants experiencing higher grade CRS (Grade 2 and above) and any grade ICANS. This may be indicative that ≥Grade 2 CRS or any grade ICANS are early indicators for the development of other neurotoxicity after a period of recovery from CRS and/or ICANS. Therefore, ≥Grade 2 CRS or any grade ICANS may represent an opportunity for early intervention and more aggressive supportive care (including steroids), especially in patients treated with a high tumor burden, that may mitigate the risk for	• At the first sign of neurotoxicity, neurology consultation and evaluation should be considered. <u>Movement and Neurocognitive Toxicity (ie, Parkinsonism)</u>: • If neurologic or psychiatric symptoms consistent with a cluster of movement and neurocognitive toxicity are noted, contact the medical monitor and refer the participant immediately to a neurologist for a full evaluation. • Consider early and aggressive supportive care including steroids in patients presenting with higher grade CRS or any grade ICANS and handwriting assessments for early detection of neurotoxicity symptoms, and extended monitoring and reporting time for neurotoxicity for the duration of the study. • Consider reducing baseline burden of disease with bridging chemotherapy prior to infusion with cilta-cel in patients with high tumor burden. • Therapy directed at reduction or elimination of CAR-T cells, including chemotherapy, may be considered for patients who develop neurotoxicity that remains unresponsive to other interventions. • Greater than or equal to Grade 2 CRS or any grade ICANS may represent an opportunity for early intervention and more aggressive supportive care (including steroids)

Table 2: Important Identified and Potential Risks with Mitigation Strategies for Study Participants (cilta-cel OOS and cilta-cel)

Risks of Clinical Significance	Risk Characterization and Rationale	Mitigation Strategies
	developing late, other neurotoxicity. Infection and sepsis were seen concurrently in many of these patients.	especially in patients treated with high tumor burden, may mitigate the risk of developing neurotoxicity later, after resolution of CRS. • Infection and sepsis were seen concurrently in many of these patients.
	• Cranial Nerve Palsies: Occurrence of 7th, 3rd, 5th, and 6th cranial nerve palsy, some of which were bilateral, worsening of cranial nerve palsy after improvement, and occurrence of peripheral neuropathy in patients with cranial nerve palsy have been reported in trials of cilta-cel. Median time of onset of symptoms was 62 days (range: 4 to 136 days), median duration of peripheral neuropathies was 256 days (range: 2 to 465 days) including those with ongoing neuropathy.	Cranial Nerve Palsies: • Monitor patients for signs and symptoms of cranial nerve palsies. Consider management with short-course systemic corticosteroids, depending on the severity and progression of signs and symptoms.
	• Peripheral Neuropathy: Occurrence of peripheral neuropathy, including sensory, motor, or sensorimotor, have been reported in trials of cilta-cel. Median time of onset of symptoms was 62 days (range: 4 to 136 days), median duration of peripheral neuropathies was 256 days (range: 2 to 465 days) including those with ongoing neuropathy	Peripheral Neuropathy: • Monitor patients for signs and symptoms of peripheral neuropathies. Consider management with short-course systemic corticosteroids, depending on the severity and progression of signs and symptoms.
	• Guillain-Barré Syndrome: A fatal outcome following Guillain-Barré syndrome has been reported after treatment with cilta-cel in another ongoing study. Symptoms reported include those consistent with Miller-Fisher variant of GBS, motor weakness, speech disturbances, and polyradiculoneuritis.	Guillain-Barré Syndrome: • Monitor for signs and symptoms of GBS after cilta-cel infusion. Consider treatment with IVIG and escalate to plasmapheresis, depending on toxicity severity per institutional guidelines.

Table 2: Important Identified and Potential Risks with Mitigation Strategies for Study Participants (cilta-cel OOS and cilta-cel)

Risks of Clinical Significance	Risk Characterization and Rationale	Mitigation Strategies
Prolonged or Recurrent Cytopenia	Participants may exhibit cytopenias for several weeks following lymphodepleting chemotherapy and cilta-cel OOS infusion. In Study 68284528MMY2001 (N=97), 30% (29/97) of patients experienced prolonged Grade 3 or 4 neutropenia and 41% (40/97) of patients experienced prolonged Grade 3 or 4 thrombocytopenia that had not resolved by Day 30 following cilta-cel infusion. In 31% (29/95) of patients who recovered from Grade 3 or 4 neutropenia after 1 month, the median time to recovery from cilta-cel infusion was 1.8 months (range: 1.0 to 3.7 months). In 52% (32/61) of patients who recovered from Grade 3 or 4 thrombocytopenia after 1 month, the median time to recovery from cilta-cel infusion was 1.9 months (range: 1.1 to 8.5 months).	• Blood counts should be monitored after cilta-cel OOS infusion and provide supportive care (eg, irradiated packed red blood cells [PRBCs] and platelets, granulocyte colony-stimulating factor for neutropenia) as outlined by institutional guidelines. • The use of myeloid growth factors, particularly granulocyte-colony stimulating factor (G-CSF), should be avoided during CRS. Pegylated myeloid growth factors (ie, pegfilgrastim) are prohibited until Day 100. • Prolonged neutropenia may increase the risk of infection. Severe thrombocytopenia may increase the risk of bleeding. Monitor hematological parameters and provide supportive care as outlined by institutional guidelines. • Parvovirus B19 monitoring by PCR should be considered in participants experiencing prolonged neutropenia or a decline in neutrophil counts following recovery.
Serious Infection	• Administration of cilta-cel OOS may increase the risk of infection due to cytopenias or hypogammaglobulinemia. • HBV reactivation, in some cases resulting in fulminant hepatitis, hepatic failure and death, may occur in participants treated with drugs directed against B cells. HBV reactivation has occurred in participants who appear to have resolved hepatitis B infection. • Subjects receiving cilta-cel may be at a higher risk of severe/fatal outcomes from COVID-19 infection compared with patients who are receiving standard of care therapy. Subjects should be reminded of the importance of vaccines and other preventative measures. Investigators should consider prophylaxis (eg, Evusheld, if available) and antiviral medications (eg, Paxlovid, if available) for patients diagnosed with COVID-19 infection, as noted in Section 10.6, Appendix 6.	• Do not administer cilta-cel OOS infusion to participants with active infection. • Participants should be monitored frequently for infection and should have blood cultures obtained, serum inflammatory markers (CRP), and/ or and empiric antibiotics administered as appropriate, based on clinical judgment and per institutional standards. • Perform screening for hepatitis B virus (HBV), hepatitis C virus (HCV), and human immunodeficiency virus (HIV) and monitor as clinically indicated, and initiate treatment as appropriate. Routinely monitor HBV DNA and AST/ALT for participants with risk of HBV reactivation. Prophylaxis for participants at high risk of HBV reactivation is recommended per institutional guidance. • Immunocompromised patients are at risk for opportunistic infections; prophylactic use of antibiotics, antivirals, or antifungals should be considered.

Table 2: Important Identified and Potential Risks with Mitigation Strategies for Study Participants (cilta-cel OOS and cilta-cel)

Risks of Clinical Significance	Risk Characterization and Rationale	Mitigation Strategies
		• Extended use of anti-microbial therapies for at least 6 month or consistent with post ASCT consensus guidelines after CAR-T dosing are recommended (Section 10.13, Appendix 13) • The safety of immunization with live viral vaccines has not been studied. Vaccination with live virus vaccines is not recommended for at least 6 weeks prior to the start of lymphodepleting chemotherapy, and until immune recovery following treatment with cilta-cel.

Abbreviations: ALT=alanine aminotransferase; ASCT=autologous stem cell transplant; AST=aspartate aminotransferase; CAR-T=chimeric antigen receptor-T (cells); CMV=cytomegalovirus; CRP=C-reactive protein; CRS=cytokine release syndrome; DMSO=dimethyl sulfoxide; G-CSF=granulocyte-colony stimulating factor; HBV=hepatitis B virus; ICANS=Immune-Effector Cell-Associated Neurotoxicity Syndrome; ICE=Immune-Effector Cell-associated Encephalopathy; ICP=intracranial pressure; IgG=Immunoglobulin G; IVIG=intravenous immunoglobulin; MRI=magnetic resonance imaging; OOS=out-of-specifications; PCR=polymerase chain reaction; TLS=tumor lysis syndrome.

Table 3: Other Potential Risks and Mitigation Strategies for Study Participants (cilta-cel)

Risks of Clinical Significance	Risk Characterization and Rationale	Mitigation Strategies
Tumor Lysis Syndrome (TLS)	Although TLS is uncommon in participants with multiple myeloma, participants must be monitored closely for symptoms of TLS	• Monitor closely for TLS with frequent monitoring of chemistry parameters (ie, hyperkalemia, hyperuricemia, hyperphosphatemia, and hypocalcemia), and follow guidance for management in protocol. • High risk participants, ie, those with a high tumor burden (≥60% plasma cell infiltrate on the bone marrow biopsy or aspirate [whichever is higher] or a participant with multiple extramedullary disease sites or plasmacytomas), should be treated prophylactically in accordance with local standards. (eg, extra hydration; diuretics; allopurinol; and primary or secondary uricosuric agents, as indicated).
Hypogammaglobulinemia	Hypogammaglobulinemia may occur in participants receiving cilta-cel OOS. Hypogammaglobulinemia was reported as an adverse event in 12% of patients; laboratory IgG levels fell below 500 mg/dL after infusion in 92% (89/97) of patients treated with cilta-cel. Hypogammaglobulinemia either as an adverse reaction or a laboratory IgG level below 500 mg/dL, after infusion occurred in 94% (91/97) of patients treated with cilta-cel. Thirty-eight percent of patients received intravenous immunoglobulin (IVIG) post cilta-cel for either an adverse reaction or prophylaxis.	• Monitor immunoglobulin levels after treatment and more frequently, if clinically indicated. Treat according to local guidelines, including administration of Ig replacement and monitoring for infection. • Participants with IgG <400 mg/dL or recurrent infections (including HBV reactivation) should be considered for prophylactic IV or subcutaneous IgG per institutional guidelines. • Vaccination with live virus vaccines is not recommended for at least 6 weeks prior to the start of lymphodepleting chemotherapy.
Second primary malignancy (SPM)	Second primary malignancy is a theoretical possibility due to the risk of lentiviral insertion (DNA integration) of the lentiviral vector.	• Second primary malignancies should be managed per institutional standards. • Second primary malignancies must be reported during the duration of the study, irrespective of when they occur, and subsequently will be collected in a long-term follow-up study yearly until 15 years post dosing of cilta-cel OOS.

Table 3: Other Potential Risks and Mitigation Strategies for Study Participants (cilta-cel)

Risks of Clinical Significance	Risk Characterization and Rationale	Mitigation Strategies
		• A tumor sample should be collected and DNA, RNA or protein analysis may be performed to investigate the presence of lentiviral elements. • SPM is an adverse event of special interest (AESI).
Hypersensitivity reactions	Allergic reactions may occur with the infusion of cilta-cel. Hypersensitivity reactions have occurred in 5% of patients following cilta-cel infusion. All reactions were Grade 1 and symptoms included flushing (n=4), chest discomfort (n=2), tachycardia (n=1), wheezing (n=1), term or (n=1), and burning sensation (n=1).Serious hypersensitivity reactions including anaphylaxis, may be due to dimethyl sulfoxide (DMSO), dextran 40, or residual kanamycin in cilta-cel.	• Participants should be carefully monitored for 2 hours after infusion for signs and symptoms of severe reaction • Participants should be treated urgently per institutional standards, according to the severity of the hypersensitivity reaction avoiding corticosteroid use if possible. • Participants should receive premedication (ie, antihistamine, antipyretic) prior to cilta-cel OOS dosing as noted in Section 6.1.1.

Abbreviations: DMSO=dimethyl sulfoxide; ICANS=Immune-Effector Cell-Associated Neurotoxicity Syndrome; ICE=Immune-Effector cell-associated Encephalopathy; IgG=Immunoglobulin G; IVIG=intravenous immunoglobulin; TLS=tumor lysis syndrome; MRI=magnetic resonance imaging; OOS=out-of-specifications; PCR=polymerase chain reaction; SPM=second primary malignancy.

2.3.2. Benefits for Study Participation

Potential benefits for the participant are that the drug product (cilta-cel OOS) may elicit a treatment effectiveness with a safety profile comparable to the commercial drug product that met the specification criteria.

2.3.3. Benefit-Risk Assessment for Study Participation

The benefit/risk will be determined for each individual participant ahead of enrollment into the study and must be determined as positive by both, the sponsor's medical review as well as by the treating physician/principal investigator. The benefit/risk assessment by medical evaluation includes assessment of the out-of-specifications' potential impact on cilta-cel´s safety and efficacy, the participant's alternative treatment options, medical need, and assessment of potential immediate hazards of not receiving the cilta-cel OOS. While clinical information of out-of-specifications release criteria drug product is limited, the following outcomes have been observed in participants within the Legend-2 study, where study participants received a dose below the target dose per USPI or locally approved label.

- In Legend-2, participants were treated with LCAR-B38M CAR-T cells, which expresses the identical CAR and provides supporting benefit-risk data.

- The safety and efficacy summary of Legend-2 is described in the latest edition of the IB (IB JNJ-68284528). There were 13 participants in Legend-2 study who received a dose in range of 0.1×10^6 to 0.5×10^6 cells/kg, out of 13 participants, 9 participants achieved PR or better. Albeit changes in the methodology of cell-count and manufacturing changes have been implemented for commercial cilta-cel, these data are seen supportive in the assessment of benefit/risk of cilta-cel OOS for a dose below the target dose per USPI or locally approved label.

- In study 68284528MMY2001, based on release specification criteria, 4 out of 97 participants received a drug product that was out of specification. Two participants received a cilta-cel infusion which did not meet the requirement for a single dose of 0.5×10^6 CAR-positive cells/kg/bag specification and hence these 2 participants were dosed with 2 cilta-cel infusion bags each to achieve the target dose. Two other participants received a product that was above the accepted natural killer (NK) cell value range. Of these 4 participants, 2 achieved VGPR and 2 achieved a sCR. There were no clinically significant AE signals reported for these participants.

As part of this open-label study, emerging safety and efficacy data will be closely monitored by the study responsible physician and study team. A Data Review Committee (DRC) will regularly review aggregated outcomes and can trigger additional safety analysis and reviews as indicated. Clinically important information with updated guidance on OOS and potential impact on safety and efficacy will be made available to investigators as appropriate.

It is assumed that cilta-cel OOS will display similar safety and efficacy as cilta-cel, as of the 1 September 2020 clinical data cut-off, 97 participants had received cilta-cel infusion in Study 68284528MMY2001. The safety profile is in-line with observations from the Legend-2 study. Refer to the latest edition of Investigator's Brochure (IB JNJ-68284528) for a complete description of the safety and efficacy outcomes of Study 68284528MMY2001.

Thus, taking into account the measures taken to minimize risk to participants of this study, the potential risks identified in association with cilta-cel are justified by the anticipated benefits that may be afforded to participants with multiple myeloma.

3. OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	
• To evaluate the efficacy of cilta-cel OOS	• Overall Response of partial response or better (ie, ORR), as defined by the International Myeloma Working Group (IMWG) response criteria and assessed by the investigator. Time frame: Screening Phase through End of Study (EOS) (Month 24 after cilta-cel OOS infusion)/Early withdrawal
Secondary	
• To assess the safety of cilta-cel OOS	• Incidence and severity of treatment emergent adverse events, serious adverse events, adverse events of special interest, abnormalities in safety (laboratory assessments), vital signs, and physical examinations
• To further characterize the efficacy of cilta-cel OOS	• Partial Response (PR)/very good partial response (VGPR)/complete response (CR)/stringent complete response (sCR) rate and clinical benefit rate (CBR=ORR [sCR+CR+VGPR+PR]+MR [minimal response]), as defined by the IMWG response criteria, duration of response (DOR), progression-free survival (PFS), overall survival (OS) and minimal residual disease (MRD)-negative rate.
• To determine whether replication competent lentivirus is present in participants that receive cilta-cel OOS	• Presence of replication competent lentivirus
Exploratory	
• To characterize the pharmacokinetics and pharmacodynamics of cilta-cel OOS	• Biomarkers including baseline expression of BCMA in MM cells, depletion of BCMA expressing cells, systemic cytokine concentrations, and CAR-T PK parameters such as expansion and persistence via monitoring CAR-T positive cell counts, and CAR transgene levels
• To assess the immunogenicity of cilta-cel OOS	• Presence of anti-cilta-cel OOS antibodies.

Abbreviations: BCMA=B-cell maturation antigen; CAR-T=Chimeric antigen receptor-T cells; CBR=clinical benefit rate; CR=complete response; DOR=duration of response; EOS=End of Study; IMWG=International Myeloma Working Group; MM=multiple myeloma; MRD=minimal residue disease; MR=minimal response; OOS=Out-of-Specifications; ORR=overall response rate; OS=overall survival; PFS=progression-free survival; PK=pharmacokinetics; PR=partial response; sCR=stringent complete response; VGPR=very good partial response.

Refer to Section 8, Study Assessments and Procedures for evaluations related to endpoints.

HYPOTHESIS

The study hypothesis is that cilta-cel OOS will demonstrate similar safety and efficacy to data from study 68284528MMY2001, as assessed by the primary and secondary endpoints.

4. STUDY DESIGN

4.1. Overall Design

This is an open-label, single-arm multicenter Phase 2 study to evaluate the safety and efficacy of cilta-cel OOS in adult participants (≥18 years) with multiple myeloma as described in cilta-cel USPI (or locally approved label, respectively), and whose final manufactured cilta-cel does not meet the commercial release specifications.

Upon written notification of the cilta-cel being OOS, the treating physician can request the sponsor to activate an exceptional release process, during which cilta-cel OOS will be assessed individually by the sponsor for the expected benefit/risk profile. If the benefit/risk profile is deemed favorable, the treating physician/principal investigator will initiate screening procedures upon obtaining informed consent. If eligible, the treating physician/principal investigator can formally request the shipment of the cilta-cel OOS for administration within the study. Exceptional Release of OOS Product Request Form must be completed and signed off by the treating physician/principal investigator before releasing cilta-cel OOS to the participant.

The study will be conducted in following 5 phases:

- Screening Phase,
- Lymphodepleting chemotherapy,
- Cilta-cel OOS Administration,
- Post infusion, and
- Post-treatment

Cilta-cel OOS will not be administered to a participant whose medical condition does not meet the criteria for CAR-T infusion. Non-eligible medical conditions include active uncontrolled infection or condition where an administration of cilta-cel OOS constitutes serious health risk to the participant.

Eligible participants may continue bridging therapy (ie, anti-plasma cell directed treatment between apheresis and the first dose of the lymphodepleting chemotherapy) as clinically indicated (ie, to maintain disease stability while waiting for availability of cilta-cel). Bridging therapy and lymphodepleting chemotherapy will be considered as part of standard-of-care and are prescribed by the treating physician, if clinically indicated.

Lymphodepleting chemotherapy consists of IV cyclophosphamide 300 mg/m^2 and fludarabine 30 mg/m^2 daily for 3 days per USPI or locally approved label. Cilta-cel OOS will be administered at a total targeted dose of 0.75×10^6 CAR-positive viable T cells/kg (range: 0.5 to 1.0×10^6 CAR-positive viable T cells/kg) or per exceptional release criteria determined alternative dose, 5 to 7 days after start of the lymphodepleting chemotherapy.

Efficacy evaluations include myeloma protein measurements and imaging as indicated for enrolled participants to evaluate response and disease progression. Efficacy evaluations will be measured from Screening Phase through end of study by the investigator per IMWG consensus recommendations for multiple myeloma treatment response criteria (Section 10.10, Appendix 10).

Blood, serum and bone marrow samples will be collected for assessment of cilta-cel OOS PK, MRD-negative rate, and predictive biomarkers of response or resistance to cilta-cel OOS.

Safety evaluations will be assessed by adverse events, laboratory test results, vital sign measurements, physical examination findings, handwriting assessments, assessment of Immune-Effector Cell-associated Encephalopathy (ICE) Tool scores, and assessment of Eastern Cooperative Oncology Group (ECOG) performance status grade.

The safety profile will be evaluated at DRC meetings during the study. Follow-up of participants will continue to include all SAEs and delayed AEs, disease progression, and survival during the Post-treatment Phase. All study evaluations will be conducted according to the SoA, Table 1.

Following the cilta-cel OOS infusion, the participant will be followed for 2 years in this study to assess response, DOR, PFS, OS, and safety. All the participants who received cilta-cel OOS will continue to be monitored for long-term safety under a separate LTFU study 68284528MMY4002 for up to 15 years after last dose of cilta-cel OOS.

No formal enrollment target is planned for this study since the number of potential participants with cilta-cel OOS is unknown at this time. Based on the current manufacturing experience with the study 68284528MMY2001, at least 20 participants are anticipated to enroll in the study.

In the event the cilta-cel is OOS, the investigator will inform the study participant that the product did not meet release specifications prior to administration. The investigator will discuss with the participant the potential risks of receiving or not receiving the product as well as alternative treatment options, which will be properly documented in the participant's study records and ICF will be obtained. If required, approval/notification from the relevant health authorities for use of the cilta-cel OOS will be obtained. The investigator should also inform or obtain approval from the IEC/IRB as per institutional guidelines, as required.

A DRC will be commissioned for this study.

Refer to Committees Structure in Section 10.3, Appendix 3, Regulatory, Ethical, and Study Oversight Considerations for details.

A diagram of the study design is provided in Section 1.2, Schema.

4.2. Scientific Rationale for Study Design

Pre-specified release specifications are intended to ensure safe and efficacious use of the drug product, a positive benefit/risk assessment may support the administration of cilta-cel that does not meet the specifications set forth in the health authority approval.

The sponsor therefore intends to provide access to OOS drug product for participants whose final manufactured cilta-cel does not meet the commercial release specifications through enrollment in this study.

The study is planned as an open-label, single-arm multicenter Phase 2 study to evaluate the safety and efficacy of cilta-cel OOS in adult participants (≥18 years) with multiple myeloma. It is planned to enroll at least 20 participants. Participation is based on the formal request from the treating physician and a written notification of availability of cilta-cel OOS after sponsor's assessment of a positive benefit to risk. Participants will be consented for study eligibility after availability of cilta-cel OOS. Safety criteria that must be met prior to starting of lymphodepleting chemotherapy and infusion of cilta-cel OOS is presented in Section 6.1.2 and Section 6.1.4, respectively.

Rationale for Pharmacokinetics and Immunogenicity Assessments

Data obtained from the cilta-cel OOS treatment in this study will provide information about the PK profile of cilta-cel OOS in participants with multiple myeloma. Therefore, samples will be obtained from all participants for PK assessments. If needed for exploration purposes, data may also be used for a population PK analysis to estimate additional PK parameters and provide information about the determinants of inter-participant variability in this population.

Immunogenicity to cilta-cel OOS is possible. Therefore, the presence of anti-cilta-cel antibodies will be determined from serum samples collected from all participants after the cilta-cel OOS treatment.

Biomarker Collection

Biomarker samples will be collected to evaluate the mechanism of action of cilta-cel OOS or help to explain interindividual variability in clinical outcomes or may help to identify population subgroups that respond differently to an intervention. The goal of the biomarker analyses is to evaluate the pharmacodynamics of cilta-cel OOS and aid in evaluating the intervention-clinical response relationship. Biomarker samples will be collected to evaluate the depth and durability of clinical response through evaluation of MRD-negative rate, using DNA sequencing of immunoglobulin genes.

Biomarker samples may be used to help address emerging issues and to enable the development of safer, more effective, and ultimately individualized therapies.

4.2.1. Study-Specific Ethical Design Considerations

The primary health risk to the study participant is an altered efficacy and/or safety profile of the drug product due to OOS which could impact the biology and clinical characteristics of cilta-cel and affect treatment outcomes. Per assessment of the principal investigator the clinical circumstances of study participants may not allow for alternative therapeutic options for the treatment of multiple myeloma, including re-apheresis, re-manufacturing cilta-cel, both with the aim to receive a drug product meeting release specification. Therefore, there is a high unmet medical need for making cilta-cel OOS available to patients without alternative treatment options for relapsed/refractory multiple myeloma (RRMM).

Cilta-cel is an approved drug for the treatment of RRMM, as per locally approved label, albeit with an OOS product. Access to the manufactured cilta-cel OOS, is dependent on a positive benefit/risk assessment and exceptional release per sponsor's medical review and principal investigator's judgment, as described below:

- In the event a cilta-cel batch does not meet release specifications, an OOS investigation by the sponsor will be initiated. The sponsor designated medical representative will contact the treating physician to inform them of the OOS product and to retrieve patient information required for medical assessment, if the treating physician initiates further benefit/risk assessment. This includes (but is not limited to) basic demographics, relevant medical history including prior lines of treatment, current clinical status, and minimum clinical data required to assess patient treatment eligibility for enrollment–per USPI per locally approved label, availability or patient access to alternative treatment options in the market or region.

- Based on the manufacturing and clinical information received the sponsor will conduct and document the benefit/risk assessment for each OOS drug product. The benefit/risk medical evaluation includes assessment of the potential OOS impact on safety and efficacy, participant's alternative options, medical need, and assessment of potential immediate hazards of not receiving the cilta-cel. If the treating physician also deems that the benefit/risk profile is favorable, and decides to request the OOS product, then the treating physician as principal investigator for the study will initiate eligibility screening procedures and formally request the shipment of the cilta-cel OOS for administration within the study by completing and signing off Exceptional Release of OOS Product Request Form.

- Exceptional release of cilta-cel OOS that has not met pre-determined release specifications is understood to be used under exceptional circumstances and only when deemed safe and appropriate for the participant. For cilta-cel OOS where the sponsor and the treating physician believe the potential benefits outweigh the potential risks for the participant, the sponsor will follow local regulations for exceptional release of the cilta-cel OOS batch.

Potential study participants will be fully informed of the risks and requirements of the study and, during the study, participants will be given any new information that may affect their decision to continue participation. They will be told that their consent to participate in the study is voluntary and may be withdrawn at any time with no reason given and without penalty or loss of benefits to which they would otherwise be entitled. Only participants who are fully able to understand the risks, benefits, and potential AEs of the study, and provide their consent voluntarily will be enrolled. The total blood volume to be collected is considered to be an acceptable amount of blood to be collected over this time period from the population in this study based upon the standard of the American Red Cross (Section 8).

4.3. Justification for Dose

As per the USPI, the recommended dose range is 0.5-1.0×10^6 CAR-positive viable T cells per kg of body weight, with a maximum dose of 1×10^8 CAR-positive viable T cells per single infusion.

Based on clinical trials, it is possible that doses below the specified dose ranges per label could also be efficacious (see also Section 2.3.3). A viable CAR-positive T cell count outside the drug product specifications may be a cause for OOS drug product for a particular participant and will be accepted for dosing within this protocol if the respective participant´s benefit-risk assessment is positive.

4.4. End of Study Definition

End of Study Definition

The end of study is defined as 2 years after the last participant has received his or her initial dose of cilta-cel OOS per Schedule of Activities (SoA). A participant is being followed for 2 years to assess response, DOR, PFS, OS, and safety. The final data from the study site will be sent to the sponsor (or designee) after completion of the final participant assessment at that study site, in the time frame specified in the Clinical Trial Agreement.

Participant Study Completion Definition

A participant will be considered to have completed the study if they have completed follow-up period of 2 years to assess response, DOR, PFS, OS, and safety after his or her initial dose of cilta-cel OOS or discontinue prematurely due to death, or has experienced a clinical endpoint that precludes further continuation in the study.

Participants who prematurely discontinue study treatment for any reason other than those mentioned above before completion of the study will not be considered to have completed the study.

5. STUDY POPULATION

Screening for eligible participants will be performed based on formal request from the treating physician and a written notification from the sponsor for availability of cilta-cel OOS. Refer to Section 5.4, Screen Failures for conditions under which the repeat of any screening procedures is allowed.

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

5.1. Inclusion Criteria

Each potential participant must satisfy all of the following criteria to be enrolled in the study:

Age

1. ≥18 years of age.

Type of Participant and Disease Characteristic

2. Eligible for treatment with cilta-cel per USPI or locally approved label.

3. Participant is suffering from serious or life-threatening multiple myeloma per USPI (or locally approved label, respectively), and re-apheresis, re-manufacturing, or other anti-myeloma directed therapies is not considered feasible or adequate per investigator.

4. A favorable participant benefit/risk assessment is concluded following the sponsor's medical review.

5. Has adequate general health status and organ function per investigator assessment and meets the criteria to receive cilta-cel OOS (see Section 6.1.4).

6 Meets the criteria to receive lymphodepleting chemotherapy (see Section 6.1.2).

Sex and Contraceptive/Barrier Requirements

7. A woman of childbearing potential must have a negative highly sensitive serum (β-human chorionic gonadotropin [β-hCG]) pregnancy test during screening and prior to the first dose of cyclophosphamide and fludarabine.

8. A woman using oral contraceptives must use an additional contraceptive method (Examples of highly effective methods of contraception are located in Section 10.5, Appendix 5, Contraceptive Guidance).

9. A woman must be (as defined in Section 10.5, Appendix 5, Contraceptive Guidance)

    a. Not of childbearing potential

    b. Of childbearing potential and

        - Practicing a highly effective method of contraception (failure rate of <1% per year when used consistently and correctly) and agrees to remain on a highly effective method while receiving study treatment and until 1 year after receiving a last dose of cilta-cel OOS infusion. The investigator should evaluate the

potential for contraceptive method failure (eg, noncompliance, recently initiated) in relationship to the first dose of study treatment. Examples of highly effective methods of contraception are located in Section 10.5, Appendix 5. Contraceptive Guidance.

10. A woman must agree not to donate eggs (ova, oocytes) for the purposes of assisted reproduction during the study and for 1 year after the last dose of study treatment. (cilta-cel OOS).

11. A male participant must agree not to donate sperm for the purpose of reproduction during the study and for a minimum 1 year after receiving the last dose of study treatment (cilta-cel OOS).

12. Male participants must agree to the following during the intervention period and for at least 1 year after the last dose of study treatment:

- Who is sexually active with a woman of childbearing potential must agree to use a barrier method of contraception (eg, condom with spermicidal foam/gel/film/cream/suppository) from the time of signing the ICF until 1 year after the last dose of study treatment (cyclophosphamide, fludarabine [standard-of-care] or cilta-cel OOS, respectively)
- Who is sexually active with a woman who is pregnant must use a condom

Informed Consent

13. Must sign an ICF indicating that he or she understands the purpose of, and procedures required for, the study and is willing to participate in the study.

5.2. Exclusion Criteria

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

Medical Conditions

1. History of active uncontrolled infection or condition where an administration of cilta-cel OOS constitutes serious health risk to the participant.

2 Known allergies, hypersensitivity, or intolerance to the excipients of cilta-cel OOS including dimethyl sulfoxide (DMSO), dextran 40, or residual kanamycin per USPI (or local approved label).

3. Criterion modified per Amendment 1

3.1. Any conditions (listed below), for which, in the opinion of the investigator, participation would not be in the best interest of the participant (eg, compromise the

well-being) or that could prevent, limit, or confound the protocol-specified assessments.

Medical conditions include:

- Uncontrolled autoimmune disease. Stable disease, controlled with or without pharmacologic treatment for at least 6 months prior to dosing could be considered.
- Overt clinical evidence of dementia or altered mental status
- Any history of Parkinson's disease or other neurodegenerative disorder
- Known active, or prior history of central nervous system (CNS) involvement or exhibits clinical signs of meningeal involvement of multiple myeloma
- Stroke within 6-months of cilta-cel dosing

4. Hepatitis B infection as defined according to Section 10.14, Appendix 14. In the event the infection status is unclear, quantitative levels are necessary to determine the infection status at Screening Phase (Hwang 2015).

5. Hepatitis C infection defined as (anti-HCV antibody positive or detectable HCV-RNA) or known to have a history of hepatitis C.

   NOTE: For participants with positive hepatitis C antibody due to prior resolved disease can be enrolled, only if a confirmatory HCV RNA test is undetectable. For participants with known history of HCV infection, confirmation of sustained virologic response is required for study eligibility, defined as undetectable HCV-RNA ≥24 weeks after completion of antiviral therapy.

6. Seropositive for HIV.

NOTE: Investigators should ensure that all study enrollment criteria have been met after screening. If a participant's clinical status changes (including any available laboratory results or receipt of additional medical records) after screening but before the first dose of study treatment is given such that he or she no longer meets all eligibility criteria, then the participant should be excluded from participation in the study. The required source documentation to support meeting the enrollment criteria are noted in Section 10.3, Appendix 3, Regulatory, Ethical, and Study Oversight Considerations.

5.3. Lifestyle Considerations

Sex and contraceptive/barrier requirements are necessary for the duration of 1 year after the last dose of study treatment (see Sections 5.1, 8.2.9, and 8.3.5).

5.4. Screen Failures

Participant Identification, Enrollment, and Screening Logs

The investigator agrees to complete a participant identification and enrollment log to permit easy identification of each participant during and after the study. This document will be reviewed by the sponsor study site contact for completeness.

The participant identification and enrollment log will be treated as confidential and will be filed by the investigator in the study file. To ensure participant confidentiality, no copy will be made. All reports and communications relating to the study will identify participants by participant identification and age at initial informed consent. In cases where the participant is not enrolled into the study, the date seen and age at initial informed consent will be used.

Individuals who do not meet the eligibility criteria for participation in this study may be re-screened and re-consented if deemed of potential benefit to the patient by the treating physician and upon the sponsor's written approval. Rescreened participants must be assigned new participant numbers.

5.5. Criteria for Temporarily Delaying Administration of Study Intervention

The criteria for temporary delay in administration of study treatment is based on participant's medical condition and the criteria described in Sections 6.1.2 and 6.1.4.

6. STUDY INTERVENTION AND CONCOMITANT THERAPY

6.1. Study Intervention Administered

For this study, study treatment refers to cilta-cel OOS, cyclophosphamide and fludarabine. Cyclophosphamide and fludarabine should be prescribed by the treating physician as per the USPI.

Study treatment administration must be captured in the source documents and the case report form (CRF). All dosing information must be recorded in the Dosage Administration page of the electronic CRF (eCRF).

Cilta-cel OOS will be provided under the responsibility of the sponsor.

6.1.1. Pre-infusion Supportive Therapy

Participants should receive premedication before cilta-cel OOS infusion as noted below (Table 4). Avoid use of prophylactic systemic corticosteroids as it may interfere with the activity cilta-cel OOS.

Table 4: Pre-infusion Medications

Medication	Dose	Administration
Antihistamine	diphenhydramine (50 mg) or equivalent	Oral - administer 1 hour (±15 minutes) prior to cilta-cel OOS infusion Or IV- start infusion 30 minutes (±15 minutes) prior to cilta-cel OOS infusion
Antipyretics	acetaminophen (650 mg to 1,000 mg) or equivalent	Oral or IV - administer 30 minutes (±15 minutes) prior to cilta-cel OOS infusion

Abbreviations: IV=intravenous; OOS=out-of-specifications.

6.1.2. Criteria for Lymphodepleting Chemotherapy (Cyclophosphamide and Fludarabine) Administration

Participants must meet the following criteria (also refer to Section 5.1) to proceed with cyclophosphamide and fludarabine dosing:

- Negative pregnancy test for women of childbearing potential up to 72 hours prior to the first dose of the lymphodepleting chemotherapy.

- No signs of active infection. For participants requiring systemic anti-microbial treatment or with temperature ≥38.0°C within 7 days prior to the first dose of lymphodepleting chemotherapy, the investigator must receive approval to proceed from the sponsor.

6.1.3. Lymphodepleting Chemotherapy (Cyclophosphamide and Fludarabine) Administration

At the completion of manufacture and quality testing of cilta-cel, written notification will be sent to the clinical site. Prior to dosing with cyclophosphamide and fludarabine, review of eligibility, safety assessments and disease characteristics should be completed per Section 6.1.2. The details regarding safety monitoring and study visits during this phase are included in the SoA (Table 1).

Administer a lymphodepleting regimen of cyclophosphamide 300 mg/m^2 intravenously daily and fludarabine 30 mg/m^2 intravenously daily for 3 days. The dose of fludarabine should be reduced to 24 mg/m^2 for participants with an estimated glomerular filtration rate of 30 to 70 mL/min/1.73 m^2. For other dose modifications, see corresponding manufacturer's prescribing information for additional guidance to account for renal insufficiency and other conditions appropriately. Administer cilta-cel OOS IV infusion 5 to 7 days after the start of the lymphodepleting regimen (the first day of conditioning is Day -7 to Day -5, and the day of cilta-cel infusion is Day 1). Cyclophosphamide and fludarabine should be administered using administration procedures and supportive care according to the site's standard of care, if clinically indicated. Cilta-cel OOS should be administered as described in the USPI or locally approved label.

If toxicities due to the lymphodepleting regimen results in delays to cilta-cel OOS dosing for more than 14 days, the lymphodepleting regimen should be re-administered after a minimum of 21 days following the first dose of the first lymphodepleting regimen.

6.1.4. Clinical Assessment Prior to cilta-cel OOS Infusion

Participants will be evaluated for safety on the day of cilta-cel OOS infusion prior to dosing. If a significant health status change (eg, clinical deterioration, rapidly progressing disease) occurs following the start of the lymphodepleting chemotherapy (see Section 6.1.2), the investigator should contact the sponsor prior to dosing.

Infusion of cilta-cel OOS should be delayed if any of the following events occur:

- Signs of active infection or inflammatory disorders. Do not administer cilta-cel OOS to participants with active infection. For participants requiring systemic anti-microbial treatment, or with temperature ≥38.0°C within 48 hours before cilta-cel OOS infusion, investigator must consult with the sponsor prior to dosing.

- Grade ≥3 non-hematologic toxicities of cyclophosphamide and fludarabine conditioning (except for Grade 3 nausea, vomiting, diarrhea, or constipation). Investigator must consult with the sponsor prior to cilta-cel OOS dosing and cilta-cel OOS infusion should be delayed until resolution of these events to Grade ≤1.

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

6.1.5. Cilta-cel OOS Administration

Cilta-cel OOS will be administered as summarized in Table 5.

Table 5: Description of Cilta-cel OOS

Intervention Name	**Cilta-cel OOS**
Type	Cell suspension of CAR positive viable T cells
Dose Formulation	The cilta-cel OOS cryopreserved drug product will be placed in a vapor shipping container along with a data logger and shipped to the site for treatment according to the clinical protocol. Preparation for administration and product infusion will be performed according to the clinical protocol and Prescribing Information.
Dosage Level	Formulated to a target dose of 0.75×10^6 CAR positive viable T cells/kg participant weight (dose range 0.5×10^6 CAR-positive viable T cells/kg to 1.0×10^6 CAR-positive viable T cells/kg). Note: out of range dose may be the reason for the OOS. In which case, the formulated dose will be the dose to be administered.
Dosage Frequency	The actual dose for study treatment administration will be based on the subject's weight (kg) at apheresis. Single IV infusion on Day 1.
Route/Regimen of Administration	Cilta-cel OOS IV infusion is to be administered under the supervision of site staff. Refer to the USPI (or locally approved label, respectively) for cilta-cel infusion instructions.
Hospitalization Requirements	The site of CAR-T infusion is determined per institutional guidance/practices. However, patients should be instructed to remain within proximity of a certified healthcare facility for at least four weeks following infusion.

Table 5: Description of Cilta-cel OOS	
Intervention Name	**Cilta-cel OOS**
	Following infusion, monitor patients at least daily for 10 days following cilta-cel OOS infusion (whether the participant will be dosed outpatient or inpatient according to institutional guidelines) at a certified healthcare facility for signs or symptoms of cytokine release syndrome and neurologic toxicities as per USPI. Monitor periodically for 4 weeks for signs and symptoms of delayed neurologic toxicity. Participants are asked to remain within close proximity of a certified healthcare facility for at least 4 weeks following infusion.
Vital signs and Clinical Safety Monitoring	Monitor vital signs as indicated in the Section 1.3 SoA (Table 1).
Use	Experimental
Investigational Medicinal Product (IMP)	Yes
Non-Investigational Medicinal Product/Auxiliary Medicinal Product (NIMP/AxMP)	No
Sourcing	Provided centrally by the sponsor
Packaging and Labeling	Cilta-cel OOS IV infusion is to be administered to individual participants under the supervision of site staff.
Current/Former Name(s) or Alias(es)	ciltacabtagene autoleucel

6.1.6. Management Guidelines for Potential Risks

6.1.6.1. Management of Cytokine Release Syndrome

At the clinical data cutoff, 1 September 2020, CRS was reported for 92 of 97 participants (94.8%) who received cilta-cel in the study 68284528MMY2001. Most participants (87 [89.7%] participants) experienced CRS AEs that were Grade 1 or 2, 3 (3.1%) participants experienced Grade 3 CRS, 1 participant experienced Grade 4 CRS, and 1 participant experienced Grade 5 CRS (see Section 2.2.6).

Symptoms indicative of CRS may include, but are not limited to, fever (with or without rigors), arthralgia, nausea, vomiting, tachypnea, hypoxia, tachycardia, hypotension, headache, confusion, tremor, delirium, dyspnea, pulmonary edema, and capillary leak (Lee 2019). Potentially life-threatening complications of CRS may include cardiac dysfunction, adult respiratory distress syndrome, neurologic toxicity, renal failure, hepatic failure, and disseminated intravascular coagulation.

Laboratory testing to monitor for disseminated intravascular coagulation, a manifestation of CRS, should be carried out in addition to daily monitoring of chemistry and hematology assessments (including ferritin and C-reactive protein [CRP]) when fever or other signs of potential CRS are present (see Table 1). In addition, pulmonary, renal and hepatic function will be monitored closely (see Table 1). Cytokine release syndrome will be captured as an AESI (see Section 8.3.1).

Rarely, severe CRS can evolve into a presentation consistent with HLH/macrophage activation syndrome (MAS) that may require additional therapy. In these cases, laboratory testing may reveal high serum levels of ferritin, lactate dehydrogenase, soluble CD25, and cytokines (such as IFNγ and IL-6), and low serum levels of fibrinogen (Neelapu 2018). Severe thrombocytopenia, low fibrinogen, and often DIC may be features of HLH, all of which combined may increase the risk of severe bleeding in these subjects. If HLH is suspected, anticoagulation should be avoided or modified based on institutional guidelines depending on platelet count and renal function. Subjects with HLH should have their platelet count and coagulation parameters very closely monitored and maximal support should be provided to avoid major bleeding complications. For example, consider platelet transfusion if platelets are less than 50×10^9/L. Under these circumstances, investigators should consider treating the subject in the ICU, so that maximal monitoring and support can be carried out during this period.

Trained clinical personnel should be prepared to intervene in the event of CRS. Resources necessary for resuscitation (ie, agents such as epinephrine and aerosolized bronchodilator; medical equipment such as oxygen, tracheostomy equipment, and a defibrillator) should be readily available. Tocilizumab must be available prior to administration of cilta-cel OOS. Vital signs and laboratory parameters must be monitored at regular intervals until normal. Additional specimens for pharmacokinetic and pharmacodynamic testing should be collected as per the schedule outlined in SoA (Section 1.3).

Infection and CRS may have a similar presentation. Therefore, investigators are strongly encouraged to evaluate for an infection at the first signs or symptoms of CRS. Cultures and imaging should be obtained: the clinical signs and symptoms should determine which tests are appropriate.

Recommendations for the clinical management of CRS are provided in Table 6. At the first sign of CRS (such as fever) participants should be immediately hospitalized for evaluation. The use of myeloid growth factors, particularly granulocyte colony-stimulating factor (G-CSF), should be avoided during CRS. Tocilizumab intervention may be considered with presenting symptom of fever per investigator discretion when other sources of fever have been eliminated and early tocilizumab should be considered in participants at high risk of severe CRS (for example, high baseline tumor burden, early fever onset, or persistent fever after 24 hours of symptomatic treatment). Other cytokine-targeting therapies (for example, IL1, TNFα) may be used based on institutional practice, especially for cases of CRS which does not respond to tocilizumab or corticosteroids.

Table 6: CRS Grading and Management Guidance

CRS Grade[a]	Tocilizumab[b]	Corticosteroids[f]
Grade 1 Temperature ≥38°C[c]	In patients with: • Early onset of fever (if onset less than 72 hours after infusion) Tocilizumab 8 mg/kg intravenously (IV) over 1 hour (not to exceed 800 mg) may be considered	N/A
Grade 2 Symptoms require and respond to moderate intervention. Temperature ≥38°C[c] with: Hypotension not requiring vasopressors, and/or, Hypoxia requiring oxygen via canula[e] or blow-by, or, Grade 2 organ toxicity.[g]	Administer tocilizumab 8 mg/kg IV over 1 hour (not to exceed 800 mg). Repeat tocilizumab every 8 hours as needed if not responsive to intravenous fluids up to 1 liter or increasing supplemental oxygen.	Consider dexamethasone 10 mg IV every 12-24 hours.
	If no improvement within 24 hours or rapid progression, repeat tocilizumab and escalate dose and frequency of dexamethasone (20 mg IV every 6 to 12 hours). If no improvement within 24 hours or continued rapid progression, switch to methylprednisolone 2 mg/kg IV every 12 hours. After 2 doses of tocilizumab, consider alternative anti-cytokine agents.[d] Do not exceed 3 doses of tocilizumab in 24 hours, or 4 doses in total.	
Grade 3 Symptoms require and respond to aggressive intervention. Temperature ≥38°C[c] with: Hypotension requiring one vasopressor with or without vasopressin, and/or, Hypoxia requiring oxygen via high-flow nasal canula[e], facemask, non-rebreather mask, or Venturi mask, or, Grade 3 organ toxicity or Grade 4 transaminitis.	Per Grade 2	Administer dexamethasone 10 mg IV every 12 hours.
	If no improvement within 24 hours or rapid progression, repeat tocilizumab and escalate dose and frequency of dexamethasone (20 mg IV every 6 to 12 hours). If no improvement within 24 hours or continued rapid progression, switch to methylprednisolone 2 mg/kg IV every 12 hours. After 2 doses of tocilizumab, consider alternative anti-cytokine agents.[d] Do not exceed 3 doses of tocilizumab in 24 hours, or 4 doses in total.	

<table>
<tr><th>CRS Grade[a]</th><th>Tocilizumab[b]</th><th>Corticosteroids[f]</th></tr>
<tr><td>Grade 4
Life-threatening symptoms. Requirements for ventilator support, continuous veno-venous hemodialysis (CVVHD).

Temperature ≥38°C[c] with:

Hypotension requiring multiple vasopressors (excluding vasopressin), and/or,

Hypoxia requiring positive pressure (e.g., CPAP, BiPAP, intubation, and mechanical ventilation),

or,

Grade 4 organ toxicity (excluding transaminitis).</td><td>Per Grade 2

After 2 doses of tocilizumab, consider alternative anti-cytokine agents[d]. Do not exceed 3 doses of tocilizumab in 24 hours, or 4 doses in total.

If no improvement within 24 hours, consider methylprednisolone (1-2 g IV, repeat every 24 hours if needed; taper as clinically indicated) or other immunosuppressants (e.g. other anti-T cell therapies).</td><td>Administer dexamethasone 20 mg IV every 6 hours.</td></tr>
</table>

Abbreviations: BiPAP bilevel positive airway pressure; CPAP continuous positive airway pressure, CRS cytokine release syndrome, NA Not Applicable.

[a] Based on ASTCT 2019 grading system (Lee et.al, 2019), modified to include organ toxicity.
[b] Refer to tocilizumab prescribing information for details.
[c] Attributed to CRS. Fever may not always be present concurrently with hypotension or hypoxia, as it may be masked by interventions such as antipyretics or anti-cytokine therapy (eg, tocilizumab or steroids). Absence of fever does not impact CRS management decision. In this case, CRS management is driven by hypotension and/or hypoxia and by the more severe symptom not attributable to any other cause.
[d] Monoclonal antibodies targeting cytokines may be considered based on institutional practice for unresponsive CRS.
[e] Low-flow nasal cannula is ≤6 L/min; high-flow nasal cannula is >6 L/min.
[f] Continue corticosteroids use until the event is Grade 1 or less; taper steroids if total corticosteroid exposure is greater than 3 days.
[g] Organ toxicity grading based on National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 5.0.

Supportive care for CRS (including but not limited to anti-pyretic agents, IV fluid support, vasopressors, supplemental oxygen) should be administered according to the clinical manifestations of the participant's illness. Similarly, ancillary testing such as B-type natriuretic peptide (BNP) assessment, echocardiograms, arterial blood gas, assessments of coagulation laboratory tests, should be performed if clinically indicated.

6.1.6.2. Neurologic Toxicities

Based on the specific mode-of-action of cilta-cel, severe or serious neurological toxicities (including CAR-T cell-related neurotoxicity, eg, ICANS) may occur (Section 6.1.6.2.1). Participants should be monitored for neurotoxicity for the duration of study (Section 6.1.6.2.2).

6.1.6.2.1. CAR-T Cell-related Neurotoxicity (Immune Effector Cell-Associated Neurotoxicity Syndrome [ICANS])

Participants should have the ICE Assessment Tool (ICE-Tool; Section 10.9, Appendix 9) performed at baseline (within 24 hours prior to infusion of cilta-cel infusion) and daily after the first symptoms of CAR-T cell-related neurotoxicity (eg, ICANS) are suspected and until resolution. Consider performing ICE-Tool more frequently until neurotoxicity symptoms resolve. Consider performing neuroimaging (eg, magnetic resonance imaging [MRI]) at Screening Phase and/or neurology consultation if pre-existing disease is suspected; see Section 8.2.

Early recognition of neurologic adverse events is critical to management. Symptoms indicative of ICANS may include, but are not limited to, speech disorders, aphasia, convulsions, disturbances in consciousness, confusion, disorientation, or coordination and balance disorders. Participants should be monitored for neurologic toxicities and advised to seek medical evaluation if they notice new onset of symptoms. If these or other neurological toxicities are observed, regardless of causality, then the sponsor's medical monitor must be consulted.

At the first sign of neurotoxicity, neurology consultation and evaluation should be considered for all neurological toxicities. Rule out alternative etiologies including infectious etiologies (eg, viral origin such as, human herpesvirus [HHV] HHV-6, HHV-7) if clinically indicated. Participants who have a lumbar puncture as part of their neurologic work up should have a sample of cerebrospinal fluid (CSF) for additional testing (eg, biomarkers) as clinically indicated. For signs of seizures or raised intracranial pressure (ICP)/cerebral edema, consider neuroimaging (CT/MRI), transfer the participant to the intensive care unit (ICU) and treat according to institutional guidelines or practices.

General management for CAR-T cell-related neurotoxicity (eg, ICANS) with or without concurrent CRS is summarized in Table 7. All neurological adverse events, including CAR-T related neurotoxicity (eg, ICANS), will be captured as an AESI (see Section 8.3.1).

Table 7: Guidelines for the Management of CAR-T Cell-related Neurotoxicity (eg, ICANS)

ICANS Grade	Presenting Symptoms[a]	Concurrent CRS	No Concurrent CRS
Grade 1	ICE score 7-9[b] or depressed level of consciousness[c]: awakens spontaneously.	Management of CRS as appropriate per Table 6. Monitoring of neurologic symptoms and consider neurology consultation and evaluation, per investigator discretion.	Monitor neurologic symptoms and consider neurology consultation and evaluation, per investigator discretion. Consider dexamethasone.
		Consider non-sedating, anti-seizure medicines (eg, levetiracetam) for seizure prophylaxis.	
Grade 2	ICE score-3-6[b] or depressed level of consciousness[c]: awakens to voice.	Administer tocilizumab per Table 6 for management of CRS. If no improvement after starting tocilizumab, administer dexamethasone[d] 10 mg intravenously every 6 hours if not already taking other corticosteroids. Continue dexamethasone use until the event is Grade 1 or less, then taper.	Administer dexamethasone[d] 10 mg intravenously every 6 hours. Continue dexamethasone use until the event is Grade 1 or less, then taper.
		Consider non-sedating, anti-seizure medicines (eg, levetiracetam) for seizure prophylaxis. Consider neurology consultation and other specialists (ie, intensivists) for further evaluation, as needed.	
Grade 3	ICE score-0-2[b] or depressed level of consciousness[c]:	Administer tocilizumab per Table 6 for management of CRS.	Administer dexamethasone[d] 10 mg intravenously every 6 hours.

	awakens only to tactile stimulus, or seizures[c], either: • any clinical seizure, focal or generalized, that resolves rapidly, or • non-convulsive seizures on EEG that resolve with intervention, or raised ICP: focal/local edema on neuroimaging[c].	In addition, administer dexamethasone[d] 10 mg intravenously with the first dose of tocilizumab and repeat dose every 6 hours. Continue dexamethasone use until the event is Grade 1 or less, then taper.	Continue dexamethasone use until the event is Grade 1 or less, then taper.
		Consider non-sedating, anti-seizure medicines (eg, levetiracetam) for seizure prophylaxis. Consider neurology consultation and other specialists (ie, intensivists) for further evaluation, as needed.	
Grade 4	ICE score-0[b] or depressed level of consciousness[c] either: • participant is unarousable or requires vigorous or repetitive tactile stimuli to arouse, or • stupor or coma, or seizures[c], either: • life-threatening prolonged seizure (>5 min), or • repetitive clinical or electrical seizures without return to baseline in between, or motor findings[c]: • deep focal motor weakness such as hemiparesis or paraparesis, or raised ICP / cerebral edema[c], with signs/symptoms such as: • diffuse cerebral edema on neuroimaging, or • decerebrate or decorticate posturing, or • cranial nerve VI palsy, or • papilledema, or • Cushing's triad.	Administer tocilizumab per Table 6 for management of CRS. As above, or consider administration of methylprednisolone 1,000 mg intravenously per day with first dose of tocilizumab and continue methylprednisolone 1,000 mg intravenously per day for 2 or more days, per investigator discretion.	As above, or consider administration of methylprednisolone 1000 mg intravenously per day for 3 days; if improves, then manage as above.
		Consider non-sedating, anti-seizure medicines (eg, levetiracetam) for seizure prophylaxis. Consider neurology consultation and other specialists (ie, intensivists) for further evaluation, as needed. In case of raised ICP/cerebral edema, refer to Table 8 for additional management guidelines.	

Abbreviations: ICANS=Immune Effector Cell-associated Neurotoxicity Syndrome, ICE=Immune Effector Cell-associated Encephalopathy; ICP=intracranial pressure; CRS=cytokine release syndrome; EEG=electroencephalogram

a Management is determined by the most severe event, not attributable to any other cause.
b If participant is arousable and able to perform Mental Status assessment, the following domains should be tested: orientation, naming, following commands, writing, and attention (see Section 10.9, Appendix 9; ICE-Tool).
c Attributable to no other cause.
d All references to dexamethasone administration are dexamethasone or equivalent.

Table 8: Guidelines for the Management of Raised ICP/Cerebral Edema[a]

- Elevate head of participant's bed to an angle of 30 degrees.
- If participant has ommaya reservoir, drain CSF to target opening pressure of <20 mmHg.
- Hyperventilation to achieve target partial pressure of arterial carbon dioxide ($PaCO_2$) of 28–30 mmHg but maintained for no longer than 24 hours.
- Consider neurology and/or neurosurgery consultation.
- Use high-dose corticosteroids with methylprednisolone IV 1 g/day, as recommended above.
- Hyperosmolar therapy with either mannitol (20 g/dL solution) or hypertonic saline (3% or 23.4%, as detailed below):
  - Mannitol: initial dose 0.5–1 g/kg; maintenance at 0.25–1 g/kg every 6 hours while monitoring metabolic profile and serum osmolality every 6 hours, and withhold mannitol if serum osmolality is ≥320 mOsm/kg, or the osmolality gap is ≥40,
  - Hypertonic saline: initial 250 mL of 3% hypertonic saline; maintenance at 50–75 mL/hour while monitoring electrolytes every 4 hours, and withhold infusion if serum Na levels reach ≥155 mEq/L,
  - For participants with imminent herniation: initial 30 mL of 23.4% hypertonic saline; repeat after 15 min, if needed.
- Consider IV anesthetics for burst-suppression pattern on electroencephalography.

a In addition to toxicity management guidelines provided in Table 7: Guidelines for the Management of CAR-T Cell-Related Neurotoxicity (ie, ICANS)

Abbreviations: CAR-T=chimeric antigen receptor-T; CSF=cerebrospinal fluid; ICANS=Immune-Effector Cell-associated Neurotoxicity Syndrome; ICP=intracranial pressure; IV=intravenous.

6.1.6.2.2. Other Neurotoxicities

Neurologic toxicity with several signs and symptoms of Parkinsonism (ie, movement and neurocognitive toxicity) distinct from ICANS have been reported in trials with cilta-cel. The median onset of Parkinsonism was 27 days (range: 14 to 108 days) from infusion of ciltacabtagene autoleucel. The median duration of Parkinsonism symptoms was 234 days (range: 62 to 482) days) including those subjects who died from MNT or had ongoing MNT at the time of death due to other cause, or with ongoing parkinsonism.

- Symptoms to watch for include:
  - movement impairments (eg, micrographia or changes in handwriting, tremors, bradykinesia, rigidity, shuffling gait, impaired balance and coordination, difficulty writing, difficulty performing activities of daily living like dressing or feeding oneself),
  - cognitive impairments (eg, memory loss or forgetfulness, disturbances in attention, mental slowness or fogginess, difficulty speaking or slurred speech, difficulty reading or understanding words),
  - personality change (eg, reduced facial expression, flat affect, reduced ability to express emotions, less communicative, disinterest in activities)
- Guillain-Barre Syndrome (GBS): Symptoms of GBS have been reported in other CARTITUDE studies and include those consistent with Miller-Fisher variant of GBS,

encephalopathy, motor weakness, speech disturbances, and polyradiculoneuritis. Monitor for signs and symptoms of GBS after cilta-cel infusion. Consider treatment with IVIG and escalate to plasmapheresis, depending on toxicity severity.

- Peripheral neuropathy: Occurrence of peripheral neuropathy, including sensory, motor, or sensorimotor, have been reported in trials of cilta-cel. Median time of onset of symptoms was 62 days (range: 4 to 136 days), median duration of peripheral neuropathies was 256 days (range: 2 to 465 days) including those with ongoing neuropathy. Monitor patients for signs and symptoms of peripheral neuropathies. Consider management with short-course systemic corticosteroids, depending on the severity and progression of signs and symptoms.
- Cranial nerve palsies: Occurrence of 7th, 3rd, 5th, and 6th cranial nerve palsy, some of which were bilateral, worsening of cranial nerve palsy after improvement, and occurrence of peripheral neuropathy in patients with cranial nerve palsy have been reported in trials of cilta-cel. Median time of onset of symptoms was 26 days (range:21 to 101 days) following infusion of cilta-cel. Median time to resolution was 70 days (range: 1 to 79 days) following onset of symptoms.

Monitor patients for signs and symptoms of cranial nerve palsies. Consider management with short-course systemic corticosteroids, depending on the severity and progression of signs and symptoms.

Of note, the delayed onset of parkinsonism was observed at a higher frequency in participants with high burden of disease and in participants experiencing higher grade CRS (Grade 2 and above) and any grade ICANS. This may be indicative that ≥Grade 2 CRS or any grade ICANS are early indicators for the development of other neurotoxicity after a period of recovery from CRS and/or ICANS. Therefore, ≥Grade 2 CRS or any grade ICANS may represent an opportunity for early intervention and more aggressive supportive care (including steroids), especially in patients treated with a high tumor burden, that may mitigate the risk for developing late, other neurotoxicity. Infection and sepsis were seen concurrently in many of these patients.

Additional monitoring and mitigation strategies include enhanced bridging therapy to reduce baseline tumor burden, early aggressive treatment of CRS and ICANS, handwriting assessments for early detection of neurotoxicity symptoms, and extended monitoring and reporting time for neurotoxicity for the duration of study.

Early detection, workup and intervention, may be important to prevent neurologic toxicity from worsening. The following is a list of potential diagnostics that should be considered in participants with new neurologic symptoms:

- Positron emission tomography/computed tomography (PET/CT) of the brain and/or brain MRI with perfusion and an electroencephalogram (EEG).
- Lumbar puncture to rule out infection (in particular John Cunningham virus [JCV], herpes zoster virus [HZV], herpes simplex virus [HSV]-1/2, HHV-6, HHV-7, Epstein-Barr virus [EBV], cytomegalovirus [CMV]).
- Serologic testing for HHV-6 and HHV-7 by polymerase chain reaction (PCR) for viremia.
- Cerebrospinal fluid flow cytometry and cytology should be considered to rule out leptomeningeal disease.

- Cerebrospinal fluid analysis to rule out paraneoplastic syndromes.
- Thiamine level (consider empiric thiamine replacement while awaiting results) (MD Anderson 2019)

Other cytokine-targeting therapies (for example, IL1) may be used based on institutional practice, especially for cases of neurotoxicity which does not respond to tocilizumab or corticosteroids.

Therapy directed at reduction or elimination of CAR-T cells, including chemotherapy, may be considered in consultation with the sponsor for participants who develop neurotoxicity that remains unresponsive to other interventions.

Per Section 8.5 of the protocol, if CSF or other relevant biological sample analysis is clinically indicated, a sample of CSF will be requested for additional analysis by the sponsor.

6.1.6.3. Tumor Lysis Syndrome

Although TLS is uncommon in participants with multiple myeloma, it has been reported after cilta-cel infusion. Participants should be monitored closely for symptoms of TLS. Management of TLS, including hyperkalemia, hyperuricemia, hyperphosphatemia, and hypocalcemia, is highly recommended. It is also required that high-risk participants, ie, those with a high tumor burden (≥60% plasma cell infiltrate on the bone marrow biopsy or aspirate [whichever is higher] or a participant with multiple extramedullary disease sites or plasmacytomas), be treated prophylactically in accordance with local standards (eg, extra hydration; diuretics; allopurinol 300 mg daily and primary or secondary uricosuric agents, as indicated).

6.1.6.4. Prolonged or Recurrent Cytopenia

Participants may exhibit cytopenias for several weeks following lymphodepleting chemotherapy and cilta-cel infusion.

In study CARTITUDE-1 (N=97), 30% (29/97) of patients experienced prolonged Grade 3 or 4 thrombocytopenia that had not resolved by Day 30 following cilta-cel infusion. In 31% (29/95) of patients who recovered from Grade 3 or 4 neutropenia after 1 month, the median time to recovery from cilta-cel infusion was 1.8 mnths (range: 1.0-3.7 mos). In 52% (32/61) of patients who recovered from Grade 3 or 4 thrombocytopenia after one month, the median time to recovery from cilta-cel infusion was 1.9 months (range: 1.1 to 8.5 months). One patient underwent autologous stem cell therapy for hematopoietic reconstitution due to prolonged thrombocytopenia.

Recurrent Grade 3 or 4 neutropenia, thrombocytopenia, lymphopenia, and anemia were seen in 63% (61/97), 18% (17/97), 60% (58/97), and 37% (36/97) after recovery from initial Grade 3 or 4 cytopenia following cilta-cel infusion. After Day 60 following cilta-cel, 31%, 12%, and 6% of patients had a recurrence of Grade 3 or higher lymphopenia, neutropenia, and thrombocytopenia, respectively, after initial recovery of their Grade 3 or 4 cytopenia [see Adverse Reactions (6.1) of USPI]. Eighty-seven percent (84/97) of patients had one, two or three or more recurrences of Grade 3 or 4 cytopenias after initial recovery of Grade 3 or 4

cytopenia. Six and 11 patients had Grade 3 or 4 neutropenia and thrombocytopenia respectively at the time of death.

Parvovirus B19 monitoring by PCR should be considered in participants experiencing prolonged neutropenia or a decline in neutrophil counts following recovery.

6.1.6.5. Hypogammaglobulinemia

Hypogammaglobulinemia can occur in patients receiving treatment with cilta-cel. Hypogammaglobulinemia was reported as an adverse event in 12% (12/97) of patients; laboratory IgG levels fell below 500 mg/dL after infusion in 92% (89/97) of patients treated with cilta-cel. Hypogammaglobulinemia either as an adverse reaction or a laboratory

IgG level below 500 mg/dL, after infusion occurred in 94% (91/97) of patients treated with cilta-cel. Thirty-eight percent of patients received intravenous immunoglobulin (IVIG) post cilta-cel for either an adverse reaction or prophylaxis. Monitor immunoglobulin levels after treatment with cilta-cel and administer IVIG for IgG <400 mg/dL. Manage per local institutional guidelines, including infection precautions and antibiotic or antiviral prophylaxis.

6.1.6.6. Serious Infections

Do not administer cilta-cel OOS infusion to participants with active infection. Administration of cilta-cel may increase the risk of infection due to cytopenias or hypogammaglobulinemia. Participants should be monitored frequently for infection and should have blood cultures obtained serum inflammatory markers (CRP), and/or empiric antibiotics administered per institutional standards. Immunocompromised participants are at risk for opportunistic infections. Prophylactic use of antibiotics, antivirals, and antifungals should be considered. Extended use of anti-microbial therapies for at least 6 month (or longer as per institutional guidelines) or consistent with post ASCT consensus guidelines after CAR-T dosing are recommended (see Section 10.13, Appendix 13). Perform screening for HBV, HCV, and HIV and monitor as clinically indicated (see HBV monitoring recommendations in Section 8.2 and Section 10.14, Appendix 14 and initiate treatment as appropriate. HBV reactivation, in some cases resulting in fulminant hepatitis, hepatic failure and death, may occur in participants treated with drugs directed against B cells such as cilta-cel. HBV reactivation has occurred in participants who appear to have resolved hepatitis B infection. Routinely monitor HBV DNA and AST/ALT for participants with risk of HBV reactivation.

Subjects receiving cilta-cel are may be at a higher risk of severe/fatal outcomes from COVID-19 infection compared with patients who are receiving standard of care therapy. Subjects should be reminded of the importance of vaccines and other preventative measures. Investigators should consider prophylaxis (eg, Evusheld, if available) and antiviral medications (eg, Paxlovid, if available) for patients diagnosed with COVID-19 infection, as noted in Appendix 10.6. The safety of immunization with live viral vaccines has not been studied. Vaccination with live virus vaccines is not recommended for at least 6 weeks prior to the start of lymphodepleting chemotherapy, and until immune recovery following treatment cilta-cel infusion.

6.1.6.7. Hypersensitivity Reactions

Allergic reactions may occur with the infusion of cilta-cel. Hypersensitivity reactions have occurred in 5% of patients following cilta-cel infusion. All reactions were Grade 1 and symptoms included flushing (n=4), chest discomfort (n=2), tachycardia (n=1), wheezing (n=1), term or (n=1), and burning sensation (n=1)..Serious hypersensitivity reactions including anaphylaxis, may be due to dimethyl sulfoxide (DMSO), dextran 40, or residual kanamycin in cilta-cel. Serious hypersensitivity reactions including anaphylaxis, may be due to dimethyl sulfoxide (DMSO), dextran 40, or residual kanamycin in cilta-cel. Participants should be carefully monitored for 2 hours after infusion for signs and symptoms of severe reaction. Participants should be treated urgently per institutional standards, avoiding corticosteroid use if possible. Participants should receive premedication (ie, antihistamine, antipyretic) prior to cilta-cel dosing as noted in Section 6.1.1.

6.1.6.8. Second Primary Malignancy

Second primary malignancy (SPM) is a theoretical possibility due to the risk of lentiviral insertion (DNA integration) of the lentiviral vector. SPMs should be managed per institutional standards. SPMs must be reported during the duration of the study, irrespective of when they occur, and subsequently will be collected in a long-term follow-up study yearly until 15 years post dosing of cilta-cel OOS (68284528MMY4002). A tumor sample should be collected, and DNA, RNA or protein analysis may be performed to investigate the presence of lentiviral elements. Second primary malignancy is an adverse event of special interest (AESI).

6.2. Preparation/Handling/Storage/Accountability

Preparation/Handling/Storage

Cilta-cel OOS is provided in a single-dose unit containing CAR-positive viable T cells based on the participant's weight at apheresis reported at the time of original commercial order of cilta-cel OOS. The cryopreserved drug product is stored at ≤-120°C, in the vapor phase of liquid nitrogen.

Cilta-cel OOS therapy contains human cells genetically modified with a lentiviral vector. Follow local biosafety guidelines applicable for handling and disposal of such products. The product is prepared from autologous blood collected by apheresis. Cilta-cel OOS may carry a risk of transmitting infectious viruses to healthcare professionals handling the product. Accordingly, healthcare professionals should employ universal precautions to avoid potential transmission of infectious diseases when handling the product.

Detailed instructions for storage conditions and handling will accompany clinical drug supplies to the clinical study sites. The storage conditions and expiry dates are indicated on the label. Refer to the USPI for additional guidance on study treatment preparation, handling, and storage.

Accountability

The investigator is responsible for ensuring that all study treatment received at the site is inventoried and accounted for throughout the study. The study treatment administered to the participant must be documented on the intervention accountability form. All study treatment will

be stored and disposed of according to the sponsor's instructions. Study site personnel must not combine contents of the study treatment containers.

Study treatment must be handled in strict accordance with the protocol and the container label, and must be stored at the study site in a limited-access area or in a locked cabinet under appropriate environmental conditions. Unused study treatment must be available for verification by the sponsor's study site monitor during on-site monitoring visits. The return to the sponsor of unused study treatment will be documented on the intervention return form. When the study site is an authorized destruction unit and study treatment supplies are destroyed on-site, this must also be documented on the intervention return form.

Potentially hazardous materials containing hazardous liquids, such as used ampules, needles, syringes and vials, should be disposed of immediately in a safe manner and therefore will not be retained for intervention accountability purposes.

Study treatment should be dispensed under the supervision of the investigator or a qualified member of the study site personnel, or by a hospital/clinic pharmacist. Study treatment will be supplied only to participants participating in the study. The investigator agrees neither to dispense the study treatment from, nor store it at, any site other than the study sites agreed upon with the sponsor. Further guidance and information for the final disposition of unused study treatments are provided in the prescribing information.

6.3. Measures to Minimize Bias: Randomization and Blinding

Randomization is not applicable as this single arm study. Participants will be enrolled if all inclusion/exclusion criteria are met.

Blinding

As this is an open study, blinding procedures are not applicable.

6.4. Study Intervention Compliance

Infusion of cilta-cel OOS will be done in the controlled environment of a qualified clinical site, under the direct observation of qualified study site personnel and the details of each administration will be recorded in the eCRF (including date, start and stop times of the IV infusion, volume infused, and weight of IV infusion bag, including the infusion line, before and after the completion of the IV infusion) Precautions associated with the use of the study treatment and concomitant medications will be reviewed by the sponsor.

Refer to the prescribing information for a description of the chain of identity and chain of custody procedures associated with cilta-cel OOS.

6.5. Dose Modification

Target dose of cilta-cel is 0.75×10^6 cells/kg with the allowed dose in the range of 0.5×10^6 cells/kg to 1.0×0^6 cells/kg. For this study, a lower dose of CAR-T cells may be the reason for OOS. Upon positive benefit/risk assessment and exceptional release participants may receive modified doses

below the target dose range. The sponsor will evaluate the safety of the dose to be administered to each participant in the current study.

6.6. Continued Access to Study Intervention After the End of the Study

Cilta-cel is a one-time treatment. Therefore, continued access study treatment after end of the study is not applicable.

6.7. Treatment of Overdose

Cilta-cel will be manufactured, formulated and provided by the sponsor for each individual participant. The maximum total dose of cells to be administered to any participant is 1.0×10^8 CAR-positive viable T cells (ie, the maximum weight adjusted dose calculated for a 100-kg participant). The dose and administration schedule may be altered for safety purposes based on emerging data. Thus, there is no risk for overdose of cilta-cel.

6.8. Concomitant Therapy

Bridging therapy (between apheresis and cilta-cel OOS administration) can be given to prevent progression of the multiple myeloma.

Concomitant therapies or treatments (except for those listed in Section 6.8.2) are those deemed necessary to provide adequate supportive care. All medications must be recorded throughout the study beginning with start of the first dose of study treatment to Day 100 after the last dose of study treatment. Concomitant therapies should also be recorded beyond Day 100 in conjunction with delayed adverse events outlined in Delayed Adverse Events in Section 8.3.1. Time Period and Frequency for Collecting Adverse Event and Serious Adverse Event Information.

All therapies (prescription or over-the-counter medications, including vaccines, vitamins, herbal supplements; non-pharmacologic therapies such as electrical stimulation, acupuncture, special diets, exercise regimens, or other specific categories of interest) different from the study treatment must be recorded in the CRF. Recorded information will include a description of the type of therapy, duration of use, dosing regimen, route of administration, and indication. Exceptions include medications used to prevent (including vaccines) and treat COVID-19 and HBV reactivation, which should be reported until 1 year after cilta-cel infusion, regardless of severity or causality (Section 10.6 Appendix 6).

The sponsor must be notified in advance (or as soon as possible thereafter) of any instances in which prohibited therapies are administered.

6.8.1. Permitted Medications

The following are examples of supportive therapies that may be used during the study:

- Standard supportive care therapies (antiemetics, antidiarrheals, anticholinergics, antispasmodics, antipyretics, antihistamines, analgesics, antibiotics and other antimicrobials, histamine receptor [H_2] antagonists or proton pump inhibitors, and other medications intended to treat symptoms or signs of disease) and therapies intended to treat CAR-T cell-related

toxicity (ie, CRS) as clinically indicated, according to institutional standards and as deemed necessary by the investigator.

- Bisphosphonates may be initiated (if not already being administered) unless contraindicated within 1 week prior to the first dose of study treatment and continued until disease progression is established. In the case of severe adverse events such as hypercalcemia, bisphosphonates may be administrated as clinically indicated, according to institutional standards and as deemed necessary by the investigator.

- Hematopoietic growth factor support and transfusions (irradiated blood products) are permitted to treat symptoms or signs of neutropenia, anemia or thrombocytopenia according to local standards of care. Non-pegylated myeloid growth factors are permitted up to 1 day prior to the start of the lymphodepleting chemotherapy (Section 6.1.2).

- Documented infectious complications should be treated with oral or IV antibiotics or other anti-infective agents as considered appropriate by the treating investigator, according to standard institutional practice.

- Chemotherapy agents used to treat CAR-T cell-related toxicities are permitted upon consultation with the sponsor (see Section 2.3.1).

6.8.2. Prohibited Therapies

There are no prohibited medications for this study; however, the following medications should be avoided when medically feasible during the study:

- Systemic corticosteroid use should be avoided, except for the treatment of CRS or CAR-T cell-related neurotoxicity (eg, ICANS), as described in Table 6 and Table 7, respectively. Alternative therapies, if feasible, should be given instead of corticosteroids.

- Any chemotherapy, anticancer immunotherapy (other than cilta-cel), or experimental therapy, except as described in Section 4.1 (bridging therapy), or protocol-specific therapies which may be used in conjunction with cilta-cel OOS.

- While in follow-up, emergency orthopedic surgery or radiotherapy is generally prohibited, but may be allowed in the absence of disease progression. Cases must be discussed and approved by the sponsor. Such emergency radiotherapy may consist of localized radiotherapy for pain control or for stabilization of an extensive bone lesion at high risk of pathologic fracture or damage to surrounding tissues.

- Nonsteroidal anti-inflammatory agents should be avoided to minimize the risk of exacerbation of potential sub-clinical myeloma-related kidney disease. Based on the investigator's clinical judgment, low dose aspirin may be continued for thromboprophylaxis.

- Other immunosuppressant agents unless used as protocol-specified pre- or post-treatment medications to treat an adverse event (eg, CRS) or medical condition (eg, autoimmune disease).

- Vaccination with live, attenuated vaccine after signing consent and in the ≤6 weeks prior to the infusion of cilta-cel OOS, and for 100 days after cilta-cel infusion OOS.

- The use of IV contrast infusions should be avoided to prevent myeloma-related kidney disease. If administration of IV contrast is necessary, then adequate precautions including hydration are indicated.

- The use of receptor activator of nuclear factor kappa-B (RANK) ligand inhibitors such as denosumab is discouraged due to their potential impact on immune function.
- Pegylated myeloid growth factors (ie, pegfilgrastim) are discouraged within the first 100 days after cilta-cel infusion OOS (Section 6.1.4).

6.8.3. Subsequent Anticancer Therapy

Subsequent anticancer therapy administered after cilta-cel OOS should be only administered after confirmed disease progression per IMWG criteria (see Section 10.10, Appendix 10) and recorded in the eCRF. The start and end date and best response should be documented in the eCRF, if available.

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Intervention

Discontinuation of study treatment is not applicable to this study as cilta-cel OOS is administered as single-dose to participants after favorable benefit-risk assessment.

7.2. Participant Discontinuation/Withdrawal From the Study

A participant will be withdrawn from the study for any of the following reasons:

- Lost to follow-up
- Withdrawal of consent
- Not being able to receive cilta-cel OOS per the decision of the sponsor or principal investigator as described in Section 4.4.

When a participant withdraws before study completion, the reason for withdrawal is to be documented in the eCRF and in the source document. If the reason for withdrawal from the study is withdrawal of consent following dosing with cilta-cel OOS, study assessments for the last visit in the Post-infusion Phase (Table 1: Day 100;) should be completed prior to withdrawal of consent, if feasible.

Withdrawal of Consent

A participant declining to return for scheduled visits does not necessarily constitute withdrawal of consent. Alternate follow-up mechanisms that the participant agreed to when signing the consent form apply as local regulations permit.

7.3. Lost to Follow-up

To reduce the chances of a participant being deemed lost to follow-up, prior to enrollment attempts should be made to obtain contact information from each participant, eg, home, work, and mobile telephone numbers and email addresses for both the participant as well as appropriate family members.

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site. A participant cannot be deemed lost to follow-up until all reasonable efforts made by the study site personnel to contact the participant are deemed futile. The following actions must be taken if a participant fails to return to the study site for a required study visit:

- The study site personnel must attempt to contact the participant to reschedule the missed visit as soon as possible, to counsel the participant on the importance of maintaining the assigned visit schedule, to ascertain whether the participant wishes to or should continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or designee must make every reasonable effort to regain contact with the participant (where possible, 3 telephone calls, e-mails, fax, and, if necessary, a certified letter to the participant's last known mailing address, or local equivalent methods. These contact attempts should be documented in the participant's medical records.
- Should the participant continue to be unreachable, they will be considered to have withdrawn from the study.
- Site personnel, or an independent third party, will attempt to collect the vital status of the participant within legal and ethical boundaries for all participants enrolled, including those who did not get study treatment. Public sources may be searched for vital status information. If vital status is determined as deceased, this will be documented, and the participant will not be considered lost to follow-up. Sponsor personnel will not be involved in any attempts to collect vital status information.

Should a study site close, eg, for operational, financial, or other reasons, and the investigator cannot reach the participant to inform them, their contact information will be transferred to another study site.

8. STUDY ASSESSMENTS AND PROCEDURES

Overview

The SoA summarizes the frequency and timing of safety and efficacy measurements, and ongoing participant review applicable to this study.

If multiple assessments are scheduled for the same timepoint, it is recommended that procedures be performed in the following sequence: Echocardiogram/MUGA, vital signs, blood draw, infusion. Urine and blood collections for assessments should be kept as close to the specified time as possible. Other measurements may be done earlier than specified timepoints if needed. Actual dates and times of assessments will be recorded in the source documentation and CRF.

Assessments are to be performed per the SoA (Table 1) and include safety and disease assessments every 84 days after Day 100. Disease evaluations should continue to be performed until confirmed disease progression, death, start of a new anticancer treatment, withdrawal of consent for study participation, or end of the study, whichever occurs first. Once disease progression is confirmed, subsequent disease assessment is not required.

The volume of blood drawn from each participant in this study is approximately 360 mL up to Day 100 and approximately 20 to 40 mL at each post-treatment visit. Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

Screening Phase

If an assessment was performed as part of the participant's routine clinical evaluation and not specifically for this study, it does not need to be repeated after signed informed consent has been obtained provided the assessments fulfill the study requirements and are performed within the specified timeframe prior to the first dose of study treatment. Retesting of abnormal clinical laboratory values that do not meet the eligibility criteria are allowed only once during the Screening Phase (to reassess eligibility). Rescreening may occur with sponsor approval.

All participants must sign an ICF prior to the conduct of any study-related procedures. The Screening Phase begins when the cilta-cel OOS is approved for exceptional release.

Lymphodepleting Chemotherapy

At the completion of manufacture and quality testing of cilta-cel, written notification will be sent to the clinical site. Prior to dosing with cyclophosphamide and fludarabine, review of eligibility, safety assessments and disease characteristics should be completed per Section 6.1.2. The details regarding safety monitoring and study visits during this phase are included in the SoA (Table 1).

Cilta-cel OOS Administration

Administration of cilta-cel OOS is fully described in Table 5.

Post-infusion

The post-infusion period starts after the completion of cilta-cel OOS infusion on Day 1 and lasts until Day 100. Any participant who receives a cilta-cel OOS should continue all subsequent post-infusion assessments per the SoA (Table 1).

During this period, participants will be monitored closely with safety and disease assessments. Participants will be asked to check their temperature at least twice daily (entering 2 temperatures including their maximum daily temperature in the provided diary) during the first 28 days (ie, upto Day 28) after cilta-cel OOS infusion and will be instructed to report any fever (≥38°C) to the study doctor immediately to initiate monitoring for development of CRS.

Hospitalization is per institutional practices/guidelines (Table 5). Participants will be provided a "wallet (study) card" with pertinent information about the study and be asked to carry this card with them for the duration of the post-infusion and post-treatment period.

Post-treatment

The post-treatment period starts on Day 101 and lasts until study completion, defined as 2 years after each participant has received the initial dose of cilta-cel OOS. Assessments are to be performed per the SoA (Table 1) and include safety and disease assessments every 84 days. Refer to Section 8.3 for additional AE collection. Disease evaluation should continue to be performed until confirmed disease progression, death, start of a new anticancer treatment, withdrawal of consent for study participation, or end of the study, whichever occurs first. Once disease progression is confirmed, subsequent disease assessment is not required.

After disease progression is documented, survival status and subsequent anticancer therapy will be obtained every 16 weeks until the end of study, unless the participant has died, is lost to follow-up, or has withdrawn consent. If the information is obtained via telephone contact, written documentation of the communication must be available for review in the source documents. If the participant has died, the date and cause of death will be collected and documented on the eCRF, if or when available. Where allowed by local law, public records may be used to document death or to obtain survival status.

After end of study, participants are offered to enroll into the long-term-follow-up study (68284528MMY4002) to assess the long-term safety of cilta-cel OOS for up to 15 years.

Following completion of this study, assessment for replication competent lentivirus (RCL) will be collected yearly until 15 years after dosing with cilta-cel OOS on a follow-up study. In case of a second primary malignancy a tumor sample should be collected, and DNA, RNA or protein analysis may be performed to investigate the presence of lentiviral elements.

At the investigator discretion and with sponsor approval, study visits in the post-treatment part of the study, starting after Day 100, may be performed remotely via telemedicine technology that connects study participants to their research coordinators and investigators or mobile study personnel per standard of care. Similarly, blood sample collection may be performed at the participant's home by mobile study personnel (ie, nurses and mobile phlebotomist) per standard-of-care, in the post-treatment period.

Monitor patients at least daily for 10 days following cilta-cel OOS infusion (whether the participant will be dosed outpatient or inpatient) at a certified healthcare facility for signs of

symptoms of cytokine release syndrome and neurologic toxicities as per USPI. Monitor periodically for 4 weeks for signs and symptoms of delayed neurologic toxicity.

Sample Collection and Handling

The actual dates and times of sample collection must be recorded in the CRF or laboratory requisition form.

Within 24 hours of study treatment infusion, if the study treatment is infused peripherally, blood samples must be drawn from a vein contralateral to the arm into which cilta-cel OOS is infused. If the study treatment is infused via a central vein line, blood samples over the subsequent 24 hours must be drawn from a vein in either arm.

Refer to the SoA (Table 1) for the timing and frequency of all sample collections.

Instructions for the collection, handling, storage, and shipment of samples are found in the laboratory manual that will be provided. Collection, handling, storage, and shipment of samples must be under the specified, and where applicable, controlled temperature conditions as indicated in the laboratory manual.

Study-Specific Materials

The investigator will be provided with the following supplies:

- Study Protocol and USPI (or locally approved label)
- Laboratory manual
- National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) (version 5.0)
- Electronic data capture (eDC) Manual
- Sample ICF
- Participant diaries and instructions/educational materials

8.1. Efficacy Assessments

Disease evaluations must be performed as specified in the SoA Table 1. Disease evaluations until confirmed disease progression, death, start of a new anticancer treatment, withdrawal of consent for study participation, or end of study, whichever occurs first. This study will use the IMWG-based response criteria (Section 10.10 Appendix 10). If it is determined that the study treatment interferes with the immunofixation assay, CR will be defined as the disappearance of the original M-protein associated with multiple myeloma on immunofixation, and the determination of CR will not be affected by unrelated M-proteins secondary to the study treatment (Durie 2006).

Quantitation of M-protein, 24-hour urine protein, serum and urine immunofixation, and free-light chain (FLC) measurements in serum and urine will be carried out per standard-of-care. Disease progression must be consistently documented across clinical study sites using the criteria in Section 10.9, Appendix 9.

All efforts should be made to collect efficacy data per standard-of-care procedures. Local laboratory data may be collected if central laboratory data is not available at a particular timepoint, however this does not include screening assessments. Documentation of the local laboratory data should be sent to the principal investigator and filed in the medical record. It is the principal investigator's responsibility to ascertain that these results are reviewed and entered into the participant's medical record and the eCRF.

8.1.1. Myeloma Protein Measurements in Serum and Urine

Assessments will be performed as specified in the SoA (Table 1):

- Serum protein electrophoresis (SPEP)
- Serum immunofixation electrophoresis
- Serum FLC assay (for participant in suspected CR/sCR and every disease assessment for participants with serum FLC only disease)
- 24-hour urine M-protein quantitation by electrophoresis (UPEP)
- Urine immunofixation electrophoresis
- Serum quantitative Immunoglobulins

Blood and 24-hour urine samples will be collected as specified in the SoA Table 1 until the development of confirmed disease progression. Disease progression based on one of the laboratory tests alone must be confirmed by at least 1 repeat investigation. Disease evaluations will continue beyond relapse from CR until disease progression is confirmed. Serum and urine immunofixation and serum FLC assays will be performed at screening and thereafter when a CR is suspected (when serum or 24-hour urine M-protein electrophoresis [by SPEP or UPEP] are 0 or non-quantifiable). For participants with light-chain multiple myeloma, serum and urine immunofixation tests will be performed routinely per the SoA (Table 1).

8.1.2. Bone Marrow Examination

Bone marrow aspirate or biopsy (biopsy alone is acceptable if aspirate is not possible) will be performed for clinical assessments and biomarker evaluations. Clinical staging (morphology and immunohistochemistry or immunofluorescence or flow cytometry) should be done by a local laboratory; cytogenetics will be done at a central laboratory. If cytogenetic results are not available by central laboratory, local laboratory data, if available, may be entered into the eCRF. Bone marrow aspirate and biopsy will also be performed to confirm CR and sCR and at PD. A portion of the bone marrow aspirate at each bone marrow aspiration should be sent to the central laboratory for flow cytometry and to monitor BCMA in CD138-positive MM cells, and checkpoint expression on T cells. Additionally, bone marrow aspirate (at central laboratory) will be performed at Day 56 post-cilta-cel infusion if not performed within the past 3 months. In the event FISH analysis does not yield diagnostic results (either centrally or locally), archived bone marrow aspirate or bone marrow clot sample may be collected for FISH analysis. In addition, MRD-negative rate will be evaluated as specified in Section 8.1.3 and in the SoA (Table 1).

8.1.3. Minimal Residual Disease Evaluations

Bone marrow aspirates will be collected to monitor MRD-negative rate to define the myeloma clones as specified in the SoA (Table 1). MRD negativity is being evaluated in the field as a potential surrogate for PFS and OS. MRD-negative rate will be evaluated using next generation sequencing (NGS) on bone marrow aspirate DNA. In the event fresh bone marrow aspirate will not be collected at prior to LD chemotherapy, or if the fresh aspirate does not yield a usable clone, non-decalcified diagnostic tissue (bone marrow aspirate slides or formalin-fixed paraffin embedded tissue) should be collected for calibration of myeloma cells to facilitate the assessment of the secondary MRD-negative rate endpoints by next generation sequencing (NGS). Bone marrow aspirate should be sent to central laboratory for MRD-negative rate evaluation as specified in the Schedule of Activities (SoA).

8.1.4. Documentation of Extramedullary Plasmacytomas

Sites of known extramedullary plasmacytomas must be documented ≤14 days prior to the first dose of the lymphodepleting chemotherapy. Clinical examination or MRI may be used to document extramedullary sites of disease. CT scan evaluations are an acceptable alternative if there is no contraindication to the use of IV contrast. Positron emission tomography (PET) scan or ultrasound tests are not acceptable to document the size of extramedullary plasmacytomas. However, PET/CT fusion scans can be used to document extramedullary plasmacytomas if the CT component of the PET/CT fusion scan is of sufficient diagnostic quality.

Extramedullary plasmacytomas should be assessed for all participants with a history of plasmacytomas or if clinically indicated at ≤14 days prior to the first dose of the lymphodepleting chemotherapy, by clinical examination or radiologic imaging. Assessment of measurable sites of extramedullary disease will be performed, measured, and evaluated locally every 4 weeks (for physical examination) for participants with a history of plasmacytomas or as clinically indicated during treatment for other participants until development of confirmed CR or confirmed disease progression. If assessment can only be performed radiologically, then evaluation of extramedullary plasmacytomas may be done every 12 weeks. The methodology used for evaluation of each disease site should be consistent across all visits. Irradiated or excised lesions will be considered not measurable, and will be monitored only for disease progression.

To qualify for VGPR or PR minimal response (MR), the sum of products of the perpendicular diameters of the existing extramedullary plasmacytomas must have decreased by over 90% or at least 50%, respectively, and new plasmacytomas must not have developed (see the disease response criteria in Section 10.9, Appendix 9). To qualify for disease progression, either the sum of products of the perpendicular diameters of the existing extramedullary plasmacytomas must have increased by at least 50%, or the longest diameter of previous lesion >1 cm in short axis must have increased at least 50%, or a new plasmacytoma must have developed. When not all existing extramedullary plasmacytomas are reported, but the sum of products of the perpendicular diameters of the reported plasmacytomas have increased by at least 50%, then the criterion for disease progression is met.

8.1.5. Skeletal Survey

A skeletal survey (including skull, entire vertebral column, pelvis, chest, humeri, femora, and any other bones for which the investigator suspects involvement by disease) is to be performed during the screening phase (or in the time interval between completion of bridging therapy and start of lymphodepleting chemotherapy, if bridging therapy is given) and evaluated by the local laboratory by either roentgenography ("X-rays") or low dose computed tomography (CT) scans without the use of IV contrast. If a CT scan is used it must be of diagnostic quality. Following cilta-cel OOS infusion, and before disease progression is confirmed, X-rays or CT scans should be performed locally, whenever clinically indicated based on symptoms, to document response or progression. Magnetic resonance imaging (MRI) is an acceptable method for evaluation of bone disease, and may be included at the discretion of the investigator; however, it does not replace the skeletal survey (see the disease response criteria in Section 10.10, Appendix 10). If a radionuclide bone scan is used at consenting, in addition to the complete skeletal survey, then both methods must be used to document disease status. These tests must be performed at the same time. Note: a radionuclide bone scan does not replace a complete skeletal survey.

If a participant presents with disease progression manifested by symptoms of pain due to bone changes, then disease progression may be documented by skeletal survey or other radiographs, depending on the symptoms that the participant experiences. If the diagnosis of disease progression is obvious by radiographic investigations, then no repeat confirmatory X-rays are necessary. If changes are equivocal, then a repeat X-ray is needed in 1 to 3 weeks.

8.2. Safety Assessments

Safety will be measured by adverse events, laboratory test results, vital signs including oxygen saturation measurements, physical examination findings (including neurological examination), assessment of ICE-Tool scores, handwriting assessments, and assessment of ECOG performance status grade. Clinically relevant changes occurring during the study must be recorded on the adverse event section of the eCRF. Clinically significant abnormalities persisting at the end of the study/early withdrawal will be followed by the investigator until resolution or until a clinically stable endpoint is reached. Safety monitoring assessments may be performed more frequently, if clinically indicated.

The study will include the following evaluations of safety according to the time points provided in the SoA (Table 1).

Details regarding the Data Review Committee is provided in Committees Structure in Section 10.3, Appendix 3, Regulatory, Ethical, and Study Oversight Considerations.

Adverse events will be reported and followed by the investigator as specified in Section 8.3, Adverse Events, Serious Adverse Events, and Other Safety Reporting, and Section 10.4, Appendix 4 Adverse Events, Serious Adverse Events, Product Quality Complaints, and Other Safety Reporting: Definitions and Procedures for Recording, Evaluating, Follow-Up, and Reporting.

Any clinically relevant changes occurring during the study must be recorded on the Adverse Event section of the CRF.

Any clinically significant abnormalities persisting at the end of the study/early withdrawal will be followed by the investigator until resolution or until a clinically stable condition is reached.

The study will include the following evaluations of safety and tolerability according to the time points provided in the SoA (Table 1).

8.2.1. Physical Examinations

The screening physical examination will include, at a minimum, participant's height, general appearance, examination of the skin, ears, nose, throat, lungs, heart, abdomen, extremities, musculoskeletal system, and lymphatic system. Thereafter, a symptom-directed physical examination will be conducted as clinically indicated at subsequent timepoints. Abnormalities will be recorded in the appropriate section of the eCRF. Body weight will be measured prior to cilta-cel OOS infusion of (SoA, Table 1). Clinically significant post-baseline abnormalities should be recorded as adverse events.

8.2.2. Vital Signs

Temperature, pulse/heart rate, respiratory rate, blood pressure and oxygen saturation monitoring will be performed as specified in the SoA (Table 1).

Vital signs including temperature, pulse/heart rate, respiratory rate, and blood pressure (systolic and diastolic) will be monitored and clinically relevant changes occurring during the study will be recorded on the adverse event section of the eCRF.

Blood pressure and pulse/heart rate measurements should be preceded by at least 5 minutes of rest in a quiet setting without distractions (eg, television, cell phones).

8.2.3. Eastern Cooperative Oncology Group (ECOG) Performance Status

The ECOG performance status scale will be used to grade changes in the participant's daily living activities (Section 10.11, Appendix 11) and will be assessed as noted in the SoA, Table 1.

8.2.4. Neurologic Examination

Magnetic resonance imaging (MRI) at Screening Phase–or neurology consultation should be considered if pre-existing disease is suspected. For participants with prior pertinent neurologic disease (eg, stroke, encephalitis) consider baseline MRI of brain and an EEG. At the first sign of neurotoxicity, neurology consultation and evaluation should be considered. CAR-T cell-related neurotoxicity (eg, ICANS) should be graded using American Society for Transplantation and Cellular Therapy (ASTCT) consensus grading. Other neurological adverse events not associated with ICANS should be graded based on NCI-CTCAE (version 5.0) throughout both phases of the study. Findings from neurological testing that support CAR-T cell-related neurotoxicity (eg, ICANS) should be reported in the CRF.

8.2.5. Immune-Effector Cell-associated Encephalopathy (ICE) Tool Scores

The ICE test was developed to provide objectivity for the grading of multiple overlapping encephalopathy terms currently included on the approved CAR-T products (Lee 2019) (Section 10.9, Appendix 9). The ICE Tool will be collected as noted in the SoA (Table 1) to guide management throughout both phases of the study. It will also be used to grade the severity of ICANS (Section 10.8, Appendix 8). All ICE Tool scores, must be reported in the eCRF.

8.2.6. Handwriting Assessment

Qualitative changes in handwriting since baseline are being explored by the sponsor as a potential early clinical predictive marker for neurotoxicity. Currently no standardized CTCAE toxicity gradings are available in the NCI-CTCAE (version 5.0). for these type of changes in handwriting. Therefore, the sponsor has developed a handwriting assessment criterion to assess participants for occurrence of the following types of changes in handwriting: micrographia, dysgraphia, or agraphia, as potential early indicators for neurotoxicity (Section 10.12, Appendix 12).

Handwriting assessments will be collected on a writing log according to the SoA, Table 1 and as instructed by the sponsor. Participants unable to write at baseline are excused from this assessment during study. The sponsor's medical monitor should immediately be notified when changes in handwriting are detected. This will prompt discussion about additional assessments to further evaluate for other neurotoxicity symptoms, further workup, as well as the potential initiation of interventions. All cases of handwriting abnormalities (ie, micrographia, dysgraphia, or agraphia) must be reported as an adverse event in the eCRF. Should a participant experience a serious CAR-T associated neurotoxicity (either ICANS or other neurotoxicity), then a copy of the handwriting assessment log should be submitted with the serious adverse event report.

8.2.7. Clinical Safety Laboratory Assessments

Blood samples for serum chemistry, hematology, infectious diseases testing, and a routine urine sample for urinalysis will be collected as noted in Section 10.2, Appendix 2, Clinical Laboratory Tests. The investigator must review the laboratory results, document this review, and record any clinically relevant changes occurring during the study in the AE section of the CRF. The laboratory reports must be filed with the source documents. Participants with Grade 3 or higher toxicity or unresolved AEs will continue to be assessed until recovery to Grade 1 or baseline, the event is deemed irreversible, the end of the study, or a maximum of 6 months, whichever occurs first.

8.2.8. Replication Competent Lentivirus (RCL)

According to Mohanlal 2016, persistence of replication competent lentivirus (RCL) or delayed adverse events related to RCL have not been reported in patients who have received lentivirus-based gene therapies. However, the potential pathogenicity of RCL requires vigilant testing to exclude the presence of RCL in peripheral blood samples of participants infused with cilta-cel OOS.

In accordance with the FDA guidance for industry on Testing of Retroviral Vector-Based Human Gene Therapy Products for Replication Competent Retrovirus During Product Manufacture and

Patient Follow-up, peripheral blood mononuclear cells for all participants in the study will be monitored for RCL-specific DNA sequences by a validated PCR method. Monitoring schedule will include analysis of participant samples at the following time points: pre-treatment, followed by testing at 3, 6, and 12 months after treatment, and yearly until end of study; participants in follow-up at the end of study will be enrolled in the separate long-term follow-up study, Protocol 68284528MMY4002, to continue monitoring for up to 15 years. If samples are negative for RCL during the first year after treatment, RCL assessments may be terminated (See Section 8.5), and yearly review of medical history will generally be sufficient for the participant. If any post-treatment samples are positive, further analysis of the RCL, and more extensive patient follow-up should be undertaken. Additional event-triggered testing for RCL may be conducted as clinically indicated as specified in Schedule of Activities (SoA).

8.2.9. Pregnancy Testing

Additional serum pregnancy tests may be performed, as determined necessary by the investigator or required by local regulation, to establish the absence of pregnancy at any time during the participation in the study.

8.3. Adverse Events, Serious Adverse Events, and Other Safety Reporting

Timely, accurate, and complete reporting and analysis of safety information, including AEs, SAEs, and product quality complaint (PQC), from clinical studies are crucial for the protection of participants, investigators, and the sponsor, and are mandated by regulatory agencies worldwide. The sponsor has established Standard Operating Procedures in conformity with regulatory requirements worldwide to ensure appropriate reporting of safety information; all clinical studies conducted by the sponsor or its affiliates will be conducted in accordance with those procedures.

Adverse events will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally acceptable representative) for the duration of the study.

Further details on AEs, SAEs, and PQC can be found in Section 10.4, Appendix 4 Adverse Events, Serious Adverse Events, Product Quality Complaints, and Other Safety Reporting: Definitions and Procedures for Recording, Evaluating, Follow-Up, and Reporting.

8.3.1. Time Period and Frequency for Collecting Adverse Event and Serious Adverse Event Information

All Adverse Events

All AEs (with the exception of HBV reactivation and delayed AEs described below) and special reporting situations, whether serious or non-serious, will be reported from the time a signed and dated ICF is obtained until 100 days after cilta-cel OOS infusion or until completion of the participant's last study-related procedure (whichever is later), which may include contact for follow-up of safety. Beyond this AE reporting period, only SAEs regardless of causality and non-serious AEs that are considered related to a study drug need to be reported until the end of the study except as defined for delayed AEs below. Events of HBV reactivations and COVID-19

infections, regardless of severity or relatedness, will be collected during the first-year post-dosing of cilta-cel OOS. See Section 10.17, Appendix 17 for additional adverse event reporting guidance.

All adverse events, regardless of seriousness, severity, or presumed relationship to study treatment, must be recorded using medical terminology in the source document and the CRF. Whenever possible, diagnoses should be given when signs and symptoms are due to a common etiology (eg, cough, runny nose, sneezing, sore throat, and head congestion should be reported as "upper respiratory infection"). The exceptions are CRS and CAR-T cell-related neurotoxicity, for which all symptoms associated with these events will be collected in the eCRF. Investigators must record in the CRF their opinion concerning the relationship of the adverse event to study therapy. All measures required for adverse event management must be recorded in the source document and reported according to the sponsor instructions.

An assessment of severity grade will be made by the investigator according to the NCI-CTCAE version 5.0, except for CRS and CAR-T cell-related neurotoxicity (eg, ICANS). Cytokine release syndrome should be evaluated according to the ASTCT consensus grading (Section 10.7, Appendix 7) (Lee 2019). CAR-T cell-related neurotoxicity (eg, ICANS) should be graded using the ASTCT consensus grading (Section 10.8, Appendix 8). In addition to capturing ICANS and CRS AEs (graded by ASTCT consensus grading), all individual symptoms of CRS (eg, fever, hypotension) and CAR-T cell-related neurotoxicity (eg, depressed level of consciousness, seizures) must be captured as individual AEs and graded by CTCAE criteria. Neurotoxicity that is not temporarily associated with CRS, or any other neurologic AEs that do not qualify as ICANS, will be graded by CTCAE criteria. Events of neurotoxicity or exacerbation of existing neurologic AEs will be reported until the end of study.

Changes in handwriting (ie, micrographia, dysgraphia, or agraphia) should be graded using the criteria outlined in Section 10.12 (Appendix 12) and reported as an AE in the eCRF. Should a participant experience a serious CAR-T associated neurotoxicity (either ICANS or other neurotoxicity), then a copy of the handwriting assessment log should be submitted with the serious AE report.

Delayed Adverse Events

The following delayed AEs need to be reported regardless of seriousness or causality until the end of study. These will continue to be collected after this study in a subsequent LTFU study (68284528MMY4002) for up to 15 years after last dose of cilta-cel.

- New primary malignancies or recurrence of pre-existing malignancy (all grades), with the exception of multiple myeloma (which should be reported as progressive disease), must be reported to the sponsor within 24 hours of awareness of the event for the duration of the study, irrespective of seriousness or causality. In the event of malignancy, a tumor sample should be collected, and vector integration site analysis may be performed for possible insertional mutagenesis.

- New incidence or exacerbation of a pre-existing neurologic disorder (all grades). Grade 3 or higher neurotoxicity and any grade movement and neurocognitive toxicity (ie, Parkinsonism) must be reported to the sponsor within 24 hours of awareness of the event for the duration of the study, irrespective of seriousness or causality.
- New incidence or exacerbation of a pre-existing rheumatologic or other autoimmune disorder (all grades)
- New incidence of Grade ≥3 hematologic disorder
- New incidence of Grade ≥3 infection

Serious Adverse Events

All serious adverse events (SAEs), as well as PQC, occurring during the study must be reported to the appropriate sponsor contact person by study site personnel within 24 hours of their knowledge of the event.

Serious adverse events (regardless of causality), including those spontaneously reported to the investigator must be reported throughout the study and subsequently will be collected yearly in ~~a~~ the long-term follow-up study (68284528MMY4002) for up to 15 years post-infusion of cilta-cel. The sponsor will evaluate any safety information that is spontaneously reported by an investigator beyond the time frame specified in the protocol. All events that meet the definition of a SAE will be reported as SAEs, regardless of whether they are considered related to study drug or protocol-specific assessments.

Information regarding SAEs will be transmitted to the sponsor using the Serious Adverse Event Form, which must be completed and signed by a physician from the study site, and transmitted to the sponsor within 24 hours. The initial and follow-up reports of an SAE should be made by facsimile (fax). Telephone reporting should be the exception and the reporter should be asked to complete the appropriate form(s) first.

Adverse Events of Special Interest

Cytokine release syndrome, neurotoxicity (including CAR-T cell-related neurotoxicity [eg, ICANS] and other neurotoxicities), prolonged and recurrent cytopenias, and second primary malignancies are adverse events of special interest and will be followed as part of standard safety monitoring activities by the sponsor, regardless of severity or causality. These events will require enhanced data collection in the eCRF, be reported to the sponsor in a timely manner, irrespective of seriousness, and followed until recovery or until there is no further improvement. For the purpose of reporting, SPMs include both new primary malignancies and recurrence of pre-existing malignancies with the exception of multiple myeloma (which should be reported as disease progression).

In addition, the following events must be reported to the sponsor using the Serious Adverse Event Form within 24 hours of awareness of the event for the duration of the study, irrespective of seriousness (eg, serious and nonserious adverse events) or causality:

- ≥Grade 3 CRS
- ≥Grade 3 neurotoxicity
- Any grade movement and neurocognitive toxicity (ie, Parkinsonism)
- Any grade second primary malignancy
- All deaths not related to disease progression occurring any time during study after receiving cilta-cel should be reported to the sponsor following expedited reporting procedures.

8.3.2. Method of Detecting Adverse Events and Serious Adverse Events

Care will be taken not to introduce bias when detecting AEs or SAEs. Open-ended and nonleading verbal questioning of the participant is the preferred method to inquire about AE occurrence.

Unsolicited Adverse Events

Unsolicited AEs are all AEs for which the participant is not specifically questioned in the participant diary.

8.3.3. Follow-up of Adverse Events and Serious Adverse Events

The investigator is obligated to perform or arrange for the conduct of supplemental measurements and evaluations as medically indicated to elucidate the nature and causality of the AE, SAE, or PQC as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.

Adverse events, including pregnancy, will be followed by the investigator as specified in Section 10.4 (Appendix 4) Adverse Events, Serious Adverse Events, Product Quality Complaints, and Other Safety Reporting: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting.

8.3.4. Regulatory Reporting Requirements for Serious Adverse Events

The sponsor assumes responsibility for appropriate reporting of AEs to the regulatory authorities. The sponsor will also report to the investigator (and the head of the investigational institute where required) all suspected unexpected serious adverse reactions (SUSARs). The investigator (or sponsor where required) must report SUSARs to the appropriate Independent Ethics Committee/Institutional Review Board (IEC/IRB) that approved the protocol unless otherwise.

8.3.5. Pregnancy

All initial reports of pregnancy in female participants or partners of male participants must be reported to the sponsor by the study site personnel within 24 hours of their knowledge of the event using the appropriate pregnancy notification form. Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs and must be reported using an SAE reporting form. Any participant who becomes pregnant during the study must discontinue further study treatment.

Follow-up information regarding the outcome of the pregnancy and any postnatal sequelae in the infant will be required.

8.3.6. Disease-Related Events and Disease-Related Outcomes Not Qualifying as Adverse Events or Serious Adverse Events

All events that meet the definition of an SAE will be reported as SAEs, regardless of whether they are protocol-specific assessments.

8.4. Pharmacokinetics

Venous blood samples will be used to evaluate the PK of cilta-cel OOS. Samples collected for PK may additionally be used to evaluate safety or efficacy aspects that address concerns arising during or after the study period. Genetic analyses will not be performed on these serum samples. Participant confidentiality will be maintained.

Venous blood samples will be collected for measurement of ciltacel-positive cellular concentration and transgene levels as specified in the SoA (Table 1). Samples will also be collected at the time of onset of suspected CRS or cilta-cell-related neurotoxicity (ie, ICANS) regardless of causality (as specified in Table 1).

The exact dates and times of sampling must be recorded on the laboratory requisition form. Refer to the laboratory manual for sample collection requirements. Collected samples must be stored under specified controlled conditions for the temperatures indicated in the laboratory manual.

8.5. Biomarkers

Biomarker assessments will focus on several objectives aligned with the objectives of the study: 1) characterization of peripheral CAR-T cell expansion and persistence as well as their memory and activation phenotypes through assessment of markers including, but not limited to, $CD4^+$, $CD8^+$, $CD25^+$, CD45RO and CCL7; 2) determine the ability of cilta-cel OOS to induce MRD negativity in participants with relapse/refractory multiple myeloma who have achieved CR; 3) immunophenotyping of other immune CAR negative cell subsets such as $CD4^+$ and $CD8^+$ T cells, regulatory B and T cells or natural killer cells; 4) assessment of serum or plasma proteins over time including, but not limited to cytokines (such as IL-6, IFN-γ, and IL-10). 5) determine the clinical benefit (ORR, DOR, PFS, and OS) of cilta-cel OOS in participants with cytogenetic modifications (del17p, t(4;14), t(14;16), or other high risk molecular subtypes). Additional biomarker samples may be collected when clinically indicated and as specified in the Schedule of Activities (SoA) to help understand unexplained adverse events including but not limited to serum or peripheral blood mononuclear cells (PBMCs).

The potential presence of Replication Competent Lentivirus (RCL) will be evaluated from whole blood samples of participants treated with cilta-cel OOS. RCL will be evaluated using a qPCR assay against the lentiviral vesicular stomatitis virus-G gene. If samples are negative for RCL during the first year after treatment RCL assessments may be terminated.

Biomarker analyses are dependent upon the availability of appropriate biomarker assays and may be deferred or not performed if during or at the end of the study it becomes clear that the analysis will have no scientific value, or if there are not enough samples or not enough responders to allow for adequate biomarker evaluation. In the event the study is terminated early or shows poor clinical efficacy, completion of biomarker assessments is based on the intended utility of the data.

Based on emerging scientific evidence, the sponsor may request additional material from, including but not limited to, previously collected bone marrow samples, whole blood, bone marrow aspirate or biopsy, or CSF, or other tissue sample during or after study completion for a retrospective analysis. For participants diagnosed with a SPM, a tumor sample should be collected. Additionally, the sponsor will receive a sample of plasmacytoma if patient relapse is suspected. Participants who have a lumbar puncture as part of their neurologic work up should have CSF sent for additional tests by the sponsor. In all cases, such analyses would be specific to research related to the study treatment(s) or diseases being investigated. If a participant dies and an autopsy is performed, specimens may be requested by the sponsor for analysis.

9. STATISTICAL CONSIDERATIONS

Statistical analysis will be done by the sponsor or under the authority of the sponsor. A general description of the statistical methods to be used to analyze the efficacy and safety data is outlined below. Specific details will be provided in the Statistical Analysis Plan. No formal statistical hypothesis testing will be performed for the study. All participants who received an infusion of cilta-cel OOS will be included in the analysis for efficacy and safety summaries. Descriptive statistics and time to event analysis as appropriate will be detailed in the statistical analysis plan. Initially, data will be reviewed by DRC after every 10 participants have been treated and followed for at least 3 months to assess efficacy and safety.

9.1. Statistical Hypotheses

No formal statistical hypothesis is planned for this study.

9.2. Sample Size Determination

Sample size is not based on statistical consideration. Based on the current manufacturing experience with the study 68284528MMY2001, at least 20 participants are anticipated to enroll in the study.

9.3. Populations for Analysis Sets

The analysis population for this study is defined as:

All **treated analysis set**, which consists all participants who received a cilta-cel OOS infusion, will be used for both efficacy and safety analyses.

9.4. Statistical Analyses

The statistical analysis plan will be finalized prior to database lock (DBL) and it will include a more technical and detailed description of the statistical analyses described in this section.

9.4.1. General Considerations

Continuous variables will be summarized using the number of observations, mean, standard deviation, coefficient of variation, median, and range as appropriate. Categorical values will be summarized using the number of observations and percentages as appropriate. For time to event data, the distribution (median and Kaplan-Meier curves) will be provided using Kaplan-Meier estimates.

9.4.1.1. Primary Endpoints

Primary Endpoint: Overall response rate is defined as the proportion of participants who achieve a PR or better (ORR) according to the IMWG response criteria (Durie 2006, 2015; Rajkumar 2011) assessed by the investigator.

9.4.1.2. Secondary Endpoints

Duration of response (DOR) will be calculated among responders (with a PR or better response) from the date of initial documentation of a response (PR or better) to the date of first documented evidence of progressive disease, as defined in the IMWG response criteria assessed by the investigator. Relapse from CR by positive immunofixation or trace amount of M-protein is not considered as disease progression. Disease evaluations will continue beyond relapse from CR until disease progression is confirmed. For participants who have not progressed, data will be censored at the last disease evaluation before the start of any subsequent anti-myeloma therapy.

Progression-free survival (PFS) defined as the time from the date of the initial infusion of cilta-cel OOS to the date of first documented disease progression, as defined in the IMWG response criteria, or death due to any cause, whichever occurs first. For participants who have not progressed and are alive, data will be censored at the last disease evaluation before the start of any subsequent anti-myeloma therapy.

Overall survival (OS) is measured from the date of the initial infusion of cilta-cel OOS to the date of the participant's death. If the participant is alive or the vital status is unknown, then the participant's data will be censored at the date the participant was last known to be alive.

All safety analyses will be made on the Safety Population.

Adverse Events

The verbatim terms used in the CRF by investigators to identify AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Section 8.3 provides information on AEs that are to be reported following initial administration of study treatment. Any AE reported at or after the initial administration of study treatment is considered to be treatment-emergent. All reported treatment-emergent AEs will be included in the analysis. For each AE, the percentage of participants who experience at least 1 occurrence of the given event will be summarized.

Summaries, listings, datasets, or participant narratives may be provided, as appropriate, for those participants who die, who discontinue intervention due to an AE, or who experience a severe or an SAE.

Parameters with predefined NCI-CTCAE (version 5.0) toxicity grades will be summarized for TEAEs. Change from baseline to the worst AE grade experienced by the participant during the study will be provided as shift tables.

Clinical Laboratory Tests

Laboratory data will be summarized by type of laboratory test. Reference ranges and markedly abnormal results (specified in the Statistical Analysis Plan) will be used in the summary of laboratory data. Descriptive statistics will be calculated for selected laboratory analyte at baseline and for observed values and changes from baseline at each scheduled time point. Changes from baseline will be presented in pre-versus post-intervention cross-tabulations (with classes for below, within, and above normal ranges). Frequency tabulations of the laboratory abnormalities will be made. A listing of participants with any laboratory results outside the reference ranges will be provided. A listing of participants with any markedly abnormal laboratory results will also be provided.

Vital Signs

Vital signs including temperature, pulse/heart rate, respiratory rate, and blood pressure (systolic and diastolic) will be summarized over time, using descriptive statistics. The percentage of participants with values beyond clinically important limits will be summarized.

Physical Examinations

Descriptive statistics of changes from baseline will be summarized at each scheduled time point.

Physical examination findings will be summarized at each scheduled time point. Descriptive statistics will be calculated at baseline and for observed values and changes from baseline at each scheduled time point. Frequency tabulations of the abnormalities will be made.

9.4.1.3. Exploratory Endpoints

Pharmacokinetics

Pharmacokinetic parameters will be estimated for individuals, and descriptive statistics will be calculated. Correlation of maximum peripheral blood concentration (C_{max}) and area under the peripheral blood concentration-time curve (AUC) with dose may also be explored. Pharmacokinetic parameters include, but are not limited to, AUC from time 0 to infinity (AUC_{inf}), AUC from time 0 to t ($AUC_{[0-t]}$), C_{max}, half-life, and time to reach maximum peripheral blood concentration (T_{max}) parameters will be calculated if sufficient data are available for estimation.

Immunogenicity Assessment

Antibodies to cilta-cel OOS will be evaluated in serum samples collected from all participants according to the SoA (Table 1). Samples will also be collected at the time onset of suspected CRS or CAR-T cell-related neurotoxicity (ie, ICANS) regardless of causality.

Additionally, serum samples should also be collected at the final visit from participants who discontinued due to progressive disease or were withdrawn from the study. These samples will be tested by the sponsor or sponsor's designee. The exact dates and times of blood sampling must be recorded on the laboratory requisition form. Refer to the laboratory manual for sample collection requirements. Collected samples must be stored under specified controlled conditions at the temperatures indicated in the Laboratory Manual.

Cilta-cel transgene concentration will also be determined to aid in the interpretation of immunogenicity data. These samples will be stored and evaluated if deemed necessary.

Serum samples will be screened for antibodies binding to cilta-cel OOS and the titer of confirmed positive samples will be reported. Other analyses may be performed to further characterize the immunogenicity of cilta-cel OOS. Genetic analyses will not be performed on these samples. Participant confidentiality will be maintained.

9.4.1.4. Biomarker Analyses

Descriptive analysis will be performed for each biomarker at baseline and for observed values and changes from baseline at each scheduled time point. These include but are not limited to CAR-positive T cell concentrations as well as cytokine levels. Descriptive associations with safety and efficacy may also be evaluated.

9.5. Interim Analysis

No formal interim analysis is planned. Initially, data will be reviewed after every 10 participants have been treated and followed for at least 3 months to assess efficacy and safety.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1. Appendix 1: Abbreviations and Definitions

AE	adverse event
AESI	adverse event of special interest
ALT	alanine aminotransferase
ASCT	autologous stem cell transplant
AST	aspartate transaminase
AxMP	Auxiliary Medicinal Product (also known as NIMP)
BCMA	B-cell maturation antigen
CAR	chimeric antigen receptor
CBR	clinical benefit rate
COVID-19	Coronavirus Disease-2019
CR	complete response
CRF	case report form
CRS	cytokine release syndrome
CSF	cerebrospinal fluid
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
DOR	duration of response
DRC	Data Review Committee
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
eDC	electronic data capture
EEG	electroencephalogram
EOS	end of study
FISH	fluorescence in situ hybridization
FLC	free-light chain
FOIA	Freedom of Information Act
GCP	Good Clinical Practice
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HHV	human herpesvirus
HLH	hemophagocytic lymphohistiocytosis
HIV	human immunodeficiency virus
HTLV	Human T cell lymphotropic virus
IB	Investigator's Brochure
ICANS	Immune-Effector Cell-associated Neurotoxicity Syndrome
ICE	Immune-Effector Cell-associated Encephalopathy
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
Ig	Immunoglobulin
IMiD	Immunomodulatory drug
IMP	Investigational Medicinal Product
IND	Investigational New Drug
IMWG	International Myeloma Working Group
IRB	Institutional Review Board
IRC	Independent Review Committee
LTFU	long-term follow-up
LD	lymphodepleting
MAS	macrophage activation syndrome
MR	minimal Response
MRD	minimal residue disease
MRI	magnetic resonance imaging
NIMP	Non-Investigational Medicinal Product

NCI	National Cancer Institute
PCR	polymerase chain reaction
PET	positron emission tomography
OS	overall survival
ORR	overall response rate
OOS	out-of-specifications
PFS	progression-free survival
PQC	Product Quality Complaint
PK	pharmacokinetics
PR	partial response
RCL	Replication Competent Lentivirus
RRMM	relapsed/refractory multiple myeloma
SAE	serious adverse events
SoA	schedule of activities
SPEP	serum protein electrophoresis
SPM	second primary malignancy
ULN	upper limit of normal
UPEP	urine protein electrophoresis
US	United States
VGPR	very good partial response
VHH	variable fragments of heavy chain antibodies
TEAE	treatment-emergent adverse event
TLS	tumor lysis syndrome
USPI	United States Prescribing Information

Definitions of Terms

Electronic source system	Contains data traditionally maintained in a hospital or clinic record to document medical care or data recorded in a CRF as determined by the protocol. Data in this system may be considered source documentation.

10.2. Appendix 2: Clinical Laboratory Tests

Protocol Required Safety Laboratory Assessments

The following tests will be performed by the local laboratory except for the calcium and albumin adjusted calcium, which will be performed at the central laboratory:

<table>
<tr><th>Laboratory Assessments</th><th colspan="3">Parameters</th></tr>
<tr><td rowspan="2">Hematology</td><td>Platelet count
Red blood cell count
Hemoglobin
Hematocrit</td><td><u>Red Blood Cell (RBC) Indices:</u>
MCV
MCH
% Reticulocytes</td><td><u>White Blood Cell (WBC) count with Differential:</u>
Neutrophils
Lymphocytes
Monocytes
Eosinophils
Basophils</td></tr>
<tr><td colspan="3">Note: A WBC evaluation may include any abnormal cells, which will then be reported by the laboratory. An RBC evaluation may include abnormalities in the RBC count, RBC parameters, or RBC morphology, which will then be reported by the laboratory. In addition, any other abnormal cells in a blood smear will also be reported.</td></tr>
<tr><td>Cluster of differentiation (CD) -CD4/CD8 Lymphocyte Panel</td><td colspan="3">Absolute number and % CD4, Absolute number and % CD8, and CD4/CD8 ratio if locally available.</td></tr>
<tr><td rowspan="2">Clinical Chemistry</td><td colspan="2">Sodium
Potassium
Chloride
Bicarbonate
Blood urea nitrogen (BUN)/Urea
Creatinine
Glucose
Aspartate aminotransferase (AST)/Serum glutamic-oxaloacetic
Alanine aminotransferase (ALT)/Serum glutamic-oxaloacetic
Gamma-glutamyltransferase (GGT)
Ferritin</td><td>Total bilirubin and Direct bilirubin, if Gilbert’s disease
Alkaline phosphatase
Creatine phosphokinase (CPK)
Lactic acid dehydrogenase (LDH)
Uric acid
Calcium and albumin-adjusted calcium
Phosphate
Albumin
Total protein
Cholesterol
Triglycerides
Magnesium
C-reactive protein
eGFR[a]</td></tr>
<tr><td colspan="3">All events of ALT (or AST) ≥3×upper limit of normal (ULN) and total bilirubin ≥2×ULN (>35% direct bilirubin) or ALT (or AST) ≥3×ULN and international normalized ratio (INR) >1.5, if INR measured which may indicate severe liver injury (possible Hy’s Law), must be reported as a serious adverse event (SAE) (excluding studies of hepatic impairment or cirrhosis).</td></tr>
</table>

Routine Urinalysis	Dipstick Specific gravity pH Glucose Protein Blood Ketones Bilirubin Urobilinogen Nitrite Leukocyte esterase	Sediment (if dipstick result is abnormal) Red blood cells White blood cells Epithelial cells Crystals Casts Bacteria
	If dipstick result is abnormal, microscopy will be used to measure sediment.	
Infectious diseases testing	Human immunodeficiency virus (HIV), Hepatitis B, Hepatitis C, Human T-cell lymphotropic virus (HTLV) and other infectious diseases will be performed within 60 days of apheresis (or sooner according to local regulations)	
Other Tests	• Serum Pregnancy Testing (β-human chorionic gonadotropin [β-hCG]) for women of childbearing potential only. • Serology: Hepatitis B: Hepatitis B surface antigen [HBsAg], anti-HBc, anti-HBs, HBV DNA quantification [for participants who are anti-HBs positive without history of vaccination or for participants who are anti-HBs positive and anti-HBc positive]; Monitor HBV DNA, AST/ALT every 3 months for one year post-dose of cilta-cel out-of-specification [OOS]; Hepatitis C: HCV antibody, HCV-RNA [for participants who are anti HCV positive]; HIV serology) (Refer Section 10.14, Appendix 14). • Coagulation (Prothrombin time/International normalized ratio, Fibrinogen, Activated partial thromboplastin time, D-dimer).	

a Calculated using modified diet in renal disease (MDRD) formula (Section 10.16, Appendix 16).

10.3. Appendix 3: Regulatory, Ethical, and Study Oversight Considerations

10.3.1. Regulatory and Ethical Considerations

Investigator Responsibilities

The investigator is responsible for ensuring that the study is performed in accordance with the protocol, current International Council for Harmonisation (ICH) guidelines on Good Clinical Practice (GCP), and applicable regulatory and country-specific requirements.

Good Clinical Practice is an international ethical and scientific quality standard for designing, conducting, recording, and reporting studies that involve the participation of human participants. Compliance with this standard provides public assurance that the rights, safety, and well-being of study participants are protected, consistent with the principles that originated in the Declaration of Helsinki, and that the study data are credible.

Protocol Amendments

Neither the investigator nor the sponsor will modify this protocol without a formal amendment by the sponsor. All protocol amendments must be issued by the sponsor, and signed and dated by the investigator. Protocol amendments must not be implemented without prior IEC/IRB approval, or when the relevant competent authority has raised any grounds for non-acceptance, except when necessary to eliminate immediate hazards to the participants, in which case the amendment must be promptly submitted to the IEC/IRB and relevant competent authority. Documentation of amendment approval by the investigator and IEC/IRB must be provided to the sponsor. When the change(s) involve only logistic or administrative aspects of the study, the IEC/IRB (where required) only needs to be notified.

During the course of the study, in situations where a departure from the protocol is unavoidable, the investigator or other physician in attendance will contact the appropriate sponsor representative listed in the Contact Information page(s), which will be provided as a separate document. Except in emergency situations, this contact should be made before implementing any departure from the protocol. In all cases, contact with the sponsor must be made as soon as possible to discuss the situation and agree on an appropriate course of action. The data recorded in the CRF and source documents will reflect any departure from the protocol, and the source documents will describe this departure and the circumstances requiring it.

Regulatory Approval/Notification

This protocol and any amendment(s) must be submitted to the appropriate regulatory authorities in each respective country, if applicable. A study may not be initiated until all local regulatory requirements are met.

Required Prestudy Documentation

The following documents must be provided to the sponsor before shipment of study treatment to the study site:

- Protocol and amendment(s), if any, signed and dated by the principal investigator.
- A copy of the dated and signed (or sealed, where appropriate per local regulations), written IEC/IRB approval of the protocol, amendments, ICF, any recruiting materials, and if applicable, participant compensation programs. This approval must clearly identify the specific protocol by title and number and must be signed (or sealed, where appropriate per local regulations) by the chairman or authorized designee.
- Name and address of the IEC/IRB, including a current list of the IEC/IRB members and their function, with a statement that it is organized and operates according to GCP and the applicable laws and regulations. If accompanied by a letter of explanation, or equivalent, from the IEC/IRB, a general statement may be substituted for this list. If an investigator or a member of the study site personnel is a member of the IEC/IRB, documentation must be obtained to state that this person did not participate in the deliberations or in the vote/opinion of the study.
- Regulatory authority approval or notification, if applicable
- Signed and dated statement of investigator (eg, Form Food and Drug Administration [FDA] 1572), if applicable
- Documentation of investigator qualifications (eg, curriculum vitae)
- Completed investigator financial disclosure form from the principal investigator, where required
- Signed and dated clinical trial agreement, which includes the financial agreement
- Any other documentation required by local regulations

The following documents must be provided to the sponsor before enrollment of the first participant:

- Completed investigator financial disclosure forms from all subinvestigators
- Documentation of subinvestigator qualifications (eg, curriculum vitae)
- Name and address of any local laboratory conducting tests for the study, and a dated copy of current laboratory normal ranges for these tests, if applicable
- Local laboratory documentation demonstrating competence and test reliability (eg, accreditation/license), if applicable

Independent Ethics Committee or Institutional Review Board

Before the start of the study, the investigator (or sponsor where required) will provide the IEC/IRB with current and complete copies of the following documents (as required by local regulations):

- Final protocol and, if applicable, amendments
- Sponsor-approved ICF (and any other written materials to be provided to the participants)
- IB (or equivalent information) and amendments/addenda
- Sponsor-approved participant recruiting materials

- Information on compensation for study-related injuries or payment to participants for participation in the study, if applicable
- Investigator's curriculum vitae or equivalent information (unless not required, as documented by the IEC/IRB)
- Information regarding funding, name of the sponsor, institutional affiliations, other potential conflicts of interest, and incentives for participants
- Any other documents that the IEC/IRB requests to fulfill its obligation

This study will be undertaken only after the IEC/IRB has given full approval of the final protocol, amendments (if any, excluding the ones that are purely administrative, with no consequences for participants, data or study conduct, unless required locally), the ICF, applicable recruiting materials, and participant compensation programs, and the sponsor has received a copy of this approval. This approval letter must be dated and must clearly identify the IEC/IRB and the documents being approved.

During the study the investigator (or sponsor where required) will send the following documents and updates to the IEC/IRB for their review and approval, where appropriate:

- Protocol amendments (excluding the ones that are purely administrative, with no consequences for participants, data or study conduct)
- Revision(s) to ICF and any other written materials to be provided to participants
- If applicable, new or revised participant recruiting materials approved by the sponsor
- Revisions to compensation for study-related injuries or payment to participants for participation in the study, if applicable
- New edition(s) of the IB and amendments/addenda
- Summaries of the status of the study at intervals stipulated in guidelines of the IEC/IRB (at least annually)
- Reports of AEs that are serious, unlisted/unexpected, and associated with the study treatment
- New information that may adversely affect the safety of the participants or the conduct of the study
- Deviations from or changes to the protocol to eliminate immediate hazards to the participants
- Report of deaths of participants under the investigator's care
- Notification if a new investigator is responsible for the study at the site
- Development Safety Update Report and Line Listings, where applicable
- Any other requirements of the IEC/IRB

For all protocol amendments (excluding the ones that are purely administrative, with no consequences for participants, data or study conduct), the amendment and applicable ICF revisions must be submitted promptly to the IEC/IRB for review and approval before implementation of the change(s).

At least once a year, the IEC/IRB will be asked to review and reapprove this study, where required.

At the end of the study, the investigator (or sponsor where required) will notify the IEC/IRB about the study completion.

Other Ethical Considerations

For study-specific ethical design considerations, refer to Section 4.2.1.

10.3.2. Financial Disclosure

Investigators and subinvestigators will provide the sponsor with sufficient, accurate financial information in accordance with local regulations to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

Refer to Required Prestudy Documentation (above) for details on financial disclosure.

10.3.3. Informed Consent Process

Each participant must give written consent according to local requirements after the nature of the study has been fully explained. The ICF(s) must be signed before performance of any study-related activity. The ICF(s) that is/are used must be approved by both the sponsor and by the reviewing IEC/IRB and be in a language that the participant can read and understand. The informed consent should be in accordance with principles that originated in the Declaration of Helsinki, current ICH and GCP guidelines, applicable regulatory requirements, and sponsor policy.

Informed consent may be obtained remotely. Refer to the Monitoring Guideline.

Before enrollment in the study, the investigator or an authorized member of the study site personnel must explain to potential participants the aims, methods, reasonably anticipated benefits, and potential hazards of the study, and any discomfort participation in the study may entail. Participants will be informed that their participation is voluntary and that they may withdraw consent to participate at any time. They will be informed that choosing not to participate will not affect the care the participant will receive Finally, they will be told that the investigator will maintain a participant identification register for the purposes of long-term follow-up if needed and that their records may be accessed by health authorities and authorized sponsor personnel without violating the confidentiality of the participant, to the extent permitted by the applicable law(s) or regulations. By signing the ICF the participant is authorizing such access It also denotes that the participant agrees to allow his or her study physician to recontact the participant for the purpose of obtaining consent for additional safety evaluations and subsequent disease-related treatments, if needed.

The participant will be given sufficient time to read the ICF and the opportunity to ask questions. After this explanation and before entry into the study, consent should be appropriately recorded by means of the participant's personally dated signature. After having obtained the consent, a copy of the ICF must be given to the participant.

If the participant is unable to read or write, an impartial witness should be present for the entire informed consent process (which includes reading and explaining all written information) and should personally date and sign the ICF after the oral consent of the participant is obtained.

10.3.4. Data Protection

Privacy of Personal Data

The collection and processing of personal data from participants enrolled in this study will be limited to those data that are necessary to fulfill the objectives of the study.

These data must be collected and processed with adequate precautions to ensure confidentiality and compliance with applicable data privacy protection laws and regulations. Appropriate technical and organizational measures to protect the personal data against unauthorized disclosures or access, accidental or unlawful destruction, or accidental loss or alteration must be put in place. Sponsor personnel whose responsibilities require access to personal data agree to keep the identity of participants confidential.

The informed consent obtained from the participant includes explicit consent for the processing of personal data and for the investigator/institution to allow direct access to his or her original medical records (source data/documents) for study-related monitoring, audit, IEC/IRB review, and regulatory inspection. This consent also addresses the transfer of the data to other entities and to other countries.

The participant has the right to request through the investigator access to his or her personal data and the right to request rectification of any data that are not correct or complete. Reasonable steps will be taken to respond to such a request, taking into consideration the nature of the request, the conditions of the study, and the applicable laws and regulations.

10.3.5. Long-Term Retention of Samples for Additional Future Research

Samples collected in this study may be stored for up to 15 years (or according to local regulations) for additional research. Samples will only be used to understand cilta-cel OOS or to understand multiple myeloma, to understand differential intervention responders, and to develop tests/assays related to cilta-cel OOS and multiple myeloma. The research may begin at any time during the study or the post-study storage period.

10.3.6. Committees Structure

Data Review Committee

A Data Review Committee (DRC) will be established to monitor data on an ongoing basis to ensure the continuing safety of the participants enrolled in this study. The committee will meet periodically to review accumulating data. After the review, DRC will make recommendations regarding the continuation of the study. Initially, data will be reviewed by DRC after every 10 participants have been treated and followed for at least 3 months to assess efficacy and safety. This committee will consist of sponsor personnel independent of the study team and include at least one

medical expert in the relevant therapeutic area and at least one statistician; committee membership responsibilities, authorities, and procedures will be documented in its charter.

10.3.7. Publication Policy/Dissemination of Clinical Study Data

All information, including but not limited to information regarding cilta-cel OOS or the sponsor's operations (eg, patent application, formulas, manufacturing processes, basic scientific data, prior clinical data, formulation information) supplied by the sponsor to the investigator and not previously published, and any data, including biomarker research data, generated as a result of this study, are considered confidential and remain the sole property of the sponsor. The investigator agrees to maintain this information in confidence and use this information only to accomplish this study and will not use it for other purposes without the sponsor's prior written consent.

The investigator understands that the information developed in the study will be used by the sponsor in connection with the continued development of cilta-cel OOS, and thus may be disclosed as required to other clinical investigators or regulatory agencies. To permit the information derived from the clinical studies to be used, the investigator is obligated to provide the sponsor with all data obtained in the study.

The results of the study will be reported in a Clinical Study Report generated by the sponsor and will contain data from all study sites that participated in the study per protocol. Recruitment performance or specific expertise related to the nature and the key assessment parameters of the study will be used to determine a coordinating investigator for the study. Results of biomarker analyses performed after the Clinical Study Report has been issued will be reported in a separate report and will not require a revision of the Clinical Study Report.

Study participant identifiers will not be used in publication of results. Any work created in connection with performance of the study and contained in the data that can benefit from copyright protection (except any publication by the investigator as provided for below) shall be the property of the sponsor as author and owner of copyright in such work.

Consistent with Good Publication Practices and International Committee of Medical Journal Editors (ICMJE) guidelines, the sponsor shall have the right to publish such primary (multicenter) data and information without approval from the investigator. The investigator has the right to publish study site-specific data after the primary data are published. If an investigator wishes to publish information from the study, a copy of the manuscript must be provided to the sponsor for review at least 60 days before submission for publication or presentation. Expedited reviews will be arranged for abstracts, poster presentations, or other materials. If requested by the sponsor in writing, the investigator will withhold such publication for up to an additional 60 days to allow for filing of a patent application. In the event that issues arise regarding scientific integrity or regulatory compliance, the sponsor will review these issues with the investigator. The sponsor will not mandate modifications to scientific content and does not have the right to suppress information. For multicenter study designs and sub-study approaches, secondary results generally should not be published before the primary endpoints of a study have been published. Similarly, investigators will recognize the integrity of a multicenter study by not submitting for publication data derived

from the individual study site until the combined results from the completed study have been submitted for publication, within 18 months after the study end date, or the sponsor confirms there will be no multicenter study publication. Authorship of publications resulting from this study will be based on the guidelines on authorship, such as those described in the International Committee of Medical Journal Editors (ICMJE) Recommendations for the Conduct, Reporting, Editing and Publication of Scholarly Work in Medical Journals, which state that the named authors must have made a significant contribution to the conception or design of the work; or the acquisition, analysis, or interpretation of the data for the work; and drafted the work or revised it critically for important intellectual content; and given final approval of the version to be published; and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Registration of Clinical Studies and Disclosure of Results

The sponsor will register and disclose the existence of and the results of clinical studies as required by law. The disclosure of the final study results will be performed after the end of study to ensure the statistical analyses are relevant.

10.3.8. Data Quality Assurance

Data Quality Assurance/Quality Control

Steps to be taken to ensure the accuracy and reliability of data include the selection of qualified investigators and appropriate study sites, review of protocol procedures with the investigator and study site personnel before the study, and periodic monitoring visits by the sponsor, and direct transmission of clinical laboratory data from a central into the sponsor's data base. Written instructions will be provided for collection, handling, storage, and shipment of samples.

Guidelines for eCRF completion will be provided and reviewed with study site personnel before the start of the study.

The sponsor will review eCRF for accuracy and completeness during on-site monitoring visits and after transmission to the sponsor; any discrepancies will be resolved with the investigator or designee, as appropriate. After upload of the data into the study database they will be verified for accuracy and consistency with the data sources.

10.3.9. Case Report Form Completion

Case report forms are prepared and provided by the sponsor for each participant in electronic format. All data relating to the study must be recorded in eCRF. All eCRF entries, corrections, and alterations must be made by the investigator or authorized study site personnel. The investigator must verify that all data entries in the CRF are accurate and correct.

The study data will be transcribed by study site personnel from the source documents onto an eCRF, if applicable. Study-specific data will be transmitted in a secure manner to the sponsor.

Worksheets may be used for the capture of some data to facilitate completion of the eCRF. Any such worksheets will become part of the participant's source documents. Data must be entered into CRF in English. The CRF must be completed as soon as possible after a participant visit and the forms should be available for review at the next scheduled monitoring visit.

All participative measurements will be completed by the same individual who made the initial baseline determinations whenever possible.

If necessary, queries will be generated in the eDC tool. If corrections to a CRF are needed after the initial entry into the CRF, this can be done in either of the following ways:

- Investigator and study site personnel can make corrections in the eDC tool at their own initiative or as a response to an auto query (generated by the eDC tool).
- Sponsor or sponsor delegate can generate a query for resolution by the investigator and study site personnel.

10.3.10. Source Documents

At a minimum, source documents consistent in the type and level of detail with that commonly recorded at the study site as a basis for standard medical care must be available for the following: participant identification, eligibility, and study identification; study discussion and date of signed informed consent; dates of visits; results of safety and efficacy parameters as required by the protocol; record of all AEs and follow-up of AEs; concomitant medication; intervention receipt/dispensing/return records; study treatment administration information; and date of study completion and reason for early discontinuation of study treatment or withdrawal from the study, if applicable.

The author of an entry in the source documents should be identifiable.

Specific details required as source data for the study and source data collection methods will be reviewed with the investigator before the study and will be described in the monitoring guidelines (or other equivalent document).

The following data will be recorded directly into the eCRF and will be considered source data:

- Race
- History of smoking
- Height and weight
- Details of physical examination
- Investigator-completed scales and assessments

The minimum source documentation requirements for Section 5.1, Inclusion Criteria and Section 5.2, Exclusion Criteria that specify a need for documented medical history are as follows:

- Referral letter from treating physician or

- Complete history of medical notes at the site
- Discharge summaries

Inclusion and exclusion criteria not requiring documented medical history must be verified at a minimum by participant interview or other protocol required assessment (eg, physical examination, laboratory assessment) and documented in the source documents.

An eSource system may be utilized, which contains data traditionally maintained in a hospital or clinic record to document medical care (eg, electronic source documents) as well as the clinical study-specific data fields as determined by the protocol. These data is electronically extracted for use by the sponsor. If eSource is utilized, references made to the CRF in the protocol include the eSource system but information collected through eSource may not be limited to that found in the CRF.

10.3.11. Monitoring

The sponsor will use a combination of monitoring techniques central, remote, or on-site monitoring to monitor this study.

The sponsor will perform on-site monitoring visits as frequently as necessary (refer to Section 10.6, Appendix 6 for monitoring during Coronavirus Disease-2019 [COVID-19]). The monitor will record dates of the visits in a study site visit log that will be kept at the study site. The nature and location of all source documents will be identified to ensure that all sources of original data required to complete the CRF are known to the sponsor and study site personnel and are accessible for verification by the sponsor study site contact. If electronic records are maintained at the study site, the method of verification must be discussed with the study site personnel.

Direct access to source documents (medical records) must be allowed for the purpose of verifying that the recorded data are consistent with the original source data. Findings from this review will be discussed with the study site personnel. The sponsor expects that, during monitoring visits, the relevant study site personnel will be available, the source documents will be accessible, and a suitable environment will be provided for review of study-related documents. The monitor will meet with the investigator on a regular basis during the study to provide feedback on the study conduct.

In addition to on-site monitoring visits, remote contacts can occur. It is expected that during these remote contacts, study site personnel will be available to provide an update on the progress of the study at the site.

Central monitoring will take place for data identified by the sponsor as requiring central review.

10.3.12. On-Site Audits

Representatives of the sponsor's clinical quality assurance department may visit the study site at any time during or after completion of the study to conduct an audit of the study in compliance with regulatory guidelines and company policy. These audits will require access to all study records, including source documents, for inspection. Participant privacy must, however, be

respected. The investigator and study site personnel are responsible for being present and available for consultation during routinely scheduled study site audit visits conducted by the sponsor or its designees.

Similar auditing procedures may also be conducted by agents of any regulatory body, either as part of a national GCP compliance program or to review the results of this study in support of a regulatory submission. The investigator should immediately notify the sponsor if he or she has been contacted by a regulatory agency concerning an upcoming inspection.

10.3.13. Record Retention

In compliance with the ICH/GCP guidelines, the investigator/institution will maintain all CRF and all source documents that support the data collected from each participant, as well as all study documents as specified in ICH/GCP Section 8, Essential Documents for the Conduct of a Clinical Trial, and all study documents as specified by the applicable regulatory requirement(s). The investigator/institution will take measures to prevent accidental or premature destruction of these documents.

Essential documents must be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents will be retained for a longer period if required by the applicable regulatory requirements or by an agreement with the sponsor. It is the responsibility of the sponsor to inform the investigator/institution as to when these documents no longer need to be retained.

If the responsible investigator retires, relocates, or for other reasons withdraws from the responsibility of keeping the study records, custody must be transferred to a person who will accept the responsibility. The sponsor must be notified in writing of the name and address of the new custodian. Under no circumstance shall the investigator relocate or dispose of any study documents before having obtained written approval from the sponsor.

If it becomes necessary for the sponsor or the appropriate regulatory authority to review any documentation relating to this study, the investigator/institution must permit access to such reports.

10.3.14. Study and Site Start and Closure

First Act of Recruitment

The first subject screened is considered the first act of recruitment and it becomes the study start date.

Study/Site Termination

The sponsor reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. Study sites will be closed upon study completion. A

study site is considered closed when all required documents and study supplies have been collected and a study site closure visit has been performed.

The investigator may initiate study site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the sponsor or investigator may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IEC/IRB or local health authorities, the sponsor's procedures, or GCP guidelines
- Inadequate recruitment of participants by the investigator
- Discontinuation of further study treatment development

10.4. Appendix 4: Adverse Events, Serious Adverse Events, Product Quality Complaints, and Other Safety Reporting: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.4.1. Adverse Event Definitions and Classifications

Adverse Event

An AE is any untoward medical occurrence in a clinical study participant administered a pharmaceutical (investigational or non-investigational) product. An AE does not necessarily have a causal relationship with the intervention. An AE can therefore be any unfavorable and unintended sign (including an abnormal finding), symptom, or disease temporally associated with the use of a medicinal (investigational or non-investigational) product, whether or not related to that medicinal (investigational or non-investigational) product. (Definition per International Council on Harmonisation [ICH]).

This includes any occurrence that is new in onset or aggravated in severity or frequency from the baseline condition, or abnormal results of diagnostic procedures, including laboratory test abnormalities.

Note: The sponsor collects AEs starting with the signing of the ICF (refer to All Adverse Events under Section 8.3.1, Time Period and Frequency for Collecting Adverse Events and Serious Adverse Events Information, for time of last AE recording).

Serious Adverse Event

An SAE based on ICH and EU Guidelines on Pharmacovigilance for Medicinal Products for Human Use is any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening (the participant was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe.)
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Is a suspected transmission of any infectious agent via a medicinal product
- Is Medically Important*

*Medical and scientific judgment should be exercised in deciding whether expedited reporting is also appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require intervention to prevent one of the other outcomes listed in the definition above. These should usually be considered serious.

If a serious and unexpected AE occurs for which there is evidence suggesting a causal relationship between the study treatment and the event (eg, death from anaphylaxis), the event must be reported as a serious and unexpected suspected adverse reaction even if it is a component of the study endpoint (eg, all-cause mortality).

Unlisted (Unexpected) Adverse Event/Reference Safety Information

An AE is considered unlisted if the nature or severity is not consistent with the applicable product reference safety information. For cilta-cel OOS, the expectedness of an AE will be determined by whether or not it is listed in the prescribing information.

10.4.2. Attribution Definitions

Assessment of Causality

The causal relationship to study intervention is determined by the investigator. The following selection should be used to assess all AEs.

Related

There is a reasonable causal relationship between study treatment administration and the AE.

Not Related

There is not a reasonable causal relationship between study treatment administration and the AE.

The term "reasonable causal relationship" means there is evidence to support a causal relationship.

10.4.3. Severity Criteria

An assessment of severity grade will be made by the investigator according to the NCI-CTCAE (version 5.0), except for CRS and CAR-T cell-related neurotoxicity (ie, ICANS). Cytokine release syndrome should be evaluated according to the ASTCT consensus grading (Section 10.7, Appendix 7). CAR-T cell-related neurotoxicity (eg, ICANS) should be graded using the ASTCT consensus grading (Section 10.8, Appendix 8). Changes in handwriting (ie, micrographia, dysgraphia, or agraphia) should be graded using the criteria outlined in Section 10.12, Appendix 12). Other neurotoxicities will be graded by CTCAE criteria. using the following categorical descriptors:

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 (ADL).*
Grade 3	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL.**
Grade 4	Life-threatening consequences; urgent intervention indicated.
Grade 5	Death related to adverse event.

Activities of Daily Living (ADL):

* Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

** Self-care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

The investigator should use clinical judgment in assessing the severity of events not directly experienced by the participant (eg, laboratory abnormalities).

10.4.4. Special Reporting Situations

Safety events of interest on a sponsor study treatment in an interventional study that may require expedited reporting or safety evaluation include, but are not limited to:

- Overdose of a sponsor study treatment
- Suspected abuse/misuse of a sponsor study treatment
- Accidental or occupational exposure to a sponsor study treatment
- Medication error, intercepted medication error, or potential medication error involving a Johnson & Johnson medicinal product (with or without patient exposure to the Johnson & Johnson medicinal product, eg, product name confusion, product label confusion, intercepted prescribing or dispensing errors)
- Exposure to a sponsor study treatment from breastfeeding
- Reporting of participant pregnancy or participant partner(s) pregnancy

Special reporting situations must be recorded in the CRF. Any special reporting situation that meets the criteria of an SAE must be recorded on the SAE page of the CRF.

Since cilta-cel will be individually manufactured and provided by the sponsor for complete administration in a one-time infusion, overdose with cilta-cel is not applicable for this study. Any special reporting situation that meets the criteria of an AE, including SAE, should be recorded on the AE/SAE page of the eCRF. Serious AEs should follow the 24-hour SAE reporting process.

10.4.5. Procedures

All Adverse Events

All AEs, regardless of seriousness, severity, or presumed relationship to study treatment, must be recorded using medical terminology in the source document and the CRF. Whenever possible, diagnoses should be given when signs and symptoms are due to a common etiology (eg, cough, runny nose, sneezing, sore throat, and head congestion should be reported as "upper respiratory infection"). The exceptions are CRS and CAR-T cell-related neurotoxicity (eg, ICANS and other neurotoxicity), for which all symptoms associated with these events will be collected in the eCRF. Investigators must record in the CRF their opinion concerning the relationship of the AE to study therapy. All measures required for AE management must be recorded in the source document and reported according to sponsor instructions.

For all studies with an outpatient phase, including open-label studies, the participant must be provided with a "wallet (study) card" and instructed to carry this card with them for the duration of the study (post-infusion and post-treatment period) indicating the following:

- Study number
- Statement, in the local language(s), that the participant is participating in a clinical study
- Investigator's name and 24-hour contact telephone number
- Local sponsor's name and 24-hour contact telephone number (for medical personnel only)
- Site number
- Participant number
- Any other information that is required to do an emergency breaking of the blind

Serious Adverse Events

All SAEs that have not resolved by the end of the study, or that have not resolved upon the participant's discontinuation from the study, must be followed until any of the following occurs:

- The event resolves
- The event stabilizes
- The event returns to baseline, if a baseline value/status is available
- The event can be attributed to agents other than the study treatment or to factors unrelated to study conduct
- It becomes unlikely that any additional information can be obtained (participant or health care practitioner refusal to provide additional information, lost to follow-up after demonstration of due diligence with follow-up efforts)

Any event requiring hospitalization (or prolongation of hospitalization) that occurs during participation in the study must be reported as an SAE, except hospitalizations for the following:

- Hospitalizations not intended to treat an acute illness or AE (eg, social reasons such as pending placement in long-term care facility).
- Surgery or procedure planned before entry into the study (must be documented in the CRF). Note: Hospitalizations that were planned before the signing of the ICF, and where the underlying condition for which the hospitalization was planned has not worsened, will not be considered SAEs. Any AE that results in a prolongation of the originally planned hospitalization is to be reported as a new SAE.
- For convenience the investigator may choose to hospitalize the participant for the duration of the intervention period.

Expected progression of disease should not be considered an AE (or SAE). However, if determined by the investigator to be more likely related to the study treatment than the underlying disease, the clinical signs or symptoms of progression and the possibility that the study treatment is enhancing disease progression, should be reported per the usual reporting requirements.

Disease progression should not be recorded as an AE or SAE term; instead, signs and symptoms of clinical sequelae resulting from disease progression/lack of efficacy will be reported if they fulfill the SAE definition (refer to Adverse Event Definitions and Classifications in Appendix 4:

Adverse Events, Serious Adverse Events, Product Quality Complaints, and Other Safety Reporting: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting). All deaths not related to disease progression occurring any time during study after receiving cilta-cel should be reported to the sponsor following expedited reporting procedures.

Information regarding SAEs will be transmitted to the sponsor using an SAE reporting form, which must be completed and signed by a physician from the study site, and transmitted in a secure manner to the sponsor within 24 hours. The initial and follow-up reports of an SAE should be made by facsimile (fax). Telephone reporting should be the exception and the reporter should be asked to complete the appropriate form(s) first.

10.4.6. Product Quality Complaint Handling

Definition

A product quality complaint (PQC) is defined as any suspicion of a product defect related to manufacturing, labeling, or packaging, ie, any dissatisfaction relative to the identity, quality, durability, reliability, or performance of a distributed product, including its labeling, drug delivery system, or package integrity. A PQC may have an impact on the safety and efficacy of the product. In addition, it includes any technical complaints, defined as any complaint that indicates a potential quality issue during manufacturing, packaging, release testing, stability monitoring, dose prepa6ation, storage or distribution of the product or the drug delivery system. The sponsor has established procedures in conformity with regulatory requirements worldwide to ensure appropriate reporting of PQC information; all studies conducted by the sponsor or its affiliates will be conducted in accordance with those procedures.

Procedures

All initial PQCs must be reported to the sponsor by the study site personnel within 24 hours after being made aware of the event.

A sample of the suspected product should be maintained under the correct storage conditions until a shipment request is received from the sponsor.

10.4.7. Contacting Sponsor Regarding Safety, Including Product Quality

The names (and corresponding telephone numbers) of the individuals who should be contacted regarding safety issues, PQC, or questions regarding the study are listed in the Contact Information page(s), which will be provided as a separate document.

10.5. Appendix 5: Contraceptive Guidance

Participants must follow contraceptive measures as outlined in Section 5.1, Inclusion Criteria. Pregnancy information will be collected and reported as noted in Section 8.3.5, Pregnancy and Section 10.4, Appendix 4 Adverse Events, Serious Adverse Events, Product Quality Complaints, and Other Safety Reporting: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting.

Definitions

Woman of Childbearing Potential (WOCBP)

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

Woman Not of Childbearing Potential

- **premenarchal**
  A premenarchal state is one in which menarche has not yet occurred.
- **postmenopausal**
  A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level (>40 IU/L or mIU/mL) in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT), however in the absence of 12 months of amenorrhea, a single follicle stimulating hormone (FSH) measurement is insufficient.

- **permanently sterile (for the purpose of this study)**
  Permanent sterilization methods include hysterectomy, bilateral salpingectomy, and bilateral oophorectomy.

Note: If the childbearing potential changes after start of the study (eg, a premenarchal woman experiences menarche) or the risk of pregnancy changes (eg, a woman who is not heterosexually active becomes active), a woman must begin a highly effective method of contraception, as described throughout the inclusion criteria.

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

Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for participants in clinical studies.

Examples of Contraceptives

EXAMPLES OF CONTRACEPTIVES[a] ALLOWED DURING THE STUDY INCLUDE:
USER INDEPENDENT **Highly Effective Methods That Are User Independent** *Failure rate of <1% per year when used consistently and correctly.*

• Implantable progestogen-only hormone contraception associated with inhibition of ovulation[b]
• Intrauterine device (IUD)
• Intrauterine hormone-releasing system (IUS)
• Bilateral tubal occlusion
• Azoospermic partner *(vasectomized or due to medical cause)* *(Vasectomized partner is a highly effective contraceptive method provided that the partner is the sole sexual partner of the woman of childbearing potential and the absence of sperm has been confirmed. If not, additional highly effective method of contraception should be used. Spermatogenesis cycle is approximately 74 days.)*
USER DEPENDENT **Highly Effective Methods That Are User Dependent** *Failure rate of <1% per year when used consistently and correctly.*
• Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation[b] – oral – intravaginal – transdermal – injectable
• Progestogen-only hormone contraception associated with inhibition of ovulation[b] – oral – injectable
• Sexual abstinence *(Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatment. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.)*
NOT ALLOWED AS SOLE METHOD OF CONTRACEPTION DURING THE STUDY (not considered to be highly effective - failure rate of ≥1% per year)
• Progestogen-only oral hormonal contraception where inhibition of ovulation is not the primary mode of action.
• Male or female condom with or without spermicide[c]
• Cap, diaphragm, or sponge with spermicide
• A combination of male condom with either cap, diaphragm, or sponge with spermicide (double-barrier methods)[c]
• Periodic abstinence (calendar, symptothermal, post-ovulation methods)
• Withdrawal (coitus-interruptus)
• Spermicides alone
• Lactational amenorrhea method (LAM)
a) Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for participants in clinical studies. b) Hormonal contraception may be susceptible to interaction with the study treatment, which may reduce the efficacy of the contraceptive method. In addition, consider if the hormonal contraception may interact with the study treatment. c) Male condom and female condom should not be used together (due to risk of failure with friction).

10.6. Appendix 6: Study Conduct During a Natural Disaster/Major Disruption/ Pandemic

GUIDANCE ON STUDY CONDUCT DURING COVID-19 PANDEMIC/NATURAL DISASTER/MAJOR DISRUPTION

It is recognized that the Coronavirus Disease-2019 (COVID-19)/major disruption may have an impact on the conduct of this clinical study due to, for example, self-isolation/quarantine by participants and study site personnel; travel restrictions/limited-access to public places, including hospitals; study site personnel being reassigned to critical tasks.

In alignment with recent health authority guidance, the sponsor is providing options for study-related participant management in the event of disruption to the conduct of the study. This guidance does not supersede any local or government requirements or the clinical judgment of the investigator to protect the health and well-being of participants and site staff. If, at any time, a participant's safety is considered to be at risk, study treatment will be discontinued, and study follow-up will be conducted.

Scheduled visits that cannot be conducted in person at the study site will be performed to the extent possible remotely/virtually or delayed until such time that on-site visits can be resumed. At each contact, participants will be interviewed to collect safety data. Key efficacy endpoint assessments should be performed if required and as feasible. Participants will also be questioned regarding general health status to fulfill any physical examination requirement.

Every effort should be made to adhere to protocol-specified assessments for participants on study treatment, including follow-up. Modifications to protocol required assessments may be permitted via COVID-19 Appendix after consultation with the participant, investigator, and the sponsor. Missed assessments/visits will be captured in the clinical trial management system for protocol deviations. Discontinuations of study treatments and withdrawal from the study should be documented with the prefix "COVID-19-related" in the CRF.

The sponsor will continue to monitor the conduct and progress of the clinical study, and any changes will be communicated to the sites and to the health authorities according to local guidance. If a participant has tested positive for COVID-19, the investigator should contact the sponsor's responsible medical officer to discuss plans for study treatment and follow-up. Modifications made to the study conduct as a result of the COVID-19 pandemic should be summarized in the clinical study report.

Testing for COVID-19 should be performed according to local guidance. If a participant has tested positive for COVID-19, the following should be reported in the eDC tool:

- all cases of COVID-19, regardless of severity or causality (including asymptomatic COVID- 19) up to 1 year after cilta-cel infusion
- all medications given to prevent (including vaccines) or treat COVID-19 up to 1 year after cilta-cel infusion

GUIDANCE SPECIFIC TO THIS PROTOCOL

These emergency provisions are meant to ensure participant safety on study while site capabilities are compromised by COVID-19-related restrictions. As restrictions are lifted and the acute phase of the COVID-19 pandemic resolves, sites should revert to original protocol conduct as soon as feasible.

- Missed assessments will be captured in the clinical trial management system for protocol deviations, with the actual visit date documented or reason for withdrawals specified; discontinuations of study treatments and withdrawal from the study will be captured with the prefix "COVID-19-related" in the CRF.
- Any changes in cilta-cel OOS treatment (eg, dose) due to COVID-19 reasons will be recorded.
- Protocol required laboratory tests and assessments may be performed at a nearby hospital when they cannot be done at the site. Verification of information outside of the study site may be obtained by the site and entered into the eCRF, as appropriate. Any biomarker specimen may be obtained whenever the participant is able to return to the site.
- When on-site monitoring visits are not feasible (eg, due to local regulations, restrictions, and guidance), the Site Manager may arrange to conduct site monitoring visits and activities remotely. Additional on-site monitoring visits may be needed in the future to catch up on source data verification.
- Investigator judgment is required to assess:
  - Information necessary to collect protocol required assessments to assess Response and Disease Progression according to IMWG criteria, if necessary.
  - Telemedicine visits with or without local laboratory/local Oncologists that would be sufficient to cover the planned visits, as long as, Telemedicine platform complies to privacy standards for local Telemedicine process.

RECOMMENDATIONS FOR COVID-19 VACCINATION FOR CILTA-CEL RECIPIENTS

It is recommended that participants can receive prophylactic COVID-19 vaccination when locally available, at the discretion of investigator judgment or institutional practice, and in compliance with the cilta-cel study protocol and local labels for the vaccine.

General guidance for consideration is as follows:

- Many vaccines against COVID-19 are being developed with different technologies and platforms, and may have safety and efficacy profiles that are not fully characterized even after preliminary health authority approval. However, the benefit-risk ratio of receiving a COVID-19 vaccine among patients with multiple myeloma participating in cilta-cel studies is considered to be positive, and should be considered for administration while in compliance with the study protocol and when not otherwise contraindicated for use in the vaccine label.
- Per protocol, live attenuated vaccines must be completed at least 6 weeks prior to lymphodepletion therapy or initiated at least 100 days after cilta-cel infusion. There are no specific timing restrictions for inactivated vaccines, which include vaccines that use

alternative technology like mRNA or replication-incompetent viral vectors, per protocol. Enrollment into an interventional clinical trial for an experimental vaccine is prohibited during study. Any vaccination, including COVID-19 vaccinations, must be recorded on the concomitant medication page of the eCRF.

- While not specifically required per protocol, it is encouraged to complete the COVID-19 vaccine series at least 2 weeks prior to lymphodepletion, and to delay vaccination for at least 3 months after cilta-cel infusion, to maximize immune response.
- No data is currently available to suggest that COVID-19 vaccines pose specific or additional safety risk beyond other vaccines for cancer patients undergoing treatment. Theoretically, a diminished immune response may occur in immunocompromised patients, and therefore these patients may have reduced vaccine effectiveness.

For additional information for reference or guidance, several organizations and journals have published recommendations for COVID-19 vaccine administration in cancer patients, including:

- European Society for Blood and Marrow Transplantation (EBMT): https://www.ebmt.org/covid-19-and-bmt
- ASTCT: https://www.hematology.org/covid-19/ash-astct-covid-19-vaccination-for-hct-and-car-t-cell-recipients
- National Comprehensive Cancer Network (NCCN): https://www.nccn.org/covid-19/pdf/COVID-19_Vaccination_Guidance_V2.0.pdf
- Centers for Disease Control and Prevention (CDC): https://www.cdc.gov/vaccines/covid-19/info-by-product/clinical-considerations.html
- Nature Reviews Clinical Oncology: COVID-19 vaccine guidance for patients with cancer participating in oncology clinical trials. Desai A, Gainor JF, Hegde A. et al. (March 15, 2021). DOI: 10.1038/s41571-021-00487-z: https://www.nature.com/articles/s41571-021-00487-z
- Investigators should inform patients that emerging data show that patients receiving cilta-cel are possibly at higher risk of severe/fatal outcomes from COVID-19 infection compared with patients receiving standard of care therapy (Section 6.1.5.8).
- Based on guidance from the organizations listed above, the following measures should be implemented to minimize subjects' risk of severe COVID-19 infection:
- Subjects, particularly those who are less than 6 to 9 months from cilta-cel infusion, should be reminded that the ongoing pandemic is still putting them at risk of contracting COVID-19. Investigators should ask subjects to continue to limit their risk of exposure to infected individuals as much as possible and strictly adhere to prevention measures such as proper masking, hand hygiene, social distancing, and avoiding travel and public transportation to the extent possible.
- Investigators should discuss with subjects the importance of COVID-19 vaccines in the prevention of severe illness, hospitalization, and death from COVID-19. Subjects should assume that any vaccination administered prior to lymphodepletion and cilta-cel infusion no longer provides protection. For this reason, it is strongly recommended that all subjects receive a full COVID-19 vaccination series (eg, a primary series of 3 vaccines and a 4th booster dose for mRNA vaccines; note: mRNA vaccines are recommended), no sooner than

3 months after cilta-cel infusion, regardless of vaccination status prior to cilta-cel. In addition, if not already vaccinated, caregivers, family, and household contacts should be advised to receive COVID 19 vaccination as well.

- Investigators should consider prophylaxis (eg, Evusheld, if available in the region) to reduce subjects' risk of severe/fatal COVID during the first 6 to 9 months after cilta-cel. It is critical that subjects understand that multiple myeloma patients (even those who have not received CAR-T therapy) may not seroconvert until after the 3rd vaccine dose and as a result they may remain at a very high risk of severe COVID-19 for at least 2 to 3 months after starting vaccination.
- Investigators should instruct subjects to notify them or study site staff immediately if they are diagnosed with COVID 19, even if they are asymptomatic, so that appropriate treatment measures can be determined.
- If available in the region, antivirals (eg, Paxlovid or other available agents) should be considered early after COVID-19 diagnosis. Subjects may remain asymptomatic or have minimal symptoms for a period of time prior to deteriorating. Investigators should make subjects aware that these drugs may potentially significantly lower their risk of severe COVID-19 infection.

10.7. Appendix 7: Cytokine Release Syndrome ASTCT Consensus Grading System

Grade	Toxicity
Grade 1	Fever[a] (Temperature ≥38°C)
Grade 2	Fever[a] (Temperature ≥38°C) with either: • Hypotension not requiring vasopressors • And/or[c] hypoxia requiring low-flow nasal cannula[b] or blow-by.
Grade 3	Fever[a] (Temperature ≥38°C) with either: • Hypotension requiring a vasopressor with or without vasopressin, • And/or[c] hypoxia requiring high-flow nasal cannula[b], facemask, nonrebreather mask, or Venturi mask.
Grade 4	Fever[a] (Temperature ≥38°C) with either: • hypotension requiring multiple vasopressors (excluding vasopressin), • And/or[c] hypoxia requiring positive pressure (eg, CPAP, BiPAP, intubation and mechanical ventilation).
Grade 5	Death

Abbreviations: BiPAP=bilevel positive airway pressure; CPAP=continuous positive airway pressure, CRS=cytokine release syndrome; NCI CTCAE=National Cancer Institute Common Terminology Criteria for Adverse Events.

a Fever not attributable to any other cause. In participants who have CRS then receive antipyretics or anticytokine therapy such as tocilizumab or steroids, fever is no longer required to grade subsequent CRS severity. In this case, CRS grading is driven by hypotension and/or hypoxia.

b Low-flow nasal cannula is defined as oxygen delivered at ≤6 L/minute or blow-by oxygen delivery. High-flow nasal cannula is defined as oxygen delivered at >6 L/minute.

c CRS grade is determined by the more severe event: hypotension or hypoxia not attributable to any other cause.

Note: Organ toxicities associated with CRS may be graded according to NCI CTCAE (version 5.0), but they do not influence CRS grading.

Source: Lee 2019

10.8. Appendix 8: Immune-Effector Cell-associated Neurotoxicity Syndrome (ICANS) ASTCT Consensus Grading System[a,b]

Neurotoxicity Domain	Grade 1	Grade 2	Grade 3	Grade 4
ICE Score	7-9	3-6	0-2	0 (participant is unarousable and unable to perform ICE).
Depressed Level of Consciousness	Awakens spontaneously.	Awakens to voice.	Awakens only to tactile stimulus.	Participant is unarousable or requires vigorous or repetitive tactile stimuli to arouse. Stupor or coma.
Seizure	N/A	N/A	Any clinical seizure, focal or generalized, that resolves rapidly; or Non-convulsive seizures on EEG that resolve with intervention.	Life-threatening prolonged seizure (>5 min); or Repetitive clinical or electrical seizures without return to baseline in between.
Motor Findings	N/A	N/A	N/A	Deep focal motor weakness such as hemiparesis or paraparesis.
Raised Intracranial Pressure / Cerebral Edema	N/A	N/A	Focal/local edema on neuroimaging.	Diffuse cerebral edema on neuroimaging; or Decerebrate or decorticate posturing; or Cranial nerve VI palsy; or Papilledema; or Cushing's triad.

Abbreviations: EEG=electroencephalogram; ICANS=Immune-Effector Cell-associated Neurotoxicity Syndrome ICE=Immune-Effector Cell-associated encephalopathy; ICP=intracranial pressure; N/A=not applicable; NCI CTCAE=National Cancer Institute Common Terminology Criteria for Adverse Events.

a Toxicity grading according to Lee 2019.

b ICANS grade is determined by the most severe event (ICE score, level of consciousness, seizure, motor findings, raised ICP/cerebral edema) not attributable to any other cause.

Note: all other neurological adverse events (not associated with ICANS) should continue to be graded with NCI CTCAE version 5.0 during the study.

10.9. Appendix 9: Immune-Effector Cell-associated Encephalopathy (ICE) Tool

Immune-Effector Cell-Associated Encephalopathy (ICE) Tool[a]
Orientation: Orientation to year, month, city, hospital: • **4 points** **Naming**: Name 3 objects (eg, point to clock, pen, button): • **3 points** **Following commands**: (eg, Show me 2 fingers or Close your eyes and stick out your tongue): • **1 point** **Writing**: Ability to write a standard sentence (eg, Our national bird is the bald eagle): • **1 point** **Attention**: Count backwards from 100 by 10: • **1 point**
a: ICE-Tool Scoring: • Score 10: No impairment • Score 7-9: Grade 1 ICANS • Score 3-6: Grade 2 ICANS • Score 0-2: Grade 3 ICANS • Score 0 due to participant unarousable and unable to perform ICE assessment: Grade 4 ICANS

Abbreviations: ICANS=Immune-Effector Cell-associated Neurotoxicity Syndrome ICE= Immune-Effector Cell-associated encephalopathy.

10.10. Appendix 10: Criteria for Response to Multiple Myeloma Treatment

Response	Response Criteria
Stringent complete response	• CR as defined below, *plus* • Normal FLC ratio, *and* • Absence of clonal PCs by immunohistochemistry or 2- to 4-color flow cytometry
Complete response[a]	• Negative immunofixation of serum and urine, *and* • Disappearance of any soft tissue plasmacytomas, *and* • <5% PCs in bone marrow • No evidence of initial monoclonal protein isotype(s) on immunofixation of the serum and urine.[b]
Very good partial response[a]	• Serum and urine M-component detectable by immunofixation but not on electrophoresis, *or* • ≥90% reduction in serum M-component plus urine M-component <100 mg/24 hours
Partial response	• ≥50% reduction of serum M-protein and reduction in 24-hour urinary M-protein by ≥90% or to < 200 mg/24 hours • If serum and urine M-protein are not measurable, a decrease ≥50% in the difference between involved and uninvolved FLC levels is require in place of the M-protein criteria • If serum and urine M-protein are not measurable, and serum free-light assay is also not measurable, ≥50% reduction in bone marrow PCs is required in place of M-protein, provided baseline percentage was ≥30% • In addition to the above criteria, if present at baseline, ≥50% reduction in the size of soft tissue plasmacytomas is also required
Minimal response	• ≥25% but ≤49% reduction of serum M-protein *and* reduction in 24-hour urine M-protein by 50% to 89% • In addition to the above criteria, if present at baseline, ≥50% reduction in the size of soft tissue plasmacytomas is also required
Stable disease	• Not meeting criteria for sCR, CR, VGPR, PR, MR, or progressive disease
Progressive disease[c]	Any one or more of the following criteria: • Increase of 25% from lowest response value in any of the following: – Serum M-component (absolute increase must be ≥0.5 g/dL), *and/or* – Urine M-component (absolute increase must be ≥200 mg/24 hours), *and/or* – Only in participants without measurable serum and urine M-protein levels: the difference between involved and uninvolved FLC levels (absolute increase must be > 10 mg/dL) – Only in participants without measurable serum and urine M-protein levels and without measurable disease by FLC levels, bone marrow PC percentage (absolute increase must be ≥10%). • Appearance of a new lesion(s), ≥50% increase from nadir in SPD of >1 lesion, or ≥50% increase in the longest diameter of a previous lesion >1 cm in short axis • Definite development of new bone lesions or definite increase in the size of existing bone lesions • ≥50% increase in circulating plasma cells (minimum of 200 cells per μL) if this is the only measure of disease

Abbreviations: CR=complete response; FLC=free-light chain; IgA=immunoglobulin A; IgG=immunoglobulin G; IgM=immunoglobulin M; MR=minimal response; PC=plasma cell; PR=partial response; sCR=stringent complete response; SPD=sum of the products of the maximal perpendicular diameters of measured lesions; VGPR=very good partial response.

a Clarifications to the criteria for coding CR and VGPR in participants in whom the only measurable disease is by serum FLC levels: CR in such participants indicates a normal FLC ratio of 0.26 to 1.65 in addition to CR criteria listed above. VGPR in such participants requires a ≥90% decrease in the difference between involved and uninvolved FLC levels. For participants achieving very good partial response by other criteria, a soft tissue plasmacytoma must decrease by more than 90% in the sum of the maximal perpendicular diameter (SPD) compared with baseline.

b In some cases it is possible that the original M-protein light-chain isotype is still detected on immunofixation but the accompanying heavy-chain component has disappeared; this would not be considered as a CR even though the heavy-chain component is not detectable, since it is possible that the clone evolved to one that secreted only light chains. Thus, if a participant has IgA lambda myeloma, then to qualify as CR there should be no IgA detectable on serum or urine immunofixation; if free lambda is detected without IgA, then it must be accompanied by a different heavy-chain isotype (IgG, IgM, etc.).

c Clarifications to the criteria for coding progressive disease: bone marrow criteria for progressive disease are to be used only in participants without measurable disease by M-protein and by FLC levels; "25% increase" refers to M-protein, and FLC, and does not refer to bone lesions, or soft tissue plasmacytomas and the "lowest response value" does not need to be a confirmed value.

Notes: All response categories (CR, sCR, VGPR, PR, MR, and progressive disease) require 2 consecutive assessments made at any time before the institution of any new therapy; CR, sCR, VGPR, PR, MR, and stable disease categories also require no known evidence of progressive or new bone lesions if radiographic studies were performed. VGPR and CR categories require serum and urine studies regardless of whether disease at baseline was measurable on serum, urine, both, or neither.

Radiographic studies are not required to satisfy these response requirements. Bone marrow assessments need not be confirmed. For progressive disease, serum M-component increases of ≥1 g/dL are sufficient to define relapse if lowest M-component is ≥5 g/dL.

Source: Adapted from Durie 2015; Rajkumar 2011; Kumar 2016.

10.11. Appendix 11: Eastern Cooperative Oncology Group Performance Status Grade

Grade	Eastern Cooperative Oncology Group Performance Status
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, eg, light house work, office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead

Source: Eastern Cooperative Oncology Group, Robert Comis MD, Group Chair (Oken 1982).

10.12. Appendix 12: Handwriting Adverse Event Toxicity Grading Criteria

Adverse Event Term	Grade 1	Grade 2
Micrographia: abnormally small or cramped handwriting	Mildly smaller letters or reduced spacing (eg, <50% decrease from baseline)	Moderate to severely smaller letters or reduced spacing (eg, ≥50% decrease from baseline)
Dysgraphia: illegible writing or writing that takes an unusually long time or great effort	Mildly slower writing, impaired straightness of line, difficulty in completing task from baseline; most words are legible	Moderate to severely slower writing, impaired straightness of line, difficulty in completing task from baseline; most words are illegible
Agraphia: pathologic loss of the ability to write	Able to write part of a sentence (3 or more words); noted change from baseline	Able to write just 1 to 2 words, or unable to write any words; noted change from baseline

10.13. Appendix 13: Anti-microbial Prophylaxis Recommendations

Participants should receive antimicrobial prophylaxis per recommendations below or per institutional standards.

Prophylaxis	Therapy	Start	Stop
Anti-Bacterial	Fluoroquinolones (Levofloxacin - 500 mg PO or IV daily, or equivalent) *Suggested Alternative for participants with allergy to quinolones*: Cefpodoxime-200 mg PO twice a day	At neutropenia onset (ANC <500/µL) OR by Day-1 of CAR-T infusion	At Neutropenia resolution (for example, ANC ≥500/µL)
Anti-Fungal	Fluconazole - 400 mg daily (or equivalent) *Alternatives*: Caspofungin or Micafungin Prolonged neutropenia >3 weeks - Consider switching to Posaconazole, *or* per institutional guidelines	At neutropenia onset (ANC <500/µL) OR by Day-1 of CAR-T infusion	At Neutropenia resolution (for example, ANC ≥500/µL)
Anti-Viral	Acyclovir-400-800 mg PO twice a day (dose to be adjusted per institutional guidelines) *Alternative*: Valacyclovir - 500 mg PO twice a day	By Day-1 of CAR-T infusion	Suggested for at least 12 months post infusion
***Pneumocystis* Pneumonia (PCP)**	Pentamidine (per institutional guidelines) followed by Trimethoprim-sulfamethoxazole - 1 DS tablet PO daily or 1 SS tablet PO daily *Alternatives*: Pentamidine (per institutional guidelines), *or* Dapsone - 100 mg PO daily or 50 mg PO bid, *or* Atovaquone - 1500 PO daily	By Day-1 of CAR-T infusion Pentamidine (or alternative) Day 28 (or when cytopenia recovers) Trimethoprim-sulfamethoxazole–1 DS tablet PO daily or 1 SS tablet PO daily	Suggested duration: 6 months post-infusion OR until CD4 count ≥200 cells/µL, (whichever is longer)

Note: Consider CMV serology at baseline, monitor with PCR testing as clinically indicated per institution guidance.
Abbreviations: ANC=absolute neutrophil count; bid=twice a day; CD4=cluster of differentiation 4; CMV=cytomegalovirus; IV=intravenous; DS=double strength; PCR=polymerase chain reaction; PO=per oral; SS=single strength.

10.14. Appendix 14: Hepatitis B Virus Screening

The following hepatitis B virus screening guide is to be used to determine participant eligibility for the study:

Eligibility based on hepatitis B virus test results			
	Hepatitis B test result		
Action	**Hepatitis B surface antigen (HBsAg)**	**Hepatitis B surface antibody (anti-HBs)**	**Hepatitis B core antibody (anti-HBc)**
Exclude	+	— *or* +	— *or* +
Include	—	—	—
	—	+*#	+#
	—	—	+#
	—	+*	—

Abbreviations: ALT=alanine aminotransferase; AST=aspartate aminotransferase; HBc=hepatitis B core; HBs=hepatitis B surface; HBsAg=hepatitis B surface antigen; HBV=hepatitis B virus; OOS=out-of-specifications.

Notes:

* Participants who are anti-HBs positive and without history of vaccination, should have HBV-DNA quantification test. Participants with positive HBV-DNA should be excluded. Participants with negative HBV-DNA can be enrolled. If required by local country guidelines on HBV prevention, HBV-DNA and AST/ALT laboratories should be performed every 3 months for the first 12 months after cilta-cel OOS administration. If there is evidence of HBV reactivation initiate treatment as appropriate per institutional guidance.

\# Participants with positive anti-HBc and either positive or negative anti-HBs should have HBV-DNA quantification test. Participants with positive HBV-DNA should be excluded. Participants with negative HBV-DNA can be enrolled; however, HBV-DNA and AST/ALT laboratories should be performed every 3 months for the first 12 months after cilta-cel OOS administration. If there is evidence of HBV reactivation initiate treatment as appropriate per institutional guidance.

Note: To minimize the number of times a participant would need to visit the clinic, the post-treatment follow-up visit (every 28 days post Day 112 [±7 days]) can be coordinated with the AST/ALT assessment every 12 weeks (±7 days).

10.15. Appendix 15: Cilta-cel OOS Outpatient Administration Guidelines

When evaluating the suitability for outpatient administration, if allowed by local regulations and institutional guidance among other considerations, investigators should assess the participant's clinical status and the health care facility capability to safely manage outpatient logistics. General recommendations for each of these considerations are provided below:

1. Clinical consideration

General guidance for clinical considerations for a participant that is suitable for outpatient administration and follow-up includes the following:

- Not requiring packed red blood cell or platelet transfusions more frequently than every 2 days
- No presence of an indwelling central line (with the exception of a peripherally inserted central catheter [PICC] line) given risk of infection in the setting of cytopenia
- No fever or active infection (bacterial, fungal, viral) since study enrollment
- No Grade 3 or higher non-hematologic toxicities of cyclophosphamide and fludarabine including nausea, vomiting, and diarrhea
- No clinically significant coagulopathy that would increase the risk of bleeding in the setting of cytopenia
- No high tumor burden defined as at least 60% plasma cell infiltration of the marrow and/or the presence of extramedullary disease
- No risk factors for developing clinically significant tumor lysis syndrome and requiring management with increased hydration, allopurinol, or rasburicase. Patients who are receiving prophylactic treatment for TLS are eligible for outpatient infusion, if deemed stable by the investigator
- No rapidly progressing disease
- No deterioration in neurologic status, including mental status changes such as confusion or increased somnolence. The only exception is confusion or somnolence that has resolved and must be attributed to diphenhydramine premedication for cilta-cel OOS.
- The following laboratory parameters:
  - eGFR of ≥40 mL/min/1.73 m^2
  - AST and ALT≤3 times the upper limit of normal

2. Logistical consideration for qualified healthcare facility

The following should be considered for outpatient administration and follow-up:

- Site must discuss with participants how to the presenting signs and symptoms of recognize signs of CAR-T associated toxicities (including but not limited to CRS, neurotoxicities, infections, etc.) as presented in the participant wallet card
- Site must provide participants with educational material including but not limited to emergency contact information
- Participant is required to stay within 30 minutes of transportation to the hospital and remain in the company of a competent adult at all times until Day 14.

- Participant must comply with all the protocol requirement procedures, including measuring and recording of body temperature twice per day, and coming to the site for safety assessments according to the SoA (Table 1).
- Admission to the hospital is required at any time in the event of any presenting signs and symptoms of CRS and/or neurotoxicity.
- Participants who experience CRS and/or neurotoxicity, can be discharged from the hospital when they are afebrile for 24 hours and signs and symptoms of CRS and/or neurotoxicity or other clinically significant adverse event have resolved.
- If a patient is admitted for CRS and/or ICANs, upon discharge from the hospital, the participant must stay locally within 1 hour of transportation to the hospital and remain in the company of a competent adult at all times for 1 additional week, or up to study Day 21, whichever is sooner.

10.16. Appendix 16: Formulas for Estimating Glomerular Filtration Rate

Modified Diet in Renal Disease (MDRD) Formula

For serum creatinine in **mg/dL**, the estimated glomerular filtration rate (eGFR) for the MDRD formula is:

eGFR (MDRD) mL/min per $1.73m^2$= 175 x [serum creatinine (mg/dL)]$^{-1.154}$ x [age]$^{-0.203}$ x [1.212 if black] x [0.742 if female]

For serum creatinine in **µmol/L**, the eGFR for the MDRD formula is:

eGFR (MDRD) mL/min per $1.73m^2$= 175 x [serum creatinine (µmol/L)/88.4]$^{-1.154}$ x [age]$^{-0.203}$ x [1.212 if black] x [0.742 if female]

Source: Levey (2006)

10.17. Appendix 17: Adverse Event Reporting Guidance for 68284528MMY2005 Study

Reporting guidelines for Adverse Events in study 68284528MMY2005 in eCRF:

<table>
<tr><th colspan="5">Duration of 68284528MMY2005 Study</th><th rowspan="2">LTFU Study:
Up to 15 Years after cilta-cel</th></tr>
<tr><th>Signing of ICF</th><th>Day 1
cilta-cel</th><th>Day 100
Post cilta-cel</th><th>1 Year
Post cilta-cel</th><th>End of
Study</th></tr>
<tr><td colspan="3">All AEs, regardless of causality</td><td colspan="2">Related AEs, per investigator</td><td></td></tr>
<tr><td colspan="6">All SAEs, regardless of causality</td></tr>
<tr><td rowspan="6"></td><td colspan="3">HBV Reactivation, all grades regardless of causality or seriousness
COVID-19 Infection, all grades regardless of causality or seriousness, including asymptomatic infection</td><td colspan="2">≥Grade 3 HBV Reactivation (regardless of causality or seriousness)
≥Grade 3 COVID-19 Infection (regardless of causality or seriousness)</td></tr>
<tr><td colspan="5">New or Recurrent Malignancy (all grades, regardless of causality or seriousness)*^</td></tr>
<tr><td colspan="5">New or Exacerbation of Neurologic Disorder (all grades, regardless of causality or seriousness)</td></tr>
<tr><td colspan="5">New or Exacerbation of Autoimmune Disorder (all grades, regardless of causality or seriousness)</td></tr>
<tr><td colspan="5">≥Grade 3 Hematologic Disorder (regardless of causality or seriousness)</td></tr>
<tr><td colspan="5">≥Grade 3 Infection (regardless of causality or seriousness)</td></tr>
</table>

* For reporting purposes, this includes both new primary malignancies and recurrence of pre-existing malignancies with the exception of recurrent multiple myeloma (ie. disease progression).

^ In the event of malignancy, a tumor sample should be collected, and vector integration site analysis may be performed for possible insertional mutagenesis.

Expedited reporting guidelines for study 68284528MMY2005 to Sponsor GMS:

Duration of 68284528MMY2005 Study		
Signing of ICF	**Day 1 cilta-cel**	**End of Study**
Expedited Reporting* of all SAEs (regardless of causality) for duration of study.	Expedited Reporting* of all SAEs, and following AESIs (regardless of causality or seriousness): • ≥Grade 3 CRS • ≥Grade 3 Neurotoxicity • New or Recurrent Malignancy (any grade)	

* Expedited reporting includes reporting to Sponsor Global Medical Safety within 24 hours via SAE Fax Form or other defined SAE reporting process per protocol.

Abbreviations: AE=adverse events; AESIs=adverse events of special interest; CRS=cytokine release syndrome; GMS=global medical safety; ICF=informed consent form; LTFU=long-term follow-up; SAEs=serious adverse events.

10.18. Appendix 18: Protocol Amendment History

The Protocol Amendment Summary of Changes Table for the current amendment is located directly before the Table of Contents (TOC).

Amendment 1 (26 May 2021)

Overall Rationale for the Amendment: The overall reasons for this amendment are to include recommendations from Safety Management Team (SMT) for Coronavirus Disease-2019 (COVID-19) vaccinations for cilta-cel recipients, to align reporting of adverse events (AEs), which includes any non-serious AEs related to study treatment, serious AEs (SAEs) regardless of causality, and delayed AEs. Tumor lysis syndrome (TLS) is no longer required to be monitored as an adverse event of special interest (AESI). Potential risks associated with cilta-cel and its management guidelines are updated to align with latest edition of investigator brochure and other cilta-cel study protocols. The end of study (EOS) definition is updated to align with other cilta-cel study protocols. The definition of treatment emergent adverse events (TEAEs) is updated to include any AE reported at or after the initial administration of study treatment.

A Protocol Amendment Summary of Changes Table for current amendment is provided below. The updates are indicated in bold text and strike-through for the deleted text, wherever applicable.

Section number and Name	Description of Change	Brief Rationale
10.6. Appendix 6: Study Conduct During a Natural Disaster	Appendix was updated to include 'Recommendations for COVID-19 vaccination for cilta-cel recipients'.	To align with recommendations from Safety Management Team.
Synopsis-Safety Evaluations; 4.1. Overall Design	Text updated to include that participants follow-up will continue to include all SAEs and delayed AEs during Post-treatment Phase.	To align with adverse event reporting guidance.
1.3. Schedule of Activities (SoA)-Adverse events (AEs); 8.3.1. Time Period and Frequency for Collecting Adverse Event and Serious Adverse Event Information-Delayed AEs, Serious AEs	Adverse event text modified to include the reporting of following: • All SAEs regardless of causality, and any nonserious adverse events considered related to study treatment until end of study (EOS). • For participants who progress before Day 100 post cilta-cel, AEs/SAEs should still be reported until 100 days post cilta-cel or until resolution, whichever is later. • Delayed AE**s** (regardless of causality) will be collected from the time of cilta-cel infusion and for the duration of the study, and subsequently in a separate long-term follow-up study for up to 15 years after last administration of cilta-cel • Events of hepatitis B virus [HBV] reactivations should be reported during the first year post dosing of cilta-cel. • A note on second primary malignancies (SPM) was deleted and corresponding footnote 'q' was revised to include 'a new or recurrent malignancy'. • A new appendix added for AE reporting and guidance. (Appendix 18)	To ensure continuous data collection of non-serious AEs (related to study treatment) from signing of ICF until EOS and requirement of reporting of AEs/SAEs data for participants showing disease progression before Day 100. To define reporting duration for HBV reactivations and long-term collection of delayed AEs, for consistency with other cilta-cel study protocols.

Section number and Name	Description of Change	Brief Rationale
8.3.1. Time Period and Frequency for Collecting Adverse Event and Serious Adverse Event Information-Adverse Events of Special Interest	Grade 3 tumor lysis syndrome (TLS) was deleted as adverse event of special interest (AESI) and text updated to include that AESIs **will require enhanced data collection in the electronic CRF (eCRF).** Reporting of SPM updated as: '**For the purpose of reporting, second primary malignancies include both new primary malignancies and recurrence of pre-existing malignancies with the exception of multiple myeloma (which should be reported as disease progression)**'.	To align with recent IB update for TLS and adverse event reporting guidance for SPM.
8.3.1. Time Period and Frequency for Collecting Adverse Event and Serious Adverse Event Information-All adverse events; 10.4.5. Procedures-All adverse events	Overall, the text of 'All adverse events' was aligned to include details to be recorded in eCRF. Additionally, the new text added '**The exceptions are cytokine release syndrome (CRS) and chimeric antigen receptor-T (CAR-T) cell-related neurotoxicity (eg, Immune Effector Cell-Associated Neurotoxicity [ICANS] and other neurotoxicity), for which all symptoms associated with these events will be collected in the eCRF.**'	To ensure early detection, characterizing, monitoring, and reporting of CRS and CAR-T cell-related neurotoxicity.
1.3. Schedule of Activities (SoA); 4.4. End of Study Definition; 8. Study Assessments and Procedures-Post-treatment; 10.4.3. Severity Criteria; 10.4.4. Special Reporting Situations	• The end of study (EOS) definition was updated as '2 years after **each** participant has received his or her initial dose of cilta-cel OOS'. The term 'last participant' from EOS definition was deleted. • The footnote 'b' of SoA was revised for EOS definition. • Text updated to include severity grading for CRS, CAR-T cell related cell neurotoxicity, and handwriting assessments. • New text added that 'overdose' is not applicable as cilta-cel infusion administered as a one-time infusion. • Text related to AE reporting as follows: '**Any special reporting situation that meets the criteria of an AE, including SAE, should be recorded on the AE/SAE page of the eCRF. Serious AEs should follow the 24-hour SAE reporting process**'.	To clarify EOS definition and to align the text of severity criteria and special reporting situations with other cilta-cel study protocols.
3. Objectives and Endpoints-Secondary	Secondary endpoint revised to include 'severity' of treatment-emergent adverse events.	To be consistent with definition of treatment-emergent adverse events.
9.4.1.2. Secondary Endpoints-Adverse Events	The subsection of AEs was updated as below: "The verbatim terms used in the CRF by investigators to identify AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). **Section 8.3 provides information on AEs that are to be reported**	To update treatment emergent AEs and to include severity criteria for assessment of TEAEs.

Section number and Name	Description of Change	Brief Rationale
	following initial administration of study treatment. Any AE reported at or after the initial administration of study treatment is considered to be treatment-emergent. ~~Any AE occurring at or after the initial administration of study treatment through the day of last dose plus 30 days is considered to be treatment-emergent.~~ All reported treatment-emergent AEs will be included in the analysis. For each AE, the percentage of participants who experience at least 1 occurrence of the given event will be summarized". Severity criteria was clarified as 'Parameters with predefined National Cancer Institute Common Terminology Criteria for Adverse Event (NCI-CTCAE) (version 5.0) toxicity grades will be summarized **for treatment emergent adverse events (TEAEs)**'.	
5.2. Exclusion Criteria; 6.1.2. Criteria for Conditioning Regimen (Cyclophosphamide and Fludarabine)	• Exclusion criterion 3 was updated to include medical conditions that may result in exclusion from the study. • New exclusion criteria (4, 5, and 6) were added to include viral infections (HBV, hepatitis C [HCV], and human immunodeficiency virus [HIV]), respectively. • Criteria for lymphodepleting chemotherapy was updated for medical conditions to align with modified exclusion criterion 3.	Criterion 3 modified to align with other cilta-cel study protocols. As CAR-T therapy may increase risks of viral infections, new exclusion criteria are added.
2.3.1. Risks for Study Participation-Table 2, Table 3; 6.1.5.1. Management of Cytokine Release Syndrome; 6.1.5.4. Other Neurotoxicities; 6.1.5.5. Tumor Lysis Syndrome 6.1.5.6. Cytopenia; 6.1.5.7. Hypogammaglobulinemia; 6.1.5.8. Infections; 6.1.5.9. Hypersensitivity Reactions 6.1.5.10. Second Primary Malignancy;	Text of Table 2 and Table 3 were aligned to management guidelines for potential risks and included new guidelines to risk characterization and mitigation strategies, wherever applicable. The key updates are listed below: • To notify the sponsor if participant is experiencing Grade 2 or higher CRS. • Recommendation to use cytokine targeting therapies for CRS and for other neurotoxicities, which do not respond to tocilizumab or corticosteroids. • Language of 'Other neurotoxicities' aligned to include movement impairments, cognitive impairments, and personality changes. • Table (Other neurotoxicities) updated to include: **Infection and sepsis were seen concurrently in many of these patients**. • Additional monitoring and mitigation strategies added to ensure early detection of neurotoxicity and extended monitoring and reporting time for the study duration. • TLS is no longer to be reported as an AESI.	To make text consistent with latest management guidance for potential risks associated with cilta-cel.

Section number and Name	Description of Change	Brief Rationale
	• Titles of subsections (6.1.5.6. and 6.1.5.8.) updated to 'Prolonged Cytopenia' and 'Serious Infections', respectively. • A subsection (Cytopenia) was updated to include the risk of bleeding in case of severe thrombocytopenia and its monitoring per institutional guideline. • Table 3 (Prolonged cytopenia) mitigation strategy updated to include supportive care to be provided along with monitoring of blood counts. • A subsection (Hypogammaglobulinemia) updated to include 'HBV reactivation' as one of the recurrent infection and administration of subcutaneous immunoglobulin (IgG) to be considered. • A subsection (Infections) updated to include following: '**Immunocompromised participants are at risk for opportunistic infections. Prophylactic use of antibiotics, antivirals, and antifungals should be considered**'. • Table 3 (Serious Infection) text aligned to Appendix 14 for HBV infections. • A subsection (Hypersensitivity Reactions) updated to specify the names of premedication prior to cilta-cel dosing. • A subsection (SPM) clarified lentiviral insertion as (DNA integration) of the lentiviral vector.	
6.8.2. Prohibited Therapies; 6.1.2. Criteria for Conditioning Regimen (Cyclophosphamide and Fludarabine)	• Text updated to include prohibition of receptor activator of nuclear factor kappa-B (RANK) ligand inhibitors and medical condition such as autoimmune disease. • Vaccination with live, attenuated vaccine to be delayed for atleast 6 weeks instead of 4 weeks prior to lymphodepleting chemotherapy. • Section 6.1.2. title revised to include 'lymphodepleting chemotherapy' instead of 'conditioning regimen'.	To avoid potential impact to immune function prior to cilta-cel infusion. To align terminology with other cilta-cel study protocols.
2.3.1. Risks for Study Participation-Table 3; 5.2. Exclusion Criteria; 6.1.5.9. Hypersensitivity Reactions	The drug 'ampicillin' was deleted.	Ampicillin is no longer used in manufacturing process.
2.2.6. Clinical Studies-Exposure, Conclusion; 6.1.5.1. Management of Cytokine Release Syndrome	• Text updated to include latest safety and efficacy data from the clinical study report and recent edition of IB update for the study 68284528MMY2001.	To align with recent IB updates.

Section number and Name	Description of Change	Brief Rationale
	• An AESI-CRS was updated to clarify that an excluded participant with 97-day CRS event was due to complication of hemophagocytic lymphohistiocytosis (HLH).	
1.3. Schedule of Activities (SoA) 8.1.2. Bone Marrow Examination	The SoA was updated for following: • Assessment of 'Immunophenotyping and Pharmacokinetics [PK] (Whole blood)' was revised to 'Immunophenotyping' testing and to be performed at Day 1 infusion. • A note added to assessment of bone marrow aspirate and core biopsy: 'Fluorescence in situ hybridization (FISH) testing required to be performed at central laboratory.' • 'Baseline' assessment was deleted from minimal residual disease (MRD) bone marrow aspirate testing. • The PK sampling was deleted from the footnotes 'n' and 'p'. • The footnote 'o' was updated to include that PK-CAR transgene samples would be collected **at least annually until EOS** instead of 'every 6 months post 1-year'. **Additional event-triggered testing for PK CAR transgene may be conducted as clinically indicated.** • The footnote 'i' was updated to include requirement of FISH testing prior to lymphodepleting chemotherapy. • A note added to serology testing and corresponding footnote 'e' updated as '**For participants at risk of HBV reactivation**, monitor HBV DNA, aspartate aminotransferase (AST)/alanine aminotransferase (ALT) every **12 weeks (±7 days)…'** and text cross-referred to Appendix 14. • A note added to infectious disease testing that it should be performed as indicated clinically. • A footnote 'r' updated to include testing of an additional Ig samples may be required.	To delete 'PK' sampling from immunophenotyping testing as it is redundant. To accurately reflect required assessments (ie, FISH testing) and timepoints for MRD (bone marrow aspirate) testing. To perform PK CAR transgene testing per request received from health authority and to align with other cilta-cel study protocols.
6.1.5.3. CAR-T Cell-related Neurotoxicity (Immune Effector Cell-Associated Neurotoxicity Syndrome [ICANS])	PK sampling was deleted from cerebrospinal fluid (CSF) testing.	To remove the PK testing as it is not required and will not be done on CSF samples.
8. Study Assessments and Procedures-Study-Specific Materials	Interactive web response system (IWRS) manual was deleted from the list of study-specific materials.	IWRS will not be used in this study.
8.2.7. Clinical Safety Laboratory Assessments	Text updated to include: '**Participants with Grade 3 or higher toxicity or unresolved AEs**	To align with AE reporting guidance.

Section number and Name	Description of Change	Brief Rationale
	will continue to be assessed until recovery to Grade 1 or baseline, the event is deemed irreversible, the end of the study, or a maximum of 6 months, whichever occurs first'	
10.4.6. Product Quality Complaint Handling-Definition	Definition updated to include: '**The sponsor has established procedures in conformity with regulatory requirements worldwide to ensure appropriate reporting of product quality complaint (PQC) information; all studies conducted by the sponsor or its affiliates will be conducted in accordance with those procedures**.'	To align with Janssen global practices
10.2. Appendix 2: Clinical Laboratory Tests	An assessment updated to include cluster of differentiation (CD)-CD4/CD8 Lymphocyte Panel.	To align with laboratory requirements.
10.13. Appendix 13: Anti-microbial Prophylaxis Recommendations	• Antimicrobial prophylaxis should be started by Day-1 of CAR-T infusion. • A following note added: 'Consider cytomegalovirus (CMV) serology at baseline, monitor with PCR testing as clinically indicated per institution guidance'. • For pneumocystis pneumonia: – pentamidine should be administered by Day -1 of CAR-T infusion, or as an alternative treatment. – Drug and dosage regimen added for Day 28.	To align with antimicrobial prophylaxis guidelines.
10.14. Appendix 14: Hepatitis B Virus Screening	A note added: '**To minimize the number of times a participant would need to visit the clinic, the post-treatment follow-up visit (every 28 days post Day 112 [±7 days]) can be coordinated with the AST/ALT assessment every 12 weeks (±7 days).**'	To align with HBV guidelines.
Throughout the protocol; 10.1. Appendix 1: Abbreviations and definitions; 11. References	The term 'conditioning regimen' updated to 'Lymphodepleting chemotherapy'. The abbreviation list was updated. Added a new publication on HBV screening. Minor grammatical, formatting, and spelling changes were made.	Minor errors were noted.

11. REFERENCES

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INVESTIGATOR AGREEMENT

I have read this protocol and agree that it contains all necessary details for carrying out this study. I will conduct the study as outlined herein and will complete the study within the time designated

I will provide copies of the protocol and all pertinent information to all individuals responsible to me who assist in the conduct of this study. I will discuss this material with them to ensure that they are fully informed regarding the study intervention, the conduct of the study, and the obligations of confidentiality.

Coordinating Investigator (where required):

Name (typed or printed): _____

Institution and Address: _____

_____

_____

_____

Signature: _____ Date: _____

(Day Month Year)

Principal (Site) Investigator:

Name (typed or printed): _____

Institution and Address: _____

_____

_____

_____

Telephone Number: _____

Signature: _____ Date: _____

(Day Month Year)

Sponsor's Responsible Medical Officer:

Name (typed or printed): PPD

Institution: Janssen Research & Development

Signature: [electronic signature appended at the end of the protocol] Date: _____

(Day Month Year)

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

Signature

User	Date	Reason
PPD	02-Sep-2022 12:10:41 (GMT)	Document Approval