Individuals using assistive technology may not be able to fully access the information contained in this file. For assistance, please call 800-835-4709 or 240-402-8010, extension 1. CBER Consumer Affairs Branch or send an e-mail to: ocod@fda.hhs.gov and include 508 Accommodation and the title of the document in the subject line of your e-mail.

NDA/BLA Clinical Review and Evaluation

Disclaimer: In this document, the sections labeled as "Data" and "The Applicant's Position" are completed by the Applicant, which do not necessarily reflect the positions of the FDA.

Application Type	Efficacy Supplement BLA
Application Number(s)	125746/74
Priority or Standard	Standard
Submit Date(s)	June 06, 2023
Received Date(s)	June 06, 2023
PDUFA Goal Date	April 05, 2024
Division/Office	Division of Clinical Evaluation Hematology/Office of Therapeutic Product
Review Completion Date	April 5, 2024
Established Name	ciltacabtagene autoleucel
(Proposed) Trade Name	CARVYKTI
Pharmacologic Class	CAR-T cell therapy
Code name	JNJ68284528
Applicant	Janssen Biotech, Inc
Formulation(s)	Cell suspension for infusion
Dosing Regimen	0.5-1.0 x10^6 CAR-positive viable T cells per kg body weight with a maximum of 1.0×10^8 CAR-positive T cells in a single dose infusion
Applicant Proposed Indication(s)/Population(s)	The treatment of adult patients with relapsed or refractory multiple myeloma, who have received at least 1 prior line of therapy, including a proteasome inhibitor, and an immunomodulatory agent, and are refractory to lenalidomide
Recommendation on Regulatory Action	Regular approval
Recommended Indication(s)/Population(s) (if applicable)	The treatment of adult patients with relapsed or refractory multiple myeloma who have received at least 1 prior line of therapy, including a proteasome inhibitor and an immunomodulatory agent, and are refractory to lenalidomide

Table of Contents

Disclaimer: In this document, the sections labeled as "Data" and "The Applicant's Position" are completed by the Applicant and do not necessarily reflect the positions of the FDA.

Table of Tables (Applicant)

Table of Tables (FDA)

Disclaimer: In this document, the sections labeled as "Data" and "The Applicant's Position" are completed by the Applicant and do not necessarily reflect the positions of the FDA.

Table of Figures (Applicant)

Table of Figures (FDA)

Reviewers of Multi-Disciplinary Review and Evaluation (If Applicable)

Clinical Reviewer	Helkha Peredo-Pinto, MD, MPH
MOR Team Leader	Bindu Kanapuru, MD
Branch Chief (CHB)	Robert Sokolic, MD
Division Director (DCEH) (Acting)	Lola Fashoyin-Aje, MD, MPH
OCE Director (or designate)	Marc Theoret, MD
Office of Clinical Evaluation	Lola Fashoyin-Aje, MD, MPH

Abbreviations: CHB, Clinical Hematology Branch; DCEH: Division of Clinical Evaluation Hematology; OCE: Oncology Center of Excellence

Glossary (Applicant)

ADA	anti-drug antibodies (to cilta-cel)
ADR	adverse drug reaction
AE	adverse event
ALT	alanine aminotransferase
ARDS	Acute Respiratory Distress Syndrome
ASCT	autologous stem cell transplantation
AST	aspartate aminotransferase
ASTCT	American Society for Transplantation and Cellular Therapy
$AUC_{0\text{-}28d}$	area under the analyte concentration-time curve from time 0 to 28 days
$AUC_{0\text{-}56d}$	area under the analyte concentration-time curve from time 0 to 56 days
BCMA	B-cell maturation antigen
BLA	Biologics License Application
CAR	chimeric antigen receptor
CAR-T	chimeric antigen receptor T (cells)
(b) (4)	
CD	cluster of differentiation
CFR	Code of Federal Regulations
CI	confidence interval
Cilta-cel	ciltacabtagene autoleucel
C_{max}	maximum observed concentration
CMH	Cochran Mantel Haenszel
COVID-19	coronavirus disease 2019
CPW	constant piecewise weighted
CR	complete response
CRCL	creatinine clearance
CRF	case report form
CRS	cytokine release syndrome
CSR	clinical study report
CTC	Common Terminology Criteria
CTCAE	Common Terminology Criteria for Adverse Events
DE	disease evaluation
DMC	data monitoring committee
DNA	deoxyribonucleic acid
DOR	duration of response
DPd	daratumumab, pomalidomide, and dexamethasone

ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EORTC	European Organization for Research and Treatment of Cancer
EQ-5D-5L	EuroQol Five Dimension Questionnaire E-R exposure-response
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HLH	hemophagocytic lymphohistiocytosis
HR	hazard ratio
HRQoL	health-related quality of life
ICANS	Immune Effector Cell-associated Neurotoxicity Syndrome
ICH	International Conference for Harmonisation
Ide-cel	idecabtagene vicleucel
IFN	interferon
Ig	immunoglobulin
IL	interleukin
IMiD	immunomodulatory drug
IMWG	International Myeloma Working Group
IQR	interquartile range
IRC	independent review committee
ISS	International Staging System
ITT	intent-to-treat
IV	intravenous
LV	lentivirus(al)
MAS	macrophage activation syndrome
MedDRA	Medical Dictionary for Regulatory Activities
MID	minimum importance difference
mITT	modified intent-to-treat
MR	minimal response
MRD	minimal residual disease
MySIm-Q	Multiple Myeloma Symptom and Impact Questionnaire
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Events
NDA	new drug application
NE	not evaluable
NGF	next-generation flow
NGS	next-generation sequencing

ORR	overall response rate
OS	overall survival
PABAK	prevalence-adjusted-bias-adjusted kappa
PFS	progression-free survival
PFS2	progression-free survival on next-line therapy
PGIS	Patient Global Impression of Severity
PI	proteasome inhibitor
PK	pharmacokinetic(s)
PML	progressive multifocal leukoencephalopathy
PR	partial response
PRO	patient-reported outcome
PT	preferred term
PVd	pomalidomide, bortezomib, and dexamethasone
QLQ-C30	Quality of Life Questionnaire Core-30 item
RCL	replication-competent lentivirus
SAE	serious adverse event
SAP	statistical analysis plan
sBCMA	soluble B-cell maturation antigen
sBLA	supplemental Biologics License Application
SC	subcutaneous(ly)
sCR	stringent complete response
SOC	system organ class
SPM	second primary malignancy
$t_{1/2}$	apparent terminal elimination half-life
TEAE	treatment-emergent adverse event
t_{last}	actual sampling time of last measurable (non-below quantification limit) analyte concentration
TLS	tumor lysis syndrome
ULN	upper limit of normal
US	United States
USPI	United States Prescribing Information
VGPR	very good partial response

Glossary (FDA)

AE	adverse event
BCMA	B-cell maturation antigen

CAR	chimeric antigen receptor
CAR-T	chimeric antigen receptor T (cells)
CD	cluster of differentiation
CI	confidence interval
cilta-cel	ciltacabtagene autoleucel
CR	complete response
CRR	complete response rate
CRS	cytokine release syndrome
DPd	daratumumab, pomalidomide, and dexamethasone
ETASU	Elements to Assure Safe Use
FDA	Food and Drug Administration
HLH	hemophagocytic lymphohistiocytosis
HR	hazard ratio
ICANS	immune effector cell-associated neurotoxicity syndrome
IMiD	immunomodulatory drug
IMWG	International Myeloma Working Group
IQR	interquartile range
IRC	independent review committee
ITT	intent-to-treat
LV	lentivirus(al)
MAS	macrophage activation syndrome
MM	multiple myeloma
MRD	minimal residual disease
NE	not evaluable
NT	neurotoxicity
ORR	overall response rate
OS	overall survival
PFS	progression-free survival
PI	proteasome inhibitor
PMR	postmarketing requirement
PO	orally
PRO	patient-reported outcome
PVd	pomalidomide, bortezomib, and dexamethasone
REMS	Risk Evaluation and Mitigation Strategies
SAE	serious adverse event
RRMM	relapsed refractory multiple myeloma

sBLA	supplemental Biologics License Application
sCR	stringent complete response
TEAE	treatment-emergent adverse event

1 Executive Summary

1.1. Product Introduction

Ciltacabtagene autoleucel (CARVYKTI; hereafter referred to as cilta-cel) is a BCMA-directed chimeric antigen receptor T (CAR-T) cell therapy composed of human autologous T cells that are genetically modified by a lentiviral (LV) vector to express a BCMA-targeting CAR. The CAR comprises two complementary llama-derived single domain antibodies that bind to human BCMA, a human cluster of differentiation (CD)8α hinge and transmembrane domain, the 4-1BB intracellular signaling domain, and the CD3ζ cytoplasmic signaling domain. Binding of the CAR to BCMA-expressing target cells leads to T cell signaling through the 4-1BB and CD3ζ domains and subsequent activation of CAR-positive T cells. Antigen-induced activation results in CAR-T cell proliferation, cytokine secretion, and subsequent cytolytic killing of BCMA-expressing cells.

To manufacture cilta-cel drug product, T cells are enriched from patient apheresis material. The enriched T cells are activated and transduced with the nonreplicating LV vector encoding the CAR. The LV-vector-transduced cells are expanded, formulated into a suspension, and cryopreserved in an infusion bag.

Cilta-cel is currently approved for the treatment of adult patients with relapsed refractory multiple myeloma (RRMM) after four or more prior lines of therapy, including a proteosome inhibitor, an immunomodulatory agent, and an anti-CD38 monoclonal antibody (traditional approval, February 28, 2022).The recommended dose range is $0.5\text{-}1.0\times10^6$ chimeric antigen receptor (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-dose infusion.

On June 6, 2023, the Applicant submitted a supplemental application for cilta-cel. The currently proposed Indication is: CARVYKTI is a BCMA-directed genetically modified autologous T cell immunotherapy indicated for the treatment of adult patients with RRMM who have received at least 1 prior line of therapy, including a proteasome inhibitor and an immunomodulatory agent, and are refractory to lenalidomide. The Applicant requests approval of this indication at the current approved dosage.

1.2. Conclusions on the Substantial Evidence of Effectiveness

Substantial evidence of the safety and effectiveness of cilta-cel for the proposed indication n derives from one adequate and well-controlled study, CARTITUDE-4 with supportive evidence from Study CARTITUDE-2. CARTITUDE-4 is a Phase 3, randomized (1:1), open-label, multicenter study that compares cilta-cel to standard therapy in adults with relapsed and lenalidomide-refractory multiple myeloma (MM) after one to three prior lines of therapy including a PI and an immunomodulatory drug (IMiD). CARTITUDE-4 enrolled a total of 419 patients who were

randomized to receive cilta-cel or one of two standard-of-care regimens, either pomalidomide, bortezomib, and dexamethasone (PVd) or daratumumab, pomalidomide, and dexamethasone (DPd). Patients received cilta-cel as a single infusion at a dose range of 0.41-1.08x10^6 CAR+ viable cells/kg following lymphodepletion therapy with fludarabine and cyclophosphamide.

The primary efficacy outcome measure for CARTITUDE-4 was progression-free survival (PFS) as determined by a blinded independent review committee (IRC) using the International Myeloma Working Group (IMWG) 2016 criteria. Key secondary efficacy outcome measures in hierarchical testing order were rate of CR or better (CRR), overall response rate (ORR), overall MRD negativity rate, overall survival (OS) and time to worsening of symptoms in the MySIm-Q total symptom score. The limitations of the MRD and PRO data being exploratory.

CARTITUDE-4 met its primary endpoint (data cutoff of November 1, 2022), demonstrating a statistically significant and clinically meaningful improvement in PFS in patients randomized to the cilta-cel arm compared to patients randomized to the standard therapy arm (hazard ratio [HR] was 0.41 [95% confidence interval (CI): 0.30, 0.56] based on a stratified log-rank test; p-value <0.0001). The median PFS was not reached in the cilta-cel arm (95% CI: 22.8, not evaluable [NE]), and was 12 months (95% CI: 9.8, 14) in the standard therapy arm.

The IRC-assessed CR rate was statistically significant; 74% (95% CI: 67, 79) in the cilta-cel arm compared to 22% (95% CI: 16, 28) in the standard therapy arm. Similarly, the ORR was higher at 85% (95% CI:79, 89) in the cilta-cel arm compared to 67% (95% CI: 61, 74) in the standard therapy arm. At the time of the primary analysis of PFS, overall survival (OS) was immature (information fraction of 34%). FDA considered cilta-cel effects on OS as part of the safety assessment.

A higher proportion of patient randomized to cilta-cel compared to standard therapy experienced death in with first 10 months following randomization (n=29/208;14% vs. n=25/211;12%). Of the 29 deaths that occurred in the CARVYKTI arm within the first 10 months of randomization, 10 deaths occurred prior to CARVYKTI infusion, and 19 deaths occurred after CARVYKTI infusion. Of the 10 deaths that occurred prior to CARVYKTI infusion, all occurred due to disease progression. Of the 19 deaths that occurred after CARVYKTI infusion, 3 occurred due to disease progression, and 16 occurred due to adverse events. The most common adverse events were due to infection (n=12). The higher early mortality with cilta-cel was observed across multiple prognostic subgroups and was observed even in the absence of individual poor prognostic factors. In the safety analysis population, there was also a higher rate of fatal adverse reaction that occurred within 90 days from starting treatment with cilta-cel in the as treated population compared to in the standard therapy arm (5% versus 0%).

FDA convened a meeting of the Oncologic Drugs Advisory Committee (ODAC) to discuss the increased risk for early deaths in the cilta-cel arm and the risk-benefit assessment of cilta-cel for the proposed indication. Voting members of the ODAC were asked to vote on whether the risk-

benefit assessment for cilta-cel for the proposed indication favorable; the ODAC voted 11 to 0 in favor of cilta-cel.

The primary evidence of the safety of cilta-cel for the proposed indication is based on CARTITUDE-4; CARTITUDE-2 provides support evidence of safety. The primary analysis of safety was conducted in patients enrolled in CARTITUDE-4 who received conformal cilta-cel in the investigational arm (n=188) and patients who received standard therapy (n=208). All patients experienced an adverse event (AE) (cilta-cel arm: 100%; standard therapy arm: 100%). The most common (≥5 %) Grade 3 to 4 treatment-emergent adverse events (TEAEs) in the cilta-cel arm were hypogammaglobulinemia (9%), pneumoniae (9%), bacterial infection (6 %), and pneumonia (11 %), viral infection (6 %), in the standard therapy arm. The Grade 3 to 4 toxicity rate was slightly higher in the standard therapy arm (cilta-cel arm: 92%; standard therapy: 94%). Serious adverse events (SAEs) occurred in 34% and 39% of subjects in the cilta-cel and standard therapy arms, respectively.

Cytokine release syndrome (CRS) and neurotoxicity (NT) associated with cilta-cel therapy are serious, life-threatening, and can be fatal. Treatment algorithms to mitigate these AEs, as implemented in the study, permit the benefits of treatment to outweigh these risks. Increased risk of secondary malignancies due to insertional mutagenesis is a known risk; during this study, a T-cell lymphoma was attributed to the study product. A postmarketing requirement, (PMR) long-term follow-up registry study will be required to follow recipients of the commercial product for short term and long-term toxicity up to 15 years.

In conclusion, CARTITUDE-4 provides substantial evidence of effectiveness of cilta-cel for patients with relapsed and lenalidomide-refractory MM after one to three prior lines of therapy, including a PI and an IMiD. CARTITUDE-4 demonstrates clinical benefit through clinically meaningful improvements in PFS, complete response rate (CRR), ORR and the potential for durable duration of response in the proposed patient population. The most common serious risks of cilta-cel have been characterized and are mitigated through product labeling and a REMS. The observed higher rate of early death observed in CARTITUDE-4 does not have a clear etiology but as discussed in the ODAC, may represented frontloaded risks associated with the treatment and its administration. CARTITUDE-4 was not designed to provide definitive information on how this risk can be mitigated. Treatment with cilta-cel may require careful consideration of individual patient characteristics, disease characteristics, the therapeutic context among other factors. The risk of increase early mortality with cilta-cel will be included under Warning and Precautions section of the USPI. The ODAC members assessed the risks acceptable in the indicated population.

The review team recommends traditional approval of cilta-cel at the currently approved dosage, for the treatment of adult patients with RRMM who have received at least one prior line of therapy, including a proteasome inhibitor (PI) and an immunomodulatory agent, and are refractory to lenalidomide.

The recommendation for approval was based on demonstration of substantial evidence of effectiveness and favorable benefit-risk of cilta-cel in the indicated population based on data from the Phase 3 CARTITUDE-4 study. Study CARTITUDE-2 provides supportive evidence for safety.

BLA Clinical Review and Evaluation
sBLA 125746/74, CARVYKTI (ciltacabtagene autoleucel)
Clinical Reviewer: Helkha Peredo-Pinto MD, MPH

Benefit-Risk Summary and Assessment

The benefit-risk assessment for cilta-cel in the indicated population is primarily based on the results of CARTITUDE-4, a Phase 3, randomized (1:1), open label, multicenter study. A total of 419 patients with relapsed and lenalidomide-refractory multiple myeloma (MM) after one to three prior lines of therapy, including a proteosome inhibitor (PI) and an immunomodulatory drug (IMiD) were enrolled. The primary efficacy endpoint was progression-free survival (PFS) as determined by a blinded independent review committee using the International Myeloma Working Group (IMWG) 2016 criteria. Key secondary efficacy outcome measures in hierarchical testing order were CR or better (CRR), overall response rate (ORR), overall MRD negativity rate, overall survival (OS) and time to worsening of symptoms in the MySIm-Q total symptom scoreare.

CARTITUDE-4 demonstrated a statistically significant and clinically meaningful improvement in PFS for cilta-cel compared to standard therapy (hazard ratio [HR] was 0.41 [95% confidence interval (CI): 0.30, 0.56]; p-value <0.0001). Median PFS was not reached in the cilta-cel arm (95% CI: 22.8, not evaluable [NE]), and was 12 months (95% CI: 9.8, 14) in the standard therapy arm. CRR and ORR were also improved in the cilta-cel arm compared to standard therapy (CRR 74% (68, 80) vs. 22% (95% CI: 17, 29) standard therapy; ORR 85% (95% CI: 70, 89) cilta-cel vs. 68 (95% CI: 61, 74) in the standard therapy). At the time of the primary analysis of PFS, overall survival (OS) was immature (information fraction of 34%); FDA considered cilta-cel effects on OS as part of the safety assessment (5% vs 0%).

The rate of adverse reactions of cilta-cel, including the rate of the serious risks such as Grade 3 or higher CRS, was similar to prior studies. However, in CARTITUDE-4, a signal of increased early deaths was observed in patients randomized to cilta-cel compared to patients randomized to standard therapy. Specifically, a higher proportion of patient randomized to cilta-cel compared to standard therapy experienced death in with first 10 months following randomization (n=29/208;14% vs. n=25/211;12%). The higher early mortality with cilta-cel was observed across multiple prognostic subgroups and was observed even in the absence of individual poor prognostic factors. In the safety analysis population, there was also a higher rate of fatal adverse reaction that occurred within 90 days from starting treatment with cilta-cel arm compared to in the standard therapy arm (5% versus 0%). The increased risk of early deaths and the benefit risk of cilta-cel for the indicated population was discussed at an oncologic drug advisory committee meeting. The ODAC voted 10-0 that the benefit-risk was favorable in the context of the PFS benefit. *Version date: March 25, 2024 (ALL NDA/ BLA reviews)*

Overall, the benefit of treatment with cilta-cel outweighs its risks in the indicated population of adult patients with relapsed or refractory multiple myeloma, who have received at least 1 prior line of therapy, including a proteasome inhibitor and an immunomodulatory agent, and are refractory to lenalidomide. The risks can be mitigated through product labeling and REMS.

1.3. Benefit-Risk Assessment (BRA)

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Multiple Myeloma (MM) is the second most common hematological malignancy. • Therapy for patients with relapsed or refractory MM (RRMM) has improved considerably over the years.	• RRMM is a serious and life-threatening condition with need for effective and safe salvages therapies.
Current Treatment Options	• Current standard therapy for MM consists of combination regimens that include proteosome inhibitors (PI)s (e.g., bortezomib, ixazomib, and carfilzomib), immunomodulatory (IMiD) agents (e.g., thalidomide, lenalidomide, and pomalidomide), and monoclonal antibodies directed against myeloma cell surface antigens (e.g., daratumumab, elotuzumab, and isatuximab). Additional treatment options include the use of autologous hematopoietic stem cell transplantation. • Treatment for relapsed disease typically consists of	• Despite the availability of multiple therapies, RRMM remains an incurable disease.

	triplet regimens, including at least two active drug classes other than steroids and at least one drug from a class to which the patient has not been exposed. • Doublet and triplet regimens containing monoclonal antibodies such as the anti-CD38 monoclonal antibodies daratumumab and isatuximab, combined with a steroid and either an IMiD or a PI, can be highly effective and demonstrate benefit, including increased OS, in randomized controlled studies (Cowan et al 2022).	
Benefit	• CARTITUDE-4 demonstrated a statistically significant and clinically meaningful improvement in PFS (HR=0.41; 95% CI: 0.30, 0.56; p-value <0.0001), CRR (74% [95% CI: 67, 70] vs 22% [95% CI: 16, 28]; p <0.0001), and ORR (85% [95% CI: 79, 89] versus 67% [95% CI: 61, 74]; p <0.0001) compared to standard therapy in patients with RRMM after one to three prior lines of therapy and who are lenalidomide refractory. Median PFS was not reached for the cilta-cel arm compared to 12 months for the standard therapy arm. The treatment effect was consistent across major groups. • CRR and ORR were also improved in the cilta-cel arm compared to standard therapy (CRR 74% [95% CI: 68,	• Based on the improvement in PFS, CRR, and ORR in a randomized Phase 3 study, ciltacabtagene autoleucel has demonstrated meaningful clinical benefit compared to standard therapy in patients with RRMM after one to three prior lines of therapy and who are lenalidomide refractory.

	80] vs. 22% [95% CI: 17, 29] standard therapy; ORR 85% [95% CI: 70, 89] cilta-cel vs. 68 [95% CI: 61, 74] in the standard therapy).	
Risk and Risk Management	• OS results from the CARTITUDE-4 study demonstrated an early detriment in OS in subjects randomized to the cilta-cel arm compared to those randomized to standard therapy. In the ITT population deaths due to AEs were higher in the cilta-cel arm (11%, n=20) compared to the deaths in the standard therapy arm (8%, n=16). In the safety analysis population, death events that occurred within 90 days from starting treatment were also higher in the cilta-cel arm compared to the standard therapy arm (5% versus 0%). The increased risk of early deaths and the benefit risk of cilta-cel for the indicated population was discussed at an oncologic drug advisory committee meeting. The ODAC voted 11 to 0 that the benefit-risk was favorable in the context of the PFS benefit. • The substantial risks of CARVYKTI are CRS, NT (includes ICANS, parkinsonism, GBS, peripheral neuropathy, cranial nerve palsy), HLH/MAS, prolonged and recurrent cytopenias, infections, and persistent hypogammaglobulinemia.	• Risk of early death will be added to the Warnings and Precautions section of the approved USPI. • There is a Black box Warning for CRS, Neurologic Toxicities (ICANS, parkinsonism and GBS), HLH/MAS, and Prolonged and Recurrent Cytopenia. • The Warnings and Precautions section of the label details the potential risks. The approved label for CARVYKTI includes a Risk Evaluation and Mitigation Strategy (REMS) with Elements to Assure Safe Use (ETASU) will be issued to mitigate the risks of CRS and NT associated with CARVYKTI after approval.

	• CRS and NT were mitigated in the study by careful site selection and training of investigators. • Long-term risk of secondary malignancy due to insertional mutagenesis from replication competent lentivirus in the genetically modified product remains a concern.	

1.4. Patient Experience Data

Patient Experience Data Relevant to this Application (check all that apply)

Check if Submitted	Type of Data	Section Where Discussed, if Applicable
☒	Patient-reported outcome	Section 8.1 Review of Relevant Individual Trials Used to Support Efficacy Section 8.3 Study Results
☐	Observer-reported outcome	
☐	Clinician-reported outcome	
☐	Performance outcome	
☐	Patient-focused drug development meeting summary	
☐	FDA Patient Listening Session	
☐	Qualitative studies (eg, individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel)	
☐	Observational survey studies	
☐	Natural history studies	
☐	Patient preference studies	
☐	Other: (please specify)	
☐	**If no patient experience data were submitted by Applicant, indicate here.**	
Check if Considered	**Type of Data**	**Section Where Discussed, if Applicable**
☐	Perspectives shared at patient stakeholder meeting	
☐	Patient-focused drug development meeting summary	
☐	FDA Patient Listening Session	
☐	Other stakeholder meeting summary report	
☐	Observational survey studies	
☐	Other: (please specify)	

X

Cross-Disciplinary Team Leader

2 Therapeutic Context

2.1. Analysis of Condition

The Applicant's Position:

Multiple myeloma is a malignant disorder of the plasma cells, characterized by uncontrolled and progressive proliferation of a plasma cell clone, and accounts for approximately 10% of hematological malignancies (Rodriguez-Abreu 2007; Rajkumar 2011). The disease leads to progressive morbidity and eventual mortality by lowering resistance to infection and causing significant skeletal destruction (with bone pain, pathological fractures, and hypercalcemia), renal insufficiency, anemia, bony lesions, bacterial infections, hyperviscosity, and secondary amyloidosis (Orlowski 2013). Despite advances in available therapies, multiple myeloma remains incurable. All patients eventually relapse and become refractory to existing treatments.

The incidence of multiple myeloma is approximately 1.5-fold higher in men than in women (Padala 2021; Turesson 2010). The prevalence of multiple myeloma increases with age, with a median age at diagnosis of approximately 66 to 70 years (Turesson 2010; Kazandjian 2016). Black and African American patients have a higher incidence of multiple myeloma compared with other ethnicities (>2-fold higher than white patients), representing approximately 20% of the patients with multiple myeloma in the US (Gormley 2021). Multiple myeloma incidence and mortality appears highest in Western Europe, the US, Canada, and Australia, with age-standardized incidence rates in these regions ranging from 4.6 to 5.8 per 100,000 persons in 2016 (Cowan 2018).

Worldwide, there are an estimated 80,000 deaths annually due to multiple myeloma and approximately 24,300 and 12,800 patients with this disease die annually in Europe and the US, respectively (Ferlay 2013; Cancer.net 2020 The estimated 5-year survival rate for patients with multiple myeloma is approximately 54% (Cancer.net 2020). With each successive relapse, symptoms return, HRQoL worsens, and the chance and DOR typically decrease. Therefore, there remains a significant and critical unmet need for new therapeutic options directed at alternative mechanisms of action that can better control the disease; provide deeper, more sustained responses; and yield better long-term outcomes including maintenance of HRQoL.

The FDA's Assessment:
FDA generally agrees with the Applicant's analysis of condition. Despite the availability of multiple approved treatment options, MM remains incurable.

2.2. Analysis of Current Treatment Options

Data:

There are several approved triplet regimens for patients with multiple myeloma that has relapsed after 1 to 3 prior lines of therapy; however, these regimens have largely been tested in lenalidomide-naïve or lenalidomide-sensitive patients. The pivotal Phase 3 studies (ASPIRE [carfilzomib, lenalidomide, and dexamethasone; Stewart 2015], ELOQUENT-2 [elotuzumab, lenalidomide, and dexamethasone; Lonial 2015], Tourmaline-MM1 [ixazomib, lenalidomide, and dexamethasone; Moreau 2016], and POLLUX [daratumumab, lenalidomide, and dexamethasone; Dimopoulos 2016]) excluded lenalidomide-refractory patients because these studies randomized against lenalidomide plus dexamethasone control arms.

Lenalidomide is a key backbone agent in the treatment of multiple myeloma, in the frontline setting, as maintenance following ASCT, and in relapsed disease. As lenalidomide is typically administered until disease progression, most patients will become lenalidomide-refractory and refractoriness to lenalidomide is associated with poorer outcomes (Lecat 2021). Importantly, as detailed below, with almost all combination therapies studied, lenalidomide-refractory patients had poorer outcomes than their lenalidomide-sensitive or non-exposed counterparts.

More recently, a number of studies evaluated combinations of a monoclonal antibody, with a PI or with pomalidomide. These studies included substantial proportions of lenalidomide-refractory patients: 93% in ICARIA (isatuximab, pomalidomide, dexamethasone; Bringhen 2021), 80% in APOLLO (DPd; Dimopoulos 2021), 70% in OPTIMISMM (PVd; Richardson 2019), 33% in CANDOR (carfilzomib, dexamethasone, and daratumumab; Usmani 2022), and 33% in IKEMA (isatuximab, carfilzomib, and dexamethasone; Moreau 2021). Among lenalidomide-refractory patients treated with the triplet regimens in these studies, median PFS was 11.4 months in ICARIA, 9.9 months in APOLLO, and 9.5 months in OPTIMISMM, with longer median PFS noted in CANDOR (median 28.1 months) and IKEMA (median PFS for lenalidomide-refractory subgroup not reported), both of which used an anti-CD38 monoclonal antibody in combination with carfilzomib and

dexamethasone. The sustained response shown in these studies relies on ongoing therapy until progression of disease, potentially resulting in cumulative toxicity and significant treatment burden.

CAR-T cell-based therapies offer potential advantages over other T-cell redirection therapeutic strategies. While other therapies require prolonged exposure, generally until progression of disease, CAR-T cell therapy is completed after a single infusion due to its in vivo expansion and long-term disease response. The anti-BCMA CAR-T therapy, ide-cel, is indicated for the treatment of adult patients with relapsed or refractory multiple myeloma after 4 or more prior lines of therapy, including an IMiD, a PI, and an anti-CD38 monoclonal antibody, with a reported ORR of 72% and a median DOR of 11.0 months (ABECMA [idecabtagene vicleucel] USPI 2021). A median PFS of 8.8 months has been reported (Munshi 2021).

More recently, in the Phase 3 KarMMa-3 study, at a median follow-up of 18.6 months, ide-cel significantly improved PFS versus standard regimens (median [95% CI] 13.3 [11.8 to 16.1] versus 4.4 [3.4 to 5.9] months; HR 0.49; 95% CI 0.38 to 0.65; p<0.001) (Rodríguez-Otero 2023).

Cilta-cel is a genetically modified autologous T-cell immunotherapy that binds to BCMA. The novel design comprises a structurally differentiated CAR-T with 2 BCMA-targeting single domain antibodies to confer avidity. Cilta-cel received FDA approval for the treatment of adult patients with relapsed or refractory multiple myeloma after 4 or more prior lines of therapy, including an IMiD, a PI, and an anti-CD38 monoclonal antibody, with an ORR of 97.9% (CARVYKTI USPI 2023).

To note, differential treatment patterns for multiple myeloma have been reported, with older patients and Black/African American and Hispanic patients less likely to undergo ASCT (Kanapuru 2022; Fiala 2017). Black/African American and Hispanic patients are also less likely to receive novel therapies for multiple myeloma, and to receive these later than white patients (Ailawadhi 2019; Derman 2020).

A summary of the treatment armamentarium for relapsed and/or refractory multiple myeloma is provided in Table 1.

Table 1: Applicant - Summary of Treatment Armamentarium for Relapsed and/or Refractory Multiple Myeloma

Product (s) Name	Relevant Indication	Year of Initial Approval/ Current Type of Approval*	Dosing/Administration	Efficacy Information[a]	Important Safety and Tolerability Issues
FDA-approved Treatments Available During MMY3002					
Pomalidomide/ Dexamethasone	In combination with dexamethasone for adult patients with multiple myeloma who have received at least 2 prior therapies including lenalidomide and a PI and have demonstrated disease progression on or within 60 days of completion of the last therapy.	2013/ Full Approval	In combination with dexamethasone: 4 mg once daily orally on Days 1 through 21 of each 28 day cycle until disease progression.	Open-label, randomized Study MM-003; ORR: 23.5% Median PFS: 3.6 months Median OS: 12.4 months. (POMALYST [pomalidomide] USPI 2023).	Embryo-fetal toxicity, venous and arterial thromboembolism, deep venous thrombosis, pulmonary embolism, myocardial infarction, and stroke.
Daratumumab	Treatment of adult patients with multiple myeloma as monotherapy, in patients who have received at least 3 prior lines of therapy including a PI and an IMiD or who are double refractory to a PI and an IMiD.	2015/ Full Approval	16 mg/kg IV infusion: Weeks 1 to 8 weekly (total 8 doses), Weeks 9 to 24 every 2 weeks (total 8 doses), Week 25 onwards until disease progression every 4 weeks.	Open-label, randomized Study SIRIUS ORR: 29.2% Median PFS: 3.7 months Median DOR: 7.4 month Median OS: 17.5 months. (DARZALEX [daratumumab] USPI 2023; Lonial 2016)	Severe and/or serious infusion-related reactions, neutropenia and thrombocytopenia induced by background therapy, embryofetal toxicity.
Carfilzomib	As a single agent for the treatment of patients with relapsed or refractory multiple myeloma who have received 1 or more lines of therapy.	2016/ Full Approval	20/27 mg/m^2 IV infusion twice weekly in Cycles 1 through 12, on Days 1, 2, 8, 9, 15, and 16 of each 28 day cycle. From	Open-label, randomized Study FOCUS (Hajek 2017); ORR: 19.1% Median PFS: 3.7 months	New onset or worsening of pre-existing cardiac failure, cardiomyopathy, myocardial ischemia, and myocardial infarction including fatalities, acute renal

Product (s) Name	Relevant Indication	Year of Initial Approval/ Current Type of Approval*	Dosing/Administration	Efficacy Information[a]	Important Safety and Tolerability Issues
			Cycle 13, administered on Days 1, 2, 15, and 16 of each 28 day cycle. Continued until disease progression or unacceptable toxicity.	Median DOR: 7.2 months Median OS: 10.2 months.	failure and TLS, ARDS, acute respiratory failure, pulmonary arterial hypertension, dyspnea, hypertension, thrombocytopenia, hepatic failure, thrombotic microangiopathy, embryofetal toxicity.

Selinexor/ Dexamethasone	In combination with dexamethasone for the treatment of adult patients with relapsed or refractory multiple myeloma who have received at least 4 prior therapies and whose disease is refractory to at least 2 PIs, at least 2 IMiDs, and an anti-CD38 monoclonal antibody.	2019/ Accelerated Approval	In combination with dexamethasone: 80 mg taken orally on Days 1 and 3 of each week until disease progression or unacceptable toxicity.	Open-label, single arm Study STORM; ORR: 25.3%; Median DOR: 3.8 months (XPOVIO [selinexor] USPI 2019).	Thrombocytopenia, neutropenia, severe gastrointestinal toxicities, severe or hyponatremia, serious and fatal infections, neurological toxicities, embryofetal toxicity.
Treatments Available During MMY3002 and since Withdrawn from the US Market					
Belantamab mafodotin	Treatment of adult patients with relapsed or refractory multiple myeloma who have received at least 4 prior therapies, including an anti-CD38 monoclonal antibody, a PI, and an IMiD.	2020/ Accelerated Approval; withdrawn from US market in 2022	2.5 mg/kg IV infusion once every 3 weeks until disease progression or unacceptable toxicity.	Open-label, randomized Study DREAMM-2; ORR: 31% Median DOR: Not reached; 73% of responders had a duration of response ≥6 months (BLENREP [belantamab mafodotin] USPI 2020).	Ocular toxicity, thrombocytopenia, infusion-related reactions, embryofetal toxicity.
Melflufen flufenamide	In combination with dexamethasone for the treatment of adult patients with relapsed or refractory multiple myeloma who have received at least 4 prior lines of therapy and whose disease is refractory to at least one PI, 1 IMiD, and 1 CD38-directed monoclonal antibody.	2021/ Accelerated Approval; withdrawn from US market in 2021	In combination with dexamethasone: 40 mg IV on Day 1 of each 28 day cycle.	Pivotal, single arm Study HORIZON; ORR: 23.7% Median DOR: 4.2 months. (PEPAXTO [melphalan flufenamide] USPI 2021).	Thrombocytopenia, neutropenia and febrile neutropenia, anemia, fatal infections, secondary malignancies, embryofetal toxicity.

Product (s) Name	Relevant Indication	Year of Initial Approval/ Current Type of Approval•	Dosing/Administration	Efficacy Information[a]	Important Safety and Tolerability Issues
FDA-approved Treatments Approved After the Start of MMY3002					
Isatuximab	In combination with pomalidomide and dexamethasone for the treatment of adult patients with multiple myeloma who have received at least 2 prior therapies including lenalidomide and a PI.	2020/ Full Approval	In combination with pomalidomide and dexamethasone: 10 mg/kg actual body weight IV infusion every week for 4 weeks followed by every 2 weeks until disease progression or unacceptable toxicity.	Open-label randomized Study ICARIA-MM 93% of patients were refractory to lenalidomide. Median PFS: 11.5 months (11.4 months for lenalidomide-refractory patients) ORR: 60.4% Median DOR: 13.3 months Median OS: not reached. (SARCLISA [isatuximab-irfc] USPI 2020; Bringhen 2021).	Infusion-related reactions, neutropenia, febrile neutropenia, and neutropenic infections, SPM, embryofetal toxicity.
Idecabtagene vicleucel (ide-cel)	Treatment of adult patients with relapsed or refractory multiple myeloma after 4 or more prior lines of therapy, including an IMiD, a PI, and an anti-CD38 monoclonal antibody.	2021/ Full Approval	After lymphodepletion (cyclophosphamide 300 mg/m^2+ fludarabine 30 mg/m^2 x 3), patients received 150–450 × 10^6 CAR-positive T cells (target dose range).	Single arm Study KarMMa. ORR: 72% Median DOR: 11.0[b] months (ABECMA [idecabtagene vicleucel] USPI 2021) Randomized, open-label KarMMa-3: Median PFS: 13.3 months (Rodríguez-Otero 2023).	Neutropenia, CRS, anemia, thrombocytopenia, neurologic toxicity, HLH/MAS, hypersensitivity reactions, infections, hypogammaglobulinemia and secondary malignancies.
Teclistamab	Treatment of adult patients with relapsed or refractory multiple myeloma who have received at	2022/ Accelerated Approval	Step-up doses of teclistamab 0.06 mg/kg and 0.3 mg/kg by SC	Single-arm, open-label Study MajesTEC-1 ORR: 61.8%	CRS, neurologic toxicity, ICANS, hepatotoxicity, serious infections, neutropenia, febrile neutropenia,

	least 4 prior lines of therapy, including a PI, an IMiD, and an anti-CD38 monoclonal antibody.		injection followed by 1.5 mg/kg once weekly until disease progression or unacceptable toxicity.	Median DOR: Not reached; estimated 6-month DOR rate of 90.6%; estimated 9-month DOR rate 66.5%. (TECVAYLI [teclistamab-cqyv] USPI 2022)	hypersensitivity, embryofetal toxicity.

Product (s) Name	**Relevant Indication**	**Year of Initial Approval/ Current Type of Approval***	**Dosing/Administration**	**Efficacy Information[a]**	**Important Safety and Tolerability Issues**
Ciltacabtagene autoleucel (cilta-cel)	Treatment of adult patients with relapsed or refractory multiple myeloma after 4 or more prior lines of therapy, including a PI, an IMiD, and an anti-CD38 monoclonal antibody.	2022/ Full Approval	After lymphodepletion (cyclophosphamide 300 mg/m^2+ fludarabine 30 mg/m^2 x 3), patients received 0.5-1.0 × 10^6 CAR-positive viable T cells per kg of body weight.	Open-label, single-arm, multicenter Study MMY2001 ORR: 97.9% Median DOR: 21.8 months (CARVYKTI [ciltacabtagene autoleucel] USPI 2023).	Lymphopenia, neutropenia, WBC decreased, anemia, thrombocytopenia, CRS, neurologic toxicities, HLH/MAS, infections, hypersensitivity reactions, secondary malignancies.

*Accelerated approval or full approval.
[a] Data presented from arm of interest for randomized study.
[b] 300 to 460 × 10^6 CAR-positive T cells.

The Applicant's Position:

Despite the classes of drugs available, patients with relapsed and lenalidomide-refractory multiple myeloma have worse outcomes than their lenalidomide-sensitive or non-exposed counterparts with almost all combination therapies studied.

Moving CAR-T therapy to an earlier line of treatment will allow patients with a less compromised immune system, who have less prior exposure to immunomodulatory and cytotoxic therapy, to benefit from this form of immunotherapy. Furthermore, given the attrition rates among patients with multiple myeloma, CAR-T therapy in earlier lines of therapy would greatly increase the number of patients who are able to benefit from this treatment. Finally, CAR-T represents a single administration of treatment in contrast to currently available therapies that are typically given until disease progression, including the regimens available in the control arm of Study 68284528MMY3002 (CARTITUDE-4; hereafter referred to as Study MMY3002).

Study MMY3002 was conducted to determine whether treatment with cilta-cel would provide efficacy benefit compared with standard therapy (investigator's choice of PVd or DPd) in participants with relapsed and lenalidomide-refractory multiple myeloma. This sBLA utilizes a clinical cutoff date of 01 November 2022 (corresponding to a median duration of follow-up of 15.9 months) and represents the protocol specified interim analysis of PFS, when approximately 188 PFS events (75% of total planned 250 PFS events) have been accumulated. As of the time of the clinical cutoff, 187 PFS events have occurred.

The Applicant will demonstrate in the sections below that cilta-cel improves outcomes in participants with lenalidomide-refractory multiple myeloma who have relapsed following 1 to 3 prior lines of therapy.

The FDA's Assessment:

FDA generally agrees with the Applicant's analysis of current treatment options for patients with RRMM. The FDA does not agree nor can verify the efficacy information provided in the Applicant's table above, which is based on published literature. FDA refers to the package insert of the approved products for efficacy information in this regard.

Current standard therapy for MM consists of combination regimens that include proteosome inhibitors (PI)s (e.g., bortezomib, ixazomib, and carfilzomib), immunomodulatory (IMiD) agents (e.g.,

thalidomide, lenalidomide, and pomalidomide), and monoclonal antibodies directed against myeloma cell surface antigens (e.g., daratumumab, elotuzumab, and isatuximab). Additional treatment options include the use of autologous hematopoietic stem cell transplantation. Upon disease relapse, considerations impacting the choice of subsequent therapy include whether the patient is on maintenance therapy at the time of relapse and whether their disease is refractory to maintenance therapies such as lenalidomide or bortezomib. Treatment for relapsed disease typically consists of triplet regimens, including at least two active drug classes other than steroids and at least one drug from a class to which the patient has not been exposed.

Patients with Lenalidomide-refractory MM are a population that has the benefit of a variety of contemporary regimens with established benefit. Doublet and triplet regimens containing monoclonal antibodies such as the anti-CD38 monoclonal antibodies daratumumab and isatuximab, combined with a steroid and either an IMiD or a PI, can be highly effective and demonstrate benefit, including increased OS, in randomized controlled studies (Cowan et al. 2022).

3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

The Applicant's Position:

The initial approval for cilta-cel was granted on 28 February 2022 by the US FDA for the treatment of adults with relapsed or refractory multiple myeloma after 4 or more prior lines of therapy, including a PI, an IMiD, and an anti-CD38 monoclonal antibody. Approval was granted on the basis of the Phase 1b/2 Study 68284528MMY2001 (CARTITUDE-1; hereafter referred to as Study MMY2001), conducted in a heavily pretreated patient population (median of 6 lines of prior therapy), which demonstrated an ORR for cilta-cel of 97.9% (95 of 97 participants) in the All Treated analysis set at median duration of follow-up of 18 months (CARVYKTI USPI 2023). The rate of sCR was 78.4% (all CRs were sCRs); the rate of VGPR was 16.5%. At an updated analysis based on median duration of follow-up of 27.7 months (Martin 2023), responses continued to deepen, with an sCR rate of 82.5%; median DOR and median PFS were not reached.

The current submission supports cilta-cel for the treatment of participants with multiple myeloma who have received 1 to 3 prior lines of therapy including a PI and IMiD and who are refractory to lenalidomide.

The FDA's Assessment:
FDA agrees that RRMM after four or more prior lines of therapy, including a PI, an IMiD, and an anti-CD38 monoclonal antibody, is the only approved indication for cilta-cel.

3.2. Summary of Presubmission/Submission Regulatory Activity

The Applicant's Position:

Key FDA interactions and agreements for this sBLA are summarized below in Table 2.

Table 2: Applicant - Cilta-cel Health Authority Interactions

Date	Description
01 February 2019	Orphan Drug Designation granted for the treatment of multiple myeloma (Designation 2018-6721).
11 September 2019	Type B End-of-Phase 2 meeting to obtain the Agency's review and agreement on Phase 3 registration study in participants with multiple myeloma (Study MMY3002).
29 March 2021	Type C Meeting to Discuss the Multiple Myeloma Symptom and Impact Questionnaire (MySIm-Q) Patient-reported Outcome Instrument and the Psychometric Analysis Plan
24 June 2022	Type B Meeting to Discuss the Proposed Format and Content for the Planned Ciltacabtagene Autoleucel Supplemental Biologic License Application.
28 March 2023	Type B pre sBLA meeting to obtain the Agency's review of the topline results from Study MMY3002 and guidance on sBLA submission plans.

The FDA's Assessment:
Development of cilta-cel for treatment of RRMM was conducted under investigational new drug application 18080. A summary of the regulatory actions and key interactions with FDA regarding cilta-cel is provided in Table 1.

Table 1: FDA – Key Regulatory Milestones for Cilta-cel Development, CARTITUDE-4

Date	Purpose and/or Key FDA Comments
Sep 11, 2019	Type B EOP2 meeting to obtain the FDA's agreement on the Phase 3 registration study (CARTITUDE-4).
Mar 29, 2021	At a Type C meeting FDA expressed concerns regarding the clinical importance and relevance of the MySIm-Q PRO content. FDA recommended that the MM manifestations and response to treatment be selected and separately analyzed. Additional clinical expert input should be obtained to confirm clinical relevance and impact of the selected symptoms. FDA also recommended to provide adequate a rationale for why MySImQ is better than other PRO instruments used in MM population.
June 24, 2022	Type B Meeting to discuss the proposed format and content for the planned cilta-cel Supplemental Biologic License Application.
Mar 28, 2023	Type B pre-sBLA meeting to obtain the Agency's review of the topline results from Study CARTITUDE-4 and guidance on sBLA submission plans. FDA reiterated that computerized algorithm remains unvalidated from regulatory perspective and, given the open-label nature of the study, IRC assessment of the primary and secondary endpoints should be conducted and submitted for the initial sBLA. The efficacy analysis for PFS using the standard, "unweighted," stratified log-rank test will be considered as the primary efficacy analysis for regulatory purposes.
Jun 6, 2023	The Sponsor submitted efficacy supplement based on PFS results from the first interim analysis of CARTITUDE-4, with a cutoff date of November 1, 2022.
Aug 5, 2023	A filing notification was sent to the Applicant for a standard review. The filing letter identified the early potential OS detriment observed in the cilta-cel arm compared to the standard therapy arm in CARTITUDE-4 as a potential review issue.
Oct 3, 2023	The Applicant submitted a 120-day Safety Update with a clinical cutoff of April 17, 2023.
Dec 8, 2023	T-con in which FDA communicated its decision to convene an oncology drug advisory committee to obtain committee's input regarding the benefit-risk of cilta-cel for the indicated population given the observed early OS detriment with cilta-cel.
Jan 7, 2024	Applicant submitted an exploratory analysis evaluating the early mortality with cilta-cel.

Source: Modified from Applicant clinical study report page 32 and FDA records
Abbreviations: EOP2, End-of-Phase 2; IRC, independent review committee; OS, overall survival; PFS, progression-free survival; PRO, patient-reported outcome; sBLA, supplemental biologics license application

4 Significant Issues From Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Compliance and Biologics Quality (OCBQ)

Clinical site inspections were conducted for this application. Bioresearch Monitoring (BIMO) inspection assignments were issued for two domestic and two international clinical study sites participating in the conduct of Study CARTITUDE-4. The inspections reports did not identify any concerns.

Table 2: FDA – Sites for BIMO Inspection, CARTITUDE-4

Site ID	Institution	Country	FDA 483 Form Issued
O30-ES10001	HOSP. UNIV. 12 DE OCTUBRE	Spain	No
O30-ES10003	INST. CAT. D'ONCOLOGIA-BADALONA	Spain	No
O30-US10004	The Ohio State University	United States	No
O30-US10028	Medical College of Wisconsin	United States	No

Source: FDA analysis and BIMO's memo dated March 13, 2024
Abbreviation: BIMO, bioresearch monitoring

4.2. Product Quality

Eight patients (SUBJID: (b) (6) received nonconforming products in the cilta-cel arm. These eight patients were excluded from the safety analysis but included in the efficacy analysis (ITT). Refer to the Office of Product Quality review for specific recommendations regarding product quality. The FDA Product Quality review team recommended approval.

4.3. Devices and Companion Diagnostic Issues

No companion diagnostic was requested with this submission.

Refer to Section 8.1.3 Study Results regarding the issues related to the Clonal Seq MRD assay used for response assessment in the study.

4.4. Office of Pharmacovigilance

CARVYKTI has an ongoing postmarketing requirement (PMR) study to monitor for long-term risk of

secondary malignancies. As per the original BLA approval, the PMR study is expected to be completed on June 30, 2041. The important identified risk of hematologic malignancies of T cell and myeloid origin will be monitored through a PMR LTFU registry study (MMY4004) for recipients in the postmarketing setting, and through routine pharmacovigilance activities. The Applicant will include a summary of any interim reports for the PMR LTFU registry study in periodic safety reports. In addition, the Applicant is conducting the following activities: collecting information on cases of second primary malignancies using a topic of interest questionnaire, submitting expedited reports to FAERS for cases of secondary malignancy of T cell origin, and performing interval analysis of all cases of second primary malignancies, including cases of AML, MDS, and T cell malignancies, and cumulative analysis of "biologically relevant" hematological malignancies in periodic safety reports. This safety concern is labeled in the following sections of the USPI:

- Boxed Warning for secondary hematological malignancies, including MDS and AML, and T cell malignancies
- Section 5.10, Warnings and Precautions: Secondary Malignancies
- Section 6.1, Clinical Trials Experience, 6.3 Post Marketing Experience
- Section 17, patient Counseling Information
- Medication guide

5 Summary of Nonclinical Pharmacology/Toxicology Findings

The Applicant's Position:

Nonclinical pharmacology, PK, and toxicology findings were provided in the original cilta-cel BLA 125746.0. Since the original cilta-cel BLA, new tissue expression profile data for BCMA in normal (non-diseased) human brain samples are available and are described below:

A survey of the literature to evaluate the normal tissue expression profile of BCMA demonstrated that expression and distribution of BCMA on normal tissues is well-characterized and shown to be restricted to plasma cells and subsets of mature B cells (Kalled 2005; Laâbi 1992; Laabi 1994; Ng 2004; O'Connor 2004). Further, BCMA expression was not detected in normal (non-diseased) human brain (107 formalin-fixed, paraffin-embedded cerebrum, basal ganglia, cerebellum, brainstem samples; 63 unique donors without known brain disease) by 2 independent immunohistochemistry assays and in situ hybridization (Marella 2022).

The FDA's Assessment:

Please refer to the original BLA application 125746/0 for details. No new PT information was submitted for this efficacy supplement.

6 Clinical Pharmacology

The Applicant's Position:

6.1. Pharmacology and PK Characteristics

Data:

PK

The clinical pharmacology results from Study MMY2001 were provided in the original cilta-cel BLA 125746.0. The primary clinical pharmacology data supporting this supplemental BLA submission comes from Study MMY3002. Additional supporting data are provided from Cohorts A and B of Study 68284528MMY2003 (CARTITUDE-2; hereafter referred to as Study MMY2003).

The conclusions from the clinical pharmacology analyses from Study MMY3002 remained consistent with those in the previous submission (BLA 125746.0). PK measurements using both transgene and cellular levels were concordant and showed similar expansion and persistence profiles. The key PK findings for Study MMY3002 in participants who received cilta-cel as study treatment based on transgene level data are summarized below:

- After a single infusion of a target dose of 0.75×10^6 CAR-positive viable T cells/kg, cilta-cel transgene levels in blood generally became detectable starting between Day 7 and Day 10. In Study MMY3002, the median time to reach peak levels of cilta-cel expansion in peripheral blood was 12.8 days post-infusion. High interindividual variability was observed for the cilta-cel transgene exposure including C_{max} and $AUC_{0\text{-}28d}$ of transgene levels in blood.
- After cell expansion, the persistence phase of the cilta-cel transgene levels was observed. Based on PK data from Study MMY3002, the mean $t_{1/2}$ of cilta-cel was 21.8 days. The median t_{last} for cilta-cel was 83 days (range: 13 to 631 days).

In Study MMY2003, mean $t_{1/2}$ values of cilta-cel transgene levels for Cohorts A and B were 38.3 and 11.0 days, respectively. The t_{last} values were 183 days (range: 21 to 332 days) for Cohort A and 97 days (range: 27 to 331 days) for Cohort B. Interindividual variability was high for each study, with overlapping PK exposure ranges between Cohort A and B.

Impact of Intrinsic and Extrinsic Factors on PK

Intrinsic and extrinsic factors affecting PK were evaluated in Study MMY3002 and Study MMY2003 (Cohorts A and B), using a population-based modeling approach. None of the investigated participant demographics or baseline characteristics had a statistically significant effect on population PK model parameters in the covariate analysis.

No dose adjustment is recommended based on any of these factors.

Age, Sex, Body Weight, Race: The impact of age, sex, body weight, and race on cilta-cel CAR transgene PK parameters was evaluated in a population PK analysis. A covariate search showed no impact on PK parameters. Cilta-cel CAR transgene C_{max} and $AUC_{0\text{-}28d}$ were similar between males and females, across age breakdowns (≥65 versus <65 years), across different body weight groups (ie, <70, 70 to 85, and >85 kg), and across races (non-White versus White and non-Asian versus Asian).

Hepatic and Renal Impairment: No dedicated hepatic or renal impairment studies were performed and no major changes in cilta-cel exposure are anticipated in patients with hepatic or renal insufficiency. Population PK analysis confirmed that cilta-cel CAR transgene C_{max} and $AUC_{0\text{-}28d}$ were similar in participants with mild hepatic dysfunction (defined as total bilirubin ≤ ULN and AST > ULN, or ULN < total bilirubin ≤1.5×ULN) and participants with normal hepatic function, and in participants with mild renal dysfunction (defined as 60 mL/min ≤ CRCL <90 mL/min) or moderate renal dysfunction (defined as 30 mL/min ≤ CRCL <60 mL/min) and participants with normal renal function (CRCL ≥90 mL/min).

Manufactured Product Characteristics: There was no apparent relationship between CAR transgene C_{max} and $AUC_{0\text{-}28d}$ and manufactured product characteristics.

LV Manufacturing Processes: No difference in blood PK results was observed between cilta-cel that was produced using LV manufactured at the (b) (4) facility (hereafter referred to as (b) (4) LV) and LV manufactured at the (b) (4) facility (hereafter referred to as

(b) (4) LV) from Study MMY3002.

Medications Used to Treat CRS and ICANS: No dedicated drug-drug interaction studies were performed for cilta-cel. Cilta-cel is a single dose cell therapy treatment and no interactions with concomitant medications are expected. The impact of concomitant administration of tocilizumab and corticosteroids to mitigate risks of CRS events and ICANS on cilta-cel PK was assessed in the population PK analysis. Median CAR transgene C_{max} and $AUC_{0\text{-}28d}$ were higher among participants who received tocilizumab or corticosteroids for CRS or ICANS management compared with participants who did not receive these medications. For anakinra, due to limited participants receiving this therapy (n=6), the comparison of PK exposure was not explored. However, no conclusion regarding the effect of tocilizumab, corticosteroids, or anakinra on cilta-cel PK can be drawn due to the confounding concurrence of CRS and overlapping exposure range.

Pharmacodynamics

sBCMA in Serum: After a single cilta-cel infusion, sBCMA decreased in all participants, with mean serum concentrations reaching nadir levels around the lower quantifiable concentration value at Day 56. Increases from nadir were seen in some participants, but levels generally remained lower than baseline sBCMA. This reversal of sBCMA levels likely reflect a reproduction of normal BCMA-positive plasma cells.

Cytokine Profiling: Across all participants, levels of IL-6, IL-10, IFN-gamma, and IL-2 receptor alpha increased post-infusion and peaked at Days 7 to 14. The serum levels of all cytokines generally returned to baseline levels within 2 to 3 months post-infusion. A positive association was observed between median C_{max} and $AUC_{0\text{-}56d}$ of IL-6, IL-10, IFN-gamma, and IL-2 receptor alpha with the worst grade of CRS experienced by the participants.

MRD Negativity: At the time of the clinical cutoff (29 August 2022), cilta-cel improved MRD negativity at 10^{-5} sensitivity versus PVd/DPd (60.6% [126 of 208] versus 15.6% [33 of 211]) in the ITT analysis set.

RCL: As of the clinical cutoff (29 August 2022), no positive samples for RCL had been detected in any participants at any of the collection timepoints.

Immunogenicity

The overall ADA incidence was 21.0% in Study MMY3002 in participants who received cilta-cel as study treatment (n=176) as of the immunogenicity data cutoff date of 29 August 2022. To date, there has been no clear association between ADA and cilta-cel exposure and persistence based on current data.

Based on the current data, there was no evidence to suggest an association between ADA and efficacy endpoints (PFS, OS, DOR, ORR, CR/sCR, VGPR or better, and MRD negativity), or safety (CRS, ICANS, other neurotoxicities, and SPM).

Exposure and Dose Relationship with Efficacy and Safety:

The E-R analyses were conducted on efficacy and safety data from the Phase 3 Study MMY3002 in participants who received cilta-cel as study treatment only (n=176).

There were no clear E-R relationships for the examined efficacy endpoints including PFS, OS, DOR, rate of CR/sCR, VGPR or better, ORR, and overall MRD negativity rate with the 2 PK exposure metrics, CAR transgene C_{max} and $AUC_{0\text{-}28d}$.

A trend of higher median cilta-cel CAR transgene systemic levels was observed in participants with CRS or CAR-T neurotoxicity (ICANS or other neurotoxicities). However, given the overlapping CAR transgene levels across AE categories and limited number of participants with ≥Grade 3 CRS (2 participants in Study MMY3002) and ICANS (8 participants in Study MMY3002), this observation needs to be interpreted with caution. In addition, no difference in the CAR transgene systemic exposure was observed between participants without and with SPM.

The Applicant's Position:

Overall, the clinical pharmacology findings support the approved dose of 0.75×10^6 CAR-positive viable T cells/kg (range: 0.5×10^6 to 1.0×10^6 CAR-positive viable T cells/kg) of cilta-cel is highly efficacious and safe, providing therapeutic benefit in patients with multiple myeloma.

The FDA's Assessment:

Following is a summary of CARVYKTI PK/PD data per the Clinical Pharmacology Reviewer: After a single dose intravenous infusion at the target dose of 0.75×10^6 CAR-positive cells/kg, CARVYKTI

exhibited an initial expansion phase followed by a rapid decline and then a slower decline, with both transgene and cellular persistence over months. The median T_{max} of CAR transgene levels in blood was 12.8 days. High inter-subject variability was observed for the CARVYKTI transgene exposure including Cmax and AUC. CD3+CAR+ T cells were also detected in bone marrow on Day 28 post-infusion. No intrinsic and extrinsic factors was found to have clinical meaningful impact on CARVYKTI exposure (Cmax and AUC). No clear exposure-response (E-R) relationships for efficacy were observed. Subjects with cytokine release syndrome (CRS) or immune effector cell-associated neurotoxicity syndrome (ICANS) had higher CAR T cell exposure compared to subjects without CRS or ICANS. However, the exposure range of CARVYKTI in subjects with CRS or ICANS and subjects without CRS or ICANS overlapped. There was no clear evidence that the observed anti-product antibodies impact CARVYKTI kinetics of initial expansion and persistence, efficacy, or safety. No subjects tested positive for replication-competent lentivirus (RCL) testing at the time of data cutoff date.
The proposed dosing regimen of CARVYKTI administered by intravenous (IV) injection has demonstrated clinical efficacy with a tolerable safety profile; therefore, the proposed dosing regimen is acceptable. Refer to the Clinical Pharmacology review memo for more details.

7 Sources of Clinical Data

7.1. Table of Clinical Studies

Data:

The efficacy and safety of cilta-cel in participants with multiple myeloma who have received 1 to 3 prior lines of therapy, including a PI and IMiD, and who are refractory to lenalidomide, is established in Study MMY3002. Supportive efficacy and safety data are provided from Cohorts A and B from Study MMY2003.

Details for these studies are provided in Table 3.

Table 3: Applicant - Listing of Clinical Trials Relevant to this sBLA for Ciltacabtagene Autoleucel

Trial Identity NCT No.	Trial Design	Regimen/ Schedule/ Route	Study Endpoints	Treatment Duration/Follow-up/Cutoff date	No. of Patients Treated	Study Population	No. of Centers and Countries
Open-label Study to Support Efficacy and Safety							
Main Study: MMY3002 NCT04181827	Phase 3, randomized, open-label, multicenter study to compare the efficacy of cilta-cel with standard therapy, investigator's choice of PVd or DPd	Cilta-cel, cyclophosphamide, and fludarabine: IV Pomalidomide: Oral Bortezomib and Daratumumab: SC Dexamethasone: IV or oral **Arm A** For PVd (21-day cycles): Pomalidomide on Days 1 to 14 of each cycle; Bortezomib on Days 1, 4, 8, and 11 (Cycles 1 to 8) and on Days 1 and 8 (Cycle 9 onwards); Dexamethasone on Days 1, 2, 4, 5, 8, 9, 11, and 12 (Cycles 1 to 8) and Days 1, 2, 8, and 9 (Cycle 9 onwards). For DPd (28-day cycles): Daratumumab weekly on Days 1, 8, 15, and 22 (Cycles 1 and 2), every 2 weeks on Days 1 and 15 (Cycles 3 to 6) and every 4 weeks on Day 1 (Cycle 7 onwards); Pomalidomide on Days 1 to 21 of each cycle; Dexamethasone on Days 1, 8, 15,	Primary Endpoint: PFS. Secondary Endpoints: rate of CR/sCR, overall MRD negative rate; rate of MRD negativity in participants with CR/sCR at 12 months ±3 months; rate of sustained MRD negative status; OS; ORR; PFS2; incidence and severity of AEs; PK and pharmacodynamic markers; HRQoL.	Cutoff date of 01 November 2022 Median duration of follow-up: 15.9 months	Planned: Approximately 400 participants randomized 1:1 to Arm A or Arm B: **Arm A:** standard therapy with either PVd or DPd **Arm B:** Cilta-cel As of data cutoff: **Arm A:** n=211 randomized, n=208 treated **Arm B:** n=208 randomized, n=208 received any part of study treatment (176 received cilta-cel as study treatment; 20 progressed prior to cilta-cel	Participants with relapsed and lenalidomide-refractory multiple myeloma: Men or women ≥18 years of age with documented diagnosis of multiple myeloma according to IMWG diagnostic criteria who have received 1 to 3 prior lines of therapy and are refractory to lenalidomide.	81 sites in Europe (Belgium, Denmark, France, Germany, Greece, Italy, Netherlands, Poland, Spain, Sweden, and United Kingdom), North America (US), and other regions (Australia, Israel, Japan, and Republic of Korea)

		and 22 of each cycle (Cycles 1 and 2), weekly (Cycle 3 onwards). **Arm B** At least 1 cycle of bridging therapy with either PVd or DPd, followed by conditioning regimen of cyclophosphamide + fludarabine for 3 days followed by cilta-cel			infusion and received treatment with cilta-cel as subsequent therapy).		

Trial Identity NCT No.	Trial Design	Regimen/ Schedule/ Route	Study Endpoints	Treatment Duration/Follow-up/Cutoff date	No. of Patients Treated	Study Population	No. of Centers and Countries
		administered 5 to 7 days after the start of the conditioning regimen.					
Study to Support Safety and Efficacy							
Cohorts A and B from Study MMY2003 NCT04133636	Phase 2, multicohort, open-label, multicenter study to evaluate the overall MRD negative rate of participants who receive cilta-cel	Cilta-cel, cyclophosphamide, and fludarabine: IV Conditioning regimen consisted of cyclophosphamide + fludarabine in 3 daily doses followed by cilta-cel. Cohorts A and B: Bridging therapy as needed after apheresis and prior to administration of conditioning regimen.	Primary Endpoint: MRD negativity rate.	Cutoff date of 08 October 2021 (Cohort A); 01 June 2022 (Cohort B) Median duration of follow-up: 14.3 months (Cohort A); 18.0 months (Cohort B)	Planned: **Cohort A:** approximately 40 participants **Cohort B:** approximately 20 participants As of cutoff dates: **Cohort A:** n=26 enrolled, n=20 received cilta-cel[a] **Cohort B:** n=21 enrolled, n=19 received cilta-cel.	Men and women ≥18 years of age with documented multiple myeloma according to IMWG diagnostic criteria. Participants were not permitted to have received prior therapies targeted to BCMA. **Cohort A**: 1 to 3 prior lines of therapy including a PI and an IMiD; refractory to lenalidomide. **Cohort B**: 1 prior line of therapy including a PI and an IMiD and early disease relapse (disease progression ≤12 months after ASCT, or after start of front-line therapy without ASCT).	**Cohort A:** Belgium (2) Israel (2) Spain (2) US (5) **Cohort B:** France (1) Netherlands (2) Spain (2) US (5)

[a] Cohort A was originally designed to enroll approximately 20 participants, all of whom would receive cilta-cel manufactured using (b) (4) LV. The protocol was later amended to

increase enrollment to approximately 40 participants to gain experience with cilta-cel manufactured using (b) (4) LV. The results of the primary analysis for the first 26 enrolled participants (Cohort A initial group; clinical cutoff date 08 October 2021) are used as supportive data for this submission.

The FDA's Assessment:
FDA agrees with the Applicant's summary of clinical studies relevant to the sBLA presented in Applicant's Table 3. CARTITUDE-4 data was analyzed in support of efficacy and safety in the indicated population. Data from CARTITUDE-2 was not used to support the efficacy in the indicated population; CARTITUDE-2 data were only supportive of safety.

8 Statistical and Clinical Evaluation

8.1. Review of Relevant Individual Trials Used to Support Efficacy

8.1.1. Pivotal Study MMY3002

The Applicant's Description:

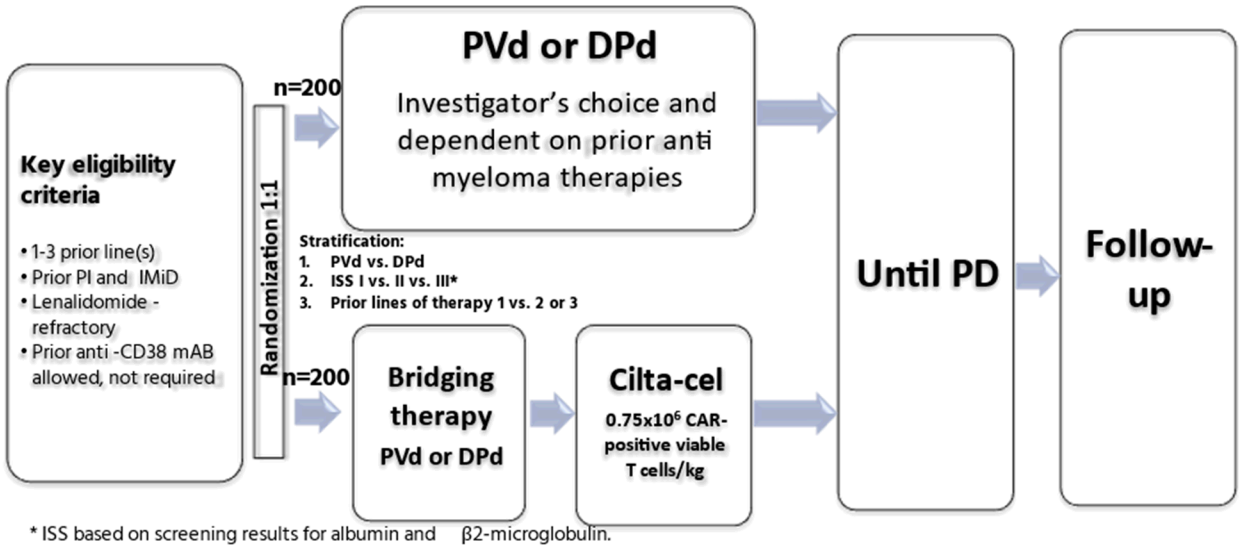
The primary evidence of efficacy and safety for cilta-cel in participants with multiple myeloma who have received 1 to 3 prior lines of therapy including a PI and IMiD and who are refractory to lenalidomide is based on data from Study MMY3002.

Basic Study Design

Study MMY3002 is an ongoing Phase 3, randomized study comparing cilta-cel versus standard therapy (investigator's choice of PVd or DPd) in participants with relapsed and lenalidomide-refractory multiple myeloma.

Approximately 400 participants were planned to be randomized 1:1 to receive either standard therapy (Arm A) or cilta-cel (Arm B). Randomization was stratified by investigator's choice of PVd or DPd, ISS (I versus II versus III), and number of prior lines of therapy (1 versus 2 or 3). The schematic overview of the study flow chart is presented in Figure 1. The primary and secondary objectives and endpoints of Study MMY3002 are presented in Table 4.

Figure 1: Applicant - Schematic Overview of the Study



Source: Study MMY3002 CSR Figure 1 - Schematic Overview of the Study.
Key eligibility criteria: the target study population consisted of adults with multiple myeloma who had received 1 to 3 prior line(s) of therapy, including prior exposure to a PI and an IMiD, and who were refractory to lenalidomide. Prior anti-CD38 monoclonal antibody treatment was permitted.
This was a randomized, active-control study in which participants received treatment with investigator's choice of PVd or DPd (determined prior to screening based on participant's prior exposure to anti-myeloma therapies) or cilta-cel (0.75×106 CAR- positive viable T-cells /kg; subsequent to bridging therapy with PVd or DPd). Approximately 400 participants were to be randomized in a 1:1 ratio to the standard therapy arm (PVd or DPd; Arm A) or the cilta-cel arm (Arm B).
Randomization was stratified by investigator's choice of PVd or DPd, ISS (I vs. II vs. III), and number of prior lines of therapy (1 vs. 2 or 3).
The study was conducted in 3 phases: Screening, Treatment, and Follow-Up. Participants were monitored for efficacy until confirmed progressive disease.

Intervention Groups and Duration

Arm A: Prior to screening, the investigator determined if the participant was to be treated with PVd or DPd, as standard therapy based on the participant's prior exposure to anti-myeloma therapies. Participants in Arm A received standard therapy as outlined in Section 3.4.1 of the CSR for Study MMY3002. Participants started standard therapy within 7 days after randomization.

Participants randomized to Arm A received standard therapy until confirmed progressive disease, death, intolerable toxicity, withdrawal of consent, or end of study. Participants who discontinued standard therapy for any reason, other than progressive disease or withdrawal of consent,

continued to be followed for response assessment until confirmed progressive disease or the start of a subsequent anti-myeloma therapy. After confirmed progressive disease, participants were followed for survival status, subsequent anti-myeloma therapies, and the occurrence of SPM every 16 weeks until the end of the study.

Arm B: Participants randomized to Arm B underwent apheresis to acquire peripheral blood mononuclear cells. Following apheresis, participants received bridging therapy with either PVd or DPd (determined by the investigator prior to screening and based on the participant's prior anti-myeloma therapy). After cilta-cel production and product release, participants received a conditioning regimen of cyclophosphamide and fludarabine, as outlined in Section 3.4.1 of the CSR for Study MMY3002. Cilta-cel was administered 5 to 7 days after the start of the conditioning regimen. Each cilta-cel drug product underwent testing to satisfy a series of pre-specified release criteria before administration to the participant.

Participants had intensive monitoring for safety, PK, biomarkers, and efficacy during the first 112 days after cilta-cel administration (post-infusion follow-up). During the post-treatment follow-up, participants continued to be monitored for efficacy until confirmed progressive disease, death, or withdrawal of consent. After confirmed progressive disease, participants were followed for survival, subsequent anti-myeloma therapies, SPM, and other delayed AEs every 16 weeks until the end of the study. All participants who received cilta-cel will continue to be monitored for long-term safety under a separate study for up to 15 years after cilta-cel administration.

Study Location

The study enrolled from 81 sites across 16 countries in Europe (61.3% of participants), North America (15.3%), and Other regions (Australia, Israel, Japan, and Republic of Korea; 23.4%). Although the incidence of patients of African descent in Western Europe is lower than in the US, the standards of therapy and treatment are very similar between these regions.

Key Inclusion and Exclusion Criteria

The eligibility criteria for the study are appropriate for the population under investigation.

Key inclusion criteria: Participants ≥18 years of age with a documented diagnosis of multiple myeloma according to IMWG diagnostic criteria, with an ECOG Performance Status score of 0 or 1, and:

1. Measurable disease at screening as defined by any of the following: Serum M-protein level ≥0.5 g/dL or urine M-protein level ≥200 mg/24 hours; or light chain multiple myeloma without measurable disease in the serum or the urine: Serum free light chain ≥10 mg/dL and abnormal serum free light chain ratio;
2. Received 1 to 3 prior lines of therapy including a PI and IMiD (participants must have undergone at least one complete cycle of treatment for each line of therapy, unless progressive disease was the best response to the line of therapy);
3. Be refractory to lenalidomide per IMWG consensus guidelines; and
4. Documented evidence of progressive disease by IMWG criteria based on investigator's determination on or within 6 months of their last regimen.

Key exclusion criteria:

Participants with prior treatment with CAR-T therapy directed at any target, any previous therapy that is targeted to BCMA, active malignancies other than the disease being treated under study, antitumor therapies within specific timeframes prior to randomization, and received an allogenic stem cell transplant within 6 months or an ASCT ≤12 weeks before apheresis.

Dose Discontinuation

Specific rules for discontinuation of study treatment are outlined in the study protocol. A participant could not receive cilta-cel if: the investigator believed that for safety reasons or tolerability reasons (eg, AE) it was in the best interest of the participant to discontinue study treatment; the participant received concurrent (non-protocol) anticancer treatment (with exception of bridging therapy); the participant refused further study treatment; noncompliance with study treatment or procedure requirements; the participant became pregnant prior to infusion; and signs of active infection or Grade ≥3 non-hematologic toxicity related to cyclophosphamide and fludarabine occurred and precluded retreatment with cyclophosphamide and fludarabine prior to cilta-cel infusion. Participants who had confirmed progressive disease after bridging therapy were permitted to be infused with cilta-cel if requested by the investigator and discussed with the sponsor.

Administrative Structure

An Independent Data Monitoring Committee, consisting of 2 clinicians and one statistician, was established to review safety data periodically (approximately every 6 months), and review efficacy

and safety results at the planned interim analysis for the primary efficacy endpoint.

Procedures, Schedule and Evaluations

The Time and Events Schedule provided in the study protocol details the planned frequency and timing of screening, safety, efficacy measurements, PK, and biomarker sampling during the conduct of the study.

For both Arm A and Arm B, disease status was evaluated according to the IMWG consensus recommendations for multiple myeloma. MRD was monitored using Next Generation Sequencing on bone marrow aspirate DNA.

The primary endpoint and response-based secondary endpoints were determined using a computerized algorithm that has been used previously in the daratumumab registration studies MMY3003 (POLLUX), MMY3004 (CASTOR), MMY3006 (CASSIOPEIA), MMY3007 (ALCYONE), MMY3008 (MAIA), and MMY3013 (APOLLO). In addition, results from the computerized algorithm were shown to have high concordance with IRC results in CARTITUDE-1.

In addition, for supportive analysis of the primary endpoint and major secondary response-related endpoints, the disease status evaluation for each participant was assessed by an IRC. The IRC was composed of 3 physicians with expertise and clinical experience in the diagnosis and management of multiple myeloma; however, they had no direct involvement in the conduct of the study. The IRC review was conducted in a blinded manner and used the 2016 IMWG consensus criteria in combination with clinical judgment to assess progressive disease and response.

Participants randomized to Arm B had blood and serum samples collected for assessment of cilta-cel PK, immunogenicity, and biomarkers.

Data regarding participants' HRQoL was captured using PRO measures in both treatment arms.

Safety evaluations included a review of AEs, laboratory test results, vital sign measurements, physical examination findings (including neurological examination), assessments of cardiac function and ECOG performance status, and assessments using the Immune Effector Cell-associated Encephalopathy tool (only for Arm B).

Concurrent Medications

Throughout the study, investigators were allowed to prescribe any concomitant medications or treatments deemed necessary to provide adequate supportive care, except for those listed as prohibited therapies. All concomitant medications were recorded during screening. Thereafter, selected concomitant medications were reported. Selected concomitant medications consisted of any medication given for an AE or SAE, therapeutically or prophylactically, as described in the study protocol.

Treatment Compliance

Participants were asked to return containers of pomalidomide and dexamethasone at each study visit and pill counts were used to assess compliance. Bortezomib and daratumumab administration was done in the controlled environment of a qualified clinical site, under the direct observation of qualified study-site personnel. Apheresis, infusion of cyclophosphamide and fludarabine and infusion of cilta-cel were done in the controlled environment of a qualified clinical site, under the direct observation of qualified study-site personnel and the details of administration were recorded in the eCRF.

End of Study Definition

The end of study will occur when approximately 250 deaths have occurred in the study. A participant was considered to have completed the study if he or she had either died before the end of the study, was not lost to follow-up, had not withdrawn consent for study participation or study terminated by sponsor.

The FDA's Assessment:
FDA agrees with the Applicant's description of the study design and the patient population. CARTITUDE-4 was a Phase 3, open-label, randomized, multicenter clinical study evaluating the safety and efficacy of cilta-cel in adult subjects with RRMM who have received at least one to three prior lines of systemic therapy, including a PI and an IMiD, and are lenalidomide refractory.

Treatment: Treatment in CARTITUDE-4 was administered as follows:

- Standard therapy arm: Subjects randomized to the standard therapy arm were administered one of the following two standard therapy regimens chosen prior to randomization: PVd or DPd, as per the investigator's decision based on prior therapies.

Subjects started standard therapy within 7 days after randomization and were treated until confirmed progressive disease, death, intolerable toxicity, withdrawal of consent, or end of study. Subjects who discontinued standard therapy for any reason, other than progressive disease or withdrawal of consent, continued to be followed for response assessment until confirmed progressive disease or the start of a subsequent anti-myeloma therapy.

- Cilta-cel arm: Subjects randomized to cilta-cel B underwent leukapheresis. Following apheresis, participants received bridging therapy while product was manufactured. After cilta-cel production and product release, subjects received a lymphodepletion chemotherapy regimen of fludarabine (30 mg/m^2) and cyclophosphamide (300 mg/m^2) intravenously for three consecutive days. A single infusion of cilta-cel was administered 5 to 7 days after the start of the lymphodepletion at a median dose of 0.7×10^6 cells/kg.

  - Bridging therapy: Included either PVd or DPd at investigator discretion (determined prior randomization) as follows: PVd in 21-day cycles (pomalidomide PO (orally) 4 mg/day, bortezomib subcutaneously 1.3 mg/m^2, dexamethasone PO 20 mg/day) or DPd in 28-day cycles (daratumumab subcutaneously 1,800 mg, pomalidomide PO 4 mg/day, dexamethasone PO, or 40 mg intravenously weekly). Of note, the protocol allowed one cycle of bridging therapy additional cycles could be administered based on patient status and cilta-cel availability. Cycle 2 and following cycles of bridging therapy could be truncated to allow for adequate washout prior lymphodepletion. In CARTITUDE-4 investigator selected the optimal bridging therapy from the protocol-specified regimens based on clinical considerations like the standard therapy arm. The study was not designed to compare the outcome based on each regimen.

- Patients were stratified based on the type of therapies (PVd vs. DPd), ISS score (I vs II or III) and number of previous lines (1 vs, 2 or 3)

Monitoring: For efficacy, subjects were evaluated for disease response by computerized assessment at the times indicated in the schedule of assessments (Appendix 17.3: Table 38, Table 39, and Table 40). Disease response was evaluated using the 2016 IMWG consensus criteria (Kumar 2016). All subjects in the study were also evaluated for disease response by an IRC (central assessment) using the 2016 IMWG 2016.

Subjects underwent safety assessments throughout the conduct of the study, as summarized in the schedule of assessments (Appendix 17.3: Table 38, Table 39, and Table 40). Safety assessments

included monitoring of AEs and concomitant medications, clinical laboratory analyses, vital signs measurements, neurological assessments, electrocardiograms, echocardiograms, physical examinations, and testing for replication-competent retrovirus and antibodies to the anti-CD19 CAR. Details on long-term follow-up assessments are in Appendix 17.3: Table 38, Table 39, and Table 40.

Study Endpoints

The Applicant's Description:

Table 4: Applicant - Primary and Secondary Objectives and Endpoints

Objectives	Endpoints
Primary	
To compare the efficacy of cilta-cel with standard therapy, either PVd or DPd	PFS
Secondary	
To further compare the efficacy of cilta-cel with standard therapy, either PVd or DPd	Rate of CR/sCR; Overall MRD negative rate; Rate of MRD negativity in participants with CR/sCR at 12 months ±3 months; Rate of sustained MRD negative status; OS; ORR; PFS2
To assess the safety profile of cilta-cel	Incidence and severity of AEs
To characterize the PK and pharmacodynamics of cilta-cel	PK and pharmacodynamic markers including but not limited, to systemic cytokine concentrations, and markers of CAR-T cells, T cell expansion (proliferation), and persistence via monitoring CAR-T positive cell counts and CAR transgene level.
To assess the immunogenicity of cilta-cel	Presence of anti-cilta-cel antibodies
To evaluate the impact of cilta-cel treatment on the HRQoL of participants compared with standard therapy, either PVd or DPd	Time to worsening of symptoms using the MySIm-Q total symptom score Change from baseline in HRQoL subscale scores from the EORTC QLQ-C30, MySIm-Q, EQ-5D-5L, PGIS, and the PRO-CTCAE items.

The FDA's Assessment:

FDA agrees with the description of primary and secondary endpoints listed in the Applicant's Table 4. FDA has the following comments:

- For the purpose of regulatory decision-making, Food and Drug Administration/Center for Biologics Evaluation and Research accepted the IRC efficacy assessment using IMWG 2016 consensus criteria.

- MRD evaluated by next-generation sequencing (Adaptive clonoSEQ version 2.0 Assay) was a secondary endpoint for the study. The primary analysis for MRD negative response was based on a threshold of 10^{-5} for those with CR/sCR..

SAP and Amendments

The Applicant's Description:

The detailed planned analyses for Study MMY3002, including definitions of the analysis sets, derived variables, and statistical methods, and determination of sample size, as well as amendment history, are described in the final version of the SAP provided in Appendix 9 of the CSR for Study MMY3002.

SAP Amendments

There were 2 amendments to the initial version of the SAP (dated 28 September 2020), both of which are fully described in the amendment history of the SAP.

Hypothesis

The primary hypothesis of Study MMY3002 was that cilta-cel would significantly improve PFS compared with standard therapy in participants who had previously received 1 to 3 prior lines of therapy, that included a PI and an IMiD, and who were refractory to lenalidomide.

Sample Size Consideration

The sample size calculation was performed based on the assumption that cilta-cel can reduce the risk of progressive disease or death by 35%, ie, HR (cilta-cel versus standard therapy) of 0.65, which translated into a median PFS of 20 months for the cilta-cel arm, assuming the median PFS for the standard therapy arm was 13 months. Approximately 400 (200/treatment arm) participants were to be randomized to observe a total of 250 PFS events to achieve approximately 90% power to detect this HR with a log-rank test (2-sided alpha of 0.05). The sample size calculation took into consideration an estimated annual dropout rate of 5% and one interim analysis for efficacy.

Level of Significance

The primary hypothesis was tested at the 0.05 significance level (overall). The exact significance

level for superiority at the interim analysis of PFS was determined based on the observed number of events using the O'Brien-Fleming boundaries as implemented by the Lan-DeMets alpha spending method. Additional details are provided in the SAP.

Primary Endpoint and Analysis Methods

The primary endpoint, PFS, was defined as the duration from the date of randomization to the date of first documented disease progression, as defined in the IMWG criteria, or death due to any cause, whichever occurred first. For participants who had not progressed and were alive, data were censored at the last DE before the start of any subsequent anti-myeloma therapy.

The primary analysis consisted of a CPW stratified log-rank test for the comparison of the PFS distribution between the 2 treatment arms, where the weight was 0 for the log-rank statistic for the first 8 weeks post-randomization, and 1 afterwards, to account for the delayed effect due to the same bridging therapies. Stratification factors used in the stratified analyses included: investigator's choice of PVd versus DPd, ISS at screening (I versus II versus III), and number of prior lines of therapy (1 versus 2 or 3). The Kaplan-Meier method was used to estimate the distribution of overall PFS for each treatment. The treatment effect in terms of HR and its 2-sided 95% CI were estimated using a stratified Cox regression model, similarly, only PFS events that occurred more than 8 weeks post-randomization were included, with treatment as the sole explanatory variable. The unweighted stratified log-rank test was performed as sensitivity analysis of PFS.

Major Secondary Endpoints and Analysis Methods

Comparison of CR/sCR rate, ORR, and overall MRD negativity rate were conducted using the stratified CMH test. The stratified CMH estimate of odds ratio and its 95% CI and p-value would be reported.

An unweighted stratified log-rank test was used for the comparison of OS distribution between the 2 treatment arms and the Kaplan-Meier method was used to estimate OS distribution for each treatment arm. The treatment effect in terms of HR and its 2-sided 95% CI were estimated using a stratified Cox's regression model with treatment as the sole explanatory variable.

For time to worsening of symptoms in the MySIm-Q total symptom score, analysis methods were similar to those for OS.

Full details of the planned analyses are provided in the SAP.

As requested by the FDA at the 28 March 2023 Type B pre-sBLA meeting, in addition to the pre-specified sensitivity analyses based on investigator assessment, sensitivity analyses of the primary endpoint (PFS) and major secondary response-related efficacy endpoints (ORR, CR or better response) based on the overall IRC assessment were performed. In addition, the PABAK (Byrt 1993) statistics and 95% CI were calculated for agreement between computerized algorithm assessment and IRC assessment for progressive disease (progressive disease versus no progressive disease) and response (PR or better versus no response, CR or better response versus less than CR).

The FDA's Assessment:

The Applicant's description of the statistical analysis plan is acceptable. The FDA has the following comments regarding the statistical analysis plan:

- The FDA does not consider the computer algorithm as validated for regulatory purposes.
- Given the open-label nature of the study, an IRC assessment of the primary and key secondary endpoints was used for regulatory decision making.
- The analysis of primary and key secondary efficacy endpoints per computer algorithm assessment will be considered as a sensitivity analysis only.
- The efficacy analysis for PFS using the standard, "unweighted," stratified log-rank test, which includes all PFS events that have occurred in the study post randomization, will be considered as the primary efficacy analysis for regulatory purposes.
- The PFS analysis based on the stratified constant piecewise-weighted log-rank test, where the weight is 0 for the events that have occurred in the first 8 weeks post randomization and 1 afterwards, will be considered as a sensitivity analysis.
- For the efficacy assessment of the primary and major secondary endpoints, the intercurrent events will be handled as follows: for the intercurrent event of two or more missed consecutive disease assessments, the primary approach should be hypothetical; for one missed disease assessment, the primary approach should be composite strategy.

Protocol Amendments

The Applicant's Description:

There were 4 global amendments to the original protocol dated 25 October 2019, all of which are fully described in the study protocol. The Applicant does not believe that any of the amendments

impacted the integrity of the study or the interpretation of the results.

The FDA's Assessment:
Changes to the original protocol throughout the study are listed in Table 3. FDA agrees that changes to the protocol did not impact the integrity of the results.

Table 3: FDA – Protocol Amendments, CARTITUDE-4

Characteristics	Reason for the Amendment	# of Subjects Enrolled
Amendment #1 Mar 20, 2020	Adding other neurotoxicities as a safety risk and implementing additional monitoring and risk minimization measures for cilta-cel.	375
Amendment #2 Jul 2, 2021	• To provide guidance on study conduct during the COVID-19 pandemic. • To enable increased patient access by allowing patients with a serum+--M-spike of 0.5 g/dL or greater to meet criteria for measurable disease. • To revise safety reporting requirements to allow extended data collection.	24
Amendment #3 Jun 14, 2022	• To inform investigators that subjects receiving cilta-cel are possibly at a higher risk of severe/fatal outcomes from COVID-19 infection compared with subjects who are receiving standard of care therapy, and to provide additional guidance for prevention and mitigation. • To provide additional guidance for HLH.	0
Amendment #4 Aug 18, 2022	Increasing the required number of PFS events to trigger the interim analysis to 75% of the total PFS events observed.	0

Source: Modified from Applicant's clinical study report Table 1 page 41
Abbreviations: COVID-19, Coronavirus Disease 2019; HLH, hemophagocytic lymphohistiocytosis; PFS, progression-free survival

8.1.2. Supportive Study MMY2003 (Cohorts A and B)

Study MMY2003 is a Phase 2, multicohort, open-label, single-arm multicenter study to determine the safety and efficacy of cilta-cel (alone or with other treatment regimens) in adult participants with multiple myeloma in various clinical settings (Table 3). The cohorts included identical (Cohort A) or closely related (Cohort B) study populations, treatment regimens, and safety data collection methods as used in pivotal Study MMY3002.

8.1.3. Study MMY3002 Results

Compliance with GCP

Data:

This study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with GCP and applicable regulatory requirements. The study protocol and amendments were reviewed by an Independent Ethics Committee or Institutional Review Board. Participants or their legally acceptable representatives provided their written consent to participate in the study after having been informed about the nature and purpose of the study, participation/termination conditions, and risks and benefits of treatment.

The Applicant's Position:

This study was conducted in accordance with the CFR governing the protection of human participants (21 CFR part 50), Institutional Review Boards (21 CFR part 56), and the obligation of clinical investigators to GCP (21 CFR 312.50 to 312.70).

The FDA's Assessment:

The submission was adequately organized and integrated to accommodate the conduct of a complete clinical review without unreasonable difficulty.

Financial Disclosure

Data:

All the principal investigators and subinvestigators participating in Study MMY3002 were assessed for financial disclosures as defined in 21 CFR part 54, and 2 investigators had disclosable financial interests. Further details of financial disclosure are provided in Section 17.2.

The Applicant's Position:

The Applicant has adequately assessed clinical investigators for any financial interest/arrangements. A Form FDA 3455 is included in the sBLA submission for the investigators disclosing significant payments and includes steps taken to minimize potential bias. Further details are provided in Section 17.2.

The FDA's Assessment:
Two U.S. investigators disclosed significant payments for consulting honoraria exceeding $25,000 US dollars, which were unrelated to the conduct of the study and investigational product.

Both participated as sub-investigators at site US10028, Medical College of Wisconsin. This site enrolled 27 out of 419 total enrolled subjects across 81 sites globally. One of the sub-investigators had one subject under her care on Arm A (Subject (b) (6) who withdrew from treatment in March 2021. The second sub-investigator had 10 enrolled patients under his care who consented between October 10, 2020, and September 13, 2021. The sub-investigator resigned from Medical College of Wisconsin in 2021.The FDA agrees with the Applicnat that there was no evidence of bias in the results.

Patient Disposition

Data:

The ITT analysis set consisted of the 419 participants randomized: 211 participants to Arm A (standard therapy) and 208 participants to Arm B (cilta-cel). Of these, 416 participants received any part of study treatment and comprised the safety analysis set (Arm A: 208 participants; Arm B: 208 participants). Three participants were randomized to Arm A but not treated. Further details are provided in Section 4.1 of the CSR for Study MMY3002.

Of the 208 participants treated in Arm A, 48 participants discontinued from the study; of these, 5 participants died while receiving study treatment, 41 participants died during the survival follow-up, and 2 participants withdrew consent from further study treatment and from survival follow-up. As of the 01 November 2022 clinical cutoff date, 160 participants were still on study, with 77 participants ongoing on study treatment, 82 participants ongoing in survival follow-up, and one participant ongoing in the pre-progressive disease post-treatment follow-up.

Of the 208 participants treated in Arm B, 39 participants discontinued from the study, all due to death, including:

- 11 participants who died without receiving cilta-cel, of whom 2 participants died during study treatment prior to cilta-cel infusion and 9 participants progressed prior to cilta-cel infusion and died during survival follow-up
- 16 participants who died during the post-infusion/post-treatment phase, following cilta-cel infusion as study treatment

- 2 participants who died during survival follow-up, after starting subsequent therapy
- 10 participants who received cilta-cel as subsequent therapy and died during survival follow up

As of the clinical cutoff, 169 participants were still on study, with 143 participants ongoing in post-treatment follow-up and 26 participants ongoing in survival follow up.

In Arm A, most participants (127) remained on study treatment until at least Cycle 9. Thirteen participants (6.3%) discontinued in Cycles 1 to 2 and 58 participants (29.7%) discontinued in Cycles 3 to 6.

In Arm B, there were no study treatment discontinuations after apheresis and prior to the start of bridging therapy. A total of 32 participants discontinued study treatment in Arm B, with 30 participants (14.4%) discontinuing on or after bridging therapy and prior to the start of the conditioning regimen, most commonly due to progressive disease (28 participants [13.5%]). Two participants discontinued study treatment prior to cilta-cel infusion due to death (one due to an AE and one due to progressive disease). Two participants (1.0%) discontinued on or after the conditioning regimen and prior to the start of cilta-cel, both due to progressive disease.

One hundred seventy-six (176) participants received cilta-cel as study treatment, without progression prior to receiving cilta-cel. Of the 32 participants who discontinued study treatment prior to receiving cilta-cel (all of whom discontinued due to a PFS event), 20 participants received cilta-cel administered as subsequent anti-myeloma therapy.

The Applicant's Position:

The efficacy analysis set (ITT; all participants who were randomized in the study) forms the basis of the sBLA review concerning the benefit of cilta-cel in the intended population of adult participants with relapsed or refractory multiple myeloma who have received 1 to 3 prior lines of therapy, including a PI and an IMiD, and who are refractory to lenalidomide. These results are presented in this document, the proposed USPI, the CSR for Study MMY3002, Summary of Clinical Efficacy, and Clinical Overview. Cilta-cel specific efficacy and safety data are also presented for the participants who received cilta-cel as study treatment (n=176), in order to inform on the efficacy and safety of cilta-cel in this subgroup of the ITT. In addition, as noted above, 20 participants received cilta-cel as subsequent therapy, after progression on bridging therapy.

The FDA's Assessment:

At the cutoff date of November 1, 2022, a total of 419 subjects were randomized, 208 in the cilta-cel arm and 211 in the standard therapy arm. Thirty-two subjects randomized to the cilta-cel arm (15% of the total number randomized to cilta-cel) had discontinued the study treatment, and 51 subjects randomized to the standard therapy arm (24% of the subjects randomized to standard therapy) had discontinued in the arm. There were 39 (19%) deaths in the cilta-cel arm and 47 (22%) deaths in the standard therapy arm. Three subjects, all of whom had been randomized to the standard of care arm, were not treated (0.7% of all subjects randomized to both arms combined). Table 4 shows reasons for treatment and study discontinuation in the ITT population.

Table 4: FDA – Reasons for Treatment and Study Discontinuation, ITT Population, CARTITUDE-4

Reasons for Discontinuation	Cilta-cel N=208 n (%)	Standard Therapy N=211 n (%)	Total N=419 n (%)
Treatment discontinuation	32 (15) ^	131 (63)	163 (39)
Adverse event	0	3 (1.4)	3 (0.7)
Death	2 (1)	5 (2.4)	7 (1.7)
Progressive disease	30 (14)	117 (56)	147 (35)
Physician decision	0	1 (0.5)	1(0.2)
Withdrawal by patient	0	5 (2.4)	5 (1.2)
Study discontinuation	39 (19)	51 (24)	90 (22)
Death	39 (19)	47 (22)	86 (21)
Withdrawal by subject	0	4 (2)	4 (1)

Source: FDA analysis, data cutoff date November 1, 2022

^ Twenty subjects received cilta-cel after disease progression as subsequent therapy and 12 subjects did not receive cilta-cel.

Abbreviations: n (%), number of subjects with the specified characteristic; N, number of subjects in the specified group, or the total sample

Protocol Violations/Deviations

Data:

Major protocol deviations were those that had the potential to impact participants' rights, safety, or well-being, or the integrity and/or result of the clinical study and included the following: entered but did not satisfy eligibility criteria; received a disallowed concomitant treatment; and received wrong treatment or incorrect dose; and other. As of the database lock for the CSR for Study MMY3002, major protocol deviations were reported for 8 participants (3.8%) in Arm A and 12 participants (5.8%) in Arm B (Table 5). As described in Section 12 of the CSR for Study MMY3002, retrospective evaluation following database lock revealed that 2 additional participants in Arm A had major protocol deviations.

Table 5: Applicant - Summary of Participants With Major Protocol Deviations; Intent-to- Treat Analysis Set (Study 68284528MMY3002)

	Arm A	Arm B	Total
Analysis set: intent-to-treat	211	208	419
Participants with major protocol deviation	8 (3.8%)	12 (5.8%)	20 (4.8%)
Type of major protocol deviation			
Entered but did not satisfy criteria	1 (0.5%)	0	1 (0.2%)
Received a disallowed concomitant treatment	1 (0.5%)	1 (0.5%)	2 (0.5%)
Received wrong treatment or incorrect dose	4 (1.9%)	5 (2.4%)	9 (2.1%)
Other	2 (0.9%)	7 (3.4%)	9 (2.1%)

	Arm A	Arm B	Total

Key: Arm A = PVd or DPd; Arm B = A sequence of apheresis, bridging therapy (PVd or DPd), conditioning regimen (cyclophosphamide and fludarabine), and Cilta-cel infusion.
Key: PVd = pomalidomide-bortezomib-dexamethasone; DPd = daratumumab-pomalidomide-dexamethasone.
Note: Percentages calculated with the number of participants in each treatment group as denominator.
Note: Intent-to-treat analysis set consists of participants who were randomized in the study.

Modified from [TSIDEV01.RTF] [PROD/JNJ-68284528/MMY3002/DBR_CSR/RE_CSR/TSIDEV01.SAS] 03FEB2023, 17:38

The Applicant's Position:

The major protocol deviations identified in the ITT analysis set were typical of those observed in randomized Phase 3 clinical studies and did not lead to the exclusion of data from the analyses or impact the interpretation of the results.

The FDA's Assessment:

Based on the efficacy cutoff date of November 1, 2022, there were 12 subjects (6%) in the cilta-cel arm and 10 (5 %) in the standard therapy arm with major protocol deviations as stated before. FDA agrees with the Applicant's position that these protocol deviations did not impact the interpretation of results.

Table of Demographic Characteristics

Data:

A summary of demographic characteristics for the ITT analysis set is presented in Table 6. The median age of participants was 61.0 years for Arm A and 61.5 years for Arm B, with only small numbers of participants aged >75 years (1.9% in both arms). In both arms, there was a higher proportion of male participants (Arm A: 58.8%; Arm B: 55.8%). Approximately 75% of participants in both arms were White (Arm A: 74.4%; Arm B: 75.5%). Overall, 8.6% of participants were Asian (Arm A: 9.5%; Arm B: 7.7%), 3.1% were Black or African American (Arm A: 3.3%; Arm B: 2.9%), and 0.5% were American Indian or Alaska Native (Arm A: 0.5%; Arm B: 0.5%).

Among the 64 participants enrolled in the US, 9 participants (14.1%; 5 participants in Arm A and 4 participants in Arm B) were Black or African American.

Table 6: Applicant - Summary of Demographic Characteristics; Intent-to-Treat Analysis Set (Study 68284528MMY3002)

	Arm A	Arm B	Total
Analysis set: intent-to-treat	211	208	419
Age, years			
Category, n (%)			
< 65	131 (62.1%)	126 (60.6%)	257 (61.3%)
65 - 75	76 (36.0%)	78 (37.5%)	154 (36.8%)

Table 6: Applicant – Summary of Demographic Characteristics; Intent-to-Treat Analysis Set (Study 68284528MMY3002)

	Arm A	Arm B	Total
> 75	4 (1.9%)	4 (1.9%)	8 (1.9%)
Mean (SD)	60.4 (9.09)	59.7 (10.09)	60.1 (9.60)
Median	61.0	61.5	61.0
Range	(35; 80)	(27; 78)	(27; 80)
Sex			
Female	87 (41.2%)	92 (44.2%)	179 (42.7%)
Male	124 (58.8%)	116 (55.8%)	240 (57.3%)
Race			
American Indian or Alaska Native	1 (0.5%)	1 (0.5%)	2 (0.5%)
Asian	20 (9.5%)	16 (7.7%)	36 (8.6%)
Black or African American	7 (3.3%)	6 (2.9%)	13 (3.1%)
White	157 (74.4%)	157 (75.5%)	314 (74.9%)
Not reported	26 (12.3%)	28 (13.5%)	54 (12.9%)
Ethnicity			
Hispanic or Latino	10 (4.7%)	18 (8.7%)	28 (6.7%)
Not Hispanic or Latino	165 (78.2%)	152 (73.1%)	317 (75.7%)
Not reported	36 (17.1%)	38 (18.3%)	74 (17.7%)

Key: Arm A = PVd or DPd; Arm B = A sequence of apheresis, bridging therapy (PVd or DPd), conditioning regimen (cyclophosphamide and fludarabine), and cilta-cel infusion.
Key: PVd = pomalidomide-bortezomib-dexamethasone; DPd = daratumumab-pomalidomide-dexamethasone.
Key: ECOG=Eastern Cooperative Oncology Group
[a] The latest non-missing ECOG score on or prior to Apheresis/Cycle 1 Day 1 (C1D1) is used. All patients met the inclusion criteria of ECOG score of 0 or 1 prior to randomization.
Note: Intent-to-treat analysis set consists of subjects who were randomized in the study.

Modified from [TSIDEM01.RTF] [PROD/JNJ-68284528/MMY3002/DBR_CSR/RE_CSR/TSIDEM01.SAS] 24FEB2023, 11:43

The Applicant's Position:

Participants in this study are representative of the intended population of patients with relapsed and lenalidomide-refractory multiple myeloma. The demographic groups in whom cilta-cel is to be used are adequately represented and evaluated in the study.

The FDA's Assessment:

Demographic data for CARTITUDE-4 are summarized in Table 5. The median age of the study population was 61 years, which is younger than the median age of 69 years at diagnosis in the United States. Only two percent of the study population was 75 years or older compared to the prevalence of multiple myeloma in 75 years and older population in the US (35%) (Palumbo et al, 2011). Racial and ethnic minorities (3% Black, 7% Hispanic or Latino) were underrepresented in the study. Only 15% of the of subjects were enrolled from the United States.

Table 5: FDA – Demographic Characteristics, ITT Population, CARTITUDE-4

Characteristic	Cilta-cel N=208 n (%)	Standard Therapy N=211 n (%)	Total N=419 n (%)
Age (years)	-	-	-
Median (range)	61.5 (27-78)	61(35-80)	61 (27-80)
<65	126 (61)	131 (62)	257 (61)
65-75	78 (37.5)	76 (36)	154 (37)
>75	4 (1.9)	4 (1.9)	8 (1.9)
Sex	-	-	-
Male	116 (56)	124 (59)	240 (57)
Female	92 (44)	87 (41)	179 (43)
Race	-	-	-
Asian	16 (8)	20 (10)	36 (9)
Black	6 (3)	7 (3)	13 (3)
White	157 (76)	157 (74)	314 (75)
Other	1 (0.5)	1 (0.5)	2 (0.50)
Not reported	28 (14)	26 (12)	54 (13)
Hispanic or Latino ethnic group	-	-	-
Yes	18 (9)	10 (5)	28 (7)
No	152 (73)	165 (78)	317(76)
Not reported	38 (18)	36 (17)	80(19)
Geographic region	-	-	-
Europe	128 (61.5)	129 (61)	257(61)
United States	32 (15.4)	32 (15)	64(15)
Asia	27 (13)	25 (12)	529(12)
Australia	21 (10)	25 (12)	46(11)

Source: FDA analysis
Abbreviations: n (%), number of subjects with the specified characteristic; N, number of subjects in the specified group, or the total sample

Other Baseline Characteristics (eg, Disease Characteristics, Important Concomitant Drugs)

Data:

Disease Characteristics

All 419 participants (100.0%) in the ITT analysis set had detectable disease. All but 2 participants (0.5%; both in Arm B) had measurable disease at baseline. The 2 participants who did not have measurable disease at baseline had measurable disease at screening and were therefore eligible to be enrolled in the study. A majority of participants in both arms had a baseline ECOG score of 0 (Arm A: 57.3%; Arm B: 54.8%). IgG was the most common Ig isotype, reported for 51.2% of participants in Arm A and 54.3% of participants in Arm B. The median time from multiple myeloma diagnosis to randomization was 3.4 years for Arm A and 3.0 years for Arm B.

Of the participants with baseline cytogenetic data reported, 62.9% of participants in Arm A and 59.4% of participants in Arm B had at least one high-risk abnormality, most commonly gain/amp(1q) (51.0% and 43.0%, respectively). The presence of soft-tissue plasmacytomas was noted for 16.6% of participants in Arm A and 21.2% of participants in Arm B; the sponsor considered both bone-based soft tissue plasmacytoma and extramedullary plasmacytomas under the inclusive term 'soft-tissue plasmacytomas'.

General Medical History

Most participants (Arm A: 97.2%; Arm B: 97.1%) had at least one comorbidity reported in their medical history, with hypertension, anemia, back pain, insomnia, and bone pain the most commonly reported PTs. One hundred two participants (48.3%) in Arm A and 118 participants (56.7%) in Arm B had one or more PT associated with neurologic disorders reported in their medical history.

Prior Therapies

Per protocol, all participants (100.0%) received 1 to 3 prior lines of multiple myeloma therapy, prior PI, and prior IMiD therapy. In both treatment arms, participants received a median of 2 prior lines of therapy, with approximately one-third of participants receiving one prior line and two-thirds receiving 2 or 3 prior lines. A total of 26.1% of participants in Arm A and 25.5% of participants in Arm B were triple-class exposed (PI, IMiD, and anti-CD38 monoclonal antibody), with 4.7% of participants in Arm A and 6.7% of participants in Arm B penta-exposed (at least 2

PIs, at least 2 IMiDs, and at least one anti-CD38 antibody). A total of 87.7% of participants in Arm A and 82.2% of participants in Arm B received one or more prior ASCT. Few participants received prior allogeneic transplantation (Arm A: 0.5%; Arm B 1.4%).

Most participants (98.6% in each treatment arm) were refractory to their last line of prior therapy. Consistent with study entry criteria, 100.0% of participants in both arms were refractory to lenalidomide. Almost half the participants in both arms were refractory to any PI (Arm A: 45.5%; Arm B: 49.5%). Refractoriness to any anti-CD38 antibody was reported for 21.8% of participants in Arm A and 24.0% of participants in Arm B.

Notably, prior daratumumab use (25.6% and 24.5% in Arms A and B, respectively) was comparable to US real world exposure data around the time of study initiation (4.2% to 13.6% and 24.2% to 36.4% for first- and second-line use of daratumumab-containing regimens, respectively, in 2019 [data on file]. Additional analysis of US real world data from the Flatiron Health Core Registry for multiple myeloma patients (N=15,002 with line of therapy data available) was conducted to assess daratumumab exposure in a cohort of patients meeting key eligibility criteria of Study MMY3002 during the time period corresponding to enrollment in Study MMY3002 (2020 to 2021). Among the 1,496 patients who were lenalidomide refractory, exposed to a PI, with a line of therapy following eligibility, 328 patients met the key eligibility criteria during this time period. In this cohort, prior daratumumab exposure in patients who were first eligible after 1, 2, or 3 prior lines of therapy was 6.3%, 17%, and 17%, respectively [data on file].

The Applicant's Position:

Baseline disease characteristics of the ITT analysis set were representative of the intended US patient population studied to evaluate the unmet needs and treatment patterns for relapsed and lenalidomide-refractory multiple myeloma. Thus, the clinical activity seen for cilta-cel in Study MMY3002 is believed to be generalizable to the relapsed and lenalidomide-refractory multiple myeloma patient population that will be encountered in clinical practice.

The FDA's Assessment:

The key baseline characteristics of subjects enrolled in Study CARTITUDE-4 are shown in Table 6. The majority of subjects enrolled had an Eastern Cooperative Oncology Group Performance status of 0 or 1. Adverse prognostic features such as high-risk cytogenetics, presence of extramedullary plasmacytoma, International Staging System Stage III, and high tumor burden were balanced

across the two arms. The FDA notes that there is no accepted cut-off criteria for high or low tumor burden. Of the 394 subjects for whom baseline cytogenetic data were available, high-risk cytogenetics (presence of t(4:14), t(14:16), or 17p13 del) were present in 34% of subjects. Nineteen percent of the subjects had extramedullary disease.

Table 6: FDA – Baseline Disease Characteristics, ITT Population, CARTITUDE-4

Characteristics	Cilta-cel N=208	Standard Therapy N=211	All N=419
ECOG performance status score %	-	-	-
0/1/2	55/44/1	57/42/1	56/43/1
International Staging System stage %	-	-	-
I/II/III	65/30/6	63/30/7	64/30/6
Time since diagnosis (years)	-	-	-
Median (range)	3.0 (0.3-18)	3.4 (0.4-22)	3.2 (0.3-22)
Extramedullary disease n (%)	-	-	-
Yes	44 (21)	35 (17)	79 (19)
No	164 (79)	176 (83)	340 (81)
Bone marrow plasma cells n (%)	-	-	-
N	206	208	414
≤30	133 (65)	121 (58)	254 (61)
>30-<60	31 (15)	44 (21)	75 (18)
≥60%	42 (20)	43/208 (21)	85 (20)
Cytogenetic risk n (%)	-	-	-
N	207	210	417
Standard	111 (54)	122 (58)	233 (55.8)
High (excluding gain/amp (1q)	73 (35)	69 (33)	142 (34)
del(17p)	49 (24)	43 (21)	92 (22)
t(4;14)	30 (15)	30 (14)	60 (14)
t(14;16)	3 (2)	7 (3)	10 (2)
Missing data	15/207 (7)	8/210 (4)	23 (5)

Source: FDA analysis
Abbreviations: ECOG, Eastern Cooperative Oncology Group; ITT, intent-to-treat; n (%), number of subjects with the specified characteristic; N, number of subjects in the specified group, or the total sample

Prior therapies for subjects on the CARTITUDE-4 study are summarized in Table 7. The majority of the subjects had an autologous stem cell transplant and received one or two prior lines of therapies. Only 50% of subjects had received a prior PI, and 15% of the subjects were triple-class refractory. None of the subjects received four or more lines of therapy, the population currently approved to receive cilta-cel.

Table 7: FDA – Prior Therapies, ITT Population, CARTITUDE-4

Characteristic	Cilta-cel N=208 n (%)	Standard Therapy N=211 n (%)	Total N=419 n (%)
Prior lines of therapy	-	-	-
1	68 (33)	68 (32)	136 (32)
2	83 (40)	87 (41)	170 (41)
3	57 (27)	56 (27)	113 (27)
Prior autologous transplant*	-	-	-
Yes	171 (82)	185 (88)	356 (85)
No	37 (18)	26 (16)	63 (15)
Refractory status-	-	-	-
Lenalidomide	208 (100)	211 (100)	419 (100)
Any IMiD	208 (100)	211 (100)	419 (100)
Any PI	103 (50)	96 (45)	199 (47)
Any anti-CD38 antibody	50 (24)	46 (22)	96 (23)
Triple-class	30 (14)	33 (16)	63 (15)
Penta-refractory	2 (1)	1 (0.5)	3 (1)

Source: FDA analysis
* Four subjects in the study (three subjects in cilta-cel arm) had prior allogeneic transplant.
Abbreviations: IMiD, immunomodulatory drug; ITT, intent-to-treat; n (%), number of subjects with the specified characteristic; N, number of subjects in the specified group, or the total sample; PI, proteasome inhibitor

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Data:

Treatment Compliance

Administration of bortezomib and daratumumab and apheresis, infusion of cyclophosphamide and fludarabine, and infusion of cilta-cel were performed in the controlled environment of a qualified clinical site, under the direct observation of qualified study-site personnel. Details of administration were recorded in the eCRF.

In Arm A, the median relative dose intensity (ratio of total dose actually received to total dose planned) was 91.7% for bortezomib, 77.6% for pomalidomide, 82.3% for dexamethasone, and 95.7% overall for daratumumab (87.5% in Cycles 1 to 2, 100.0% in Cycles 3 to 6 and Cycles 7+).

In Arm B, the median relative dose intensity was 87.5% for bortezomib, 85.7% for pomalidomide, 87.5% for dexamethasone, and 83.3% for daratumumab.

Exposure data for participants in Arm A and Arm B are provided in Section 8.2.2, Overall Exposure.

Concomitant Medications

All participants in both arms received concomitant medications during treatment (defined as either ongoing before first dose of study treatment or started during treatment). A summary of concomitant medication usage, including concomitant medications administered for specific situations is provided in Section 4.5.2 of the CSR for Study MMY3002.

The Applicant's Position:

The study treatment administered was in compliance with the study protocol and the concomitant medications administered were similar to those administered in other myeloma CAR-T studies.

The FDA's Assessment:
FDA agrees with the Applicant's assessment. The FDA has the following comment regarding bridging therapies.

In the cilta-cel arm (n=208), 100% of the subjects in the ITT population started at least one cycle of bridging therapy during cilta-cel manufacture. The median time from randomization to initiation of bridging therapy was 7 days (range 2-19 days). The most common bridging used was DPd (87.5 %) followed by PVd (12.5 %). The median number of bridging cycles started was 2.0 (range: 1 to 6 cycles); 162 subjects (77.9%) started at least 2 cycles of bridging therapy. Most of the subjects (59%) received two cycles of bridging; 22% received one cycle, 16% received three cycles, and 2.5% received four cycles.

No substantial difference between the two arms on the time to start of study treatment in the standard therapy or to start bridging therapy in the cilta-cel arm was observed.

The median relative dose intensity was lower for bortezomib and for daratumumab (88% and 83% respectively) in the cilta-cel compared to bortezomib and daratumumab (92% and 96% respectively) in the standard therapy. This might be related to the truncation of cycle 2+ to allow for adequate washout period for the LD in the cilta-cel arm.

Efficacy Results – Primary Endpoint (Including Sensitivity Analyses)

Data:

As discussed in the SAP, because both treatment arms were expected to receive the same therapy for approximately 2 cycles (approximately 8 weeks) after randomization per the study design, no separation of the Kaplan-Meier curves was expected initially. Given that a regular log-rank test would generally lead to a loss of power in such scenario of non-proportional hazards, the primary analysis of the PFS endpoint utilized a CPW log-rank test, where the weight was 0 for the first 8 weeks post-randomization, and 1 afterwards.

At a median follow-up of 15.9 months, a PFS event was reported for 57.8% of participants in Arm A and for 31.3% of participants in Arm B; median PFS was 11.8 months (95% CI: 9.7, 13.8) for Arm A and NE (95% CI: 22.8, NE) for Arm B (Table 7). The HR of 0.26 (95% CI: 0.18, 0.38; p<0.0001) indicates a 74% reduction in the risk of death or progression for Arm B as compared with Arm A. The 12-month PFS rates were 48.6% for Arm A and 75.9% for Arm B.

Table 7: Applicant – Summary of Progression-free Survival Based on Computerized Algorithm by Constant Piecewise Weighted (CPW) Log-rank Test; Intent-to-treat Analysis Set (Study 68284528MMY3002)

	Arm A	Arm B
Analysis set: intent-to-treat	211	208
Progression-free survival (PFS)		
Number of events (%)	122 (57.8%)	65 (31.3%)
Number of censored (%)	89 (42.2%)	143 (68.8%)
Kaplan-Meier estimate (months)		
25% quantile (95% CI)	4.11 (3.38, 5.32)	12.91 (7.29, 17.97)
Median (95% CI)	11.79 (9.66, 13.77)	NE (22.83, NE)
75% quantile (95% CI)	20.96 (20.63, NE)	NE (NE, NE)
P-value[a]		<0.0001
Hazard ratio (95% CI)b		0.26 (0.18, 0.38)
6-month PFS rate % (95% CI)	66.5 (59.5, 72.5)	82.7 (76.8, 87.2)
12-month PFS rate % (95% CI)	48.6 (41.5, 55.3)	75.9 (69.4, 81.1)
18-month PFS rate % (95% CI)	35.7 (28.0, 43.4)	67.8 (60.0, 74.5)
24-month PFS rate % (95% CI)	18.7 (6.8, 35.2)	56.4 (43.7, 67.3)

Table 7: Applicant - Summary of Progression-free Survival Based on Computerized Algorithm by Constant Piecewise Weighted (CPW) Log-rank Test; Intent-to-treat Analysis Set (Study 68284528MMY3002)

	Arm A	Arm B

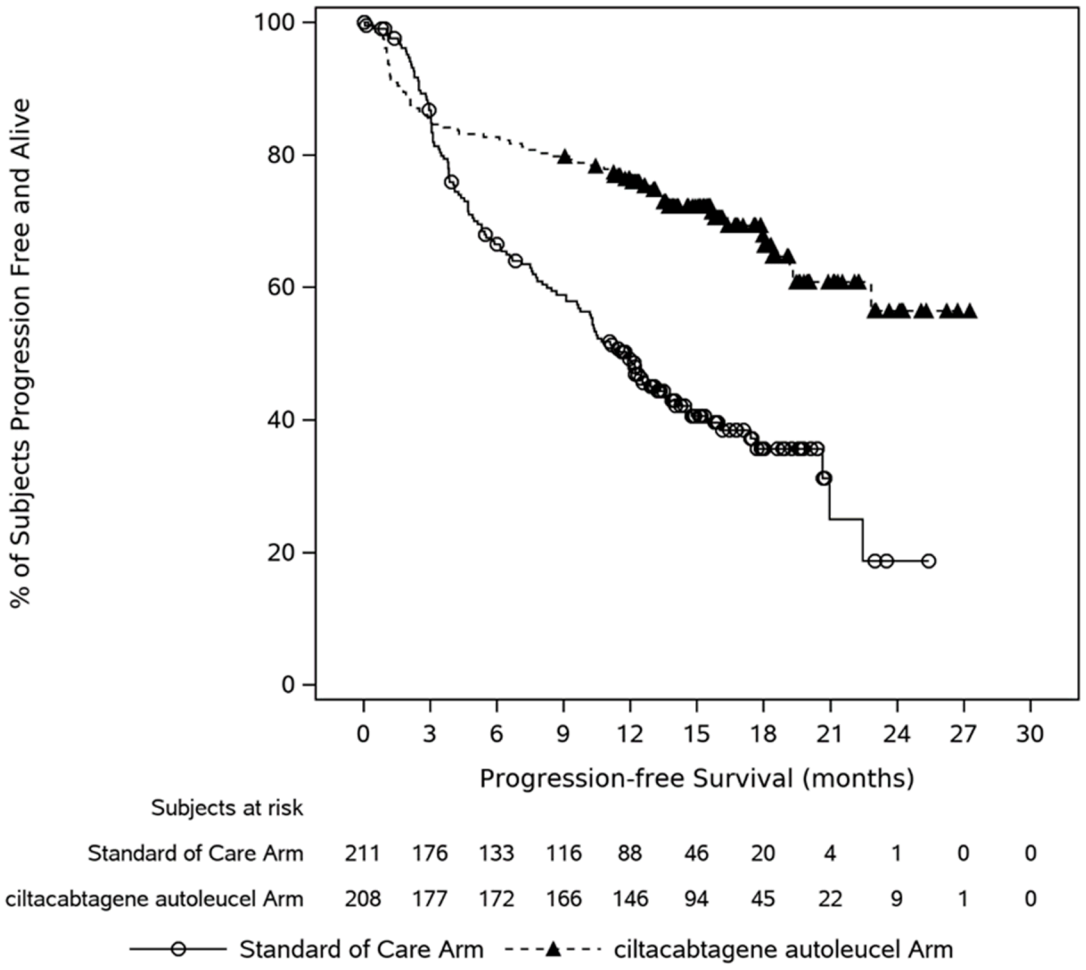
Key: Arm A = PVd or DPd; Arm B = A sequence of apheresis, bridging therapy (PVd or DPd), conditioning regimen (cyclophosphamide and fludarabine), and cilta-cel infusion.
Key: PVd = pomalidomide-bortezomib-dexamethasone; DPd = daratumumab-pomalidomide-dexamethasone.
Key: CI = confidence interval; CPW=constant piecewise weighted.
[A] p-value is based on the CPW log-rank test (weight=0 in the log-rank statistic for the first 8 weeks post-randomization, and 1 afterwards) stratified with investigator's choice (PVd or DPd), ISS staging (I, II, III) and number of prior lines (1 vs. 2 or 3) as randomized.
[B] Hazard ratio and 95% CI from a Cox proportional hazards model with treatment as the sole explanatory variable and stratified with investigator's choice (PVd or DPd), ISS staging (I, II, III) and number of prior lines (1 vs. 2 or 3) as randomized, including only PFS events that occurred more than 8 weeks post-randomization. A hazard ratio <1 indicates an advantage for Arm B.
Note: Intent-to-treat analysis set consists of subjects who were randomized in the study.
Modified from [TEFPFS01_CPW.RTF] [PROD/JNJ-68284528/MMY3002/DBR_CSR/RE_CSR/TEFPFS01_CPW.SAS] 13FEB2023, 18:18

The Kaplan-Meier curves for PFS (Figure 2) crossed at approximately 3 months after randomization, with 8 PFS events in Arm A and 22 PFS events in Arm B during the first 8 weeks post-randomization. During the first 8 weeks post-randomization, participants in both arms were intended to receive standard therapy with PVd/DPd either as study treatment (Arm A) or bridging therapy (Arm B). All 22 events in Arm B occurred before cilta-cel infusion. Twenty-one of the events were due to progressive disease and one participant died 3 days after apheresis due to an AE of respiratory failure. The 2 arms were well balanced in terms of baseline demographic and disease characteristics. Possible reasons for the imbalance in PFS events were investigated and it was found that the relative dose intensity of PVd/DPd was lower in Arm B than in Arm A in the first 3 cycles. This may have contributed to early PFS events observed in Arm B.

While the median time from first apheresis to cilta-cel infusion was 79 days, for 17 out of 22 participants the PFS events in Arm B occurred within 1 week of the planned end date of their first cycle of bridging therapy (day of progression range: Study Day 3 to 34). As such, the

availability of cilta-cel was not considered a contributing factor for these early progression events. No other causes could be identified, and the imbalance may further be due to random variability.

Figure 2: Applicant - Kaplan-Meier Plot for Progression-free Survival Based on Computerized Algorithm; Intent-to-Treat Analysis Set (Study 68284528MMY3002)



Key: Standard of Care Arm = PVd or DPd; ciltacabtagene autoleucel Arm = A sequence of apheresis, bridging therapy (PVd or DPd), conditioning regimen (cyclophosphamide and fludarabine), and cilta-cel infusion.
Key: PVd=pomalidomide-bortezomib-dexamethasone; DPd=daratumumab-pomalidomide-dexamethasone.
Note: Intent-to-treat analysis set consists of subjects who were randomized in the study.

Modified from [GEFPFS01X.RTF] [PROD/JNJ-68284528/MMY3002/DBR_CSR/RE_CSR/GEFPFS01X.SAS] 26APR2023, 17:46
Figure 2: Kaplan-Meier Plot for PFS Based on Computerized Algorithm; Intent-to-Treat Analysis Set (Study 68284528MMY3002)
In the first 8 weeks, 22 PFS events were observed on Arm B (ciltacabtagene autoleucel Arm) compared with 8 on Arm A (Standard of Care Arm). Of note, the 2 Kaplan-Meier curves crossed at around 3 months after randomization, by which time 27 and 31 PFS

events had occurred in Arm A and Arm B, respectively. The curves continue to separate throughout the study.
Subjects at risk in Arm A (Standard of Care Arm): Month 0, 211 subjects; Month 3, 176; Month 6, 133; Month 9, 116; Month 12, 88; Month 15, 46; Month 18, 20; Month 21, 4; Month 24, 1; Month 27, 0; Month 30, 0.
Subjects at risk in Arm B (ciltacabtagene autoleucel Arm): Month 0, 208 subjects; Month 3, 177; Month 6, 172; Month 9, 166; Month 12, 146; Month 15, 94; Month 18, 45; Month 21, 22; Month 24, 9; Month 27, 1; Month 30, 0.

A standard 'unweighted' stratified log-rank test of PFS was performed as a planned sensitivity analysis to support the primary analysis. The results of this unweighted test (HR: 0.40 [95% CI:

0.29, 0.55], p<0.0001) and all other planned sensitivity and supplementary analyses of PFS were consistent with the results from the primary analysis. Sensitivity analysis of PFS was also performed using a composite handling strategy that treats death or progression immediately after one missed DE as event at the last DE prior to the missed DE, and censored at the last DE prior to the missed Des for death or progression immediately after at least 2 consecutive missed Des. The results of this sensitivity analysis (HR:0.41 [95% CI: 0.30, 0.56]) are also consistent with the primary analysis.

Piecewise analysis of PFS (by intervals of 0 to ≤3 months, 3 to ≤12 months, 12 to ≤24 months, and >24 months) was performed to evaluate the treatment effect under non-proportional hazards. Following the period 0 to ≤3 months, in which the rate of PFS events was slightly higher in Arm B (14.9%) than in Arm A (12.8%), the rate of PFS events in all time periods thereafter was higher for Arm A.

The PFS results were consistent across all pre-specified subgroups, with HRs favoring Arm B over Arm A, including subgroups for participants with one prior line of therapy, ISS Stage III, high tumor burden, and high-risk cytogenetics (see Section 5.1.2.1.1 of the CSR for Study MMY3002). The PFS results were also consistent across subgroups for sex, age, and race.

Subgroups with small sample size (fewer than 10 participants in either treatment arm) were suppressed as the estimations would be unreliable with wide Cis; these subgroups include age >75 years, African American race, unknown cytogenetic risk at study entry, penta-refractory status, and certain subgroups of prior exposure (pomalidomide, both bortezomib and pomalidomide, and both daratumumab and pomalidomide). Efficacy parameters for the Black or African American subgroup versus others are discussed further in Section 8.1.3, Additional Analyses Conducted on the Individual Trial.

Additional analysis was conducted to determine the level of agreement on disease progression assessment (progressive disease and no progressive disease) between IRC assessment and assessment by computerized algorithm. This analysis demonstrated complete concordance between the 2 approaches, as indicated by PABAK=1.00 (95% CI: 1.00, 1.00) and observed agreement of 100.0%.

The Applicant's Position:

A one-time infusion of cilta-cel demonstrated a statistically significant and clinically meaningful improvement in PFS, compared with the standard therapy arm. With a median duration of follow-up of 15.9 months, median PFS in the cilta-cel arm was not reached compared with a median PFS of 11.8 months for the standard therapy arm. Across all clinically relevant subgroups evaluated, PFS was consistently highly in favor of the cilta-cel arm. Robustness of the treatment effect in PFS was also demonstrated from all sensitivity and supplementary analyses, including high concordance between the IRC assessment and assessment by computerized algorithm.

Piecewise analysis of PFS by time period indicated that while the rate of PFS events was slightly higher in Arm B (14.9%) than in Arm A (12.8%) during the period 0 to ≤3 months, in all subsequent time periods thereafter, the rate of PFS was higher in Arm A. The 2 randomized arms were well balanced in terms of baseline characteristics, and the schedules of disease assessment were similar. Therefore, the imbalance in PFS events observed in the first 3 months may have been due to several factors, including random variability or the lower relative dose intensity of PVd/DPd as bridging therapy in Arm B compared with Arm A during the first 3 cycles of treatment (see further detail in Section 5.1.2 of the CSR for Study MMY3002).

In Arm B, the observed rate of early PFS events prior to cilta-cel infusion was as expected based on the equivalent period in the APOLLO study for a similar subgroup of participants treated with DPd. Participants in the APOLLO study who received 1 to 3 prior lines of therapy and were lenalidomide-refractory (n=102) had a PFS rate of 90.1% in the first 8 weeks of the study, almost identical to the PFS rate observed on Arm B in Study MMY3002 (89.4%). Contrary to what was expected, participants in Arm A appeared to perform better than comparable participants from the experimental arm of the APOLLO study in the first 3 months (PFS rate of 96.1% for participants in Arm A), and very similarly afterwards. Kaplan-Meier plots of the 3 treatment groups are provided in Section 4.1.3.1 of the Clinical Overview.

The FDA's Assessment:

Treatment with cilta-cel in CARTITUDE-4 demonstrated a statistically significant improvement in PFS as assessed by the IRC according to IMWG consensus criteria (2016), compared to in the standard therapy arm; HR was 0.41 (95% CI: 0.30, 0.56; p-value <0.0001). Median PFS was not reached for the cilta-cel arm compared to 12 months for the standard therapy arm.

Table 8 and Figure 1 below summarize the analysis of PFS.

Table 8: FDA – Progression-Free Survival Per IRC, ITT Population, CARTITUDE-4

Category	Cilta-cel (N=208)	Standard Therapy (N=211)
Progression-free survival	-	-
Number of events, n (%)	65 (31)	122 (58)
Progression, n (%)	48 (23)	118 (56)
Death, n (%)	17 (8)	4 (2)
Number of censored, n (%)	143 (69)	89 (42)
KM estimate: median, months (95% CI)	NE (22.8, NE)	12 (9.8, 14)
Hazard ratio (95% CI)	0.41 (0.30, 0.56)	-
p-value[1]	<0.0001	-

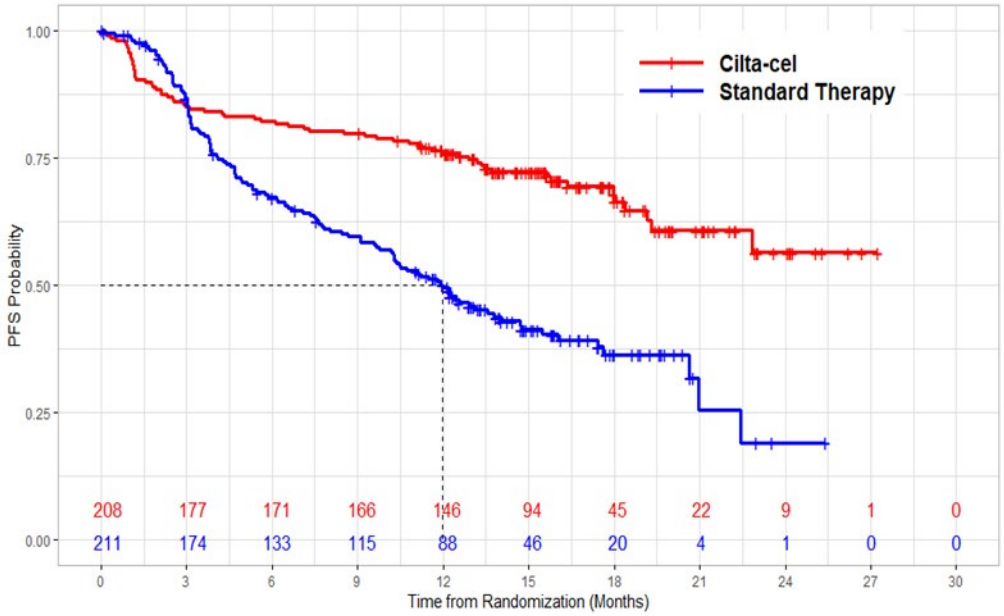
Source: FDA analysis, data cutoff November 1, 2022

1. One-sided stratified log-rank test.

Median follow-up for PFS is 15.8 (95% CI: 15.4, 16.1) months for the cilta-cel arm and 15.3 (95% CI: 14.3, 16.8) months for the standard therapy arm.

Abbreviations: CI, confidence interval; IA, interim analysis; IRC, independent review committee; ITT, intent-to-treat; KM, Kaplan-Meier; n (%), number of subjects with the specified characteristic; N, number of subjects in the specified group, or the total sample; NE, not evaluable

Figure 1: FDA – Progression-Free Survival Per IRC, ITT Population, CARTITUDE-4



Source: FDA, data cutoff November 1, 2022
Abbreviations: IRC, independent review committee; ITT, intent-to-treat; PFS, progression free survival

- The FDAs analysis was based on the IRC assessment based on 2016 IMWG consensus criteria.
- Treatment with cilta-cel in CARTITUDE-4 demonstrated a statistically significant improvement in PFS as assessed by the IRC compared to in the standard therapy arm, with an HR of 0.41 (95% CI: 0.30, 0.56; p-value <0.0001). Overall, the observed estimate of the treatment effect on PFS appears reliable based on balanced prognostic factors across treatment arms and the blinded independent assessment of the PFS endpoint.
- There is early crossing of PFS curves which is limited to the first 3 months. However, on follow up there is a robust and sustained PFS advantage. The PFS results are mature with 75% information fraction, and the lower PFS is limited to a very short period of time. There are several possible causes of the early PFS detriment, e.g., inadequate bridging therapy or randomness due to very limited number of early events.
- A higher proportion of PFS events in the cilta-cel arm occurred early in the study and are attributable to deaths compared to in the standard arm (cilta-cel arm: 8%, n=17; standard therapy arm 2%, n=4).
- FDA conducted additional analyses (safety) to evaluate the increase rate of early death observed in the CARTITUDE-4.

- Although PFS has been accepted as primary endpoint and has supported traditional approval in MM trials, OS is always evaluated at the time of the primary PFS assessment. Particularly for therapies with significant toxicity, assessment of overall survival is important to ensure that there is a favorable benefit risk assessment. FDAs analysis of OS is described in Efficacy Results – Secondary and Other Relevant Endpoints.

Data Quality and Integrity

Data:

See also Section 8.1.3, Compliance with GCP.

A protocol appendix with COVID-19-specific guidance was implemented with global Amendment 2 (issued 02 July 2021) and further refined with global Amendment 3 (issued 14 June 2022).

Because more deaths were attributed to COVID-19 in Arm B (7 participants) than in Arm A (one participant), an Urgent Safety Measure to prevent COVID-19 infection and mitigate potential COVID-19-related risks was implemented across the cilta-cel development program. Additionally, the Sponsor extended the reporting requirements of COVID-19 infection to 1 year post-cilta-cel infusion to allow for continued monitoring of clinical study participants. No additional deaths due to COVID-19 have since been reported for participants in Arm B.

The Applicant's Position:

It is the Applicant's position that there are no issues related to data quality and integrity. A review of all available information indicated that there was minimal impact of COVID-19 on the integrity of the study and study data, assessment of participant safety, and adequacy of data completeness or quality.

The FDA's Assessment:
FDA agrees that there are no issues related to data quality and integrity.

Efficacy Results – Secondary and Other Relevant Endpoints

Data:

Rate of CR/sCR

The rate of CR or better (sCR + CR) was 21.8% (95% CI: 16.4%, 28.0%) for Arm A and 73.1% (95%

CI: 66.5%, 79.0%) for Arm B (Table 8); the stratified CMH estimate of odds ratio was 10.3 (95% CI: 6.5, 16.4; p<0.0001). Similar rates of CR or better were observed for the sensitivity analysis in which determination of response was based on investigator assessment.

In analysis of the 176 participants in Arm B who received cilta-cel infusion as study treatment, the rate of CR or better was 86.4% (95% CI: 80.4%, 91.1%).

ORR

The ORR (sCR + CR + VGPR + PR) was 67.3% (95% CI: 60.5%, 73.6%) for Arm A and 84.6% (95% CI: 79.0%, 89.2%) for Arm B (Table 8), the stratified CMH estimate of odds ratio was 3.0 (95% CI: 1.8, 5.0; p<0000.1). Similar rates of overall response were observed for the sensitivity analysis in which determination of response was based on investigator assessment.

In analysis of the 176 participants in Arm B who received cilta-cel infusion as study treatment, the ORR was 99.4% (95% CI: 96.9%, 100.0%).

Additional analysis was conducted to determine the level of agreement on response assessment (PR or better response and no response; CR or better response and less than CR) between IRC assessment and assessment by computerized algorithm. This analysis demonstrated a high degree of concordance between the 2 approaches for PR or better response and no response (PABAK=1.00 [95% CI: 0.99, 1.00] and observed agreement of 99.8%) and for CR or better response and less than CR (PABAK=0.99 [95% CI: 0.97, 1.00] and observed agreement of 99.3%).

Table 8: Applicant – Summary of Overall Best Confirmed Response Based on Computerized Algorithm; Intent-to-treat Analysis Set (Study 68284528MMY3002)

	Arm A		Arm B			
	n (%)	95% CI for %	n (%)	95% CI for %	Odds Ratio (95% CI)[a]	P-value[b]
Analysis set: intent-to-treat	211		208			
Response category						
Stringent complete response (sCR)	32 (15.2%)	(10.6%, 20.7%)	121 (58.2%)	(51.2%, 65.0%		
Complete response (CR)			14 (6.6%)	(3.7%, 10.9%)	31 (14.9%)	(10.4%, 20.5%)

	Arm A		Arm B			
	n (%)	95% CI for %	n (%)	95% CI for %	Odds Ratio (95% CI)[a]	P-value[b]
Very good partial response (VGPR)	50 (23.7%)	(18.1%, 30.0%)	17 (8.2%)	(4.8%, 12.8%)		
Partial response (PR)	46 (21.8%)	(16.4%, 28.0%)	7 (3.4%)	(1.4%, 6.8%)		
Minimal response (MR)	11 (5.2%)	(2.6%, 9.1%)	1 (0.5%)	(0.0%, 2.6%)		
Stable disease (SD)	47 (22.3%)	(16.8%, 28.5%)	13 (6.3%)	(3.4%, 10.5%)		
Progressive disease (PD)	6 (2.8%)	(1.1%, 6.1%)	17 (8.2%)	(4.8%, 12.8%)		
Not evaluable (NE)	5 (2.4%)	(0.8%, 5.4%)	1 (0.5%)	(0.0%, 2.6%)		
Overall response (sCR + CR + VGPR + PR)	142 (67.3%)	(60.5%, 73.6%)	176 (84.6%)	(79.0%, 89.2%)	3.00 (1.81, 4.97)	<0.0001
Clinical benefit (Overall response + MR)	153 (72.5%)	(66.0%, 78.4%)	177 (85.1%)	(79.5%, 89.6%)	2.39 (1.42, 4.01)	0.0010
VGPR or better (sCR + CR + VGPR)	96 (45.5%)	(38.6%, 52.5%)	169 (81.3%)	(75.3%, 86.3%)	5.89 (3.70, 9.40)	<0.0001
CR or better (sCR + CR)	46 (21.8%)	(16.4%, 28.0%)	152 (73.1%)	(66.5%, 79.0%)	10.30 (6.48, 16.35)	<0.0001

Table 8: Applicant – Summary of Overall Best Confirmed Response Based on Computerized Algorithm; Intent-to-treat Analysis Set (Study 68284528MMY3002)

Key: Arm A = PVd or DPd; Arm B = A sequence of apheresis, bridging therapy (PVd or DPd), conditioning regimen (cyclophosphamide and fludarabine), and cilta-cel infusion.
Key: PVd = pomalidomide-bortezomib-dexamethasone; DPd = daratumumab-pomalidomide-dexamethasone.
Key: CI = confidence interval.
[A] Mantel-Haenszel estimate of the common odds ratio for stratified tables is used. An odds ratio > 1 indicates an advantage for Arm B. The stratification factors are: Investigator's choice (PVd or DPd), ISS staging (I, II, III) and number of prior lines of therapy (1 vs. 2 or 3) as randomized.
[B] P-value from the Cochran Mantel-Haenszel Chi-Squared test.
Note: Intent-to-treat analysis set consists of subjects who were randomized in the study.
Note: Response was assessed by computerized algorithm, based on International Myeloma Working Group (IMWG) consensus criteria (Kumar 2016).
Note: Percentages are calculated with the number of subjects in each group as denominator.

Modified from: [TEFRESP01.RTF] [PROD/JNJ-68284528/MMY3002/DBR_CSR/RE_CSR/TEFRESP01.SAS] 13FEB2023, 18:18

Overall MRD Negativity Rate

Overall MRD negativity rate is defined as the proportion of participants who had MRD negative status (at 10^{-5}) by bone marrow aspirate after the date of randomization and prior to the start of subsequent anti-myeloma therapy.

The MRD negativity rate (10^{-5}) as measured by NGS was approximately 4-fold higher for participants in Arm B compared with participants in Arm A (Arm A: 15.6%; Arm B: 60.6%; odds ratio=8.7; 95% CI: 5.42, 13.90; p<0.0001).

In analysis of the 176 participants in Arm B who received cilta-cel infusion as study treatment, the overall MRD negativity rate (at 10^{-5} threshold) was 71.6%.

OS

OS was analyzed using an unweighted stratified log-rank test and was based on the ITT analysis

set (Arm A: n=211; Arm B: n=208). As of the time of clinical cutoff, 47 participants (22.3%) in Arm A and 39 participants (18.8%) in Arm B had died. OS data may suggest a trend towards improved survival for Arm B versus Arm A (HR=0.78; 95% CI: 0.50, 1.20; p=0.2551); however, the OS data are yet to be mature to provide a reliable estimate for median OS. The estimated OS rates at 12 months were 83.6% (95% CI: 77.8%, 88.0%) for Arm A and 84.1% (95% CI: 78.4%, 88.4%) for Arm B.

Piecewise analysis of OS (by intervals of 0 to ≤3 months, >3 to ≤6 months, >6 to ≤9 months, >9 to ≤12 months, >12 to ≤24 months, and >24 months from randomization) indicated that the period of greatest imbalance between arms was for the period 0 to ≤3 months, in which one death (0.5%) was reported for Arm A versus 7 deaths (3.4%) for Arm B. For all time periods thereafter, the rate of deaths was similar between arms or lower in Arm B. The higher number of deaths in Arm B during the first 3-month period post randomization was largely due to progression in participants prior to receiving cilta-cel.

Time to Worsening of Symptoms in the MySIm-Q Total Symptom Score

Time to worsening of symptoms in the MySIm-Q total symptom score was considered as a major secondary endpoint for the study. This endpoint could not be tested formally at the current interim analysis because it follows OS in the hierarchical testing order and OS was not significant as of the clinical cutoff due to immaturity of the data.

Time to worsening of symptoms in the MySIm-Q total symptom score was defined as a worsening by MID compared with baseline without subsequent improvement to a score above this level. Most participants (Arm A: 78.2%; Arm B: 85.6%) were censored as of the time of clinical cutoff. The median time to a sustained worsening of multiple myeloma symptoms was longer for Arm B: median 18.9 months (95% CI: 16.8, NE) for Arm A and 23.7 months (95% CI: 22.1, NE) for Arm B, with a HR of 0.42 (95% CI: 0.26, 0.68). Data from other PRO instruments were supportive of the MySIm-Q results.

The Applicant's Position:

Treatment with a single infusion of cilta-cel was highly efficacious in this population of participants with relapsed and lenalidomide-refractory multiple myeloma in Study MMY3002, with 73.1% of participants in the Arm B ITT analysis set achieving a CR or better, compared with 21.8% of participants in Arm A. For the 176 participants in Arm B who received cilta-cel infusion as

study treatment, the ORR was 99.4% and the rate of CR or better was 86.4%. The high degree of concordance on response assessment by IRC and assessment by computerized algorithm demonstrated robust and reliable results. These findings are further supported by improvements in overall MRD negativity rate, OS data that may suggest a trend towards improved survival in Arm B, and PROs.

All of the major secondary endpoints (rate of CR/sCR, ORR, overall MRD negativity rate, OS, time to worsening of symptoms in the MySIm-Q total symptom score) support the benefit of cilta-cel compared with standard therapy in this patient population.

The FDA's Assessment:

The FDA agrees with the Applicant that CR/sCR and ORR per IRC, were significantly higher in the cilta-cel arm compared to the standard therapy arm (one-sided p-value <0.0001 based on a stratified Cochran-Mantel-Haenszel test).

Results of the analysis of the key secondary endpoints, CR/sCR and ORR by IRC, are summarized in Table 9.

Table 9: FDA – Rate of CR/sCR and ORR Per IRC, ITT Population, CARTITUDE-4

Response Parameter	Cilta-cel (N=208)	Standard Therapy (N=211)
sCR, n (%)	137 (66)	38 (18)
CR, n (%)	17 (8)	9 (4)
VGPR, n (%)	16 (8)	49 (23)
PD, n (%)	18 (9)	6 (3)
Rate of CR/sCR	-	-
n (%)	154 (74)	47 (22)
p-value[1]	<0.0001	
Odds ratio (95% CI)	10.6 (6.6, 16.8)	
ORR (sCR+CR+VGPR+PR)	-	-
n (%)	176 (85)	143 (68)
p-value[1]	<0.0001	
Odds ratio (95% CI)	2.9 (1.8, 4.9)	

Source: FDA analysis, data cutoff January 1, 2022
1. One-sided Cochran-Mantel-Haenszel test controlling for pooled strata.
Abbreviations: CI, confidence interval; CR, complete response; IRC, Independent Review Committee; ITT, intent-to-treat; MR, minimal response; n (%), number of subjects with the specified characteristic; N, number of subjects in the specified group, or the total sample; NE, not evaluable; ORR, overall response rate; PD, progressive disease; PR, partial response; sCR, stringent complete response; VGPR, very good partial response

The FDA does not agree with the Applicant's characterization of the other secondary endpoints of MRD, OS and the MySlm-Q scores. The FDAs analysis and interpretation of these secondary endpoints are shown below.

Overall MRD Negativity Rate

The reported calibration in 81% and 84% of the subjects with bone marrow aspirate samples in the cilta-cel arm and standard therapy arm ITT populations, respectively (p.98 clinical study report). Indicates that there is a high rate of calibration failure rate (>20%). The rate of calibration failure is higher than the reported rates with the clonoSEQ next-generation sequencing assay (Costa et al. 2021). Additionally, the Applicant reported that further samples were unevaluable for MRD at $10^{-5,}$ (p.97 clinical study report). Therefore, the MRD was evaluable in only 69% (144/208) and 48% (101/211) of the ITT population in the cilta-cel arm and standard therapy arm. The data raise concerns regarding the reliability of the MRD response assessments for regulatory purposes. These significant issues noted have an impact on the strength and validity of the MRD results. Therefore, the MRD data was not considered robust enough to support inclusion in the United States Prescribing Information.

Overall Survival

At the time of the data cutoff, the study observed 86 deaths out of 250 total OS events planned (34% information fraction), with heavy censoring in both arms (81% for cilta-cel arm, 78% for the standard therapy arm) due to immature OS data.

Of the 86 deaths in the ITT population, 39 were in the cilta-cel arm and 47 in the standard therapy arm. While the standard therapy arm reached a median OS of 26.7 months, the cilta-cel arm hasn't reached its median yet. This is further illustrated in Table 10 and Figure 2.

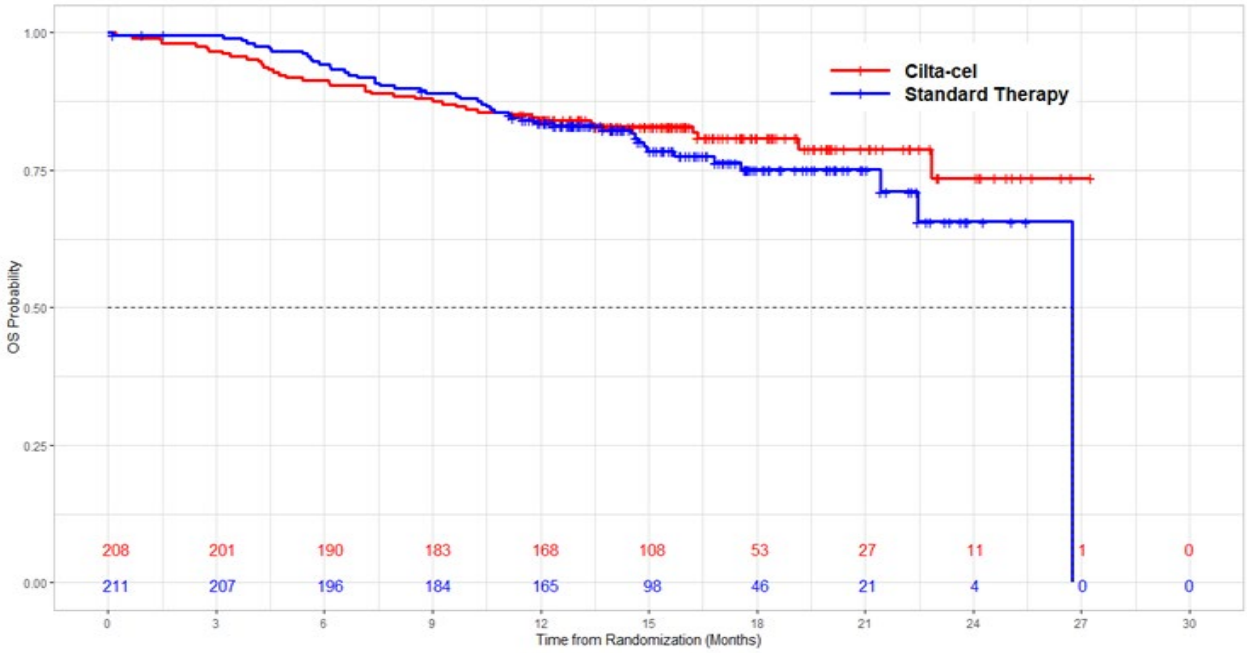
Table 10: FDA – Overall Survival, Interim Analysis, ITT Population, CARTITUDE-4

Category	Cilta-cel (N=208)	Standard Therapy (N=211)
Overall survival	-	-
Deaths, n (%)	39 (19)	47 (22)
Censored, n (%)	169 (81)	164 (78)
Study cutoff	169 (81)	160 (76)
Withdrawal by subject	0	4 (2)

Category	Cilta-cel (N=208)	Standard Therapy (N=211)
Median, months (95% CI)	NE (NE, NE)	26.7 (22.5, NE)
Hazard ratio (95% CI)	0.78 (0.51, 1.20)	
p-value[1]	0.26	

Source: FDA analysis, data cutoff January 1, 2022
1. One-sided stratified log-rank test.
Median follow-up for OS is 16.0 (95% CI: 15.6, 16.8) months for the cilta-cel arm and 15.9 (95% CI: 15.2, 16.6) months for the standard therapy arm.
Abbreviations: CI, confidence interval; ITT, intent-to-treat; n (%), number of subjects with the specified characteristic; N, number of subjects in the specified group, or the total sample; NE, not evaluable

Figure 2: FDA – Kaplan-Meier Curves for OS, ITT Population, CARTITUDE-4



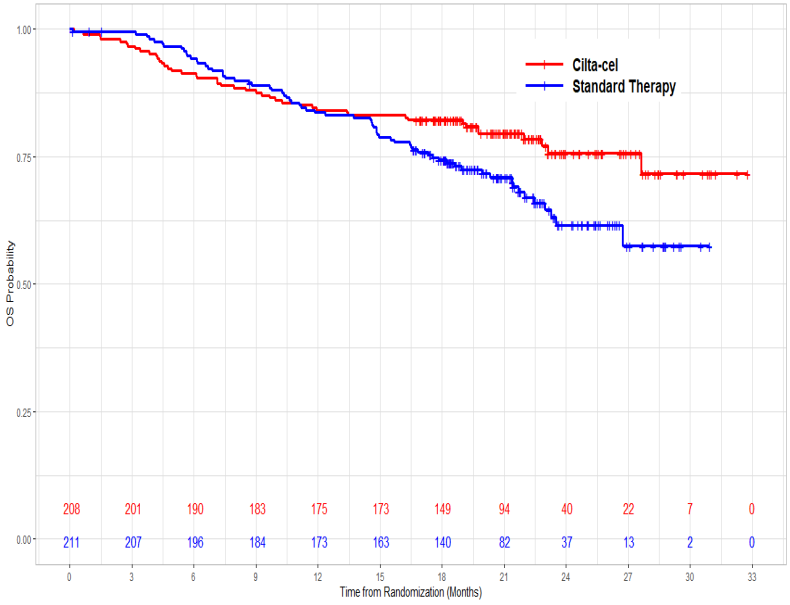
Source: FDA analysis, data cutoff November 1, 2022
Abbreviations: ITT, intent-to-treat; OS, overall survival

- In the Kaplan Meier plot for OS (Figure 2), a crossing of the curves indicates that the treatment effect constancy assumption cannot be made (i.e., nonproportional hazards). In this scenario, average HR is an unreliable summary statistic to quantify the treatment effect.
- The median OS estimate for the standard therapy arm should be interpreted with caution as the last subject in the at-risk set died at 26.7 months, leading to an immediate OS probability drop from ~65% to 0% at that timepoint. The median OS estimates may become more reliable with longer follow-up OS data.

- OS results from the CARTITUDE-4 study demonstrated an observed early detriment in OS in subjects randomized to the cilta-cel arm compared to those randomized to standard therapy.
- A higher proportion of patient randomized to cilta-cel compared to standard therapy experienced death in with first 10 months following randomization (n=29/208;14% vs. n=25/211;12%).
- The impact of early deaths and additional analysis is described further in Section 8.2.4 Safety Results

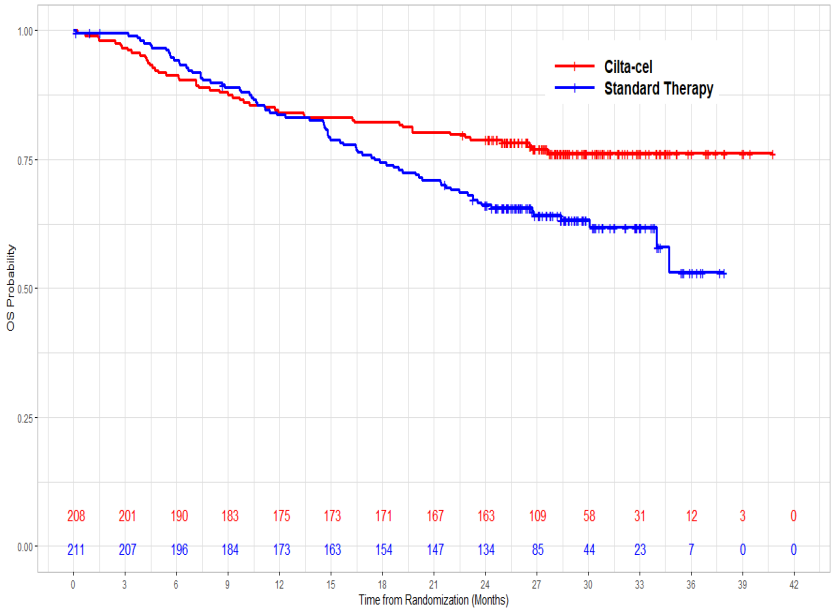
During the FDA review period, the Applicant provided an updated Kaplan-Meier curves based on the clinical cutoff of April 17, 2023, for the 120-Day Safety Update (IF 44%) Figure 3. Most recently, the Applicant provided another OS update with the cutoff of December 13, 2023, as shown in Figure 4 with information fraction of 50%. Of note, both are unplanned analyses for OS, and no statistical testing was performed. While there is further separation of the curves, the OS data is still immature with only 50% Information fraction at the latest unplanned data cut-off. In addition, as we can see from the two KM curves for OS, our major concern regarding the early OS detriment still evident with longer follow-up OS data.

Figure 3. FDA- Kaplan-Meier Curves for OS, ITT Population, at 120-Day Safety Update



Data cutoff date April 17, 2023

Figure 4. FDA- Kaplan-Meier Curves for OS, ITT Population



Data cutoff date December 13, 2023

Patient-Reported Outcomes

As patient-reported outcome (PRO) data describe patient experiences and quality of life, such data are always welcomed by FDA. While quality of life data are important, there are several limitations with the PRO data from Study CARTITUDE-4 as noted in Table 1. The PRO data are considered exploratory as they have not been statistically evaluated according to the prespecified hierarchical testing strategy.

Dose/Dose Response

Data and The Applicant's Position:

Not applicable as a single dose was tested.

The FDA's Assessment:
Not applicable.

Durability of Response

Data:

As most responders' DOR data (56.3% of participants in Arm A and 81.3% of participants in Arm B with PR or better) was censored at the time of clinical cutoff, DOR data were not mature. Median DOR was 16.6 months (95% CI: 12.9, NE) for Arm A and NE (95% CI: NE, NE) for Arm B. Twelve-month event-free rates were 63.0% (95% CI: 54.2%, 70.6%) for Arm A and 84.7% (95% CI: 78.1%, 89.4%) for Arm B.

The Applicant's Position:

DOR data are not mature at this time.

The FDA's Assessment:

FDA agrees.

Persistence of Effect

Data:

No formal evaluations of persistence of efficacy and/or tolerance have been conducted. With a median duration of follow-up of 15.9 months for the ITT analysis set, the data are yet to be mature to provide a reliable estimate for median OS. Please refer to Section 8.1.3, Durability of Response for DOR results and to Section 8.1.3, OS for OS results.

The Applicant's Position:

DOR and OS data are not mature at this time.

The FDA's Assessment:
FDA agrees that DOR and OS data were not mature at the time of the submission of the efficacy supplement. However, the FDA consider OS as both an efficacy and safety endpoint. The FDAs concerns with the high rate of early deaths in the cilta-cel arm compared to the standard arm and the OS data are described in Efficacy Results – Secondary and Other Relevant Endpoints.

Additional Analyses Conducted on the Individual Trial

Data:

Subgroup Analysis by Race

A summary table for key efficacy parameters, including PFS, is provided for the Black or African American subgroup versus others in the CSR for Study MMY3002. Efficacy results, including PFS, ORR, and DOR were consistent between Black or African American participants and other participants.

Subgroup Analysis by LV Manufacturing Site

To meet demand for LV, the Applicant introduced a (b) (4) LV manufacturing process at the Janssen Vaccines, (b) (4) facility during the conduct of Study MMY3002. The LV produced at this facility is referred to as (b) (4) LV; LV produced at (b) (4) is referred to as (b) (4) LV. Among the 176 participants in Arm B who received cilta-cel infusion as study treatment, 90 participants received cilta-cel manufactured using (b) (4) LV and 86 participants received cilta-cel manufactured using (b) (4) LV.

Comparable efficacy was observed regardless of LV ((b) (4) versus (b) (4) used to manufacture the cilta-cel product, with a 12-month PFS rate of 87.8% (95% CI: 79.0%, 93.0%) for the (b) (4) LV subgroup, and 91.6% (95% CI: 83.2%, 95.9%) for the (b) (4) LV subgroup. Efficacy results by LV subgroup are provided for major secondary endpoints in Section 5.1.3 of the CSR for Study MMY3002.

Drug Product Release Status

Eight participants received cilta-cel that did not meet all pre-specified release criteria, either as study treatment (6 participants) or as subsequent therapy (2 participants). Further details of cilta-cel product that did not meet all pre-specified release criteria are provided in the CSR for Study MMY3002.

Key efficacy endpoints were examined by drug product release status. The small number of participants who received out-of-specification cilta-cel prevents a definitive conclusion regarding clinical efficacy.

Participants Who Received Cilta-cel as Subsequent Therapy in MMY3002

In accordance with the study protocol, participants in Arm B who progressed before cilta-cel infusion and therefore met the primary endpoint were still eligible to receive cilta-cel as subsequent systemic anti-myeloma therapy. In addition to being included in the primary PFS analysis, study data for the 20 participants who received cilta-cel as subsequent therapy were summarized separately in order to provide a comprehensive assessment of efficacy and safety for the enrolled population. Data for these 20 participants are presented in the CSR for Study MMY3002.

The Applicant's Position:

Comparable efficacy results were observed across subgroups examined by race and LV manufacturing site.

The FDA's Assessment:
The results of the subgroups should be interpreted with caution since no formal testing was planned for the subgroup analyses and the sample size in each subgroup was not planned to power such analyses for detecting the same magnitude of the treatment effect as the overall population. Thus, the subgroup analysis results are considered exploratory only. For additional FDA analysis of increased early deaths and the OS data please see Section 8.2.4. Safety Results

8.1.4. Integrated Review of Effectiveness

The FDA's Assessment:
The effectiveness of cilta-cel for the proposed indication derives from Study CARTITUDE-4. CARTITUDE-4 is a Phase 3, randomized (1:1), open-label, multicenter study that compares cilta-cel to standard therapy in adults with relapsed and lenalidomide-refractory multiple myeloma (MM) after one to three prior lines of therapy including a PI and an immunomodulatory drug (IMiD). CARTITUDE-4 enrolled a total of 419 patients who were randomized to receive cilta-cel or one of two standard-of-care regimens, either pomalidomide, bortezomib, and dexamethasone (PVd) or daratumumab, pomalidomide, and dexamethasone (DPd). Patients received cilta-cel as a single infusion at a dose range of 0.41-1.08 x 10^6 CAR+ viable cells/kg following lymphodepletion therapy with fludarabine and cyclophosphamide.

The primary efficacy outcome measure for CARTITUDE-4 is progression-free survival (PFS) as determined by a blinded independent review committee (IRC) using the International Myeloma Working Group (IMWG) 2016 criteria. Key secondary efficacy outcome measures in hierarchical

testing order are rate of CR or better (CRR), overall response rate (ORR), overall MRD negativity rate, overall survival (OS) and time to worsening of symptoms in the MySIm-Q total symptom score.

CARTITUDE-4 met its primary endpoint (data cutoff of November 1, 2022), demonstrating a statistically significant and clinically meaningful improvement in PFS in patients randomized to the cilta-cel arm compared to patients randomized to the standard therapy arm (hazard ratio [HR] was 0.41 [95% confidence interval (CI): 0.30, 0.56] based on a stratified log-rank test; p-value <0.0001). The median PFS was not reached in the cilta-cel arm (95% CI: 22.8, not evaluable [NE]), and was 12 months (95% CI: 9.8, 14) in the standard therapy arm.

The IRC-assessed CR rate was statistically significant; 74% (95% CI: 67, 79) in the cilta-cel arm compared to 22% (95% CI: 16, 28) in the standard therapy arm. Similarly, the ORR was higher at 85% (95% CI:79, 89) in the cilta-cel arm compared to 67% (95% CI: 61, 74) in the standard therapy arm. At the time of the primary analysis of PFS, overall survival (OS) was immature (information fraction of 34%). FDA considered cilta-cel effects on OS as part of the safety assessment. Results from the interim OS analysis (~34% IF) done at the time of the final PFS analysis showed an OS detriment for approximately 10 months after randomization.

A higher proportion of patient randomized to cilta-cel compared to standard therapy experienced death in with first 10 months following randomization (n=29/208;14% vs. n=25/211;12%). Of the 29 deaths that occurred in the CARVYKTI arm within the first 10 months of randomization, 10 deaths occurred prior to CARVYKTI infusion, and 19 deaths occurred after CARVYKTI infusion. Of the 10 deaths that occurred prior to CARVYKTI infusion, all occurred due to disease progression. Of the 19 deaths that occurred after CARVYKTI infusion, 3 occurred due to disease progression, and 16 occurred due to adverse events. The most common adverse events were due to infection (n=12). The higher early mortality with cilta-cel was observed across multiple prognostic subgroups and was observed even in the absence of individual poor prognostic factors. In the safety analysis population, there was also a higher rate of fatal adverse reaction that occurred within 90 days from starting treatment with cilta-cel in the as treated population compared to in the standard therapy arm (5% versus 0%).

FDA convened a meeting of the Oncologic Drugs Advisory Committee (ODAC) to discuss the increased risk for early deaths in the cilta-cel arm and the risk-benefit assessment of cilta-cel for the proposed indication. Voting members of the ODAC were asked to vote on whether the risk-benefit assessment for cilta-cel for the proposed indication favorable; the ODAC voted 11 to 0 in favor of cilta-cel.

8.1.5. Assessment of Efficacy Across Trials

Data:

The positive clinical efficacy of cilta-cel compared with standard therapy in pivotal Study MMY3002 is supported by data from Study MMY2003, which enrolled identical (Cohort A) or closely related (Cohort B) study populations. Baseline characteristics for the participants who received cilta-cel in Cohort A and Cohort B of Study MMY2003 are presented in the CSRs for Study MMY2003 Cohort A and Study MMY2003 Cohort B.

Key efficacy findings from the 2 studies are presented side-by-side in Table 9.

Table 9: Applicant – Summary of Key Efficacy Findings From Study MMY3002, Study MMY2003 Cohort A, and Study MMY2003 Cohort B

	Study MMY3002		Study MMY2003 Cohort A (Initial Group)	Study MMY2003 Cohort B
Analysis Set	**ITT** Arm B: 208	176[a]	**mITT**[b] 20	**mITT**[b] 19
Median Duration of Follow-up	16.0 months	16.03 months	14.3 months	18.04 months
12-month PFS Rate	75.9%[c]	89.7%[c]	75.0%[d]	89.5%[d]
CR or Better Rate	73.1% (95% CI: 66.5%, 79.0%)	86.4% (95% CI: 80.4%, 91.1%)	85.0% (95% CI: 62.1%, 96.8%)	89.5% (95% CI: 66.9%, 98.7%)
ORR	84.6% (95% CI: 79.0%, 89.2%)	99.4% (95% CI: 96.9%, 100.0%)	95.0% (95% CI: 75.1%, 99.9%)	100.0% (95% CI: 82.4%, 100.0%)
MRD Negativity	60.6%	71.6%	80.0%[e]	73.7%[e]

Table 9: Applicant – Summary of Key Efficacy Findings From Study MMY3002, Study MMY2003 Cohort A, and Study MMY2003 Cohort B

	Study MMY3002		Study MMY2003 Cohort A (Initial Group)	Study MMY2003 Cohort B
OS	39 participants (18.8%) had died 12-month OS rate was 84.1% (95% CI: 78.4, 88.4)[f]	18 participants (10.2%) had died 12-month OS rate was 92.6% (95% CI: 87.6, 95.6)[f]	4 participants (20.0%) had died 12-month OS rate was 95.0% (95% CI: 69.5, 99.3)[g]	3 participants (15.8%) had died 12-month OS rate was 94.7% (95% CI: 68.1, 99.2)[g]

[a] Arm B participants who received cilta-cel as study treatment.
[B] The mITT Analysis Set for Study MMY2003 (Cohort A and Cohort B) included participants who received cilta-cel infusion at the target dose of 0.75×10^6 CAR-positive viable T cells/kg and within the range of 0.5 to 1.0×10^6 CAR-positive viable T cells/kg. The mITT Analysis Set is used for all efficacy analyses unless otherwise specified.
[C] PFS is the primary endpoint for Study MMY3002. For Study MMY3002, PFS was counted from the date of randomization to the date of first documented disease progression.
[D] For Study MMY2003, PFS was counted from the date of the initial infusion of cilta-cel.
[E] MRD negativity, assessed via NGS or NGF, is the primary endpoint for Study MMY2003.
[F] For Study MMY3002, OS was counted from date of randomization to date of death.
[G] For Study MMY2003, OS was counted from date of initial infusion to date of death.

Modified from Mod2.7.3/SCE/Tab32

The Applicant's Position:

Efficacy findings from supportive Study MMY2003 (Cohort A and Cohort B) were consistent with efficacy findings for the 176 participants who received cilta-cel as study treatment in pivotal Study MMY3002. The depth and durability of response were comparable across the studies.

The FDA's Assessment:
Study CARTITUDE-4 was the primary study supporting efficacy of cilta-cel in the indicated population.

8.1.6. Integrated Assessment of Effectiveness

Data:

Refer to efficacy results in Section 8.1.3 for assessment of efficacy in Study MMY3002 and to Section 8.1.5 for assessment of efficacy across Studies MMY3002 and MMY2003 (Cohort A and

Cohort B).

The FDA's Assessment:

Substantial evidence of effectiveness of cilta-cel for the proposed indication derives from Study CARTITUDE-4. CARTITUDE-4 is a Phase 3, randomized (1:1), open-label, multicenter study that compares cilta-cel to standard therapy in adults with relapsed and lenalidomide-refractory multiple myeloma (MM) after one to three prior lines of therapy including a PI and an immunomodulatory drug (IMiD). CARTITUDE-4 enrolled a total of 419 patients who were randomized to receive cilta-cel or one of two standard-of-care regimens, either pomalidomide, bortezomib, and dexamethasone (PVd) or daratumumab, pomalidomide, and dexamethasone (DPd). Patients received cilta-cel as a single infusion at a dose range of 0.39-1.08 x 10^6 CAR+ viable cells/kg following lymphodepletion therapy with fludarabine and cyclophosphamide.

The primary efficacy outcome measure for CARTITUDE-4 is progression-free survival (PFS) as determined by a blinded independent review committee (IRC) using the International Myeloma Working Group (IMWG) 2016 criteria. Key secondary efficacy outcome measures in hierarchical testing order are rate of CR or better (CRR), overall response rate (ORR), overall MRD negativity rate, overall survival (OS) and time to worsening of symptoms in the MySIm-Q total symptom score. Patient reported outcomes were additional efficacy endpoints, evaluated in an exploratory fashion.

CARTITUDE-4 met its primary endpoint (data cutoff of November 1, 2022), demonstrating a statistically significant and clinically meaningful improvement in PFS in patients randomized to the cilta-cel arm compared to patients randomized to the standard therapy arm (hazard ratio [HR] was 0.41 [95% confidence interval (CI): 0.30, 0.56] based on a stratified log-rank test; p-value <0.0001). The median PFS was not reached in the cilta-cel arm (95% CI: 22.8, not evaluable [NE]), and was 12 months (95% CI: 9.8, 14) in the standard therapy arm.

The IRC-assessed CR rate was statistically significant; 74% (95% CI: 67, 79) in the cilta-cel arm compared to 22% (95% CI: 16, 28) in the standard therapy arm. Similarly, the ORR was higher at 85% (95% CI:79, 89) in the cilta-cel arm compared to 67% (95% CI: 61, 74) in the standard therapy arm. At the time of the primary analysis of PFS, overall survival (OS) was immature (information fraction of 34%). Accordingly, FDA considered cilta-cel effects on OS as part of the safety assessment. A higher proportion of patient randomized to cilta-cel compared to standard therapy experienced death in with first 10 months following randomization (n=29/208;14% vs. n=25/211;12%). Of the 29 deaths that occurred in the cilta-cel arm within the first 10 months of randomization, 10 deaths occurred prior to cilta-cel infusion, and 19 deaths occurred after cilta-cel

infusion. Of the 10 deaths that occurred prior to cilta-cel infusion, all occurred due to disease progression, and none occurred due to adverse events. Of the 19 deaths that occurred after cilta-cel infusion, 3 occurred due to disease progression, and 16 occurred due to adverse events. The higher early mortality with cilta-cel was observed across multiple prognostic subgroups and was observed even in the absence of individual poor prognostic factors. In the safety analysis population, there was also a higher rate of fatal adverse reaction that occurred within 90 days from starting treatment with cilta-cel in the as treated population compared to in the standard therapy arm (5% versus 0%).

FDA convened a meeting of the Oncologic Drugs Advisory Committee (ODAC) to discuss whether the results of CARTITUDE-4 are sufficient to support a positive risk-benefit assessment of cilta-cel for the proposed indication and if the risk of early death associated with cilta-cel treatment is acceptable in the context of PFS benefit. The ODAC were asked to vote whether the risk-benefit assessment for cilta-cel for the proposed indication was favorable. the ODAC voted 11 to 0 in favor of cilta-cel.

In conclusion, CARTITUDE-4 provides substantial evidence of effectiveness of cilta-cel for patients with relapsed and lenalidomide-refractory MM after one to three prior lines of therapy, including a PI and an IMiD. CARTITUDE-4 demonstrates clinical benefit through clinically meaningful improvements in PFS, complete response rate (CRR),and ORR. The most common serious risks of cilta-cel have been characterized and are mitigated through product labeling and a REMS. The observed higher rate of early death observed in CARTITUDE-4 does not have a clear etiology but as discussed in the ODAC, may represented frontloaded risks associated with the treatment and its administration. CARTITUDE-4 was not designed to provide definitive information on how this risk can be mitigated. Treatment with cilta-cel may require careful consideration of individual patient characteristics, disease characteristics, the therapeutic context among other factors. The risk of increase early mortality with cilta-cel will be included under Warning and Precautions section of the USPI.

The review team recommends traditional approval of cilta-cel at the currently approved dosage, for the treatment of adult patients with RRMM who have received at least one prior line of therapy, including a proteasome inhibitor (PI) and an immunomodulatory agent, and are refractory to lenalidomide. Also see FDA's assessment in Section 8.1.3.

8.2. Review of Safety

8.2.1. Safety Review Approach

Data:

The safety profile for cilta-cel comes primarily from data from the Phase 3 Study MMY3002. Comparison of AEs occurring in Arm A and Arm B used the safety analysis set (N=416), which included all participants who received any part of study treatment (Arm A=208; Arm B=208). This analysis allowed for a standardized assessment of safety associated with the complete treatment interventions being evaluated.

Among the 208 participants in the safety analysis set for Arm B, the following participant cohorts were also utilized for analyses of safety:

- 176 participants who received cilta-cel as study treatment (used for summaries of cilta-cel specific events including CRS, CAR-T cell neurotoxicity, and other neurologic AEs).
- 20 participants whose disease progressed prior to cilta-cel infusion and who received cilta-cel as subsequent therapy, with safety data for these participants presented separately as supporting data.
- Total of 196 participants who received cilta-cel either as study treatment or as subsequent therapy.

Additional supporting data are provided from Study MMY2003 Cohorts A and B that used identical or closely related study populations, treatment regimens, and safety data collection methods as Study MMY3002.

The Applicant's Position:

The safety data supporting this sBLA submission for cilta-cel come primarily from 416 participants in the safety analysis set of Study MMY3002 and are supported by data from 39 participants from Study MMY2003 (20 participants in Cohort A and 19 participants in Cohort B). The Applicant believes that this safety experience is sufficient to allow adequate characterization of the safety profile of cilta-cel and provide appropriate guidance to both physician and patient on what to expect from treatment with this therapy.

The FDA's Assessment:
The safety analysis was done on all subjects who received at least one dose of PVd, DPd, and cilta-cel. Safety was summarized according to the treatment actually received and was based on 396 of 419 patients; subjects who received cilta-cel not conforming to the release criteria proposed for the to-be-marketed product were excluded from the safety analysis. A 120-day safety update was submitted (clinical cutoff: April 17, 2023). The submission included data from subjects who received cilta-cel (conforming and nonconforming product) either as study treatment or as subsequent therapy (N=196). The safety population included in this safety update did not exclude subjects who received nonconforming product.

Data from Study MMY3002 was included as supportive of safety only.

8.2.2. Review of the Safety Database

Overall Exposure

Data:

Primary Safety Data – Study MMY3002

The median duration of follow-up for the 419 participants in the ITT analysis set of Study MMY3002 (which comprised 416 participants in the safety analysis set and an additional 3 participants who did not start study treatment and therefore were not in the safety analysis set) was 15.9 months.

Arm A: The median duration of study treatment for Arm A was 4.8 months (range: 0.5 to 19.9 months) for the 26 participants who received PVd and 11.8 months (range: 0.5 to 25.2 months) for the 182 participants who received DPd. The median number of treatment cycles started in Arm A was 12.0 (range: 1 to 28 cycles). Thirteen participants (6.3%) started 1 or 2 cycles of treatment, 58 participants (27.9%) started 3 to 6 cycles of treatment, 10 participants (4.8%) started 7 to 8 cycles of treatment, and 137 participants (65.9%) started 7 or more cycles of treatment.

Arm B: All 208 participants randomized to Arm B underwent apheresis and received bridging therapy (PVd or DPd). Of these, 176 participants (84.6%) received the conditioning regimen of cyclophosphamide and fludarabine infusion followed by cilta-cel infusion as study treatment.

Apheresis

All 208 participants randomized to Arm B completed apheresis. One hundred ninety-three participants (92.8%) underwent a single apheresis attempt and 15 participants (7.2%) underwent 2 apheresis attempts.

Bridging therapy

All 208 participants randomized to Arm B started at least one cycle of bridging therapy as required per protocol. Additional cycles of bridging therapy could be given based on a participant's clinical status and timing of availability of cilta-cel. The median number of bridging cycles started was 2.0 (range: 1 to 6 cycles); 162 participants (77.9%) started at least 2 cycles of bridging therapy. One hundred sixty-eight participants (80.8%) started 1-2 cycles of bridging therapy and 40 participants (19.2%) started 3 to 6 cycles of bridging therapy.

Among the 208 participants in the ITT analysis set for Arm B, 154 participants (74.0%) had a decrease in tumor burden (defined as change in serum M-protein, urine M-protein, or difference between involved and uninvolved free light chain) between baseline and administration of the conditioning regimen.

Cyclophosphamide and Fludarabine Conditioning

Arm B participants were to receive a conditioning regimen prior to cilta-cel infusion. The median total dose of cyclophosphamide infusion was 891.6 mg/m^2 (range: 705 to 1490 mg/m^2). The median total dose of fludarabine infusion was 88.7 mg/m^2 (range: 58 to 96 mg/m^2).

Supportive care, including pre-infusion medication, associated with administration of the conditioning regimen was directed by local standard of care.

Cilta-cel Infusion

Cilta-cel infusion occurred 5 to 7 days after the start of the conditioning regimen. The median time from first apheresis to cilta-cel infusion was 79.0 days (IQR: 68 to 90 days). The median time from receipt to release for cilta-cel was 44.0 days (IQR 35 to 52 days). The median total number of CAR-positive viable T cells infused was 53.1×10^6 (range: 22.7 to 106.5×10^6 cells), with a median of 0.71×10^6 cells/kg administered (range: 0.39 to 1.07×10^6 cells/kg).

Supportive Safety Data – Study MMY2003

As of the clinical cutoff dates of 08 October 2021 and 01 June 2022, 26 participants had been enrolled into Cohort A and 21 participants into Cohort B of Study MMY2003, respectively, and underwent apheresis.

In Cohort A, 20 participants completed the conditioning regimen and received cilta-cel infusion. The median duration of follow-up for these participants was 14.3 months (range, 3.3 to 19.0 months).

In Cohort B, 19 participants completed the conditioning regimen and received cilta-cel infusion. The median duration of follow-up for these participants was 18.0 months (range, 5.2 to 26.3 months).

The Applicant's Position:

In Study MMY3002, 416 participants were included in the safety analysis set, comprising 208 participants in Arm A and 208 participants in Arm B, of whom 176 participants received cilta-cel as study treatment and 20 participants received cilta-cel as subsequent therapy. Supportive safety information is provided from 39 participants from Study MMY2003 (20 participants in Cohort A and 19 participants in Cohort B).

The Applicant will continue to monitor these participants within the long-term follow-up Study 68284528MMY4002 for up to 15 years after cilta-cel administration, for possible complications of LV integration and potential delayed AEs, including SPMs. Initial toxicity (up to 112 days post-cilta-cel infusion) has already been studied as of the clinical cutoff.

In conclusion, the safety data from Study MMY3002 and Cohort A and Cohort B of Study MMY2003 are sufficient to allow adequate characterization of the safety profile of cilta-cel administered after fewer prior lines of therapy than cilta-cel is currently approved for.

The FDA's Assessment:

- Safety was assessed in all subjects who received conforming cilta-cel. Subjects randomized and not treated were excluded from the safety analysis (N=188). For the standard therapy arm, safety analysis included all subjects who received any study treatment (N=208).

- The safety review was based on the primary cutoff date of November 1, 2022, with a median follow-up of 15.6 months (range: 2.4, 27.3 months) in the cilta-cel arm. For the standard therapy arm, the median follow-up for the safety population was 15.9 months (range: 0.1, 26.7 months).

Relevant Characteristics of the Safety Population

Data:

Primary Safety Data – Study MMY3002

Table of Demographic Characteristics

Baseline characteristics were analyzed for the ITT analysis set, which comprised all 419 participants randomized (416 participants in the safety analysis set and 3 participants who did not start study treatment and therefore were not in the safety analysis set). Baseline characteristics for the ITT analysis set of Study MMY3002 are presented in Section 8.1.3, Table of Demographic Characteristics.

Other Baseline Characteristics (eg, Disease Characteristics, Important Concomitant Drugs)

Other baseline characteristics for the ITT analysis set of Study MMY3002 are presented in Section 8.1.3, Other Baseline Characteristics (eg, Disease Characteristics, Important Concomitant Drugs.

Supportive Safety Data – Study MMY2003

Baseline characteristics for the participants who received cilta-cel in Cohort A and Cohort B of Study MMY2003 are presented in the CSRs for Study MMY2003 Cohort A and Study MMY2003 Cohort B.

The Applicant's Position:

As stated in Section 8.1.3, participants enrolled into Study MMY3002 had demographic and baseline disease characteristics representative of the intended population of patients with relapsed and lenalidomide-refractory multiple myeloma.

The FDA's Assessment:
As stated earlier, FDA's safety analysis set included all 188 subjects from Study CARTITUDE-4 who received cilta-cel at the target dose of 0.75×10^6 cells/kg administered. Demographic characteristics

for subjects in the safety analysis set are presented in Table 11. The median age was 61 (range: 27 to 80 years old). White and non-Hispanic were the predominant race and ethnic groups, and the majority of the subjects were treated outside of the United States.

Table 11: FDA – Demographic Characteristics, Safety Population, CARTITUDE-4

Characteristics	Cilta-cel N=188 n (%)	Standard Therapy N=208 n (%)	Total N=396 n (%)
Age (years)	-	-	-
Median (range)	61.5 (27-78)	61 (35-80)	61 (27-80)
<65	112 (60)	129 (62)	241 (61)
65-75	72 (38)	75 (36)	147 (37)
>75	4 (2.1)	4 (1.9)	8 (2)
Sex	-	-	-
M	108 (57)	122 (59)	230 (58)
F	80 (43)	86 (41)	166 (42)
Race	-	-	-
White	143 (76)	157 (75)	300 (76)
Not reported	23 (12)	25 (12)	48 (12)
Asian	15 (8)	18 (9)	33 (8)
Black Or African American	6 (3.2)	7 (3.4)	13 (3.3)
American Indian or Alaska Native	1 (0.5)	1 (0.5)	2 (0.5)
Ethnicity	-	-	-
Not Hispanic or Latino	138 (73)	162 (78)	300 (76)
Not reported	33 (18)	36 (17)	69 (17)
Hispanic Or Latino	17 (9)	10 (4.8)	27 (7)
Region group	-	-	-
Europe	113 (60)	128 (62)	241 (61)
Other	45 (24)	48 (23)	93 (23)
U.S.	30 (16)	32 (15)	62 (16)
ECOG Perf Status Score at Baseline	-	-	-
0	106 (56)	118 (57)	224 (57)
1	82 (44)	89 (43)	171 (43)
2	0	1 (0.5)	1 (0.3)

Source: FDA analysis
Abbreviations: ECOG, Eastern Cooperative Oncology Group; n (%), number of subjects with the specified characteristic; N, number of subjects in the specified group, or the total sample

Baseline disease characteristics for the subjects in CARTITUDE-4 are presented in Table 12. The two arms were well-balanced and represented the known disease characteristics of a population of patients with RRMM.

Table 12: FDA – Baseline Disease Characteristics, Safety Population, CARTITUDE-4

Characteristics	Cilta-cel N=188	Standard Therapy N=208	All N=396
ECOG performance status score %	-	-	-
0/1/2	56/44/0	57/43/0.5	57/43/1
International Staging System stage %	-	-	-
I/II/III	68/27/6	63/30/7	65/29/6
Time since diagnosis (years)	-	-	-
Median (range)	3.2 (0.3-16)	3.4 (0.4-22)	3.4 (0.3-22)
Extramedullary disease n (%)	-	-	-
Yes	36 (19)	34 (16)	70 (18)
No	152 (81)	174 (84)	326 (82)
Bone marrow plasma cells n (%)	-	-	-
N	186 (99)	205 (99)	391 (99)
≤30	121 (64)	119 (57)	240 (61)
>30-<60	29 (15)	44 (21)	73 (18)
≥60	36 (19)	42 (20)	78 (20)
Cytogenetic risk n (%)	-	-	-
N	187 (99)	208 (100)	395(100)
Standard	102 (54)	121 (58)	223 (56)
High (excluding gain/amp (1q))	73 (35)	69 (33)	142 (34)
del(17p)	47 (25)	42 (20)	89 (23)
t(4;14)	24 (13)	30 (14)	54 (14)
t(14;16)	3 (2)	7 (3)	10 (2.5)
Missing data	11 (6)	8 (4)	19 (5)

Source: FDA analysis
Abbreviations: ECOG, Eastern Cooperative Oncology Group; ITT, intent-to-treat; n (%), number of subjects with the specified characteristic; N, number of subjects in the specified group, or the total sample

Adequacy of the Safety Database

Data and Applicant's Position:

As of the 01 November 2022 clinical cutoff date, the median duration of follow-up for the 419 participants in the ITT analysis set of Study MMY3002 was 15.9 months (Arm A: 15.9 months; Arm B: 16.0 months). The safety analysis set of Study MMY3002 included 416 participants who received any part of study treatment and comprised 208 participants in Arm A and 208 participants in Arm B. As of the clinical cutoff date, the median duration of follow- up in supportive study MMY2003 was 14.3 months for the 20 participants in Cohort A and 18.0 months for the 19 participants in Cohort B. These safety data are considered to be adequate to assess the safety of cilta-cel in the treatment of participants with relapsed and lenalidomide-

refractory multiple myeloma after 1 to 3 prior lines of therapy, to provide guidance regarding management of toxicities, and for an assessment of the benefit-risk profile of cilta-cel in the target population.

The FDA's Assessment:
The reviewer agrees that the safety database is considered adequate to identify the most common AEs and support the benefit-risk assessment. As stated in the analysis of the ITT population, representation of minorities in the study was suboptimal.

8.2.3. Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

Data:

Steps to be taken to ensure the accuracy and reliability of data in Study MMY3002 included 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 Applicant, and direct transmission of clinical laboratory data from a central laboratory into the Applicant's database. Monitors were responsible for reviewing adherence to the protocol; compliance with GCP; and the completeness, accuracy, and consistency of the data.

All available data as of the clinical cutoff date were included in the safety assessment presented in the sBLA.

See also Section 8.1.3, Data Quality and Integrity, for information related to data integrity/quality related to the COVID-19 pandemic.

The Applicant's Position:

There were no issues regarding data quality identified by the Applicant; thus, the Applicant does not anticipate any issues with the safety review or the quality of the overall submission that would affect the FDA's ability to perform the review.

The FDA's Assessment:
FDA acknowledges the Applicant's position; the review did not uncover any data integrity issues. FDA agrees that the sBLA submission was complete and of adequate quality.

Categorization of AEs

Data:

TEAE definitions for Study MMY3002 are provided in Section 5.2.1 of the CSR.

Severity of AEs was graded according to the NCI-CTCAE v5.0, except for CRS and ICANS. CRS and ICANS were evaluated according to the ASTCT consensus grading system.

The Applicant's Position:

The recording, coding, and categorization of AEs is considered by the Applicant to be reasonable and appropriate and is consistent with typical clinical development practices for oncology agents and CAR-T therapy, specifically.

The FDA's Assessment:

- Because CAR-T cell therapy is preceded by bridging therapy and conditioning chemotherapy, it is often difficult to parse out the causality of AEs. Therefore, adverse drug reactions were defined by the reviewer as any TEAE occurring after the start of cilta-cel infusion regardless of perceived relationship and causality with the investigational product.
- The Applicant reported AEs by preferred terms, which may underestimate the incidence of some AEs. To minimize underestimation of AEs, FDA grouped preferred terms that represent the same disease process. The reviewer utilized a grouping strategy for comprehensive analyses of AEs that is consistent with the grouping practices for review of similar agents within this class of therapies.
- The Applicant's definition of TEAEs is acceptable. Note that the terms AEs and TEAEs are used interchangeably in this review except when discussing AEs that occurred during the leukapheresis or chemotherapy conditioning periods where the AEs were considered not treatment emergent.
- In general, all grade AEs were counted by maximum toxicity (max tox) grade (i.e., multiple incidences of the same AE in one subject are counted once at the worst grade for this subject). For example, for Grade 3 AEs, the number of subjects who experienced any event with a max tox Grade of 3 was counted. This is different from the number of subjects who had a Grade 3 event, which is typically larger, as some also had Grade 4 or 5 events.

Routine Clinical Tests

Data:

In addition to monitoring for AEs, safety evaluations in Study MMY3002 included clinical laboratory assessments, vital signs, 12-lead ECGs, assessments of cardiac function by echocardiogram and/or multi-gated acquisition scans, and physical examinations. Laboratory data were classified into CTC grades according to the NCI-CTCAE v5.0 (where applicable).

For hematology and clinical chemistry parameters, changes from baseline by visit, the worst on-treatment toxicity grade, and shifts from baseline to worst toxicity grade on study were analyzed.

The Applicant's Position:

The assessment methods and timepoints for collection and analysis of safety measures other than AEs were appropriate for the disease and indication investigated.

The FDA's Assessment:
Overall, the schedule of testing in CARTITUDE-4 is considered adequate for the assessment of safety.

8.2.4. Safety Results

Pivotal Safety Data – Study MMY3002

The FDA's Assessment:

Major Safety Results

Table 13 summarizes the major safety results. A higher proportion of subjects in the cilta-cel arm experienced Grade 4 events. Similarly, AEs leading to death were higher in the cilta-cel (11%) compared to the standard therapy arm (8%).

Table 13: FDA – Summary of Safety, Safety Population, CARTITUDE-4

Adverse Event	Cilta-cel N=188	Standard Therapy N=208	Total N=396
Any TEAE	188 (100)	208 (100)	396 (100)
Any Grade 3-4	173 (92)	196 (94)	369 (93)
Grade 3	39 (21)	73 (35)	112 (28)
Grade 4	120 (64)	117 (56)	237 (60)
Serious AEs	64 (34)	34 (39)	98 (25)
AEs leading to death*	20 (11)	16 (8)	36 (9)

Source: FDA analysis and Applicant's response to information request, data cutoff November 1, 2022
* Excludes death from progressive disease.
Abbreviations: AE, adverse events; N, number of subjects in the specified group, or the total sample; SAE, serious adverse events; TEAE, treatment-emergent adverse event

Deaths

Data:

As of the clinical cutoff date of 01 November 2022, a total of 85 deaths had occurred in the safety analysis set during the study: 46 deaths (22.1%) in Arm A and 39 deaths (18.8%) in Arm B (Table 10), including 11 participants who had not received cilta-cel. In addition, one Arm A participant who was not included in the safety analysis set died after randomization but prior to starting study treatment.

Progressive disease was noted as the primary cause of death for 30 participants (14.4%) in Arm A and 14 participants (6.7%) in Arm B. Of the 14 deaths due to progressive disease in Arm B, 8 participants had not received cilta-cel and 4 had received cilta-cel as subsequent therapy.

A summary of deaths that occurred during the study, including the primary causes of death, is provided in Table 10.

Table 10: Applicant - Summary of Deaths and Primary Cause of Death; Safety Analysis Set (Study 68284528MMY3002)

	Arm A	Arm B
Analysis set: safety	208	208
Total number of subjects who died during study	46 (22.1%)	39 (18.8%)
Primary cause of death		

Treatment-emergent adverse event	5 (2.4%)	10 (4.8%)
Progressive disease	30 (14.4%)	14 (6.7%)
Other[a]	11 (5.3%)	15 (7.2%)

Key: Arm A = PVd or DPd; Arm B = A sequence of apheresis, bridging therapy (PVd or DPd), conditioning regimen (cyclophosphamide and fludarabine), and cilta-cel infusion.
Key: PVd = pomalidomide-bortezomib-dexamethasone; DPd = daratumumab-pomalidomide-dexamethasone.
[a] The reason for deaths (not due to disease progression) will be reported as AE if the AE is treatment-emergent, otherwise reported as other if the AE is non-treatment-emergent.
Note: Percentages calculated with the number of subjects in each treatment group as denominator.
Note: Safety analysis set consists of subjects who received any part of study treatment.
Note: Study treatment start refers to Cycle 1 Day 1 for Arm A and the initial apheresis for Arm B.

Modified from [TSFDTH01.RTF] [PROD/JNJ-68284528/MMY3002/DBR_CSR/RE_CSR/TSFDTH01.SAS] 20FEB2023, 17:46

TEAEs were reported as the primary cause of death for 5 participants (2.4%) in Arm A and 10 participants (4.8%) in Arm B. For the 5 deaths in Arm A due to TEAEs, causes of death were COVID-19 pneumonia, PML, respiratory tract infection, septic shock, and pulmonary embolism. Of the 10 deaths in Arm B due to TEAEs, one participant died due to respiratory failure prior to cilta-cel infusion, 7 (3.4%) participants died due to COVID-19 pneumonia, one due to pneumonia, and one due to neutropenic sepsis. For 4 participants in Arm B, the TEAE reported as the primary cause of death was considered as related to cilta-cel (COVID-19 pneumonia for 3 participants and neutropenic sepsis for one participant).

Fatal AEs that were not considered treatment-emergent (shown as Other in Table 10) were reported as the primary cause of death for 11 (5.3%) participants in Arm A and 15 (7.2%) participants in Arm B. Of the 11 deaths in Arm A, all participants died after start of subsequent therapy. Of the 15 deaths in Arm B, 2 participants died prior to cilta-cel infusion and after start of subsequent therapy. Seven deaths occurred more than 112 days after infusion of cilta-cel and were not considered as related to study treatment. Six deaths occurred in participants who received cilta-cel as subsequent therapy.

The Applicant's Position:

Although most cilta-cel related TEAEs were manageable in this population of participants with pre-treated relapsed and lenalidomide-refractory multiple myeloma, 9 participants in Arm B had a TEAE after cilta-cel infusion that was reported as the primary cause of death, with 4 participants experiencing TEAEs reported as the primary cause of death considered as related to cilta-cel

(COVID-19 pneumonia for 3 participants and neutropenic sepsis for one participant). Five participants in Arm A had a TEAE reported as the primary cause of death. This mortality rate is comparable with the safety profile of the current understanding of CAR-T therapy.

The FDA's Assessment:

Table 14 summarizes all deaths in the safety population reported on the CARTITUDE-4 study. Overall, AEs were the most common cause of reported for deaths that occurred ≤90 days in the cilta-cel arm compared to no deaths due to AEs in the standard therapy arm.

Table 14: FDA – Deaths, Safety Population, CARTITUDE-4

Deaths	Cilta-cel N=188	Standard Therapy N=208	All N=396
Total deaths, n (%)	25 (13)	46 (22)	71 (18)
TEAE, n (%)	20 (11)	16 (8)	36 (9)
Progressive disease, n (%)	5 (3)	30 (14)	35 (9)
Deaths ≤90 days after treatment start, n (%)	9 (5)	0	9 (2.2)
TEAE, n (%)	8 (4)	0	8 (2)
Progressive disease, n (%)	1(0.5)	0	1(0.2)
Deaths >90 days after treatment start, n (%)	16 (8.5)	46 (22)	62 (16)
TEAE, n (%)	12 (6.4)	16 (8)	28 (7)
Progressive disease, n (%)	4 (2)	30 (14)	34 (9)

Source: FDA analysis, data cutoff November 1, 2022
Death day is from treatment start for each treatment. Only deaths that occurred after infusion of conformal cilta-cel are included in this table. TEAE deaths include all deaths from AEs, including AEs after disease progression and after initiation of subsequent anti-myeloma therapy.
Abbreviations: n (%), number of subjects with the specified characteristic; N, number of subjects in the specified group, or the total sample; TEAE, treatment-emergent adverse event

Table 15 lists the FDA-assessed primary cause of death due to AEs of each treatment arm. FDA replicated the Applicant's analysis. When grouping terms, the most frequent cause of death was infections (13 [7%] and 8 [4%]) in the cilta-cel arm and standard therapy arm, respectively). The infections included pneumoniae (9 subjects [5%]), hemorrhage (3 subjects [2%]), and sepsis (3 subjects [2%]). This reviewer agrees that overall, the types of AEs leading to death were generally representative of a population with RRMM, and more subjects in the cilta-cel arm experienced AEs leading to death.

Table 15: FDA – TEAEs as Primary Cause of Death, Safety Population, CARTITUDE-4

Category	Cilta-cel N=188 (n/%)	Standard Therapy N=208 (n/%)	Total N=396 (n/%)
Total deaths	25 (13)	46 (22)	71 (18)
Adverse events	20 (11)	16(8)	36 (9)
COVID-19 pneumonia	7 (4)	1 (0.5)	8 (20)
Pneumonia^	2 (1)	4 (2)	6 (2)
Sepsis	3 (2)	2 (1)	5 (1)
Hemorrhage*	4 (2)	2 (1)	6 (1.5)
CMV colitis	1 (0.5)	0	1 (0.2)
Multiorgan failure	1 (0.5)	2 (1)	3 (0.7)
Acute myeloid leukemia	1 (0.5)	0	1 (0.2)
Cardiorespiratory arrest	1 (0.5)	0	1 (0.2)
Cardiogenic shock	0	1 (0.5)	1 (0.2)
JC virus	0	1 (0.5)	1 (0.2)
Progressive multifocal leukoencephalopathy	0	1 (0.5)	1 (0.2)
Pulmonary embolism	0	1 (0.5)	1 (0.2)
Respiratory distress	0	1 (0.5)	1 (0.2)

Source: FDA analysis and review of death narratives. This table represents the primary AE causing death as assessed by FDA's review of the narratives. Deaths are not grouped under SOC but grouped term. Data cutoff November 1, 2022
^ Pneumoniae includes influenza pneumoniae, respiratory infection, pneumoniae, and pneumocystis jiroveci pneumonia.
* Hemorrhage includes intraparenchymal bleeding, intracranial hemorrhage, retroperitoneal bleed, and subdural hematoma.
Abbreviations: CMV, cytomegalovirus; COVID-19, Coronavirus Disease 2019; JC, John Cunningham; n (%), number of subjects with the specified characteristic; N, number of subjects in the specified group, or the total sample; TEAE, treatment adverse event

As presented in Section 8.1.3, the OS results from the CARTITUDE-4 study demonstrated an increased rate of early deaths in the cilta-cel arm compared to the standard therapy arm. This increased rate of early deaths is reflected in the Kapan-Meier curves as a crossing hazards pattern favoring the standard therapy arm up to approximately 11 months.

FDA conducted additional descriptive analyses to characterize the risk of deaths by specific time periods, based on the ITT population; the results of these analyses are shown below in Table 16. These analyses indicate that at least until approximately 10 months, the rate of deaths attributable to AEs continues to be higher in the cilta-cel arm.

Table 16: FDA – Deaths, ITT Population, CARTITUDE-4

Parameter	Cilta-cel N=208	Standard Therapy N=211	Total N=419
Total deaths, ITT n (%)	39 (18.8)	47 (22)	86 (20)
Progressive disease	17 (8)	30 (15)	47(11)
Adverse event	22 (11)	17 (7)	39 (9)
Death 0 to ≤10 months n (%)	**29 (14)**	**25 (12)**	**54 (13)**
Progressive disease	13 (6)	15 (7)	28 (7)
Adverse event	16 (8)	10 (5)	26 (6)
Death >10 to ≥15 months n (%)	10 (5)	22 (10)	32 (8)
Progressive disease	4 (2)	15 (7)	19 (5)
Adverse event	6 (3)	7 (3)	13 (3)

Source: FDA analysis, data cutoff November 1, 2022
Abbreviations: ITT, intent-to-treat; n (%), number of subjects with the specified characteristic; N, number of subjects in the specified group, or the total sample

As is shown in the Table 38, 14% of the patients in the cilta-cel arm died in the first 10 months compared to 12% in the standard therapy arms.

Due to the increased rate of death in the cilta-cel arm in the first 10 months, FDA further analyzed deaths occurred in the first 10 months post randomization. Table 17 shows the death in the first 10 months post randomization prior to and after cilta-cel/standard therapy in the ITT population.

Table 17: FDA – Death in the First 10 Months Post Randomization Prior to and After Cilta-cel/Standard Therapy, ITT Population, CARTITUDE-4

Category	Cilta-cel N=208 n (%)	Standard Therapy N=208 n (%)
Total	29 (14)	25 (12)
Prior to cilta-cel/standard therapy	10 (5)	0
PD	10 (5)	1(0.5)
AE	0	0
After cilta-cel/standard therapy	19 (9)	24 (11)
PD	3 (2)	15 (7)
AE	16 (8)	9 (4)

Source: FDA analysis, data cutoff November 1, 2022
Abbreviations: AE, adverse event; ITT, intent-to-treat; n (%), number of subjects with the specified characteristic; N, number of subjects in the specified group, or the total sample; PD, progressive disease

Since the majority of patients died from disease progression prior to cilta-cel infusion, we analyzed the bridging therapy administration among the patients who did not progressed or died early compared to patients who died or progressed prior to cilta-cel infusion within 10 months of

randomization in the safety population.

Table 18: FDA – Bridging Therapy Summary, Safety Population, CARTITUDE-4

Category	Receiving Cilta-cel N=170	Progressed or died early N=18	Total Safety Population N=188
Received bridging therapy n (%)	170 (100)	18 (100)	188 (100)
Time from rdz. to start of BT	-	-	-
Median (range)	7.0 (2; 19)	7.5 (3; 13)	7.0 (2; 19)
Type of BT (%)	-	-	-
DPd	152 (89)	12 (67)	164 (87)
PVd	18 (11)	6 (33)	24 (13)
Duration of bridging therapy (days)	-	-	-
Median (range)	50 (16; 186)	48 (14; 130)	50 (14; 186)
Number of cycles n (%)	-	-	-
1	37 (22)	3 (17)	40 (21)
2	102 (60)	11 (61)	113 (60)
3	28 (17)	3 (17)	31 (17)
≥4	3 (2)	1 (6)	4 (2)
Median (range)	2.0 (1; 6)	2.0 (1; 4)	2.0 (1; 6)
Time from LK to product release (days)	-	-	-
Median (range)	54.5 (33; 180)	61.5 (40; 120)	56.0 (33; 180)

Source: Adapted from Applicant's response to FDA IR dated Mar 26, 2024 (TSIEX01_BR_IR). Data cutoff November 1, 2022
Abbreviations: BT, =bridging therapy; DPd, daratumumab-pomalidomide-dexamethasone; LK, leukapheresis; n (%), number of subjects with the specified characteristic; N, number of subjects in the specified group, or the total sample; PVd, pomalidomide-bortezomib-dexamethasone; rdz., randomization

Overall, the rate of bridging therapy administration was comparable between these two groups. The median time from randomization to start of bridging therapy and the median duration of bridging therapies were also similar between the two groups. Bridging therapy cycles were truncated and modified in the event of cytopenia or infections and in some instances more than one regimen was administered as bridging. Refer to Appendix 17.4 for additional bridging therapy safety analyses.

A higher proportion of patients randomized to cilta-cel compared to standard therapy experienced death in with first 10 months following randomization (n=29/208;14% vs. n=25/211;12%). Of the 29 deaths that occurred in the cilta-cel arm within the first 10 months of randomization, 10 deaths occurred prior to cilta-cel infusion, and 19 deaths occurred after cilta-cel infusion. Of the 10 deaths that occurred prior to cilta-cel infusion, all occurred due to disease progression, and none occurred due to adverse events. Of the 19 deaths that occurred after cilta-cel infusion, 3 occurred due to disease progression, and 16 occurred due to adverse events. The most common adverse

events were due to infection (n=9). The higher early mortality with cilta-cel was observed across multiple prognostic subgroups and was observed even in the absence of individual poor prognostic factors. In the safety analysis population, there was also a higher rate of fatal adverse reaction that occurred within 90 days from starting treatment with cilta-cel in the as treated population compared to in the standard therapy arm (5% versus 0%).

FDA conducted exploratory analyses to assess whether any prognostic subgroup was associated with a higher early mortality in the cilta-cel arm. No prognostic subgroup was associated with or was driving this observed higher early mortality. The study was not designed to identify a subgroup of patients who experienced higher early mortality with cilta-cel.

FDA convened a meeting of the Oncologic Drugs Advisory Committee (ODAC) to discuss whether the results of CARTITUDE-4 are sufficient to support a positive risk-benefit assessment of cilta-cel for the proposed indication and if the risk of early death associated with cilta-cel treatment is acceptable in the context of PFS benefit. Voting members of the ODAC were asked to vote on whether the risk-benefit assessment for cilta-cel for the proposed indication favorable; the ODAC voted 11 to 0 in favor of cilta-cel.

SAEs

Data:

Serious TEAEs by MedDRA SOC and PT (reported at a frequency of at least 2%) overall and events of Grade 3 or 4 are summarized by treatment arm in Table 11.

Table 11: Applicant – Number of Subjects with Treatment-emergent Serious Adverse Events with Frequency of at Least 2% by System Organ Class, Preferred Term, and Toxicity Grade 3 or 4; Safety Analysis Set (Study 68284528MMY3002)

	Arm A		Arm B	
	Total	Grade 3 or 4	Total	Grade 3 or 4
Analysis set: safety	208		208	
Total number of subjects with serious TEAE	81 (38.9%)	70 (33.7%)	92 (44.2%)	67 (32.2%)
MedDRA system organ				

class/preferred term				
Infections and infestations	51 (24.5%)	47 (22.6%)	50 (24.0%)	40 (19.2%)
COVID-19 pneumonia	9 (4.3%)	9 (4.3%)	12 (5.8%)	10 (4.8%)
Pneumonia	9 (4.3%)	7 (3.4%)	6 (2.9%)	5 (2.4%)
Blood and lymphatic system disorders	9 (4.3%)	9 (4.3%)	15 (7.2%)	14 (6.7%)
Febrile neutropenia	5 (2.4%)	5 (2.4%)	5 (2.4%)	5 (2.4%)
Nervous system disorders	3 (1.4%)	2 (1.0%)	14 (6.7%)	5 (2.4%)
Facial paralysis	1 (0.5%)	0	9 (4.3%)	1 (0.5%)
General disorders and administration site conditions	7 (3.4%)	2 (1.0%)	8 (3.8%)	1 (0.5%)
Pyrexia	5 (2.4%)	2 (1.0%)	4 (1.9%)	0
Immune system disorders	1 (0.5%)	0	7 (3.4%)	1 (0.5%)
Cytokine release syndrome	1 (0.5%)	0	7 (3.4%)	1 (0.5%)
Metabolism and nutrition disorders	3 (1.4%)	1 (0.5%)	7 (3.4%)	4 (1.9%)
Hypercalcaemia	2 (1.0%)	1 (0.5%)	5 (2.4%)	3 (1.4%)
Gastrointestinal disorders	3 (1.4%)	2 (1.0%)	6 (2.9%)	5 (2.4%)
Diarrhoea	0	0	5 (2.4%)	4 (1.9%)

Table 11: Applicant - Number of Subjects with Treatment-emergent Serious Adverse Events with Frequency of at Least 2% by System Organ Class, Preferred Term, and Toxicity Grade 3 or 4; Safety Analysis Set (Study 68284528MMY3002)

	Arm A		Arm B	
	Total	Grade 3 or 4	Total	Grade 3 or 4

Key: Arm A = PVd or DPd; Arm B = A sequence of apheresis, bridging therapy (PVd or DPd), conditioning regimen (cyclophosphamide and fludarabine), and cilta-cel infusion.
Key: PVd = pomalidomide-bortezomib-dexamethasone; DPd = daratumumab-pomalidomide-dexamethasone.
Key: TEAE = treatment-emergent adverse event.
Note: Adverse events are reported using MedDRA version 25.0.
Note: Percentages calculated with the number of subjects in each treatment group as denominator.
Note: Safety analysis set consists of subjects who received any part of study treatment.
Note: The output includes the diagnosis of CRS and ICANS along with other AEs and the symptoms of CRS or ICANS are excluded.

Modified from [TSFAE07.RTF] [PROD/JNJ-68284528/MMY3002/DBR_CSR/RE_CSR/TSFAE07.SAS] 20FEB2023, 17:45

The Applicant's Position:

Serious TEAEs were reported for 38.9% of participants in Arm A and for 44.2% of participants in Arm B. The only serious TEAE reported for at least 5% of participants in either treatment arm was COVID-19 pneumonia, reported for 4.3% of participants in Arm A and for 5.8% of participants in Arm B. The overall incidence of serious TEAEs in Arm B was driven by events under the SOCs of Blood and lymphatic system disorders (Arm A: 9 participants [4.3%]; Arm B: 15 participants [7.2%; mainly cytopenias]), Nervous system disorders (Arm A: 3 participants [1.4%]; Arm B: 14 participants [6.7%; mainly cranial nerve palsies]), and Immune system disorders (Arm A: one participant [0.5%]; Arm B: 7 participants [3.4%; all CRS]), reflecting TEAEs known to be associated with cilta-cel treatment. These data do not impact the current understanding of the known safety profile of CAR-T therapy.

The FDA's Assessment:

Table 19 summarizes all nonfatal SAEs in ≥2% of the safety population. Nonfatal serious events were reported in 71 (38%) and 81 (39%) subjects in the cilta-cel and the standard therapy arms, respectively. The most frequently reported SAEs Grade 3 or higher in ≥2% or more of subjects in the CARTITUDE-4 study were Pneumoniae (9%), viral infection (3%), sepsis (3%), neutropenia (2%), and CRS (2%) in the cilta-cel arm. Pneumoniae (12%), viral infection (6%), upper respiratory tract infection (4%), bacterial infection (3%), and febrile neutropenia (2%) were reported in the standard therapy arm. Other serious TEAEs in the cilta-cel arm included CRS and cranial nerve palsies, which are known AEs associated with CAR-T cell therapy.

Table 19: FDA – Nonfatal Serious Treatment-Emergent Adverse Events Occurring in ≥2% of the Safety Population, CARTITUDE-4

System Organ Class	Cilta-cel N=188 All Grades n (%)	Cilta-cel N=188 Grade 3-4 n (%)	Standard Therapy N=208 All Grades n (%)	Standard Therapy N=208 Grade 3-4 n (%)
Any nonfatal serious TEAE	66 (35)	39 (21)	78 (37)	67 (32)
Infections and infestations	-	-	-	-
Pneumoniae (GT)	19 (5)	9 (5)	24 (12)	22 (11)
Viral infection (GT)	12 (6)	5 (3)	12 (6)	12 (6)
Upper respiratory tract infection	3 (2)	2 (1)	9 (4)	8 (4)
Bacterial infection	3 (2)	3 (2)	7 (3)	7 (3)
Sepsis	5 (3)	5 (3)	3 (1.4)	1(0.5)

System Organ Class	Cilta-cel N=188 All Grades n (%)	Cilta-cel N=188 Grade 3-4 n (%)	Standard Therapy N=208 All Grades n (%)	Standard Therapy N=208 Grade 3-4 n (%)
Blood and lymphatic system disorders	-	-	-	-
Febrile neutropenia	0	0	5 (2)	5 (2)
Neutropenia	4 (2)	4 (2)	1 (0.5)	1 (0.5)
Nervous system disorders				
Encephalopathy	4 (2)	1 (0.5)	2 (1)	2 (1)
Cranial nerve palsies	10 (5)	2 (1)	1 (0.5)	0
Gastrointestinal disorders	-	-	-	-
Diarrhea	4 (2)	3 (2)	0	0
Immune system disorders	-	-	-	-
Cytokine release syndrome	12 (6)	4 (2)	1 (0.5)	0

Source: Applicant's IR response, data cutoff November 1, 2022
Abbreviations: GT, grouped term; n (%), number of subjects with the specified characteristic; N, number of subjects in the specified group, or the total sample; TEAE, treatment-emergent adverse event

TEAEs and Adverse Reactions

Data:

At least one TEAE of any grade was reported for all participants in the safety analysis set. The most frequently reported TEAEs of any grade (≥20% of participants in either treatment arm) included the following events:

- Within the SOC of Blood and lymphatic system disorders: neutropenia, anemia, thrombocytopenia, and lymphopenia
- Within the SOC of Immune system disorders: CRS and hypogammaglobulinemia
- Within the SOC of Gastrointestinal disorders: nausea, diarrhea, and constipation
- Within the SOC of General disorders and administration site conditions: fatigue
- Within the SOC of Infections and infestations: COVID-19
- Within the SOC of Nervous system disorders: headache
- Within the SOC of Psychiatric disorders: insomnia

ADRs are events that are considered to be reasonably associated with the use of cilta-cel based on a comprehensive assessment of available AE information. The assessment was based on all TEAEs and laboratory abnormalities reported following cilta-cel infusion among the 176 Arm B participants who received cilta-cel as study treatment in Study MMY3002. This assessment was

guided by the definition of ADRs from the ICH guideline entitled, E6: GCP, Consolidated Guidance. Each TEAE was assessed as a single term or within a grouped term and determined to be an ADR or not an ADR based on the combined assessment of incidence, plausibility, medical judgment, and case review of individual participant profiles, as necessary. Determination of ADRs focused on assessment of individual cases in addition to overall trends in the analysis sets.

Serious ADRs were reported for 58 participants (33.0%) who received cilta-cel as study treatment in Study MMY3002, most commonly (≥5% of participants) pneumonia (9.1%), viral infection (6.8%), and cranial nerve palsies (5.7%).

ADRs identified from Study MMY3002 are summarized in Table 12 and Table 13. To note, of the 8 participants who had a Grade 5 infection under the grouped term of pneumonia, 7 participants had COVID-19 pneumonia and one participant had pneumonia.

Table 12: Applicant – Adverse Reactions (≥10%) in Multiple Myeloma Patients Treated with Cilta-cel in Study MMY3002 (N=176)

System Organ Class	Adverse Reaction	Incidence (%)		
		All Grades	Grade 3-4	Grade 5
Infections and infestations	Upper respiratory tract infection[1]	46 (26.1%)	2 (1.1%)	0
	Viral infection[2]	43 (24.4%)	8 (4.5%)	0
	Bacterial infection[3]	25 (14.2%)	10 (5.7%)	0
	Pneumonia[4]	24 (13.6%)	7 (4.0%)	8 (4.5%)
Immune system disorders	Cytokine release syndrome	134 (76.1%)	2 (1.1%)	0
	Hypogammaglobulinaemia	86 (48.9%)	15 (8.5%)	0
Metabolism and nutrition disorders	Decreased appetite	19 (10.8%)	1 (0.6%)	0
Nervous system disorders	Headache	44 (25.0%)	0	0
Vascular disorders	Hypotension[5]	36 (20.5%)	4 (2.3%)	0
Respiratory, thoracic and mediastinal disorders	Cough[6]	28 (15.9%)	0	0
	Hypoxia	18 (10.2%)	4 (2.3%)	0
Gastrointestinal disorders	Diarrhea[7]	49 (27.8%)	6 (3.4%)	0

Table 12: Applicant - Adverse Reactions (≥10%) in Multiple Myeloma Patients Treated with Cilta-cel in Study MMY3002 (N=176)

System Organ Class	Adverse Reaction	Incidence (%)		
		All Grades	Grade 3-4	Grade 5
	Nausea	35 (19.9%)	0	0
	Constipation	18 (10.2%)	0	0

Musculoskeletal and connective tissue disorders	Musculoskeletal pain[8]	61 (34.7%)	3 (1.7%)	0
General disorders and administration site conditions	Pyrexia	136 (77.3%)	10 (5.7%)	0
	Fatigue[9]	52 (29.5%)	4 (2.3%)	0
	Edema[10]	21 (11.9%)	1 (0.6%)	0
	Pain[11]	19 (10.8%)	2 (1.1%)	0

Adverse events are reported using MedDRA version 25.0

[1]Upper respiratory tract infection includes Bronchitis, Nasal congestion, Nasopharyngitis, Pharyngitis, Respiratory tract infection, Rhinitis, Rhinorrhoea, Rhinovirus infection, Sinusitis, Upper respiratory tract infection, and Viral pharyngitis.

[2]Viral infection includes Adenovirus infection, Asymptomatic COVID-19, COVID-19, Cytomegalovirus infection, Cytomegalovirus infection reactivation, Cytomegalovirus viraemia, Hepatitis B reactivation, Herpes simplex reactivation, Herpes virus infection, Herpes zoster, Influenza, Lymphadenitis viral, Metapneumovirus infection, Parainfluenzae virus infection, Parvovirus B19 infection, Parvovirus infection, Respiratory syncytial virus infection, Respiratory tract infection viral, and Rotavirus infection.

[3]Bacterial infection includes Bordetella infection, Bronchitis bacterial, Campylobacter infection, Catheter site infection, Cellulitis, Chalazion, Citrobacter infection, Clostridium difficile colitis, Device related infection, Gingivitis, Perichondritis, Pyelonephritis acute, Salmonellosis, Skin infection, Staphylococcal infection, Superinfection bacterial, Vascular access site infection, and Vascular device infection.

[4]Pneumonia includes Bronchopulmonary aspergillosis, COVID-19 pneumonia, Lower respiratory tract infection, Metapneumovirus pneumonia, Pneumonia, Pneumonia moraxella, Pneumonia pseudomonal, and Pneumonia streptococcal.

[5]Hypotension includes Hypotension, and Orthostatic hypotension.

[6]Cough includes Cough, Productive cough, and Upper-airway cough syndrome.

[7]Diarrhea includes Colitis, and Diarrhoea.

[8]Musculoskeletal pain includes Arthralgia, Back pain, Bone pain, Bursitis, Musculoskeletal chest pain, Musculoskeletal pain, Myalgia, Myositis, Neck pain, Non-cardiac chest pain, Osteoarthritis, Pain in extremity, Plantar fasciitis, Rotator cuff syndrome, Spinal pain, and Tendonitis.

[9]Fatigue includes Asthenia, Fatigue, and Malaise.

[10]Edema includes Face oedema, Generalised oedema, Hypervolaemia, Oedema, Oedema peripheral, and Peripheral swelling.

[11]Pain includes Anorectal discomfort, Catheter site pain, Flank pain, Inflammatory pain, Pain, Pain in jaw, Pain of skin, Pelvic pain, Rhinalgia, and Sacral pain.

Modified from: [TSFADR01A_US.RTF] [JNJ-68284528/Z_ADR/DBR_SBLA_2023/RE_SBLA_2023/PROD/TSFADR01A_US.SAS]
17APR2023, 16:35

Table 13: Applicant - Laboratory Abnormalities Following Treatment with Cilta-cel Based on CTCAE[a] in Study MMY3002 (N=176)

Laboratory Abnormality	Any Grade (%)	Grade 3 or 4 (%)
Anemia	176 (100.0%)	52 (29.5%)
Lymphopenia	176 (100.0%)	174 (98.9%)
White blood cell decreased	176 (100.0%)	166 (94.3%)
Neutropenia	175 (99.4%)	167 (94.9%)
Thrombocytopenia	168 (95.5%)	78 (44.3%)

Fibrinogen decreased	15 (8.5%)	12 (6.8%)
Hypoalbuminemia	112 (63.6%)	0
Alanine aminotransferase increased	95 (54.0%)	7 (4.0%)
Aspartate aminotransferase increased	86 (48.9%)	6 (3.4%)
Gamma Glutamyl Transferase increased	83 (47.2%)	12 (6.8%)
Hypocalcemia	80 (45.5%)	1 (0.6%)
Hypokalemia	73 (41.5%)	9 (5.1%)
Hypomagnesemia	69 (39.2%)	4 (2.3%)
Alkaline phosphatase increased	66 (37.5%)	6 (3.4%)
Hyponatremia	54 (30.7%)	5 (2.8%)
Hypertriglyceridaemia	40 (22.7%)	5 (2.8%)
Blood bilirubin increased	23 (13.1%)	1 (0.6%)

[a]CTCAE = Common Terminology Criteria for Adverse Events version 5.0
Note: Lab assessments following cilta-cel infusion until the start of subsequent therapy are included in the analysis.
Modified from [TSFLAB01A_US.RTF] [JNJ-68284528/Z_ADR/DBR_SBLA_2023/RE_SBLA_2023/PROD/TSFLAB01A_US.SAS]
17APR2023, 16:35

The Applicant's Position:

Overall, the TEAEs and ADRs were manageable and consistent with the known mechanism of action of cilta-cel and prior experience reported for CAR-T therapy.

The FDA's Assessment:

We generally agree with the Applicant's description of the common AEs. The FDA conducted their own analysis based on FDA grouped terms on patients treated with conforming cilta-cel (N=188) as shown below.

Incidence of AEs are presented by system organ class and by the individual AEs in Table 20. Among the common TEAEs, higher rates of CRS, hypogammaglobulinemia, bacterial infections, encephalopathy, and parkinsonism were noted in the cilta-cel arm compared to standard therapy. Grade 3 to 4 hypogammaglobulinemia, CRS, bacterial infection, pneumoniae, encephalopathy, and parkinsonism were higher in the cilta-cel arm compared to the standard therapy arm.

TEAEs, which occurred in 10% or more of subjects, are listed in Table 20.

Table 20: FDA – Treatment-Emergent Adverse Events Occurring in ≥10% of Subjects, GT Safety Population, CARTITUDE-4

System Organ Class	Cilta-cel N=188 All Grades n (%)	Cilta-cel N=188 Grade 3-4 n (%)	Standard Therapy N=208 All Grades n (%)	Standard Therapy N=208 Grade 3-4 n (%)
Any TEAE	188 (100)	151 (80)	208 (100)	190 (91)
General disorders and administration site conditions	-	-	-	-
Pyrexia	148 (79)	9 (5)	33 (16)	4 (2)
Fatigue (GT)	53 (28)	5 (3)	104 (50)	7 (3)
Edema	21(11)	2 (1)	(20)	(1)
Immune system disorders	-	-	-	-
Hypogammaglobulinemia	176 (94)	16 (9)	149 (72)	-
Cytokine release syndrome	146 (78)	6 (3)	1 (0.5)	1 (0.5)
Gastrointestinal disorders	-	-	-	-
Diarrhea (GT)	50 (27)	6 (3)	56 (27)	5 (2)
Nausea	38 (20)	0	37 (18)	2(1)
Constipation	21(10)	0	44 (21)	2(1)
Infections and infestations	-	-	-	-
Upper respiratory infection	47 (25)	2 (1)	83 (40)	10 (5)
Viral infection (GT)	44 (23)	8 (4)	76 (37)	12 (6)
Bacterial infection (GT)	28 (15)	12 (6)	36 (17)	9 (4)
Pneumonia	27 (14)	17 (9)	38 (18)	23 (11)
COVID-19	17 (9)	4 (2)	42 (20)	4 (2)
Nervous system disorders	-	-	-	-
Headache	35 (19)	0	28 (14)	0
Encephalopathy (GT)	20 (11)	3 (2)	9 (4)	2 (1)
Dizziness (GT)	16 (9)	1 (0.5)	37 (18)	8 (4)
Neuropathy (GT)	13 (7)	1 (0.5)	38 (19)	1 (0.5)
Musculoskeletal and connective tissue disorders	-	-	-	-
Musculoskeletal pain (GT)	64 (34)	3 (2)	98 (47)	9 (4)
Respiratory, thoracic, and mediastinal disorders	-	-	-	-
Cough	28 (15)	0	18	0
Hypoxia	22 (12)	6(3)	1	1
Vascular disorders	-	-	-	
Hypotension (GT)	44 (23)	7 (4)	6 (3)	0
Hemorrhage (GT)	17 (9)	2(1)	29 (14)	0

System Organ Class	Cilta-cel N=188 All Grades n (%)	Cilta-cel N=188 Grade 3-4 n (%)	Standard Therapy N=208 All Grades n (%)	Standard Therapy N=208 Grade 3-4 n (%)
Psychiatric disorders	-	-	-	-
Sleep disorder	11 (6)	1 (0.5)	52 (25)	6 (3)

Source: FDA analysis, data cutoff November 1, 2022
AE, presented for Arm B in the output, is any AE that occurred on or after cilta-cel infusion (Day 1), either as study treatment or subsequent therapy, until Day 112 or start of subsequent therapy, whichever earlier, or any AE that is considered related to cilta-cel infusion, either as study treatment or subsequent therapy, regardless of event onset. Hypogammaglobulinemia is a composite of events reported in ADAE dataset and laboratory values of IgG < 500 mg/dl following treatment administration.
For listing of GT please refer to Appendix 17.5.
Abbreviations: COVID-19, Coronavirus Disease 2019; GT, grouped term; n (%), number of subjects with the specified characteristic; N, number of subjects in the specified group, or the total sample; SOC, system organ class; TEAE, treatment adverse event.

The most common all grades and Grade 3 and 4 laboratory hematologic and nonhematologic abnormalities that occurred in ≥10% of subjects are depicted in Table 21. Overall, all Grade 3 and 4 laboratory abnormalities were observed in a higher proportion of subjects in the cilta-cel arm compared to the standard therapy arm.

Hematologic laboratory abnormalities were expected in both arms; however, the rate of Grade 3 and 4 hematologic toxicity was higher in the cilta-cel arm compared to the standard therapy arm.

Table 21: FDA – Laboratory Abnormalities Occurring in ≥10% of the Safety Population, CARTITUDE-4

Laboratory Abnormality	Cilta-cel N=188 All Grades n (%)	Cilta-cel N=188 Grade 3-4 n (%)	Standard Therapy N=208 All Grades n (%)	Standard Therapy N=208 Grade 3-4 n (%)
Anemia	188 (100)	61 (34)	202 (97)	33 (11)
Lymphocyte count decreased	188 (100)	185 (99)	182 (88)	129 (62)
Neutrophil count decreased	187 (99)	178 (95)	203 (98)	182 (88)
Platelet count decreased	177 (94)	82 (44)	181 (87)	42 (20)
White blood cell decreased	188 (100)	177 (94)	207 (100)	143 (69)
ALT increased	96 (51)	6 (3)	57 (27)	7 (3)
ALK increased	76 (41)	8 (4)	53 (26)	0
AST increased	86 (46)	11(6)	30 (14)	4 (2)
Potassium decreased	28 (15)	4 (2)	14 (7)	3 (1)
Phosphorus decreased	20 (10)	4 (3)	8 (4)	1 (0.5)

Source: FDA analysis and Applicant response to information request, data cutoff November 1, 2022
Laboratory tested are graded according to National Cancer Institute (NCI) common terminology criteria for adverse events (CTCAE version 5.0).
Laboratory values included in the analysis are for standard therapy arm, lab assessments on or after the study treatment start until 30 days after the last dose of study treatment or start a subsequent therapy, whichever earlier. For cilta-cel arm, lab assessment on or after cilta-cel infusion until Day 112 or start subsequent therapy, whichever earlier.
Abbreviations: ALK, alkaline phosphatase; ALT, Alanine aminotransferase; AST, Aspartate aminotransferase; n (%), number of subjects with the specified characteristic; N, number of subjects in the specified group, or the total sample

The overall AEs after cilta-cel treatment are consistent with those seen for the already approved indication of RRMM and with other anti-BCMA CAR T cell products and are considered of acceptable severity given its efficacy.

Table 19 above will serve as the basis for the ADR table of the USPI. The laboratory abnormalities incidence will be presented in a separate table that is derived from the ADLB dataset and not from the ADAE dataset since the ADLB is more accurate and will capture all laboratory abnormalities rather than just the ones recorded as AEs.

Other clinically important adverse reactions that occurred in less than 10% of patients are included in the USPI.

Adverse Events of Special Interest (Arm B)

Adverse Events of Special Interest (AESIs) are summarized in Table 22.

Table 22: FDA – Summary of Adverse Events of Special Interest, Safety Population, CARTITUDE-4

AESI	Cilta-cel N=188 Any Grade n (%)	Cilta-cel N=188 Grade ≥3 n (%)	Standard Therapy N=208 Any Grade n (%)	Standard Therapy N=208 Grade ≥3 n (%)
CRS	146 (77)	6 (3)	1(1)	0
Neurotoxicity	44 (23)	8 (4)	0	0
HLH/MAS	2 (1)	1(0.5)	1 (2)	0
Infections	107 (57)	46 (25)	148 (71)	47 (23)
Secondary primary malignancy	8 (4)	N/A	14 (7)	N/A
Hematologic neoplasm	3 (2)	1(0.5)	0	-
Cytopenia	-	-	-	-
Neutropenia	187 (99)	178 (95)	203 (98)	182 (87)
Thrombocytopenia	177 (94)	82 (44)	181 (87)	42 (20)

Source: FDA analysis, data cutoff November 1, 2022
Abbreviations: CRS, cytokine release syndrome; HLH, hemophagocytic lymphohistiocytosis; MAS, macrophage activation syndrome; n (%), number of subjects with the specified characteristic; N, number of subjects in the specified group, or the total sample; N/A, not applicable

CRS

Data:

Among the Arm B participants who received cilta-cel as study treatment (n=176), most participants (134 participants [76.1%]) experienced CRS, generally of Grade 1 (93 participants [52.8%]) or Grade 2 (39 participants [22.2%]) severity. Two participants (1.1%) experienced Grade 3 CRS.

The median time from initial cilta-cel infusion to first onset of CRS was 8.0 days (range: 1 to 23 days) and the median duration of CRS was 3.0 days (range: 1 to 17 days).

Most participants (131 participants [74.4%]) received supportive measures to treat CRS and CRS symptoms, most commonly analgesics/anti-inflammatories (95 participants [54.0%]), anti-infectives (91 participants [51.7%]), and the IL-6 receptor antagonist tocilizumab (71 participants [40.3%]). Vasopressors were administered to 2 participants (1.1%). Oxygen was required as a supportive measure to treat CRS for 17 participants (9.7%). No participant required intubation as a supportive measure to treat CRS. As of the database lock, CRS was considered as recovered or resolved for 133 of 134 participants. As described further in Section 12 of the CSR for Study MMY3002, the outcome was incorrectly entered in the database for the CRS event that was recorded as not resolved; subsequent to database lock the outcome for this event was corrected

to recovered or resolved.

The Applicant's Position:

CRS is a known risk associated with CAR-T therapy. In Study MMY3002, CRS was reported for 134 participants (76.1%) who received cilta-cel as study treatment, which was as expected for a CAR-T therapy. CRS was manageable for the majority of participants. Most events of CRS were mild, with 132 of the 134 participants experiencing Grade 1 or 2 events. No Grade 4 or 5 CRS was reported. A lower incidence of Grade 3 or higher CRS was observed in Study MMY3002 (1.1%) than in the more refractory population of Study MMY2001, in which CRS occurred in 92 of 97 participants (95%) receiving cilta-cel, with Grade 3 or higher CRS in 5 participants (5%; CARVYKTI USPI 2023). This difference may be due in part to more effective bridging therapy in Study MMY3002, with 74.0% of participants in the ITT analysis set for Arm B having a decrease in tumor burden between baseline and administration of the conditioning regimen. In conclusion, results from Study MMY3002 suggest that the use of cilta-cel in patients with earlier relapsed disease may contribute to a lower incidence of CRS.

The FDA's Assessment:

CRS occurred in 146 subjects (78%) in the safety analysis set, including ≥Grade 3 (severe, life threatening, or fatal) in 3% of the subjects. See Table 23. The median time to onset of CRS was 8 days (range: 1 to 23 days), and the median duration of CRS was 3 days (range: 1 to 17 days). Median time to CRS resolution was 3 days (range: 1 to 17 days).

Table 23: FDA – Cytokine Release Syndrome, Safety Population, CARTITUDE-4

Parameters	**Cilta-cel N=188**
Subjects with CRS	146 (78%)
Maximum toxicity grade	-
Grade 1	95 (50%)
Grade 2	45 (24%)
Grade 3	4 (2%)
Grade 4	2 (1%)
Grade 5	0
Time from initial infusion to first onset (days)	-
Median (range)	8.0 (1; 23)
Interquartile range	(6.0; 8.0)

Parameters	Cilta-cel N=188
Duration	-
Median (range)	3.0 (1; 17)
Interquartile range	(2.0; 5.0)
Time to resolution	-
Median (range)	3.0 (1; 17)
Interquartile range	(2.0; 5.0)
Outcome	-
Recovered or resolved	143 (76%)
Not recovered or not resolved	2 (1%)
Recovered or resolved with sequelae	1 (0.5%)

Source: FDA analysis and Applicant response to information request, data cutoff November 1, 2022
Abbreviations: CRS, cytokine release syndrome; N, number of subjects in the specified group, or the total sample

Key manifestations of CRS occurring in ≥10% of subjects included fever (78%), hypotension (21%), and hypoxia (11%) and nausea. Grade ≥3 events that were associated with CRS and occurred in >1% of subjects included fever (5%), hypotension (3%), and hypoxia (3%)

Of the 188 patients who received CARVYTI in clinical trials, 44% (44/188) patients received tocilizumab; 51% (27/188) received a single dose, while 17% (31/188) received more than 1 dose of tocilizumab. Overall, 7% (14/188) of patients received at least one dose of corticosteroids for treatment of CRS. The CRS profile observed in the CARTITUDE-4 study was generally consistent with previous experience with Cilta-cel.

CAR-T Cell Neurotoxicity

Data:

CAR-T cell neurotoxicity is a known risk associated with CAR-T therapy. Of the Arm B participants who received cilta-cel as study treatment (n=176), 36 participants (20.5%) experienced one or more treatment-emergent CAR-T cell neurotoxicity events, with 5 participants (2.8%) experiencing Grade 3 or 4 events. No Grade 5 neurotoxicity events were reported. CAR-T cell neurotoxicity was categorized as ICANS or Other Neurotoxicity determined by the investigator to be related to CAR-T therapy and occurring after recovery of CRS and/or ICANS. To provide a more comprehensive overview, the cranial nerve palsy and peripheral neuropathy categories of Other Neurotoxicity below include participants with cranial nerve palsy and peripheral neuropathy regardless of whether the AE was considered CAR-T Cell Neurotoxicity by the investigator.

ICANS and Other Neurotoxicity are not mutually exclusive, 2 participants had events in both categories.

ICANS

- 8 participants (4.5%) experienced ICANS, including 6 participants (3.4%) with a Grade 1 event and 2 participants (1.1%) with a Grade 2 event. No participants experienced Grade 3 or higher events, evaluated according to the ASTCT consensus grading system. Six participants (3.4%) had ICANS concurrent with CRS.
- The median time from initial cilta-cel infusion to first onset of ICANS was 9.5 days (range: 6 to 15), and the median duration of ICANS was 2.0 days (range: 1 to 6).
- Four participants (2.3%) received supportive measures to treat ICANS, and all events of ICANS were considered as recovered or resolved.
- Eight participants (4.5%) experienced TEAEs considered as symptoms of ICANS. The most commonly reported (≥1%) symptoms of ICANS included dysgraphia (4 participants [2.3%]) and headache (2 participants [1.1%]). With the exception of Grade 2 dysmetria and Grade 3 syncope, each reported for one participant (0.6%), all treatment-emergent symptoms of ICANS were of Grade 1 toxicity.

Other Neurotoxicities

- 30 participants (17.0%) experienced an event of Other Neurotoxicity with onset following cilta-cel infusion, including 4 (2.3%) participants with events with maximum toxicity of Grade 3. No fatal events were reported. The median time from initial cilta-cel infusion to first onset of other neurotoxicities was 21.0 days (range: 1 to 113); onset of other neurotoxicities occurred within 30 days of cilta-cel infusion for 24 participants and >30 days after cilta-cel infusion for 6 participants.

Movement and Neurocognitive TEAEs:

- One participant developed movement and neurocognitive TEAEs with maximum toxicity of Grade 1, with an AE onset at 85 days following cilta-cel infusion. These AEs were ongoing as of the time of clinical cutoff.

  Cranial Nerve Palsies:

  – 16 participants (9.1%) experienced presentation of cranial nerve palsies, all of which were considered CAR-T cell neurotoxicity by the investigator. Two participants (1.1%)

experienced events of a maximum toxicity of Grade 3, with no Grade 4 or fatal events reported.

- The median time from cilta-cel infusion to first onset of cranial nerve palsies was 21.0 days (range: 17 to 60). As of the clinical cutoff, 14 participants (8.0%) had recovered and 2 participants (1.1%) had ongoing cranial nerve palsies.

Peripheral Neuropathies

- 13 participants (7.4%) experienced an event of peripheral neuropathy, with events in 5 participants considered CAR-T cell neurotoxicity by the investigator and events in 8 participants after cilta-cel, but not considered CAR-T cell neurotoxicity by the investigator. Maximum toxicity was Grade 1 for 6 participants (3.4%), Grade 2 for 6 participants (3.4%), and Grade 3 for one participant (0.6%). No Grade 4 or fatal AEs were reported.
- The median time from cilta-cel infusion to first onset of peripheral neuropathy was 57.0 days (range: 1 to 225). As of the clinical cutoff, 7 (4.0%) participants had recovered and 6 (3.4%) participants had ongoing peripheral neuropathy.

Guillain-Barré Syndrome

- As of the clinical cutoff, no events of Guillain-Barré syndrome were reported.

The Applicant's Position:

ICANS and other neurotoxicities are described in the literature as known risks associated with CAR-T cell infusions. In Study MMY3002, 36 of 176 Arm B participants (20.5%) who received cilta-cel as study treatment experienced one or more treatment-emergent CAR-T cell neurotoxicity events, with 5 participants (2.8%) experiencing Grade 3 or 4 events. In Study MMY2001, neurologic toxicity occurred following cilta-cel infusion in 26% of participants, with 11% participants experiencing Grade 3 or higher events (CARVYKTI USPI 2023). ICANS was reported for 4.5% of participants who received cilta-cel as study treatment in Study MMY3002 (versus 23% in Study MMY2001 [CARVYKTI USPI 2023]), with no Grade 3 or 4 ICANS events (versus 3% in Study MMY2001 [CARVYKTI USPI 2023]). Mitigation strategies put in place in Study MMY3002, together with proper and early treatment may have contributed to a low incidence of ICANS and other neurotoxicities.

The FDA's Assessment:

Among the 188 subjects in the cilta-cel arm, 44 subjects (23%) experienced CAR-T cell NT, including immune effector cell-associated neurotoxicity syndrome (ICANS) in 14 subjects (7%) and Other NT in 35 subjects (19%). See Table 24 and Table 25.

- ICANS: Most subjects experienced Grade 1 or 2 ICANS. One subject had a Grade 3. The median time to onset of ICANS was 9 days (range: 3 to 15 days) with a median duration of 2 days (range: 1 to 21 days). Median time to resolution was 2 days (range: 1 to 21 days). Eleven subjects had ICANS concurrent with CRS.
- Other NT: Among the subjects who experienced other NT, most subjects experienced Grade 1 or 2 events; six subjects (3%) experienced Grade 3 toxicity. The following NT categories were reported in CARTITUDE-4:
  - Movement and Neurocognitive toxicities: 2 subjects (1%), all Grade ≤2
  - Cranial Nerve Palsy: 16 subjects (8.5%); maximum toxicity was Grade 2 for 14 subjects (7%) and Grade 3 for 2 subjects (1%)
  - Peripheral Neuropathies: 14 subjects (7%). Maximum toxicity was Grade 1 for 5 subjects (3%) and Grade 2 for 8 subjects (4%); only 1 subject had a Grade 3 event.

Table 24: FDA – CAR-T Cell Neurotoxicity, Safety Population, CARTITUDE-4

Parameter	ICANS	Peripheral Neuropathies	Cranial Nerve Palsies
Total	14 (7%)	14 (7%)	16 (8%)
Maximum toxicity grade	-	-	-
Grade 1	10 (5%)	14 (7%)	-
Grade 2	3 (2%)	8 (4%)	14 (7%)
Grade 3	1 (0.5%)	1 (0.5%)	2 (1%)
Grade 4	0	0	0
Grade 5	0	0	0
CRS	-	-	-
With concurrent CRS	11 (6%)	-	-
Without concurrent CRS	3 (2%)	-	-
Time from initial infusion to first onset (days)	-	-	-
Median (range)	9.0 (2; 15)	51.0(1; 225)	21.0 (17; 60)
Interquartile range	(7; 10)	(31; 113)	(20; 25)
Duration	-	-	-
Median (range)	2.0 (2; 21)	167.5 (1; 503)	-
Interquartile range	(1; 2)	(1; 503)	-
Time to recovery	-	-	-
Median (range)	2.0 (1; 21)	36.5(1; 215)	61 (15; 209)
Interquartile range	(1; 2)	(7; 174)	(34; 95)

Parameter	ICANS	Peripheral Neuropathies	Cranial Nerve Palsies
Outcome	-	-	-
Recovered or resolved	13 (7%)	8 (4%)	14 (7%)
Not recovered or not resolved	1 (0.5%)	8 (4%)	2 (1%)

Source: Modified from Applicant Response to FDA IR dated Jan 25, 2024 (TSFAE25A_CSR_IRPART3OF3). Data cutoff November 1, 2022
Abbreviations: CRS, cytokine release syndrome; ICANS, Immune Effector Cell-associated Neurotoxicity Syndrome; N, number of subjects in the specified group, or the total sample

Table 25: FDA – CAR-T Cell Neurotoxicity Symptoms in ≥1% of Subjects by System Organ Class Preferred Term, Safety Population, CARTITUDE-4

Parameters	CAR-T Cell NT All Grades n (%)	CAR-T Cell NT Grade 3 or 4 n (%)	ICANS All Grades n (%)	ICANS Grade 3 or 4 n (%)	Other Neurotoxicity All Grades n (%)	Other Neurotoxicity Grade 3 or 4 n (%)
Number of subjects with NT	44 (23)	8 (4)	14 (7)	3 (2)	35 (19)	6 (3)
System organ class/preferred term	-	-	-	-	-	-
Nervous system disorders	-	-	-	-	-	-
Neurological disorders NEC	-	-	-	-	-	-
Dysgraphia	7 (4)	0	6 (3)	0	1 (0.5)	0
Dysarthria	3 (2)	0	2 (1)	0	1 (0.5)	0
Hypoaesthesia	3 (2)	0	0	0	3 (2)	0
Aphasia	2 (1)	0	1 (0.5)	0	2 (1)	0
Neuralgia	2 (1)	1 (0.5)	0	0	2 (1)	1 (0.5)
Cranial nerve disorders (excl neoplasms)	-	-	-	-	-	-
Facial paralysis	11(6)	1 (0.5)	0	0	11 (6)	1 (0.5)
Facial paresis	5 (3)	0	0	0	5 (3)	0
Encephalopathies	-	-	-	-	-	-
Immune effector cell-associated neurotoxicity syndrome	14 (7)	1 (0.5)	14 (7)	1 (0.5)	0	0
Headache	10 (5)	0	3 (2)	0	7 (4)	0
Peripheral neuropathies	-	-	-	-	-	-
Peripheral sensory neuropathy	4 (2)	0	0	0	4 (2)	0
Movement disorders (incl parkinsonism)	-	-	-	-	-	-
Micrographia	2 (1)	0	0	0	2 (1)	0
Parkinsonism	2 (1)	0	0	0	2 (1)	0
Reduced facial expression	2 (1)	0	0	0	2 (1)	0
Tremor	2 (1)	0	1 (0.5)	0	1 (0.5)	0
Bradykinesia	1 (0.5)	0	0	0	1 (0.5)	0
Extrapyramidal disorder	1 (0.5)	0	0	0	1 (0.5)	0
Mental impairment disorders	-	-	-	-	-	-

Parameters	CAR-T Cell NT All Grades n (%)	CAR-T Cell NT Grade 3 or 4 n (%)	ICANS All Grades n (%)	ICANS Grade 3 or 4 n (%)	Other Neurotoxicity All Grades n (%)	Other Neurotoxicity Grade 3 or 4 n (%)
Disturbance in attention	2 (1)	0	0	0	2 (1)	0
Amnesia	1 (0.5)	0	0	0	1 (0.5)	0
Psychiatric disorders	-	-	-	-	-	-
Deliria (incl confusion)	5 (3)	1 (0.5)	5 (3)	1 (0.5)	0	0
Confusional state	5 (3)	1 (0.5)	5 (3)	1 (0.5)	0	0
Sleep disorders and disturbances	-	-	-	-	-	-
Insomnia	2 (1)	0	0	0	2 (1)	0
Depressed mood disorders and disturbances	2 (1)	0	0	0	2 (1)	0
Depression	1 (0.5)	0	0	0	1 (0.5)	0
Psychomotor retardation	1 (0.5)	0	0	0	1 (0.5)	0
Mood disorders and disturbances NEC	2 (1)	0	0	0	2 (1)	0
Apathy	1 (0.5)	0	0	0	1 (0.5)	0
Flat affect	1 (0.5)	0	0	0	1 (0.5)	0
Mood altered	1 (0.5)	0	0	0	1 (0.5)	0
Disturbances in thinking and perception	-	-	-	-	-	-
Bradyphrenia	1 (0.5)	0	1 (0.5)	0	0	0
Eye disorders	-	-	-	-	-	-
Vision disorders	3 (2)	0	1 (0.5)	0	2 (1)	0
General system disorders NEC						
Gait disturbance	3 (2)	0	1 (0.5)	0	2 (1)	0

Source: Modified from Applicant Response to FDA IR dated Jan 25, 2024 (TSFAE25A_CSR_IRPART3OF3). Data cutoff November 1, 2022
Abbreviations: CAR, chimeric antigen receptor; ICANS, Immune Effector Cell-Associated Neurotoxicity Syndrome; n (%), number of subjects with the specified characteristic; N, number of subjects in the specified group, or the total sample; NT, neurotoxicity

Second Primary Malignancy

Data:

For Arm A and Arm B, SPMs are AEs of special interest, including both new primary malignancies and recurrence of pre-existing malignancies with the exception of multiple myeloma (which should be considered and reported as progressive disease).

Fourteen participants (6.7%) in the Arm A safety analysis set and 9 participants (4.3%) in the Arm B safety analysis set had an SPM event during the study. Three PTs, all categorized under

cutaneous/non-invasive malignancies, were reported for more than one participant each: basal cell carcinoma, squamous cell carcinoma of skin, and Bowen's disease. Three participants (1.4%) in Arm B had an SPM of hematologic malignancies, including acute myeloid leukemia, myelodysplastic syndrome, and CAR-positive peripheral T-cell lymphoma unspecified, each reported for one participant (0.5%). Additional details are provided in Section 5.2.1.5.3 of the CSR for Study MMY3002.

The Applicant's Position:

There is a potential risk of SPM due to possible viral insertion (DNA integration) of the LV vector. With the exception of the event of CAR-positive peripheral T-cell lymphoma unspecified in one participant, no events of SPM reported for Arm B participants were considered by the investigator to be related to cilta-cel. Life-long monitoring of patients for SPM and collection of patient samples for testing for SPM of T-cell origin in the event of a secondary malignancy are recommended (CARVYKTI USPI 2023).

The FDA's Assessment:

Three subjects (2%) in the cilta-cel arm and no subjects in the standard therapy arm had hematologic second primary malignancy, including AML, MDS, and T cell lymphoma. The case of T cell lymphoma was considered related to cilta-cel. The median time to onset of hematologic malignancies from cilta-cel arm was 159 days (range 56-301). Below a summary of the SPM cases as the data cutoff of November 1, 2022.

Subject (b) (6) is a 74-year-old woman who received 2 prior lines of therapy, including oral melphalan and lenalidomide. Past medical history included past breast cancer and breast cancer recurrence as well as ongoing essential thrombocythemia. She received cilta-cel on (b) (6) with a VGPR as best response from Day 29 after cilta-cel infusion. MDS was diagnosed on Day 56 after cilta-cel infusion with no treatment reported. Bone marrow biopsy entering the study (Jun 2021), showed dysplastic characteristics with maturation disturbances in all 3 lineages and presence of two TP53 mutations and a DNMT3A mutation (per investigator communication). The subject died on Day 200 after cilta-cel infusion due to intracranial hemorrhage. At that time the MDS was not resolved. A bone marrow sample was collected close to MDS onset and CAR transgene analysis was negative. No RCL was detected at any available time point, including within +/- 3 months of MDS onset.

Subject (b) (6) is a 62-year-old man who re received 3 prior lines of therapy, including high-dose melphalan with ASCT and lenalidomide. He received cilta-cel on (b) (6) with sCR as

best response from Day 56 after cilta-cel infusion. On Day 301 after cilta-cel infusion), AML was reported and treated with azacitidine and venetoclax. Molecular pathology of the bone marrow showed del9q. On Day 472 after cilta-cel infusion), the subject died due to AML. A bone marrow sample for CAR transgene analysis. Was not evaluable by qPCR or ISH/IHC assays. No RCL was detected on Day 196 after cilta-cel infusion; RCL samples on day 321 and day 365 after cilta-cel infusion, were not evaluable by qPCR assay.

Subject (b) (6) is a 51-year-old man who bridging therapy with DPd. On Day 134 post cilta-cel infusion he presented with skin lesion on the left side of a nare which was biopsied. Biopsy compatible with peripheral T cell lymphoma (PTCL) NOS (D159); further evaluation confirmed disseminated disease. 90-100% of cell (node biopsy) expressed the BCMA CAR, 91% of the lymph node biopsy clonal (TCR sequencing). The clone was not detected in pheresis and earlier samples. The clone was first detected in drug product via TCR sequencing. A bone marrow biopsy done 5.5 months post-treatment showed MRD negativity for myeloma at sensitivity of 10e-5; however, a monoclonal CD4/8 negative T cell population was identified representing 40% of the lymphocytes. Subject was initiated on steroids due to progression of the cutaneous lesion. A research assay performed at the study site showed BCMA CAR on the CD4/8 negative T cell population in the blood/marrow and on a lymph node biopsy. The subject was initiated on treatment with CHOEP (multiagent chemotherapy) for the treatment of T cell lymphoma and attained a clinical response.
In January 2023, the subject experienced PTCL-NOS relapse (progression in bone marrow and lymph nodes); treatment with cisplatin was initiated (Day 331 post ciltacabtagene autoleucel infusion). One month later, additional treatments for PTCL included alemtuzumab, gemcitabine, and dexamethasone. On Day 348, CAR T-cell re- expansion was detected in peripheral blood (135 absolute CAR+ T-cells/ μL [~18.3%]). At the time of this reported relapse, the subject remained in complete response for multiple myeloma. The subject is awaiting allogenic stem cell transplant (ASCT) for the treatment of PTCL-NOS

The following language will be incorporate in the USPI label: T-cell malignancies have occurred following treatment of hematologic malignancies with BCMA- and CD19-directed genetically modified autologous T-cell immunotherapies, including CARVYKTI. Mature T-cell malignancies, including CAR-positive tumors, may present as soon as weeks following infusion, and may include fatal outcomes *[see Boxed Warning, Adverse Reactions (6.1, 6.3), Patient Counseling Information (17)]*.

At the time of 120-safety update report, two additional hematological malignancies were reported

in the cilta-cel arm bring the total number of myeloid malignancies to five (MDS=3, AML=1, MDS transformed to AML=1). The rate of MDS/AML will be updated in the USPI to inform providers.

No cases of MDS/AML have been reported in the standard therapy arm.

Other Significant Adverse Events (Arm A and Arm B)

Cytopenias

Data:

Most participants in the safety analysis set in both treatment arms (Arm A: 88.9%; Arm B: 93.8%) experienced a treatment emergent cytopenia-associated AE.

- Grade 3 or 4 events were reported for 86.1% of participants in Arm A and for 93.8% of participants in Arm B.
- Neutropenia was the most frequently reported treatment-emergent cytopenia-associated AE, reported for 85.1% of participants in Arm A (Grade 3 or 4: 82.2%) and for 89.9% of participants in Arm B (Grade 3 or 4: 89.9%).
- Febrile neutropenia of all grades was reported for 8 participants (3.8%) in Arm A and for 11 participants (5.3%) in Arm B; serious TEAEs of febrile neutropenia were reported for 5 participants (2.4%) in each arm.
- Serious cytopenia TEAEs included anemia (1 participant [0.5%] in Arm A and 4 participants [1.9%] in Arm B), neutropenia (1 participant [0.5%] in Arm A and 4 participants [1.9%] in Arm B), and thrombocytopenia (0 participants in Arm A and one participant [0.5%] in Arm B).
- Among Arm B participants who received cilta-cel as study treatment (n=176), Grade 3 or 4 events of neutropenia had not recovered to ≤Grade 2 by Day 30 for 26.1% of participants and by Day 60 for 10.2% of participants. After Day 60, 23.3% of participants had a recurrence of Grade 3 or 4 neutropenia after initial recovery.
- Among Arm B participants who received cilta-cel as study treatment (n=176), Grade 3 or 4 events of thrombocytopenia had not recovered to ≤Grade 2 by Day 30 for 26.1% of participants and by Day 60 for 10.8% of participants. After Day 60, 4.5% of participants had a recurrence of Grade 3 or 4 thrombocytopenia after initial recovery.

The Applicant's Position:

Prolonged or recurrent cytopenia is a known risk associated with CAR-T therapy. Participants may

exhibit cytopenia for several weeks following lymphodepleting chemotherapy and cilta-cel infusion. In Study MMY3002, rates of prolonged cytopenias were low and manageable with supportive care, with only approximately 10% of Grade 3 or 4 events of thrombocytopenia, neutropenia, and lymphopenia not recovered to ≤ Grade 2 by Day 60. Among the 176 participants who received cilta-cel as study treatment in Study MMY3002, 26.1% had prolonged Grade 3 or 4 neutropenia beyond Day 30 (compared with 30% in Study MMY2001 [CARVYKTI USPI 2023]) and 26.1% of participants had prolonged Grade 3 or 4 thrombocytopenia beyond Day 30 (compared with 41% in Study MMY2001 [CARVYKTI USPI 2023]). In Study MMY3002, after Day 60, 23.3% of participants had recurrent Grade 3 or 4 neutropenia (compared with 12% in Study MMY2001 [CARVYKTI USPI 2023]) and 4.5% of participants had recurrent thrombocytopenia (compared with 6% in Study MMY2001 [CARVYKTI USPI 2023]).

Cytopenia can increase the risk of infection. Rates of Grade 3 or 4 treatment-emergent infection were comparable between Studies MMY3002 (27.3% of 176 participants who received cilta-cel as study treatment) and MMY2001 (23% [CARVYKTI USPI 2023]).

The FDA's Assessment:

Among the 188 subjects in the safety population, Grade 3 or higher cytopenia not resolved by Day 30 following cilta-cel infusion (based on laboratory values) were reported as follows: lymphopenia (29% of the subjects), neutropenia (25%), thrombocytopenia (29%), and anemia (3%). Prolonged cytopenia not recovered by Day 60 was observed in 11%, 10%, 14, and 3% of the subjects experiencing lymphopenia, neutropenia, thrombocytopenia, and anemia, respectively. Table 26 shows the prolonged and recurrent cytopenias.

Table 26: FDA – Prolonged and Recurrent Cytopenia, Safety Population, CARTITUDE-4

Laboratory	Grade 3-4 After Day 1 Dosing n (%)	Grade 3-4 Not Recovered by Day 30 n (%)	Grade 3-4 Not Recovered by Day 60 n (%)	Occurrence of Grade 3-4 After Day 60 n (%)
Lymphopenia	188 (100)	55(29)	20 (11)	33 (18)
Neutropenia	178 (95)	47 (25)	19 (10)	44 (23)
Thrombocytopenia	82 (44)	54 (29)	26 (14)	8 (4)
Anemia	64 (34)	5 (3)	5 (3)	8 (4)

Source: Applicant's response to information request dated Jan 29, 2024 (TSFAE37_CSR Part2of3), data cutoff November 1, 2022
The lab with the worst toxicity grade will be used for a calendar day. Recovery definition: must have two consecutive Grade ≤2 results from separate days if recover period ≤10 days.
Abbreviations: n (%), number of subjects with the specified characteristic

Sixty-two percent (116/188) of the patients had one, two or three or more recurrence of Grade 3

or 4 cytopenias after initial recovery of Grade 3 or 4 cytopenia. Eight and thirteen patients had Grade 3 or 4 neutropenia and thrombocytopenia, respectively, at the time of death.

Hypogammaglobulinemia

Data:

One hundred and forty-nine participants (71.6%) in Arm A and 189 participants (90.9%) in Arm B had either treatment-emergent hypogammaglobulinemia or post-baseline IgG level <500 mg/dL:

- 13 participants (6.3%) in Arm A and 88 participants (42.3%) in Arm B had a TEAE of hypogammaglobulinemia.
- 147 participants (70.7%) in Arm A and 188 participants (90.4%) in Arm B had a post-baseline laboratory finding of IgG level <500 mg/dL.
- 26 participants (12.5%) in Arm A and 137 participants (65.9%) in Arm B received IV Ig.

The Applicant's Position:

Hypogammaglobulinemia is common in patients with multiple myeloma, in part due to the underlying disease and in part due to myeloma-directed therapy. Hypogammaglobulinemia is a well-known effect of CAR-T products based on their mechanism of action. As cilta-cel targets BCMA expressing plasma cells, as well as B-cells, resulting in disruption of normal B-cell maturation into plasma cells, there is a risk of hypogammaglobulinemia, which was reflected by the incidence of hypogammaglobulinemia in Study MMY3002. Post-baseline laboratory findings of IgG level <500 mg/dL were reported in 70.7% of participants in Arm A and 90.4% of participants in Arm B.

The FDA's Assessment:
Hypogammaglobulinemia occurred in 177 subjects (94%; i.e., immunoglobulin G level <500mg/dl), and 132 subjects (70%) received intravenous immunoglobulin post cilta-cel infusion.

Infections

Data:

Treatment-emergent infections were reported for 148 participants (71.2%) in the Arm A safety analysis set (Grade 3 or 4: 47 participants [22.6%]) and for 127 participants (61.1%) in the Arm B safety analysis set (Grade 3 or 4: 47 participants [22.6%]). The most common Grade 3 or 4

infections (≥2% of participants in either treatment arm) were COVID-19 pneumonia and pneumonia. A Grade 5 infection was reported for 4 participants (1.9%) in Arm A (1 participant each with respiratory tract infection, COVID-19 pneumonia, septic shock, and PML) and for 9 participants (4.3%) in Arm B (7 participants with COVID-19 pneumonia, one participant with pneumonia, and one participant with neutropenic sepsis).

For infections in which the pathogen was identified, viral infections were reported for 36.5% of participants in Arm A and 28.8% of participants in Arm B (most commonly COVID-19 for 20.2% and 8.7%), bacterial infections for 10.1% and 15.9%, respectively (most commonly Escherichia urinary tract infection for 0 and 2.9%), and fungal infections for 9.1% and 5.8%, respectively (most commonly oral candidiasis for 2.9% and 1.0%). Hepatitis B reactivation was reported for one participant (0.5%) in Arm B.

Among the 176 Arm B participants who received cilta-cel as study treatment, treatment-emergent infections were reported for 114 participants (64.8%). Grade 3 or 4 treatment-emergent infections were reported for 39 participants (22.2%), including infections with an unspecified pathogen in 20 participants (11.4%), viral infections in 12 participants (6.8%), bacterial infections in 15 participants (8.5%), and fungal infections in 2 participants (1.1%). Nine participants (5.1%) had Grade 5 treatment-emergent infections, including COVID-19 pneumonia in 7 participants (4.0%), pneumonia in one participant (0.6%) and neutropenic sepsis in one participant (0.6%). For 2 participants who received cilta-cel as study treatment, non-treatment emergent infections were reported as primary cause of death, including pneumocystics jirovecii pneumonia in one participant and cytomegalovirus colitis (with herpes simplex virus type 1 hepatitis) in one participant.

There was a decrease over time in the incidence of Grade 3 or higher treatment-emergent infections with onset after cilta-cel infusion among the 176 Arm B participants who received cilta-cel as study treatment: from 15.3% in the ≤3 months window, to 8.1% in the >3 to ≤6 months window, to 8.4% in the >6 to ≤12 months window, to 5.1% in the >12 to ≤24 months window. No Grade 3 or higher infections had first onset >24 months after cilta-cel infusion.

The Applicant's Position:

Infections are common in patients with myeloma, in part due to the underlying disease and in part due to myeloma-directed therapy. In Study MMY3002, treatment-emergent infections were

reported for 71.2% of participants in Arm A and for 61.1% of participants in Arm B, with 22.6% of participants in both treatment arms experiencing Grade 3 or 4 treatment-emergent infections.

As Study MMY3002 was conducted in its entirety during the COVID-19 pandemic, COVID- related deaths were observed in both arms. An imbalance of COVID-19 related deaths prompted an Urgent Safety Measure to prevent COVID-19 infection and mitigate potential COVID-19- related risks. Subsequently, no additional deaths due to COVID-19 were reported for Arm B participants.

The FDA's Assessment:
Grade ≥3 infections occurred in 46 subjects (25%) in the cilta-cel arm and 47 subjects (23%) in the standard therapy arm. The most common Grade 3 or 4 infections in the cilta-cel arm were bacterial infection (12 subjects [6%]) and sepsis (10 subjects [5%]) compared to pneumonia (22 subjects [11%]) and viral infection (11 subjects [5%]) in the standard therapy arm. Infection by high level grouped term is shown in Table 27.

Table 27: FDA – Infections, Safety Population, CARTITUDE-4

High Level Group Term	Cilta-cel Arm N=188 Grade 3 or 4 n (%)	Cilta-cel Arm N=188 Grade 5 n (%)	Standard Therapy N=208 Grade 3 or 4 n (%)	Standard Therapy N=208 Grade 5 n (%)
Total	35(19)	11 (6)	47 (23)	6(3)
Infections pathogen unspecified	20(11)	3(2)	26(13)	3(1)
Viral infectious	11(6)	7(4)	27(13)	3(1)
Bacterial infectious	12(6)	1(0.5)	11(5)	0
Fungal infectious	1(0.5)	0	2(1)	0

Source: FDA analysis, data cutoff November 1, 2022
Abbreviations: n (%), number of subjects with the specified characteristic; N, number of FDA subjects in the specified group, or the total sample.

In subjects receiving cilta-cel, the median time to onset of Grade 3 or higher infection was 61 days (range: 1 to 626 days; interquartile range [IQR] of 11, 112). Median time to resolution was 44 days (range: 3 to 59 days; IQR of 6, 14.5). Median duration was 11 days (range: 1, 59 days; IQR of 6, 19).

Hemophagocytic Lymphohistiocytosis/Macrophage Activation Syndrome

The FDA's Assessment:
Hemophagocytic lymphohistiocytosis (HLH)/macrophage activation syndrome (MAS) is an inflammatory reaction that involves the activation of macrophages and T cells. It can be primary or secondary (sometimes associated with viral disease). In the context of CAR-T cell therapy, HLH/MAS has been seen in patients after the CAR-T cells are administered.

HLH/MAS occurred in 2 of the 188 subjects in the cilta-cel arm. Subject (b) (6) developed a Grade 1 HLH/MAS 8 days post cilta-cel infusion, resolved by Day 28 post cilta-cel infusion.

Subject (b) (6) had Grade 4 toxicity that started 10 days post cilta-cel infusion and was ongoing at the data cutoff date of November 1, 2022.

Tumor Lysis Syndrome

Data:

No treatment-emergent event of TLS was reported in Arm A or in Arm B participants who received cilta-cel as study treatment.

The Applicant's Position:

While TLS may be a life-threatening condition, no treatment-emergent cases of TLS were observed in participants who received cilta-cel as study treatment in Study MMY3002. The management of TLS is well known in clinical hematology/oncology practice.

The FDA's Assessment:
FDA agrees.

Other Significant Adverse Events (Arm B)

Other Neurologic AEs

Data:

Among the 176 Arm B participants who received cilta-cel as study treatment, 79 participants (44.9%) experienced other neurologic AEs (regardless of causality), including 5 participants (2.8%) with a Grade 3 or 4 event and one participant (0.6%) with a Grade 5 event.

All-grade events reported for more than 5% of participants included headache (37 participants [21.0%]) and dizziness (14 participants [8.0%]). Grade 3 or 4 events included somnolence, syncope, spinal cord compression, suicidal ideation, and suicide attempt, each reported for one participant (0.6%). None of the Grade 3 or 4 events was considered as related to cilta-cel. One participant (0.6%) experienced a maximum Grade 5 event of hemorrhage intracranial on Study Day 293 that was assessed by the investigator as not related to cilta-cel.

The Applicant's Position:

Other neurologic AEs were reported in Study MMY3002 and were mostly mild. It is recommended that patients are monitored for signs and symptoms of neurologic events after cilta-cel infusion.

The FDA's Assessment:
FDA agrees.

Hypersensitivity and Cilta-cel Infusion-related Reactions

Data:

Among the 176 Arm B participants who received cilta-cel as study treatment, 4 participants (2.3%) experienced hypersensitivity and cilta-cel infusion-related reactions, most commonly non-cardiac chest pain in 2 participants (1.1%). All events were of Grade 1 toxicity. For 3 participants, the event had first onset on Day 1 (ie, the initial cilta-cel infusion date) and one participant had first onset on Day 2. All 4 participants were able to complete cilta-cel infusion.

The Applicant's Position:

Allergic reactions may occur with the infusion of cilta-cel. Serious hypersensitivity reactions, including anaphylaxis, may be due to the dimethylsulfoxide in cilta-cel. Patients should be carefully monitored for 2 hours after cilta-cel infusion for signs and symptoms of severe reaction. Patients should be treated promptly and managed appropriately according to the severity of the hypersensitivity reaction (CARVYKTI USPI 2023).

The FDA's Assessment:
Hypersensitivity reactions occurred in eight (4%) of the subjects in the cilta-cel arm. All reactions were Grade 1.

Dropouts and/or Discontinuations Due to Adverse Effects

Data:

TEAEs leading to withdrawal of any component of study treatment were reported for 29 participants (13.9%) in Arm A and for 6 participants (2.9%) in Arm B. PTs reported for more than 2 participants in total included insomnia (4 participants [1.9%] in Arm A, 0 participants in Arm B) and hyperglycemia (3 participants [1.4%] in Arm A, 0 participants in Arm B).

The Applicant's Position:

The incidence of specific TEAEs leading to discontinuation of study treatment was low.

The FDA's Assessment:
FDA agrees.

Dose Interruption/Reduction Due to Adverse Effects

Data:

In Arm A, cycle delays were reported for 138 participants (66.3%). The most common reason for cycle delay was AE for 115 participants (55.3%), including COVID-19 related AE in 18 participants (8.7%).

Cyclophosphamide and Fludarabine Conditioning

Among the 176 Arm B participants who received cilta-cel as study treatment, 11 participants (6.3%) experienced a delay in administration of the conditioning regimen. For 8 participants (4.5%), these delays were due to AE. No dose adjustments for the conditioning regimen (abortion or interruption) were reported.

Cilta-cel Infusion

Among the 176 Arm B participants who received cilta-cel as study treatment, cilta-cel infusion was interrupted for 2 participants (1.1%) due to AE. Cilta-cel infusion was delayed for 9 participants (5.1%), with delays due to AE reported for 7 participants (4.0%). All cilta-cel infusions were completed. Additional details of the cilta-cel infusion delays and interruptions is provided in Section 4.6.2.2.3 of the CSR for Study MMY3002.

The Applicant's Position:

In Arm A, cycle delays were reported for 66.3% of participants, primarily due to AEs. In Arm B, the incidence of delays and interruptions to cilta-cel infusion due to AEs was low. All cilta-cel infusions were completed.

The FDA's Assessment:
FDA agrees with the Applicant's assessment.

Laboratory Findings

Data:

The following trends were observed for selected clinical chemistry parameters for participants in Arm B (safety analysis set):

- Mean AST values remained within normal limits.
- Mean ALT values increased during bridging therapy, then decreased on the day of cilta-cel infusion. Mean ALT values then increased to a maximum on Day 14, followed by a return to baseline levels by Day 84.
- Mean CRP values fluctuated during bridging therapy and returned to baseline at the time of the conditioning regimen. A steady increase in mean values was observed until Day 7, with a return to baseline levels by Day 21.
- Mean ferritin values increased rapidly during bridging therapy and returned to baseline levels at the start of the conditioning regimen. A steady increase was observed until Day 14, followed by a return to baseline levels by Day 84.

Grade 3 or 4 cytopenia TEAEs were reported for 86.1% of participants in Arm A and for 93.8% of participants in Arm B. Among the 176 participants in Arm B who received cilta-cel as study treatment, most Grade 3 or 4 cytopenias had onset and recovery to Grade 2 or better within 60 days following cilta-cel infusion.

The Applicant's Position:

Laboratory data were as expected based on the current understanding of CAR-T therapy.

The FDA's Assessment:
FDA agrees.

Vital Signs

Data:

Fewer than 10% of participants in either arm had clinically important abnormal vital sign measurements at any post-baseline measurement prior to subsequent therapy.

The Applicant's Position:

There were no clinically meaningful differences between the 2 treatment arms with respect to vital sign assessment results during the study.

The FDA's Assessment:
FDA agrees.

Electrocardiograms

Data:

For all participants, 12-lead ECG was performed at screening and as clinically indicated during the treatment phase. For Arm A (both PVd and DPd), 12-lead ECG was performed at end of treatment. For Arm B, 12-lead ECG was performed as clinically indicated during the post infusion follow-up phase.

One participant in Arm A and 2 participants in Arm B had baseline ECG findings of normal, or abnormal but not clinically significant, followed by abnormal clinically significant ECG findings post-baseline.

The Applicant's Position:

Based on review of the data, there is no evidence that cilta-cel affects ECG parameters.

The FDA's Assessment:
FDA agrees.

Immunogenicity

Data:

The overall incidence of antibodies to cilta-cel (ADA) was 21.0% among participants who received cilta-cel as study treatment in Study MMY3002 (n=176). Based on the current data, there was no clear association between ADA status and cilta-cel exposure and persistence.

The impact of ADAs on safety outcomes was analyzed based on an immunogenicity data cutoff date of 29 August 2022 and a safety clinical data cutoff date of 01 November 2022. The presence of ADAs had no apparent impact on safety outcomes among participants who received cilta-cel as

study treatment, including CRS, ICANS, other neurotoxicities, and SPMs. All CRS and ICANS

TEAEs experienced by ADA-positive participants were Grades 1 or 2 in severity, although it should be noted that there were only 2 Grade 3 TEAEs of CRS and no Grade 3 TEAEs of ICANS among all 176 participants who received cilta-cel as study treatment. It should also be noted that the overall number of participants who experienced CRS, ICANS, other neurotoxicities, or SPMs and were ADA-positive was small, which limits a definitive conclusion regarding the impact of ADA on the clinical safety of cilta-cel.

The Applicant's Position:

Based on the current data, there was no evidence to suggest an association between ADA and safety.

The FDA's Assessment:

Immunogenicity in CARTITUDE-4, was analyzed among the 186 evaluable subjects who received within specification CARVYKTI, 39 subjects (21%) were positive for anti-drug antibodies (ADA) of CARVYKTI (anti-cilta-cell antibodies) with low peak titers (range 1:7 to 1:896). The impact of ADA on CARVYKTI's PK. Efficacy and safety were evaluated. The presence of ADA appeared to have no evident impact on CARVYKTI's safety outcomes, as per clin-pharm review. Due to the small sample size of subjects who experienced AEs and were positive for ADA, there was no definitive conclusion regarding the impact of ADA on clinical safety of CARVYKTI. For details, refer to clinical pharmacology review.

Participants Who Received Cilta-cel as Subsequent Therapy in Study MMY3002

Safety data for the 20 participants in Arm B of Study MMY3002 who received cilta-cel as subsequent therapy are presented in Section 6.3 of the CSR for Study MMY3002.

Compared with cilta-cel administered as study treatment (n=176), cilta-cel administered as subsequent therapy (n=20) was associated with higher rates of all-grade CRS (17/20 [85.0%] participants versus 134/176 [76.1%] participants), Grade 3 or Grade 4 CRS (5/20 [25.0%] participants versus 2/176 [1.1%] participants), all-grade ICANS (7/20 [35.0%] participants versus 8/176 [4.5%] participants), Grade 3 or Grade 4 ICANS (2/20 [10.0%] participants versus 0/176 participants), Other Neurotoxicity (7/20 [35.0%] participants versus 30/176 [17.0%] participants), and Grade 3 or 4 thrombocytopenia (13/20 [65.0%] participants versus 71/176

[40.3%] participants).

Supportive Safety Data – Study MMY2003

Safety findings for participants treated with cilta-cel in Cohorts A and B from Study MMY2003 were consistent with those for Arm B participants in Study MMY3002 who received cilta-cel as study treatment.

Cohort A

AEs, especially Grade 3 or 4 cytopenias, were common but usually recovered to ≤Grade 2 within 2 months of cilta-cel infusion for most participants. All 20 participants experienced at least one Grade 3 or 4 TEAE. Serious TEAEs were reported for 40.0% of participants; CRS (15.0%) and diarrhea (10.0%) were the only serious TEAEs reported in ≥10% of participants.

Lower-grade CRS occurred in most participants and all CRS, including 2 participants with Grade 3 or 4 CRS, resolved by the clinical cutoff with a median duration of 3.0 days (range, 2 to 12 days).

Six participants experienced treatment-emergent CAR-T cell neurotoxicity, including Grade 1 or 2 ICANS (3 participants) and Other Neurotoxicity for an additional 3 participants. The latter category included one participant with serious Grade 4 peripheral sensorimotor neuropathy. No movement and neurocognitive TEAEs were observed.

Treatment-emergent infections of bacterial, viral, fungal, or unspecified origin were reported for 45.0% of participants, including one participant (5.0%) with Grade 3 or 4 COVID-19, sepsis, and sinusitis aspergillus, followed by Grade 5 COVID-19 pneumonia. The event of Grade 5 COVID-19 pneumonia was the only TEAE identified by investigator as the primary cause of death.

Laboratory abnormalities typically showed maximum worsening between Days 7 and 14 after cilta-cel infusion followed by gradual recovery to, or improvement beyond, baseline measurements.

As of the clinical cutoff, there were no reports of SPM or TLS.

In summary, the safety profile for Cohort A was consistent with previous experience and no new safety concern was identified.

Cohort B

Eighteen (94.7%) participants experienced at least one Grade 3 or 4 TEAE (Grade 3: 5.3%; Grade 4: 89.5%). Grade 3 or 4 cytopenias were common (94.7%), and mostly occurred during the first month after cilta-cel infusion. No participant experienced a TEAE with an outcome of death (Grade 5). Serious TEAEs were reported for 36.8% of participants. No single PT was reported as a serious TEAE in more than one participant.

TEAEs of CRS were common (84.2%) but most (78.9%) were low grade. All CRS events resolved and had a duration of ≤7 days; median duration was 4.0 days (range, 1 to 7 days).

TEAEs of CAR-T cell neurotoxicity were experienced by 26.3% of participants, including ICANS (5.3%) and other neurotoxicities (21.1%). Movement and neurocognitive TEAEs were reported in one male participant who had risk factors of high tumor burden and had previously experienced Grade 4 CRS.

No participant experienced TLS. One participant was diagnosed with a Grade 2 non-serious SPM of prostate cancer, which was considered by the investigator to be not related to cilta-cel.

Grade 3 or higher infections were reported in 21.1% of participants including device-related infection, septic shock, vascular device infection, COVID-19 pneumonia, pneumonia viral, and pseudomonal bacteremia (1 participant each).

In summary, the safety profile for Cohort B was consistent with the mechanism of action of CAR-T therapy and with previous experience; no new safety concern was identified.

FDA Position:

FDA did not conduct an independent analysis to verify the results described above. Also, that the patients who received cilta-cel (n=20) as subsequent therapy are included in the n=188 safety population

8.2.5. Analysis of Submission-Specific Safety Issues

Data:

The information on the specific safety issues such as CRS, neurotoxicity, TLS, SPM, cytopenias, hypogammaglobulinemia, and infections is provided in Section 8.2.4.

The Applicant's Position:

Cilta-cel has a safety profile generally consistent with the mechanism of action of CAR-T therapy and other BCMA CAR-T ide-cel therapy. CRS, neurotoxicity, TLS, SPM, cytopenias, hypogammaglobulinemia, and infections are known risks of CAR-T therapy that can be managed by monitoring and mitigation strategies.

The FDA's Assessment:
The clinical reviewer for safety did not independently verify the data reported by the Applicant for Study CARTITUDE-2. No formal assessment of safety data from CARTITUDE-2 was conducted.

8.2.6. COA Analyses Informing Safety/Tolerability

Data:

Please refer to Section 8.1.3, for information on results for COA endpoints, including results for the major secondary endpoint of time to worsening of symptoms in the MySIm-Q total symptom score.

The PRO-CTCAE was used to evaluate the impact of cilta-cel treatment on the HRQoL of participants. Low rates of symptoms were reported by participants across both arms throughout the treatment period as measured by the PRO-CTCAE items: nausea, vomiting, diarrhea, shortness of breath, rash, dizziness, headache, and fatigue. Most symptoms were reported as being present at baseline (prior to treatment) and while on therapy. Headache and fatigue were most frequently reported as being mild to moderate in severity. Participants were more likely to report fatigue as interfering with usual or daily activities.

The Applicant's Position:

Assessment of HRQoL, symptoms, and functioning using PRO instruments, including the MySIm-Q and PRO-CTCAE, suggest a quality-of-life trend favoring cilta-cel treatment.

The FDA's Assessment:
The MySIM-Q data was not formally tested since it follows OS in the statistical hierarchy; therefore, no conclusions can be made from it or other collected PROs. This data should be treated as purely exploratory.

8.2.7. Safety Analyses by Demographic Subgroups

Data:

Age

The incidence of TEAEs was examined separately for participants <65 years old, those between 65 and 75 years, and those >75 years. In general, the small numbers of participants in the >75 years age subgroup in both arms (4 participants in each treatment arm) limit the conclusions that can be drawn from these analyses.

Grade 3 or 4 TEAEs occurred at similar rates across age subgroups and in both arms, the incidence of TEAEs considered by the investigator to be related to any component of the treatment regimen was similar for the <65 years and 65 to 75 years subgroups. A similar observation was made for the incidence of serious TEAEs by age subgroups in Arm A. In Arm B, serious TEAEs occurred at similar rates across age subgroups. No important differences were noted in the incidence of specific TEAEs between the <65 years and 65 to 75 years subgroups, while the small number of participants aged >75 years precludes meaningful interpretations for that subgroup. Further details are provided in Section 5.1.1 of the Summary of Clinical Safety.

Race

The incidence of TEAEs was examined separately for Black or African American participants, and those of other races. In general, the small numbers of Black or African American participants in both arms (7 participants in Arm A and 6 participants in Arm B) limit the conclusions that can be drawn from these analyses.

The incidence of CRS, ICANS, and Other Neurotoxicity among Arm B participants who received cilta-cel as study treatment (n=176) was examined separately for those who were Black or African American (n=6) and those who were of other races (n=170). Of the 134 participants who experienced CRS, 3 were Black or African American. CRS recovered for these 3 participants (versus 130 participants of other races). The median time from initial cilta-cel infusion to first onset of CRS was 6.0 days (range: 6 to 7 days; versus 8.0 days [range: 1 to 23 days]) among participants of other races), and the median duration of CRS was 3.0 days (range: 3 to 4 days; versus 3.0 days [range: 1 to 17 days] among participants of other races). None of the Black or African American participants experienced ICANS or Other Neurotoxicity.

Total CAR-positive Viable T-cells Infused

The incidence of TEAEs among Arm B participants who received cilta-cel as study treatment (n=176) was examined separately for participants who were infused with less than the median number of CAR-T positive T cells (n=88) and for participants infused with the median number or more CAR-T positive T cells (n=88). The overall incidence of cilta-cel-related TEAEs was similar

between the 2 subgroups: 98.9% and 95.5%, respectively. The incidence of Grade 3 or 4 TEAEs was also similar between the subgroups: 93.2% and 92.0%, respectively. There were no clinically meaningful differences in the incidence of specific TEAEs, including CRS, for the infusion subgroups examined.

Bone Marrow Plasma Cells at Baseline

For each treatment arm, the incidence of TEAEs was examined separately for participants in the safety analysis set (Arm A: n=208; Arm B: n=208) who presented with ≤30%, >30% to <60%, and ≥60% plasma cells (based on the highest value obtained) at baseline.

In both arms, the incidence of TEAEs considered by the investigator to be related to any component of the treatment regimen was similar across subgroups and Grade 3 or 4 TEAEs also occurred at similar rates across the 3 subgroups. No clear trend was seen for the incidence of serious TEAEs. Within each treatment arm, there were no clinically meaningful differences in the incidence of specific TEAEs for the baseline bone marrow subgroups examined, except for all-grade CRS among Arm B participants, as described further in Section 5.1.3 of the Summary of Clinical Safety.

LV Manufacturing Site

As described in Section 8.1.3, both (b) (4) LV and (b) (4) LV were used in cilta-cel manufacturing during Study MMY3002. The incidence of TEAEs among Arm B participants who received cilta-cel as study treatment (n=176) was examined separately for participants who were infused with cilta-cel manufactured with (b) (4) LV (n=90) and with cilta-cel manufactured with (b) (4) LV (n=86). The overall incidence of cilta-cel-related AEs was similar between the subgroups: 100.0% and 94.2%, respectively. The incidences of Grade 3 or 4 TEAEs (92.2% and 93.0%, respectively) and of serious TEAEs (34.4% and 36.0%, respectively) were also similar between the subgroups.

There were no clinically meaningful differences in the incidence of specific TEAEs, including CRS, CAR-T Cell Neurotoxicity, and Other Neurologic AEs for the LV subgroups examined.

Additional Subgroup Analyses

The incidence of TEAEs was also examined for subgroups for renal function, hepatic function, and tumor burden at baseline. As discussed further in Section 5.1 of the Summary of Clinical Safety, there were no clinically meaningful differences in the incidence of specific TEAEs for these subgroups.

The incidence of TEAEs among Arm B participants who received cilta-cel as study treatment was examined for participants who were infused with cilta-cel within-specification drug product and for participants infused with out-of-specification drug product. As discussed further in Section 5.2.2 of the Summary of Clinical Safety, overall, the relatively small number of participants who received out-of-specification cilta-cel as study treatment (6 participants) limits the comparisons that can be made between the 2 subgroups.

The Applicant's Position:

There were no clinically meaningful differences in the cilta-cel AE profile across the subgroups examined for age, race (including Black or African American participants), total CAR-positive viable T-cells infused, bone marrow % plasma cells at baseline, renal function, hepatic function, tumor burden at baseline, and LV manufacturing site.

The FDA's Assessment:
Geriatric population: Of the 188 patients in CARTITUDE-4 that received cilta-cel, 38% were 65 to 75 years of age, and 2% were 75 years of age or older. In 112 patients less than 65 years of age, all grade and Grade 3 and higher neurologic toxicities occurred in 16% (18/112) and 3% (3/112) respectively. Of the 76 patients ≥65 years of age, all grade and Grade 3 and higher neurologic toxicities occurred in 34% (26/76) and 7% (5/76) respectively.

FDA, in general, agrees with the Applicant's position. No excess toxicity was observed in subjects by group age.

The majority of the subjects enrolled in CARTITUDE-4 were White; therefore, comparative analyses for other races are not informative.

8.2.8. Specific Safety Studies/Clinical Trials

Not applicable.

The FDA's Assessment:
Not applicable.

8.2.9. Additional Safety Explorations

Human Carcinogenicity or Tumor Development

Not applicable.

The FDA's Assessment:
Not applicable.

Human Reproduction and Pregnancy

Not applicable.

The FDA's Assessment:
Not applicable.

Pediatrics and Assessment of Effects on Growth

Not applicable.

The FDA's Assessment:
Not applicable.

8.2.10. Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

Data:

A cumulative review was performed on all medically confirmed postmarketing cilta-cel cases received by the Global Medical Safety global safety database from 28 February 2022 (cilta-cel international birth date) through 31 January 2023. A cumulative total of 141 relevant postmarketing cases associated with 290 events were identified. Almost all cases originated from the US (94%; 133/141).

The most common (≥2%) PTs in these cases were CRS (13%; 37/290); disease progression, ICANS, and pyrexia (4%; 12/290 each); therapeutic product effect incomplete (reported term: "very good partial response" [6 events] and "partial response" [1 event]; 2%; 7/290); and HLH and neurotoxicity (2%; 6/290 each), all of which are consistent with the known safety profile for cilta-cel and/or the relapsed or refractory multiple myeloma population under review.

Among the 141 cases, there were 14 fatal cases (10%; 14/141) with the following 17 fatal PTs: death (3 events); multiple organ dysfunction syndrome and septic shock (2 events each); and adenovirus infection, cardiac arrest, cerebral hemorrhage, COVID-19, CRS, HLH, ICANS, respiratory failure, sepsis, and septic embolus (1 event each). Most of these fatal events are consistent with the known safety profile for cilta-cel and/or complications arising from CRS, HLH, ICANS, serious infections, or advancing multiple myeloma.

In addition, the following AEs of interest were reviewed for the 141 cilta-cel cases: CRS (including HLH), neurologic toxicities (including ICANS and other neurotoxicities), prolonged or recurrent cytopenia (excluding anemia), serious infections, hypogammaglobulinemia, and SPMs. Consistent with the known safety profile for cilta-cel, the most frequent (≥5%) AEs of interest were CRS including HLH (8%; 38/475) and neurologic toxicities including ICANS and other neurotoxicities (6%; 27/475). HLH was reported in a small number of the cases (1%; 6/475), most of which were observed concurrently with CRS (1%; 5/475); ICANS was reported in about half of the cases reporting neurologic toxicities (2.5%; 12/475).

The Applicant's Position:

Overall, upon review of the postmarketing safety data for cilta-cel, no new significant safety information was identified. A review of the events pertaining to the important identified and potential risks for cilta-cel did not indicate an increase in frequency or severity and the events observed were consistent with the known safety profile for cilta-cel. The Applicant will continue to monitor all cilta-cel reported cases. No change to the current risk minimization is warranted at this time based on the postmarketing safety data.

The FDA's Assessment:
Cases of myelodysplastic syndrome and acute myeloid leukemia have been reported in the postmarketing setting.

Expectations on Safety in the Postmarket Setting

Data:

As discussed in Section 8.2.10, Safety Concerns Identified Through Postmarket Experience, upon review of the postmarketing safety data for cilta-cel, no new significant safety information was identified.

The Applicant's Position:

Safety in the postmarket setting is expected to remain consistent with the known safety profile for cilta-cel.

The FDA's Assessment:
Postmarketing registry study MMY4004 is a PMR to assess the long-term safety and risk of secondary malignancies occurring after treatment with cilta-cel. The study will include at least 1,500 adult patients with RRMM after four or more prior lines of therapy, including a PI, an immunomodulatory agent, and an anti-CD38 monoclonal antibody. Enrolled patients will be followed for 15 years after product administration. The study milestones as are follows:

- Final protocol submission: April 30, 2022
- Study completion date: June 30, 2041
- Final report submission: June 30, 2042

The Applicant proposed to recruit 200 additional patients for the postmarketing registry study upon approval of the newly proposed indication to ensure that patients who receive earlier line therapy are also being monitored for the occurrence of secondary malignancies. This proposal is acceptable to DPV and OTP and is consistent with what has been done for other CAR-T cell products. At the time of action due date a PMC for final OS analysis has not been agree yet.

8.2.11. Integrated Assessment of Safety

Data:

The safety profile for cilta-cel was manageable and consistent with the current understanding of CAR-T therapy.

With a median follow-up of 15.9 months, the overall safety profile of cilta-cel was manageable and consistent with the current understanding of CAR-T therapy and comparable between study

arms. Cilta-cel specific TEAEs of CRS and CAR-T cell neurotoxicity were generally low-grade and reversible. Of note, the low incidence of movement and neurocognitive TEAEs in Study MMY3002 indicates a beneficial effect of the risk management measures for early detection and management of neurotoxicities implemented across the cilta-cel clinical development program.

Subgroup analyses performed for the 176 Arm B participants who received cilta-cel as study treatment show that there are no clinically meaningful differences in the safety profile of cilta-cel for any of the subgroups examined. Of note, no association was found between cilta-cel safety and the LV used for manufacturing cilta-cel, and no new safety concerns were seen for participants who received out-of-specification product.

Compared with data from Study MMY2001, which included a population of patients with more heavily pretreated relapsed or refractory multiple myeloma, safety data from Study MMY3002 suggests an improvement in rate and reduction in severity of cilta-cel specific events such as CRS, ICANS and movement and neurocognitive TEAEs. Supportive safety data for the use of cilta-cel in an earlier disease setting comes from Cohorts A and B from Study MMY2003, which included similar patient populations as Study MMY3002. Safety findings for both cohorts were generally consistent with Study MMY3002.

The Applicant's Position:

Based on the totality of data, the overall safety profile of cilta-cel is considered acceptable for the treatment of patients with relapsed and lenalidomide-refractory multiple myeloma who have received 1 to 3 prior lines of therapy.

The FDA's Assessment:

The Applicant submitted additional supportive safety data for studies of cilta-cel in subjects with RRMM (CARTITUDE-2). We analyzed the data from the three studies (CARTITUDE-1, CARTITUDE-2, and CARTITUDE-4), but no new safety signal was identified. Study CARTITUDE-1 was the primary study for the approved RRMM, and the data were reviewed in the original Biologics License Application submission.

Studies/Clinical Trials Used to Evaluate Safety

Table 28 lists the three clinical studies included in the safety population of cilta-cel (N=324).

Table 28: FDA – Clinical Trials to Evaluate Safety of Ciltacabtagene Autoleucel (N=324)

Study No.	Primary Objective	Study Design	Dosage	No. of Subjects	Subject Population	Study Status
CARTITUDE-1	Safety Efficacy	Single-arm, open- label, multicenter Phase 1b/2 study	Single dose cilta-cel (0.75 $\times 10^6$ CAR+ T cells/ kg) IV	97	R/R MM after failure of 4 or more prior lines of systemic therapy	Completed
CARTITUDE-4	Safety Efficacy	Phase 3, randomized, open-label, parallel-group, multicenter trial	Single dose cilta-cel (0.75 $\times 10^6$ CAR+ T cells/ kg) IV	188	R/R MM after failure of 1 line of prior therapy, and lenalidomide refractory	Ongoing Primary CSR, (data cutoff 01 Nov 2022)
CARTITUDE-2	Safety	Phase 2, open-label, single-arm multicenter trial	Single dose cilta-cel (0.75×10^6 CAR+ T cells/kg) IV	39	R/R MM after failure of 1 line of prior therapy and lenalidomide refractory	Completed CSR (data cutoff 8 Oct 2021 [Cohort A] and 01 Jun 2022 [Cohort B])

Source: sBLA 125746/74 Module 5.2: Tabular listing of Clinical Studies
Abbreviations: CAR, chimeric antigen receptor; CSR, clinical study report; IV, intravenous; R/R MM, relapsed/refractory multiple myeloma

Demographics of Pooled Safety Populations

Baseline demographics and disease characteristics of the pooled safety population (n=324) are displayed in Table 29 and Table 30.

Table 29: FDA – Baseline Demographics Characteristics of the Pooled Safety Population (N=324)

Parameter	CARVYKTI N=324
Age (years)	-
N	324
Mean (StD)	60.1 (9.49)
Median (Min, Max)	61 (27;78)
Interquartile range	(54.0; 68.0)
Age Group, n (%)	-
<65 years	209 (64.5%)
≥65 to <75 years	103 (31.8%)
≥75 years	12 (3.7%)

Parameter	CARVYKTI N=324
Screening ECOG PS, n (%)	-
0	164 (50.6%)
1	156 (48.1%)
2	4 (1.2%)
Sex, n (%)	-
Female	132 (40.7%)
Male	192 (59.3%)
Race, n (%)	-
White	244 (75.3%)
Unknown	33 (10.2%)
Asian	17 (5.2%)
Black or African	27 (8.3%)
Other[a]	3 (1)

Source: FDA analysis, data cutoff November 1, 2022
a. American Indian or Alaska Native (2) and Pacific Islander.
Abbreviations: ECOG, Eastern Cooperative Oncology Group; max, maximum; min, minimum; n (%), number of subjects with the specified characteristic; N, number of subjects in the specified group, or the total sample; PS, performance status; StD, standard deviation

Table 30: FDA – Baseline Disease Characteristics, Pooled Safety Population (N=324)

Characteristics	All N=324
International Staging System stage %	-
I	213 (66)
II	83 (26)
III	28 (7)
Time since diagnosis (years)	-
Median (range)	3.7 (0.3-18)
Interquartile range	(2.09; 6.41)
Extramedullary disease n (%)	-
Yes	61 (19)
No	263 (81)
Bone marrow plasma cells n (%)	-
N	321
≤30	208 (65)
>30-<60	49 (15)
≥60	64 (20)

Characteristics	All N=324
Cytogenetic risk n (%)	-
N	306
Standard	188 (61)
High	107 (35)
del(17p)	72 (24)
t(4;14)	27 (9)
t(14;16)	10 (3)
Missing data	11 (4)

Source: FDA analysis, data cutoff November 1, 2022
Abbreviations: n (%), number of subjects with the specified characteristic; N, number of subjects in the specified group, or the total sample

Categorization of Adverse Events

The same FDA-grouped terms were used to recode the AEs that were coded in dictionary code AE columns in AE datasets. A copy of the FDA-grouped terms was sent for the Applicant to add a column to the datasets with the FDA grouped terms. The pooled analysis of the safety data that was summarized from the three studies was based on the agreed upon FDA-grouped terms.

Safety Results

Deaths

Table 31 shows the incidence of deaths reported in the safety population (N=324) in the three cilta-cel studies combined (CARTITUDE-1, CARTITUDE-2, and CARTITUDE-4).

Table 31: FDA – Summary of Deaths Safety Population

Parameter	CARTITUDE-1 N=97	CARTITUDE-4 N=188	CARTITUDE-2 N=39	Total N=324
All deaths	30 (31)	25 (13)	7 (18)	62 (19)
Disease progression	14 (14)	5 (3)	5 (13)	24 (7)
Adverse events	15 (16)	20 (12)	2 (5)	37 (11)
Other causes[a]	1 (1)	0	0	1 (0.3%)
Fatal AEs ≤30 days after CAR-T infusion	0	2 (1)	0	2 (0.6%)
Fatal AEs >30 days after CAR-T infusion	15 (16)	18 (10)	2 (5)	35 (11)
Fatal AEs ≤90 days after CAR-T infusion	1 (1)	8 (4)	0	9 (3)
Fatal AEs >90 days after CAR-T infusion	14 (14)	12 (6)	2 (5)	28 (9)

Source: FDA analysis of ADSL, and Applicant's response to IR dated Mar 19, 2024 (TSFDTH01_ISS_FDA_IR). Data cutoff November 1, 2022
a. CARTITUDE-4, all death not due to disease progression are reported here as due to adverse events.
Abbreviations: AE, adverse event; CAR-T, chimeric antigen receptor T (cells); N, number of subjects in the specified group, or the total sample

Amongst the 324 subjects treated with cilta-cel, 44 subjects or 14% died within 90 days of CAR-T cell infusion. AEs were the most common cause of deaths (11%) in the safety population.

Nonfatal Serious Adverse Events

Table 32 shows the pooled, nonfatal, serious adverse events in 324 subjects who received cilta-cel in the three studies. The incidence of nervous system disorders was higher in the CARTITUDE-1 study compared to in the CARTITUDE 4 and CARTITUDE-2 studies. Incidence of infections disorders was comparable among the three studies. Notably, there was a higher incidence of SPM in the CARTITUDE-4 study.

Table 32: FDA – Nonfatal Serious Adverse Events in Recipients of Cilta-cel Across Studies

System Organ Class and Preferred Term	CARTITUDE-1 N=97 n (%)	CARTITUDE-4 N=188 n (%)	CARTITUDE-2 N=39 n (%)	TOTAL N=324 n (%)
Subjects with any serious any Grade 3 or 4 TEAE	35 (36)	39 (21)	12 (31)	86 (27)
Blood and lymphatic system disorders	7 (7)	7 (4%)	5 (13)	19 (6)
Febrile neutropenia	3 (3)	0	2 (5)	5 (2)
Immune system disorders	4 (4)	4 (2)	3 (8)	11 (3)
Cytokine release syndrome	4 (4)	7 (4)	5 (13)	19 (6)
Nervous system disorders	11 (11)	4 (2)	2 (5)	17 (5)
Encephalopathy	5 (5)	1 (0.5)	1 (3)	7 (2)
Cranial nerve palsies	1 (1)	2 (1)	0	3 (1)
Motor dysfunction	3 (3)	0	0	3 (1)
Neuropathy peripheral	1 (1)	1 (0.5)	1 (3)	3 (1)
Infections and infestations	18 (19)	24 (13)	5 (13)	47 (15)
Pneumonia	7 (7)	9 (5)	2 (5)	18 (6)
Viral infection	2 (2)	5 (3)	0	7 (2)
Sepsis	6 (6)	5 (3)	2 (5)	13 (4)
Bacterial infection	2 (2)	3 (2)	1 (3)	6 (2)
Upper respiratory tract infection	3 (3)	2 (1)	0	5 (2)
Myelitis	0	1 (0.5)	0	1 (0.3)

System Organ Class and Preferred Term	CARTITUDE-1 N=97 n (%)	CARTITUDE-4 N=188 n (%)	CARTITUDE-2 N=39 n (%)	TOTAL N=324 n (%)
Gastrointestinal disorders	1 (1)	3 (2)	2 (5)	6 (2)
Diarrhea	0	3 (2)	2 (5)	5 (2)
Renal disorders	4 (4)	1 (0.5)	0	5 (2)
Renal failure	4 (4)	1 (0.5)	0	5 (2)
Secondary primary malignancies	0	3 (3)	0	3 (2)
Acute myeloid leukemia	0	1(0.5)	0	1(0.3)
Myelodysplastic syndrome	0	1 (0.5)	0	1 (0.3)
Peripheral T cell lymphoma unspecified	0	1 (0.5)	0	1 (0.3)

Source: Adapted from Applicant's response to FDA IR dated Mar 19, 2024 (TSFAE49_ISS_FDA_IR). Data cutoff November 1, 2022
Abbreviations: n (%), number of subjects with the specified characteristic; N, number of subjects in the specified group, or the total sample; TEAE, treatment-emergent adverse event

Common Adverse Events

Table 33 shows the incidence of TEAEs (Grade 1 to 5) that occurred in ≥10% of the safety population (N=324 subjects) in the three cilta-cel studies combined (CARTITUDE-1, CARTITUDE-4, and CARTITUDE-2).

Table 33: FDA – TEAE (Grade 1-5) in >10% Recipients of Cilta-cel Across Studies by SOC and PT

System Organ Class and Preferred Term	CARTITUDE-1 N=97 n (%)	CARTITUDE-4 N=188 n (%)	CARTITUDE-2 N=39 n (%)	TOTAL N=324 n (%)
Immune system disorders	-	-	-	-
Cytokine release syndrome	92 (95)	146 (78)	35 (90)	273 (84)
Hypogammaglobulinaemia	92 (93)	90 (48)	6 (15.4%)	188 (58)
Infections and infestations	-	-	-	-
Upper respiratory tract infection	27 (28)	47 (25)	12 (31)	86 (26)
Viral infection	21 (23)	44 (23)	2 (5)	67 (21)
Bacterial infection	8 (8)	29 (15)	8 (21)	45 (14)
Pneumonia	13 (14)	27 (14)	4 (10)	44 (14)
General disorders and administration site conditions	-	-	-	-
Fatigue	46 (47)	52 (28)	15 (39)	113 (35)
Edema	22 (23)	20 (11)	9 (23)	51 (16)
Pyrexia	93(96)	148 (79)	9 (23)	250 (77)
Pain	14 (14)	19 (10)	3 (8)	36 (11)
Gastrointestinal disorders	-	-	-	-
Diarrhea	32 (33)	50 (27)	12 (31)	94 (29)
Nausea	30 (31)	36 (20)	8 (21)	74 (23)
Constipation	21 (22)	19 (10)	7 (18)	47 (15)
Vomiting	19 (20)	10 (5)	5 (13)	34 (11)

System Organ Class and Preferred Term	CARTITUDE-1 N=97 n (%)	CARTITUDE-4 N=188 n (%)	CARTITUDE-2 N=39 n (%)	TOTAL N=324 n (%)
Nervous system disorders	-	-	-	-
Headache	26 (27)	43 (23)	10 (26)	79 (20)
Encephalopathy	29 (30)	20 (11%)	8 (21)	57 (18)
Dizziness	22 (23)	15 (8)	6 (15)	43 (13)
Motor dysfunction	17 (16)	11 (6)	7 (18)	35 (11)
Metabolism and nutrition disorders	-	-	-	-
Decreased appetite	28 (29)	18 (10)	5 (13)	51 (16)
Musculoskeletal and connective tissue disorders	-	-	-	
Musculoskeletal pain	47 (48)	64 (34)	16 (41.0%)	127 (139)
Respiratory, thoracic and mediastinal disorders	-	-	-	-
Cough	38 (39)	28 (15)	6 (15)	72 (22)
Dyspnea	22 (23)	17 (9)	6 (15)	45 (14)
Vascular disorders	-	-	-	-
Hypertension	18 (19)	13 (7)	4 (10)	35 (10)

Source: Adapted from Applicant's response to FDA IR dated Mar 19, 2024 (TSFAE49_ISS_FDA_IR; CARVYKTI USPI 2021). Data cutoff November 1, 2022

Abbreviations: n (%), number of subjects with the specified characteristic; N, number of subjects in the specified group, or the total sample; PT, preferred term; SOC, system organ class; TEAE, treatment-emergent adverse event

Table 34 shows the incidence of TEAEs (Grade 3 or higher) that occurred in ≥2% of the safety population in the three cilta-cel studies combined (CARTITUDE-1, CARTITUDE-4, and CARTITUDE-2).

Table 34: FDA – Grade 3 and Higher AEs in ≥2% of 324 Subjects Treated With Cilta-cel by SOC and PT

System Organ Class and Preferred Term	CARTITUDE 1 N=97 n (%)	CARTITUDE-4 N=188 n (%)	CARTITUDE-2 N=39 n (%)	TOTAL N=324 n (%)
Blood and lymphatic system disorders	-	-	-	-
Febrile neutropenia	9 (9)	3 (3)	4 (10)	16 (5)
Immune system disorders	-	-	-	-
Hypogammaglobulinaemia	2 (2)	16 (9)	0	18 (6)
Cytokine release syndrome	4 (4)	6 (3)	16 (9)	13 (4)
Infections and infestations	-	-	-	-
Pneumonia	13 (13)	17 (9)	3 (8)	33 (10)
Sepsis	7 (7)	13 (7)	3 (8)	23 (7)
Bacterial infection	4 (4)	12 (6)	2 (5)	18 (6)
Viral infection	5 (5)	8 (4)	1 (3)	14 (4)

System Organ Class and Preferred Term	CARTITUDE 1 N=97 n (%)	CARTITUDE-4 N=188 n (%)	CARTITUDE-2 N=39 n (%)	TOTAL N=324 n (%)
General disorders	-	-	-	-
Fatigue	6 (6)	4 (2)	2 (5)	12 (4)
Gastrointestinal disorders	-	-	-	-
Diarrhea	1 (1)	5 (3)	3 (8)	9 (3)
Nausea	30 (31)	36 (20)	8 (21)	74 (23)
Constipation	21 (22)	19 (10)	7 (18)	47 (15)
Vomiting	19 (20)	10 (5)	5 (13)	34 (11)
Nervous system disorders	-	-	-	-
Encephalopathy	5 (6)	2 (1)	1 (3)	8 (3)
Motor dysfunction	4 (3)	0	2 (5)	6 (2)
Metabolism and nutrition disorders	-	-	-	-
Decreased appetite	28 (29)	18 (10)	5 (13)	51 (16)
MSK and connective tissue disorders	-	-	-	-
Musculoskeletal pain	1 (1)	3 (2)	3 (8)	7 (2)
Respiratory, thoracic and mediastinal disorders	-	-	-	-
Hypoxia	3 (3)	2 (8)	3 (8)	8 (3)
Dyspnea	2 (2)	3 (2)	2 (5)	7 (2)
Renal and urinary disorders	4 (4)	6 (3)	2 (5)	12 (4)
Renal failure	4 (4)	6 (3)	2 (5)	12 (4)
Vascular disorders	-	-	-	-
Hypertension	6 (6)	6 (3)	1 (3)	13 (4)
Hemorrhage	4 (4)	3 (2)	0	7 (2)

Source: Adapted from Applicant's response to FDA IR dated Mar 19, 2024 (TSFAE49_ISS_FDA_IR; CARVYKTI USPI 2022). Data cutoff November 1, 2022

Abbreviations: AE, adverse event; MSK, musculoskeletal; n (%), number of subjects with the specified characteristic; N, number of subjects in the specified group, or the total sample; PT, preferred term; SOC, system organ class; TEAE, treatment-emergent adverse event

Clinical Test Results

Table 35 shows the incidence of new or worsening laboratory abnormalities by lab shift treatment-emergent hematology laboratory results in the safety population in the three cilta-cel studies combined (CARTITUDE-1, CARTITUDE-4, and CARTITUDE-2).

Table 35: FDA – New or Worsening Hematologic Laboratory Abnormalities by Laboratory Shift Analysis

Parameter	Subjects n	All Grade n (%)	Grade 3-4 n (%)	Grade 3 n (%)	Grade 4 n (%)
Hematology	-	-	-	-	-
Hemoglobin decrease	324 (100)	324 (100)	0	148 (46)	0
Platelet decrease	324 (100)	310 (96)	13 (4)	60 (19)	94 (29)

Parameter	Subjects n	All Grade n (%)	Grade 3-4 n (%)	Grade 3 n (%)	Grade 4 n (%)
Neutrophil decrease	324 (100)	323 (100)	45 (14)	70 (22)	241 (74)
Chemistry	-	-	-	-	-
Potassium increase	324 (100)	19 (6)	0	2 (1)	0
ALT increase	324 (100)	188 (58)	0	17 (5)	1 (0.3)

Source: Adapted from Applicant's response to FDA IR dated Mar 19, 2024 (TSFAE49_ISS_FDA_IR). Data cutoff November 1, 2022
Abbreviations: ALT, alanine aminotransferase; n (%), number of subjects with the specified characteristic

Adverse Events of Special Interest

Table 36 shows the adverse events of special interest (AESIs) by FDA grouped preferred terms in the safety population in the three cilta-cel studies combined (CARTITUDE-1, CARTITUDE-4, and CARTITUDE-2).

Table 36: FDA – AE of Special Interest in 324 Recipients of Cilta-cel

AESI	CARTITUDE 1 N=97 n (%)	CARTITUDE 1 N=97 n (%)	CARTITUDE-4 N=188 n (%)	CARTITUDE-4 N=188 n (%)	CARTITUDE-2 N=39 n (%)	CARTITUDE-2 N=39 n (%)	TOTAL N=324 n (%)	TOTAL N=324 n (%)
-	All Grades	Grade 3 or higher	All Grades	Grade 3 or higher	All Grades	Grade 3 or higher	All Grades	Grade 3 or higher
CRS	92 (95)	5 (5)	146 (78)	6 (3)	35 (90)	3 (8)	273 (84)	14 (4)
Pyrexia	92 (95)	5 (5)	146 (78)	10 (5)	31 (80)	3 (8)	269 (83)	18 (6)
Hypotension	40 (41)	8 (8)	39 (21)	6 (3)	15 (39)	3 (8)	94 (29)	17 (5)
Hypoxia	6 (6)	1 (1)	21 (11)	4 (2)	4 (10)	3 (8)	31 (10)	8 (3)
Chills	14 (14)	0	4 (2)	0	2 (5)	0	20 (6)	0
Headache	7 (7)	0	8 (4)	0	2 (5)	0	17 (5)	0
Sinus tachycardia	10 (10)	0	3 (2)	0	3 (8)	0	16 (5)	0
Tachycardia	4 (4)	0	2 (1)	0	4 (10)	0	10 (3)	0
CAR-T Cell NT	25(26)	11(11)	44 (23)	8 (4)	9 (23)	2(5)	78 (24)	21(6)
ICANS	17 (18)	3 (3)	14 (7)	1 (1)	4 (10)	0	35 (11)	4 (1)
Confusional state	4 (4)	0	5 (3)	1 (0.5)	1 (3)	0	10 (3)	1 (0.3)
Dysgraphia	2 (2)	0	6 (3)	0	1 (3)	0	9 (3)	0
Aphasia	8 (8)	0	3 (2)	0	0	0	6 (2)	0
Gait disturbance	2 (2)	0	1 (0.5)	0	1 (3)	0	4 (1)	0

AESI	CARTITUDE 1 N=97 n (%)	CARTITUDE 1 N=97 n (%)	CARTITUDE-4 N=188 n (%)	CARTITUDE-4 N=188 n (%)	CARTITUDE-2 N=39 n (%)	CARTITUDE-2 N=39 n (%)	TOTAL N=324 n (%)	TOTAL N=324 n (%)
-	All Grades	Grade 3 or higher	All Grades	Grade 3 or higher	All Grades	Grade 3 or higher	All Grades	Grade 3 or higher
Headache	1 (1)	0	3 (2)	0	0	0	4 (1)	0
Disturbance in attention	2 (2)	0	0	0	1 (3)	0	3 (1)	0
Lethargy	2 (2)	0	1 (0.5)	0	0	0	3 (1)	0
Somnolence	2 (2)	0	1 (0.5)	0	0	0	3 (1)	0
Tremor	2 (2)	0	1 (0.5)	0	0	0	3 (1)	0
Depressed LOC	1 (1)	1 (1)	1 (0.5)	1 (0.5)	0	0	2 (0.6)	2 (0.6)
Dysarthria	0	0	2 (1)	0	0	0	2 (0.6)	0
Slow speech	1 (1)	0	0	0	1 (3)	0	2 (0.6)	0
Peripheral neuropathies	7 (7)	2 (2)	13 (7)	1 (0.5)	2 (5)	1 (3)	22 (7)	4 (1)
Cranial nerve palsies	3 (3)	1 (1)	16 (7)	2 (1)	2 (5)	0	21 (7)	3 (1)
Movement and neurocognitive	6 (6)	5 (5)	2 (1)	0	1 (2)	1 (3)	9 (3)	6 (1.9)
Infections	59(57)	21(20)	57(107)	19(35)	20(51)	8 (21)	136 (42)	48 (15)
Bacterial infections	9 (9)	2 (2)	27 (14)	13 (6)	6 (15)	1 (3)	42 (13)	16 (5)
Infections – pathogen unspecified	38 (39)	17 (18)	67 (36)	23 (12)	14 (36)	4 (10)	119 (37)	44 (14)
Febrile neutropenia	10 (10)	9 (9)	3 (2)	3 (2)	6 (15)	6 (15)	19 (6)	18 (6)
Fungal infections	1 (1)	1(1)	10 (5)	1(1)	3 (8)	1 (3)	14 (4)	3(1)
Viral infections	22(23)	7 (7)	53 (28)	18 (10)	5 (13)	3 (8)	80 (24)	28 (9)

Source: Adapted from Applicant's response to FDA IR dated Mar 19, 2024 (TSFAE49_ISS_FDA_IR; CARVYKTI USPI 2022). Data cutoff November 1, 2022
Abbreviations: LOC, level of consciousness; MSK, musculoskeletal; NT, neurotoxicity

Table 37 shows a summary of time to onset and time to recovery of the AESIs in the safety population in the three cilta-cel studies combined (CARTITUDE-1, CARTITUDE-4, and CARTITUDE-2). The AESIs are comparable across the three cilta-cel studies. The clinical review team will present the pooled data in the label.

Table 37: FDA – Summary of AESI With Onset and Recovery in 324 Recipients of Cilta-cel

Adverse Event of Special Interest	CARTITUDE-1 N=97	CARTITUDE-4 N=188	CARTITUDE-2 N=39	Total N=324
CRS	-	-	-	-
Time from infusion to onset (days)	-	-	-	-
N	92	146	35	273
Median (range)	7.0 (1; 12)	8.0 (1; 23)	7.0 (5; 11)	7.0 (1; 23)
Interquartile range	(5.0; 8.0)	(6.0; 8.0)	(7.0; 8.0)	(6.0; 8.0)

Adverse Event of Special Interest	CARTITUDE-1 N=97	CARTITUDE-4 N=188	CARTITUDE-2 N=39	Total N=324
Time to recovery (days)	-	-	-	-
N	91	144	35	270
Median (range)	4.0 (1; 40)	3.0 (1; 17)	4.0(1; 12)	4.0 (1; 40)
Interquartile range	(3.0; 6.0)	(2.0; 5.0)	(2.0; 5.0)	(3.0; 5.0)
ICANS	-	-	-	-
Time from infusion to onset (days)	-	-	-	-
N	17	14	4	35
Median (range)	8.0 (3; 26)	9.0 (2; 15)	9.0 (7; 11)	8.0 (2; 26)
Interquartile range	(6.0; 8.0)	(7.0; 10.0)	(7.5; 10.5)	(7.0; 10.0)
Time to recovery (days)	-	-	-	-
N	16	13	4	33
Median (range)	4.0 (1; 12)	2.0 (1; 21)	3.0 (1; 4)	3.0 (1; 21)
Interquartile range	(3.0; 6.0)	(1.0; 2.0)	(2.0; 3.5)	(2.0; 4.0)
Peripheral neuropathies	-	-	-	-
Time from infusion to onset (days)	-	-	-	-
N	7	13	2	22
Median (range)	66.0 (4; 914)	46.0 (1; 189)	205.5 (96; 315)	57.5 (1; 914)
Interquartile range	(44.0; 136.0)	(31.0; 101.0)	(96.0; 315.0)	(34.0; 113.0)
Time to recovery (days)	-	-	-	-
N	3	8	0	11
Median (range)	62.0 (2; 138)	36.5 (1; 215)	-	58.0 (1; 215)
Interquartile range	(2.0; 138.0)	(7.0; 174.0)	-	(6.0; 158.0)
Cranial nerve palsy	-	-	-	-
Time from infusion to onset (days)	-	-	-	-
N	3	16	2	21
Median (range)	26.0 (21; 101)	21.0 (17; 60)	25.5 (22; 29)	22.0 (17; 101)
Interquartile range	(21.0; 101.0)	(20.0; 24.5)	(22.0; 29.0)	(21.0; 25.0)
Time to recovery (days)	-	-	-	-
N	3	14	2	19
Median (range)	70.0 (1; 79)	61.0 (15; 209)	89.5 (51; 128)	66.0 (1; 209)
Interquartile range	(1.0; 79.0)	(34.0; 95.0)	(51.0; 128.0)	(34.0; 95.0)
Movement and neurocognitive toxicity	-	-	-	-
Time from infusion to onset (days)	-	-	-	-
N	6	2	1	9
Median (range)	64.0 (14; 914)	59.5 (34; 85)	38.0 (38; 38)	38.0 (14; 914)
Interquartile range	(15.0; 108.0)	(34.0; 85.0)	(38.0; 38.0)	(27.0; 101.0)

Adverse Event of Special Interest	CARTITUDE-1 N=97	CARTITUDE-4 N=188	CARTITUDE-2 N=39	Total N=324
Time to recovery (days)	-	-	-	-
N	1	0	0	1
Median (range)	523.0 (523; 523)	-	-	523.0 (523; 523)
Interquartile range	(523.0; 523.0)	-	-	(523.0; 523.0)

Source: Adapted from Applicant's response to FDA IR dated Mar 19, 2024 (TSFAE49_ISS_FDA_IR). Data cutoff November1, 2022
Abbreviations: AESI, adverse event of special interest; CRS, cytokine release syndrome; ICANS, Immune Effector Cell-associated Neurotoxicity Syndrome; N, number of subjects in the specified group, or the total sample

SUMMARY AND CONCLUSIONS

8.3. Statistical Issues

The FDA's Assessment:

Study CARTITUDE-4 met the prespecified criteria for demonstrating a statistically significant improvement in the primary endpoint of PFS for subjects treated with cilta-cel compared to the subjects treated with standard therapy. The first interim OS analysis was immature at the time of the primary PFS analysis (34%). The OS curves showed detriment in the first 10 months with subsequent crossing and heavy censoring following 10 months. The average HR for OS and the medians are not interpretable.

8.4. Conclusions and Recommendations

The FDA's Assessment:

The safety and effectiveness of cilta-cel for the proposed indication derives from Study CARTITUDE-4 and Study CARTITUDE-2. CARTITUDE-4 is a Phase 3, randomized (1:1), open-label, multicenter study that compared cilta-cel to standard therapy in adults with relapsed and lenalidomide-refractory MM after one to three prior lines of therapy including a PI and an IMiD. CARTITUDE-4 enrolled a total of 419 patients who were randomized to receive cilta-cel or one of two standard-of-care regimens, either PVd or DPd. Patients received cilta-cel as a single infusion at a dose range of 0.41-1.08x10^6 CAR+ viable cells/kg following lymphodepletion therapy with fludarabine and cyclophosphamide.

The primary efficacy outcome measure for CARTITUDE-4 is PFS as determined by a blinded IRC using the IMWG 2016 criteria. Key secondary efficacy outcome measures in hierarchical testing order are rate of CR or better (CRR), ORR, overall MRD negativity rate, OS, and time to worsening of symptoms in the MySIm-Q total symptom score. Patient reported outcomes were additional efficacy endpoints, evaluated in an exploratory fashion.

CARTITUDE-4 met its primary endpoint (data cutoff of November 1, 2022), demonstrating a statistically significant and clinically meaningful improvement in PFS in patients randomized to the cilta-cel arm compared to patients randomized to the standard therapy arm (HR was 0.41 [95% CI: 0.30, 0.56] based on a stratified log-rank test; p-value <0.0001). The median PFS was not reached in the cilta-cel arm (95% CI: 22.8, not evaluable [NE]), and was 12 months (95% CI: 9.8, 14) in the standard therapy arm.

The IRC-assessed CR rate was statistically significant; 74% (95% CI: 67, 79) in the cilta-cel arm compared to 22% (95% CI: 16, 28) in the standard therapy arm. Similarly, the ORR was higher at 85% (95% CI:79, 89) in the cilta-cel arm compared to 67% (95% CI: 61, 74) in the standard therapy arm. At the time of the primary analysis of PFS, overall survival (OS) was immature (information fraction of 34%). Accordingly, FDA considered cilta-cel effects on OS as part of the safety assessment.

A higher proportion of patient randomized to cilta-cel compared to standard therapy experienced death in with first 10 months following randomization (n=29/208;14% vs. n=25/211;12%). Of the 29 deaths that occurred in the cilta-cel arm within the first 10 months of randomization, 10 deaths occurred prior to cilta-cel infusion, and 19 deaths occurred after cilta-cel infusion. Of the 10 deaths that occurred prior to cilta-cel infusion, all occurred due to disease progression, and none occurred due to adverse events. Of the 19 deaths that occurred after cilta-cel infusion, 3 occurred due to disease progression, and 16 occurred due to adverse events. The higher early mortality with cilta-cel was observed across multiple prognostic subgroups and was observed even in the absence of individual poor prognostic factors. In the safety analysis population, there was also a higher rate of fatal adverse reaction that occurred within 90 days from starting treatment with cilta-cel in the as treated population arm compared to in the standard therapy arm (5% versus 0%).

FDA convened a meeting of the ODAC to discuss whether the results of CARTITUDE-4 are sufficient to support a positive risk-benefit assessment of cilta-cel for the proposed indication and if the risk of early death associated with cilta-cel treatment is acceptable in the context of PFS benefit. Voting members of the ODAC were asked to vote on whether the risk-benefit assessment for cilta-cel for the proposed indication favorable; the ODAC voted 11 to 0 in favor of cilta-cel.

The primary evidence of the safety of cilta-cel for the proposed indication derives from CARTITUDE-4; CARTITUDE-2 provides support evidence of safety. The primary analysis of safety was conducted in patients enrolled in CARTITUDE-4 who received conformal cilta-cel in the investigational arm (n=188) and patients who received standard therapy (n=208). All patients experienced an AE (cilta-cel arm: 100%; standard therapy arm: 100%). The most common (≥5 %)

Grade 3 to 4 TEAEs in the cilta-cel arm were hypogammaglobulinemia (9%), Pneumoniae (9%), bacterial infection (6 %), and pneumonia (11 %), viral infection (6 %), in the standard therapy arm. The Grade 3 to 4 toxicity rate was slightly higher in the standard therapy arm (cilta-cel arm: 92%; standard therapy: 94%). SAEs occurred in 34% and 39% of subjects in the cilta-cel and standard therapy arms, respectively.

CRS and NT associated with cilta-cel therapy are serious, life-threatening, and can be fatal. Treatment algorithms to mitigate these AEs, as implemented in the study, permit the benefits of treatment to outweigh these risks. Increased risk of secondary malignancies due to insertional mutagenesis is a known risk; during this study, a T-cell lymphoma was attributed to the study product. A PMR long-term follow-up registry study will be required to follow recipients of the commercial product for short term and long-term toxicity up to 15 years.

In conclusion, CARTITUDE-4 provides substantial evidence of effectiveness of cilta-cel for patients with relapsed and lenalidomide-refractory MM after one to three prior lines of therapy, including a PI and an IMiD. CARTITUDE-4 demonstrates clinical benefit through clinically meaningful improvements in PFS, CRR, ORR, and the potential for durable duration of response in the proposed patient population. The most common serious risks of cilta-cel have been characterized and are mitigated through product labeling and a REMS. The observed higher rate of early death observed in CARTITUDE-4 does not have a clear etiology but as discussed in the ODAC, may represented frontloaded risks associated with the treatment and its administration. CARTITUDE-4 was not designed to provide definitive information on how this risk can be mitigated. Treatment with cilta-cel may require careful consideration of individual patient characteristics, disease characteristics, the therapeutic context among other factors. The risk of increase early mortality with cilta-cel will be included under Warning and Precautions section of the USPI. The ODAC members assessed the risks acceptable in the indicated population.

The review team recommends traditional approval of cilta-cel at the currently approved dosage, for the treatment of adult patients with RRMM who have received at least one prior line of therapy, including a PI and an immunomodulatory agent, and are refractory to lenalidomide.

The recommendation for approval was based on demonstration of substantial evidence of effectiveness and positive benefit-risk in the indicated patient population as assessed in the Phase 3 CARTITUDE-4 study.

X X

Primary Clinical Reviewer Clinical Team Leader

9 Advisory Committee Meeting and Other External Consultations

The FDA's Assessment:
FDA convened a meeting of the ODAC to discuss the results of the randomized controlled study CARTITUDE-4, which provides the primary evidence of cilta-cel's safety and effectiveness for the proposed indication. Specifically, FDA requested the Committee's input on the the higher rate of early deaths associated with cilta-cel and the benefit-risk profile of cilta-cel for the proposed indication based on the results of the CARTITUDE-4 study. The ODAC voted 11 to 0 in favor of cilta-cel.

10 Pediatrics

The Applicant's Position:

No new information is provided in the current submission. Cilta-cel is indicated for adults with multiple myeloma and is not studied in pediatric patients. A request for waiver of pediatrics studies in children below 18 years of age is included in Module 1.9.1.

The FDA's Assessment:
Not applicable.

11 Labeling Recommendations

Data:

Summary of Significant Labeling Changes (High level changes and not direct quotations)		
Section	**Applicant's Proposed Labeling**	**FDA's Proposed Labeling**
Section 1 Indications and Usage	Indicated population updated to: • patients with RRMM who received at least 1 prior line of therapy • removal of prior therapy including an anti-CD38 antibody and addition of refractory to lenalidomide	CARVYKTI is indicated for the treatment of adult patients with relapsed or refractory multiple myeloma who have received at least 1 prior line of therapy, including a proteasome inhibitor and an immunomodulatory agent, and are refractory to lenalidomide.
Warnings and Precautions Section 5.1 Cytokine Release Syndrome	Addition of data from Study MMY3002 (CARTITUDE-4). • Incidence of CRS • Duration of CRS • Symptoms of CRS Guidance added to evaluate patients with progressive symptoms of CRS or refractory CRS for evidence of HLH/MAS	Added increased early mortality associated with cilta-cel observed in CARTITUDE-4 under Section 5.1
Warnings and Precautions Section 5.2 Neurologic Toxicities	Addition of data from Study MMY3002 (CARTITUDE-4). • Overall incidence of neurologic toxicity • Incidence of subtypes of neurologic toxicity: ICANS, parkinsonism, immune mediated myelitis, peripheral neuropathy, and cranial nerve palsies	Adding pooled data of Neurologic Toxicities from CARTITUDE-1 and CARTITUDE-4 instead of describing the studies individually
Warnings and Precautions Section 5.3 Hemophagocytic Lymphohistiocytosis (HLH)/Macrophage Activation Syndrome (MAS)	Addition of data from Study MMY3002 (CARTITUDE-4).	Adding pooled data of HLH/MAS from CARTITUDE-1 and CARTITUDE-4 instead of describing the studies individually
Warnings and Precautions Section 5.5 Prolonged and Recurrent Cytopenias	Addition of data from Study MMY3002 (CARTITUDE-4).	Adding pooled data of Prolonged and Recurrent Cytopenias from CARTITUDE-1 and CARTITUDE-4 instead of describing the studies individually DA will complete this section

Summary of Significant Labeling Changes (High level changes and not direct quotations)		
Section	**Applicant's Proposed Labeling**	**FDA's Proposed Labeling**
Warnings and Precautions Section 5.6 Infections	Addition of data from Study MMY3002 (CARTITUDE-4). • Overall incidence of infections • Fatal infections • Increased rate of fatal COVID-19 infections in patients treated with cilta-cel	Adding pooled data of Infections from CARTITUDE-1 and CARTITUDE-4 instead of describing the studies individually
Warnings and Precautions Section 5.7 Hypogammaglobulinemia	Addition of data from Study MMY3002 (CARTITUDE-4).	Adding pooled data of Hypogammaglobulinemia from CARTITUDE-1 and CARTITUDE-4 instead of describing the studies individually
Warnings and Precautions Section 5.8 Hypersensitivity Reactions	Addition of data from Study MMY3002 (CARTITUDE-4).	Adding pooled data of Hypersensitivity from CARTITUDE-1 and CARTITUDE-4 instead of describing the studies individually A will complete this section
Section 6.1 Clinical Trials Experience	Addition of data from Study MMY3002 (CARTITUDE-4). • Median dose and dose range • Demographics • Median duration of follow-up • Common and clinically important ADRs • Laboratory abnormalities (cytopenias)	This section includes ADRs, and laboratory abnormalities observed in CARTITUDE-4 based FDA's adjudication and FDA's grouped terms The safety population includes all the patients who received conforming cilta-cel product. (N=188)
Section 6.2 Immunogenicity	Addition of data from Study MMY3002 (CARTITUDE-4).	Update with data of all the patients who received conformal cilta-cel product in CARTIUDE-4
Section 6.3 Postmarketing Experience		FDA ejected the deletion of Section 6.3. This section was included as part of the Safety Labeling Change Notification
Section 8.5 Geriatric Use	Addition of data from Study MMY3002 (CARTITUDE-4).	Updated to include data from Study CARTITUDE-4
Section 12.3 Pharmacokinetics	Addition of data from Study MMY3002 (CARTITUDE-4).	Updated to include data from CARTITUDE-4.

Disclaimer: In this document, the sections labeled as "Data" and "The Applicant's Position" are completed by the Applicant and do not necessarily reflect the positions of the FDA.

Section 14 Clinical Studies	Addition of data from Study MMY3002 (CARTITUDE-4). • Study disposition and demographics • Dosing information including time from day of receipt of apheresis material to release of product for infusion • Efficacy data: PFS, CR or better rate, ORR, MRD negativity rate, and OS	This section is updated to include efficacy data from CARTITUDE-4 with the following revisions: In table 8: Removed results for OS since the data is immature. Removed results for Minimal Residual Disease negative rate due to missing data and high rates of failure. Request to add a paragraph with DOR for PR and better. Request to include KM curve for OS with data cutoff date of November 1, 2022 Remove the efficacy results for subgroups that received CARVYKTI as study treatment and as subsequent therapy) Remove Patient Reported Outcomes: MySIM-Q data was not formally tested and was considered exploratory data.
Boxed Warning		Updated to include the safety related labeling change language for T-cell malignancies with CARVYKTI

The Applicant's Position:

The draft label includes the relevant conclusions based on the population enrolled in Study MMY3002 and the currently approved indication for cilta-cel to support the following combined indication:

CARVYKTI is a BCMA-directed genetically modified autologous T cell immunotherapy indicated for the treatment of adult patients with relapsed or refractory multiple myeloma, who have received at least 1 prior line of therapy, including a PI, and an immunomodulatory agent, and are refractory to lenalidomide.

The FDA's Assessment:

The agreed upon and negotiated information in the prescribing information for cilta-cel provide adequate directions for use to support the indication seeking by the Applicant. See Table above and final approved prescribing information for more information.

12 Risk Evaluation and Mitigation Strategies (REMS)

The FDA's Assessment:
Based on review of available data from the Phase 3 clinical trial and supportive Phase 1/2 clinical trials, the safety concerns for Carvykti continue to warrant a REMS Program with ETASU to mitigate the risks of CRS and neurological toxicity and to ensure the benefits outweigh the risks for use of the product. The Applicant submitted a REMS major modification that included revisions to the REMS materials to address the new indication and labeling changes proposed in sBLA 125746/74.

The REMS requires hospital sites to be specially certified and have on-site, immediate (within two hours of infusion) access to tocilizumab. Under STN 125746/74, there were no major changes to the REMS Document or REMS Hospital Enrollment Form. The REMS website screenshot was updated to align with the revisions to the USPI (indication statement and Boxed Warning). DPV recommends approval of CARVYKTI REMS Modification under STN 125746/74

Please see the final version of the REMS Document, REMS materials, and package insert submitted by the Applicant for the final agreed-upon content and language, including product indication and dosing. For details, please refer to OBPV/DPV clinical reviewer's memo dated April 02, 2024

13 Postmarketing Requirements and Commitment

The FDA's Assessment:

The Applicant is conducting a postmarketing registry study, which we are considering as a PMR. This study is observational and focuses on short-term toxicity, AE documentation, and long-term follow-up for evaluation of secondary malignancies. The original plan was to enroll approximately 1,500 patients and follow each patient for 15 years. The study (protocol 68284528MMY4004) has been amended to add 200 additional patients who receive cilta-cel as an earlier line treatment.

The important identified risk of hematologic malignancies of T cell and myeloid origin will be monitored through a PMR LTFU registry study (MMY4004) for recipients in the postmarketing setting, and through routine pharmacovigilance activities. The Applicant will include a summary of any interim reports for the PMR LTFU registry study in periodic safety reports. In addition, the Applicant is conducting the following activities: collecting information on cases of second primary malignancies using a topic of interest questionnaire, submitting expedited reports to FAERS for cases of secondary malignancy of T cell origin, and performing interval analysis of all cases of second primary malignancies, including cases of AML, MDS, and T cell malignancies, and cumulative analysis of "biologically relevant" hematological malignancies in periodic safety reports. Of note, there is no new safety PMR with approval of STN 125746/74. The LTFU registry study will further assess the incidence and severity of the serious risk of secondary malignancy, as well as other selected AEs, in patients treated with Carvykti in the postmarket setting and will include up to 15-years of participant follow-up. (The safety PMR#1 with the initial approval of STN 125746/0 on February 28, 2022, remains unchanged.). Class SLC language will be added to the label Section 5.10. Please refer to OBPV/DPV clinical reviewer's memo dated April 02, 2024.

The following PMC was agreed on April 5, 2023:

Submit the final overall survival report and datasets for the CARTITUDE-NCT04181827 clinical trial, titled "A Phase 3 Study Comparing JNJ-68284528, a Chimeric Antigen Receptor T (CAR T) Cell Therapy Directed Against B-cell Maturation Antigen (BCMA), versus Pomalidomide, Bortezomib and Dexamethasone (PVd) or Daratumumab, Pomalidomide and Dexamethasone (DPd) in Participants With Relapsed and Lenalidomide-Refractory Multiple Myeloma.

Final Protocol Submission: 08/2022

Study/Trial Completion Date: 08/2031

Final Report Submission: 02/2032

14 Chief, Clinical Hematology Branch

X

15 Oncology Center of Excellence (OCE) Signatory

This application was reviewed by the Oncology Center of Excellence (OCE) per the OCE Intercenter Agreement. My signature below represents an approval recommendation for the clinical portion of this application under the OCE.

X

Marc Theoret, MD

16 Division Director (DCEH)

X

17 Appendices

17.1. References

The Applicant's References:

ABECMA (idecabtagene vicleucel) USPI. Celgene Corporation, a Bristol-Myers Squibb Company; 2021.

Ailawadhi S, Parikh K, Abouzaid S, et al. Racial disparities in treatment patterns and outcomes among patients with multiple myeloma: a SEER-Medicare analysis. Blood Adv. 2019;3(20):2986-2994.

BLENREP (belantamab mafodotin-blmf) USPI. GlaxoSmithKline; 2020.

Bringhen S, Pour L, Vorobyev V, et al. Isatuximab plus pomalidomide and dexamethasone in patients with relapsed/refractory multiple myeloma according to prior lines of treatment and refractory status: ICARIA-MM subgroup analysis. Leuk Res. 2021;104:106576.

Byrt T, Bishop J, Carlin JB. Bias, prevalence and kappa. J Clin Epidemiol. 1993;46(5):423-429.

Cancer.net 2020. Multiple myeloma statistics. Available from: http://www.cancer.net/cancer-types/multiple-myeloma/statistics. Accessed 04 October 2022.

CARVYKTI (ciltacabtagene autoleucel) USPI. Horsham, PA: Janssen Biotech, Inc. and Somerset, NJ: Legend Biotech; 2023.

Cowan AJ, Allen C, Barac A, et al. Global burden of multiple myeloma: A systematic analysis for the global burden of disease study 2016. JAMA Oncol. 2018;4:1221-1227.

DARZALEX (daratumumab) USPI. Janssen; 2023.

Derman BA, Jasielec J, Langerman SS, Zhang W, Jakubowiak AJ, Chiu BCH. Racial differences in treatment and outcomes in multiple myeloma: a multiple myeloma research foundation analysis. Blood Cancer J. 2020;10(8):80.

Dimopoulos MA, Oriol A, Nahi H, et al. Daratumumab, lenalidomide, and dexamethasone for multiple myeloma. N Engl J Med. 2016;375(14):1319-1331.

Dimopoulos MA, Terpos E, Boccadoro M, et al. Daratumumab plus pomalidomide and

dexamethasone versus pomalidomide and dexamethasone alone in previously treated multiple myeloma (APOLLO): an open-label, randomised, phase 3 trial. Lancet Oncol. 2021;22(6):801-812.

Ferlay J, Steliarova-Foucher E, Lortet-Tieulent J, et al. Cancer incidence and mortality patterns in Europe: estimates for 40 countries in 2012. Eur J Cancer. 2013;49(6):1374-1403.

Fiala MA, Wildes TM. Racial disparities in treatment use for multiple myeloma. Cancer. 2017;123(9):1590-1596.

Gormley N, Fashoyin-Aje L, Locke T, et al. Recommendations on eliminating racial disparities in multiple myeloma therapies: a step toward achieving equity in healthcare. Blood Cancer Discov. 2021;2(2):119-124.

Hajek R (2017), Masszi T, Petrucci MT, et al. A randomized phase III study of carfilzomib vs low-dose corticosteroids with optional cyclophosphamide in relapsed and refractory multiple myeloma (FOCUS). Leukemia. 2017;31:107-114.

Kalled SL. The role for BAFF in immune function and implications for autoimmunity. Immunol Rev. 2005;204;43-54.

Kanapuru B, Fernandes LL, Fashoyin-Aje LA, et al. Analysis of racial and ethnic disparities in multiple myeloma US FDA drug approval trials. Blood Adv. 2022;6(6):1684-1691.

Kazandjian D. Multiple myeloma epidemiology and survival: A unique malignancy. Semin Oncol. 2016;43(6):676-681.

Kumar S, Paiva B, Anderson KC et al. International Myeloma Working Group consensus criteria for response and minimal residual disease assessment in multiple myeloma. Lancet Oncol. 2016;17:e328-e346.

Laâbi Y, Gras MP, Carbonnel F, et al. A new gene, BCM, on chromosome 16 is fused to the interleukin 2 gene by a t(4;16)(q26;p13) translocation in a malignant T cell lymphoma. EMBO J. 1992;11(11):3897–3904.

Laabi Y, Gras MP, Brouet JC, Berger R, Larsen CJ, Tsapis A. The BCMA gene, preferentially expressed during B lymphoid maturation, is bidirectionally transcribed. Nucleic Acids Res. 1994;22(7):1147-1154.

Lecat CSY, Taube JB, Wilson W, et al. Defining unmet need following lenalidomide refractoriness: real-world evidence of outcomes in patients with multiple myeloma. Front Oncol. 2021;11:703233.

Lonial S, Dimopoulos MA, Palumbo A, et al. Elotuzumab therapy for relapsed or refractory multiple myeloma. N Engl J Med. 2015;373(7):621-631.

Lonial S, Weiss BM, Usmani SZ, et al. Daratumumab monotherapy in patients with treatment-refractory multiple myeloma (SIRIUS): an open-label, randomised, phase 2 trial. Lancet. 2016;387(10027):1551-1560.

Marella M, Yao X, Carreira V, et al. Comprehensive BCMA expression profiling in adult normal human brain suggests a low risk of on-target neurotoxicity in BCMA-targeting multiple myeloma therapy. J Histochem Cytochem. 2022;70(4):273-287.

Martin T, Usmani SZ, Berdeja JG, et al. Ciltacabtagene autoleucel, an anti-B-cell maturation antigen chimeric antigen receptor T-cell therapy, for relapsed/refractory multiple myeloma: CARTITUDE-1 2-year follow-up. J Clin Oncol. 2023;41(6):1265-1274.

Moreau P, Masszi T, Grzasko N, et al. Oral ixazomib, lenalidomide, and dexamethasone for multiple myeloma. N Engl J Med. 2016;374(17):1621-1634.

Moreau P, Dimopoulos MA, Mikhael J, et al. Isatuximab, carfilzomib, and dexamethasone in relapsed multiple myeloma (IKEMA): a multicentre, open-label, randomised Phase 3 trial. Lancet. 2021; 397: 2361–2371.

Munshi NC, Anderson LD Jr, Shah N, et al. Idecabtagene vicleucel in relapsed and refractory multiple myeloma. N Engl J Med. 2021;384(8):705-716.

Ng LG, Sutherland AP, Newton R, et al. B cell-activating factor belonging to the TNF family (BAFF)-R is the principal BAFF receptor facilitating BAFF costimulation of circulating T and B cells. J Immunol. 2004;173(2):807-817.

O'Connor BP, Raman VS, Erickson LD, et al. BCMA is essential for the survival of long-lived bone marrow plasma cells. J Exp Med. 2004;199(1):91-98.

Orlowski RZ. Why proteasome inhibitors cannot ERADicate multiple myeloma. Cancer Cell. 2013;24(3):275-277.

Padala SA, Barsouk A, Barsouk A, et al. Epidemiology, staging, and management of multiple myeloma. Med Sci (Basel). 2021;9(1):3.

PEPAXTO (melphalan flufenamide) USPI. Oncopeptides Inc.; 2021.

POMALYST (pomalidomide) USPI. Bristol Myers Squibb; 2023.

Rajkumar SV, Harousseau JL, Durie B, et al. Consensus recommendations for the uniform reporting of clinical trials: report of the International Myeloma Workshop Consensus Panel 1. Blood. 2011;117(18):4691-4695.

Richardson PG, Oriol A, Beksac M, et al. Pomalidomide, bortezomib, and dexamethasone for patients with relapsed or refractory multiple myeloma previously treated with lenalidomide (OPTIMISMM): a randomised, open-label, phase 3 trial. Lancet Oncol. 2019;20(6):781-794.

Rodriguez-Abreu D, Bordoni A, Zucca E. Epidemiology of hematological malignancies. Ann Oncol. 2007;18 Suppl 1:i3-i8.

Rodríguez-Otero P, Ailawadhi S, Arnulf B, et al. Ide-cel or standard regimens in relapsed and refractory multiple myeloma. N Engl J Med. 2023;388(11):1002-1014.

SARCLISA (isatuximab-irfc) USPI. Sanofi; 2020.

Stewart AK, Rajkumar SV, Dimopoulos MA, et al. Carfilzomib, lenalidomide, and dexamethasone for relapsed multiple myeloma. N Engl J Med. 2015;372(2):142-152.

TECVAYLI (teclistamab-cqyv) USPI. Janssen; 2022.

Turesson I, Velez R, Kristinsson SY, Landgren O. Patterns of improved survival in patients with multiple myeloma in the twenty-first century: a population-based study. J Clin Oncol. 2010;28(5):830-834.

Usmani SZ, Quach H, Mateos MV, et al. Carfilzomib, dexamethasone, and daratumumab versus carfilzomib and dexamethasone for patients with relapsed or refractory multiple myeloma (CANDOR): updated outcomes from a randomised, multicentre, open-label, Phase 3 study. Lancet Oncol. 2022;23(1):65–76.

XPOVIO (selinexor) USPI. Karyopharm Therapeutics Inc.; 2019.

The FDA's References:

Cowan AJ, Green DJ, Kwok M, Lee S, Coffey DG, Holmberg LA, Tuazon S, Gopal AK, Libby EN. Diagnosis and Management of Multiple Myeloma: A Review. JAMA. 2022 Feb 1;327(5):464-477. doi: 10.1001/jama.2022.0003. PMID: 35103762.

Costa LJ, Derman BA, Bal S, Sidana S, Chhabra S, Silbermann R, Ye JC, Cook G, Cornell RF, Holstein SA, Shi Q, Omel J, Callander NS, Chng WJ, Hungria V, Maiolino A, Stadtmauer E, Giralt S, Pasquini M, Jakubowiak AJ, Morgan GJ, Krishnan A, Jackson GH, Mohty M, Mateos MV, Dimopoulos MA, Facon T, Spencer A, Miguel JS, Hari P, Usmani SZ, Manier S, McCarthy P, Kumar S, Gay F, Paiva B. International harmonization in performing and reporting minimal residual disease assessment in multiple myeloma trials. Leukemia. 2021 Jan;35(1):18-30.

Kumar S, Paiva B, Anderson KC, Durie B, Landgren O, Moreau P, Munshi N, Lonial S, Bladé J, Mateos MV, Dimopoulos M, Kastritis E, Boccadoro M, Orlowski R, Goldschmidt H, Spencer A, Hou J, Chng WJ, Usmani SZ, Zamagni E, Shimizu K, Jagannath S, Johnsen HE, Terpos E, Reiman A, Kyle RA, Sonneveld P, Richardson PG, McCarthy P, Ludwig H, Chen W, Cavo M, Harousseau JL, Lentzsch S, Hillengass J, Palumbo A, Orfao A, Rajkumar SV, Miguel JS, Avet-Loiseau H. International Myeloma Working Group consensus criteria for response and minimal residual disease assessment in multiple myeloma. Lancet Oncol. 2016 Aug;17(8):e328-e346.

Palumbo A, Anderson K. Multiple myeloma. N Engl J Med. 2011; 364:1046–1060

Rajkumar SV, Harousseau JL, Durie B, Anderson KC, Dimopoulos M, Kyle R, Blade J, Richardson P, Orlowski R, Siegel D, Jagannath S, Facon T, Avet-Loiseau H, Lonial S, Palumbo A, Zonder J, Ludwig H, Vesole D, Sezer O, Munshi NC, San Miguel J; International Myeloma Workshop Consensus Panel 1. Consensus recommendations for the uniform reporting of clinical trials: report of the International Myeloma Workshop Consensus Panel 1. Blood. 2011 May 5;117(18):4691-5.

17.2. Financial Disclosure

The Applicant's Position:

The Applicant has adequately assessed clinical investigators from covered Studies MMY3002 and MMY2003 for any financial interests/arrangements as defined in 21 CFR Part 54.

Two US investigators disclosed significant payments for consulting honoraria exceeding $25,000 USD. These investigators participated as subinvestigators, and enrolled/treated 10 participants and one participant, respectively, in Study MMY3002. Financial certifications and disclosures are provided in Module 1.3.4.

No disclosable financial interests were found for investigators from Study MMY2003.

The FDA's Assessment:
The table was filled by the Applicant and confirmed by the FDA. Please see Section 8.1.2.

Covered Clinical Study (Name and/or Number):* 68284528MMY3002

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 1135		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 2		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0		

Significant payments of other sorts: 2 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in study: 0 Sponsor of covered study: 0		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 13		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from Applicant)

*The table above should be filled by the applicant, and confirmed/edited by the FDA.

Covered Clinical Study (Name and/or Number):* 68284528MMY2003

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 416		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		

If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)):

Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: N/A

Significant payments of other sorts: N/A

Proprietary interest in the product tested held by investigator: N/A

Significant equity interest held by investigator in study: N/A

Sponsor of covered study: N/A

Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☒ (Request details from Applicant) – N/A
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☒ (Request information from Applicant) – N/A
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☐	No ☒ (Request explanation from Applicant) – N/A

*The table above should be filled by the applicant and confirmed/edited by the FDA.

17.3. Schedule of Assessments

Table 38: FDA – Schedule for Standard Therapy Arm

	Notes	Treatment Phase (21-day cycle)						End of Treatment	Post-Treatment Follow-up Phase	
		Cycles 1 to 8				Cycles 9 and beyond				
		Day 1[a] (±1 day)	Day 4 (±1 day)	Day 8 (±1 day)	Day 11 (±1 day)	Day 1 (±2 days)	Day 8 (±2 days)	Within 30 days of last dose (±3 days)	Pre-PD every 28 days (±3 days)	Post-PD (every 16 wk±14 days)
STUDY PROCEDURES										
Physical examination		Symptom-directed physical examination as clinically indicated								
ECOG		On Day 1 of C1 to C5, and Day 1 of Cycles 9, 13, 17 and Day 1 every 8 cycles thereafter								
TTE or MUGA Scan		As clinically indicated. Monitor subjects for clinical signs or symptoms of cardiac failure or cardiac ischemia. Evaluate promptly if cardiac toxicity is suspected								
12-lead ECG		As clinically indicated						X		
Weight		X				X				
Vital signs	Including oxygen saturation	X	X	X	X	X	X	X		
LABORATORY ASSESSMENTS – TO BE PERFORMED LOCALLY										
CBC with differential	See Section 10.2	X	C1-C3	C1-C3	C1-C3	X		X		
Full metabolic panel	See Section 10.2	X		C1 only		X		X		
HBV-DNA	Including AST/ALT; see Section 10.6	For subjects at risk for HBV reactivation, monitor HBV DNA and AST/ALT every 12 weeks (±14 days) until 6 months after the last dose of study treatment								
Serum or urine pregnancy test	For WOCBP with regular or irregular menstrual cycles. Pregnancy tests must have a minimum sensitivity of 25 mIU/mL	Within 24 hours prior to the first dose of PVd, every week for the first 4 weeks, and then every 3 weeks starting from C3D1, or every 2 weeks for WOCBP with irregular menses Additional pregnancy testing done as clinically indicated and/or consistent with any country specific requirements as per local prescribing information for pomalidomide.						X (+7) days		
STUDY INTERVENTION ADMINISTRATION										
Pomalidomide	PO; see Section 6.1.4 for full dosing details.	Days 1 to 14 of each 21-day cycle								
Bortezomib	SC; see Section 6.1.2 for full dosing details At least 72 hours should elapse between consecutive doses of bortezomib.	X	X	X	X	X	X			
Dexamethasone	PO; see Section 6.1.1 for full dosing details.	Cycles 1 to 8 Days 1, 2, 4, 5, 8, 9, 11, and 12 of a 21-day cycle Cycles 9 and beyond Days 1, 2, 8, and 9 of a 21-day cycle								
ACCOUNTABILITY/EXPOSURE CHECK										
Pill count	For pomalidomide and dexamethasone	X (C2 onward)				X		X		
DISEASE EVALUATIONS (SERUM AND, URINE): SEE SECTION 8.1 FOR EFFICACY ASSESSMENTS. BLOOD AND 24-HOUR URINE: TO BE SENT TO THE CENTRAL LABORATORY[c]										
Quantitative immunoglobulins	Includes IgG, IgA, IgM. Testing for IgD and IgE is only required for subjects identified as having IgD- or IgE-type myeloma during screening. - Central laboratory	X (±7 days starting with Cycle 2)				X (±7 days)		X	X	
SPEP	Central laboratory	X (±7 days starting with Cycle 2)				X (±7 days)		X	X	

	Notes	Treatment Phase (21-day cycle)						End of Treatment	Post-Treatment Follow-up Phase	
		Cycles 1 to 8				Cycles 9 and beyond				
		Day 1[a] (±1 day)	Day 4 (±1 day)	Day 8 (±1 day)	Day 11 (±1 day)	Day 1 (±2 days)	Day 8 (±2 days)	Within 30 days of last dose (±3 days)	Pre-PD every 28 days (±3 days)	Post-PD (every 16 wk±14 days)
UPEP (24-hour urine)	Central laboratory	X (±7 days starting with Cycle 2)				X (±7 days)		X	X	
Serum FLC and SIFE/UIFE	Central laboratory	For subjects with measurable disease only by light chain criteria, serum FLC and SIFE/UIFE will be performed at C1D1 and with every disease evaluation (±7 days starting with Cycle 2); For subjects with measurable disease by serum and/or urine M spike: serum FLC and SIFE/UIFE will be performed at C1D1 and when CR is suspected or maintained								
OTHER DISEASE EVALUATIONS										
Bone marrow aspirate and core biopsy	Disease characterization (morphology and either immunohistochemistry or flow cytometry performed locally).	To confirm CR (including sCR)								
MRD (bone marrow aspirate)	Central laboratory	Sample should be collected: • At time of suspected CR or sCR.[b] • At 6, 12, 18, and 24 months[b] (±21 days) from C1D1 regardless of whether or not CR is achieved • Yearly (±3 months) thereafter until PD for subjects that are in CR or sCR 24 months after C1D1[b]								
Imaging: Skeletal survey or whole-body MRI or low-dose whole-body CT or PET/CT with diagnostic CT component		As clinically indicated to document PD								
Plasmacytoma assessment by PET/CT with diagnostic CT component. MRI or CT is acceptable		For subjects with a history of plasmacytoma - For assessment by physical examination (if applicable), every 21 days (±7 days) - For assessment by radiology, ie, at C5D1 (±14 days) and then every 12 weeks (±14 days) As clinically indicated for other subjects								
PATIENT REPORTED OUTCOMES (PRO) AND MEDICAL RESOURCE UTILIZATION (MRU): PRO ASSESSMENTS TO BE COMPLETED BEFORE ANY CLINICAL TESTS OR PROCEDURES THAT WOULD INFLUENCE THE SUBJECT'S PERCEPTIONS OF THEIR CURRENT HEALTH										
EORTC QLQC30		on Day 1 of C1 to C5, and Day 1 of Cycles 9, 13, 17 and every 8 cycles thereafter until PD								
MySIm-Q		on Day 1 of C1 to C5, and Day 1 of Cycles 9, 13, 17 and every 8 cycles thereafter until PD								
EQ-5D-5L		on Day 1 of C1 to C5, and Day 1 of Cycles 9, 13, 17 and every 8 cycles thereafter until PD								X
PRO-CTCAE		on Day 1 of C1 to C5, and Day 1 of Cycles 9, 13, 17 and every 8 cycles thereafter until PD								
PGIS		on Day 1 of C1 to C5, and Day 1 of Cycles 9, 13, 17 and every 8 cycles thereafter until PD								
MRU		Collected continuously from randomization for 33 weeks including in the event of PD before 33 weeks								
ONGOING SUBJECT REVIEW										
Adverse event		Continuous from the time of signing of ICF until 30 days after last dose or until the start of subsequent anti-myeloma therapy, whichever is earlier; thereafter, continue to report any adverse events/serious adverse events considered related to study treatment until EOS								
Second primary malignancy		Continuous from randomization until EOS								
Concomitant therapy		Continuous reporting of selected concomitant therapy from the time of signing of ICF until 30 days after last dose or until the start of subsequent anti-myeloma therapy, whichever is earlier; thereafter, continue to report concomitant therapy given for any adverse events/serious adverse events considered related to study treatment until EOS								

	Notes	Treatment Phase (21-day cycle)						End of Treatment	Post-Treatment Follow-up Phase	
		Cycles 1 to 8				Cycles 9 and beyond				
		Day 1[a] (±1 day)	Day 4 (±1 day)	Day 8 (±1 day)	Day 11 (±1 day)	Day 1 (±2 days)	Day 8 (±2 days)	Within 30 days of last dose (±3 days)	Pre-PD every 28 days (±3 days)	Post-PD (every 16 wk±14 days)
Subsequent anti-myeloma therapy										X
Survival									X	X

Abbreviations: ALT=alanine aminotransferase; AST=aspartate aminotransferase; C=Cycle; CBC=complete blood count; CR=complete response; CT=computed tomography; CTCAE=Common Terminology Criteria for Adverse Events; D=Day; ECOG=Eastern Cooperative Oncology Group; ECG=electrocardiogram; EORTC-QLQ-C30=European Organization for Research and Treatment of Cancer Quality of Life Questionnaire; EOS=end of study; EQ-5D-5L=EuroQol Five Dimension Questionnaire; FLC=free light chain; ICF=informed consent form; Ig=immunoglobulin; MRD=minimal residual disease; MRI=magnetic resonance imaging; MRU=medical resource utilization; MUGA= multiple-gated acquisition; MySIm-Q: Multiple Myeloma Symptom and Impact Questionnaire PD=progressive disease; PET=positron emission tomography; PGIS=Patient Global Impression of Severity; PO=oral; PRO=patient reported outcome; PVd=pomalidomide, bortezomib, and dexamethasone; SC=subcutaneous; sCR=stringent CR; SIFE=serum immunofixation; SPEP=serum M-protein quantitation by electrophoresis; TTE=transthoracic echocardiogram; UIFE= urine immunofixation; UPEP=urine M-protein quantitation by electrophoresis; wk=week; WOCBP=woman of childbearing potential

a. Start of PVd should be within 7 days after randomization. Assessments and procedures on Cycle 1 Day 1 to be performed prior to administration of study intervention.
b. A scheduled timepoint will not be collected if a bone marrow aspirate for central MRD evaluation was performed within the last 3 months of that timepoint.
c. Local laboratory assessments may be used under specified circumstances (see Section 8.1.6)

	Notes	Treatment Phase (28-day cycle)							End of Treatment	Post-Treatment Follow-up Phase	
		Cycles 1 and 2				Cycles 3-6		Cycles 7 and beyond			
		Day 1[a] (±1 day)	Day 8 (±1 day)	Day 15 (±1 day)	Day 22 (±1 day)	Day 1 (±1 day)	Day 15 (±1 day)	Day 1 (±3 days)	Within 30 days of last dose (±3 days)	Pre-PD every 28 days (±3 days)	Post-PD every 16 wk (± 14 days)
STUDY PROCEDURES											
Physical examination		Symptom-directed physical examination as clinically indicated									
ECOG		On Day 1 of C1 to C4, and Day 1 of Cycles 7, 10, 13 and every 6 cycles thereafter									
TTE or MUGA Scan		As clinically indicated. Monitor subjects for clinical signs or symptoms of cardiac failure or cardiac ischemia. Evaluate promptly if cardiac toxicity is suspected.									
12-lead ECG		As clinically indicated							X		
Spirometry test (ie, FEV1)	Subjects with known or suspected COPD only	As clinically indicated									
Weight		X				X		X			
Vital signs	Including oxygen saturation	X	X	X	X	X	X	X	X		
LABORATORY ASSESSMENTS – TO BE PERFORMED LOCALLY											
Blood group and type assessment and indirect antiglobulin test (IAT) results	IAT to be done prior to first dose of daratumumab. Results placed on subject identification wallet card; See Section 10.2	X									
CBC with differential	See Section 10.2	X	X	X	X	X		X	X		
Full metabolic panel	See Section 10.2	X		C1 only		X		X	X		
HBV-DNA	Including AST/ALT; see Section 10.6	For subjects at risk for HBV reactivation monitor HBV DNA and AST/ALT every 12 weeks (±14 days) until 6 months after the last dose of study treatment									
Serum or urine pregnancy test	For WOCBP with regular or irregular menstrual cycles. Pregnancy tests must have a minimum sensitivity of 25 mIU/mL	Within 24 hrs prior to the first dose of DPd, every week for the first 4 weeks and then every 28 days or every 14 days for WOCBP with irregular menses. Additional pregnancy testing done as clinically indicated and/or consistent with any country specific requirements as per local prescribing information for pomalidomide							X (+7 days)		
STUDY INTERVENTION ADMINISTRATION											
Pre- and post-injection medications for daratumumab subjects	PO or IV: see Sections 6.5.1.4 and 6.5.1.5 for full dosing details	X	X	X	X	X	X	X			
Daratumumab	SC; see Section 6.1.3 for full dosing details	X[b]	X	X	X	X	X	X			
Pomalidomide	PO; see Section 6.1.4 for full dosing details	On Days 1 to 21 of each 28-day cycle									
Dexamethasone	PO or IV; see Section 6.1.1 for full dosing details.	Days 1, 8, 15, and 22 of each 28-day cycle									
ACCOUNTABILITY/EXPOSURE CHECK											
Pill count	For pomalidomide and dexamethasone	X (C2 onward)				X		X	X		

	Notes	Treatment Phase (28-day cycle)							End of Treatment	Post-Treatment Follow-up Phase	
		Cycles 1 and 2				Cycles 3-6		Cycles 7 and beyond			
		Day 1[a] (±1 day)	Day 8 (±1 day)	Day 15 (±1 day)	Day 22 (±1 day)	Day 1 (±1 day)	Day 15 (±1 day)	Day 1 (±3 days)	Within 30 days of last dose (±3 days)	Pre-PD every 28 days (±3 days)	Post-PD every 16 wk (± 14 days)
DISEASE EVALUATIONS (SERUM AND URINE): SEE SECTION 8.1 FOR EFFICACY ASSESSMENTS. BLOOD AND 24-HOUR URINE: TO BE SENT TO THE CENTRAL LABORATORY[d]											
Quantitative immunoglobulins	Includes IgG, IgA, IgM. Testing for IgD and IgE is only required for subjects identified as having IgD- or IgE-type myeloma at screening. Central laboratory	X (±7 days starting with Cycle 2)				X (±7 days)		X (±7 days)	X	X	
SPEP	Central laboratory	X (±7 days starting with Cycle 2)				X (±7 days)		X (±7 days)	X	X	
UPEP (24-hour urine)	Central laboratory	X (±7 days starting with Cycle 2)				X (±7 days)		X (±7 days)	X	X	
Serum FLC and SIFE/UIFE	Central laboratory	For subjects with measurable disease only by light chain criteria, serum FLC and SIFE/UIFE will be performed at C1D1 and with every disease evaluation (±7 days starting with Cycle 2). For subjects with measurable disease by serum and/or urine M spike: serum FLC and SIFE/UIFE will be performed at C1D1 and when CR is suspected or maintained									
DSIFE	Central laboratory	To confirm a VGPR or better in subjects with IgG kappa myeloma when daratumumab interference is suspected based on SPEP and SIFE results. DSIFE is not required once CR/sCR is confirmed.									
OTHER DISEASE EVALUATIONS											
Bone marrow aspirate and core biopsy	Disease characterization (morphology and either immunohistochemistry or flow cytometry performed locally).	To confirm CR (including sCR).									
MRD (bone marrow aspirate)	Central laboratory	Sample should be collected: • At time of suspected CR or sCR.[c] • At 6, 12, 18, and 24 months[c] (±21 days) from C1D1 regardless of whether or not CR is achieved • Yearly (±3 months) thereafter until PD for subjects that are in CR or sCR 24 months after C1D1[c]									
Imaging: Skeletal survey or whole-body MRI or low-dose whole body CT or PET/CT with diagnostic CT component		As clinically indicated to document PD									

	Notes	Treatment Phase (28-day cycle)							End of Treatment	Post-Treatment Follow-up Phase	
		Cycles 1 and 2				Cycles 3-6		Cycles 7 and beyond			
		Day 1[a] (±1 day)	Day 8 (±1 day)	Day 15 (±1 day)	Day 22 (±1 day)	Day 1 (±1 day)	Day 15 (±1 day)	Day 1 (±3 days)	Within 30 days of last dose (±3 days)	Pre-PD every 28 days (±3 days)	Post-PD every 16 wk (± 14 days)
Plasmacytoma assessment by PET/CT with diagnostic CT component. MRI or CT is acceptable		For subjects with a history of plasmacytoma - For assessment by physical examination (if applicable), every 28 days (±7 days) - For assessment by radiology, ie, at C4D1 (±14 days) and then every 12 weeks (±14 days) As clinically indicated for other subjects									
PATIENT REPORTED OUTCOMES (PRO) AND MEDICAL RESOURCE UTILIZATION (MRU): PRO ASSESSMENTS TO BE COMPLETED BEFORE ANY CLINICAL TESTS OR PROCEDURES THAT WOULD INFLUENCE THE SUBJECT'S PERCEPTIONS OF THEIR CURRENT HEALTH											
EORTC-QLQ-C30		on Day 1 of C1 to C4, and Day 1 of Cycles 7, 10, 13 and every 6 cycles thereafter until PD									
MySIm-Q		on Day 1 of C1 to C4, and Day 1 of Cycles 7, 10, 13 and every 6 cycles thereafter until PD									
EQ-5D-5L		on Day 1 of C1 to C4, and Day 1 of Cycles 7, 10, 13 and every 6 cycles thereafter until PD									X
PRO-CTCAE		on Day 1 of C1 to C4, and Day 1 of Cycles 7, 10, 13 and every 6 cycles thereafter until PD									
PGIS		on Day 1 of C1 to C4, and Day 1 of Cycles 7, 10, 13 and every 6 cycles thereafter until PD									
MRU		Collected continuously from randomization for 33 weeks including in the event of PD before 33 weeks									
ONGOING SUBJECT REVIEW											
Adverse event		Continuous from the time of signing of ICF until 30 days after last dose or until the start of subsequent anti-myeloma therapy, whichever is earlier; thereafter, continue to report any adverse events/serious adverse events considered related to study treatment until EOS									
Second primary malignancy		Continuous from randomization until EOS									
Concomitant therapy		Continuous reporting of selected concomitant therapy from the time of signing of ICF until 30 days after last dose or until the start of subsequent anti-myeloma therapy, whichever is earlier; thereafter, continue to report concomitant therapy given for any adverse events/serious adverse events considered related to study treatment until EOS									
Subsequent anti-myeloma therapy											X
Survival										X	X

Abbreviations: ALT=alanine aminotransferase; AST=aspartate aminotransferase; C=Cycle; CBC=complete blood count; COPD=chronic obstructive pulmonary disease; CR=complete response; CT=computed tomography; CTCAE=Common Terminology Criteria for Adverse Events; D=Day; DPd=daratumumab, pomalidomide, and dexamethasone; DSIFE=daratumumab-specific immunofixation electrophoresis; ECOG=Eastern Cooperative Oncology Group; ECG=electrocardiogram; EORTC-QLQ-C30=European Organization for Research and Treatment of Cancer Quality of Life Questionnaire; EOS=end of study; EQ-5D-5L=EuroQol Five Dimension Questionnaire; FCL=free light chain; FEV1=forced expiratory volume (in 1 second); FLC=free light chain; HBV=hepatitis B virus; IAT=indirect antiglobulin test; ICF=informed consent form; Ig=immunoglobulin; IV=intravenous; MRD=minimal residual disease; MRI=magnetic resonance imaging; MRU=medical resource utilization; MUGA= multiple-gated acquisition; MySIm-Q: Multiple Myeloma Symptom and Impact Questionnaire; PD=progressive disease; PET=positron emission tomography; PGIs=Patient Global Impression of Severity; PO=oral; PRO=patient reported outcome; SC=subcutaneous; sCR=stringent CR; SIFE=serum immunofixation; SPEP=serum M-protein quantitation by electrophoresis; TTE=transthoracic echocardiogram; UIFE= urine immunofixation; UPEP=urine M-protein quantitation by electrophoresis; VGPR=very good partial response; wk=week; WOCBP=women of childbearing potential

[a] Start of DPd should be within 7 days after randomization. Assessments and procedures on Cycle 1 Day 1 to be performed prior to administration of study intervention
[b] Subjects should be observed following Cycle 1 Day 1 daratumumab administration for 6 hours at the site where daratumumab is administered.
[c] A scheduled timepoint will not be collected if a bone marrow aspirate for central MRD evaluation was performed within the last 3 months of that timepoint.
[d] Local laboratory assessments may be used under specified circumstances (see Section 8.1.6)

Source: Clinical Protocol (MMY3002 Amendment 4) Table 2 to Table 5 pg. 32 to pg. 48

Table 39: FDA – Schedule of Activities for Cilta-Cel: Apheresis and Bridging Therapy

	Notes	Apheresis (3 to 6 days after randomization)[c]	Treatment Phase			
			Bridging Therapy Cycle (21-day cycle for PVd or 28-day cycle for DPd)[a]			
			Day 1 (PVd or DPd) (±1 day)	Day 4 (PVd), Day 8 (PVd or DPd) (±1 day)	Day 11 (PVd), Day 15 (DPd) (±1 day)	Day 22 (DPd) (±1 day)
STUDY PROCEDURES						
Physical examination	Symptom-directed exam	X (≤72 hrs prior to apheresis)	Symptom-directed as clinically indicated			
ECOG		X (≤72 hrs prior to apheresis)				
TTE or MUGA scan		As clinically indicated. Monitor subjects for clinical signs or symptoms of cardiac failure or cardiac ischemia. Evaluate promptly if cardiac toxicity is suspected.				
12-lead electrocardiogram		As clinically indicated				
Spirometry test (ie, FEV1)	Subjects with known or suspected COPD only		As clinically indicated (for DPd only)			
Weight		X (dose calculation)				
Vital signs	Including oxygen saturation. If bortezomib or daratumumab administration is planned to be omitted, vital signs for the planned day can also be omitted.	X	X (prior to 1st dose)	X	X	X (only DPd)
LABORATORY ASSESSMENTS – TO BE PERFORMED LOCALLY						
Blood group and type assessment and indirect antiglobulin test (IAT) results	IAT to be done prior to first dose of daratumumab. Results placed on subject identification wallet card; see Section 10.2		X (only DPd)			
Complete blood count with differential	See Section 10.2. If bortezomib or daratumumab administration is planned to be omitted, CBC assessments on those days can be done locally but need to be reviewed by the Investigator.	X (≤72 hrs prior to apheresis)	X	X (only for first 2 cycles for DPd)	D11 (PVd) or D15 (DPd)	X (only DPd) (only for first 2 cycles)
Full metabolic panel	See Section 10.2. If bortezomib or daratumumab administration is planned to be omitted, chemistry assessments on those days can be done locally but need to be reviewed by the Investigator.	X (≤72 hrs prior to apheresis)	X		D11 (PVd) or D15 (DPd)	
Infectious disease testing	HIV, hepatitis B, hepatis C, HTLV, and other infectious disease testing as needed for apheresis in EU and Israel and for other countries as required per local regulations	X				
Serum or urine pregnancy test	For WOCBP with regular or irregular menstrual cycles. Pregnancy tests must have a minimum sensitivity of 25 mIU/mL.	Within 72 hrs prior to apheresis	Within 10-14 days (if the first pregnancy test falls out of required 10-14 days prior to first dose of PVd or DPd) AND within 24 hours prior to the start of PVd or DPd, every week for the first 4 weeks and 28 (+7) days after the last dose of pomalidomide. Additional pregnancy testing done as clinically indicated and/or consistent with any country specific requirements as per local prescribing information for pomalidomide			
OUTPATIENT ADMINISTRATION: IN CONSULTATION WITH AND APPROVAL OF THE SPONSOR. SEE SECTION 10.16						
Evaluation for outpatient suitability	See Section 10.16	X				

	Notes	Apheresis (3 to 6 days after randomization)[c]	Treatment Phase: Bridging Therapy Cycle (21-day cycle for PVd or 28-day cycle for DPd)[a]			
			Day 1 (PVd or DPd) (±1 day)	Day 4 (PVd), Day 8 (PVd or DPd) (±1 day)	Day 11 (PVd), Day 15 (DPd) (±1 day)	Day 22 (DPd) (±1 day)
ASSESSMENTS PRIOR TO APHERESIS						
Criteria for apheresis	See Section 6.1.5.2	X				
STUDY INTERVENTION ADMINISTRATION: INVESTIGATOR'S CHOICE PVD (1 CYCLE)						
Pomalidomide	PO; see Section 6.1.4 for full dosing details		On Days 1 to 14 of a 21-day cycle			
Bortezomib	SC; see Section 6.1.2 for full dosing details		X	D4, D8	D11	
Dexamethasone	PO; see Section 6.1.1 for full dosing details.		Days 1, 2, 4, 5, 8, 9, 11, and 12 of a 21-day cycle			
STUDY INTERVENTION ADMINISTRATION: INVESTIGATOR'S CHOICE DPD (1 CYCLE)						
Pre- and post-injection medications for daratumumab	PO or IV; see Sections 6.5.1.4 and 6.5.1.5		X	D8	D15	X
Daratumumab	SC; see Section 6.1.3 for full dosing details		X[b]	D8	D15	X
Pomalidomide	PO: see Section 6.1.4 for full dosing details		On Days 1 to 21 of a 28-day cycle			
Dexamethasone	PO or IV; see Section 6.1.1 for full dosing details		X	D8	D15	X
DISEASE EVALUATIONS (SERUM AND URINE): SEE SECTION 8.1 FOR EFFICACY ASSESSMENTS. BLOOD AND 24-HOUR URINE: TO BE SENT TO THE CENTRAL LABORATORY.[d]						
Quantitative immunoglobulins	Includes IgG, IgA, IgM. Testing for IgD and IgE is only required for subjects identified as having IgD- or IgE-type myeloma during screening - Central laboratory	X	X (±7 days) (Day 1 of each cycle of bridging therapy starting from cycle 2)			
SPEP	Central laboratory	X	X (±7 days) (Day 1 of each cycle of bridging therapy starting from cycle 2)			
UPEP (24-hour urine)	Central laboratory	X	X (±7 days) (Day 1 of each cycle of bridging therapy starting from cycle 2)			
Serum FLC and SIFE/UIFE	Central laboratory	X	X (±7 days) (Day 1 of each cycle of bridging therapy starting from cycle 2)			
OTHER DISEASE EVALUATIONS						
Plasmacytoma assessment by physical exam		X (≤72 hrs prior to apheresis) (if applicable)	For subjects with a history of plasmacytoma. For assessment by physical examination (if applicable), Day 1 of each bridging cycle starting from Cycle 2 (±7 days)			
Biopsy of EM plasmacytoma	If biopsy of EM plasmacytoma is clinically indicated, a sample should be sent to the central lab	The sponsor should receive a sample of plasmacytoma if a plasmacytoma biopsy is performed for any reason				
PATIENT REPORTED OUTCOMES (PRO) AND MEDICAL RESOURCE UTILIZATION (MRU): PRO ASSESSMENTS TO BE COMPLETED BEFORE ANY CLINICAL TESTS OR PROCEDURES THAT WOULD INFLUENCE THE SUBJECT'S PERCEPTIONS OF THEIR CURRENT HEALTH						
EORTC QLQ-C30		X (≤72 hour window)	X[e]			
MySIm-Q		X(≤72 hour window)	X[e]			
EQ-5D-5L		X(≤72 hour window)	X[e]			
PRO-CTCAE		X(≤72 hour window)	X[e]			

	Notes	Apheresis (3 to 6 days after randomization)[c]	Treatment Phase			
			Bridging Therapy Cycle (21-day cycle for PVd or 28-day cycle for DPd)[a]			
			Day 1 (PVd or DPd) (±1 day)	Day 4 (PVd), Day 8 (PVd or DPd) (±1 day)	Day 11 (PVd), Day 15 (DPd) (±1 day)	Day 22 (DPd) (±1 day)
PGIS		X(≤72 hour window)	X[e]			
Medical resource utilization		Collected continuously from randomization until 33 weeks regardless of PD before 33 weeks.				
PHARMACOKINETIC AND BIOMARKER SAMPLING						
Immunophenotyping (whole blood)[f]		X				
Soluble BCMA sample (serum)		X				
CyTOF/PBMC (TCRSeq)/Plasma (whole blood)[g]		X				
ONGOING SUBJECT REVIEW						
Adverse event		Continuous from the time of signing of ICF				
Second primary malignancy		Continuous from randomization				
Concomitant therapy		Continuous reporting of selected concomitant therapy from the time of signing of ICF[h]				

Abbreviations: BCMA=B-cell maturation antigen; COPD=chronic obstructive pulmonary disease; CT=computed tomography; CTCAE=Common Terminology Criteria for Adverse Events; CyTOF=cytometry by time of flight; D=Day; DPd=daratumumab, pomalidomide, and dexamethasone; ECOG=Eastern Cooperative Oncology Group; EQ-5D-5L=EuroQol Five Dimension Questionnaire; EU=European Union; FEV1=Forced Expiratory Volume (in 1 second); FLC=free light chain; HIV=human immunosuppressant virus; IAT= indirect antiglobulin test; ICF=informed consent form; IV=intravenous; MRI=magnetic resonance imaging; MUGA=multiple-gated acquisition; MySIm-Q: Multiple Myeloma Symptom and Impact Questionnaire; PET=positron emission tomography; PO=oral; PRO=patient reported outcome; PVd=pomalidomide, bortezomib, and dexamethasone; SC=subcutaneous; SIFE=serum immunofixation; SPEP=serum protein electrophoresis; TCR=T-cell receptor; TTE=transthoracic echocardiogram; UIFE=urine immunofixation; UPEP=urine protein electrophoresis; WOCBP=woman of childbearing potential

[a] Bridging therapy should be started after apheresis but no more than 7 days after randomization. If more than 2 cycles of bridging therapy are indicated, daratumumab will be administered on Days 1 and 15. Safety laboratory assessments may be performed prior to initiating bridging therapy.
[b] Subjects should be observed following Cycle 1 Day 1 daratumumab administration for 6 hours at the site where daratumumab is administered.
[c] Assessments and procedures to be performed prior to apheresis
[d] Local laboratory assessments may be used under specified circumstances (see Section 8.1.6)
[e] Only to be done for the first cycle of bridging therapy given
[f] Recollect blood samples for immunophenotyping prior to the second apheresis for subjects who require a repeat apheresis.
[g] Recollect blood sample for CyTOF/PBMC (TCRSeq)/Plasma prior to the second apheresis for subjects who require a repeat apheresis.
[h] 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).

Source: Clinical Protocol (MMY3002 Amendment 4) Table 2 to Table 5 pg. 32 to pg. 48

Table 40: FDA – Schedule of Activities for Cilta-Cel: Treatment, Post-Infusion, Follow-Up, and Post-Treatment Follow-Up Phases

	Notes	Treatment Phase		Post-Infusion Follow-up Phase (CAR-T Day 1 to Day 112)[a]											Post-Treatment Follow-up Phase				
		Conditioning Regimen	JNJ-68284528																
		CAR-T Day -5, -4, -3 (Window for start: Day -7 to Day -5)	CAR-T Day 1	Day 3	Day 7 (±1 d)	Day 10 (±1 d)	Day 14 (±1 d)	Day 21 (±1 d)	Day 28 (±2 d)	Day 35 (±2 d)	Day 42 (±2 d)	Day 56 (±2 d)	Day 84 (±2 d)	Day 112 (±2 d)	Day 140 (±2 d)	Day 168 (±2 d)	Day 196 then every 28 d (±3 d)	At PD[b]	Post PD Every 16 wks (±14 d)
STUDY PROCEDURES																			
Physical examination	Complete physical exam including neurologic exam on CAR-T Day 1; symptom-directed exam thereafter		X (prior to CAR-T infusion)	Symptom-directed physical examination as clinically indicated															
ECOG		X (prior to 1st dose only)	X						X					X	Every 12 wks x 2, then every 24 wks				
TTE or MUGA		As clinically indicated. Monitor subjects for clinical signs or symptoms of cardiac failure or cardiac ischemia. Evaluate promptly if cardiac toxicity is suspected.																	
12-lead ECG		As clinically indicated																	
ICE neurologic test			X (≤24 hrs prior to infusion)[c]	ICE test must be repeated at any incidence of suspected CAR-T cell-related neurotoxicity (eg, ICANS). Perform at least daily until ICANS is resolved.															
Handwriting sample			X (≤24 hrs prior to infusion)[c]	X	X	X	X	X	X	X	X	X	Perform every 28 days up to and including Day 196						
Weight		X (prior to 1st dose only)	X																
Vital signs	Including oxygen saturation	X	X (multiple times)[d]	X	X	X	X	X	X			X	X	X	Every 12 wks				
Temperature			Measure and record temperature at least twice every day[e]																
LABORATORY ASSESSMENTS: TO BE PERFORMED LOCALLY																			
CBC with differential	See Section 10.2	X (prior to 1st dose only)	X (prior to infusion)	X	X	X	X	X	X			X	X	X	Every 12 weeks (±7 days) x2 and then every 6 months (± 14 days) until EOS				
CD4/CD8 Lymphocyte panel[f]	See Section 10.2	X (prior to 1st dose only)	X (prior to infusion)	X	X	X	X	X	X			X	X	X	Every 4 weeks until 1 year after CAR-T				
CAR-T chemistry	See Section 10.2	X (prior to 1st dose only)	X (prior to infusion)	X	X	X	X	X	X			X	X	X					

	Notes	Treatment Phase		Post-Infusion Follow-up Phase (CAR-T Day 1 to Day 112)[a]											Post-Treatment Follow-up Phase				
		Conditioning Regimen	JNJ-68284528																
		CAR-T Day -5, -4, -3 (Window for start: Day -7 to Day -5)	CAR-T Day 1	Day 3	Day 7 (±1 d)	Day 10 (±1 d)	Day 14 (±1 d)	Day 21 (±1 d)	Day 28 (±2 d)	Day 35 (±2 d)	Day 42 (±2 d)	Day 56 (±2 d)	Day 84 (±2 d)	Day 112 (±2 d)	Day 140 (±2 d)	Day 168 (±2 d)	Day 196 then every 28 d (±3 d)	At PD[b]	Post PD Every 16 wks (±14 d)
Coagulation	PT/INR, aPTT, fibrinogen, D-dimer		As clinically indicated, ie, for subjects who have fever or other signs of potential CRS																
Serum or urine pregnancy test	For WOCBP with regular or irregular menstrual cycles. Pregnancy tests must have a minimum sensitivity of 25 mIU/mL.	Within 72 hours prior to 1st dose	As clinically indicated or as mandated by local regulations, whichever is more stringent																
HBV-DNA	Including AST/ALT, see Section 10.6		For subjects at risk for HBV reactivation monitor HBV DNA and AST/ALT every 12 weeks (±14 days) until 1-year post-dose of JNJ-68284528.																
OUTPATIENT ADMINISTRATION: IN CONSULTATION WITH AND APPROVAL OF THE SPONSOR. SEE SECTIONS 10.16 AND 10.17																			
Evaluation for outpatient suitability	See Section 10.16		X (predose)																
Subjects with discharge on Days 10 to 13	See Section 10.16					Daily phone calls during business days from site staff, Days 10-14													
ASSESSMENTS PRIOR TO CONDITIONING REGIMEN AND ADMINISTRATION OF JNJ-68284528																			
Criteria for conditioning regimen	See Section 6.1.5	X (≤72 hours of 1st dose only)																	
Criteria for JNJ-68284528 administration	See Section 6.1.5.5		X (predose)																
STUDY INTERVENTION ADMINISTRATION																			
Cyclophosphamide/ fludarabine		X																	
Pre-infusion medication	See Section 6.1.5.6		X																

	Notes	Treatment Phase		Post-Infusion Follow-up Phase (CAR-T Day 1 to Day 112)[a]											Post-Treatment Follow-up Phase				
		Conditioning Regimen	JNJ-68284528																
		CAR-T Day -5, -4, -3 (Window for start: Day -7 to Day -5)	CAR-T Day 1	Day 3	Day 7 (±1 d)	Day 10 (±1 d)	Day 14 (±1 d)	Day 21 (±1 d)	Day 28 (±2 d)	Day 35 (±2 d)	Day 42 (±2 d)	Day 56 (±2 d)	Day 84 (±2 d)	Day 112 (±2 d)	Day 140 (±2 d)	Day 168 (±2 d)	Day 196 then every 28 d (±3 d)	At PD[b]	Post PD Every 16 wks (±14 d)
JNJ-68284528	See CPTTM and IPPI		X																
ACCOUNTABILITY/EXPOSURE CHECK																			
Pill count	For pomalidomide and dexamethasone given as part of bridging therapy	X (prior to 1st dose only)																	
DISEASE EVALUATIONS (SERUM AND URINE): SEE SECTION 8.1 FOR EFFICACY ASSESSMENTS. BLOOD AND 24-HOUR URINE: TO BE SENT TO THE CENTRAL LABORATORY.[f] DISEASE EVALUATION SHOULD CONTINUE TO BE PERFORMED UNTIL CONFIRMED PD, DEATH, START OF A NEW ANTI-MYELOMA TREATMENT, WITHDRAWAL OF CONSENT FOR STUDY PARTICIPATION, OR STUDY COMPLETION, WHICHEVER OCCURS FIRST.																			
Quantitative immunoglobulin[g]	Includes IgG, IgA, IgM. Testing for IgD and IgE is only required for subjects identified as having IgD- or IgE-type myeloma during screening. Central laboratory	X (≤7 days before 1st dose)							X			X	X	X	X	X	X	X	
SPEP	Central laboratory	X (≤7 days before 1st dose)							X			X	X	X	X	X	X	X	
UPEP (24-hour urine)	Central laboratory	X (≤7 days before 1st dose)							X			X	X	X	X	X	X	X	
Serum FLC and SIFE/UIFE	Central laboratory	X (≤7 days before 1st dose)							For subjects with measurable disease only by light chain criteria, serum FLC and SIFE/UIFE will be performed at CAR-T Day 28, 56, 84, 112 and then every 28 days. For subjects with measurable disease by serum and/or urine M spike: serum FLC and SIFE/UIFE will be performed when CR is suspected or maintained									

	Notes	Treatment Phase		Post-Infusion Follow-up Phase (CAR-T Day 1 to Day 112)[a]											Post-Treatment Follow-up Phase				
		Conditioning Regimen	JNJ-68284528																
		CAR-T Day -5, -4, -3 (Window for start: Day -7 to Day -5)	CAR-T Day 1	Day 3	Day 7 (±1 d)	Day 10 (±1 d)	Day 14 (±1 d)	Day 21 (±1 d)	Day 28 (±2 d)	Day 35 (±2 d)	Day 42 (±2 d)	Day 56 (±2 d)	Day 84 (±2 d)	Day 112 (±2 d)	Day 140 (±2 d)	Day 168 (±2 d)	Day 196 then every 28 d (±3 d)	At PD[b]	Post PD Every 16 wks (±14 d)
DSIFE	Central laboratory DSIFE is not required after bridging therapy and prior to conditioning regimen	X[h]							To confirm a VGPR or better in subjects with IgG kappa myeloma when daratumumab interference is suspected based on SPEP and SIFE results.										
OTHER DISEASE EVALUATIONS																			
Bone marrow aspirate and core biopsy	Disease characterization (morphology and either immunohistochemistry or flow cytometry; performed locally)												• To confirm CR (including sCR) (bone marrow biopsy and aspirate) (local lab) • At time of PD or EOS bone marrow biopsy and aspirate should be sent to the central lab (Section 8.1.4) • Bone marrow not required if PD prior to CAR-T infusion						
MRD (bone marrow aspirate)	Central laboratory											X	Sample should be collected: • At time of suspected CR or sCR • At 6 (D196), 12 (D364), 18 (D532), and 24 (D700) months[i] (±21 days) from JNJ-68284528 regardless of whether or not CR is achieved • Yearly (±3 months) thereafter until PD for subjects that are in CR or sCR 24 months after JNJ-68284528 infusion[i]						
Imaging: Skeletal survey or low-dose whole body CT or whole-body MRI or PET/CT with diagnostic CT component									Performed as clinically indicated to document PD										

	Notes	Treatment Phase		Post-Infusion Follow-up Phase (CAR-T Day 1 to Day 112)[a]											Post-Treatment Follow-up Phase				
		Conditioning Regimen	JNJ-68284528																
		CAR-T Day -5, -4, -3 (Window for start: Day -7 to Day -5)	CAR-T Day 1	Day 3	Day 7 (±1 d)	Day 10 (±1 d)	Day 14 (±1 d)	Day 21 (±1 d)	Day 28 (±2 d)	Day 35 (±2 d)	Day 42 (±2 d)	Day 56 (±2 d)	Day 84 (±2 d)	Day 112 (±2 d)	Day 140 (±2 d)	Day 168 (±2 d)	Day 196 then every 28 d (±3 d)	At PD[b]	Post PD Every 16 wks (±14 d)
Biopsy of EM plasmacytoma	If biopsy of EM plasmacytoma is clinically indicated, a sample should be sent to the central lab		The sponsor should receive a sample of plasmacytoma if a plasmacytoma biopsy is performed for any reason.																
Plasmacytoma assessment by PET/CT with diagnostic CT component. MRI or CT is acceptable		X (For assessment by physical examination, if applicable)[j]							For subjects with a history of plasmacytoma for assessment by physical examination (if applicable), ie, CAR-T Day 28, 56, 84, 112 and then every 28 days (±7 days) - for assessment by radiology, ie, CAR-T Day 84 and then every 12 weeks (±14 days) As clinically indicated for other subjects									
PATIENT REPORTED OUTCOMES (PRO) AND MEDICAL RESOURCE UTILIZATION (MRU): PRO ASSESSMENTS TO BE COMPLETED BEFORE ANY CLINICAL TESTS OR PROCEDURES THAT WOULD INFLUENCE THE SUBJECT'S PERCEPTIONS OF THEIR CURRENT HEALTH																			
EORTC QLQ-C30		X[k]							X					X	X[l]				
MySIm-Q		X[k]							X					X	X[l]				
EQ-5D-5L		X[k]							X					X	X[l]				X
PRO-CTCAE		X[k]							X					X	X[l]				
PGIS		X[k]							X					X	X[l]				
MRU		Collected continuously for 33 weeks including in the event of PD before 33 weeks																	
PHARMACOKINETIC AND BIOMARKER ASSESSMENTS																			
Cytokine profiling (serum)[n]		X (≤7 days prior to 1st dose)	Pre-dose 2 hours post-dose (±10 min)	X	X	X	X	X	X			X	X	X					
PK CAR transgene levels sample (whole blood)[m]			Pre-dose	X	X	X	X		X			X	X	X	Every 8 wks up to 1 yr			X or EOS	
Soluble BCMA sample (serum)			Pre-dose	X	X	X	X		X			X	X	X	Every 8 wks up to 1 yr			X or EOS	
Immunogenicity ADA sample for CAR-T (serum)[n]			Pre-dose				X					X		X				X or EOS	

	Notes	Treatment Phase		Post-Infusion Follow-up Phase (CAR-T Day 1 to Day 112)[a]											Post-Treatment Follow-up Phase				
		Conditioning Regimen	JNJ-68284528																
		CAR-T Day -5, -4, -3 (Window for start: Day -7 to Day -5)	CAR-T Day 1	Day 3	Day 7 (±1 d)	Day 10 (±1 d)	Day 14 (±1 d)	Day 21 (±1 d)	Day 28 (±2 d)	Day 35 (±2 d)	Day 42 (±2 d)	Day 56 (±2 d)	Day 84 (±2 d)	Day 112 (±2 d)	Day 140 (±2 d)	Day 168 (±2 d)	Day 196 then every 28 d (±3 d)	At PD[b]	Post PD Every 16 wks (±14 d)
Immunophenotyping (whole blood)[n, m]	Samples also collected at suspected CR	X (≤7 days before 1st dose)	Pre-dose		X	X	X	X	X	X	X	X	X	X	Every 8 wks up to 1 yr			X or EOS	
Flow cytometry (bone marrow aspirate)									X	• At time of suspected CR/sCR • 6 months (D 196) after CAR-T infusion in subjects who have not had a bone marrow within the last 3 months								X or EOS	
CyTOF (bone marrow aspirate)									X	• At time of suspected CR/sCR • 6 months (D 196) after CAR-T infusion in subjects who have not had a bone marrow within the last 3 months								X or EOS	
CyTOF/PBMC (TCRSeq)/ Plasma (whole blood)			Pre-dose			X	X	X	X	X	X	X		X				X or EOS	
RCL (whole blood)			Pre-dose	At approximately 3 (Day 84), 6 (Day 196), and 12 (Day 364) months (±1 month); then yearly (±3 months) until EOS, and then yearly (±3 months) for up to 15 years after cilta-cel infusion in a separate long-term follow- up study. Yearly collection of RCL samples is not required if all assessments within the first year are negative. Sites will be notified if a subject's sample is positive for RCL; otherwise RCL is no longer required to be collected after the 12-month visit. Additional samples may be collected triggered by events which may be relevant to RCL per clinical assessment.															
Serum protein analysis		X (≤7 days prior to 1st dose)	Pre-dose	Additional serum protein sample will be taken at each SIFE/SPEP evaluation, as well as at each MRD sample collection															
ONGOING SUBJECT REVIEW																			
Adverse event		Continuous from the time of signing ICF until 30 days after the last dose of bridging therapy or until CAR-T Day 112, whichever is later, regardless if subjects progress before CAR-T Day 112; thereafter, continue to report all SAEs regardless of causality, and any non-serious adverse events considered related to study treatment until EOS.[o,p] Events of HBV reactivations and COVID-19 infection should be reported during the first year post-dosing of JNJ-68284528. Subjects who progress prior to CAR-T infusion and are not able to receive CAR-T infusion, adverse events/serious adverse events should still be reported until PD or until the start of subsequent anti-myeloma therapy, whichever is earlier.															
Delayed Adverse Events			Continuous from Day1 of CAR-T infusion until EOS (with the exception of second primary malignancy, which is collected from the time of randomization until EOS)[o,p,q]																
Concomitant therapy		Continuous reporting of selected concomitant therapy from the time of signing ICF until 30 days after the last dose of bridging therapy or until CAR-T Day 112, whichever is later; regardless if subjects progress before CAR-T Day 112, thereafter, continue to report concomitant therapy given for any non-serious adverse events considered related to study treatment or all serious adverse event regardless of causality or delayed adverse events until EOS. Medications for the prevention and treatment of COVID-19 (including vaccines) and HBV reactivation should be reported until 1 year after cilta-cel infusion (Appendix 10.29).															

	Notes	Treatment Phase		Post-Infusion Follow-up Phase (CAR-T Day 1 to Day 112)[a]										Post-Treatment Follow-up Phase				
		Conditioning Regimen	JNJ-68284528															
		CAR-T Day -5, -4, -3 (Window for start: Day -7 to Day -5)	CAR-T Day 1	Day 3	Day 7 (±1 d)	Day 10 (±1 d)	Day 14 (±1 d)	Day 21 (±1 d)	Day 28 (±2 d)	Day 35 (±2 d)	Day 42 (±2 d)	Day 56 (±2 d)	Day 84 (±2 d)	Day 112 (±2 d)	Day 140 (±2 d)	Day 168 (±2 d)	Day 196 then every 28 d (±3 d)	At PD[b]	Post PD Every 16 wks (±14 d)
Subsequent anti-myeloma therapy																		X
Survival																		X

Abbreviations: ADA=anti-drug antibody; ALT=alanine aminotransferase; aPTT=activated partial thromboplastin time; AST=aspartate aminotransferase; BCMA=B-cell maturation antigen; CAR-T=chimeric antigen receptor T-cell; CBC=complete blood count; CPTTM=Cell Therapy Product Procedures Manual; CR=complete response; CRS=cytokine release syndrome; CT=computed tomography; CTCAE=Common Terminology Criteria for Adverse Events; CyTOF=cytometry by time of flight; D=Day; DPd= daratumumab, pomalidomide, and dexamethasone; ECOG=Eastern Cooperative Oncology Group; ECG=electrocardiogram; EOS=end of study; EQ-5D-5L=EuroQol Five Dimension Questionnaire; and dexamethasone; FLC=free light chain; HBV=hepatitis B virus; ICANS=Immune Effector Cell-associated Neurotoxicity Syndrome; ICE=Immune Effector Cell-associated Encephalopathy assessment tool; ICF=informed consent form; INR=international normalized ratio; IPPI=investigational product preparation instructions; MM=multiple myeloma; MRD=minimal residual disease; MRI=magnetic resonance imaging; MRU=medical resource utilization; MUGA=multiple-gated acquisition; MySIm-Q: Multiple Myeloma Symptom and Impact Questionnaire; PD=progressive disease; PET=positron emission tomography; PGIS=Patient Global Impression of Severity; PK=pharmacokinetic; PRO=patient reported outcome; PT=prothrombin time; PVd=pomalidomide, bortezomib, and dexamethasone; sCR=stringent CR; RCL=replication competent lentivirus; SIFE=serum immunofixation; SPEP=serum protein electrophoresis; TCR=T-cell receptor; TTE=transthoracic echocardiogram; UIFE= urine immunofixation; UPEP=urine protein electrophoresis; VGPR=very good partial response; wks=weeks; WOCBP=woman of childbearing potential.

[a] For subjects who discontinue due to PD or withdrawal of consent before CAR-T Day 112, the Day 112 assessments should be performed prior to discontinuation, if feasible.
[b] For subjects who discontinue due to PD or withdrawal of consent after CAR-T Day 112 but before end of study should have the assessments at PD performed prior to discontinuation, unless these assessments were performed within 14 days prior to discontinuation. End of study is when approximately 250 deaths have occurred
[c] Pre-infusion ICE test and handwriting assessment should be performed before pre-medication with diphenhydramine
[d] Immediately before the start of infusion, at the end of infusion, and 0.5 hours (±5 min), 1 hours (±10 min), and 2 hours (±10 min) after end of infusion. Monitor until normalized after a CRS event. For subjects who are hospitalized, hematology and chemistry laboratory evaluations, vital signs, and oxygen saturation should be performed at least daily or more as clinically indicated.
[e] Temperature will be checked at least twice a day. Subjects will be provided with a thermometer and instructed on the use of the thermometer and entering temperature in a diary. Diary will be reviewed at each visit, then collected on CAR-T Day 28 and stored with subject source documents.
[f] Local laboratory assessments may be used under specified circumstances (see Section 8.1.6).
[g] Additional immunoglobulin samples may be collected as clinically indicated for safety and treated according to institutional guidelines (see Section 6.1.6.6).
[h] Only for IgG kappa MM subjects who received DPd for bridging therapy and who are SIFE positive following bridging therapy.
[i] A scheduled timepoint will not be collected if a bone marrow aspirate for central MRD evaluation was performed within the last 3 months of that timepoint.
[j] Assessment to be performed as close to prior to the first dose as possible.
[k] PRO questionnaires to be completed on the first day, prior to the start of the conditioning regimen
[l] Every 12 weeks x 2 (D196 ± 3 days, D280 ± 3days), then every 24 weeks
[m] After Day 112, CAR transgene levels, and CAR+ T cell counts will be measured every 8 weeks through 1 year. After 1 year, PK CAR transgene levels and CAR+ T cell counts (immunophenotyping) will be measured at least annually until EOS or PD, whichever is earlier. Additional event-triggered testing for PK CAR transgene levels and CAR+ T cell counts may be conducted as clinically indicated.
[n] 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 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.

[o] Delayed AEs will be collected regardless of causality from the time of JNJ-68284528 administration (with the exception of SPMs, which are collected from the time of randomization) until the end of study, and subsequently in a separate long-term follow-up study for up to 15 years after last administration of JNJ-68284528. For subjects diagnosed with 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
[p] Delayed AEs include new malignancies or recurrence of pre-existing malignancy (all grades), new incidence or exacerbation of pre-existing neurologic disorder (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.
[q] For additional information, refer to Section 8.3.1.
[r] CD4/CD8 panel should be done for newly enrolled subjects. Subjects enrolled under amendment #1 that have re-consented to amendment #2 and have received cilta-cel are not required to do the CD4/CD8 lymphocyte panel.

Source: Clinical Protocol (MMY3002 Amendment 4) Table 2 to Table 5 pg. 32 to pg. 48

17.4. Additional Safety Analyses Conducted by FDA

Table 41: FDA – Adverse Events, Bridging Therapy Period, Safety Population, CARTITUDE-4

Parameter	CARTITUDE-4 N=188
Any AE	185 (98)
Any grade 3-4 AE	151 (80)
Any grade 5 AE	0
Any SAE	27 (14)
Any AE related to BT	170 (90)
Any grade 3-4 AE related to BT	141 (75)
Any grade 5 AE related to BT	0
Any SAE related to BT	16 (9)

Source: Adapted from Applicant's response to FDA IR dated Mar 26, 2024 (TSFAE01_BR_IR). Data cutoff November 1, 2022
Abbreviations: AE, adverse event; BT, bridging therapy; N, number of subjects in the specified group, or the total sample

Table 42: FDA – Nonfatal Serious Adverse Events, Bridging Therapy Period, Safety Population, CARTITUDE-4

System Organ Class and FDA Grouped Preferred Term	CARTITUDE-4 N=188 All Grades n (%)	CARTITUDE-4 N=188 Grade 3 or Higher n (%)
Total	27 14)	23 (12)
Infections and infestations	14 (8)	10 (5)
Pneumonia	9 (5)	7 (4)
Blood and lymphatic system disorders	6 (3)	6 (3)
Febrile neutropenia	5 (3)	5 (3)

Source: Adapted from Applicant's response to FDA IR dated 26Mar2024, TSFAE49_BR_IR. Data cutoff November 1, 2022
Abbreviations: n (%), number of subjects with the specified characteristic; N, number of subjects in the specified group, or the total sample

Table 43: FDA – Adverse Events, Bridging Therapy Period, >10% Safety Population, CARTITUDE-4

System Organ Class and FDA Grouped Preferred Term	CARTITUDE-4 N=188 All Grades n (%)	CARTITUDE-4 N=188 Grade 3 or Higher n (%)
Total	185 (99)	151 (80)
Blood and lymphatic system disorders	-	-
Neutropenia	144 (77)	140 (75)
Thrombocytopenia	58 (31)	39 (21)
Anemia	44 (23)	25 (13)
Lymphopenia	23 (12)	20 (11)
Leukopenia	16 (9)	14 (7)

System Organ Class and FDA Grouped Preferred Term	CARTITUDE-4 N=188 All Grades n (%)	CARTITUDE-4 N=188 Grade 3 or Higher n (%)
Infections and infestations	-	-
Upper respiratory tract infection	23 (12)	1 (0.5)
Pneumonia	11 (6)	8 (4)
General disorders	-	-
Fatigue	51 (27)	2 (1)
Edema	23 (12)	0
Pyrexia	17 (9)	0
Pain	11 (6)	0
Gastrointestinal disorders	-	-
Diarrhea	23 (12)	1 (0.5)
Constipation	20 (11)	1 (0.5)
Nausea	17 (9)	0
Nervous system disorders	-	-
Neuropathy peripheral	22 (12)	0
Motor dysfunction	21 (11)	0
Dizziness	15 (8)	3 (2)
Headache	12 (6)	0
Sleep disorder	12 (6)	1 (0.5)
Metabolism and nutrition disorders	-	-
Hypokalemia	14 (7)	1 (0.5)
MSK and connective tissue disorders	-	
Musculoskeletal pain	48 (26)	4 (2)
Respiratory, thoracic and mediastinal disorders	-	-
Dyspnea	20 (11)	1 (0.5)
Cough	10 (5)	0
Vascular disorders	-	-
Hemorrhage	11 (6)	0

Source: Adapted from Applicant's response to FDA IR dated 26Mar2024, TSFAE07_BR_IR. Data cutoff November 1, 2022
Abbreviations: MSK, musculoskeletal; n (%), number of subjects with the specified characteristic; N, number of subjects in the specified group, or the total sample

17.5. FDA Grouped Terms

Table 44: FDA Grouped Terms

Group Term	Preferred Terms Included
Abdominal pain	Abdominal discomfort, abdominal pain, abdominal pain lower, abdominal pain upper, abdominal tenderness, defaecation urgency, dyspepsia, gastritis
Acidosis	Acidosis, blood bicarbonate decreased, blood lactic acid increased, lactic acidosis, metabolic acidosis
Adjustment disorder	Adjustment disorder with anxiety, adjustment disorder with mixed anxiety and depressed mood
Anemia	Anaemia, hypochromic anaemia, iron deficiency anaemia, normocytic anaemia, pallor
Aphasia	Aphasia, disorganised speech, dysarthria, dysphemia, slow speech, speech disorder
Ataxia	Ataxia, balance disorder, dyskinesia, dysmetria, gait disturbance, hand-eye coordination impaired
Bacterial infection	Abscess limb, anal abscess, appendicitis, arthritis infective, bacterial pericarditis, Bordetella infection, breast cellulitis, bronchitis bacterial, campylobacter infection, catheter site infection, cellulitis, chalazion, cholecystitis infective, Citrobacter infection, Clostridium difficile colitis, Clostridium difficile infection, device-related infection, diverticulitis, ecthyma, endophthalmitis, Enterococcal infection, erysipelas, Escherichia infection, eye infection, folliculitis, Gardnerella infection, gingivitis, Haemophilus infection, Helicobacter infection, hordeolum, impetigo, infected dermal cyst, infection, Klebsiella infection, Ludwig angina, lung abscess, mastitis, mastoiditis, meningitis listeria, nail infection, oral infection, osteomyelitis, paronychia, perichondritis, periodontitis,

	perirectal abscess, peritonitis, post procedural infection, prostatitis, Pseudomonas infection, pustule, pyelonephritis acute, pyoderma, respiratory tract infection bacterial, salmonellosis, sinusitis bacterial, skin infection, soft tissue infection, Staphylococcal infection, Staphylococcal skin infection, Streptococcal infection, superinfection bacterial, tooth abscess, tooth infection, vascular access site infection, vascular device infection
Blindness	Blindness, blindness unilateral
Bradycardia	Bradyarrhythmia, bradycardia, heart rate decreased, sinus bradycardia
Cardiac arrhythmias	Arrhythmia, atrial fibrillation, atrial flutter, atrioventricular block complete, atrioventricular block first degree, atrioventricular block second degree, bundle branch block left, extrasystoles, heart rate irregular, supraventricular extrasystoles, supraventricular tachycardia, ventricular extrasystoles, ventricular tachycardia
Cardiac failure	Cardiac failure, cardiac failure acute, cardiac failure chronic, cardiac failure congestive, cardiogenic shock, cardiomyopathy, ejection fraction decreased, ischaemic cardiomyopathy, left ventricular dilation, left ventricular dysfunction, n-terminal prohormone brain natriuretic peptide increased
Chest pain	Angina pectoris, chest discomfort, chest pain
Cholecystitis	Cholecystitis, cholecystitis acute
Coagulopathy	Activated partial thromboplastic time prolonged, antithrombin III decreased, blood fibrinogen decreased, coagulation test abnormal, coagulation time shortened, coagulopathy, disseminated intravascular coagulation, hypofibrinogenaemia, international normalised ratio increased, prothrombin level increased, prothrombin time prolonged, thrombin time prolonged
Conjunctivitis	Conjunctivitis, conjunctivitis bacterial, conjunctivitis viral

Cough	Cough, productive cough, upper-airway cough syndrome
Cranial nerve palsies	Bell's palsy, cranial nerve paralysis, facial nerve disorder, facial paralysis, facial paresis, gaze palsy, IIIrd nerve palsy, tongue paralysis, trigeminal palsy, VIth nerve paralysis, vocal cord paralysis
Deafness	Deafness, deafness bilateral, deafness neurosensory, deafness unilateral
Delirium	Agitation, delirium, delusion, disorientation, euphoric mood, hallucination, hallucination (auditory), hallucination (visual), irritability, restlessness
Depression	Anhedonia, decreased interest, depressed mood, depression, major depression, suicidal ideation
Diarrhea	Colitis, Diarrhoea
Dizziness	Dizziness, dizziness exertional, dizziness postural, presyncope, syncope, vertigo
Dysgeusia	Ageusia, dysgeusia, taste disorder
Dyspnea	Acute respiratory distress syndrome, acute respiratory failure, bronchospasm, dyspnoea, dyspnoea exertional, orthopnoea, respiratory failure, tachypnoea, wheezing
Ecchymosis	Application site bruise, catheter site bruise, ecchymosis, increased tendency to bruise
Edema	Conjunctival oedema, face oedema, fluid overload, fluid retention, generalised oedema, hypervolaemia, localised oedema, oedema, oedema peripheral, oral leukoedema, palatal oedema, periorbital oedema, periorbital swelling, peripheral swelling, pharyngeal oedema, pulmonary congestion, pulmonary oedema, scrotal oedema, skin oedema, swelling, swelling face, swollen tongue

Encephalopathy	Amnesia, apraxia, bradyphrenia, cognitive disorder, confusional state, depressed level of consciousness, disturbance in attention, encephalopathy, immune effector cell-associated neurotoxicity syndrome, incoherent, lethargy, leukoencephalopathy, loss of consciousness, memory impairment, mental disorder, mental impairment, mental status changes, noninfective encephalitis, psychomotor retardation, slow response to stimuli
Fatigue	Asthenia, exercise tolerance decreased, fatigue, malaise
Fracture	Femur fracture, fibula fracture, foot fracture, hip fracture, humerus fracture, pathological fracture, rib fracture, spinal compression fracture, spinal fracture, stress fracture, subchondral insufficiency fracture, thoracic vertebral fracture, tibia fracture, tooth fracture, wrist fracture
Fungal infection	Aspergillus infection, body tinea, Candid infection, cerebral aspergillosis, dermatophytosis, fungal foot infection, fungal infection, fungal skin infection, Onychomycosis, oral candidiasis, sinusitis aspergillus, tinea infection, tinea pedis, tongue fungal infection, vulvovaginal candidiasis, vulvovaginal mycotic infection
Gastroenteritis	Campylobacter colitis, Campylobacter gastroenteritis, enteritis, enteritis infectious, enterocolitis, enterocolitis bacterial, enterocolitis infectious, enterocolitis viral, enterovirus infection, gastroenteritis, gastroenteritis Escherichia coli, gastroenteritis bacterial, gastroenteritis cryptosporidial, gastroenteritis norovirus, gastroenteritis rotavirus, gastroenteritis salmonella, gastroenteritis viral, gastroenteritis fungal infection, gastroenteritis infection, gastroenteritis viral infection, Helicobacter gastritis, large intestine infection
Graft versus host disease	Graft versus host disease in gastrointestinal tract, graft versus host disease in skin
Headache	Head discomfort, headache, migraine, procedural headache, sinus headache, tension headache

Hemorrhage	Anal haemorrhage, catheter site haemorrhage, cerebral haemorrhage, conjunctival haemorrhage, contusion, diarrhoea haemorrhagic, epistaxis, eye contusion, gastric haemorrhage, gastric ulcer haemorrhage, gastrointestinal haemorrhage, haematemesis, haematochezia, haematoma, haematospermia, haematotympanum, haematuria, haemoptysis, haemorrhage, haemorrhage intracranial, haemorrhage subcutaneous, haemorrhoidal haemorrhage, infusion site haematoma, lower gastrointestinal haemorrhage, melaena, mouth haemorrhage, oral contusion, pharyngeal haemorrhage, post procedural haemorrhage, pulmonary alveolar haemorrhage, pulmonary haemorrhage, rectal haemorrhage, retinal haemorrhage, retroperitoneal haemorrhage, subarachnoid haemorrhage, subcutaneous haematoma, subdural haematoma, subdural haemorrhage, upper gastrointestinal haemorrhage, vaginal haemorrhage
Hyperammonemia	Ammonia increased, hyperammonaemia
Hyperbilirubinemia	Blood bilirubin increased, hyperbilirubinaemia
Hyperferritinemia	Hyperferritinaemia, serum ferritin increased
Hyperglycemia	Blood glucose increased, hyperglycaemia
Hyperphosphatemia	Blood phosphorus increased, hyperphosphataemia
Hypertension	Essential hypertension, hypertension
Hyperuricemia	Blood uric acid increased, hyperuricaemia
Hypoalbuminaemia	Blood albumin decreased, hypoalbuminaemia
Hypocapnia	Carbon dioxide decreased, hypocapnia
Hypogammaglobulinaemia	Blood immunoglobulin G decreased, globulins decreased, hypogammaglobulinaemia, hypoglobulinaemia, immunoglobulins decreased
Hypoproteinaemia	Hypoproteinaemia, protein total decreased
Hypotension	Hypotension, orthostatic hypotension

Hypoxia	Hypoxia, oxygen consumption decreased, oxygen saturation decreased, PO2 decreased
Injection site reaction	Catheter site erythema, catheter site irritation, catheter site vesicles, infusion site extravasation, infusion site urticaria, infusion site warmth, injection site bruising, injection site discomfort, injection site erythema, injection site haematoma, injection site pain, injection site pruritis, injection site rash, injection site swelling
Leukocytosis	Leukocytosis, white blood cell count increased
Leukopenia	Leukopenia, white blood cell count decreased
Lymphocytosis	Lymphocyte count increased, lymphocytosis
Lymphopenia	CD4 lymphocytes decreased, lymphocyte count decreased, lymphocyte percentage decreased, lymphopenia
Monocytopenia	Monocyte count decreased, monocytopenia
Monocytosis	Monocyte count increased, monocytosis
Motor dysfunction	Agraphia, bradykinesia, cogwheel rigidity, coordination abnormal, dysgraphia, dystonia, extrapyramidal disorder, eyelid ptosis, head titubation, micrographia, motor dysfunction, muscle rigidity, muscle spasms, muscle spasticity, muscle tightness, muscle twitching, muscular weakness, myoclonus, parkinsonism, posture abnormal, stereotypy
Mucositis	Aphthous ulcer, mouth ulceration, oral blood blister, oral mucosal blistering, stomatitis
Musculoskeletal pain	Arthralgia, back pain, bone contusion, bone pain, bursa disorder, bursitis, joint stiffness, limb discomfort, muscle strain, musculoskeletal chest pain, musculoskeletal discomfort, musculoskeletal pain, musculoskeletal stiffness, myalgia, myopathy, myositis, neck pain, non-cardiac chest pain, osteoarthritis, pain in extremity, plantar fasciitis, rotator cuff syndrome, spinal osteoarthritis, spinal pain, temporomandibular joint syndrome, tendonitis

Neuropathy peripheral	Neuropathy peripheral, peripheral motor neuropathy, peripheral sensorimotor neuropathy, peripheral sensory neuropathy, polyneuropathy
Neutropenia	Granulocytopenia, neutropenia, neutrophil count decreased
Olfactory disorders	Anosmia, hyposmia, olfactory dysfunction, parosmia
Oral pain	Gingival discomfort, gingival pain, glossodynia, laryngeal pain, oral pain, oropharyngeal pain
Pain	Anorectal discomfort, axillary pain, bladder pain, breast pain, cancer pain, catheter site pain, discomfort, ear pain, eye pain, facial pain, flank pain, fracture pain, gastrointestinal pain, groin pain, inflammatory pain, lymph node pain, odynophagia, pain, pain in jaw, pain of skin, pelvic pain, pleuritic pain, procedural pain, proctalgia, prostatic pain, rhinalgia, sacral pain, sinus pain, skin burning sensation, stoma site pain, suprapubic pain, testicular pain, thyroid pain, toothache, tumour pain, urinary tract pain
Paresis	Diplegia, hemiparesis, hemiplegia, monoparesis, monoplegia, ophthalmoplegia, paralysis, paresis, peroneal nerve palsy
Pericardial effusion	Pericardial effusion, pericardial effusion malignant
Personality changes	Affect lability, apathy, flat affect, indifference, personality change, reduced facial expression
Pneumonia	Atypical pneumonia, bronchopulmonary aspergillosis, COVID-19 pneumonia, lower respiratory tract infection, lower respiratory tract infection viral, lung consolidation, lung infiltration, metapneumovirus pneumonia, organising pneumonia, pneumocystis jirovecii pneumonia, pneumonia, pneumonia aspiration, pneumonia bacterial, pneumonia cryptococcal, pneumonia haemophilus, pneumonia influenzal, pneumonia klebsiella, pneumonia legionella, pneumonia moraxella, pneumonia parainfluenzae viral, pneumonia pneumococcal, pneumonia pseudomonal, pneumonia respiratory syncytial viral, pneumonia staphylococcal, pneumonia streptococcal, pneumonia viral, pulmonary mycosis

Rash	Bullous haemorrhagic dermatosis, dermatitis, dermatitis acneiform, dermatitis allergic, dermatitis contact, dermatitis exfoliative generalised, dermatitis psoriasiform, drug eruption, ear pruritus, eczema, erythema, erythema multiforme, erythema of eyelid, papule, perineal rash, pityriasis lichenoides et varioliformis acuta, rash, rash erythematous, rash macular, rash maculo-papular, rash morbilliform, rash papular, rash pruritic, rash pustular, rash vesicular, rosacea, skin reaction, statis dermatitis, toxic erythema of chemotherapy, urticaria
Reflexes abnormal	Areflexia, glabellar reflex abnormal, hyporeflexia, palmomental reflex, postural reflex impairment, reflexes abnormal
Renal failure	Acute kidney injury, blood creatinine increased, chronic kidney disease, creatinine renal clearance decreased, renal failure, renal impairment, renal injury
Seizure	Epilepsy, seizure, status epilepticus
Sepsis	Bacteraemia, bacterial sepsis, bacterial toxaemia, candida sepsis, device-related bacteraemia, device-related sepsis, enterococcal bacteraemia, enterococcal sepsis, escherichia bacteraemia, escherichia sepsis, fungaemia, haemophilus sepsis, neutropenic sepsis, pseudomonal bacteraemia, pseudomonal sepsis, sepsis, sepsis pasteurella, septic shock, staphylococcal bacteraemia, staphylococcal sepsis, streptococcal bacteraemia, streptococcal sepsis, systemic candida, systemic mycosis, urosepsis
Sleep disorder	Hypersomnia, insomnia, sleep disorder, sleep terror, somnolence
Tachycardia	Heart rate increased, sinus tachycardia, tachycardia, tachycardia paroxysmal
Thrombocytopenia	Platelet count decreased, thrombocytopenia

Thrombosis	Axillary vein thrombosis, cerebral infarction, cerebral venous thrombosis, cerebrovascular accident, deep vein thrombosis, device-related thrombosis, embolism, jugular vein thrombosis, pulmonary embolism, subclavian vein thrombosis, thrombosis, thrombosis in device, vena cava thrombosis, venous thrombosis, venous thrombosis limb
Transaminase elevation	Alanine aminotransferase increased, aspartate aminotransferase, aspartate aminotransferase increased, transaminases increased
Tremor	Essential tremor, resting tremor, tremor
Upper respiratory tract infection	Acute sinusitis, bronchitis, chronic sinusitis, laryngitis, nasal congestion, nasopharyngitis, paranasal sinus discomfort, pharyngeal inflammation, pharyngitis, pharyngotonsillitis, respiratory tract congestion, respiratory tract infection, rhinitis, rhinorrhoea, rhinovirus infection, sinus congestion, sinusitis, tonsillitis, upper respiratory tract congestion, upper respiratory tract infection, upper respiratory tract infection bacterial, viral pharyngitis, viral upper respiratory tract infection
Urinary tract infection	Cystitis, escherichia urinary tract infection, urinary tract infection, urinary tract infection bacterial, urinary tract infection viral
Valve disorders	Mitral valve disease, tricuspid valve disease, tricuspid valve incompetence

Viral infection	Adenovirus infection, adenovirus test positive, asymptomatic COVID-19, BK virus infection, bronchitis viral, COVID-19, coronavirus infection, cytomegalovirus chorioretinitis, cytomegalovirus colitis, cytomegalovirus infection, cytomegalovirus infection reactivation, cytomegalovirus syndrome, cytomegalovirus test positive, cytomegalovirus viraemia, Epstein-Barr virus infection reactivation, hepatitis B, hepatitis B DNA assay positive, hepatitis B reactivation, herpes ophthalmic, herpes simplex, herpes simplex reactivation, herpes virus infection, herpes zoster, herpes zoster disseminated, human herpesvirus 6 infection, human metapneumovirus test positive, human rhinovirus test positive, influenza, JC polyomavirus test positive, JC virus infection, lymphadenitis viral, meningitis viral, metapneumovirus infection, norovirus infection, oral herpes, oral viral infection, parainfluenzae virus infection, parvovirus B19 infection, parvovirus infection, polyomavirus viraemia, post herpetic neuralgia, progressive multifocal leukoencephalopathy, respiratory syncytial virus infection, respiratory tract infection viral, rotavirus infection, SARS-CoV-2 test positive, viral infection, viral uveitis
Vision blurred	Vision blurred, visual acuity reduced, visual impairment
Visual field defect	Hemianopia, visual field defect
Weight decreased	Abnormal loss of weight, weight decreased
Xerosis	Dry eye, dry mouth, dry skin, xerosis

Source: FDA and Applicant response to IR dated December 18, 2023.
Abbreviations: BK, human polyomavirus 1; COVID-19, Coronavirus Disease 2019; JC, John Cunningham