

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	Biologics Licensing Application
Application Number(s)	BLA 125746/0
Priority or Standard	Priority
Submit Date(s)	Rolling BLA 3/31/2021
Received Date(s)	3/31/2021
PDUFA Goal Date	2/28/2022
Division/Office	DCEPT/OTAT and OCE
Review Completion Date	10/29/2021
Established Name	ciltacabtagene autoleucl
(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 x 10 ⁸ CAR-positive T cells in a single dose infusion
Applicant Proposed Indication(s)/Population(s)	Treatment of adult patients with relapsed or refractory multiple myeloma who previously received a proteasome inhibitor, an immunomodulatory agent and an anti-CD38 antibody.
Recommendation on Regulatory Action	Regular Approval
Recommended Indication(s)/Population(s) (if applicable)	Treatment of adult patients with relapsed or refractory multiple myeloma, after four or more prior lines of therapy, including a proteasome inhibitor, an immunomodulatory agent and an anti-CD38 monoclonal antibody.

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Reviewers of Multi-Disciplinary Review and Evaluation

Regulatory Project Manager	Nadia Whitt and Rachel Blasdell
Clinical Reviewer	Kavita Natrajan, MD (Safety)/ Megha Kaushal, MD (Efficacy)
Clinical Team Leader/Branch Chief	Bindu Kanapuru, MD/Bindu George, MD
Division Director (DCEPT)	Tejashri Purohit-Sheth, MD
Deputy Center Director (OCE)	Marc Theoret, MD
Office Director (or designated signatory authority)	Wilson Bryan, MD

Glossary

ADA	anti-drug (cilta-cel) antibodies
AE	adverse event
AESI	adverse events of special interest
ALT	alanine aminotransferase
AST	aspartate aminotransferase
ASTCT	American Society for Transplantation and Cellular Therapy
AUC	area under the analyte concentration-time curve
BCMA	B-cell maturation antigen
BLA	biologics license application
BQL	below quantification limit
C _{max}	maximum observed serum concentration
CAR-T	chimeric antigen receptor T (cells)
CD	cluster of differentiation
CFR	Code of Federal Regulations
CI	confidence interval
COVID	coronavirus disease
CR	complete response
CRCL	creatinine clearance
CRF	case report form
CRS	cytokine release syndrome
CSR	clinical study report
CT	computed tomography
CTC	Common Terminology Criteria
%CV	coefficient of variation
DNA	deoxyribonucleic acid
DOR	duration of response

eCRF	electronic case report form
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EORTC QLQ	European Organization for Research and Treatment of Cancer quality of life questionnaire
EQ-5D-5L	EuroQol Five Dimension Questionnaire
E-R	exposure-response
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GHS	global health status
HLH	hemophagocytic lymphohistiocytosis
HRQoL	health related quality of life
ICANS	immune effector cell associated neurotoxicity syndrome
ICE	immune effector Cell-associated Encephalopathy
ICF	informed consent form
ICH	Council for Harmonisation
IFN-gamma	interferon gamma
Ig	immunoglobulin
IL	interleukin
IL-1 β	interleukin 1 beta
IL-2RA	IL-2 receptor alpha
IMiD	immunomodulatory drug
IMWG	International Myeloma Working Group
IND	Investigational New Drug
INR	International Normalization Rate
IRC	Independent Review Committee
ISE	integrated summary of effectiveness
ISS	International Staging System
ITT	intent to treat
IV	intravenous
IVIG	intravenous immunoglobulin
LLOQ	lower quantifiable concentration
LV	lentiviral
LVV	lentiviral vector
MedDRA	Medical Dictionary for Regulatory Activities
MDS	myelodysplastic syndrome
mITT	modified intent-to-treat
MM	multiple myeloma
mPFS	median progression free survival
MRD	minimal residual disease
MRI	magnetic resonance imaging
MUGA	multigated acquisition
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event

NDA	new drug application
NK	natural killer
OPQ	Office of Pharmaceutical Quality
ORR	overall response rate
OS	overall survival
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PET	positron emission tomography
PD	progressive disease
PFS	progression-free survival
PGIC	Patient Global Impression of Change
PGIS	Patient Global Impression of Severity
PI	proteasome inhibitor
PK	pharmacokinetics
PRO	patient reported outcome
RCL	replication competent lentivirus
RP2D	recommended Phase 2 dose
RRMM	relapsed or refractory multiple myeloma
SAP	statistical analysis plan
sBCMA	soluble BCMA
SD	standard deviation
SET	Safety Evaluation Team
SOC	standard of care
SPM	second primary malignancy
$t_{1/2}$	half-life
TEAE	treatment emergent adverse event
TNF- α	tumor necrosis factor-alpha
TTR	time to response
ULN	upper limit of normal
USPI	United States prescribing information
VGPR	very good partial response

1. Executive Summary

1.1. Product Introduction

Drug: ciltacabtagene autoleucl (cilta-cel; non-proprietary name); CARVYKTI (commercial product)

Pharmacological Class: CAR-T cell product

Approved Indication: Treatment of adult patients with relapsed or refractory multiple myeloma, after four or more prior lines of therapy, including a proteasome inhibitor, an immunomodulatory agent and an anti-CD38 monoclonal antibody.

Proposed Indication: Treatment of adult patients with relapsed or refractory multiple myeloma who previously received a proteasome inhibitor, an immunomodulatory agent and an anti-CD38 antibody.

Dosing Regimen: Dose range of 0.5 to 1.0 x 10⁶ viable CAR-positive T cells per kg of body weight with a maximum dose of 1.0 x 10⁸ viable CAR-positive T cells in a single infusion

1.2. Conclusions on the Substantial Evidence of Effectiveness

The review team recommends regular approval of CARVYKTI, for the following indication:

CARVYKTI is a cell suspension consisting of autologous T cells that are genetically modified ex vivo with a lentiviral vector (LV) encoding a chimeric antigen receptor (CAR) targeting the B cell maturation antigen (BCMA).

The approval of CARVYKTI in adult patients with relapsed or refractory multiple myeloma (RRMM) who have received four or more prior lines of therapy including a proteasome inhibitor, an immunomodulatory agent and an anti-CD38 monoclonal antibody is based on the totality of evidence from CARTITUDE-1 (68284528MMY2001 or MMY2001), which demonstrated a favorable benefit-risk profile in the indicated patient population.

CARTITUDE-1 was a phase 1b/2, single arm, multicenter trial in patients with RRMM previously treated with at least three prior lines of therapy. Patients received 0.5 -1 x10⁶ CAR positive viable T cells per kg of body weight.

Efficacy

- The primary endpoint in CARTITUDE-1 was Overall Response Rate (ORR), defined as partial response (PR) or better according to the International Myeloma Working Group (IMWG) response criteria and as assessed by an independent review committee (IRC).
- The primary efficacy analysis was based on 97 patients who received CAR T cell infusion (cilta-cel) on the CARTITUDE-1 study. As product release specifications were revised, during the BLA review, the total number of patients in the CARTITUDE 1 study (n=97) who received cilta-cel (n=97) and the product intended for marketing (CARVYKTI) (n=80) differ. Determination of efficacy for regulatory recommendation is based on the efficacy results from the 97 patients who received cilta-cel.
- The ORR in the 97 patients who received cilta-cel was 97.9% [95% CI: 92.7, 99.7], above the pre-specified null hypothesis rate of 30%.
- Among the 95 patients with overall response, the median duration of response (DOR) was 21.8 months with a median duration of follow up of 18 months.
- The efficacy for the CARVYKTI subgroup (n=80) is comparable to the efficacy of those who received cilta-cel.

Safety

The primary safety analysis included all 97 patients in the CARTITUDE-1 study who were treated with one dose of cilta-cel within a dose range of $0.5-1.0 \times 10^6$ viable CAR-T cells/kg. Additional safety data from studies CARTITUDE-2 (MMY2003) and CARTITUDE-4 (MMY3002) obtained via information requests (IRs) for specific toxicities e.g., cranial nerve palsies was reviewed as supportive data.

The most common non-laboratory adverse reactions (incidence $\geq 20\%$) included fever, cytokine release syndrome (CRS), hypogammaglobulinemia, hypotension, musculoskeletal pain, fatigue, infections-pathogen unspecified, cough, chills, diarrhea, nausea, encephalopathy, decreased appetite, upper respiratory tract infection, headache, tachycardia, dizziness, dyspnea, edema, viral infections, coagulopathy, constipation, and vomiting. The most common (incidence $\geq 10\%$) grade 3 or 4 laboratory abnormalities included lymphopenia (99%), neutropenia (98%), leukopenia (98%), anemia (72%), thrombocytopenia (63%) and increased aspartate aminotransferase (21%).

Serious adverse events (SAEs) occurred in 53 (55%) patients and included CRS, hemophagocytic lymphohistiocytosis (HLH), infections, febrile neutropenia, cardiac arrhythmias, pericardial effusion, tumor lysis syndrome, encephalopathy, parkinsonism, neuropathy, paresis, dizziness, motor dysfunction, renal failure, dyspnea, hypoxia, pleural effusion, diplopia, nausea, pyrexia, fatigue, hemorrhage and hypotension.

All patients (100%) experienced severe (\geq Grade 3) treatment emergent AE (TEAE). The most common laboratory and non-laboratory ($\geq 10\%$) severe TEAEs were cytopenias (lymphopenia, neutropenia, leukopenia, anemia, thrombocytopenia), aspartate transaminase elevation, febrile neutropenia, infections-pathogen unspecified and viral, febrile neutropenia and hypotension, fatigue, hypophosphatemia, hyponatremia and increased blood alkaline phosphatase.

Nine patients had fatal adverse reactions. Fatal adverse reactions included - 2 patients with acute myeloid leukemia (AML), 3 patients with neurologic toxicity (NT) with 1 of these 3 patients having pulmonary embolism and cerebrovascular accident as other causes of death, 1 patient with CRS/HLH (hemophagocytic lymphohistiocytosis) and 3 patients with infection- sepsis, pneumonia and lung abscess in 1 patient each.

Any grade CRS occurred in 92 (95%) patients and NT [includes Immune Effector Cell Associated Neurotoxicity Syndrome (ICANS) and non-ICANS NT occurred in 25 (26%) patients. Grade 3 or higher CRS and NT occurred in 5% and 11% of patients respectively. Prolonged cytopenias (Grade 3 or 4 cytopenia that had not resolved by day 30 following cilta-cel infusion)- thrombocytopenia, neutropenia, lymphopenia and anemia occurred in 41%, 30%, 12% and 1% of patients respectively. One patient required autologous stem cell transplant (rescue) for prolonged grade 4 thrombocytopenia.

New safety signals identified include NT other than ICANS- parkinsonism, cranial nerve palsies, Guillain Barre syndrome (GBS), and peripheral sensory and motor neuropathy, and recurrent grade 3 or 4 cytopenias after initial recovery from grade 3 or 4 cytopenia.

The USPI will include boxed warning for CRS, HLH, NT including ICANS, parkinsonism, GBS, and prolonged and recurrent cytopenias. CRS and NT have been included in the Risk Evaluation and Mitigation Strategy (REMS) with elements to assure safe use (ETASU). The "Warnings and Precautions" section of the label (section 5) will also include the other adverse events of special interest- secondary malignancies, hypogammaglobulinemia, serious infections, and hypersensitivity reactions. No events of lentiviral competent replication have been reported. A post-marketing requirement (PMR) registry study to follow recipients of the commercial product for short-and long-term toxicities for up to 15 years will be issued.

In summary despite the serious and severe toxicity associated with cilta-cel and lymphodepleting chemotherapy, the magnitude of benefit, including overall response and persistence of response supports a favorable benefit risk profile and regular approval of CARVYKTI, for the R/R multiple myeloma patient population who have received 4 or more prior lines of therapy including a PI, IMiD and a CD38 monoclonal antibody. The indicated patient population is a population with life-threatening and fatal disease with few treatment options. Use of a REMS is considered essential to the mitigation of some of the life-

threatening toxicities as outlined above.

The recommended indication includes a requirement for receipt of 4 or more lines of therapy for receipt of CARVYKTI and reflects the patient population assessed to support the benefit risk for approval.

1.3. Benefit-Risk Assessment (BRA)

Benefit-Risk Summary and Assessment

Multiple myeloma (MM) is a plasma cell malignancy that accounts for approximately 1-2% of all cancers and approximately 17% of hematologic malignancies in the United States (1). MM is diagnosed most frequently among people aged 65-74 with a median age at diagnosis of 69 years. Despite the availability of multiple treatments, including alkylating agents, corticosteroids, immunomodulatory drugs (IMiDs), proteasome inhibitors (PIs) and monoclonal antibodies (mAbs), MM is thought to be an incurable disease. Most patients experience recurring remissions and relapses, and the goal of treatment is often aimed at creating longer periods of time without disease progression. Improving outcomes in patients with relapsed/refractory disease is an unmet medical need.

The review team recommends approval of CARVYKTI for the treatment of adult patients with multiple myeloma after four or more prior lines of therapy, including a proteasome inhibitor, an immunomodulatory agent and an anti-CD38 monoclonal antibody.

The approval of CARVYKTI in is based on the totality of evidence from Study CARTITUDE-1, a phase 1/2b, single arm trial in patients with RRMM previously treated with at least 3 prior lines of therapy.

The study met the primary endpoint of ORR, defined as PR or better according to the IMWG response criteria and as assessed by an independent review committee (IRC). The ORR was 97.9% [95% CI: 92.7, 99.7], which was above the pre-specified null hypothesis rate of 30%. Among the 95 patients with overall response, the median duration of response (DOR) was 21.8 months with a median duration of follow up of 18 months.

The safety profile of CARVYKTI is generally consistent with the known safety profile of other CAR products and includes cytokine release syndrome (CRS), hemophagocytic lymphohistiocytosis (HLH)/macrophage activation syndrome (MAS), immune effector cell associated neurologic syndrome (ICANS; referred to as neurologic toxicity in other products), infections, hypogammaglobulinemia, and prolonged cytopenias. Risk of secondary malignancies is present- both from the lymphodepletion regimen and the CAR-T therapy. Additional safety concerns include neurologic toxicity other than ICANS

(that is typically seen with CAR-T therapy)- neurologic toxicity with parkinsonism, cranial nerve palsies, Guillain Barre syndrome, peripheral sensory and motor neuropathy, and recurrent grade 3 or 4 cytopenias after initial recovery from grade 3 or 4 cytopenia and hypersensitivity reaction. Risk Evaluation and Mitigation Strategy (REMS) with Elements to Assure Safe Use (ETASU) will be issued for CRS and NT to ensure safe use of CARVYKTI after approval. The safety profile in the context of a REMS with ETASU is acceptable for this patient population with a serious and life-threatening disease.

The most common non-laboratory adverse reactions (incidence $\geq 20\%$) included fever, cytokine release syndrome (CRS), hypogammaglobulinemia, hypotension, musculoskeletal pain, fatigue, infections-pathogen unspecified, cough, chills, diarrhea, nausea, encephalopathy, decreased appetite, upper respiratory tract infection, headache, tachycardia, dizziness, dyspnea, edema, viral infections, coagulopathy, constipation, and vomiting. The most common (incidence $\geq 10\%$) grade 3 or 4 laboratory abnormalities included lymphopenia (99%), neutropenia (98%), leukopenia (98%), anemia (72%), thrombocytopenia (63%) and increased aspartate aminotransferase (21%).

The results of the CARTITUDE-1 study support regular approval of CARVYKTI in patients with RRMM who have received 4 or more prior lines of therapy. The recommended indication differs slightly from the indication sought by the Applicant and is based on the population enrolled in the CARTITUDE-1 study; only 17 patients received only 3 lines of therapy. A sample size of 17 patients from a single arm trial is considered insufficient to assess the magnitude of benefit in this population. Furthermore, the fatal and life-threatening risks such as parkinsonism and GBS, unique to CARVYTKTI raise substantial concerns to warrant additional information through ongoing studies to better understand risk minimizing strategies and reliably evaluate the benefit in this patient population in which options for other available therapies exist. A PMR will be issued to further characterize the short- and long-term toxicities of CARVYKTI.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	<ul style="list-style-type: none"> 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 with approval of multiple new therapies with improvement in response rate and progression free survival (PFS). However, MM remains incurable, with a 5-year survival rate of 52%. 	RRMM is a serious and life-threatening condition with need for effective and safe salvage therapies.
Current Treatment Options	<ul style="list-style-type: none"> Multiple drugs approved for use in MM and numerous combination regimens are considered standard of care. Potential treatments include alkylating agents, corticosteroids, immunomodulatory drugs (IMiDs), proteasome inhibitors and monoclonal antibodies. Daratumumab in combination with carfilzomib and dexamethasone was approved in 2020 for treatment of adult patients with multiple myeloma who have received 1 to 3 prior therapies. Selinexor, a nuclear export inhibitor in combination with dexamethasone has regular approval for treatment of penta-refractory myeloma population with at least four prior therapies. Belantamab mafodotin, a BCMA-directed antibody and microtubule inhibitor conjugate received accelerated approval in relapsed or refractory population who has received 4 prior therapies including an anti-CD 38 antibody, a PI and an IMiD. Abecma, a CAR T cell product was approved in 2020 for treatment of adult patients with multiple myeloma who have received 4 prior lines of therapy. 	Despite the availability of multiple therapies, RRMM remains an incurable disease.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Benefit	<ul style="list-style-type: none"> The clinical benefit of CARVYKTI was established in CARTITUDE-1, a phase 1/2b, a single arm, open-label, multicenter trial in patients with RRMM previously treated with at least 3 prior lines of therapy. The primary endpoint was ORR assessed by independent review committee (IRC) was 97.9 % [95 % CI 92.7, 99.7] with an sCR rate of 78.4%. The median DOR was 21.8 months. 	<p>The ORR, CR rate and DOR at the recommended dose range observed in CARTITUDE-1 provides substantial evidence of benefit of cilta-cel in the indicated patient population.</p>
Risk and Risk Management	<ul style="list-style-type: none"> The most 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. CRS and NT were mitigated in the trial 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 	<p>The available evidence indicated that the risks, while substantial, does not outweigh the benefit in this patient population with RRMM.</p> <p>There is a Black box Warning for CRS, Neurologic Toxicities (ICANS, parkinsonism and GBS), HLH/MAS, and Prolonged and Recurrent Cytopenia.</p> <p>The Warnings and Precautions section of the label details the potential risks. A Risk Evaluation and Mitigation (REMS) with Elements to Assure Safe Use (ETASU) will be issued to mitigate the risks of CRS and NT associated with CARVYKTI after approval.</p>

Dimension	Evidence and Uncertainties	Conclusions and Reasons
		The PMR study will follow 1500 recipients of the commercial product (CARVYKTI) for 15 years for secondary malignancies and other safety signals.

1.4. Patient Experience Data

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

<input type="checkbox"/>	The patient experience data that was submitted as part of the application, include:	Section where discussed, if applicable
	<input type="checkbox"/> Clinical outcome assessment (COA) data, such as	[e.g., Section 6.1 Study endpoints]
✓	<input type="checkbox"/> Patient reported outcome (PRO)	Section 8.1.2 Efficacy Results -Secondary Endpoints
	<input type="checkbox"/> Observer reported outcome (ObsRO)	
	<input type="checkbox"/> Clinician reported outcome (ClinRO)	
	<input type="checkbox"/> Performance outcome (PerfO)	
	<input type="checkbox"/> Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)	
	<input type="checkbox"/> Patient-focused drug development or other stakeholder meeting summary reports	[e.g., Section 2.1 Analysis of Condition]
	<input type="checkbox"/> Observational survey studies designed to capture patient experience data	
	<input type="checkbox"/> Natural history studies	
	<input type="checkbox"/> Patient preference studies (e.g., submitted studies or scientific publications)	
	<input type="checkbox"/> Other: (Please specify)	
<input type="checkbox"/>	Patient experience data that was not submitted in the application, but was considered in this review.	

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).

Worldwide, there were an estimated 80,000 deaths due to multiple myeloma (MM) and approximately 24,300 and 12,800 patients with this disease die annually in Europe and the United States, respectively (Ferlay 2013; Cancer.net 2020). The estimated 5-year survival rate for patients with MM is approximately 54% (Cancer.net 2020). With each successive relapse, symptoms return, health related quality of life (HRQoL) worsens, and the chance and duration of response typically decreases. 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.

FDA Assessment

FDA agrees with the Applicant's analysis of condition. Despite the availability of multiple approved treatment options, MM remains incurable. Improving outcomes such as durability of response and/or demonstrating an increase in magnitude of response particularly complete response in patients with limited treatment options may address an unmet medical need.

Analysis of Current Treatment Options

Data:

Despite multiple therapeutic options, MM remains incurable. All patients eventually relapse and become refractory to existing treatments. Median overall survival in patients who have received at least 3 prior lines of therapy and are refractory to both an immunomodulatory imide drug (IMiD) and a PI is only 13 months (Kumar 2017). The reported overall response rate (ORR) for approved therapies for the population of heavily pre-treated and refractory patients with MM, is approximately 30% for therapies belonging

to the classes of IMiD, PI, anti-cluster of differentiation (CD)38 antibody, inhibitor of nuclear transport, and anti-B-cell maturation antigen (BCMA) antibody drug conjugate (Table 1). The ORR reported for the anti-BCMA chimeric antigen receptor T (cells) (CAR-T) therapy recently approved by the FDA (idecabtagene vicleucl) was 73%.

In a recently published retrospective chart review, investigators from 14 academic institutions analyzed 275 patients who developed refractory disease to anti-CD38 monoclonal antibody treatment ([Gandhi 2019](#)). This observational study was derived from real-world data and supports the lack of options for patients who had prior exposure to a PI, IMiD, and anti-CD38 monoclonal antibody therapy. Patients were heavily pre-treated with a median of 4 lines of therapy (range: 1 to 16). The median overall survival for the entire cohort was 8.6 months, ranging from 11.2 months for patients not simultaneously refractory to an IMiD and PI to 5.6 months for penta refractory patients (refractory to anti-CD38, 2 PIs, and 2 IMiDs). Among patients who received ≥ 1 subsequent treatment after becoming refractory to anti-CD38 therapy (90% of patients in the study), the response rate averaged 31%, with a median progression-free survival (PFS) and median overall survival of 3.4 months and 9.3 months, respectively. The median overall survival for patients who received no further treatment was 1.3 months.

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	Important Safety and Tolerability Issues
FDA Approved Treatments					
Pomalidomide/ Dexamethasone	Pomalidomide, in combination with dexamethasone, is indicated for adult patients with MM 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.	Pomalidomide 4 mg once daily orally with or without food on Days 1 through 21 of each 28-day cycle until disease progression. Pomalidomide is given in combination with dexamethasone.	Open-label, randomized StudyMM-003 (San Miguel 2013); ORR: 31% Median PFS: 4.0 months Median DOR: 7 months Median OS: 12.7 months.	<ul style="list-style-type: none"> Embryo-fetal toxicity Pomalidomide is contraindicated in pregnancy. Pomalidomide is a thalidomide analogue. Thalidomide is a known teratogen that causes severe life-threatening birth defects Venous and Arterial Thromboembolism Deep venous thrombosis, pulmonary embolism, myocardial infarction, and stroke occur in patients with MM treated with pomalidomide.
Daratumumab	Daratumumab is indicated for the treatment of adult patients with MM 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.	Daratumumab 16 mg/kg actual body weight administered as an IV infusion according to the following dosing schedule: Weeks 1 to 8 weekly (total 8 doses), Weeks 9 to 24 every two weeks (total 8 doses), Week 25 onwards until disease progression every 4 weeks.	Open-label, randomized Study SIRIUS (Lonial 2016); ORR: 29.2%; Median PFS: 3.7 months Median DOR: 7.4 month Median OS: 17.5 months.	<p>Daratumumab can cause:</p> <ul style="list-style-type: none"> Severe and/or serious infusion-related reactions including anaphylactic reactions. Daratumumab binds to CD38 on RBCs and results in a positive Indirect Antiglobulin Test (Indirect Coombs test). Blood transfusion centers should be notified of this interference with serological testing. Neutropenia and thrombocytopenia induced by background therapy. Fetal harm in a pregnant woman, depletion of fetal immune cells, and decreased bone density.

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	Important Safety and Tolerability Issues
Carfilzomib ^a	Carfilzomib is indicated as a single agent for the treatment of patients with RRMM who have received 1 or more lines of therapy.	2016/ Full Approval	Carfilzomib is administered in 20/27 mg/m ² twice weekly regimen by 10-minute IV infusion in cycles 1 through 12, on Days 1, 2, 8, 9, 15, and 16 of each 28-day cycle. From Cycle 13, administered on Days 1, 2, 15, and 16 of each 28-day cycle. The recommended starting dose is 20 mg/m ² in Cycle 1 on Days 1 and 2. If tolerated, the dose is escalated to 27 mg/m ² on Day 8 of Cycle 1 and thereafter is continued until disease progression or unacceptable toxicity.	Open-label, randomized Study FOCUS (Hajek 2017); ORR: 19.1% Median PFS: 3.7 months Median DOR: 7.2 months Median OS: 10.2 months.	Carfilzomib can cause: <ul style="list-style-type: none"> • New onset or worsening of pre-existing cardiac failure (eg, congestive heart failure, pulmonary edema, decreased ejection fraction), cardiomyopathy, myocardial ischemia, and myocardial infarction including fatalities • Acute renal failure and TLS, including fatal outcomes for both • ARDS and acute respiratory failure in approximately 2% of patients • Pulmonary arterial hypertension in approximately 2% of patients, with Grade 3 or greater in less than 1%. • Dyspnea in 25% of patients, with 4% Grade 3 or greater. • Hypertension, including hypertensive crisis and hypertensive emergency, venous thromboembolic events (including deep venous thrombosis and pulmonary embolism), infusion-related reactions, including life-threatening reactions, fatal or serious cases of hemorrhage • Thrombocytopenia with platelet nadirs observed between Day 8 and Day 15 of each 28-day cycle, with recovery to baseline platelet count usually by the start of the next cycle • Hepatic failure, fatal cases in 2% of patients

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	Important Safety and Tolerability Issues
					<ul style="list-style-type: none"> • Thrombotic microangiopathy, including TTP/HUS, PRES, and PML • Fetal harm in a pregnant woman.

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	Important Safety and Tolerability Issues
Selinexor/ Dexamethasone	Selinexor in combination with dexamethasone is indicated for the treatment of adult patients with RRMM 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.	Selinexor 80 mg taken orally on Days 1 and 3 of each week until disease progression or unacceptable toxicity in combination with dexamethasone 20 mg taken orally with each dose of selinexor on Days 1 and 3 of each week.	Open-label, single arm Study STORM (Chari 2019) ORR: 26.2%; Median PFS: 3.7 months Median DOR: 4.4 months Median OS: 8.6 months.	Selinexor can cause: <ul style="list-style-type: none"> • Life-threatening thrombocytopenia, potentially leading to hemorrhage • Life-threatening neutropenia, potentially increasing the risk of infection • Severe gastrointestinal toxicities (nausea/vomiting, diarrhea, anorexia/weight loss), severe or life-threatening hyponatremia, serious and fatal infections, and life-threatening neurological toxicities • Fetal harm in a pregnant woman • New onset or exacerbation of cataract.
Belantamab mafodotin	Belantamab mafodotin is indicated for the treatment of adults with RRMM who have received at least 4 prior therapies, including an anti-CD38 monoclonal antibody, a PI, and an IMiD.	2020/ Accelerated Approval.	Belantamab mafodotin 2.5 mg/kg of actual body weight given as an IV infusion over approximately 30 minutes once every 3 weeks until disease progression or unacceptable toxicity.	Open-label, randomized Study DREAMM-2 (Lonial 2020); ORR: 31% Median PFS: 2.9 months Median DOR: 11.0 months.	Belantamab mafodotin can cause: <ul style="list-style-type: none"> • Changes in the corneal epithelium resulting in changes in vision, including severe vision loss and corneal ulcer, and symptoms, such as blurred vision and dry eyes • Thrombocytopenia and infusion-related reactions • Fetal harm in a pregnant woman because it contains a genotoxic compound (the microtubule inhibitor, MMAF) and it targets actively dividing cells.

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	Important Safety and Tolerability Issues
Melflufen flufenamide	Melflufen flufenamide is indicated in combination with dexamethasone for the treatment of adult patients with RRMM who have received at least 4 prior line of therapy and whose disease is refractory to at least one PI, 1 IMiD, and 1 CD38-directed monoclonal antibody.	2021/ Accelerated Approval.	Melflufen flufenamide 40 mg IV on Day 1 of each 28-day cycle plus once weekly oral dexamethasone at a dose of 40 mg (20 mg in patients older than 75 years).	Pivotal, single arm Study Horizon (Richardson 2021); ORR: 26% Median PFS: 3.9 months Median DOR: 4.4 months.	<p>Patients who received melflufen flufenamide with dexamethasone reported:</p> <ul style="list-style-type: none"> • Thrombocytopenia in 99% of 157 patients (26% Grade 3 and 54% Grade 4). Thrombocytopenia may lead to hemorrhage (Any Grade hemorrhage in 28% of 157 patients, 3.2% Grade 3, and Grade 4 in <1 % of patients) • Neutropenia in 95% of 157 patients (41% Grade 3 and 40% Grade 4). Febrile neutropenia in 6% of patients. Neutropenia may lead to infection • Anemia in 84% of 157 patients (50% Grade 3) • Fatal infections in <1% of 157 patients (Any Grade infection in 58%, Grade 3 in 20% and Grade 4 in 1.9% of patients). Respiratory tract infection in 24% (5% Grade ≥3), pneumonia in 13% (11% Grade ≥3), and sepsis in 3.8% (3.2% Grade ≥3) of patients • Secondary malignancies such as myelodysplastic syndromes or acute leukemia in MM patients • Fetal harm in a pregnant woman because it is genotoxic and targets actively dividing cells.

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	Important Safety and Tolerability Issues
Idecabtagene vicleucel (ide-cel)	Idecabtagene vicleucel is indicated for the treatment of adult patients with RRMM 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+ T cells (target dose range).	Single arm Study KarMMa (Munshi 2021); ORR: 73% Median PFS: 8.8 ^b months Median DOR: 10.7 ^b months.	Patients who received Ide-cel reported: <ul style="list-style-type: none"> • Neutropenia (91%), CRS (84%), anemia (70%), and thrombocytopenia (63%) • Neurotoxicity developed in 18% patients • Four treatment related deaths (bronchopulmonary aspergillosis, gastrointestinal hemorrhage, CRS, and cytomegaloviral pneumonia).

Keys: ARDS=Acute Respiratory Distress Syndrome; CRS=cytokine release syndrome;; DOR=duration of response; HUS= hemolytic uremic syndrome; IMiD=immunomodulatory drug; IV=intravenous; MM=multiple myeloma; MMAF=monomethyl auristatin F; ORR=overall response rate; OS=overall survival; PFS=progression-free survival; PI=proteasome inhibitor; PML=progressive multifocal leukoencephalopathy;; PRES=posterior reversible encephalopathy syndrome; RBC=red blood cell; RRMM= relapsed or refractory multiple myeloma; TLS=tumor lysis syndrome; TTP= thrombotic thrombocytopenic purpura.

*Accelerated approval or full approval

^a Data presented from arm of interest for randomized study

^b 150 × 10⁶ to 450 × 10⁶ CAR+ T cells

The Applicant's Position

There is an unmet need for new treatment options beyond the current classes of anti-myeloma therapies for the treatment of adult subjects with relapsed or refractory MM (RRMM), whose prior regimens included a PI, an IMiD, and an anti-CD38 antibody and who had disease progression on or after the last regimen. Ciltacabtagene autoleucel (cilta-cel) a genetically modified autologous BCMA-targeted CAR T-cell therapy with its unique mechanism of action, is expected to address this unmet medical need, and provide a targeted treatment option with a favorable benefit-risk profile for patients with RRMM. Idecabtagene vicleucel (ide-cel), an anti-BCMA CAR-T therapy, recently received FDA approval for the treatment of adult patients with RRMM after 4 or more prior lines of therapy, including an IMiD, a PI, and an anti-CD38 monoclonal antibody. The Applicant will demonstrate in the sections below that cilta-cel has deep and durable responses in the 3 or more prior lines of therapy setting, which remains an area of high unmet need.

FDA 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 verified efficacy information in this regard. FDA notes that additional regimens are approved for patients with RRMM who have received at least 2 prior lines of therapy, including daratumumab in combination with pomalidomide and dexamethasone (DPd), isatuximab in combination with pomalidomide and dexamethasone (Isa-Pd) and elotuzumab in combination with Pd (EPd).

FDA recommends at least 4 or more prior lines of therapy, as will be discussed below in the review.

3. Regulatory Background

3.1 U.S. Regulatory Actions and Marketing History

The Applicant's Position:

Cilta-cel (JNJ-68284528) is not currently registered (or approved) in the US or any other part of the world. The current submission supports cilta-cel treatment of adult patients with RRMM, who previously received a PI, an IMiD, and an anti-CD38 antibody.

FDA Assessment

FDA agrees with the Applicant's position that cilta-cel is not currently registered or approved anywhere in the world.

Summary of Pre-submission/Submission Regulatory Activity

The Applicant's Position:

The Sponsor submitted Investigational New Drug (IND) 18080 on 27 April 2018 to the United States of America (US) FDA to support the investigation of cilta-cel in the treatment of subjects with RRMM. The notification that the study was safe to proceed was provided on 25 May 2018.

The clinical development program was designed after consultation with global health authorities. Key FDA interactions and agreements are summarized below in Table 2.

Table 2: Applicant - Cilta-cel Health Authority Interactions

Date	Description
10 Jan 2018	Pre-IND Type B Meeting to discuss the development program.
24 Aug 2018	Type C Meeting to obtain agency feedback regarding the additional manufacturing site for clinical supplies of cilta-cel in (b) (4).
14 Dec 2018	Type C Meeting to seek the Agency's review and concurrence on the proposal to introduce (b) (4) as an additional manufacturing facility for JNJ-68284528 clinical and commercial Drug Product manufacturing.
01 Feb 2019	Orphan Drug Designation granted for the treatment of MM (Designation 2018-6721).
27 Jun 2019	Type B End of Phase 1 Meeting is to obtain Agency review and agreement on the proposed recommended Phase 2 dose, the clinical development plan in subjects with RRMM, and the sufficiency of the clinical plan and nonclinical package for registration.
21 Aug 2019	Type C Meeting seeking review and concurrence on the proposal to introduce LV manufacture at a Janssen Vaccines, (b) (4) using a (b) (4) process.
14 Feb 2020	Type B Meeting to discuss and obtain initial agreement with the Agency regarding the proposed content and format for the initial BLA for cilta-cel.
27 May 2020	Agreed initial pediatrics study plan (iPSP)- Agreement Letter.
18 Aug 2020	Type B Meeting to obtain review and agreement on the comparability strategy for LVV and Drug Product for cilta-cel and present clinical efficacy and safety data from 68284528MMY2001.
28 Aug 2020	Type C Meeting to obtain review and feedback on proposed Expanded Access Program strategy, objectives and study design of the draft Protocol Elements Document and Managed Access Program.
24 Sep 2020	Conditional acceptance of proprietary name CARVYKTI.
02 Oct 2020	Type B Meeting to obtain review and agreement to the 68284528MMY4002 long-term follow-up study and a post-marketing registry study to assess the safety of cilta-cel.

Table 2: Applicant - Cilta-cel Health Authority Interactions

Date	Description
08 December 2020	Type B Pre-BLA Meeting to obtain the Agency’s review of the topline results from 68284528MMY2001, the proposed REMS strategy and guidance on BLA submission plans.
10 December 2020	FDA grants Rolling Review for BLA 125746.

Keys: BLA=biologics license application; FDA=Food and Drug Administration; IND=investigational New Drug; iPSP=initial pediatrics study plan; LV=Lentiviral; LVV=Lentiviral Vector; MM=multiple myeloma; RRMM=relapsed or refractory multiple myeloma

FDA Assessment

FDA agrees with the Applicant’s table summarizing the pre-submission/submission regulatory activity relevant to this 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)

FDA Assessment

Clinical site inspections were conducted for this application. Bioresearch Monitoring (BIMO) inspection assignments were issued for five domestic clinical study sites participating in the conduct of study CARTITUDE-1. The inspections did not reveal substantive findings that impact the data submitted in this Biologics License Application (BLA).

Site #	Study Site Location
US10001	Sarah Cannon Research Institute Nashville, TN
US10003	University of Chicago Chicago, IL
US10007	University of California, San Francisco San Francisco, CA
US10021	Mayo Clinic Rochester Rochester, MN
US10026	University of Pittsburgh Medical Center Pittsburgh, PA

Several discrepancies were observed during the inspection of Study Site US10003 which were characterized by the review team as minor, and no further action was indicated.

Product Quality

FDA Assessment

Refer to the Office of Product Quality review for specific recommendations regarding product quality. The FDA Product Quality review team recommended approval.

4.2 Devices and Companion Diagnostic Issues

FDA Assessment

No companion diagnostic was requested with this submission. Refer to Section 8.1.2 Study Results regarding the issues related to the Clonal Seq MRD assay used for response assessment in the trial.

5. Summary of Nonclinical Pharmacology/Toxicology Findings

The Applicant's position

5.1 Pharmacology

Primary Pharmacology

Analysis of normal tissue expression of BCMA demonstrates BCMA is highly restricted in normal human tissue supporting that on-target/off-tumor toxicity is not a major safety concern. The dual BCMA targeting domain of cilta-cel was selected for its in vitro (b) (4)

In vitro co-culture assays evaluating cytotoxicity and cytokine release have demonstrated antigen specific on-target functional activity of cilta-cel towards BCMA-expressing human MM cells lines and no off-target effects towards BCMA-negative human cell lines. Binding assessments against (b) (4)

assays with BCMA-positive or BCMA-negative cell lines suggest a low-risk for off-target recognition and functional consequences in patients. [Source: Mod2.6.2/Sec2.1]

In vivo efficacy studies using a MM xenograft in immunodeficient mice demonstrated tumor growth inhibition and a significant survival benefit. CAR gene copy number quantification of whole blood from these mice demonstrated expansion and persistence of cilta-cel. [Source: Mod2.6.2/Sec2.2]

Cilta-cel is a patient-specific cell therapy product and lacks cross-reactivity to a relevant nonclinical species.

Secondary Pharmacology

No secondary pharmacology studies have been conducted.

Safety Pharmacology

Safety pharmacology studies were not conducted because there is no relevant species for the nonclinical safety assessment of cilta-cel. While there is restricted expression of BCMA on B-lineage cells, cytokine release syndrome (CRS), the main toxicity of CAR-T therapy, may affect safety pharmacology parameters ([Shalabi et al. 2020](#); [Hay et al. 2017](#); [Burstein et al. 2018](#)).

5.2 Pharmacokinetics

Allometric scaling methods or predictive pharmacokinetic (PK)/pharmacodynamic models are not currently available to allow translations of effective doses demonstrated in this model to predict therapeutically active clinical doses. Due to the restricted expression of the BCMA target in a hematological condition, which is primarily abundant in blood and bone marrow spaces, biodistribution of cilta-cel was not evaluated.

5.3 Toxicology

The nonclinical toxicology program of cilta-cel was designed to characterize the on-target specificity to BCMA and evaluate the risk of off-tumor/on-target toxicity or off-tumor/off-target toxicity. Standard in vivo models cannot accurately assess the on-target toxicological characteristics of cilta-cel because it is generated from human T cells and neither mouse nor monkey are pharmacologically relevant species. [Source: *Mod2.6.2/Sec2.1.1.3*]

5.3.1 General Toxicity

Single-dose Toxicity

Both mouse and (b) (4) monkey were considered as potential nonclinical species for the safety assessment of cilta-cel but the CAR in cilta-cel is not cross-reactive to BCMA in these species. In vivo studies were limited to the efficacy studies due to the nature of the product and lack of cross-reactivity.

Repeat-dose Toxicity

Repeat-dose toxicity studies have not been conducted for cilta-cel given there is no relevant nonclinical species and that cilta-cel is administered as a single dose to patients.

5.3.2 Genetic Toxicology

Conventional genotoxicity studies were not conducted with cilta-cel. As indicated in the Council for Harmonisation Safety Pharmacology guideline (ICH S6[R1]) and ICH S2(R1) guidance, genotoxicity studies routinely conducted for pharmaceuticals are not appropriate for a biotechnology pharmaceutical such as cilta-cel.

Although traditional carcinogenicity and genotoxicity studies were not conducted due to the advanced cancer indication and the lack of appropriate test models and pharmacologically relevant species, the risk for insertional mutagenesis occurring during the manufacturing of cilta-cel following transduction of autologous human T cells with a lentiviral vector (LVV) was assessed based on a weight-of-evidence risk assessment, a lentiviral (LV) integration site analysis on preinfusion cilta-cel, and a cytokine independent growth assay. Cilta-cel does not demonstrate uncontrolled growth in the absence of exogenous cytokine supplementation, and the distribution of integration of LVV in cilta-cel is random/semi-random and does not cluster at known oncogenic hotspots of concern. [Source: Mod2.6.6/Sec4]

5.3.3 Carcinogenicity

Carcinogenicity studies were not performed for cilta-cel. Cilta-cel is a human specific CAR-T cell product and lacks cross reactivity to rodent BCMA precluding the conduct of traditional rat and mouse bioassays.

5.3.4 Reproductive and Developmental Toxicology

Pregnancy risk was considered through a weight-of-evidence assessment and cilta-cel is not expected to be teratogenic. Moreover, since T cells are transduced ex vivo in (b) (4) cells, germ-line transmission of cilta-cel is not anticipated. [Source: Mod2.6.6/Sec6]

FDA Assessment

Please refer to the pharmacology/toxicology review memo for details.

6. Clinical Pharmacology

The Applicant's Position

Pharmacology and Pharmacokinetic Characteristics

The targeted dose (equivalent to the recommended Phase 2 dose [RP2D]) is a single infusion of cilta-cel 0.75×10^6 CAR-positive viable T cells/kg (range: $0.5-1.0 \times 10^6$ CAR-positive viable T cells/kg, with a maximum total dose of 1.0×10^8 CAR-positive viable T cells).

Cilta-cel pharmacology information is based on the evaluable data obtained from 97 subjects (29 in Phase 1b, 68 in Phase 2) with RRMM in Study 68284528MMY2001 (hereafter referred to as MMY2001). All subjects treated in the study received the RP2D (median dose administered: 0.709×10^6 cells/kg [range: $0.51-0.95 \times 10^6$ cells/kg]). The median dose administered was similar in Phase 1b (0.722×10^6 cells/kg [range: $0.52-0.89 \times 10^6$ cells/kg]) and Phase 2 (0.707×10^6 cells/kg [range: $0.51-0.95 \times 10^6$ cells/kg]).

Subjects underwent apheresis to acquire peripheral blood mononuclear cells. Cilta-cel was generated from the subjects' T cells selected from the apheresis product. After cilta-cel production and product release, subjects received a conditioning regimen of cyclophosphamide 300 mg/m^2 and fludarabine 30 mg/m^2 daily, administered intravenously for 3 consecutive days. Cilta-cel was administered as a single intravenous (IV) infusion on Day 1 (5 to 7 days after the start of the conditioning regimen).

Dose and Cellular Kinetics Relationship

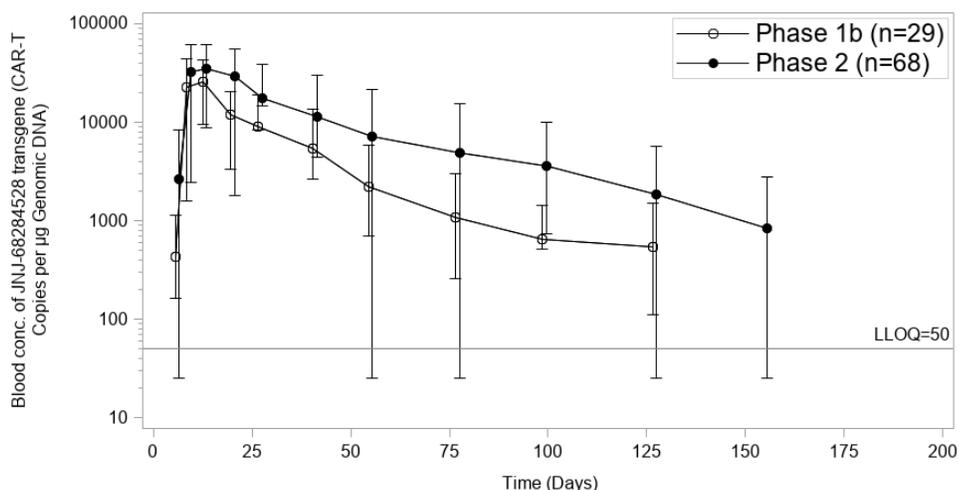
Cilta-cel PK was characterized by transgene levels and CAR-positive cells in peripheral blood. In the bone marrow, cilta-cel acts by direct interaction with BCMA⁺ cells present in MM patients. Therefore, the concentration of CAR-T cells and their persistence was also evaluated in bone marrow samples.

Pharmacokinetic measurements using both transgene and cellular levels were concordant and showed similar expansion and persistence profiles. Following a single infusion, cilta-cel exhibited an initial expansion phase followed by a rapid decline, and then a slower decline with both transgene and cellular persistence over months.

The key cellular PK findings for the study overall (Phase 1b and Phase 2 combined and comparisons between the phases) based on transgene level data (Figure 1):

- After a single infusion of a median dose of 0.709×10^6 CAR-positive viable T cells/kg (range: $0.51\text{-}0.95 \times 10^6$ cells/kg), mean cilta-cel transgene levels in blood samples were below the quantification limit (below quantification limit [BQL]; <50 CAR-T copies per μg genomic deoxyribonucleic acid [DNA]) until Day 7 or 10 in both Phase 1b and Phase 2. The median time to reach peak levels of cilta-cel expansion in peripheral blood was 12.7 days (range: 8.7 to 54.6 days) post-infusion. Cilta-cel mean apparent terminal elimination half-life ($t_{1/2}$) values were shorter in Phase 1b compared with Phase 2 (16.4 and 25.4 days, respectively), but ranges were overlapping and interindividual variability was high (coefficient of variation [%CV]: 109.2% to 125.0%).
- After cell expansion, the persistence phase of the cilta-cel transgene levels was observed for all subjects. The median time to last measurable (non-BQL) cilta-cel transgene level included all 97 subjects and was comparable in Phase 1b (95.9 days [range: 26.2 to 438.0 days]) and Phase 2 (99.7 days [range: 20.0 to 240.0 days]). Among 57 out of 97 subjects who had cilta-cel transgene levels returned to the pre-dose baseline level of BQL at the time of the data cutoff, the median time to return to BQL was shorter in Phase 1b than Phase 2, but ranges were overlapping. Overall, the median time to return to BQL was 79.7 days (range: 27.0 to 275.0 days) post-infusion.
- Cilta-cel transgene exposure parameters maximum observed analyte concentration (C_{max}), area under the analyte concentration-time curve (AUC) from time 0 to 28 days ($\text{AUC}_{0\text{-}28\text{d}}$), AUC from time 0 to 6 months ($\text{AUC}_{0\text{-}6\text{m}}$), and AUC from time 0 to time of last measurable (non-BQL) analyte concentration ($\text{AUC}_{0\text{-}\text{last}}$) showed higher mean values in Phase 2 than in Phase 1b, but with high interindividual variability (%CV: 49.8% to 123.6%) and different sample sizes (29 in Phase 1b and 68 in Phase 2). Overall, the mean (standard deviation [SD]) cilta-cel transgene values was 48501 (27362) copies/ μg genomic DNA for C_{max} , 504561 (385428) copies*day/ μg genomic DNA for $\text{AUC}_{0\text{-}28\text{d}}$, 1036998 (1348041) copies*day/ μg genomic DNA for $\text{AUC}_{0\text{-}6\text{m}}$, and 990124 (1182015) copies*day/ μg genomic DNA for $\text{AUC}_{0\text{-}\text{last}}$.
- Bone marrow transgene levels also declined over time and exhibited high interindividual variability (%CV: 156.5% to 202.3%). Detectable cilta-cel transgene exposures in bone marrow indicate a distribution of cilta-cel from systemic circulation to bone marrow.
- The observed cilta-cel CAR transgene PK-time data were adequately described by a 2-compartment model (with a fast and a slow decline rate from each compartment, respectively) and a chain of 4 transit compartments with a lag time empirically representing the process from infused CAR-T cell to measurable CAR transgene.

Figure 1: Applicant - Semi-logarithmic Mean Blood Concentration-time Profiles of Cilta-cel Transgene Levels After a Single Infusion



CAR-T=chimeric antigen receptor T cell; DNA=deoxyribonucleic acid; LLOQ=lower quantifiable concentration; SD=standard deviation.

On the logarithmic scale, if the SD was higher than the mean, the lower errors bars were modified by adding the mean and blocking the minimum values of the error bars to half the lower limit of quantification.

Alternate Dosing Regimens for Specific Sub-populations Based on Intrinsic/Extrinsic Factors

Intrinsic and extrinsic factors affecting PK were evaluated using a population-based modeling approach. None of the investigated subject demographics, baseline characteristics (eg, age, sex, body weight, race, hepatic impairment, renal impairment), or manufactured product 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_{0-28d} were similar across age breakdowns (≥ 65 vs < 65 years), between males and females, across different body weight groups (ie, < 70 , 70 to 85, and > 85 kg), and across races.

Hepatic and Renal Impairment: No dedicated hepatic or renal impairment studies were performed and no major changes in cilta-cel exposure are anticipated in subjects with hepatic or renal insufficiency. Population PK analysis confirmed that cilta-cel CAR

transgene C_{max} and AUC_{0-28d} were similar in subjects with mild hepatic dysfunction (defined as total bilirubin \leq upper limit of normal [ULN] and aspartate aminotransferase $>$ ULN, or ULN $<$ total bilirubin $\leq 1.5 \times$ ULN) and subjects with normal hepatic function, and in subjects with mild renal dysfunction (defined as $60 \text{ mL/min} \leq$ creatinine clearance [CRCL] $< 90 \text{ mL/min}$) and subjects with normal renal function (CRCL $\geq 90 \text{ mL/min}$).

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

Drug-drug Interactions

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.

Pharmacodynamics

Soluble BCMA (sBCMA): After a single cilta-cel infusion, sBCMA decreased in all subjects with mean serum concentrations reaching nadir levels around the lower quantifiable concentration (LLOQ) value at Day 78 in Phase 1b and at Day 100 in Phase 2. Increases from nadir were seen in some subjects, but levels remained lower than baseline sBCMA. This reversal of sBCMA levels may reflect a reproduction of BCMA⁺ plasma cells.

Cytokine Profile: Thirteen cytokines (interferon [IFN]-gamma, Interleukin 1 beta [IL-1 β], IL-2, IL-4, IL-6, IL-8, IL-10, tumor necrosis factor-alpha [TNF- α], IL-5, IL-17A, IL-13, IL-2 receptor alpha [IL-2RA], and IL-12/IL-23p40) were evaluated in Study MMY2001. Across all subjects, levels of IL-6, IL 10, IFN-gamma, and IL-2RA increased post-infusion and peaked at Days 7 to 14 coinciding with expansion of cilta-cel and the onset of CRS. The serum levels of all cytokines generally returned to baseline levels within 2 to 3 months post-infusion.

Immunogenicity: The overall incidence of antibodies to cilta-cel was 15.5%. Based on the current data, there was no clear evidence to suggest an association between anti-drug antibodies and cilta-cel kinetics of initial expansion and persistence, efficacy, or safety.

Replication Competent Lentivirus (RCL): At the time of the clinical cutoff date, no positive samples for RCL had been detected in any subjects at any of the collection timepoints.

Exposure and Dose Relationship with Efficacy and Safety

Exposure-response (E-R) analyses evaluated the relationship between 2 exposure metrics, CAR transgene C_{max} and AUC_{0-28d} , and efficacy (ORR, duration of response

[DOR], progression-free survival [PFS], and overall survival [OS]) and safety (AEs of clinical interest: CRS, immune effector cell associated neurotoxicity syndrome [ICANS], and other neurotoxicities [including movement and neurocognitive treatment emergent adverse events [TEAEs]) endpoints.

The majority of treated subjects were responders (ORR=96.9%), and it was not feasible to draw a conclusion on the E-R relationship between systemic cilta-cel CAR transgene level and ORR. Similarly, the E-R relationship between systemic cilta-cel CAR transgene level and disease progression, as measured by DOR, PFS, and OS, could not be evaluated due to the limited number of subjects and events (deaths or disease progression).

The median systemic CAR transgene levels (C_{max} and AUC_{0-28d}) were higher in subjects with CRS, ICANS, other neurotoxicities (including movement and neurocognitive TEAEs), and movement and neurocognitive TEAEs than in subjects without these AEs. However, CAR transgene levels across AE categories were overlapping and this observation needs to be interpreted with caution. No apparent trend with the infused cilta-cel total dose (over the narrow target dose range) was observed for any of these safety endpoints. This was expected since only 1 target dose level (0.75×10^6 CAR-positive viable T cells/kg [range: $0.5-1.0 \times 10^6$ CAR-positive viable T cells/kg) of cilta-cel was investigated in Study MMY2001. [Source: Mod2.7.2/Fig13, Fig14, Fig15, Fig16]

Drug-biologic interactions particularly in relation to risk mitigation medications on dose expansion.

As described above, cilta-cel is administered as a single IV infusion at a targeted dose (RP2D) of 0.75×10^6 CAR-positive viable T cells/kg (range: $0.5-1.0 \times 10^6$ CAR-positive viable T cells/kg, with a maximum total dose of 1.0×10^8 CAR-positive viable T cells).

Bridging Therapy: If clinically indicated, short term bridging therapy (anti-plasma cell directed treatment between apheresis and the first dose of the lymphodepletion conditioning regimen) was allowed to maintain disease stability for subjects waiting for cilta-cel manufacturing. Bridging therapy was assessed as a covariate of interest in the population PK analysis to identify correlations with individual PK parameters. None of the covariates explored and tested had a statistically significant effect on the systemic cilta-cel level.

Medications Used to Treat CRS and ICANS: The impact of concomitant administration of tocilizumab, corticosteroids, and anakinra 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_{0-28d} were higher among subjects who received tocilizumab, corticosteroids, or

anakinra for CRS or ICANS management compared with subjects who did not receive these medications. 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.

FDA Assessment

Refer to the Clinical Pharmacology review memo.

7. Sources of Clinical Data

7.1 Table of Clinical Studies

Data:

The efficacy and safety of cilta-cel in subjects with RRMM is established in Study MMY2001. Supportive safety data are provided from Study MMY2003 and the Japan cohort of Study MMY2001. Details for these studies are provided in Table 3.

Table 3: Applicant - Listing of Clinical Trial Relevant to this BLA for Ciltacabtagene autoleucl

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
<i>Open-label Study to Support Efficacy and Safety</i>								
Main Study: 68284528MMY2001	NCT03548207	Phase 1b/2 Open-label, multicenter study	Conditioning regimen consisted of IV cyclophosphamide (300 mg/m ²) and fludarabine (30 mg/m ²) in 3 daily doses. The dose of IV infusion of cilta-cel is 0.75 x 10 ⁶ CAR-positive viable T cells/kg (range: 0.5-1.0 x 10 ⁶ CAR-positive viable T cells/kg) derived from the subject's T cells.	Primary endpoint: ORR Secondary endpoints: VGPR or better rate, MRD negativity rate, CBR, DOR, TTR, PFS, and OS. HRQol will also be evaluated	Subjects received a single IV infusion of cilta-cel on Day 1 (5 to 7 days after the start of the conditioning regimen). As of the cutoff date of 11 February 2021: The median duration of follow-up was 18.0 months (range 1.5 months to 30.5 months)	Main Study: N=97 (Phase 1b: n= 29; Phase 2: n= 68)	Men and women ≥18 years of age, with documented diagnosis of MM according to IMWG diagnostic criteria whose prior lines of therapy included a PI, an IMiD, and an anti-CD38 antibody and who had disease progression on or after the last prior regimen	US (16)
<i>Study to Support Safety</i>								
68284528MMY2001: Phase 2 Japan Cohort	NCT03548207	Phase 1b/2 Open-label, multicenter study	Conditioning regimen consisted of IV cyclophosphamide (300 mg/m ²) and fludarabine (30 mg/m ²) in 3 daily doses. The dose of IV infusion of cilta-cel is 0.75 x 10 ⁶	Primary endpoint: ORR Secondary endpoints: VGPR or better rate, MRD negativity rate, CBR, DOR, TTR, PFS, and OS.	Subjects received a single IV infusion of cilta-cel on Day 1 (5 to 7 days after the start of the conditioning regimen). As of the cutoff date of 01	N=9	Men and women ≥20 years of age, with documented diagnosis of MM according to IMWG diagnostic criteria whose prior lines of therapy included a PI, an IMiD, and an anti-CD38 antibody and who had disease	JPN (4)

Table 3: Applicant - Listing of Clinical Trial Relevant to this BLA for Ciltacabtagene autoleucl

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
			CAR-positive viable T cells/kg (range: 0.5-1.0 x 10 ⁶ CAR-positive viable T cells/kg) derived from the subject's T cells.	HRQol will also be evaluated	September 2020: The median duration of follow-up was 2.4 months (range 0.9 months to 5.2 months) at clinical cutoff.		progression on or after the last prior regimen	
68284528MMY2003	NCT04133636	Phase: 2 Multicohort, open-label, multicenter study.	Conditioning regimen consisted of IV cyclophosphamide (300 mg/m ²) and fludarabine (30 mg/m ²) in 3 daily doses. The dose of IV infusion of cilta-cel is 0.75 x 10 ⁶ CAR-positive viable T cells/kg (range: 0.5-1.0 x 10 ⁶ CAR-positive viable T cells/kg) derived from the subject's T cells. Cohorts A, B, and C: Bridging therapy as needed after apheresis and prior to administration of conditioning regimen.	Primary endpoint: MRD negativity rate	Conditioning regimen for 3 days followed by cilta-cel administered 5 to 7 days after the start of the conditioning regimen. Cohorts A, B, and C: Bridging therapy as needed after apheresis and prior to administration of conditioning regimen. Cohort D: One 28-day cycle of lenalidomide after apheresis and prior to administration	N=18 Cohort A: n=13 Cohort B: n=1 Cohort C: n=2 Cohort D: n=2	Men and women ≥18 years of age with documented MM according to IMWG diagnostic criteria. Subjects were enrolled in cohorts according to the following criteria: Cohort A: 1-3 prior lines of therapy including PI and IMiD Cohort B: 1 line of prior therapy including PI and IMiD Cohort C: Previously treated with PI, IMiD, anti-CD38 monoclonal	Belgium (2) France (3) Germany (3) Israel (2) Netherlands (2) Spain (2) US (17)

Table 3: Applicant - Listing of Clinical Trial Relevant to this BLA for Ciltacabtagene autoleucl

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
			Cohort D: cilta-cel plus lenalidomide Subjects with MM without CR after 4 to 8 total cycles of initial therapy, including induction, high dose chemotherapy, and ASCT with or without consolidation		of conditioning regimen (alternative bridging therapy permissible with sponsor approval). Lenalidomide maintenance as early as Day 21 and up to 2 years post cilta-cel infusion, beginning with the 6th Cohort D subject. As of the cutoff date of 23 July 2020: The median duration of follow-up was 1.6 months (range, 0.1 to 5.2 months).		antibody, and BCMA-directed therapy Cohort D: Subjects who did not achieve CR after 4 to 8 total cycles of initial therapy, including induction, high-dose chemotherapy, and ASCT with or without consolidation	

Keys: ASCT=autologous stem cell transplantation; BCMA=B-cell maturation antigen; CAR= chimeric antigen receptor; CBR= clinical benefit rate; CD= cluster of differentiation; CR=complete response;; DOR= duration of response; HRQol=health related quality of life; IMiD=immunomodulatory drug; IMWG=International Myeloma Working Group; IV=intravenous; mg=milligram; µg=microgram; MM=multiple myeloma; mL=milliliter; MRD=minimal residual disease; ORR=overall response rate; OS=overall survival; PI=proteasome inhibitor; PK=pharmacokinetics; PFS=progression-free survival; RRMM=relapsed or refractory MM; TTR=time to response; VGPR=very good partial response.

FDA Assessment

FDA agrees with the Applicant's summary of clinical trials relevant to the BLA presented in Applicant Table 3. CARTITUDE-1 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; general observations on safety pertaining to specific adverse events e.g., cranial nerve palsies was included in the label from ongoing studies of cilta-cel (CARTITUDE-2 and CARTITUDE-4).

8. Statistical and Clinical Evaluation

8.1 Review of Relevant Individual Trials Used to Support Efficacy

8.1.1 68284528MMY2001/CARTITUDE-1

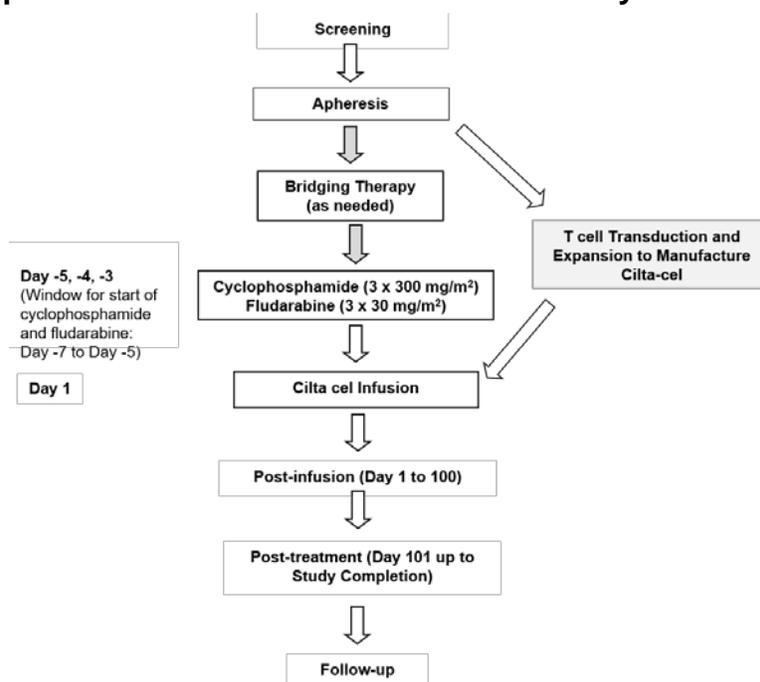
The primary evidence of efficacy and safety for cilta-cel is based on data from Phase 1b-2 of the ongoing Phase 2 Study MMY2001.

Trial Design

The Applicant's Description:

Basic Study Design: MMY2001 was a Phase 1b-2, open-label study to evaluate cilta-cel in adult subjects with RRMM, whose prior regimens included a PI, an IMiD, and an anti-CD38 antibody and who had disease progression on or after the last prior regimen. The study comprised of 2 parts, in Phase 1b part, a minimum of 24 and up to 50 subjects were to receive treatment to confirm treatment safety and provide information to be used in the selection of a RP2D for further investigation in the Phase 2 part of the study. The schematic overview of the study flow chart is presented in Figure 2.

Figure 2: Applicant - Schematic Overview of the Study Flow Chart



- **Single-arm Study Design:** A single-arm design was chosen for the MMY2001 study due to the lack of established standard of care options for use as a concurrent control for this patient population. Specifically, other available options considered for this patient population including selinexor (median progression free survival [mPFS]=3.7 months), belantamab mafodotin-blmf (mPFS=2.8 months) or investigator choice (mPFS=3.4 months), based on the MAMMOTH study; (Gandhi 2019) were deemed to be unreasonable given the known mPFS of the LEGEND-2 study (mPFS=18 months) when the MMY2001 study was initiated. Given the perceived lack of equipoise to randomize patients between cilta-cel and any of the aforementioned available standards of care, a single-arm study design was selected for the MMY2001 study.
- **Phase 1b-2:** The MMY2001 study was designed such that, in Phase 1b part of the study safety of cilta-cel was confirmed and RP2D was established and in the Phase 2 part of the study efficacy of the selected RP2D of cilta-cel was further evaluated.

Bridging Therapy: The median length of time from initial apheresis to cilta-cel infusion was ^{(b) (4)} days and receipt to release (calculated from the day after the receipt of leukapheresis material at the manufacturing facility up to, and inclusive of the day on which the CAR-T product is released for shipment to the clinical trial site) was a median of 29 days. When clinically indicated, short term treatment with bridging therapy was allowed for subjects waiting for cilta-cel manufacture. Bridging therapy was limited to a treatment the subject had previously received and generated a response of stable disease or better. Per protocol, subjects in complete response (CR) or better after receiving bridging therapy were not permitted to receive cilta-cel.

Trial location: 16 sites across US, treated a total of 97 subjects (113 subjects enrolled).

Choice of control group: Not applicable as this was a single-arm study.

Diagnostic criteria: Diagnosis of MM was documented according to International Myeloma Working Group (IMWG) diagnostic criteria. Multiple myeloma was defined as clonal bone marrow plasma cells $\geq 10\%$ or biopsy-proven bony or extramedullary plasmacytoma, any one or more of the following myeloma defining events: evidence of end organ damage that can be attributed to the underlying plasma cell proliferative disorder, specifically hypercalcemia (serum calcium >0.25 mmol/L [>1 mg/dL] higher than the ULN or >2.75 mmol/L [>11 mg/dL]), renal insufficiency (creatinine clearance <40 mL per min or serum creatinine >177 μ mol/L [>2 mg/dL]), anemia (hemoglobin value of >20 g/L below the lower limit of normal, or a hemoglobin value <100 g/L), and bone lesions (one or more osteolytic lesions on skeletal radiography, computed tomography [CT], or positron emission tomography [PET]-CT), and any one or more of the following biomarkers of malignancy (clonal bone marrow plasma cell percentage $\geq 60\%$,

involved:uninvolved serum free light chain ratio ≥ 100 , >1 focal lesions on magnetic resonance imaging [MRI] studies).

Key inclusion and exclusion criteria: The eligibility criteria for the study are appropriate for the population under investigation.

- **Key inclusion criteria:** Subjects ≥ 18 years of age with a documented diagnosis of MM according to IMWG diagnostic criteria, with an Eastern Cooperative Oncology Group (ECOG) Performance Status score of 0 or 1, with 1) Measurable disease at screening as defined by any of the following: Serum M-protein level ≥ 1.0 g/dL or urine M-protein level ≥ 200 mg/24 hours; or light chain MM without measurable disease in the serum or the urine: Serum immunoglobulin free light chain ≥ 10 mg/dL and abnormal serum immunoglobulin kappa lambda free light chain ratio; with 2) Received at least 3 prior lines of therapy or were double refractory to a PI and an IMiD (induction with or without hematopoietic stem cell transplant and with or without maintenance therapy was considered a single regimen), subjects were to have undergone at least 1 complete cycle of treatment for each regimen (unless progressive disease [PD] was the best response); with 3) Received a PI, an IMiD, and anti-CD38 antibody (prior exposure could have been from different monotherapy or combination regimens); and with 4) Documented disease progression during, or within 12 months, of the most recent anti-myeloma therapy.
- **Key exclusion criteria:** Subjects with prior treatment with CAR-T therapy directed at any target, any therapy that is targeted to BCMA, diagnosed or treated for invasive malignancy other than MM, prior antitumor therapy prior to apheresis, and received an allogenic stem cell transplant within 6 months or an autologous stem cell transplant ≥ 12 weeks before apheresis.

Dose and Administration Schedule Selection: A staggered enrollment strategy was used in Phase 1b to allow for an observation period between dosing of the first 4 subjects. An observation period of 4 weeks was implemented between the first and second subjects followed by a 2-week observation period between the second and third subjects and between the third and fourth subjects.

The conditioning regimen of cyclophosphamide 300 mg/m^2 and fludarabine 30 mg/m^2 daily for 3 doses led to lymphodepletion and helped promote CAR-T cell expansion in the subject. Cyclophosphamide 300 mg/m^2 and fludarabine 30 mg/m^2 before cilta-cel infusion (Day 1) was consistent with the lymphodepletion regimen used in the marketed CAR-T products [Kymriah 2020](#) and [Yescarta 2020](#).

Cilta-cel was administered at a targeted infused dose of 0.75×10^6 CAR-positive viable T cells/kg (range: $0.5\text{-}1.0 \times 10^6$ CAR-positive viable T cells/kg with a maximum total dose of 1.0×10^8 CAR-positive viable T cells) for this Phase 1b-2 study.

Study Treatment: Cilta-cel was administered in a single infusion at a target dose of 0.75×10^6 CAR-positive viable T cells/kg (range: 0.5 to 1.0×10^6 CAR-positive viable T cells/kg). Each cilta-cel drug product underwent testing to satisfy a series of pre-specified release criteria before administration to the subject. The sponsor performed a benefit/risk evaluation on any cilta-cel product that did not meet the pre-specified release criteria to determine if that product could be considered for use (with consultation of the investigator and health authority where applicable).

Dose discontinuation: Specific rules for dose discontinuation are outlined in the study protocol. A subject 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 subject to discontinue study treatment
- Grade ≥ 3 nonhematologic toxicity related to cyclophosphamide and fludarabine occurred, and precluded retreatment with cyclophosphamide and fludarabine prior to cilta-cel infusion
- The subject received concurrent (non-protocol) anticancer treatment (with exception of sponsor-approved bridging therapy)
- Confirmed disease progression per IMWG criteria between the time of conditioning therapy and infusion of cilta-cel
- Subject refused further study treatment
- Noncompliance with study treatment or procedure requirements

Administrative structure: For the primary efficacy analysis, the disease status evaluation for each subject was assessed by an Independent Review Committee (IRC).

A Safety Evaluation Team (SET) was established to ensure safety monitoring and sponsor oversight during the Phase 1b part of the study. The SET was chaired by the sponsor Study Responsible Physician. Membership included the study principal investigators, a sponsor clinical scientist, safety physician, statistician, clinical pharmacologist, and additional sponsor staff, as appropriate. The SET reviewed all available treatment-emergent data (eg, PK, pharmacodynamics, safety, and efficacy) at predefined enrollment milestones (after 6 subjects at the same dose completed the dose evaluation period) to evaluate the need for dose level escalation or de-escalation. The SET could advise on modifications in study conduct, including whether hospitalization, local stay, or staggered dosing with cilta-cel was required for subsequent subjects or stopping further enrollment if treatment-emergent toxicity was believed to result in an unfavorable risk-benefit profile.

Procedures and schedule: The Time and Events Schedule provided in Table 4 and Table 5 detail the planned frequency and timing of screening, safety, efficacy measurements, PK, and biomarker sampling during the conduct of Study MMY2001.

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 medications (excluding study treatment and prior antineoplastic treatments), surgeries and vaccinations administered from screening to apheresis through 100 days after infusion of cilta-cel, or until the start of subsequent systemic anticancer treatment, if earlier were recorded in the electronic case report form (eCRF).

Anti-myeloma therapy (medications which the subject had previously received) was permitted during bridging therapy. Pre-infusion supportive treatment included antihistamine and antipyretic (IV or oral) prior to cilta-cel infusion. Subsequent anticancer therapy administered after cilta-cel was administered only after confirmed PD per IMWG criteria.

Treatment compliance: Apheresis 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.

Subject completion, discontinuation, or withdrawal: A subject was considered to have completed the study if he or she died before the end of the study, had not been lost to follow-up or had not withdrawn consent for study participation before the end of the study, defined as 2 years after the last subject had received his or her initial dose of cilta-cel. Subjects were withdrawn from treatment due to confirmed disease progression per IMWG criteria between the time of conditioning therapy and infusion of cilta-cel, or investigator discontinued the subjects study treatment for safety or tolerability reasons, or Grade 3 nonhematologic toxicity related to cyclophosphamide and fludarabine occurred, or subjects received concurrent (non-protocol) anticancer treatment or refused further study treatment or due to noncompliance with study treatment or procedure requirements.

Table 4: Applicant - Time and Events Schedule for Study Procedures/ Assessments

	Screening Phase	Apheresis	Cyclophosphamide and fludarabine conditioning regimen	JNJ-68284528 Infusion	Post Infusion (Day 1 to Day 100) (any subject who received an infusion of JNJ-68284528 should continue all subsequent assessments) ^a										Post-treatment (Day 101 and up to Study Completion) ^b
					Day 3	Day 7 (± 1 day)	Day 10 (± 1 day)	Day 14 (± 1 day)	Day 21 (± 1 day)	Day 28 (± 2 days)	Day 42 (± 2 days)	Day 56 (± 2 days)	Day 78 (± 2 days)	Day 100 (± 2 days) ^b	
Screening Assessments															
Informed consent ^a	X Before the 1 st study related procedure														
Eligibility criteria	X														
Demography, Medical History	X														
Disease Characteristics ^d			X (prior to start of conditioning regimen)												
ECOG	X		Prior to 1 st dose only	X								X		X	
Physical Examination	X		A symptom-directed physical examination should be performed as clinically indicated												
Height	X														
12-lead ECG	X											X			
Echocardiogram or MUGA scan	X (≤8 weeks of apheresis)		For subjects who receive bridging therapy that includes agents with known cardiac toxicity (per prescribing information), assessment of cardiac function should be repeated after completion of bridging therapy and prior to the start of the conditioning regimen, then again as clinically indicated if the subject develops signs/symptoms of heart failure												
ICE neurological test				X (≤24 hours)	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.										

Table 4: Applicant - Time and Events Schedule for Study Procedures/ Assessments

	Screening Phase	Apheresis	Cyclophosphamide and fludarabine conditioning regimen	JNJ-68284528 Infusion	Post Infusion (Day 1 to Day 100) (any subject who received an infusion of JNJ-68284528 should continue all subsequent assessments) ^a										Post-treatment (Day 101 and up to Study Completion) ^b	
					Day 3	Day 7 (± 1 day)	Day 10 (± 1 day)	Day 14 (± 1 day)	Day 21 (± 1 day)	Day 28 (± 2 days)	Day 42 (± 2 days)	Day 56 (± 2 days)	Day 78 (± 2 days)	Day 100 (± 2 days) ^b		(every 28 days after day 100) ^c (± 7 days)
	≤28 days prior to apheresis ^a	Upon enrollment	Day -5,* -4, -3 (assessments may be conducted ≤72 hours predose) *Window for start of conditioning regimen: Day -7 to Day -5	Day 1 (Infusion)												
				prior to infusion) ^q												
Handwriting sample				X (≤24 hours prior to infusion) ^q	X	X	X	X	X	X	X (also on Day 35)	X	X	X	X	up to Day 184
Safety Criteria (prior to apheresis and conditioning regimens)																
Safety criteria		X	≤72 hours of the 1 st dose only.	X												
Laboratory Assessments																
Hematology ^e	X	X (within 24 hours prior to apheresis)	Prior to 1 st dose only	X (predose)	X	X	X	X	X	X	X	X	X	X	X	
Chemistry ^e	X	X (≤72 hour window)	Prior to 1 st dose only	X (predose)	X	X	X	X	X	X	X	X	X	X	X	
Serology ^f	X															
Coagulation (PT/INR, aPTT, fibrinogen, D-dimer)	X				As clinically indicated for subjects who have fever or other signs of potential CRS											

Table 4: Applicant - Time and Events Schedule for Study Procedures/ Assessments

	Screening Phase	Apheresis	Cyclophosphamide and fludarabine conditioning regimen	JNJ-68284528 Infusion	Post Infusion (Day 1 to Day 100) (any subject who received an infusion of JNJ-68284528 should continue all subsequent assessments) ^a										Post-treatment (Day 101 and up to Study Completion) ^b
					Day 3	Day 7 (± 1 day)	Day 10 (± 1 day)	Day 14 (± 1 day)	Day 21 (± 1 day)	Day 28 (± 2 days)	Day 42 (± 2 days)	Day 56 (± 2 days)	Day 78 (± 2 days)	Day 100 (± 2 days) ^b	
Urinalysis	X				As clinically indicated										
Serum Pregnancy test (in subjects with childbearing potential)	X	X (≤72 hour window)	Prior to 1 st dose only		As clinically indicated										
Infectious Disease Testing ⁿ	X (within 60 days of apheresis, as applicable per local regulations)														
Study Intervention Administration															
Weight	X	X (for JNJ-68284528 dose calculation)	Prior to 1 st dose only	X											
Vital signs, including oxygen saturation	X	X	X	X ^g	X	X	X	X	X	X		X			
Temperature					Measure at least twice a day ^h										
Apheresis		X													
Cyclophosphamide and fludarabine			X												
Pre-infusion medication for				X											

Table 4: Applicant - Time and Events Schedule for Study Procedures/ Assessments

	Screening Phase	Apheresis	Cyclophosphamide and fludarabine conditioning regimen	JNJ-68284528 Infusion	Post Infusion (Day 1 to Day 100) (any subject who received an infusion of JNJ-68284528 should continue all subsequent assessments) ^a										Post-treatment (Day 101 and up to Study Completion) ^b	
					Day 3	Day 7 (± 1 day)	Day 10 (± 1 day)	Day 14 (± 1 day)	Day 21 (± 1 day)	Day 28 (± 2 days)	Day 42 (± 2 days)	Day 56 (± 2 days)	Day 78 (± 2 days)	Day 100 (± 2 days) ^b		(every 28 days after day 100) ^c (± 7 days)
requirements prior to dosing with JNJ-68284528)	≤28 days prior to apheresis ^a	Upon enrollment	Day -5,* -4, -3 (assessments may be conducted ≤72 hours predose) *Window for start of conditioning regimen: Day -7 to Day -5	Day 1 (Infusion)												
JNJ-68284528 (See SIPP and IPI for administration of JNJ-68284528)				X ^e												
Serum and Urine Disease Evaluations for efficacy assessments. Blood and 24-hour urine: to be sent to the central laboratory. ^s Disease evaluation should continue to be performed until confirmed disease progression, death, start of a new anticancer treatment, withdrawal of consent for study participation, or study completion, whichever occurs first.). Subjects with disease progression who receive retreatment with JNJ-68284528 must continue with disease evaluation visits.																
Serum β2-microglobulin			X (prior to first dose of conditioning regimen [≤7 days])													
Quantitative Immunoglobulins	X ⁱ		X (prior to first dose of conditioning regimen [≤7 days]) ⁱ						X		X	X	X	X	X	X
Serum M-protein quantitation by electrophoresis	X		X (prior to first dose of conditioning regimen [≤7 days])						X		X	X	X	X	X	X

Table 4: Applicant - Time and Events Schedule for Study Procedures/ Assessments

	Screening Phase	Apheresis	Cyclophosphamide and fludarabine conditioning regimen	JNJ-68284528 Infusion	Post Infusion (Day 1 to Day 100) (any subject who received an infusion of JNJ-68284528 should continue all subsequent assessments) ^a										Post-treatment (Day 101 and up to Study Completion) ^b
					Day 3	Day 7 (± 1 day)	Day 10 (± 1 day)	Day 14 (± 1 day)	Day 21 (± 1 day)	Day 28 (± 2 days)	Day 42 (± 2 days)	Day 56 (± 2 days)	Day 78 (± 2 days)	Day 100 (± 2 days) ^b	
24-hour urine protein electrophoresis sample	X ^j		X (prior to first dose of conditioning regimen [≤7 days])							X		X	X	X	X
Serum calcium corrected for albumin	X		X (prior to first dose of conditioning regimen [≤7 days])							X		X	X	X	X
Serum FLC and serum/urine immunofixation	X		Serum FLC and serum/urine immunofixation are to be performed prior to the start of conditioning regimen (≤7 days) and when CR is suspected or maintained; for subjects with measurable disease only by light chain criteria serum FLC will also be performed at every assessment when an SPEP is performed												
Other Disease Evaluations															
Bone marrow aspirate and core biopsy ^k			X (prior to first dose of conditioning regimen [≤7 days])	To confirm CR, sCR, and at disease progression (immunohistochemistry or flow cytometry). See Table 5 for additional bone marrow collection for research.											
Skeletal Survey ^l	X		As clinically indicated to assess for disease progression												
Assess extramedullary Plasmacytomas ^m			X (≤14 days prior to first dose of conditioning regimen)	Measurable sites Day 28, Day 56, Day 78, Day 100 then every 4 weeks for physical examination (if applicable) and Day 78 and Day 156 then every 12 weeks for radiologic assessment (for subjects with a history of plasmacytomas or as clinically indicated for others).											
MRD and biomarker evaluations			See Biomarker Time & Events Schedule (Table 5)												

Table 4: Applicant - Time and Events Schedule for Study Procedures/ Assessments

	Screening Phase	Apheresis	Cyclophosphamide and fludarabine conditioning regimen	JNJ-68284528 Infusion	Post Infusion (Day 1 to Day 100) (any subject who received an infusion of JNJ-68284528 should continue all subsequent assessments) ^a										Post-treatment (Day 101 and up to Study Completion) ^b
					Day 3	Day 7 (± 1 day)	Day 10 (± 1 day)	Day 14 (± 1 day)	Day 21 (± 1 day)	Day 28 (± 2 days)	Day 42 (± 2 days)	Day 56 (± 2 days)	Day 78 (± 2 days)	Day 100 (± 2 days) ^b	
Patient Reported Outcomes (PRO), Qualitative Interviews, and Medical Resource Utilization (MRU): Phase 2 only. 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; EORTC QLQ-MY20 (4 items)	X					X				X		X	X	X	X ^o
EQ-5D-5L	X					X				X		X	X	X	X ^o
PGIS	X					X				X		X	X	X	X ^o
PGIC										X		X	X	X	
Qualitative Interviews ^p	X													X (±30 days)	Day 184 (±30 days)
Medical Resource Utilization (MRU)				X				X		X		X		X	X ^r
Ongoing Subject Review After disease progression is documented, survival status and subsequent anticancer therapy will be obtained every 16 weeks until study completion															
Adverse Events	Continuous from the time of signing of ICF until 100 days after last administration of any study treatment. Second primary malignancies should be followed from the time of signing of ICF signing to study completion. CRS should be evaluated according to the ASBMT consensus grading (Lee 2019). CAR-T cell-related neurotoxicity (eg, ICANS) should be graded according to the ASBMT consensus grading. Report new neurologic AEs or exacerbation of existing neurologic AEs up to 12 months after JNJ-68284528 infusion. Events of HBV reactivations should be reported during the first-year post-dosing of JNJ-68284528.														
Concomitant medication	Continuous from the time of signing of ICF until at least 100 days after last administration of any study treatment. Concomitant usage for the treatment of AEs after 100 days should be reported.														

Abbreviations: AE=adverse event; aPTT=activated partial thromboplastin time; CR=complete response; sCR=stringent complete response; CRS= cytokine release syndrome; CT=computed tomography; D=Day; ECOG=Eastern Cooperative Oncology Group; ECG=electrocardiogram; EORTC-QLQ=European Organization for Research and Treatment of Cancer Quality of Life Questionnaire; EQ-5D-5L=EuroQol Five Dimension Questionnaire; FISH=fluorescence in situ hybridization; FLC=free light chain;

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HBV=hepatitis B virus; ICANS=immune-effector cell-associated neurotoxicity syndrome; ICE=immune effector Cell-associated Encephalopathy; ICF=informed consent form; INR=international normalized ratio; IPPI=investigational product preparation instructions; MRD=minimal residual disease; MRI=magnetic resonance imaging; MRU=medical resource utilization; MUGA=multiple-gated acquisition; PGIC=Patient Global Impression of Change; PGIS=Patient Global Impression of Severity; PRO=patient reported outcome; PT=prothrombin time; SIPP=site investigational product procedures manual; SOC=standard of care; SPEP=serum protein electrophoresis; UPEP=urine protein electrophoresis.

- a ICF must be signed before any study-related procedures are performed, and remains in effect even if the screening evaluation is not performed within the 28-day Screening Phase. Evaluations for eligibility determination performed outside the screening window may need to be repeated. For subjects who require a repeat apheresis, for assessments should be collected before the second apheresis. If the second apheresis falls outside of the 28 day window, all screening assessments (except bone marrow collection) must be repeated.
- b For subjects who discontinue the study before Day 100, including those who have not received an infusion of JNJ-68284528, the Day 100 assessments should be performed prior to withdrawal if feasible. Subjects who discontinue after Day 100 but before study completion should have urine and serum disease assessments performed prior to withdrawal if feasible at the time of discontinuation, unless performed within 14 days prior to discontinuation. Study completion is defined as 2 years after the last subject has received his or her initial dose of JNJ-68284528.
- c Post-treatment assessments to be obtained until progressive disease is documented or the start of subsequent anticancer therapy, with the exception of survival status and subsequent anticancer therapy, which are to be collected until study completion.
- d Disease characteristics cytogenetics (full karyotyping or FISH as well as molecular genetics [if applicable]), both of which may originate from prior to or during the screening period within 42 days before apheresis, or between apheresis and the conditioning regimen, as applicable. A pathologist/cytogeneticist should complete the cytogenetics data collection worksheet.
- e The first 6 subjects enrolled will be hospitalized for at least 2 weeks after infusion of JNJ-68284528. The requirement for hospitalization and local stay will be evaluated by the SET for subsequent subjects. 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.
- f Serology results performed as standard of care within 28 days prior to apheresis are acceptable; Hepatitis B: hepatitis B surface antigen (HBsAg), hepatitis B core antibody (anti-HBc), anti-HBs, HBV DNA quantification (for subjects who are anti-HBs positive without history of vaccination or-for subjects who are anti-HBs positive and anti-HBc positive); Monitor HBV-DNA, aspartate aminotransferase (AST)/ alanine aminotransferase (ALT) every 3 months for one year post-dose of JNJ-68284528. Hepatitis C: hepatitis C virus (HCV) antibody, HCV-RNA (for subjects who are anti HCV positive); human immunodeficiency virus (HIV) serology.
- g Immediately before the start of infusion, at the end of infusion, and 0.5, 1, 2 hours after end of infusion. Monitor until normalized after a CRS event.
- h Temperature will be checked at least twice a day up to Day 28. Subjects will be provided with a thermometer and instructed on the use of the thermometer and entering 2 temperatures including their maximum daily temperature in a diary. Diary will be reviewed at each visit, then collected on Day 28 and stored with subject source documents.
- i All subjects will be evaluated for immunoglobulin (Ig)G, IgA, IgM. Testing for IgD and IgE will only be performed for subjects with IgD and IgE-type myeloma.
- j UPEP sample collected as part of the standard of care and prior to the subject signing ICF may be used for analysis at the central laboratory.
- k Bone marrow morphology from an aspirate and core biopsy to be assessed locally at all time points. Additional bone marrow aspirate samples will be collected for biomarkers
- l Results from skeletal survey performed as routine follow-up within 42 days before start of apheresis may be used without these tests being repeated. The skeletal survey is to be performed by either roentgenography or low-dose CT scans without the use of IV contrast. If a CT is used it must be of diagnostic quality. Additional imaging (X-ray, CT, or MRI) will be performed as clinically indicated (eg, to document response or progression).
- m Extramedullary plasmacytomas should be assessed for all subjects with a history of plasmacytomas or if clinically indicated prior to the first dose of the conditioning regimen, by clinical examination or radiologic imaging.
- n Human immunodeficiency virus, hepatitis B, hepatitis C, human T-lymphotropic virus (HTLV), and other infectious diseases as applicable per local regulations

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- o PRO assessments to be collected every 28 days in the post-treatment Phase. For subjects with disease progression or who initiate subsequent anticancer therapy, PRO assessments should be collected every 16 weeks.
- p Subjects enrolled in the Phase 2 portion of the study will have the option of participating in pre-treatment and post-treatment semi-structured qualitative interviews.
- q Pre-infusion ICE test and handwriting sample should be performed before pre-medication with diphenhydramine
- r Medical resource evaluation data will be collected until Day 180 (±7 days).
- s Local laboratory assessments may be used under specified circumstances.

Table 5: Applicant - Time and Events Schedule for Pharmacokinetic and Biomarker Sampling

	Screening Phase	Apheresis	Cyclophosphamide and fludarabine conditioning regimen	JNJ-68284528 Infusion	Post Infusion (any subject who received infusion of JNJ-68284528 should continue all subsequent assessments) ^a and Post-treatment (Day 101 up to study completion)												At PD	At Study Completion for subjects without PD	
					Day 2	Day 3	Day 7 (± 1 day)	Day 10 (± 1 day)	Day 14 (± 1 day)	Day 21 (± 2 days)	Day 28 (± 2 days)	Day 42 (± 2 days)	Day 56 (± 2 days)	Day 78 (± 2 days)	Day 100 (± 2 days)	Day 184 (±7 days)			
	≤28 days prior to apheresis	Upon enrollment	Day -5,* -4, -3 (assessments may be conducted ≤72 hours predose) ^{b*}	Day 1 (Infusion)															
Pharmacokinetics																			
PK CAR positive T cell cellular blood sample ^c			X (prior to first dose of conditioning regimen [≤7 days])	Pre-dose (same day as dose of JNJ-68284528), Within 30 minutes Post EOI	24-hour post-EOI	X	X	X	X	X	X	X	X	X	X	X	X; then every 4 weeks up to 1 year	X	X
PK CAR transgene levels blood sample ^c			X (prior to first dose of conditioning regimen [≤7 days])	Pre-dose (same day as dose of JNJ-68284528), Within 30 minutes Post EOI	24-hour post-EOI	X	X	X	X	X	X	X	X	X	X	X	X; then every 4 weeks up to 1 year	X	X

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Table 5: Applicant - Time and Events Schedule for Pharmacokinetic and Biomarker Sampling

	Screening Phase	Apheresis	Cyclophosphamide and fludarabine conditioning regimen	JNJ-68284528 Infusion	Post Infusion (any subject who received infusion of JNJ-68284528 should continue all subsequent assessments) ^a and Post-treatment (Day 101 up to study completion)													At PD	At Study Completion for subjects without PD	
					Day 2	Day 3	Day 7 (± 1 day)	Day 10 (± 1 day)	Day 14 (± 1 day)	Day 21 (± 2 days)	Day 28 (± 2 days)	Day 42 (± 2 days)	Day 56 (± 2 days)	Day 78 (± 2 days)	Day 100 (± 2 days)	Day 184 (± 7 days)				
Soluble serum BCMA sample	≤28 days prior to apheresis	Upon enrollment	Day -5,* -4, -3 (assessments may be conducted ≤72 hours predose) ^{b*}	Day 1 (Infusion)	24-hour post-EOI	X	X	X	X	X	X	X	X	X	X	X	X; then every 4 weeks up to 1 year	X	X	
PK CAR transgene levels bone marrow sample			X (prior to first dose of conditioning regimen [≤7 days])									X		X			X			
PK CAR positive T cell bone marrow sample			X (prior to first dose of conditioning regimen [≤7 days])									X		X			X			
ADA sample (serum) ^{c,d}				Pre-dose					X		X		X	X	X	X	X	X	X	
Biomarker Sampling																				
Immuno-phenotyping (whole blood)		X	X (prior to first dose of conditioning regimen [≤7 days])	Pre-dose	24-hour post-EOI	X	X	X	X	X	X	X	X	X	X	X	X; then every 4 weeks up to 1 year	X	X	X ^e
Flow cytometry, (aspirate) (bone marrow) ^e			X (prior to first dose of conditioning regimen [≤7 days])									X		X			X	X	X	

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Table 5: Applicant - Time and Events Schedule for Pharmacokinetic and Biomarker Sampling

	Screening Phase	Apheresis	Cyclophosphamide and fludarabine conditioning regimen	JNJ-68284528 Infusion	Post Infusion (any subject who received infusion of JNJ-68284528 should continue all subsequent assessments) ^a and Post-treatment (Day 101 up to study completion)													At PD	At Study Completion for subjects without PD				
					Day 2	Day 3	Day 7 (± 1 day)	Day 10 (± 1 day)	Day 14 (± 1 day)	Day 21 (± 2 days)	Day 28 (± 2 days)	Day 42 (± 2 days)	Day 56 (± 2 days)	Day 78 (± 2 days)	Day 100 (± 2 days)	Day 184 (± 7 days)							
	≤28 days prior to apheresis	Upon enrollment	Day -5,* -4, -3 (assessments may be conducted ≤72 hours predose) ^{b*}	Day 1 (Infusion)																			
CyTOF (aspirate) (bone marrow) ^{e,f}			X (prior to first dose of conditioning regimen [≤7 days])																	X	X	X	
CyTOF/PBMC/Plasma (whole blood)		X					X	X	X	X	X			X		X	X	X	X	X	X	X ^{e,f}	
MRD (aspirate) (bone marrow)			X (prior to first dose of conditioning regimen [≤7 days])		Sample should be collected: <ul style="list-style-type: none"> For all dosed subjects at Day 28, and at 6 months, 12 months, 18 months (Day 520), and 24 months (Day 744) (± 16 days) regardless of the status of disease measured in blood and urine. For subjects with suspected CR at the time of CR and then yearly for subjects that remain on study up to disease progression. 																		
Cytogenetics (bone marrow)			X (prior to first dose of conditioning regimen [≤7 days])																	X			
Replication Competent Lentivirus (RCL) (whole blood)			X (prior to first dose of conditioning regimen [≤7 days])	Pre-dose	At approximately 3, 6, and 12 months; then yearly for 15 years post infusion																		
Cytokine profiling ^g (serum)			X (prior to first dose of conditioning regimen [≤7 days])	Pre-dose, 2hrs Post (±10 minutes)	X	X	X	X	X	X	X	X	X	X	X	X							

Table 5: Applicant - Time and Events Schedule for Pharmacokinetic and Biomarker Sampling

	Screening Phase	Apheresis	Cyclophosphamide and fludarabine conditioning regimen	JNJ-68284528 Infusion	Post Infusion (any subject who received infusion of JNJ-68284528 should continue all subsequent assessments) ^a and Post-treatment (Day 101 up to study completion)													At PD	At Study Completion for subjects without PD
					Day 2	Day 3	Day 7 (± 1 day)	Day 10 (± 1 day)	Day 14 (± 1 day)	Day 21 (± 2 days)	Day 28 (± 2 days)	Day 42 (± 2 days)	Day 56 (± 2 days)	Day 78 (± 2 days)	Day 100 (± 2 days)	Day 184 (± 7 days)			
	≤28 days prior to apheresis	Upon enrollment	Day -5,* -4, -3 (assessments may be conducted ≤72 hours predose) ^{b*}	Day 1 (Infusion)															

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

^a For subjects who discontinue the study post JNJ-68284528 infusion before Day 100, the Day 100 assessments should be performed if feasible.

^b Window for start of conditioning regimen: Day -7 to Day -5

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

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

^e Sample should also be collected at suspected CR

^f Sample should be collected at 12 months, relative to Day 1, for subjects that achieve CR/sCR and remain on study.

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

FDA Assessment

FDA agrees with the Applicant’s description of the study design and the patient population. CARTITUDE-1 is phase 1/2b single arm study evaluating CARVYKTI in adult patients with RRMM, whose prior regimens included a PI, an IMiD, and an anti-CD38 antibody and who had disease progression on or after the last prior regimen. The key eligibility criteria included patients with RRMM who had received at least 3 prior lines of therapy with limited treatment options. However, the restrictive exclusion criteria from other BCMA products allowed to enroll an overall healthier pre-treated patient population

The phase 1b and 2 data were pooled together, as the study procedures were consistent during both phases, including dose range and population enrolled.

Study Endpoints

The Applicant's Description:

Primary Endpoint: Given the single-arm nature of Study MMY2001, the primary endpoint chosen for this study is ORR, defined as the proportion of subjects who achieve a PR or better according to the IMWG response criteria, as assessed by the IRC across both Phase 1b and Phase 2 treated at the targeted RP2D dose level. Given the potential bias that may be present in investigator assessment, a 3-member IRC was empaneled to assess disease status for the primary efficacy endpoint of ORR, comprised of clinical experts without direct involvement in study conduct. Their assessment was based on clinical judgement guided by objective IMWG consensus recommendations for MM treatment response criteria. (Durie 2006; Durie 2015; Rajkumar 2011; Kumar 2016) and was used as the primary endpoint.

Secondary and Other Endpoints: The primary endpoint of ORR was supported by the additional major secondary endpoints of very good partial response (VGPR) or better rate, minimal residual disease (MRD) negativity rate, and clinical benefit rate (CBR, defined as minimal response or better according to the IMWG criteria), assessed similarly. Other protocol-specified time-to-event efficacy endpoints included DOR, Time to response (TTR), PFS, OS, and HRQoL.

VGPR or better response rate (sCR+CR+VGPR) is defined as the proportion of subjects who achieve a VGPR or better response according to the IMWG criteria, as assessed by IRC.

Minimal residual disease negativity rate is defined as the proportion of subjects who have negative MRD by bone marrow aspirate at any timepoint after initial dose of cilta-cel and before disease progression or starting subsequent therapy or retreatment with cilta-cel.

Clinical benefit rate is defined as the proportion of subjects with best response of minimal response (MR) or better (including sCR, CR, VGPR, PR, and MR).

Duration of response (DOR) is calculated among responders (with a PR or better response) from the date of initial documentation of a response (PR or better) to the date of first documented evidence of progressive disease, as defined in the IMWG criteria.

Time to response (TTR) is defined as the time between date of the initial infusion of cilta-cel and the first efficacy evaluation that the subject has met all criteria for PR or better.

Progression-free survival (PFS) defined as the time from the date of the initial infusion of cilta-cel to the date of first documented disease progression, as defined in the IMWG criteria, or death due to any cause, whichever occurs first.

Overall survival (OS) is measured from the date of the initial infusion of cilta-cel to the date of the subject's death.

Subjects HRQoL (symptoms, functioning, and overall well-being) during Phase 2 was assessed using the following PRO instruments: European Organization for Research and Treatment of Cancer quality of life questionnaire (EORTC QLQ)-C30, EuroQol Five Dimension Questionnaire (EQ-5D-5L), Patient Global Impression of Change (PGIC), Patient Global Impression of Severity (PGIS), and 4 single items from EORTC QLQ-MY20.

FDA Assessment

FDA agrees with the description of the primary efficacy endpoint of ORR and secondary endpoints. FDA has the following comments regarding the secondary endpoints:

- MRD evaluated by next-generation sequencing (NGS [Adaptive clonoSEQ version 2.0 Assay]) was a secondary endpoint on the trial. The primary analysis for MRD negative response was based on a threshold of $10e-5$ for those with CR/sCR. However, the clinical significance of MRD negativity post CAR T therapy remains unknown.
- The FDA recommended a minimum follow up period of least 9- 12 months at the time of submission for an adequate assessment of durability. Data cutoff in February 2021 allowed for at least 9 months follow up for DOR data.
- Time to event endpoints OS, PFS (secondary endpoints in this study) are uninterpretable as there is no randomization and no comparator arm. These endpoints will not be reviewed and will not be included in the label.
- As with time to event endpoints, interpretation of PROs is challenging in uncontrolled clinical trials, as it is unclear to what extent the outcomes can be attributed to the treatment effect of regimen versus underlying disease and patient characteristics. For reasons described, these data were not evaluated as part of the application review.

Statistical Analysis Plan and Amendments

The Applicant's Description:

The Statistical Analysis Plan (SAP) for Study MMY2001 was finalized and submitted to FDA on 23 September 2020. The study SAP reflected changes in the protocol (via protocol amendments) such as addition or updation of analyses as deemed clinically relevant and/or statistically appropriate based on emerging data, and updation of analysis terminology according to Estimand framework in ICH E9(R1).

The primary analysis for all efficacy endpoints was performed based on the IRC assessment of disease status using Modified intent-to-treat (mITT) analysis set, which is the same as the All Treated analysis set, since all subjects treated received cilta-cel at the targeted RP2D level (ie, within the RP2D dose range). Efficacy assessments were also performed by the sponsor using a computerized algorithm, following the IMWG Criteria (Kumar 2016) as well as per Investigator assessment.

The primary endpoint was ORR, defined as the proportion of subjects who achieved a PR or better according to the IMWG response criteria (Kumar 2016), as assessed by IRC. The ORR and its 2-sided 95% Clopper-Pearson exact confidence interval (CI) were presented, and the p-value from a 1-sided exact binomial test for the null hypothesis of $ORR \leq 30\%$ was provided. The study was to be considered successful if the lower bound of the 95% confidence interval exceeds 30%. Sensitivity analyses of ORR was performed using disease response based on the computerized algorithm and investigator assessment according to the IMWG response criteria (Kumar 2016). The prevalence -adjusted-bias-adjusted kappa (PABAK) statistics (Byrt 1993) and its 95% CI was calculated for agreement between IRC assessment and computerized algorithm assessment for response (response [PR or better] vs. no response). Supplementary analyses of ORR were performed based on the All Enrolled analysis set, and for subjects who received the cilta-cel product that met all the pre-specified release criteria based on the mITT analysis set, which is the same as the All Treated analysis set.

The major secondary endpoints of VGPR or better rate, MRD negativity rate, and CBR were analyzed similarly. The time-to-event efficacy endpoints, including DOR, PFS, and OS were estimated using the Kaplan-Meier method. Time to response was analyzed using descriptive statistics.

Subgroup analyses for ORR were analyzed for age, gender, race, International Staging System (ISS), number of lines of prior therapy, prior autologous stem cell transplant, prior allogenic stem cell transplant, refractoriness to prior therapy or last line of prior therapy, myeloma type, ECOG performance score prior to cilta-cel infusion, percentage of bone marrow plasma cells at baseline, cytogenetic risk groups, tumor BCMA expression at baseline, study site, and total CAR-positive viable T cells infused. A Forest plot is provided for the subgroups. [Source: Mod2.7.3/Fig2 (ORR)].

Subjects HRQoL (symptoms, functioning, and overall well-being) during Phase 2 was assessed using the following patient reported outcome (PRO) instruments: EORTC QLQ-C30, EQ-5D-5L, PGIC, PGIS, and 4 single items from EORTC QLQ-MY20. Patient reported outcome instruments were scored based on the instrument developer guidelines with no imputation for missing data. Change from baseline and the proportion with improvement based on meaningful change thresholds were calculated.

FDA Assessment

The Applicant's description of the SAP is acceptable. The null hypothesis threshold of 30% was based on a reference ORR of 30% based on results of daratumumab monotherapy in R/R MM. This threshold was agreed upon by the clinical review team in May 2018. The primary efficacy endpoint, ORR, was calculated along with the 2-sided 95% exact Clopper-Pearson confidence interval (CI). The p-value from a 1-sided exact binomial test with significant level of 0.025 for the null hypothesis of ORR \leq 30% was to be provided.

No interim analysis was performed.

With over 100 patients treated with CARVYKTI in the Phase 1/2 portion of the study, the study achieves 90% power to test the null hypothesis that the ORR is 30% vs. the alternative hypothesis that the ORR is 50% at a 1-sided alpha level of 0.025.

Protocol Amendments

The Applicant's Description:

There were 4 global amendments to the original protocol dated 11 April 2018, all of which are fully described in the study protocol. Key amendments are summarized in Table 6. The Applicant does not believe that any of the amendments impacted the integrity of the study or the interpretation of the results.

Table 6: Applicant - Overall Reasons for Study 68284528MMY2001 Protocol Amendments

Amendment Number (Date), subjects enrolled	Main Rationale for Amendment
Amendment 1 20 August 2018, (n=2)	The overall reason for the amendment was to add collection of additional safety information and information and provide an additional inclusion criterion (lower limit of (b) (4)) that may increase potential for successful manufacture of cilta-cel).
Amendment 2 11 March 2019, (n=21)	The overall reason for the amendment was to expand the number of subjects enrolled in the Phase 1b portion, update CRS and neurotoxicity management guidelines, update the CRS and neurotoxicity grading system to align with ASTCT guidelines published in 2019, and to add clarity to targeted sections of the protocol.
Amendment 3 30 July 2019, (n=64)	The overall reason for the amendment was to transition the study into the Phase 2 portion, describe the role of the IRC, add the MRU assessment, and to add clarity to targeted sections of the protocol.
Amendment 4 20 March 2020 (n=113)	The overall reason for the amendment was to add other neurotoxicities as a safety risk and implement additional monitoring and risk minimization measures for cilta-cel.
COVID-19 Appendix 30 April 2020 (n=113)	The overall reason for this appendix was to provide guidance on study conduct as a result of the COVID-19 pandemic.

Keys: ASTCT=American Society for Transplantation and Cellular Therapy; CRS=cytokine release syndrome; IRC=Independent Review Committee; MRU=medical resource utilization; n= Number of subjects enrolled in the study on the date of the protocol amendment.

FDA Assessment

The Applicant's description of protocol amendments is acceptable.

8.1.2 Study Results

Compliance with Good Clinical Practices

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 Good Clinical Practice (GCP)s and applicable regulatory requirements. The study protocol and amendments were reviewed by an Independent Ethics Committee or Institutional Review Board. Subjects 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 Code of Federal Regulations (CFR) governing the protection of human subjects (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).

FDA Assessment

The Applicant's description of compliance with good clinical practices is acceptable.

Financial Disclosure

Data:

All the 378 principal investigators and sub-investigators participating in Study MMY2001 were assessed for financial disclosures as defined in 21 CFR Part 54, and 1 investigator 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 biologics license application (BLA) submission for the investigator disclosing significant payments of other sorts and includes steps taken to minimize potential bias. Further details are provided in Section 17.2.

FDA Assessment

One US investigator disclosed significant payments for consulting honoraria exceeding \$25,000 USD which were unrelated to the conduct of the trial and investigational product. This investigator participated as a Principal Investigator, which screened 6 patients and enrolled/treated 3 patients in CARTITUDE-1. The Applicant states that there was no evidence of bias on the results. Due to the low number of patients enrolled on this site, the FDA agrees with the minimal potential bias of this financial disclosure.

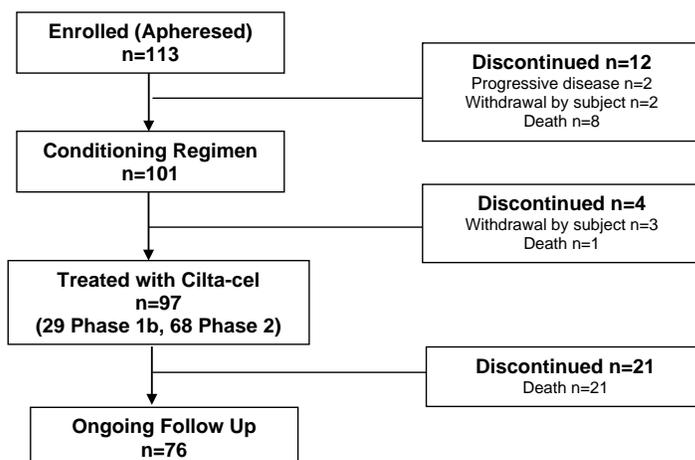
Patient Disposition

Data:

A total of 113 subjects were enrolled and underwent apheresis (All Enrolled or Intent-to-Treat [ITT] population). Ninety-seven subjects (85.8%) received a cilta-cel infusion (All treated or mITT population) at the RP2D (i.e., within the RP2D dose range).

Find the schematic presentation of subject disposition in Figure 3.

Figure 3: Applicant - Subject Study Disposition as of the Clinical Cutoff Date For Efficacy Update (11 February 2021); Study 68284528MMY2001



No subject was discontinued from the study due to inability to manufacture the cilta-cel drug product. At the time of the primary analysis (01 September 2020), the median follow-up for all 97 subjects was 12.4 months (range 1.5 months [subject died] to 24.9 months). At the time of the efficacy update (11 February 2021), the median duration of follow-up was 18.0 months.

The Applicant’s Position:

The MMY2001 study represents a highly refractory population of patients with MM who have very limited treatment options. The primary efficacy population of 97 subjects who received a cilta-cel infusion (All Treated analysis set) form the basis of the BLA review concerning the benefit of cilta-cel in the intended population, and these results are presented in this document, the proposed United States prescribing information (USPI), the MMY2001 Clinical Study Report (CSR), Summary of Clinical Efficacy, and Clinical Overview.

FDA Assessment

The FDA agrees with the Applicant’s position statement and the Subject Study Disposition as in Applicant Figure 3. At the time of the data cutoff date 02/11/2021, 37 out of the 113 enrolled patients either died (n=30) or otherwise discontinued from the study while 76 were still on study in the ongoing follow up. For efficacy analyses, the FDA utilized the cut-off date of February 11, 2021.

Protocol Violations/Deviations

Data:

As of the 11 February 2021 clinical cutoff date for the efficacy update, all protocol deviations of eligibility criteria and those deviations that could impact subject safety or primary endpoints were considered major protocol deviations. Major protocol deviations were reported for 3 subjects (1 subject received disallowed concomitant treatment during bridging therapy, 1 subject required assessment(s) of extramedullary plasmacytoma not performed according to schedule per protocol, and 1 subject received subsequent anti-myeloma therapy without disease progression).

For protocol deviations due to the COVID-19 pandemic, the sponsor captured all potential deviations, including minor protocol deviations. A comprehensive report summarizing these findings and their impact on the study was generated and is included in Module 5.3.5.2. As of the 11 February 2021 data cutoff for the efficacy update, there have been no such major protocol deviations secondary to COVID-19 pandemic. The minor protocol deviations related to COVID-19 are captured in the ADDV dataset submitted in Module 5.3.5.2. [Source: Mod5.3.5.2]

The Applicant's Position:

The three major protocol deviations identified in the primary efficacy population were typical of those observed in clinical studies and did not lead to the exclusion of data from the analyses or impact the interpretation of the results.

FDA Assessment

Based on the efficacy cut-off date of February 11, 2021, there were three protocol deviations as stated above. Two deviations were reported in the initial Clinical Study Report and included a patient who received concomitant treatment with D-PACE during bridging therapy (IRB was notified). The impact of this protocol deviation on the bridging therapy and subsequent response is unclear. The second patient had an assessment of plasmacytoma 9 months post baseline. FDA agrees with the Applicant's position that these protocol deviations did not impact the interpretation of results.

Table of Demographic Characteristics

Data:

The median age of the 97 subjects who received cilta-cel infusion was 61 years (range 43 to 78 years). Men and women were treated in similar numbers (57 men [58.8%] and 40 women [41.2%]). The majority of subjects were White (71.1%) and 17.5% were Black or African American. Baseline ECOG scores assessed prior to cilta-cel infusion ranged from 0 to 2 with 39 subjects (40.2%) having an ECOG score of 0, 54 subjects (55.7%) having an ECOG score of 1, and 4 subjects (4.1%) having an ECOG of 2 prior to infusion.

The Applicant’s Position:

Subjects treated in Study MMY2001 are representative of the intended population of subjects with RRMM and limited treatment options.

FDA Assessment

Of the 97 efficacy-evaluable patients, the median age was 61 years (range: 43 to 78 years), 59% were male, 71% were white, and 18% were black. Most patients were reported to have an International Staging System (ISS) Stage I or II. Of the 91 patients for whom baseline cytogenetic data were available, high-risk cytogenetics (presence of t(4:14), t(14:16), or 17p13 del) were present in 24% of patients. Thirteen percent of the patients had extramedullary disease.

The Demographic Information for the phase 1b, phase 2, and all treated are in the Table below:

FDA Table 1: FDA - Demographics for All Treated analysis sets

	Phase 1b + Phase 2, N (%)
N	97
<65	62 (63.9%)
65-75	27 (27.8%)
>75	8 (8.2%)
Mean (STD)	62.0 (8.38)
Median (min, max)	61 (43, 78)
Female	40 (41.2%)
Male	57 (58.8%)
American Indian or Alaska native	1 (1.0%)
Asian	1 (1.0%)
Black or African American	17 (17.5%)
Native Hawaiian or Other Pacific Islander	1
White	69 (71.1%)
Multiple	0

Not reported	8 (8.2%)
Ethnicity n (%)	
Hispanic or Latino	6 (6.2%)
Not Hispanic or Latino	85 (88.7%)
Not reported	6 (6.2%)

(Source: FDA Analysis of ADSL dataset)

Other Baseline Characteristics (eg, disease characteristics, important concomitant drugs)

Data:

All 97 treated subjects (100.0%) had detectable disease at baseline, with immunoglobulin (Ig)G the most common Ig isotype presenting in 57 subjects (58.8%). The median time from diagnosis of MM to enrollment in the study was 5.94 years (range: 1.6 to 18.2 years) and the median number of prior lines of therapy was 6 (range: 3 to 18); 17 subjects (17.5%) received exactly 3 prior lines of therapy and a majority (49 subjects [50.5%]) received 5 or more prior lines. Forty-one subjects (42.3%) of the AllTreated analysis set subject population were refractory to 5 or more agents (including at least 2 PIs, at least 2 IMiDs, and at least 1 anti-CD38 monoclonal antibody), referred to as “penta refractory”. Ninety-six subjects (99.0%) were refractory to their last prior therapy. Eighty-five subjects (87.6%) were refractory to the 3 major classes of therapeutic agents for MM (PI, IMiD, and anti-CD38 monoclonal antibody therapy), referred to as “triple-refractory.” (Table 7)

Among the 17 subjects who received exactly 3 prior lines of therapy, all were refractory to the last line of prior therapy and 12 were triple refractory to PI, IMiD, and anti-CD38 antibody.

Table 7: Applicant - Summary of Refractory Status to Prior Multiple Myeloma Therapy; All Treated Analysis Set (Study 68284528MMY2001)

	Phase 1b	Phase 2	Phase 1b + Phase 2
Analysis set: all treated	29	68	97
Refractory at any point to prior therapy	29 (100.0%)	68 (100.0%)	97 (100.0%)
Refractory Status			
PI+IMiD+anti-CD38 antibody	25 (86.2%)	60 (88.2%)	85 (87.6%)
Any PI	25 (86.2%)	62 (91.2%)	87 (89.7%)
Any IMiD	28 (96.6%)	67 (98.5%)	95 (97.9%)
Any anti-CD38 antibody	29 (100.0%)	67 (98.5%)	96 (99.0%)
At least 2 PIs + at least 2 IMiDs + 1 anti-CD38 antibody	9 (31.0%)	32 (47.1%)	41 (42.3%)
Refractory to last line of prior therapy	28 (96.6%)	68 (100.0%)	96 (99.0%)
Refractory to			

Table 7: Applicant - Summary of Refractory Status to Prior Multiple Myeloma Therapy; All Treated Analysis Set (Study 68284528MMY2001)

	Phase 1b	Phase 2	Phase 1b + Phase 2
Bortezomib	15 (51.7%)	51 (75.0%)	66 (68.0%)
Carfilzomib	21 (72.4%)	42 (61.8%)	63 (64.9%)
Ixazomib	7 (24.1%)	20 (29.4%)	27 (27.8%)
Lenalidomide	22 (75.9%)	57 (83.8%)	79 (81.4%)
Pomalidomide	22 (75.9%)	59 (86.8%)	81 (83.5%)
Thalidomide	1 (3.4%)	7 (10.3%)	8 (8.2%)
Daratumumab	27 (93.1%)	67 (98.5%)	94 (96.9%) ^b
Isatuximab	2 (6.9%)	5 (7.4%)	7 (7.2%)
(b) (4) ^a	1 (3.4%)	0	1 (1.0%)
Elotuzumab	1 (3.4%)	18 (26.5%)	19 (19.6%)
Panobinostat	3 (10.3%)	5 (7.4%)	8 (8.2%)

Key: IMiD=Immunomodulatory agent; PI=proteasome inhibitor.

^a (b) (4) is an investigational (b) (4).

^b Two additional subjects were refractory to other anti-CD38 antibodies

Note: Refractory to each medication refers to refractory to any medication-containing line.

Note: Percentages are calculated with the number of subjects in the all treated analysis set as denominator.

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Of the 91 subjects with baseline cytogenetic data reported, 23 subjects (23.7%) had at least 1 high-risk abnormality, most commonly Del17p which was present in 19 subjects (19.6%).

The Applicant's Position:

Baseline disease characteristics of the primary efficacy population were representative of the intended patient population studied to evaluate the unmet needs and treatment patterns for RRMM, Thus, the clinical activity seen for cilta-cel in Study MMY2001 are believed to be generalizable to the RRMM patient population that will be encountered in clinical practice.

FDA Assessment

CARTITUDE-1 was a Phase 1b-2, single arm, open label study evaluating CARVYKTI in patients with relapsed and/or refractory multiple myeloma who had received at least 3 lines of prior therapy. All patients received at least three lines of therapy. Out the 97 treated, there were 17 patients that received only 3 lines of therapy; 16 patients received only 4 lines of therapy; 15 patients received only 5 lines of therapy; 49 patients (50.5%) received over 5 lines of therapy.

The majority of the patients in this study received more lines of therapy (4 or more) and the population that received 3 prior lines of therapy is limited to only 17 total patients. Due to the overall small sample size, the data for this subgroup is limited.

FDA agrees that the baseline disease characteristics are representative of the RRMM population. However, FDA notes the following with regards to the demographics of the patients enrolled on the trial.

- The majority of the patients enrolled on the trial were White and of the non-Hispanic/Latino ethnicity. Although the percentage of Blacks was 18% and appropriately represented in the study, the total number of Black patients (N=18) is limited as a result of the overall total small sample size (N=97) patients.
- The median age of the patients on the trial was 61 years, much younger than the median age of 69 years old for patients diagnosed with MM in the US. Only 8 patients enrolled on the trial were >75 years old. The younger age enrolled likely reflects the stringent eligibility criteria requirement for the trial

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Data:

Apheresis, conditioning therapy, premedication, and cilta-cel were all administered per protocol in the controlled environment of a qualified clinical site by qualified healthcare professionals and the administrations were recorded in the eCRFs for each subject.

Apheresis and Bridging Therapy:

A total of 113 subjects (Phase 1b: 35; Phase 2:78) were enrolled and underwent apheresis. Bridging therapy was administered to 73 of 97 subjects (75.3%) between apheresis and initiation of the conditioning regimen. Proteasome inhibitors were used in 44 subjects (45.4%), IMiDs in 26 subjects (26.8%), and anti-CD38 antibodies in 15 subjects (15.5%). The agents most commonly used as bridging therapies ($\geq 20\%$ of subjects in the All-Treated analysis set) included dexamethasone: 62 subjects (63.9%), bortezomib: 26 subjects (26.8%), cyclophosphamide: 22 subjects (22.7%), and pomalidomide: 21 subjects (21.6%). Among the 73 subjects who received bridging therapy, 33 subjects (45.2%) had a decrease in tumor burden between screening and cilta-cel infusion which was expected to be transient due to the nature of this highly refractory population as described in the MAMMOTH study ([Gandhi 2019](#)). Among those subjects who experienced a tumor burden decrease, 15 subjects (20.5%) experienced a decrease of $>50\%$. Despite the decrease in tumor burden in some subjects, no subjects achieved complete response (CR) or better while on bridging therapy.

Thirty-six of the subjects (49.3%) who received bridging therapy experienced an increase in tumor burden between screening and cilta-cel infusion. Twenty-five subjects (34.2%) experienced an increase in tumor burden of $\geq 25\%$. Two of the subjects (2.7%) who

received bridging therapy did not experience a change in tumor burden as a result of bridging therapy and additional 2 subjects (2.7%) were not evaluable for assessment of change in tumor burden.

Baseline efficacy assessments occurred after bridging therapy and prior to the start of conditioning regimen.

Conditioning Regimen: Among the All-Enrolled subjects, 101 (89.4%) received the conditioning regimen of cyclophosphamide and fludarabine infusion and 97 subjects (85.8%) went on to receive cilta-cel. Four subjects (3.5%) received conditioning regimen but did not receive cilta-cel infusion. Two of these subjects refused future study treatment, 1 subject withdrew due to AE and 1 subject died.

Cyclophosphamide and Fludarabine Conditioning: Subjects received a conditioning regimen of cyclophosphamide 300 mg/m² IV and fludarabine 30 mg/m² IV in 3 daily doses beginning on Day 7 to Day -5. The median cumulative dose of cyclophosphamide infusion was 897.8 mg/m² (range: 748 to 946 mg/m²). The median cumulative dose of fludarabine infusion was 89.6 mg/m² (range: 45 to 95 mg/m²).

Twenty-three subjects (23.7%) had a delay in their cyclophosphamide or fludarabine conditioning regimen. These delays were due to AE for 11 subjects (11.3%) and 12 subjects (12.4%) for other reasons (eg, personal reasons, re-apheresis, rapid disease progression, etc). One subject died after the start of the conditioning regimen and prior to infusion of cilta-cel.

Cilta-cel Infusion: The first subject in the Phase 1b portion of the study was dosed with cilta-cel on 27 August 2018. The first subject in the Phase 2 portion of the study was dosed with cilta-cel on 02 July 2019.

Cilta-cel infusion occurred on Study Day 1, which was 5 to 7 days after the start of the conditioning regimen. Ninety-seven subjects received a single dose of cilta-cel (Phase 1b: 29; Phase 2: 68) at the targeted dose of 0.75×10^6 CAR-positive viable T cells/kg (range: $0.5\text{-}1.0 \times 10^6$ CAR-positive viable T cells/kg). The median time from initial apheresis to cilta-cel infusion was (b) (4) days (range: (b) (4) days). Receipt to release (R2R) for cilta-cel is a median 29 days (range: 23-64 days). Forty-nine subjects (50.5%) received the cilta-cel infusion within (b) (4) days after apheresis. The median total number of CAR-positive viable T cells infused was 54.30×10^6 (range: 23.5×10^6 to 93.1×10^6 cells). The median cilta-cel dose administered was 0.709×10^6 cells/kg (range: 0.51×10^6 to 0.95×10^6 cells/kg).

One subject in Phase 2 received a single dose of cilta-cel at the target dose followed by a retreatment at the same dose after confirmed disease progression.

Cilta-cel infusion was delayed for 1 subject (1.1%) and interrupted for 2 subjects (2.1%). In these 2 cases, infusion of cilta-cel was interrupted in order to flush the line (one due to a line malfunction and a second due to the study drug being sluggish requiring flushes to push it along). Both subjects received the planned dose of cilta-cel despite infusion interruption. Cilta-cel infusion was delayed 9 days after start of lymphodepletion to allow for clinical observation after a positive rhinovirus test in 1 subject. With exception of this 1 infusion delay, all infusions occurred within 5 to 7 days after the start of conditioning regimen as per protocol, and no subject required re-administration of the conditioning regimen due to the delay. No infusions were delayed, interrupted, or aborted due to AEs.

Subjects Receiving Cilta-cel Not Meeting Release Specifications: Four subjects (4.1%) received infusions of cilta-cel product that did not meet all pre-specified release criteria.

For 2 of these subjects, the single product bag manufactured contained a lower than specified dose, requiring 2 product infusion bags to supply the required dose. The 2 other subjects received infusions of cilta-cel which did not meet specifications of the percentage (b) (4) cells and/or natural killer (NK) cells. One subject's batch contained (b) (4) cells (release specification was (b) (4)) and contained 10% NK cells (release specification was (b) (4) NK (b) (4)). The second subject's batch contained (b) (4) cells (release specification was (b) (4)).

Note that the specification for (b) (4) and NK cells was changed during the course of the study based on clinical experience with MM subjects. The referenced specification ranges listed were in place at the time of product release.

Per protocol, infusion of the product which did not meet release specification was evaluated based on the benefit and risk to the subject. In all cases, it was determined that

the potential overall benefit outweighed the potential risk of infusion. The products were infused per the pre-defined Exceptional Releasing Procedure and all subjects received cilta-cel within target range of 0.5 to 1.0 x 10⁶ CAR-T cells/kg. Of these 4 subjects who received treatment under the Exceptional Release Procedure, 2 subjects had VGPR and 2 had sCR per IRC (based on IMWG criteria), with no clinically significant safety signals.

Rescue medications: Not applicable

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 CAR-T studies.

FDA Assessment

Bridging therapy was administered for 73 patients (75.3%). None of the patients achieved CR while on bridging therapy. FDA agrees with the Applicant's evaluation of patients post bridging therapy.

There were 113 patients who completed apheresis. The timing from apheresis to product infusion was (b) (4) days (range of (b) (4) days). There were 101 patients that received the conditioning regimen and 97 patients who received the study drug.

There were 16 patients who did not receive cilta-cel due to progressive disease (N=2), death (N=9) or withdrawal from the study (N=5).

In this study the product that met specifications for CARTITUDE -1 study is referred to as cilta-cel and the product specification that were introduced after the study was completed and during the review of the BLA phase is referred to as CARVYKTI (the commercial product or product that is to be marketed). Successful manufacturing at 100% success was noted for all patients receiving cilta-cel, the product that met specifications for the CARTITUDE-1 study. There were limitations in assessing the manufacturing failure rates for CARVYKTI. Samples for the 16 patients who did not receive cilta-cel for clinical reasons of progressive disease, death or withdrawal from CARTITUDE-1 study were not available to evaluate for the post-hoc product release specifications for CARVYKTI. For these reasons the manufacturing failure rates for CARVYKTI (the to be marketed product) could not be assessed in all 113 leukapheresed patients but was assessed in the 97 patients who were considered efficacy evaluable by virtue of having received cilta-cel.

Of the 97 patients, 80 patients received the product that met the post-hoc specifications for CARVYKTI. Of the remaining 17 patients, who failed to receive CARVYKTI, 10 failed to meet these specifications and 7 patients did not have adequate samples to complete

the analysis for product specifications. Thus, there were limitations in assessing the manufacturing failure rates for CARVYKTI (the commercial product or product that is to be marketed) in the leukapheresed population which impacts the information conveyed in the label, in that the assessment of manufacturing failure rate of CARVYKTI is limited to the 97 efficacy evaluable patients who received cilta-cel.

Efficacy Results – Primary Endpoint (Including Sensitivity Analyses Data):

The primary analysis population for efficacy and safety was the All Treated Population. The ORR (PR or better) as assessed by the IRC based on IMWG criteria (Table 8) was:

- All Treated Population (n=97): 97.9% (95% CI: 92.7% to 99.7%)
- All Enrolled Population (n=113): 84.1% (95% CI: 76.0% to 90.3%)

Table 8: Applicant - Overall Best Response Based on Independent Review Committee (IRC) Assessment; All Treated Analysis Set (Study 68284528MMY2001)

	Phase 1b + Phase 2	
	n (%)	95% CI for %
Analysis set: all treated	97	
Best response		
Stringent complete response (sCR)	78 (80.4%)	(71.1%, 87.8%)
Complete response (CR)	0	(NE, NE)
MRD-negative CR/sCR ^a	42 (43.3%)	(33.3%, 53.7%)
Very good partial response (VGPR)	14 (14.4%)	(8.1%, 23.0%)
Partial response (PR)	3 (3.1%)	(0.6%, 8.8%)
Minimal response (MR)	0	(NE, NE)
Stable disease (SD)	0	(NE, NE)
Progressive disease (PD)	1 (1.0%)	(0.0%, 5.6%)
Not evaluable (NE)	1 (1.0%)	(0.0%, 5.6%)
Overall response (sCR + CR + VGPR + PR)	95 (97.9%)	(92.7%, 99.7%)
P-value	<0.0001	
Clinical benefit (Overall response + MR)	95 (97.9%)	(92.7%, 99.7%)
VGPR or better (sCR + CR + VGPR)	92 (94.8%)	(88.4%, 98.3%)
CR or better (sCR + CR)	78 (80.4%)	(71.1%, 87.8%)

Keys: CI=confidence interval.

^a MRD-negative CR/sCR. Only MRD assessments (10⁻⁵ testing threshold) within 3 months of achieving CR/sCR until death/progression/subsequent therapy (exclusive) are considered.

Note: Response was assessed by independent review committee (IRC), based on International Myeloma Working Group (IMWG) consensus criteria (2016).

Note: Percentages are calculated with the number of subjects in the all treated analysis set as denominator.

Note: Exact 95% confidence intervals are provided.

Note: One-sided p-value from exact binomial test for the null hypothesis of overall response rate ≤30% is presented.

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The observed ORR was consistent across all subgroups examined when assessment was based on the IRC data including evaluation by age, sex, race, total CAR-T positive cells infused, baseline ECOG performance score, baseline ISS staging, lines of prior therapy, stem cell transplant history, disease type, refractory status, cytogenetic risk groups, baseline bone marrow plasma cells, baseline BCMA expression, and baseline plasmacytoma status, and study site.

A sensitivity analysis of ORR in the All Treated analysis set assessed by computerized algorithm (93.8%) was consistent with the primary analysis using IRC assessment according to IMWG response criteria (97.9%).

The Applicant's Position:

Treatment with single infusion cilta-cel among the heavily pre-treated population of subjects in Study MMY2001 (at least 3 prior lines of therapy, 99.0% of subjects refractory to last line of therapy, 87.6% triple refractory, 42.3% penta-refractory) was highly effective with 96.9% of subjects achieving a PR or better. The ORR observed in this study was higher than the approved therapies for this patient population, which have response rates of approximately 30% belonging to the classes of IMiD, PI, anti-CD38 antibody, inhibitor of nuclear transport, and anti-BCMA antibody drug conjugate and 73% for the anti-BCMA CAR-T therapy (Table 1). The ORR across multiple clinically relevant subgroups, including subjects receiving exactly 3 prior lines of therapy, was consistent with the overall study population.

FDA Assessment

The study met the objective that ORR was greater than the prespecified null hypothesis rate of 30%.

Among the 97 patients receiving cilta-cel, 95 patients (97.9%) response of PR or better based on IRC assessment. The lower limit of the 95% exact Clopper-Pearson confidence interval for ORR was 92.7% which is well above the pre-specified null hypothesis rate of 30%. Among the 95 responders, 76 (78.4%) patients had a best response of sCR, 16 (16.5%) patients had a best response of VGPR, and 3 (3.1%) patients had a best response of PR.

The VGPR and sCR rates are different from that in sponsor's CSR as the clinical review team's adjudication of the response status were changed for two patients. Two patients (Subject (b) (6) and Subj (b) (6)) were downgraded to VGPR from sCR based on the following adjudication.

It was noted that there were patients who were adjudicated as sCR as best response and who did not have bone marrow biopsy performed at the time of or within the protocol specified visit window of response adjudication. The Applicant stated that the protocol did not have a protocol specified visit "window" for repeating bone marrow procedures for CR/sCR response adjudication after a bone marrow biopsy showing <5% plasma cells had been documented.

Of the 78 (80.4%) patients who were adjudicated as sCR by IRC, all patients had a bone marrow demonstrating sCR: 67 patients had bone marrow assessments within 30

days or less of sCR response, 8 patients had bone marrow assessments within 31-60 days of sCR response, and 3 patients had bone marrow assessments >60 days of sCR response. These responses (those who had a BM assessment over the 30 days post a biochemical assessment) were noted to be durable and therefore not re-adjudicated

However, it was also noted that 17/78 had bone marrow assessments prior to the sCR date (biochemical assessment). Nine patients had these assessments within 30 days, and 8 outside of the 30-day window (7 within 31-60 days, and one after 60 days). This finding was discussed with the Applicant. They were notified that they had not provided evidence to support that if these evaluations are done in advance, that the bone marrow assessments will continue to remain negative. If no evidence could be provided, then FDA may downgrade the response, where the best response date would change to a further time period when a subsequent marrow was performed.

In a single arm trial, clarity is needed to understand the impact of bone marrow assessments that are performed before a patient achieves a CR biochemically. Subsequent bone marrow data was provided for the 8 patients and FDA adjudicated the response in relation to the timing of the assessments.

These 9 patients who were out of the 30-day window and with a bone marrow assessment prior to a biochemical response were re-adjudicated and two patients did not have subsequent marrow evaluations performed. Therefore, two patients were downgraded to VGPR and patients with subsequent marrow evaluations post a biochemical response had the best response date changed. Therefore, this did not impact the ORR, but only the downgrading of patients and durability dates. Below is the Table of the FDA assessment of the responses.

FDA Table 2: FDA - Best response Based on Independent Review Committee (IRC) Assessment for Cilta-cel Treated Analysis Set

	Phase 1b + Phase 2, N (%)
	97
ORR (sCR + CR + VGPR + PR), n (%)	95 (97.9%)
95% CI	(92.7%, 99.7%)
sCR rate, n (%)	76 (78.4%)
95% CI	(68.8%, 86.1%)
CR rate, n (%)	0
95% CI	(NE, NE)
VGPR rate, n (%)	16 (16.5%)
95% CI	(9.7.%, 25.4%)
PR rate, n (%)	3 (3.1%)
95% CI	(0.6%, 8.8%)

Progressive disease, n (%)	1 (1.0%)
Not evaluable, n (%)	1 (1.0%)

Source: FDA Analysis based on ADEFF dataset

FDA Table 3 shows the best response based on IRC for *All Enrolled Analysis Set*. The ORR for this set (n=113) is 84.1% (95% CI: 76.0%, 90.3%).

FDA Table 3: FDA - Best response per IRC for *All Enrolled Analysis Set*.

	Phase 1b + Phase 2, N (%)
	113
ORR (sCR + CR + VGPR)	95 (84.1%)
95% CI	(76.0%, 90.3%)
sCR rate, n (%)	76 (67.3%)
95% CI	(57.8%, 75.8%)
CR rate, n (%)	0
95% CI	(NE, NE)
VGPR rate, n (%)	16 (14.2%)
95% CI	(8.3%, 22%)
PR rate, n (%)	3 (2.7%)
95% CI	(0.6%, 7.6%)

Source: FDA Analysis based on ADEFF dataset

The subgroup analysis for ORR is considered exploratory and given the small numbers no conclusion can be made about the efficacy in subgroups.

As stated above, a subset of patients from those who received cilta-cel received CARVYKTI (n=80). The efficacy for this subset of patients showed a similar magnitude of efficacy, despite the smaller sample size with an ORR of 98.75% [95%CI 93.23, 99.96%].

Data Quality and Integrity Data:

See also Section 8.1.2, Compliance with GCP.

Beginning in 2020, protocol-specific contingency measures were implemented in response to the COVID-19 pandemic to assure the safety of MMY2001 participants, maintain compliance with GCP, and minimize risks to study integrity. A COVID-19 Protocol Appendix was developed and submitted to Health Authorities and trial sites in all

countries involved in the study (see Table 6). 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 subject safety, and adequacy of data completeness or quality.

The Applicant's Position:

It is the Applicant's position that there are no issues related to data quality and integrity.

FDA Assessment

FDA agrees that there no issues related to data quality and integrity.

Efficacy Results – Secondary and other relevant endpoints

Data:

Depth and Duration of Response: Deep and durable responses were induced by ciltacel as demonstrated by a VGPR or better rate of 94.8% in the AllTreated analysis set. Seventy-eight subjects (80.4%) achieved a CR or better, with all adjudicated as stringent CR (sCR) as of the 11 February 2021 data cut.

At a median follow-up of 18.0 months, median DOR was 21.8 months (95% CI [21.8 months, NE]) at the time of the 11 February 2021 clinical cutoff. The probabilities of the responders remaining in response at 9 months and 12 months were 79.7% (95% CI: 70.0%, 86.5%) and 72.9% (95% CI: 62.6%, 80.9%), respectively. The median DOR for subjects achieving CR/sCR has not yet reached.

MRD Negativity Rate: MRD was monitored in subjects using next generation sequencing (NGS) on bone marrow aspirate DNA (clonoSEQ, version 2.0). Baseline bone marrow aspirates were used to define the myeloma clones, and post-treatment samples will be used to evaluate MRD negativity.

At the time of 11 February 2021 clinical cutoff, 96 subjects (99.0%) had samples available for MRD evaluation (baseline and post-baseline sample). However, not all samples were evaluable. Identification of the clone at the baseline sample failed in samples from 20 subjects (20.6%) and samples from 2 subjects had an unsuccessful assay run.

Thirty-six of the 97 subjects were not evaluable for MRD mainly due to failure to identify the MM clone at baseline or samples that were not evaluable at the 10^{-5} level of sensitivity. In the 61 subjects with evaluable samples, a high rate of MRD negativity at the sensitivity threshold of 10^{-5} (56 subjects; 91.8%) was observed corresponding to 57.7% of the total population of 97 subjects and 42 subjects (43.3%) achieved MRD-negative CR/sCR.

Time to response: The median time to response was rapid, occurring after 1 month of treatment. The median time to first response was 0.95 months (range: 0.9 to 10.7 months), median time to best response was 2.6 months (range: 0.9 to 15.2 months), and median time to CR or better was 2.63 months (range: 0.9 to 15.2 months).

Progression-free Survival and Overall Survival: At a median duration of follow-up of 18.0 months, median PFS was 22.8 months (95% CI: 22.8, NE) and the median PFS for subjects who achieved CR/sCR has not yet reached. At 12 months post cilta-cel infusion, 76.3% of subjects (95% CI: 66.5% to 83.6%) remained progression free and median OS has not been reached. The 12 months OS rate was 87.6% (95% CI: 79.2% to 92.8%). While data continue to mature, available data suggests that there may be a positive association between depth of response and favorable PFS and OS.

Patient Reported Outcomes: Patient reported outcomes were consistent with observed clinical findings. Subjects in Phase 2 completing the PRO evaluations reported clinically meaningful improvements in HRQoL, functional status and symptoms as measured by the cancer-specific EORTC-QLQ30 and general health EQ-5D-5L. Specifically, decrement in global health status (GHS), at Day 7 was consistent with the onset of cilta-cel side effects with a mean change of -9.7 (95%CI: -15.1 to -4.4). Improvements in GHS paralleled clinical improvements with a mean change of -0.6 (95% CI: -5.9 to 4.7) at Day 28 and steadily improving over time to 19.9 (95% CI: 7.8 to 32.1) by Day 352. Subject's assessment of their physical function followed a similar trend as GHS. After an initial decline in physical functional scores between Day 1 and Day 7, a steady increase was seen through Day 352 (mean change 6.4 [95% CI: -4.1 to 16.9]). Subjects experienced reduction in the pain (Day 352 mean change -17.6 [95% CI: -32.6 to -2.6]) and fatigue (Day 352 LS mean change -17.6 [95% CI: -32.6 to -2.6]) subscales and an improvement in the future perspective subscale (Day 352 LS mean change 24.2 [95% CI: 15.5 to 33.0]).

Subjects who participated in the qualitative interviews stated that their pre-treatment expectations for symptom improvement had been met or were exceeded and described their experience with cilta-cel as better than their previous treatment experiences.

The Applicant's Position:

Administration of cilta-cel resulted in deep, durable, and rapid responses in this population of subjects with heavily pre-treated RRMM. No difference in response was seen across all subgroups analyzed demonstrating the potential for wide applicability across various subsets of MM patients. With a median DOR and a median PFS of 21.8 months and 22.8 months, respectively, available data suggests a durable response with positive long-term outcomes.

FDA Assessment**FDA Table 4: FDA - DOR results of Responders.**

	Phase 1b	Phase 2	Phase 1b +2, n (%)
Number of patients achieved PR or better, n	29	66	95
Number of events, n (%)	10 (34.5%)	21 (31.8%)	31 (32.6%)
Progression	8 (27.6%)	14 (21.2%)	22 (23.2%)
Death	2 (6.9%)	7 (10.6%)	9 (9.5%)
Censored, n (%)	19 (65.5%)	45 (68.2%)	64 (67.4%)
DOR (months)			
median	21.8	NE	21.8
95% CI	(15.9, NE)	(NE, NE)	not reported
Follow-up (months)			
median	24.0	19.8	23.6
95% CI	(22.8, NE)	(17.9, NE)	(22.8, 26.2)
Percentage of patients with response duration (%) (95% CI)*			
≥6 months	93.1% (75.1%,	81.6% (69.9%,	85.2% (76.2%, 90.9%)
≥9 months	86.2% (67.3%,	76.7% (64.4%,	79.7% (70.0%, 86.5%)
≥12 months	72.1% (51.8%,	73.5% (60.8%,	72.9% (62.6%, 80.9%)

Source: FDA Analysis based on ADEFF dataset

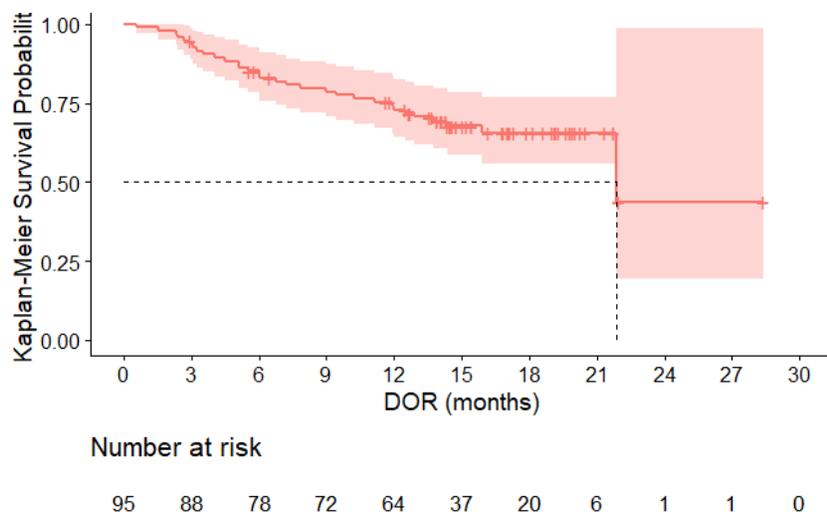
For the analysis of DOR per IRC, the overall median was 21.8 months. Its 95% CI is not reported in the table because the upper limit cannot be estimated and the lower limit estimate is the same as the median, 21.8 months. Per the statistical reviewer, the median estimate and its 95% CI lower limit are the same because the last two events happened at 15.9 and 21.8 months, leading the survival probabilities to 0.656 and 0.437, respectively, which are right above and below 0.5. This makes the median DOR and its lower limit both at 21.8 months. Therefore, due to the lack of long-term follow-up data, the observed event time of 21.8 months is the only time point whose survival probability falls within the 95% CI of 0.5.

Assessment of DOR based on IRC assessment of best response achieved is presented graphically in Figure 3. The group of CR or better did not reach its median DOR at the time of clinical cut off.

The DOR for sCR is included in the PI. Additionally, the DOR for responders with VGPR or better has also been included in the label, since there was minimal uncertainty

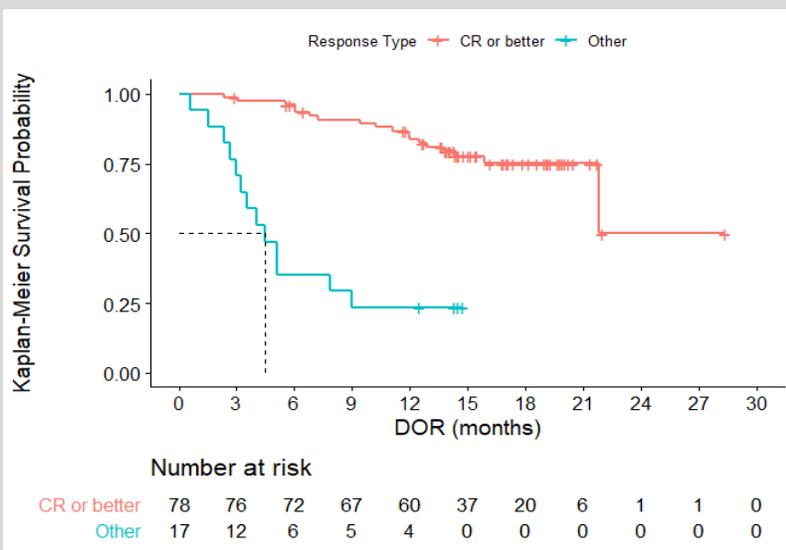
regarding the reliability on the DOR as only two patients were downgraded from sCR to VGPR.

FDA Figure 1: FDA - Kaplan-Meier curves of DOR for responders per IRC in All Treated Analysis set.



(Source: FDA statistical reviewer's analysis, Figure 3 on page 24 of Efficacy update)

FDA Figure 2: FDA - Kaplan-Meier curves of DOR for responders achieving CR versus Other responders per IRC in All Treated Analysis Set.



(Source: FDA statistical reviewer's analysis; Figure 4 of Efficacy update, page 25).

MRD:

For the MRD data, FDA noted that there were significant gaps in the MRD data. There was a 20.6% (20/97) calibration failure rate and missing data. The high rate of calibration failure rates raises concerns regarding the reliability of the MRD response assessments for regulatory purposes. The rate of calibration failure is higher than the reported rates with the clonoseq NGS assay. These significant issues noted have an impact the strength and validity of the MRD results. Therefore, the MRD data was not considered robust to support inclusion in the USPI.

PFS/OS:

The PFS and OS was not reviewed for this file. Time to event endpoints are uninterpretable in a single arm trial due to the lack of a comparator arm comparator arm.

Patient Reported Outcomes: PRO cannot be reliably assessed in a single arm open label trial. These results will not be included in the label.

Dose/Dose Response

Data:

Not Applicable as a single dose was tested.

The Applicant's Position:

[To the Applicant: Insert text here]

FDA Assessment

Not applicable. Agree with above. A single dose was tested in this study.

Durability of Response

Data:

See discussion of DOR above under secondary and other relevant endpoints.

The Applicant's Position:

[To the Applicant: Insert text here]

FDA Assessment

As above.

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 18.0 months for the All Treated analysis set, the data are yet to be mature to provide a reliable estimate for median OS. The 12-month OS rate for the All-Treated analysis set was 87.6%. Please refer to Section 8.1.2 for DOR and OS results.

The Applicant's Position:

The persistence of the efficacy is indicated by the durability of the response. The median DOR was 21.8 months. Furthermore, the probabilities of the responders remaining in response at 9 months and 12 months were 79.7% (95% CI: 70.0 to 86.5%) and 72.9% (95% CI: 62.6% to 80.9%), respectively. These data suggest that ORR and DOR is likely to predict clinical benefit (eg, OS) in this MM population with disease that has become refractory to available therapies.

FDA Assessment

For regulatory purpose, key elements of effectiveness or clinical benefit in a single arm trial are the magnitude of overall response and persistence of response. The overall and complete response rates after treatment with CARVYKTI in relapsed and refractory multiple myeloma patients and the durability of response based on 23.6 months (median follow up) after first response in the overall population and in the sCR subset provides evidence of a meaningful clinical benefit.

Efficacy Results – Secondary or exploratory COA (PRO) endpoints

Data:

The results for secondary and PRO endpoints are discussed above.

The Applicant’s Position:

The clinical outcome assessment analyses were typical of other studies for RRMM and appropriate to collect evidence of safety and tolerability of cilta-cel. Subjects in Phase 2 completing the PRO evaluations reported significant improvements in functional status and wellbeing as measured by the cancer-specific EORTC-QLQ30 and general health EQ-5D-5L. Subjects also experienced reduction in pain and fatigue with an improvement in future perspective. The qualitative interviews suggested the majority of patients reported that pre-treatment expectations for cilta-cel had been met or exceeded and their experience with cilta-cel was better than with prior MM treatments. All of these measures suggest improved HRQoL following treatment with cilta-cel.

FDA Assessment

No conclusions can be made on HRQoL based on PRO assessments in a single arm trial. Comparison of HRQoL during cilta-cel treatment cannot be compared to prior therapies for MM as stated by the Applicant given the retrospective nature of such a comparison that is subject to bias and lack of control over other factors e.g., stage of disease that impact such assessments. There was also no agreement reached between the FDA and the Applicant on PRO assessments prior to BLA submission. Hence, PRO data will not be included in the label. The clinical reviewer did not independently assess/verify PRO data.

Additional Analyses Conducted on the Individual Trial

Not Applicable.

FDA Assessment

Not applicable.

8.1.3 Integrated Review of Effectiveness

Not Applicable.

FDA Assessment

Not applicable.

8.1.4 Assessment of Efficacy Across Trials

Not Applicable.

FDA Assessment

Not applicable.

8.1.5 Integrated Assessment of Effectiveness

Data:

Refer to efficacy results in Section 8.1.2 for assessment of effectiveness.

The Applicant's Position:

Treatment with single infusion cilta-cel among the heavily pre-treated population of subjects in Study MMY2001 (at least 3 prior lines of therapy, 99.0% of subjects refractory to last line of therapy, 87.6% triple refractory, 42.3% penta-refractory) was highly effective with 97.9% of subjects achieving a PR or better. The ORR observed in this study was higher than the approved therapies with different mechanisms of action (IMiD, PI, anti-CD38 antibody, inhibitor of nuclear transport, and anti-BCMA antibody drug conjugate) in this patient population, which have response rates of approximately 30% (Table 1). Additionally, the ORR and sCR rate of cilta-cel observed in this study (97.9% and 80.4%, respectively) was higher than the anti-BCMA CAR-T therapy recently approved by the FDA (ide-cel) which had a reported ORR of 73% and a sCR rate of 28%. The ORR across multiple clinically relevant subgroups, including age, was consistent with the overall study population.

The depth of response (VGPR or better of 94.8% and sCR of 80.4%) is also unprecedented for this highly refractory patient population and may translate to improved long term outcomes in these patients. Improved long term outcomes correlate with achievement of sCR ([Kapoor 2013](#)). Median PFS was 22.8 months (95% CI: 22.8, NE) and at 12 months post cilta-cel infusion, 76.3% of subjects remained progression free. For subjects who achieved a sCR, median PFS has not yet reached. Although the median OS has not been reached, the high percentage of subjects achieving sCR is anticipated to translate to a favorable OS.

Additionally, time to response was rapid with a median time to first response of 0.95 months and time to best response of 2.6 months.

Patient reported outcomes were consistent with clinical observations, with subjects reporting improvements in symptoms, functional status and HRQoL following treatment with cilta-cel.

FDA Assessment

FDA agrees that cilta-cel was effective in the population studied, with 97.9% of patients achieving a PR or better and that these results indicate clinical benefit in the overall refractory patient population.

FDA's assessment differs with the Applicants assessment on the following aspects:

- The sCR rate by FDA analysis is 78.4% compared to 80.4% reported by the Applicant as two patients were downgraded to VGPR as discussed above.
- FDA does not agree with the Applicant's conclusions based on cross trial comparisons.
- The small number of patient enrolled limit conclusions regarding effectiveness in the subgroups including racial, ethnic and older adult subgroups.
- Time to event endpoint such as OS and PFS as well as PRO results are uninterpretable without a control arm. No conclusions can be drawn from the reported PFS, OS as well as PRO outcomes.

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 1b-2 Study MMY2001. The safety evaluation focuses on the All Treated Population, consisting of 97 subjects enrolled at 15 study sites in the United States who received cilta-cel. All subjects enrolled in the United States received cilta-cel at the recommended Phase 2 dose of 0.75×10^6 CAR-positive viable T cells/kg (range, 0.5 to 1.0×10^6 CAR-positive viable T cells/kg).

Additional supporting data are provided from 2 sources that enrolled identical or closely related study populations, treatment regimens, and safety data collection methods as were used for the main cohort of Study MMY2001:

- Study MMY2001 Japan cohort (N=9 treated). Study MMY2001 included a country-specific amendment to the Phase 2 portion of the study to evaluate population-specific safety and efficacy in a Japanese subject population.
- Study MMY2003 (N=18 treated as of the cutoff date of 23 July 2020) is a Phase 2, multicohort, open-label, multicenter study to determine the safety and efficacy of cilta-cel (alone or with other treatment regimens) in adult subjects with MM in various clinical settings. Multiple cohorts are being run in parallel with unique patient populations of unmet medical need enrolled.

The Applicant's Position:

The safety data supporting this BLA submission for cilta-cel comes primarily from 97 subjects from Study MMY2001 and is supported by 9 subjects from Japan cohort from Study MMY2001 and 18 subjects from Study MMY2003. The Applicant believes that the safety experience with the 124 subjects treated with cilta-cel, including the 97 subjects in the target indication population of RRMM with a median follow-up of 12.42 months in Study MMY2001 (as of the 01 September 2020 cutoff of the pivotal CSR), along with the supplementary safety data from the additional 27 subjects in the Japan cohort and Study MMY2003 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.

FDA Assessment

The key materials used for the safety review included:

- The BLA application electronic submission
- Applicant submissions in response to the review team's information requests (IRs)
- Proposed labeling of JNJ62284528
- Published literature
- Prior regulatory history
- Review of adverse event reports and response to IRs submitted to IND 18080 which has the cilta-cel studies

The clinical review of safety was primarily based upon analysis of 97 patients in the CARTITUDE-1 study (JNJ68284528MMY2001 or MMY2001 study; USA cohort) at the primary data cutoff of September 1, 2020. The 97 patients include those who received a dose of cilta-cel irrespective of whether study product met the final commercial specification criteria; all patients received product within the approved dose range of $0.5\text{--}1.0 \times 10^6$ viable CAR-T cells/kg and product that met clinical study release specification criteria. Per the final CMC analysis, 17 of 97 patients in CARTITUDE-1 were deemed as having manufacturing failures either because they received drug product that did not meet product release specifications or for which there were insufficient data to confirm product

release specifications for the commercial product i.e., CARVYKTI. The cilta-cel analysis datasets (ADaM datasets) were used for the safety analysis. Analyses by the clinical reviewer were performed using JMP 14.3. All narratives and case report forms (CRFs) were reviewed for all deaths and majority of adverse events of special interest (AESI) especially neurologic toxicity (NT) that occurred in the primary safety population. Adverse events (AEs) were coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 23.0, and AE severity was graded using the National Cancer Institute's (NCI) Common Toxicology Criteria for Adverse Events (CTCAE) version 5.0 except for cytokine release syndrome (CRS) and immune effector cell associated neurotoxicity syndrome (ICANS) that were graded using the 2019 ASTCT (American Society of Transplant and Cellular Therapy) criteria (Lee 2019). Some AEs are presented throughout this review as grouped terms as defined by the review team. The complete list of FDA's grouped terms is presented in APPENDIX A.

Safety data on 97 patients from the 120-day safety update for CARTITUDE-1 with a data cutoff of February 11, 2021, 9 patients in the Japan cohort of CARTITUDE-1 and 18 patients in the CARTITUDE-2 (68284528MMY2003) study were reviewed to follow up on existing toxicities in the CARTITUDE-1 study and to ensure that new and/or unusual toxicities reported in CARTITUDE-1 or CARTITUDE-2 were captured. Additionally, safety data presented by the Applicant in response to safety team's IRs from study CARTITUDE-4 (68284528MMY3002 or MMY3002 study) were also reviewed.

- CARTITUDE-2 is an ongoing, non-randomized multi-cohort study of cilta-cel that includes patients with previously untreated, and relapsed/refractory myeloma. CARTITUDE-4 is an ongoing, randomized control trial of cilta-cel versus 1 of 2 standard chemotherapy regimens in patients with relapsed/refractory myeloma with 1-3 prior lines of therapy including an IMiD and a PI. Since the dosing of cilta-cel in these trials is similar to dosing used in CARTITUDE-1, we deemed it reasonable to review some safety data from these trials especially those pertaining to rarer toxicities like Guillain-Barre syndrome, parkinsonism that have occurred following cilta-cel infusion. No specifics of safety data in ongoing trials of cilta-cel were included in the label.
- The term ciltacabtagene autoleucel (cilta-cel) refers to the non-proprietary name of the anti-BCMA CAR-T drug product used in the CARTITUDE studies (all 97 patients in CARTITUDE-1 plus patients in other ongoing trials) while CARVYKTI is the proprietary name used to describe the anti-BCMA CAR-T drug product that meets commercial release specifications in CARTITUDE-1 (n=80 in CARTITUDE-1). As stated above, 17 of 97 patients in CARTITUDE-1 were deemed to be manufacturing failures and hence are considered to have received cilta-cel but not CARVYKTI. Although only 80 patients received CARVYKTI, safety data on all 97 patients who received cilta-cel is included in the analysis and in the label, as patients who received CARVYKTI make-up for substantial proportion of those who

received cilta-cel and we therefore felt it was reasonable to extrapolate safety of cilta-cel to those who received CARVYKTI.

8.2.2 Review of the Safety Database

Overall Exposure

Data:

Primary Safety Data

Though not defined as part of study treatment, apheresis was a mandatory study intervention required to manufacture cilta-cel. Enrollment into the study (N=113) was defined as the day of apheresis.

Study treatment included both the conditioning regimen of cyclophosphamide and fludarabine followed by cilta-cel infusion. Among the 113 enrolled subjects, 101 subjects received conditioning regimen, and 97 (85.8%) subjects received conditioning regimen followed by cilta-cel infusion.

The median cilta-cel dose administered was 0.709×10^6 cells/kg (range, 0.51×10^6 to 0.95×10^6 cells/kg) and the median total number of CAR-positive viable T cells infused was 54.30×10^6 (range, 23.5×10^6 to 93.1×10^6 cells). The median time from initial apheresis to cilta-cel infusion was 47 days (range, 41 to 167 days).

Supportive Safety Data

1. Study MMY2001-Japan Cohort

Thirteen subjects had been enrolled (apheresed) in this cohort, and 9 subjects received the conditioning regimen followed by cilta-cel infusion (the All Treated Population). At the time of clinical cutoff (1 September 2020), the median duration of follow-up was 2.4 months (range, 0.9 to 5.2 months), including 3 subjects with ≥ 3 months of follow-up. Enrollment is completed for this cohort.

2. Study 68284528MMY2003

As of the 23 July 2020 clinical cutoff date, 39 subjects had been enrolled into Study MMY2003 and underwent apheresis. Four subjects (10.3%) discontinued the study after apheresis but before starting the conditioning regimen, including 1 subject who died during this period. Seventeen subjects had completed apheresis and were awaiting completion of cilta-cel product manufacturing at the time of clinical cutoff.

Eighteen subjects completed the conditioning regimen and received cilta-cel infusion (in the All Treated Population). Thirteen of the 18 subjects were enrolled into Cohort A. The 5 remaining subjects treated with cilta-cel were enrolled into Cohort B (n=1), Cohort C (n=2), and Cohort D (n=2). The median duration of follow-up was 1.6 months (range, 0.1 to 5.2 months); 5 subjects had ≥ 3 months of follow-up.

One subject had cilta-cel infusion delayed for 21 days due to a delay in cilta-cel shipment from the sponsor to the study site and for completion of a quality investigation before product release. This delay required that the conditioning regimen be readministered. Cilta-cel infusion was postponed by 8 days for another subject due to an AE (non-coronavirus disease (COVID)-19 infection).

The Applicant's Position:

A total of 124 subjects were treated and evaluated to assess the safety of cilta-cel. Ninety-seven subjects received an infusion of cilta-cel in Study MMY2001 with a median duration of follow-up of 12.4 months. Supportive safety information is provided for 9 subjects from the Japan cohort of Study MMY2001 and 18 subjects from Study MMY2003. The Applicant will continue to characterize safety of these subjects with ongoing follow-up.

FDA Assessment

Ninety-seven patients in the CARTITUDE-1 study (USA cohort) at the primary data cutoff of September 1, 2020, served as the primary population that informed cilta-cel safety. As stated previously, patients who received cilta-cel in the CARTITUDE-1 Japan cohort and study CARTITUDE-2 did not serve as the primary population for characterization of safety given the short follow-up that most of these patients had had. Additionally, study CARTITUDE-2 has different cohorts that differ in their baseline characteristics than the population in study CARTITUDE-1 e.g., line of therapy thus limiting the safety interpretability and benefit-risk assessment across studies CARTITUDE-1 and CARTITUDE-2. There was no integrated assessment of safety.

For special adverse events of interest e.g., parkinsonism, cranial nerve palsies, neuropathy etc., data from studies CARTITUDE-2 and CARTITUDE-4 (ongoing randomized trial) were incorporated into the safety assessment and to inform labeling to better help characterize these serious toxicities for healthcare providers and patients despite differences in study population. CARTITUDE-1 (USA cohort) was carried out in 2 phases-1b and 2. All 97 patients received cilta-cel in the same dose range and essentially had similar baseline characteristics of a relapsed/refractory myeloma population. Hence, no distinction was made between the study phases for the purpose of safety analyses.

All 97 patients in CARTITUDE-1 received cilta-cel in the proposed dose range of 0.5-1.0 x 10⁶ viable CAR-T cells/kg. Duration from apheresis to cilta-cel infusion is as per the Applicant's analysis. At the time of BLA submission, 4 patients were deemed to have out

of specification (OOS) product. Of these 4 patients, 2 patients were stated to have OOS product only because they received cilta-cel in 2 bags rather than 1. From a safety analysis standpoint, the two patients who received cilta-cel in 2 bags are not considered protocol deviations from the clinical safety and efficacy perspective. The remaining 2 patients had OOS product due to percentage of natural killer (NK cells) (b) (4) cells. For the purposes of safety, all 4 patients were included in the analyses since none of the deviations in the OOS product were deemed to impact safety (please also see above discussion on why 17 patients despite being deemed to have manufacturing failures due to product specification issues were still included in the safety analyses).

Relevant characteristics of the safety population:

Data:

All 97 treated subjects (100.0%) had detectable disease at baseline, with IgG the most common Ig isotype presenting in 57 subjects (58.8%). The median time from diagnosis of MM to enrollment in the study was 5.94 years (range: 1.6 to 18.2 years) and the median number of lines of prior therapy was 6 (range: 3 to 18). Of the 91 subjects with baseline cytogenetic data reported, 23 subjects (23.7%) had at least one high-risk abnormality, most commonly Del17p which was present in 19 subjects (19.6%).

Supportive Safety Data

1. Study MMY2001-Japan Cohort

All 9 subjects had detectable disease at baseline, with IgG the most common Ig isotype presenting in 8 of 9 subjects (88.9%). The median time from initial diagnosis of MM to enrollment in the study was 5.41 years (range, 3.8 to 11.3 years). Six subjects (66.7%) had high cytogenetic risk at baseline, most commonly Del17p (5 subjects [55.6%]). Baseline plasma cell count based on bone marrow biopsy/aspirate was ≤ 30 for 7 subjects (77.8%), >30 to <60 for 1 subject (11.1%), and ≥ 60 for 1 subject (11.1%).

Subjects received a median of 5 lines (range, 3 to 7 lines) of prior therapy for MM. All subjects had received prior treatment with a PI, an IMiD, and an anti-CD38 antibody therapy. Eight of 9 subjects (88.9%) were triple-refractory, 2 subjects (22.2%) were penta-refractory, and all 9 subjects were refractory to their last line of prior therapy.

2. Study 68284528MMY2003

All 18 subjects had detectable disease, with IgG the most common Ig isotype presenting in 11 subjects (61.1%). The median time from initial diagnosis of MM to enrollment was 2.60 years (range, 0.6 to 7.7 years). Subjects received a median of 2 lines of prior therapy (range, 1 to 12) for MM which varied as expected across the various cohorts; 10 subjects

(55.5%) received fewer than 3 prior lines. All subjects (100%) received a prior PI and an IMiD therapy; 11 subjects (61.1%) received anti-CD38 antibody therapy. Five subjects (27.8%) were penta-exposed (at least 2 PIs, at least 2 IMiDs, and 1 anti-CD38 antibody), and 2 subjects (11.1%) had received an antibody-drug conjugate targeting BCMA.

The Applicant’s Position:

Overall, subjects enrolled into Study MMY2001 (main and Japan Cohort) and Study MMY2003 had demographic and baseline disease characteristics representative of target population with RRMM (see also Section 8.1.2).

FDA Assessment

The baseline demographics of the primary population (USA cohort CARTITUDE-1 study) for safety analyses is shown in FDA Table 5 below.

FDA Table 5: FDA- Demographic Characteristics of Primary Safety Population: CARTITUDE-1

Demographic Group	Analysis population N = 97 (%)
Age	
<65	62 (64)
>=65	35 (36)
<75	86 (89)
>=75	11 (11)
Mean (SD)	62 (8.4)
Median (Range)	61 (43–78)
Sex	
M	57 (59)
F	40 (41)
Race	
Total	97 (100)
White	69 (71)
Black or African American	17 (18)
Not reported	8 (8)
American Indian or Alaska Native	1 (1)
Asian	1 (1)
Native Hawaiian or other Pacific Islander	1 (1)

Demographic Group	Analysis population N = 97 (%)
Ethnicity	
Total	97 (100)
Not Hispanic or Latino	85 (88)
Hispanic or Latino	6 (6)
Not reported	6 (6)
ECOG Performance Status Score at Baseline	
Total	97 (100)
1	54 (56)
0	39 (40)
2	4 (4.1)

Source: FDA Analysis of ADSL dataset

All 97 patients had received an IMiD, a PI and an anti-CD38 antibody as required by the protocol; majority had received an alkylating agent (97%; 94/97) and steroids. Ninety percent (87/97) had received an ASCT and about half of patients (48%; 47/97) had received prior radiotherapy. The percentage of patients with prior anthracycline, elotuzumab and panobinostat use was 28%, 24% and 11% respectively. Patients were heavily pre-treated with a median of 6 prior lines of therapy (range 3-18).

Adequacy of the safety database:

Data and Applicant's Position:

At the time of clinical cutoff, median duration of follow-up for 97 subjects in the pivotal Study MMY2001 and 9 subjects in the Japan Cohort of the Study MMY2001, was 12.42 months (range 1.5 months [subject died] to 24.9 months) and 2.4 months (range, 0.9 to 5.2 months), including 3 subjects with ≥ 3 months of follow-up, respectively. As of the 23 July 2020 clinical cutoff date, median duration of follow-up for 18 subjects in Study MMY2003 was 1.6 months (range, 0.1 to 5.2 months); 5 subjects had ≥ 3 months of follow-up. This safety database of 124 subjects in the All Treated Population who received a single cilta-cel infusion, is considered to be adequate to assess the safety of cilta-cel in the treatment of subjects with RRMM, to provide guidance regarding management of toxicities, and for an assessment of the benefit-risk profile of cilta-cel in the target population.

FDA Assessment

- *In general, the safety database of 97 patients in CARTITUDE-1 is considered adequate to identify the most common AEs, support the benefit-risk assessment*

and represent the target patient population. However, occurrence of rarer toxicities e.g., neurologic toxicity with parkinsonism, Guillain-Barre syndrome etc. seen in CARTITUDE-1 and/or other ongoing trials of CARVYKTI will require a larger patient population to better characterize these toxicities.

- *Cutoff of 1 year for consideration of treatment emergent NT as done for study CARTITUDE-1 is prudent given delayed onset of NT in some patients.*
- *A longer duration of follow-up for recurrent grade 3 or 4 cytopenias with attendant consequences of infection, bleeding etc. may be warranted in other trials of ciltacel.*

8.2.3 Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

Data:

The study centers/clinical sites for Study MMY2001 and Study MMY2003 were monitored by clinical research associates following study-specific monitoring plans for consistency. The data were reviewed by the Applicant's Data Management personnel in accordance with the prespecified Data Management Plan. The Applicant assigned physicians and clinical scientists responsible for conducting an ongoing clinical review. All available data as of the clinical cutoff date were included in the safety assessment presented in the BLA.

See also Section 8.1.2, for information related to data integrity/quality related to COVID-19 pandemic. As related to safety assessments, there were no issues related to the timelines for AE reporting and clinical monitoring of safety data by sponsor through the clinical cutoff. There were no meaningful changes in the AE rate after the emergence of 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.

FDA Assessment

- *FDA requested that Applicant submit new ADAE, ADSL, CRS and (includes combined CRS and NT dataset) datasets after adjudication of the safety data. Multiple revisions were made to these datasets with the latest one (at time of writing this memo) being submitted on 10.07.2021. Additional modification to these datasets has been requested given changes in death adjudication and failure of previously submitted datasets to accurately reflect the changes in adjudication.*

Version date: January 2020 (ALL NDA/ BLA reviews)

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.

- *The ADAE dataset contains the “FDAGRP” flag that reflects the term under which certain AEDECOD terms are grouped in order that a safety signal alluding to the same AE is not “diluted out” by use of different terms.*
- *Separate flags for patients receiving corticosteroids for CRS and NT termed STRCRSFL and STRNTFL were also placed by the Applicant in response to our guidance that patients with overlapping CRS and NT should be considered to have received steroids for both toxicities irrespective of the toxicity that corticosteroids were indicated for since steroids can ameliorate both toxicities.*
- *It was the clinical reviewer’s impression based on review of certain narratives (especially those pertaining to NT) and the corresponding AE data in the ADAE dataset that not all the AEs pertaining to a given toxicity were captured or were captured under a broad term that did not reflect the multiple events under that broad term e.g., parkinsonism listed in ADAE without all the AEs mentioned in the narrative e.g., stooped posture, shuffling gait, tongue protrusion etc. These terms in such instances were not also captured under any other term e.g., shuffling gait under gait disturbance. This question was posed to the Applicant (IR#44, Question#5). Applicant stated that investigators were permitted to record an overarching diagnosis as an AE in lieu of individual sign/symptoms e.g., difficulty swallowing was encompassed under parkinsonism. Thus, Applicant confirmed our impression of the issue as being correct.*

Overall, however, there were no major data issues that precluded a comprehensive safety review.

Categorization of Adverse Event

Data:

All AEs and special reporting situations, whether serious or non-serious, were to be reported from the time a signed and dated informed consent form (ICF) was obtained until 100 days after last administration of any study treatment or until the start of subsequent systemic anti-cancer therapy, if earlier. After 100 days, AEs that were considered to be related to study drug were to be reported until the end of the study. These TEAEs were included in the current analysis. Neurotoxicity irrespective of seriousness, and hepatitis B virus reactivation were to be reported during the first year after cilta-cel infusion. Second primary malignancy (SPM), irrespective of seriousness or investigator causality assessment were to be reported for the duration of the study.

All AEs were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) v5.0, with the exception of CRS and ICANS events.

In Phase 1b of the study, CRS was graded according to the criteria outlined by Lee et al (Lee 2014). In Phase 2 of the study, grading standards were updated to the American Society for Transplantation and Cellular Therapy (ASTCT) consensus grading system (Lee 2019). As a result, CRS events were re-characterized according to the new standard to allow evaluation across the entirety of the study. In an update to the Medical Dictionary for Regulatory Activities (MedDRA) v23.0, the preferred term CAR-T related encephalopathy syndrome (CRES) was replaced by ICANS. ICANS grading is derived from immune effector Cell-associated Encephalopathy (ICE) scores. As this change was implemented during study conduct, ICE scores were not collected for all subjects. ICE scores were collected for 2 subjects treated in Phase 1b and all subjects treated in Phase 2 of the study. As such, complete evaluation of ICANS as specified in the ASTCT consensus grading system across the entirety of the study is not possible.

Collection of handwriting sample and frequency of testing were added and implemented in the study procedures while the studies were on-going, so this neurotoxicity assessment results are not available for the subjects who experience micrographia before this addition was made.

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.

FDA Assessment

- *Applicant's categorization of AEs appears reasonable. Treatment emergent adverse events (TEAEs) are those AEs with onset (or worsening from baseline) within and including 100 days after last administration of any study treatment or subsequent anti-cancer therapy, whichever occurred first. Neurologic toxicity and Hepatitis B reactivation were required to be reported if they occurred within 1 year after cilta-cel infusion. Occurrence of any second primary malignancy during the study irrespective of time of occurrence is to be reported including in the long-term 15-year follow-up study. After 100 days following cilta-cel infusion only those AEs considered "related" to cilta-cel were collected till end of study.*
- *The definition of TEAE is in keeping with other CAR-T products till date. Although the protocol (version 4.0) does not specify NT within a year of study treatment as treatment-emergent, Applicant has requested reporting of such events given that some patients had delayed onset of NT.*
- *Definition of serious adverse event (SAE) includes one of the following serious criteria: fatal, life-threatening, requiring in-patient hospitalization or prolongs existing hospitalization, results in- persistent/significant disability or congenital anomaly/birth defect, suspected transmission of any infectious agent via a medicinal product or any other medically important event. SAEs were collected from informed consent till 100 days after cilta-cel infusion or subsequent anti-cancer therapy, whichever occurred earlier. AEs related to leukapheresis, bridging therapy and lymphodepleting chemotherapy were also collected.*
- *Change in grading system for CRS and NT during the different phases of CARTITUDE-1 did create some challenges. Even though CRS was regraded for phase 1b patients according to 2019 ASTCT grading as used for phase 2 patients, some neurological events were still considered as CRS symptoms. These were adjudicated as NT by the clinical reviewer. Since ICE scores were not collected during phase 1b of study CARTITUDE-1, these neurological events (where applicable) could not be appropriately graded by 2019 ASTCT grading for ICANS; however, all events were low grade (see also discussion on ICANS in AESI below).*
- *It is sometimes difficult to attribute causality to study product in a single-arm trial of CAR-T therapy given that it is preceded by lymphodepleting chemotherapy and in many instances by bridging therapy. Hence, generally, any AE occurring after cilta-cel were considered as an adverse drug reaction. However, unlike previously*

approved CAR-T products, non-specific neurologic/psychiatric symptoms (especially if they were low-grade) occurring in isolation without symptoms characteristic of ICANS e.g., insomnia were not considered to be ICANS related to cilta-cel given that these AEs can have multiple reasons unrelated to underlying CAR-T therapy. However, such AEs are counted towards the general AE tables reported in this memo and in the label.

Routine Clinical Tests

Data:

In addition to monitoring for AEs, safety evaluations included clinical laboratory data (hematology, clinical chemistry), vital signs (temperature, pulse rate, blood pressure, respiratory rate, pulse oximetry), 12-lead electrocardiogram (ECG)s, assessments of cardiac function by echocardiogram and/or multigated acquisition (MUGA) scans, and physical examinations. Hematology and clinical chemistry data were from local laboratories, and laboratory data were classified into Common Terminology Criteria (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 value on study (from treatment start to 100 days after last dose or the start of subsequent anti-cancer therapy, whichever was earlier) were analyzed. The assessment of prolonged cytopenia in Study MMY2001 (n=97) demonstrated that Grade 3 and Grade 4 cytopenia did not recover to below Grade 2 by Day 30 and Day 60.

The Applicant's Position:

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

FDA Assessment

Overall, the schedule of testing for CARTITUDE-1 is considered adequate for assessment of safety. Given occurrence of prolonged and recurrent grade 3 or 4 cytopenias in patients receiving cilta-cel, consideration for a longer period (up to a year) of formal collection and reporting of cytopenias in other trials of cilta-cel is warranted.

8.2.4 Safety Results

Primary safety data are summarized for the 97 subjects who received cilta-cel in Study MMY2001. Supportive safety data for 9 subjects from the Japan cohort of Study MMY2001 and 18 subjects from Study MMY2003 are described separately (Section 8.2.4.1), following the primary safety data. No new safety signals were identified

from the analysis of subjects from the Japan cohort of Study MMY2001 or Study MMY2003.

8.2.4.1 Pivotal Safety Data

Deaths

Data:

As off the clinical cutoff date of 1 September 2020, overall survival is a secondary efficacy endpoint in Study MMY2001, and survival data continues to be collected on all subjects including discontinuation after cilta-cel infusion. In all cases of subject death other than disease progression, the cause of death was to be reported as a Grade 5 AE for the duration of the study regardless of relatedness or causality. Subject deaths due to progressive disease, were also separately reported per protocol.

The summary of deaths that occurred during the study and the primary causes of death is provided in Table 9.

Table 9: Applicant - Summary of Deaths and Primary Cause of Death; All Treated Analysis Set (Study 68284528MMY2001)

	Phase 1b	Phase 2	Phase 1b + Phase 2
Analysis set: all treated	29	68	97
Total number of subjects who died during study	5 (17.2%)	9 (13.2%)	14 (14.4%)
Primary cause of death			
Adverse event	3 (10.3%)	6 (8.8%)	9 (9.3%)
Progressive Disease	2 (6.9%)	3 (4.4%)	5 (5.2%)
Total number of subjects who died within 30 days of the initial JNJ-68284528 infusion	0	0	0
Total number of subjects who died within 100 days of the initial JNJ-68284528 infusion	1 (3.4%)	1 (1.5%)	2 (2.1%)
Primary cause of death			
Adverse event	1 (3.4%)	1 (1.5%)	2 (2.1%)

Note: Percentages are calculated with the number subjects in the all treated analysis set as denominator.

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Treatment-emergent AEs with an outcome of death were reported for 6 subjects (6.2%), all of which were considered related to study drug (Table 10).

Table 10: Applicant - Number of Subjects with Treatment-emergent Adverse Events with Outcome of Death by System Organ Class, Preferred Term, and Relationship to Study Drug; All Treated Analysis Set (Study 68284528MMY2001)

	Phase 1b		Phase 2		Phase 1b + Phase 2	
	Total	Related	Total	Related	Total	Related
Analysis set: all treated	29		68		97	
Total number of subjects with TEAE with outcome death	1 (3.4%)	1 (3.4%)	5 (7.4%)	5 (7.4%)	6 (6.2%)	6 (6.2%)
MedDRA system organ class/preferred term						
Infections and infestations	0	0	3 (4.4%)	3 (4.4%)	3 (3.1%)	3 (3.1%)
Lung abscess	0	0	1 (1.5%)	1 (1.5%)	1 (1.0%)	1 (1.0%)
Sepsis	0	0	1 (1.5%)	1 (1.5%)	1 (1.0%)	1 (1.0%)
Septic shock	0	0	1 (1.5%)	1 (1.5%)	1 (1.0%)	1 (1.0%)
Immune system disorders	1 (3.4%)	1 (3.4%)	0	0	1 (1.0%)	1 (1.0%)
Cytokine release syndrome	1 (3.4%)	1 (3.4%)	0	0	1 (1.0%)	1 (1.0%)
Nervous system disorders	0	0	1 (1.5%)	1 (1.5%)	1 (1.0%)	1 (1.0%)
Neurotoxicity	0	0	1 (1.5%)	1 (1.5%)	1 (1.0%)	1 (1.0%)
Respiratory, thoracic and mediastinal disorders	0	0	1 (1.5%)	1 (1.5%)	1 (1.0%)	1 (1.0%)
Respiratory failure	0	0	1 (1.5%)	1 (1.5%)	1 (1.0%)	1 (1.0%)

Keys: TEAE=treatment-emergent adverse event.

Note: The output includes the diagnosis of CRS and ICANS along with other AEs and the symptoms of CRS or ICANS are excluded.

Note: Adverse events are reported using MedDRA version 23.0.

Note: Percentages are calculated with the number of subjects in the all treated analysis set as denominator.

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The Applicant's Position:

Although most cilta-cel related AEs were manageable in this population of subjects with heavily pre-treated RRMM, 9 subjects died due to AEs, 6 of which were deemed to be related to cilta-cel. All deaths occurred more than 30 days after cilta-cel infusion; 2 deaths were within 100 days of infusion (range, 45 to 694 days). This mortality rate is comparable with the safety profile of current understanding of CAR-T therapy.

FDA Assessment

As of the original data cutoff of September 1, 2020, 14 of 97 patients in CARTITUDE-1 (USA cohort) had died; 5 (5/14) of progressive disease and 9 of adverse events. As of

the 120-day safety update with data cutoff of February 11, 2021, an additional 7 patients had died- 5 of progressive disease and 2 of adverse events. Thus 21 of 97 patients have died as of the latest available data. There was no change adjudication of death from progressive disease to death due to AE. However, cause of death was changed/modified in 2 patients (see FDA Table 6 below) with AE related death.

FDA Table 6: FDA- Summary of Deaths in CARTITUDE-1 (USA Cohort)

Death Statistic	Overall N=97 N (%)
All Deaths	14 (14%)
Disease progression	5 (5)
Adverse Events	9 (9)
Other Causes	
Fatal AEs ≤ 30 days after cilta-cel	0 (0)
Fatal AEs > 30 days after cilta-cel	9 (9)

Source: FDA Analysis at September 1, 2020 data cutoff

- Clinical reviewer reviewed all death narratives to confirm cause of death. Relevant datasets and CRFs were reviewed as needed to reach a conclusion on cause of death. Disease progression was considered as cause of death when supported by imaging, biopsy, autopsy or other descriptive narratives of progression of underlying malignancy. However, presence of underlying malignancy did not automatically result in adjudication of death from progressive disease since certain complications of CAR-T therapy e.g., NT is a clinical diagnosis.*
- Applicant considered only those AEs attributed by the investigator as “related” as fatal AEs; deaths from acute myeloid leukemia and pneumonia were considered unrelated to cilta-cel as. We disagree with this approach since many a time it is impossible to rule in or rule out causality to study product, and toxicity of the entire investigational protocol including lymphodepleting chemotherapy is considered, not just toxicity attributed to CAR-T therapy. Lymphodepleting chemotherapy may have contributed to increased risk of AML and Applicant had not conducted transgene analysis to rule*

out CAR-T therapy as a cause of AML in the majority of cases (IR#19; response to Question#1). For patient with pneumonia, no neutrophil and lymphocyte counts are available at time of death. Thus, recurrent cytopenia secondary to CAR-T therapy cannot be ruled out as a predisposing cause for pneumonia. Patient did not receive any other anti-myeloma therapy following CAR-T therapy and thus there was no confounding from other therapy to explain the AE.

Final FDA adjudication of fatal events as of the 120-day safety update including those whose cause of death was changed/modified are shown in FDA Table 7 below.

FDA Table 7: FDA - Death from AE in CARTITUDE-1

USUBJID	Fatal Adverse Event	Study day of death
(b) (6)	Acute Myeloid Leukemia (bi-phenotypic)	418
	Acute Myeloid Leukemia	582
	Cytokine release syndrome/HLH	99
	Septic shock	162
	Pulmonary embolism, Neurologic toxicity (ICANS), CVA	121
	Neurologic toxicity (NT with parkinsonism)	247
	Pneumonia	109
	Acute Myeloid Leukemia	718
	Refractory ascites	445
	Neurologic toxicity (ICANS), Sepsis	45
	Lung abscess	119

Source: FDA Analysis of Deaths at February 11, 2021 cutoff (120-day safety update)

Abbreviations: HLH-hemophagocytic lymphohistiocytosis; CVA-cerebrovascular accident

*Indicates patients for whom cause of AE related death was changed/modified from that of the Applicant

^ Indicates patients who died of fatal AEs and reported in the 120-day safety update but not in the original submission

Brief narratives of the 11 patients who died of an AE (including those reported at the time of the 120-day update) are listed below

Subject (b) (6) 69-year-old white male with 6 prior lines of therapy for MM who died of biphenotypic AML on day 418 following cilta-cel infusion. CAR-T cell therapy complicated by Grade 1 CRS and Grade 1 NT that resolved. Other complications included sensory neuropathy, squamous cell cancer of the scalp, prostate cancer. AML diagnosed day 338- B cell/myeloid type; no treatment for leukemia reported. No sample for vector detection and integration was collected since death occurred prior to getting consent for the same and no sample is available (IR#19; response to Question#1).

Subject (b) (6) 54-year-old white male with 10 prior lines of therapy for MM who died of AML on day 582 following cilta-cel infusion. He achieved sCR on day 28 but progressed on day 211. Subsequently received anti-myeloma therapy including an ASCT. Diagnosed with grade 4 MDS on day 447 for which he was treated with azacitidine. Diagnosed with therapy-related AML on day 568 that was thought to have arisen from the prior MDS. Baseline bone marrow prior to cilta-cel had del 20q; AML cytogenetics- loss of -5q31, 21q22 (RUNX1). No treatment for AML reported and patient subsequently died.

Subject (b) (6) 71-year-old black male with 4 prior lines of therapy who died on day 99 following cilta-cel infusion from CRS/HLH. CRS diagnosed day 3 following cilta-cel. Subsequently, he developed worsening acute kidney injury (AKI), aminotransferase elevation, respiratory failure, disseminated intravascular coagulation (DIC), pulmonary hemorrhage in the setting of severe thrombocytopenia, sepsis, new cavitory lung lesion and left pneumothorax. Blood cultures positive for *Staphylococcus epidermidis*, *vancomycin-resistant Enterococcus faecium*; cultures remained positive despite multiple antibiotics. Patient received steroids, anakinra, cyclophosphamide, tocilizumab, etanercept for CRS; was on vasopressors for blood pressure support. Had a cardiac arrest on day 97- resuscitated and then placed on hospice care. Autopsy showed extensive histiocytic infiltration in lungs, liver, spleen and bone marrow. Other autopsy findings include hepatosplenomegaly, diffuse alveolar damage, cardiomegaly with pericardial effusion, extramedullary hematopoiesis in the spleen, marked autolysis in the pancreas, focal and global segmental glomerulosclerosis, bile duct infarcts, fluid overload and sacral pressure ulcer.

Subject (b) (6) See detailed narrative under sub-section on parkinsonism in neurologic toxicity. 58-year-old white male who died of septic shock on day 162 following cilta-cel infusion. Blood cultures positive for *Serratia marcescens*. Absolute neutrophil count (ANC) was normal on day 100 (prior to death) but no data available at time of death (IR#13 Part 1; response to Question#5); however, filgrastim was administered during event of septic shock raising the possibility of infection in the setting of neutropenia.

Subject (b) (6) See death narrative under section on neurologic toxicity. Cause of death on day 121 following cilta-cel infusion changed from respiratory failure to pulmonary embolism (PE, NT (ICANS) and cerebrovascular accident (CVA) based on autopsy report. Absolute neutrophil count not available at time of death; day 100 ANC was 1340. Patient noted to have DIC as well on autopsy report.

Subject (b) (6) See detailed narrative under sub-section of parkinsonism under NT. 58-year-old white male died of NT with parkinsonian features on day 247 following cilta-cel infusion.

Subject (b) (6) 62-year-old black male with 6 prior lines of therapy for MM who died of pneumonia on day 109 following cilta-cel infusion. Had grade 1 CRS with aminotransferase elevation that resolved. Diagnosed with influenza A on day 86 followed by hospitalization on day 95 with bilateral pneumonia with persistent positivity for influenza A and sputum culture positive for *Aspergillus fumigatus*. Patient died day 109 despite treatment with multiple antibacterial, antifungal and antiviral agents and supportive care. Absolute neutrophil count normal on day 78 but ANC and absolute lymphocyte count (ALC) not available at time of hospitalization and death (IR#13; response to Question#5); had grade 4 thrombocytopenia ongoing at death. Applicant did not include this patient in the calculation for fatal AE since investigator considered pneumonia unrelated to cilta-cel.

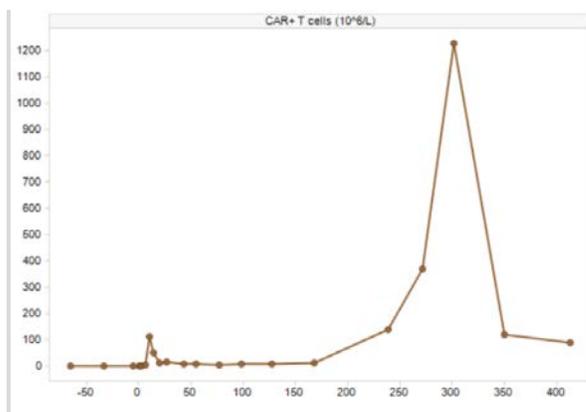
- *Clinical reviewer disagrees with Applicant assessment regarding death of USUBJID (b) (6) as not being related to therapy. Reviewer considers this AE related death to be related to investigational protocol; patient received no therapy following cilta-cel and prolonged immunosuppression has been noted with cilta-cel that may have predisposed patient to pneumonia.*

Subject (b) (6) 50-year-old black female with 8 prior lines of therapy for MM who died from AML on day 718 following cilta-cel infusion. AML was diagnosed on day 712 with death shortly thereafter. CAR-T cell therapy complicated by grade 2 CRS with aminotransferase elevation. Had sCR to therapy on day 156 followed by progressive disease on day 234 which was treated with multiple lines of therapy. Tumor sample analysis for vector detection and integration pending (IR#19; response to Question#1). This patient's death was reported at the 120-day safety update.

Subject (b) (6) 60-year-old white male with 9 prior lines of therapy for MM who died on day 445 of "refractory ascites" following cilta-cel infusion. Had Grade 1 CRS and episode of aspiration pneumonia following cilta-cel; sCR noted on day 55. Ascites reported on day 248 and attributed to non-cirrhotic portal hypertension that was a pre-existing problem. Died on day 445 from refractory ascites due to liver problems. Patient had *C.difficile* infection and robust CAR-T expansion associated with infection prior to death (see FDA Figure 3 below). This patient's death was reported at the 120-day safety update.

- *Clinical reviewer could not find non-cirrhotic portal hypertension as a prior problem and Applicant was queried about this issue (IR#32 Question 7). Applicant stated that investigator had not documented liver abnormalities under past medical history in the eCRF but following patient's death reported Grade 2 "non-alcoholic steatosis" (ongoing), "intermittent liver function abnormalities" and Grade 1 "non-cirrhotic portal fibrosis" (ongoing) to the Applicant in the SAE narrative and to the clinical database after the 120-day safety update data cutoff.*

FDA Figure 3: FDA - CAR-T cell expansion for USUBJID (b) (6)



Source: Applicant response to Question#7, IR#32

- *The explanation of refractory ascites from prior low-grade non-cirrhotic portal hypertension causing death is not satisfactory. CAR-T cell data on the ascitic fluid is not available; blood counts to rule out infection in the setting of recurrent cytopenia are also not available. Robust CAR-T cell expansion attributed to C.Difficile infection that remains above baseline expansion immediately following cilta-cel is concerning. Paucity of data precludes the clinical reviewer from concluding that death was the result of direct hepatic CAR-T cell toxicity.*

Subject (b) (6) See detailed narrative sub-section of ICANS in NT. 77-year-old male with 12 prior lines of therapy for MM died on day 45 following cilta-cel infusion from NT and sepsis in setting of pancytopenia.

- *Death adjudication due to sepsis was changed to death due to NT and sepsis based on the narrative.*

Subject (b) (6) See detailed narrative in sub-section of parkinsonism under NT. 62-year-old white male with prior lines of therapy for MM who died of lung abscess on day 119 following cilta-cel infusion.

Clinical Reviewer Comments (all deaths)

- Overall fatal AE rate was 9% (September 1, 2020, cutoff); 2 additional fatal AEs reported with 120-day safety update
- There were no deaths reported within 30 days of cilta-cel infusion. One patient died of ICANS and sepsis at day 45; one patient died of CRS/HLH at day 99. All other deaths occurred beyond 100 days of CAR-T therapy.
- Majority of deaths from neurologic toxicity and infection occurred after 4 months. Delayed neurologic toxicity especially with mixed features of parkinsonism and ICANS and recurrent and/or prolonged cytopenias especially neutropenia and lymphopenia that are risk factors for infection predispose patients to death from AE of CAR-T therapy well beyond the usual time frame for such events. Delayed or recurrent CAR-T expansion as seen in patient (b) (6) is concerning for risk of ongoing toxicity from cilta-cel. Thus, continued monitoring for these complications is warranted.

Serious Adverse Events

Data:

Serious TEAEs by MedDRA system organ class (SOC) and preferred term (reported at a frequency of at least 5% in the All Treated Population) and worst event Grade of 3 or higher are summarized for the cilta-cel in Table 11.

Table 11: Applicant - Number of Subjects with Treatment-emergent Serious Adverse Events with Frequency of at Least 5% in Total by System Organ Class, Preferred Term, and Worst Event Grade of 3 or Higher; All Treated Analysis Set (Study 68284528MMY2001)

	Phase 1b			Phase 2			Phase 1b + Phase 2		
	Total	Grade 3 or 4	Grade 5	Total	Grade 3 or 4	Grade 5	Total	Grade 3 or 4	Grade 5
Analysis set: all treated	29			68			97		
Total number of subjects with serious TEAE	11 (37.9%)	7 (24.1%)	1 (3.4%)	42 (61.8%)	22 (32.4%)	5 (7.4%)	53 (54.6%)	29 (29.9%)	6 (6.2%)
MedDRA system organ class/preferred term									
Infections and infestations	4 (13.8%)	3 (10.3%)	0	17 (25.0%)	12 (17.6%)	3 (4.4%)	21 (21.6%)	15 (15.5%)	3 (3.1%)
Pneumonia	1 (3.4%)	1 (3.4%)	0	4 (5.9%)	4 (5.9%)	0	5 (5.2%)	5 (5.2%)	0
Sepsis	1 (3.4%)	1 (3.4%)	0	4 (5.9%)	3 (4.4%)	1 (1.5%)	5 (5.2%)	4 (4.1%)	1 (1.0%)
Immune system disorders	5 (17.2%)	2 (6.9%)	1 (3.4%)	15 (22.1%)	2 (2.9%)	0	20 (20.6%)	4 (4.1%)	1 (1.0%)
Cytokine release syndrome	5 (17.2%)	2 (6.9%)	1 (3.4%)	15 (22.1%)	2 (2.9%)	0	20 (20.6%)	4 (4.1%)	1 (1.0%)
Nervous system disorders	3 (10.3%)	2 (6.9%)	0	13 (19.1%)	8 (11.8%)	1 (1.5%)	16 (16.5%)	10 (10.3%)	1 (1.0%)

Table 11: Applicant - Number of Subjects with Treatment-emergent Serious Adverse Events with Frequency of at Least 5% in Total by System Organ Class, Preferred Term, and Worst Event Grade of 3 or Higher; All Treated Analysis Set (Study 68284528MMY2001)

	Phase 1b			Phase 2			Phase 1b + Phase 2		
	Total	Grade 3 or 4	Grade 5	Total	Grade 3 or 4	Grade 5	Total	Grade 3 or 4	Grade 5
Immune effector cell-associated neurotoxicity syndrome	1 (3.4%)	1 (3.4%)	0	4 (5.9%)	1 (1.5%)	0	5 (5.2%)	2 (2.1%)	0

Keys: TEAE=treatment-emergent adverse event.

Note: The output includes the diagnosis of CRS and ICANS along with other AEs and the symptoms of CRS or ICANS are excluded.

Note: Adverse events are reported using MedDRA version 23.0.

Note: For 1 subject in Phase 1b with serious TEAE of Immune Effector Cell-Associated Neurotoxicity (ICANS), the reported term was CAR-T cell Related Encephalopathy Syndrome (CRES). The event was reported prior to publication of the ASTCT consensus grading system and graded according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 5.0 by investigator. For this subject, the maximum toxicity grade was Grade 3 according to NCI-CTCAE version 5.0.

Note: Adverse events are graded according to the NCI-CTCAE Version 5.0, with the exception of immune effector cell-associated neurotoxicity (ICANS) and cytokine release syndrome (CRS), which were evaluated according to the ASTCT consensus grading system, and adverse events associated with changes in handwriting, which were graded according to the protocol criteria.

Note: Percentages are calculated with the number of subjects in the all treated analysis set as denominator.

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The Applicant’s Position:

Overall serious TEAEs were reported in 53 subjects (54.6%) and majority were reported in Phase 2 of the study. Most commonly (≥5% subjects) reported serious TEAEs were CRS (20.6%), pneumonia (5.2%), sepsis (5.2%), and ICANS (5.2%). This mortality rate is comparable with the safety profile of current understanding of CAR-T therapy. These common AE, both overall incidence and Grade 3+ severity, are consistent with known safety profile of marketed CAR-T therapy (Table 1).

FDA Assessment

The clinical reviewer agrees with the Applicant’s assessment of SAEs. The definition of SAE in CARTITUDE-1 is detailed in section on “categorization of AE” above. It was unclear from the SAE definition if AEs occurring during the required hospitalization following cilta-cel infusion were considered as SAEs especially if there was escalation of care. Applicant clarified (IR#57) that prolongation of hospitalization beyond the period of mandatory stay following cilta-cel infusion was considered an SAE. Serious adverse events occurring in ≥ 1 % of patients in CARTITUDE-1 is shown in FDA Table 8 below.

FDA Table 8: FDA - Treatment Emergent SAEs ≥ 1% of Patients in CARTITUDE-1

SAE	All grade N (%) N=97	Grade ≥ 3 N (%) N=97
Cytokine release syndrome	20 (21)	4 (4)
Encephalopathy	10 (10)	6 (6)
Pneumonia	7 (7)	7 (7)

SAE	All grade N (%) N=97	Grade ≥ 3 N (%) N=97
Sepsis	7 (7)	7 (7)
Dyspnea	4 (4)	3 (3)
Febrile neutropenia	4 (4)	3 (3)
Viral infection	4 (4)	2 (2)
Bacterial infection	3 (3)	2 (2)
Hypoxia	3 (3)	2 (2)
Parkinsonism	3 (3)	2 (2)
Renal failure	3 (3)	3 (3)
Thrombocytopenia	3 (3)	3 (3)
Upper respiratory tract infection	3 (3)	3 (3)
Cardiac arrhythmias	3 (3)	3 (3)
Hemorrhage	2 (2)	2 (2)
Neuropathy	2 (2)	2 (2)
Neurotoxicity	2 (2)	2 (2)
Paresis	2 (2)	1 (1)
Pyrexia	2 (2)	0 (0)
Diplopia	1 (1)	1 (1)
Dizziness	1 (1)	1 (1)
Fatigue	1 (1)	1 (1)
Gastroenteritis	1 (1)	1 (1)
Haemophagocytic lymphohistiocytosis	1 (1)	1 (1)
Hypotension	1 (1)	0 (0)
Motor dysfunction	1 (1)	1 (1)
Nausea	1 (1)	1 (1)
Neutropenia	1 (1)	1 (1)
Pericardial effusion	1 (1)	1 (1)
Pleural effusion	1 (1)	1 (1)
Skin infection	1 (1)	1 (1)
Tumor lysis syndrome	1 (1)	1 (1)

Source: FDA Analysis of ADAE dataset

- The FDA assessment of SAEs in FDA Table 8 above may differ slightly in percentages of certain AEs from that of the Applicant since analysis was based on FDA group terms and not AEDECOD terms as used by the Applicant.
- Certain terms e.g., ICANS may not be listed under SAEs since this AE was grouped under encephalopathy (Refer to [FDA Table 27](#) in Appendix for complete list of preferred and group terms).

Common Adverse Events

Data:

All 97 subjects who received a cilta-cel infusion experienced 1 or more TEAEs. Consistent with the anticipated risks associated with CAR-T therapy, the most frequently reported TEAEs were cytopenias (neutropenia [95.9%], CRS (94.8%), anemia [81.4%], thrombocytopenia [79.4%], leukopenia [61.9%], and lymphopenia [52.6%]).

All 97 subjects who received a cilta-cel infusion experienced 1 or more Grade 3 or 4 TEAE. The most frequently reported Grade 3 or 4 TEAEs were cytopenias (neutropenia [94.8%], anemia [68.0%], leukopenia [60.8%], thrombocytopenia [59.8%], and lymphopenia [49.5%]).

The Applicant's Position:

Cilta-cel has a manageable safety profile generally consistent with the current understanding of CAR-T therapy.

FDA Assessment

Prolonged and recurrent cytopenias are considered under section on adverse events of special interest (AESI) although not pre-specified as such in the CARTITUDE-1 protocol. The occurrence of recurrent grade 3 or 4 cytopenia has not been reported in other approved CAR-T products to possibly because such analyses were not carried out. Treatment emergent AEs and AEs related to apheresis, bridging therapy and lymphodepleting chemotherapy are presented below.

Adverse Events Related to Apheresis

Five of 113 (4.4%) enrolled patients had AEs considered related to apheresis by the investigator. These included Grade 1 or 2 events of citrate toxicity, procedural pain, chills, and atrial fibrillation. One patient had Grade 3 hypertension. No patient had Grade 4 or 5 event related to apheresis.

Adverse Events Related to Bridging Therapy

Adverse events related to bridging whether they received cilta-cel or not is presented below.

Eighty-seven (77%, 77/113) of 113 patients undergoing apheresis (all enrolled population) received bridging therapy. Of these 87 patients, 43 (49%, 43/87) experienced an AE related to bridging as judged by the investigator with 35 (40%, 35/87) experiencing a grade 3 or 4 AE. One patient died of sepsis. The grade 3 or 4 AEs in these 87 patients include thrombocytopenia (18%), lymphopenia (21%), neutropenia (21%), anemia (16%),

febrile neutropenia (5.7%) and asthenia, peripheral edema, hyperglycemia, aminotransferase elevation, mental status changes and hypertension- all 1%.

Of the 97 patients treated with cilta-cel (all treated population), 73 (75%) received bridging, Of the 73 patients who received bridging therapy in this population, 37 (50%; 37/73; 38% of 97 total patients) had AEs associated with bridging therapy. In these 97 patients, 31 (32%) patients had the following Grade 3 or 4 events- thrombocytopenia (14.4%), neutropenia (17.5%), lymphopenia (16.5%), anemia (12.4%), febrile neutropenia (4.1%), fatigue (1%) and hypertension (1%).

Adverse Events Related to Lymphodepleting Chemotherapy

All 101 patients who received lymphodepleting chemotherapy with fludarabine and cyclophosphamide experienced an AE with the majority (100/101, 99%) having a Grade 3 or 4 event. As expected, cytopenias were the most common grade 3 or 4 AE. There were no Grade 5 events. The most common Grade 3 or 4 AEs related to lymphodepletion in these 101 patients include neutropenia (92%), anemia (64%), thrombocytopenia (51.5%), lymphopenia (57%), and febrile neutropenia (6%). Other important AEs included tumor lysis syndrome (2%), hypogammaglobulinemia (2%), parkinsonism (1%), infections (6%; included atypical/typical pneumonia, bacteremia, CMV viremia, disseminated zoster, cryptosporidium GI infection, sepsis, rhinoviral infection), confusional state (1%), respiratory failure (1%) and hyperbilirubinemia (1%). Other Grade 3 or 4 laboratory abnormalities like hypophosphatemia, hyponatremia, hypocalcemia, prolonged prothrombin time were noted in 1%-2% of patients.

- *The clinical reviewer accepted the Applicant's analysis of AEs associated with apheresis, bridging therapy and lymphodepleting chemotherapy as outlined in the CSR (and summarized above) since these are common to CAR-T products in the same or different product class given the common toxicities of these procedures (e.g., apheresis) and use of the same lymphodepletion regimen e.g., fludarabine and cyclophosphamide.*
- *Eleven patients (11%, 11/97) experienced an AE that led to a delay in lymphodepleting chemotherapy administration. Nine of 11 patients experienced a grade 3 or 4 event that included infections (4%), thrombocytopenia (2%), and pericardial effusion, acute cholecystitis, fracture of the humerus, AKI and DVT-each in 1% of patients.*

Treatment Emergent AEs

Definition of TEAE has been elucidated under section on "categorization of AE" above. TEAEs occurring in $\geq 10\%$ of patients in study CARTITUDE-1 is shown in FDA Table 9 below.

FDA Table 9: FDA - Non-laboratory Treatment Emergent AEs in ≥ 10% of Patients in CARTITUDE-1 by System Organ Class

Adverse Reaction	Any Grade (%)	Grade 3 or higher (%)
Blood and Lymphatic System Disorders		
Coagulopathy	22	2.1
Febrile Neutropenia	10	10
Cardiac Disorders		
Tachycardia	27	1
Gastrointestinal Disorders		
Diarrhea	33	1
Nausea	31	1
Constipation	22	0
Vomiting	20	0
General disorders and administrative site conditions		
Pyrexia	96	5
Fatigue	47	7
Chills	33	0
Edema	23	0
Immune system disorders		
Cytokine release syndrome	95	5
Hypogammaglobulinemia	94	2
Infections and infestations		
Infections-pathogen unspecified	41	17
Upper respiratory tract infection	28	3
Viral infections	23	7
Pneumonia	12	11
Sepsis	10	7
Bacterial infections	10	3
Metabolism and nutrition disorders		
Decreased appetite	29	1
Musculoskeletal and connective tissue disorders		
Musculoskeletal pain	48	2
Nervous system disorders		
Encephalopathy	30	6
Headache	27	0
Dizziness	23	1
Motor dysfunction	16	3
Psychiatric disorders		
Insomnia	13	0

Respiratory, thoracic and mediastinal disorders		
Cough	39	0
Dyspnea	23	3
Nasal congestion	15	0
Hypoxia	12	4
Vascular disorders		
Hypotension	51	10
Hypertension	19	6
Hemorrhage	15	4

Source: FDA Analysis of ADAE dataset

TEAEs occurring in < 10% of patients but clinically important include ataxia (8%), neuropathy (8%), rash (8%), cardiac arrhythmias (8%), chest pain (7%), renal failure (7%), hyperbilirubinemia (6%), pleural effusion (6%), tremor (6%), bradycardia (5%), delirium (5%), thrombosis (5%), gastroenteritis (4%), micrographia (4%), parkinsonism (4%), dysgraphia (3%), UTI (4%), reduced facial expression (3%), bradykinesia (2%), hemorrhage (2%), infusion related reaction (2%), neurotoxicity (2%), HLH (1%), pulmonary embolism (1%), seizure (1%), slow speech (1%) and stereotypy (1%).

One patient with febrile neutropenia was classified as having Grade 2 toxicity. This was changed to Grade 3 toxicity since by CTCAE v 5.0, febrile neutropenia at the minimum is Grade 3.

Adverse Events of Special Interest (AESI)

Cytokine Release Syndrome

Cytokine Release Syndrome was the most common AE of special interest (AESI) and reported for 92 subjects (94.8%) (Table 12). Most subjects (87 subjects [89.7%]) who experienced CRS AEs were Grade 1 or 2. Three subjects (3.1%) experienced Grade 3 CRS, 1 subject (1.0%) experienced Grade 4 CRS, and 1 (1.0%) subject experienced Grade 5 CRS. Most subjects (88 subjects, 90.7%) received supportive treatment for CRS, with 70 subjects (72.2%) receiving paracetamol and 67 subjects (69.1%) receiving tocilizumab, 21 subjects (21.6%) receiving corticosteroids, and 18 subjects (18.6%) receiving anakinra.

The median time from cilta-cel infusion to first onset of CRS was 7.0 days (range, 1 to 12 days). No subject had an onset of CRS beyond Day 30 after cilta-cel infusion. Eighty-two subjects (89.9%) experienced onset of CRS after the 3rd day following cilta-cel infusion. The median duration of CRS was 4.0 days (range: 1 to 14 days), with the exception of 1 subject who experienced Grade 5 CRS (97-day duration). Eighty-one subjects (88.0%) of subjects experienced a duration of ≤7 days.

Table 12: Applicant - Summary of Treatment-emergent Cytokine Release Syndrome (CRS) Events; All Treated Analysis Set (Study 68284528MMY2001)

	Phase 1b	Phase 2	Phase 1b + Phase 2
Analysis set: all treated	29	68	97
Number of subjects with CRS	27 (93.1%)	65 (95.6%)	92 (94.8%)
Maximum toxicity grade			
Grade 1	14 (48.3%)	35 (51.5%)	49 (50.5%)
Grade 2	10 (34.5%)	28 (41.2%)	38 (39.2%)
Grade 3	1 (3.4%)	2 (2.9%)	3 (3.1%)
Grade 4	1 (3.4%)	0	1 (1.0%)
Grade 5	1 (3.4%)	0	1 (1.0%)
Time from initial infusion of CAR-T cells to first onset of CRS (days)			
N	27	65	92
Mean (SD)	7.0 (2.01)	6.4 (2.28)	6.6 (2.21)
Median	7.0	7.0	7.0
Range	(2; 12)	(1; 10)	(1; 12)
Duration of CRS (days)			
N	27	65	92
Mean (SD)	7.0 (18.04)	5.2 (2.68)	5.7 (9.94)
Median	3.0	4.0	4.0
Range	(2; 97)	(1; 14)	(1; 97)
Interquartile range	(2.0; 4.0)	(3.0; 6.0)	(3.0; 6.0)
<=7 days	26 (96.3%)	55 (84.6%)	81 (88.0%)
Number of subjects with supportive measures to treat CRS ^a	26 (89.7%)	62 (91.2%)	88 (90.7%)
Anti-IL6 receptor Tocilizumab	23 (79.3%)	44 (64.7%)	67 (69.1%)
IL-1 receptor antagonist Anakinra	6 (20.7%)	12 (17.6%)	18 (18.6%)
Corticosteroids	6 (20.7%)	15 (22.1%)	21 (21.6%)
IV fluids	8 (27.6%)	21 (30.9%)	29 (29.9%)
Vasopressor used	2 (6.9%)	2 (2.9%)	4 (4.1%)
Oxygen used	1 (3.4%)	5 (7.4%)	6 (6.2%)
Blow-by	0	0	0
Nasal cannula low flow (\leq 6L/min)	1 (3.4%)	5 (7.4%)	6 (6.2%)
Nasal cannula high flow (>6L/min)	0	1 (1.5%)	1 (1.0%)
Face mask	0	0	0
Non-Rebreather mask	0	0	0
Venturi mask	0	0	0
Other	0	0	0
Positive pressure	1 (3.4%)	0	1 (1.0%)
Bilevel Positive Airway Pressure	1 (3.4%)	0	1 (1.0%)
Intubation/ Mechanical Ventilation	1 (3.4%)	0	1 (1.0%)
Analgesics/Antiinflammatory	20 (69.0%)	52 (76.5%)	72 (74.2%)

Table 12: Applicant - Summary of Treatment-emergent Cytokine Release Syndrome (CRS) Events; All Treated Analysis Set (Study 68284528MMY2001)

	Phase 1b	Phase 2	Phase 1b + Phase 2
Antiinfectives	14 (48.3%)	34 (50.0%)	48 (49.5%)
Antiepileptics	1 (3.4%)	0	1 (1.0%)
Other	6 (20.7%)	4 (5.9%)	10 (10.3%)
Outcome of CRS			
N	27	65	92
Recovered or resolved	26 (96.3%)	65 (100.0%)	91 (98.9%)
Not recovered or not resolved	0	0	0
Recovered or resolved with sequelae	0	0	0
Recovering or resolving	0	0	0
Fatal	1 (3.7%)	0	1 (1.1%)
Unknown	0	0	0
Missing	0	0	0

Key: CAR-T= chimeric antigen receptor T (cells); CRS = Cytokine Release Syndrome; SD=standard deviation.

^a Supportive measures to treat CRS and CRS symptoms are included.

Note: Percentages calculated with the number of subjects in the all treated analysis set as denominator, except for the outcome of CRS and duration of CRS for which percentages are calculated with the number of subjects with CRS in the all treated analysis set as denominator.

Note: CRS was originally graded by Lee criteria (Lee et al 2014) in Phase 1b and by ASTCT consensus grading system (Lee et al 2019) in Phase 2, with conversion of grade in Phase 1b to ASTCT based on data in eCRF.

Toxicity grade by ASTCT is presented in this table, for both Phase 1b and Phase 2.

Note: Time from initial infusion of CAR-T cells to first onset of CRS is calculated as first onset date of CRS - initial infusion date of CAR-T cells +1.

Modified from [TSFAE24.RTF] [JNJ-68284528\MMY2001\DBR_CSR\RE_CSR\PROD\TSFAE24.SAS] 24NOV2020, 10:49

During the study, 6 subjects (6.2%) required oxygen as a supportive measure to treat CRS. Five of these subjects required low flow oxygen support, 1 subject required high flow oxygen support. One subject (1.0%) received low flow oxygen, followed by bilevel positive airway pressure, and ultimately required intubation/mechanical ventilation as a result of CRS. This subject had 97-day duration of CRS and ultimately died on Day 99 of CRS complicated by hemophagocytic lymphohistiocytosis (HLH).

The Applicant's Position:

Cytokine Release Syndrome was the most common AE of special interest, which is as expected for a CAR-T therapy. CRS was manageable for a majority of subjects. Most events of CRS were mild with 87 of the 92 subjects experiencing Grade 1 or 2 events. All subjects recovered from CRS, with the exception of 1 fatal event complicated by HLH.

FDA Assessment

CRS was graded based on the 2019 ASTCT criteria ([Lee 2019](#)) which does not incorporate organ toxicity in the grading system; events contributing to CRS were graded

using CTCAE criteria. CRS occurred in 92 of 97 patients (95%) including \geq Grade 3 in 5% of patients (see FDA Table 10 below). One patient died of CRS/HLH (hemophagocytic lymphohistiocytosis); all other 91 patients recovered from CRS.

FDA Table 10: FDA-CRS Toxicity Grade by 2019 ASTCT Criteria

Worst CRS Toxicity Grade	Total N=97 N (%)
CRS Any Grade	92 (95)
Grade 1	49 (50)
Grade 2	38(39)
Grade 3	3(3)
Grade 4	1(1)
Grade 5	1(1)

Source: FDA Analysis of ADAE Dataset

- Worst CRS toxicity grade analysis was done using the WRCRSGR flag in ADAE and not the ACRSMAX flag since this represents the worst CRS grade by 2019 ASTCT criteria for all patients; the ACRSMAX grade represents maximum CRS toxicity grade by 2019 ASTCT criterion for patients in the phase 2b part of the study only while the LCRSMAX grade flag represents the maximum CRS grade by 2014 Lee criteria for patients in the phase 1 part of the trial. In the ADAE CRS2 dataset, ACRSMAX flag represents the maximum CRS grade by 2019 ASTCT criteria for all patients; analysis of maximum CRS grade was done in both ADAE and ADAE CRS2 datasets and results are consistent.*

Median time to CRS onset was 7 days (range 1-12 days). CRS resolved in all but one patient (91 of 92, 99%) with a median time to resolution of 4 days (range 1 to 40 days). The median duration of CRS in all patients including the patient who died of CRS was 4 days (range 1 to 97 days). The median time to maximum CRS grade was 7 days (range 2-99 days).

The most common manifestations of CRS included fever (100%), hypotension (43.5), AST (aspartate aminotransferase) elevation (22%), chills (15%), ALT (alanine aminotransferase) elevation (15%), sinus tachycardia (10%), headache (8%) and hypoxia (6.5%). Other serious events associated with CRS include acute kidney injury (AKI), ventricular tachycardia, supraventricular tachycardia, atrial flutter, angina pectoris, disseminated intravascular coagulation (DIC), hemophagocytic lymphohistiocytosis (HLH), respiratory failure, pulmonary edema and elevation of other liver enzymes-bilirubin, alkaline phosphatase and GGT (gamma glutamyl transferase). FDA Table 11 below summarizes the AEs observed in patients with CRS.

FDA Table 11: FDA-Symptoms in 92 Patients with CRS

CRS Symptoms/AEs*	All grades N (%)	Grades 3 or higher N (%)
Total	92 (100)	27 (29)
Pyrexia	92 (100)	5 (5.4)
Hypotension	40 (43.5)	8 (8.7)
AST increased	20 (21.7)	14 (15.2)
Chills	14 (15.2)	0
ALT increased	13 (14.1)	6 (6.5)
Sinus tachycardia	10 (11)	0
Headache	7 (7.6)	0
Hypoxia	6 (6.5)	1 (1)
Nausea	4 (4.3)	0
Serum Ferritin increased	4 (4.3)	1(1)
Tachycardia	4 (4.3)	0
C-reactive protein increased	3 (3.3)	2 (2.2)
Fatigue	3 (3.3)	0
Hyperbilirubinemia	3 (3.3)	2 (2.2)
Hyponatremia	3 (3.3)	0
Blood alkaline Phosphatase increased	2 (2.2)	1(1)
Dizziness	2 (2.2)	0
Dyspnea	2 (2.2)	1(1)
GGT increased	2 (2.2)	1(1)
Muscular weakness	2 (2.2)	0
Somnolence	2 (2.2)	0
Acute kidney injury	4 (4.3)	4 (4.3)
Angina Pectoris	1 (1)	1 (1)
Asthenia	1 (1)	1 (1)
Atrial Flutter	1 (1)	0
Confusional state^	1 (1)	0
DIC	1 (1)	1 (1)

CRS Symptoms/AEs*	All grades N (%)	Grades 3 or higher N (%)
Dysarthria [^]	1 (1)	0
Gait disturbance [^]	1 (1)	0
HLH	1 (1)	1 (1)
Hyperhidrosis	1 (1)	0
Hyperuricemia	1 (1)	0
Hypoalbuminemia	1 (1)	0
Hypocalcemia	1 (1)	0
Malaise	1 (1)	1 (1)
Myalgia	1 (1)	1 (1)
Orthostatic hypotension	1 (1)	0
Pulmonary edema	1 (1)	0
Respiratory failure	1 (1)	1 (1)
Supraventricular tachycardia	1 (1)	1 (1)
Ventricular tachycardia	1 (1)	1 (1)

Source: FDA Analysis of ADAE dataset; *Does not include FDA Group terms

AST: aspartate aminotransferase; ALT: alanine aminotransferase; GGT: gamma glutamyl transferase.

DIC: disseminated intravascular coagulation; HLH: hemophagocytic lymphohistiocytosis

[^]: CRS symptoms as listed by investigator; reclassified as neurologic toxicity by FDA

- Since majority (92 of 97) of patients had CRS, we did not look for additional CRS cases using the strategy of finding fever, hypoxia or hypotension within 30 days of CAR-T infusion to identify additional patients with CRS
- We looked at vasopressor and oxygen use in grade 1 and grade 2 CRS to verify accuracy of CRS grade. Five patients with grade 1 CRS were identified who had either supplemental oxygen use (USUBJID (b) (6)), hypotension with intravenous (IV) fluids use (USUBJIDs (b) (6)) or hypotension with midodrine use (USUBJID (b) (6)). Based on review of Applicant’s explanation (IR#19-response received 08.11.2021; IR#34- response received 09.20.2021), no change in grade was made.
- Resolution of CRS graded by 2019 ASTCT criteria is based on resolution of fever, hypotension, and hypoxia; organ toxicity may persist beyond resolution of these symptoms and is not included in the time to resolution. Assessment of CRS resolution based on resolution of fever may be confounded by use of corticosteroids that may mask fever.

- In the CARTITUDE-1, during phase 1b, CRS resolution was defined by the end date of last AE of hypotension, hypoxia and fever that was reported as AESI and CRS by the investigator and no longer required supplemental oxygen or vasopressor use (CRS graded by 2014 Lee in phase 1b was mapped to 2019 ASTCT CRS criteria). For phase 2 patients, CRS end date was based on the investigator report of CRS end day and could have included resolution of organ toxicity or lab abnormalities deemed to be due to CRS (IR#44; Applicant response to Question#12). Thus, CRS resolution may not have been judged by a uniform set of criteria in all patients with CRS. However, in general CRS onset, duration and organ toxicity is like other CAR-T products and in the timeframe of early CAR-T expansion.*

Thirty-two patients with CRS had one or more organ toxicities associated with CRS. Twenty patients (22%) had \geq Grade 3 organ toxicity. Median onset of organ toxicity was 8 days (range 1-15 days). Median time to resolution of organ toxicity (29/32) was 5 days (range 1 to 61 days). Cardiac organ toxicity comprised mainly of changes in heart rate or rhythm; one patient had angina pectoris. Majority (N=13) of the 17 patients with cardiac toxicity had sinus tachycardia; serious arrhythmias included atrial flutter, ventricular tachycardia and supraventricular tachycardia. Cardiac toxicity resolved in all patients. Hepatic organ toxicity occurred in 22 patients and manifested as elevation in one or more liver enzymes; all but 1 patient had resolution of toxicity. One patient had ongoing toxicity at death from HLH. Four patients had acute kidney injury; toxicity did not resolve in 2 patients -one died of HLH and the other had ongoing toxicity. Pulmonary toxicity in 6 patients consisted of hypoxia (N=4), pulmonary edema (N=1) and respiratory failure (N=1). Patient with respiratory failure died of HLH; one patient with grade 2 hypoxia had ongoing toxicity. Organ toxicities associated with CRS are shown in FDA Table 12 below.

FDA Table 12: FDA- Organ Toxicity in Patients with CRS in CARTITUDE-1

Organ Toxicity	All Grades (%) N=92 with CRS	\geq Grade 3 (%) N=92 with CRS
Any Organ toxicity	32 (35%)	20 (22%)
Hepatic	22 (24)	16 (17.4)
Cardiac	17 (18.5)	3 (3.3)
Pulmonary	6 (6.5)	2 (2.2)
Renal	4 (4.4)	4 (4.4)

Source: FDA Analysis of ADAE

- Use of the 2019 ASTCT Consensus Criteria (Lee 2019) for CRS grading has the disadvantage of not reflecting organ toxicity from CRS in the grade. Thus, patients especially with Grade 1 or Grade 2 CRS on basis of fever, hypotension and/or hypoxia but with organ toxicity e.g., cardiac arrhythmias, elevated transaminases etc. of a higher grade (grade 3 or 4) may not have been captured as having more severe grade of CRS based on organ toxicity (see previous comment on variability in adjudication of resolution of CRS). Cross-trial comparison of similar products in the same disease*

have therefore to be interpreted cautiously depending on the CRS grading systems that were used e.g., 2014 Lee criteria versus 2019 ASTCT consensus criteria.

FDA Table 13: FDA- CRS Management

Medication	Overall N=97 N (%)
Tocilizumab (With or without corticosteroids and/or anakinra)	68 (70)
Tocilizumab without corticosteroids or anakinra	40 (41)
Tocilizumab and corticosteroids	24 (25)
Corticosteroids only	1 (1)
Anakinra	18 (18)
Tocilizumab, anakinra and corticosteroids	14 (14)
Tocilizumab and anakinra	4 (4.1)

Source: Applicant analysis; response to IR#32, IR#39

- *No patient received anakinra alone; the majority (14/18) received it with both tocilizumab and steroids, while 4 patients received it with tocilizumab*
- *In the label, the statement in section 5.1 “Forty-four (45%) patients received tocilizumab without corticosteroids” includes the 4 patients wherein tocilizumab was given with anakinra (n=40 tocilizumab only + n=4 tocilizumab and anakinra). The anakinra data is not specified in the label since it is not the standard of care and the reasons for its use in CARTITUDE-1 are unclear to us (see below)*
- *Of the 18 patients who received anakinra, majority (15 of 18) received more than 1 dose*
- *The reason for the high percentage (20%) of use of anakinra (IL-1 antagonist) in the study despite study protocol not mandating its use is unclear; this data was not captured in the CRF. Since most patients had Grade 1 or 2 CRS and CRS resolved in all but 1 patient, high usage is not explained by large numbers of patients with higher grade CRS, or unresolving CRS needing alternative therapy besides standard therapy with tocilizumab (IL-6 antagonist) and/or steroids. Recent shortages of tocilizumab also do not explain higher usage of anakinra since study was completed prior to such shortage.*

- *Two of 18 patients who received anakinra were given this medication for NT in addition to CRS.*

Hemophagocytic Lymphohistiocytosis

A single patient (USUBJID (b) (6) ; see also death narratives) with HLH was reported in CARTITUDE-1. Patient died of CRS/HLH on day 99; autopsy revealed extensive histiocytic infiltration in multiple organs; clinical course and autopsy findings consistent with fatal CRS/HLH.

Five other patients have had HLH in other trials (4 patients in CARTITUDE-2 and 1 patient in CARTITUDE-4) of cilta-cel to date (Applicant response to Question #3, IR#52). Three of 5 patients reported to have Grade 4 HLH (2 in study CARTITUDE-2 and the 1 patient in MMY CARTITUDE-4) while one patient each in study MMY2003 had Grade 2 and Grade 3 HLH respectively. Four of 5 patients with HLH in these studies have died of fatal AEs.

- *Many times, it is not possible to clinically distinguish between CRS and HLH and HLH may represent a more severe form of CRS. For USUBJID(b) (6) in study CARTITUDE-1, it appears that distinction between CRS and HLH was not possible. However, clinically, patient received multiple treatments to suppress inflammation and ablate CAR-T cells without success.*
- *Although none of the other 5 cases in other studies of cilta-cel have been reported to be fatal, review of the information provided in IR#52 raises the possibility that at least 2 patients likely had Grade 5 HLH ((b) (6) in study CARTITUDE-2 and (b) (6) in study CARTITUDE-4). USUBJID(b) (6) had multiple causes for death including HLH and neurologic toxicity (NT) while USUBJID (b) (6) died of extensive intracerebral hemorrhage with “predominant DIC from CRS/HLH” reported. A 3rd patient may have died of HLH ((b) (6)) since Grade 5 subarachnoid hemorrhage on day 63 was reported; HLH had previously been considered resolved for this patient but no laboratory details available at time of death to rule in or rule out coagulopathy from HLH at time of death.*
- *Given the above cases of life-threatening and fatal HLH, this information has been included in the label and the REMS training material.*

Neurotoxicity (specific to the product class)

Data:

Neurotoxicity is a known risk associated with CAR-T therapy. Twenty subjects (20.6%) experienced 1 or more treatment-emergent CAR-T cell neurotoxicity events, half of them experiencing Grade 3 or above events. CAR-T cell neurotoxicity was categorized as ICANS or Other Neurotoxicity occurring after recovery of CRS and/or ICANS (Figure 4).

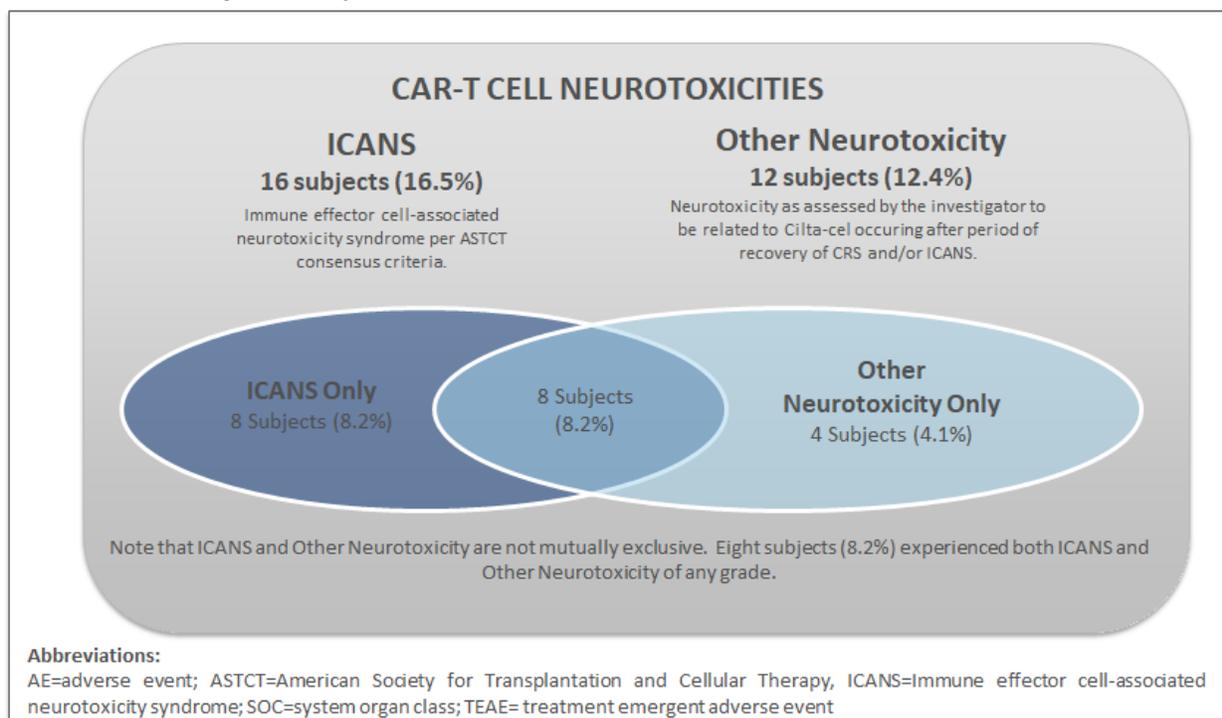
ICANS and Other Neurotoxicity are not mutually exclusive, 8 subjects had events in both categories.

- ICANS
 - Sixteen subjects (16.5%) had an ICANS event. For 15 of these subjects, ICANS occurred concurrent with CRS and for 1 subject, ICANS occurred 4 days after recovery from CRS.
 - All ICANS events occurred within 30 days of cilta-cel infusion. The median time from cilta-cel infusion to ICANS onset was 8 days (range: 3 to 12 days) and the median duration was 4 days (range: 1 to 12 days).
 - All subjects recovered from ICANS events.
 - Treatment emergent symptoms of clinical note for ICANS included: aphasia, slow speech, dysgraphia, encephalopathy, depressed level of consciousness, and confusional state.

- Other Neurotoxicity
 - Twelve subjects (12.4%) experienced Other Neurotoxicity not defined as ICANS assessed by the Investigator either due to symptoms or time of onset (ie, occurring after period of recovery from CRS and/or ICANS).
 - The median time from cilta-cel infusion to first onset of other neurotoxicities was 26.5 days (range: 11 to 108 days).
 - Four subjects had Other Neurotoxicity events with an onset within 30 days post cilta-cel infusion
 - Four subjects had Other Neurotoxicity events with an onset more than 30 days post cilta-cel infusion
 - Four subjects had Other Neurotoxicity events with mixed onset, ie, some events presented within 30 days post cilta-cel infusion and some events occurring more than 30 days post infusion
 - At the time of clinical cutoff, 6 of these 12 cases had resolved, 5 cases had not yet resolved (4 cases were ongoing at the time of death due to other causes and 1 case is ongoing), and 1 case was fatal due to neurotoxicity.

- Events reported for these 12 subjects included a variety of symptoms with varying severity including disturbances in consciousness, coordination and balance disturbances, movement disorders, mental impairment disorders, cranial nerve disorders, and peripheral neuropathies.
 - Movement and neurocognitive TEAEs
 - Although the symptoms associated with other neurotoxicity were widely varied, 5 of the 12 subjects experienced a similar presentation of movement and neurocognitive TEAEs. These included a cluster of movement (eg, micrographia, tremors, etc.), cognitive (eg, memory loss, disturbance in attention, etc.) and personality changes (eg, reduced facial expression, flat affect, etc.) TEAEs that were observed in some to progress to an inability to work or care for oneself.
 - These events had a median onset of 27.0 days from cilta-cel infusion (range: 14 to 108 days).
 - For 2 subjects, all events had an onset more than 30 days post cilta-cel infusion.
 - Three subjects had events with mixed onset, ie, some events presented within 30 days post cilta-cel infusion and some events occurring more than 30 days post infusion.
 - An analysis was performed to identify risk factors in these 5 subjects with the common presentation of neurotoxicity symptoms. The movement and neurocognitive TEAEs in these 5 subjects appear to be potentially associated with a combination of 2 or more factors such as high tumor burden, prior Grade 2 or higher CRS, prior ICANS, and high CAR-T cell expansion and persistence.
 - To minimize risk for patients in the ongoing cilta-cel clinical development program, monitoring and mitigation strategies were implemented including enhanced bridging therapy to reduce baseline tumor burden, early aggressive treatment of CRS and ICANS, handwriting assessments for early detection of neurotoxicity symptoms, and extended monitoring and reporting time for neurotoxicity up to 1-year post-cilta-cel infusion. As of the clinical cutoff, no further cases of other neurotoxicity characterized by movement and neurocognitive TEAEs have been reported.

Figure 4: Applicant - Overview of CAR-T Cell Neurotoxicities (All Treated Analysis Set)



The Applicant’s Position:

Cilta-cel has a safety profile generally consistent with the current understanding of CAR-T therapy and other BCMA CAR-T ide-cel therapy. ICANS and other neurotoxicities are described in the literature are known risks associated with CAR-T cell infusions. To manage the neurologic toxicity risks of cilta-cel in the post-marketing setting, labeling warnings and additional risk mitigation measures to assure safe use are planned. These will include controlled distribution to hospitals and associated centers that are qualified and only if the healthcare professionals involved in the treatment of a patient have completed the educational program. Patient materials will be also be provided.

FDA Assessment

Sixty-eight (70%) of 97 patients had one or more events (247 events) from Neurologic and/or Psychiatric system organ class (SOC). Of these 68 patients, twenty-five patients (26%) experienced one or more events of neurologic toxicity (NT) including Grade 3 or higher events in 11 patients (11%) that were attributed to cilta-cel. Adverse events in other SOCs may be included under the signs/symptoms of NT in these 25 patients where applicable (see below). Fifteen of 25 patients had resolution of NT. Of the 10 patients in whom NT did not resolve, 3 patients died of NT-1 with NT with parkinsonism, 1 with ICANS, and 1 with ICANS and CVA (also had PE as cause of death); 3 patients had NT

ongoing at time of death while NT was ongoing in 4 patients at time of the last known alive date. In patients who had NT ongoing at death, NT was Grade 2 in 2 patients and Grade 3 in 1 patient at time of death. Of the 3 patients who had NT ongoing at time of death, 2 patients had NT with parkinsonism (Grade 3 in 1 patient and Grade 2 in 1 patient) and 1 patient had Grade 2 peripheral neuropathy. Of the 4 patients who were known to be alive with ongoing NT, 3 patients had Grade 1 NT while 1 patient had Grade 2 NT. The ongoing NT in these 4 patients included Grade 1 parkinsonism, encephalopathy and tremor, and Grade 2 peroneal nerve palsy.

FDA Table 14: FDA- Neurologic Toxicity Grade

Worst Neurologic Toxicity Grade	Patients N (%); Total N=97
Neurologic Toxicity Any Grade	25 (26%)
Grade 1	6 (6%)
Grade 2	8 (8%)
Grade 3	7 (7%)
Grade 4	1 (1%)
Grade 5	3 (3%)

Source: FDA Analysis of ADAE dataset; Grade per CTCAE v. 5.0

- Applicant labeled neurologic toxicity as ICANS and “Other Neurotoxicity” that included those with NT with parkinsonism (Applicant uses term of “movement and neurocognitive disorder” for parkinsonism), neuropathy etc. Applicant used the flag/term- “other neurotoxicity” to indicate neurologic AEs attributed to product; the term/flag of other neurologic AEs was used to denote neurologic AEs not attributed to product.
- The clinical reviewer considered NT in a broad perspective irrespective of the subtype of NT or attribution of toxicity to the product by the Applicant. Based on data in the BLA submission for the CARTITUDE-1 study, SAE reports submitted to IND 18080 for studies CARTITUDE-1, CARTITUDE-2, and CARTITUDE-4, and Applicant responses to multiple IRs, the clinical reviewer identifies the following subcategories of NT: ICANS, parkinsonism (also referred to as NT with parkinsonism/parkinsonian features since patients have parkinsonian and non-parkinsonian features in the spectrum of NT), peripheral neuropathy (motor, sensory or combined), cranial nerve palsy (especially of the 7th cranial nerve) and Guillain Barre syndrome (GBS) as the principal NTs associated with the product. Whether some patients classified as having peripheral neuropathy and/or cranial nerve palsy could in fact have GBS or GBS variants has not been determined. Likewise, it is unclear if patients with NT with parkinsonism with some neurologic AEs reminiscent of those associated with classic ICANS (as described in the 2019 ASTCT consensus criteria) e.g., encephalopathy are having a subsequent episode of ICANS at a later timepoint following CAR-T therapy, or whether NT with parkinsonism represents a spectrum of ICANS (not reported at

time of 2019 criteria). These uncertainties will likely be clarified as these toxicities are better characterized.

- *For neurotoxicity, Applicant defined TEAE as that occurring up to a year following cilta-cel administration; beyond 1 year, events related to cilta-cel administration were reported. We reviewed all neurologic AEs after cilta-cel administration irrespective of timeframe to ensure that all delayed events beyond the time frame defined as TEAE or causality were assessed.*
- *In addition to neurologic and psychiatric SOCs, 17 neurologic events in 7 patients in study CARTITUDE-1 were in the following 5 SOCs with the following AEDECOD terms and included as symptoms of NT:*

i) General disorders and administration site conditions- gait disturbance, asthenia, fatigue, atrophy

ii) Ear and labyrinth disorders- hypoacusis

iii) Musculoskeletal and connective tissue disorders- muscular weakness, posture abnormal, muscle rigidity

iv) Eye disorders- diplopia

v) Injury, poisoning and procedural complications- fall

All patients with neurologic events in SOC other than neurologic and psychiatric SOC had neurologic events in the neurologic and/or psychiatric SOCs.

- *Two different grading for NT have been used- CTCAE v. 5.0 and 2019 ASTCT Consensus Criteria (Lee 2019) for ICANS. The above table reflects grading by CTCAE v. 5.0 of all neurologic events attributed to cilta-cel which is labeled as “neurologic toxicity”.*
- *During Phase 1b of the CARTITUDE-1 study, neurologic events of ICANS were graded using CTCAE v. 5.0; the 2019 ASTCT grading for ICANS was utilized only for the Phase 2 portion of the study. Two patients from the phase 1b portion of the study therefore had to be recoded using the 2019 ASTCT criteria. Three of 4 additional patients labeled by the clinical reviewer as having NT (see below) were in the Phase 1b part of the study. Of these 3 patients, 2 patients- USUBJID (b) (6) with AEDECOD terms of depression (days 8-10), dysarthria (days 8-9), mental impairment (day 8-9), somnolence (days 8-10) and USUBJID (b) (6) with AEDECOD terms of headache (days 2-9) and somnolence (days 8-9) likely had low grade ICANS but could not be mapped as such using ASTCT criteria. Patient (USUBJID (b) (6)) had AEDECOD terms of headache (days 2-28), confusional state (days 7-9) and myoclonus (days 42-57); headache and especially somnolence raise the possibility of*

ICANS; however, the investigator did not assess ICE scores after day 1 (ICE score 10/10 on day 1; IR#19) and hence patient was not classified as having ICANS. Patient (USUBJID (b) (6)) had impaired concentration (group term- encephalopathy Grade 2 days 28-55) that was considered as ICANS. All 6 patients are deemed to have ICANS and were included in the analysis per CTCAE grading.

- Less specific neurologic events e.g., headache, dizziness, insomnia, anxiety etc., that could be attributed to cilta-cel or have other causes e.g., other concomitant medications, were not taken into the calculation of ICANS especially if such events occurred in isolation. Less specific neurologic events occurring in patients with more classic symptoms of ICANS attributed to CAR-T cell products e.g., aphasia was included in the spectrum of ICANS for a given patient especially if such symptoms occurred in close proximity to the more classic symptoms of ICANS. Since prior reviews of CAR-T products for other products may have labeled all neurologic events as ICANS with attribution to drug product under consideration, caution must be exercised in cross-trial or cross-product comparisons of rates of ICANS. For non-ICANS NT, symptoms/signs that could clinically be indicative of NT were included e.g., falls in patients with parkinsonism.
- Applicant had included certain ICANS signs/symptoms under symptoms of CRS. These were re-classified as symptoms of ICANS in keeping with our prior review practices except for perhaps non-specific symptoms like headache especially if it occurred without other classic ICANS symptoms as discussed above. Two of the 4 additional patients (see bullet below; USUBJID (b) (6)) identified as having ICANS by the clinical reviewer had ICANS events mapped as CRS symptoms by the investigator.
- We classified 5 additional patients (USUBJIDs - (b) (6)) as having NT for a total of 25 patients with NT attributed to study product (Applicant analysis has 20 patients). Additionally, one patient (USUBJID (b) (6)) already flagged as having NT (peripheral neuropathy) was flagged as having ICANS; we subsequently did not include this patient's peripheral neuropathy since it was not verified by the investigator (see section on peripheral neuropathy). The maximum NT grade in 4 of 6 patients (USUBJIDs (b) (6)) was 1; 1 patient (USUBJID (b) (6)) had Grade 2 NT and 1 patient (USUBJID (b) (6)) had Grade 3 NT. Patient (USUBJID (b) (6)) had Grade 1 memory impairment (phase 1b part of study); patient (USUBJID (b) (6)) had Grade 3 fatigue (days 15 to ongoing), Grade 1 hallucinations (days 26-28), Grade 1 tremor (day 26-ongoing), Grade 2 fall (day 27) and grade 2 ataxia (days 26-28). Patient (USUBJID (b) (6)) was classified as having "noninfective encephalitis"; review of narrative unearthed the aforementioned symptoms; investigator had considered events as related to cilta-cel. Neurologic events in patients (USUBJIDs (b) (6)) are described in bullet #s 6 and 8 above.

- *Neurologic events not captured as NT in patients already flagged as having NT were added for the following patients (IR#34):*

i) **USUBJID (b) (6)** headache (Grade 1, days 10-11), restlessness (Grade 1, days 11-148) and facial paralysis (Grade 2, day 101-101)

ii) **USUBJID (b) (6)** - dizziness (Grade 1 days 8-9), headache (Grade 1 days 10-11) and hypoacusis (grade 1 days 14-19). Multiple other symptoms in this patient- falls, bowel incontinence, dysphagia etc., described in the narrative were not flagged in the ADAE dataset. In response to our query, Applicant stated that falls had been mapped to gait disturbance while bowel incontinence, dysphagia were placed under the verbatim term of “parkinsonism” by the investigator. Hence, the lack of detail in the ADAE dataset in such instances does not capture the full spectrum of such toxicity.

iii) **USUBJID (b) (6)** – amnesia (Grade 2 days 9-22), insomnia (Grade 1 days 10-22) and dizziness (Grade 1 days 11-22)

iv) **USUBJID (b) (6)** - Altered mental status (Grade 3 day 17-ongoing), dysarthria (Grade 3 day 28-ongoing) and depression (Grade 1 day 25-ongoing). There were several other symptoms in the narrative that were not captured in the ADAE dataset e.g., myoclonic jerks, lack of ocular movement etc. Applicant stated that some of these symptoms were part of the ICE score which in turn contributed to the ICANS grading- hence, these were not captured separately in the ADAE dataset. For some of the symptoms, Applicant stated that the site and investigator were queried but the investigatory signed off on the assessment as accurate at time of database lock.

- *Change in Grade: 2 patients (USUBJIDS (b) (6)) had maximum NT grade changed from Grade 4 to Grade 5. One patient (USUBJID (b) (6)) with NT with parkinsonism had maximum grade changed from Grade 3 to Grade 4 (see narrative in section on parkinsonism).*

i) *For patient (USUBJID (b) (6)), the clinical reviewer also disagreed with the Applicant assessment that ICANS had resolved in this patient but rather was ongoing at time of death from sepsis. However, upon further review of the narrative including the daily neurologic assessments/description of mental status provided, this patient had severe Grade 3 or 4 ICANS starting day 6 till death. Hence, Grade of NT for this patient was changed from 4 to 5 (see narrative under ICANS).*

ii) *For patient (USUBJID (b) (6)), Applicant stated that death was from respiratory failure attributed to pulmonary embolism (see bullet below). However, conclusion of autopsy report was that patient died of PE, CVA and NT due to CAR-T cell therapy. Hence, adjudication of grade of NT for this patient was changed from Grade 4 to Grade 5.*

- Narrative of 2 patients with Grade 5 ICANS (USUBJID (b) (6) and USBJID (b) (6)) are in the sub-section on ICANS below; narratives of patients with Parkinsonism who either died or had Parkinsonism at time of death (USUBJIDs (b) (6) are described in the sub-section on parkinsonism. Narrative of patient (USUBJID (b) (6)) with grade 2 NT ongoing at time of death is given in Section on Deaths.

The most common NT by FDA Group terms in all 97 patients treated with cilta-cel include encephalopathy in 23% (22/97), aphasia in 8% (8/97), ataxia in 6% (6/97), headache in 6% (6/97), delirium in 5% (5/97) and micrographia, paresis, Parkinsonism (note that 1 of 5 patients deemed to have NT with parkinsonism did not have parkinsonism recorded as an AEDECOD term in the ADAE dataset) and tremor each in 4% (4/97) of patients. Percentages of AEs in the 25 patients adjudicated to have cilta-cel related NT is in table 27 below. All but 1 patient had at least one symptom/sign (event) of NT start within 8 weeks of cilta-cel infusion. The median time to the onset of first event was 8 days (range 2-101 days). Neurologic toxicity resolved in 15 of 25 patients (60%) with a median time to resolution of 8 days (range 2-208 days). Median duration of NT in all patients including those with fatal events and NT ongoing at death or last known alive date was 62 days (range 2 to 926 days).

FDA Table 15: FDA - Neurologic Toxicity Events in 25 Patients with NT in CARTITUDE-1

FDA Group Term	All grade N (%) N = 25**	≥ Grade 3 N (%) N = 25**
Encephalopathy*	22 (88)	6 (24)
Aphasia*	8 (32)	0 (0)
Ataxia*	6 (24)	0 (0)
Headache	6 (24)	0 (0)
Delirium*	5 (20)	1 (4)
Micrographia	4 (16)	0 (0)
Paresis*	4 (16)	2 (8)
Parkinsonism	4 (16)	3 (12)
Tremor	4 (16)	0 (0)
Depression	3 (12)	0 (0)
Dizziness	3 (12)	0 (0)
Dysgraphia	3 (12)	1 (4)
Neuropathy*	3 (12)	2 (8)
Reduced facial expression	3 (12)	0 (0)
Bradykinesia	2 (8)	0 (0)
Fatigue*	2 (8)	2 (8)
Motor dysfunction*	2 (8)	1 (4)
Neurotoxicity	2 (8)	2 (8)
Atrophy	1 (4)	0 (0)
Aura	1 (4)	0 (0)
Cogwheel rigidity	1 (4)	0 (0)

FDA Group Term	All grade N (%) N = 25**	≥ Grade 3 N (%) N = 25**
Diplopia	1 (4)	1 (4)
Fall	1 (4)	0 (0)
Hypoacusis	1 (4)	0 (0)
Insomnia	1 (4)	0 (0)
Muscle rigidity	1 (4)	0 (0)
Nystagmus	1 (4)	0 (0)
Posture abnormal	1 (4)	0 (0)
Psychomotor retardation	1 (4)	0 (0)
Reflexes abnormal*	1 (4)	0 (0)
Sensory loss	1 (4)	0 (0)
Slow speech	1 (4)	0 (0)
Stereotypy	1 (4)	1 (4)
Visuospatial deficit	1 (4)	0 (0)

Source: FDA Analysis of ADAE dataset

* FDA Group Terms and AEDECOD terms-see [FDA Table 27](#)

** Calculations based on N = 25 patients with neurologic toxicity; total study population N=97

Abbreviation: NT-neurologic toxicity

- NT for each patient consisted typically of multiple AEs labeled as NT from mostly neurologic and/or psychiatric SOC, and/or less likely from other SOCs as described above. Duration of NT was calculated as the time between the earliest AE start date/day and the last AE end date/day. For patients with non-resolution of NT, the death date/day or the last known alive date/day were used to compute the duration of NT.
- AEs labeled as NT may or may not have had overlapping time courses; however, duration of NT was calculated as described above is inclusive of any time gaps between resolution of a preceding NT AE and onset of a subsequent NT AE e.g., for encephalopathy days 8-17 and Parkinsonism days 35-60, duration of NT would be calculated from day 8 to day 60. Since patients are not evaluated daily for the entire duration of NT, resolution of a given NT AE or onset of a given NT AE cannot be accurately determined. Furthermore, CAR-T cell associated NT (not limited to ICANS) can have a waxing/waning course. Assessment of duration of NT in this manner is consistent across all CAR-T product files. The Applicant had not assessed duration of NT in this manner and had calculated NT duration separately for ICANS and “other neurotoxicity” (non-ICANS NT).
- The clinical team grouped several AEs (AEDECOD terms in the ADAE dataset) under a single term (FDA Group term) as outlined in [FDA Table 27](#) whenever possible. Grouping was based on terms used in other files and clinical judgement of the group term most likely to fit the AEDECOD term under consideration e.g., mental status changes, confusion were grouped under encephalopathy. Grouped terms are used wherever applicable so that same/similar adverse events are not under-reported due

to use of different terminology in reference to the same/similar AE. Applicant was provided with the preferred (AEDECOD) terms listed under a specific FDA group term.

- No case of cerebral edema has been reported (IR#39) in CARTITUDE-1 for the USA cohort as of the February 11, 2021 (clinical cutoff for 120-day Safety Update), CARTITUDE-1 (Japan cohort) as of July 22, 2021, CARTITUDE-2 as of April 15, 2021 (clinical cutoff as in the 120-day safety update) and CARTITUDE-4 as of Applicant's Global safety database monitoring cumulative through September 10, 2021.*
- Given that all but 1 patient had onset of any NT AE within 8 weeks, we decided to keep driving restrictions for 8 weeks in the label as in other CAR-T labels. Since NT can occur even after 8 weeks especially in those with persistent or delayed CAR-T expansion, the label includes a statement that urges caution with respect to driving at onset of NT at any timepoint beyond 8 weeks.*

Categories of Neurologic Toxicity

1. Immune Effector Cell Associated Neurotoxicity Syndrome (ICANS)

Signs and symptoms of ICANS by CTCAE v 5.0 occurred in 22 of 25 patients with neurologic toxicity attributed to cilta-cel. Median time to onset was 8 days (range 1-28 days). Seventeen of 22 patients (77%) had resolution of ICANS with a median time to resolution of 6 days (range 2-143 days). Two patients died of ICANS (one of these patients had CVA and PE as additional causes of death), symptoms in 1 patient were ongoing at death from NT with parkinsonian features while 2 patients had ongoing symptoms at last known alive date. Median duration of ICANS in all patients including those in whom ICANS resolved, those who died from the toxicity or another cause, and those that had toxicity ongoing at the last known alive date is 7.5 days (range 2-927 days). In patients with ongoing toxicity, 1 patient had grade 1 toxicity at death and 2 patients had grade 3 and grade 1 toxicity respectively at last known alive date.

The most common symptoms of ICANS (by FDA Group terms; denominator of 97 patients) are encephalopathy (23%), aphasia (8%), headache (6%), delirium (4%), ataxia (3%), dizziness (3%), tremor (3%), depression (2%) and dysgraphia (2%). Other symptoms (occurring in 1% pf patients) include aura, diplopia, fall, fatigue, hypoacusis, insomnia, neurotoxicity, nystagmus, abnormal reflexes, slow speech and visuospatial deficit.

- The 2019 ASTCT Consensus Grading Criteria assess ICANS in 5 domains- the ICE (Immune effector Cell-associated Encephalopathy) score, level of consciousness, motor findings, presence or absence of cerebral edema and presence or absence of seizures. The ICE score in turn has 5 objective components encompassing orientation, naming, following commands, writing and attention. Since this grading system was used only for phase 2 portion of the study, there were patients with symptoms of ICANS in phase 1 who were unable to be graded using these criteria*

since ICE scores were not available. Additionally, ICE scores were not available for some patients in phase 2 part of the study at the time of neurologic symptoms. Therefore, in order to avoid undercounting patients with this toxicity given the lack of data for grading purposes by 2019 ASTCT criteria, we decided to use the CTCAE grade for reporting this toxicity in the label. However, since majority of patients in the Phase 2 study were managed using the ASTCT criteria and since there appears to be increasing use of ASTCT criteria in ongoing studies with cilta-cel, management guidelines for ICANS will be aligned using grade, descriptive symptoms and ICE scores that are consistent with ASTCT criteria.

- We included less specific symptoms of ICANS e.g., headache in our calculations for ICANS if the symptoms occurred during the timeframe of ICANS (as described in the literature to date) and if it occurred with other symptoms that are considered more specific for this toxicity e.g., aphasia. Symptoms occurring in $\geq 5\%$ of patients (of the total number of patients in CARTITUDE-1) are included in the label.
- Symptoms of ICANS e.g., encephalopathy occurring after the onset of NT with parkinsonian features were not considered as ICANS for labeling purposes given that we are unclear if such symptoms are a second episode of ICANS as currently described in the literature, have the same or different pathophysiology and/or represent a distinct toxicity (see also discussion on this issue under NT with parkinsonism/parkinsonian features).
- We disagreed with the Applicant's assessment that USUBJID (b) (6) had resolution of ICANS (IR#34). Review of the narrative revealed that this patient died of ICANS. Narrative for this patient is given below.

USUBJID (b) (6) : 77-year-old male with 12 prior lines of therapy and ASCT x 2 who reportedly died of sepsis on day 45 following cilta-cel infusion; received bridging therapy. Had Grade CRS for days 2-8 complicated by Grade 3 supraventricular tachycardia; Grade 3 ICANS reported on day 6. Review of neurologic assessments in the narrative reveal profound encephalopathy and aphasia till death with very few days wherein patient could have some meaningful interaction; obtunded on day 34 prior to intubation with no responsiveness or speech output; unresponsive even to sternal rub starting day 39 despite withdrawal of all sedation. Other manifestations of NT included generalized tremulousness, myoclonic jerks, absence of spontaneous limb movements, cognitive slowing, positive Babinski sign bilaterally, blurred vision, dysarthria, depression and nystagmus. Evaluation of NT revealed abnormal EEG (day 7), normal CT head except for volume loss, MRI suggestive of subacute infarcts, CSF negative for viral, fungal and mycobacterial testing and mostly acellular with 4% of all cells being CD3+ T cells. Intubated on day 34 for hypoxia; chest X-ray showed likely atelectasis bilaterally with possible aspiration pneumonia. Treated with systemic and IT (intrathecal) corticosteroids, anakinra, tocilizumab, levetiracetam. Diagnosed with sepsis on day 40; no positive blood cultures reported; sputum showed Staphylococcal

aureus and Enterococcus faecalis. Treated with antifungal and antibacterial therapy. Clinical course complicated by profound pancytopenia with last ANC (absolute neutrophil count) of 480 (day 42) and platelet count of 6000 (day 44) just prior to death on day 45. Bone marrow (day 42) showed hemosiderin laden macrophages but no definitive hemophagocytic histiocytes. No autopsy was done. Given profound NT starting early in the clinical course that continued, clinical team has determined cause of death to be NT (Grade 5); hypoxia and hypotension can be seen with severe NT as well. Patient was predisposed to sepsis given prolonged, severe pancytopenia and NT; sepsis may have contributed to death.

- We also disagreed with death adjudication for USUBJID (b) (6) as being only from respiratory failure due to pulmonary embolism (PE). Patient was adjudicated to have died from multiple causes to include ICANS, CVA and PE. Narrative provided below.

USUBJID (b) (6) : 64-year-old white female with 14 prior lines of therapy for MM including autologous and allogeneic stem cell transplant, and radiation therapy for skull plasmacytoma who died on day 121 following cilta-cel infusion; received bridging therapy. Had Grade 1 CRS days 8-14 and Grade 2 ICANS days 8-12; treated with Tocilizumab, Anakinra and steroids. Subsequent course complicated by Grade 4 febrile neutropenia on day 32 with blood cultures positive for *Pseudomonas* which resolved on day 41; developed soft tissue infection on day 41. Had recurrence of infection (Grade 3 sepsis and limb abscess-drainage positive for *clostridium difficile*, *Parabacteroides*) on day 88. Noted to have Grade 4 NT (no specifics as to what the grade 4 event(s) were), Grade 2 cerebrovascular accident, Grade 2 seizures starting day 93. Neurological events of confusion, obtundation, bilateral tremors, nystagmus seen thereafter; EEG showed diffuse cortical dysfunction with multifocal epileptiform potential on day 112; MRI revealed middle cerebral artery branch occlusion, cerebral infarct (left insular cortex); CSF analysis positive for CAR-T cells, monocytes (30%) and macrophages on day 106; patient received anti-thymocyte globulin (ATG) for NT (for CAR-T cell ablation) in addition to steroids and Anakinra for Rx of NT. Aphasia and tongue protrusion were other symptoms reported in amendment to IND (response to IR dated 03.04.2020). Other AEs during this time included DIC (this was in the narrative submitted to the IND 18080) with bleeding from rectovaginal fistula (received Amicar for this), pancytopenia including grade 4 thrombocytopenia (had received TPO agonists starting day 38), cultures positive for *Acinetobacter* (rectal swab), recto-vaginal fistula and bilateral extensive lower extremity proximal vein DVTs (Grade 4). Autopsy report concluded that cause of death was multifactorial: PE (clot extended from right hilum to right lower lobe, CVA and CAR-T cell NT i.e., ICANS (IR#13; part 1 of response). Other autopsy reports of significance include hypocellular bone marrow (increased fat to cell ratio) with hemosiderin laden macrophages and increased iron stores and significant coagulopathy (lab, gross and histopathological findings). Stringent CR achieved on day 56 and was in sCR at time of death. We re-adjudicated duration and grade of ICANS from that reported (Grade 2 days 8-12) to days 8-121 and grade 5 to include the findings later in the clinical course and the autopsy report.

2. Neurologic toxicity with Parkinsonism/Parkinsonian features

Five of 25 patients [(20%); 5% overall i.e., 5/97 study patients) with NT had a constellation of several signs/symptoms consistent with parkinsonism (see FDA Table 16 below for list of symptoms) with a median time to onset of 43 days (range 15-108 days). These patients had an admixture of parkinsonism and non-parkinsonian neurologic signs/symptoms and despite some overlap of symptoms like encephalopathy with ICANS, were considered to have NT distinct from ICANS. A 6th patient in study CARTITUDE-2 with the same toxicity has been reported. All 6 patients with parkinsonism (N=5 in CARTITUDE-1 and N=1 in CARTITUDE-2) to date are males with a median age of 60 years (range 44-77 years); all had CRS (Grade 3 in 2 patients and Grade 2 in 4 patients) and 4 of 6 patients had grade ICANS-all grade 1 (2 patients did not have ICANS). The maximum grade of parkinsonism in these 6 patients are Grade 5 in 1 patient, Grade 4 in 1 patient, Grade 3 in 3 patients and Grade 2 in 1 patient.

Neurologic toxicity with parkinsonism did not resolve in any patient; 3 patients died- 1 patient of neurologic toxicity with parkinsonism; 2 patients had parkinsonism ongoing at time of death from other causes (lung abscess, septic shock). The remaining 2 patients had toxicity ongoing at last known alive day. Median duration of toxicity in all 5 patients was 205 days (range 62-488 days). Attempted treatment (N=6; includes 1 patient from study CARTITUDE-2) including systemic chemotherapy (4/6), systemic glucocorticoids (4/6) intrathecal chemotherapy and steroids (3/6), dopaminergic agents (2/6), plasmapheresis (2/6), intravenous immunoglobulin (1/6), siltuximab (1/6) and Dasatinib (1/6) did not result in resolution of toxicity.

FDA Table 16: FDA - Parkinsonian Symptoms in 5 Patients in CARTITUDE-1

FDA Group Term	All Grade N (%) N = 5	Grade 3 or higher N (%) N = 5
Micrographia	4 (80)	0 (0)
Parkinsonism	4 (80)	3 (60)
Encephalopathy*	3 (60)	3 (60)
Reduced facial expression	3 (60)	0 (0)
Ataxia	2 (40)	0 (0)
Bradykinesia	2 (40)	0 (0)
Tremor	2 (40)	0 (0)
Cogwheel rigidity	1 (20)	0 (0)
Delirium	1 (20)	1 (20)
Depression	1 (20)	0 (0)
Dysgraphia	1 (20)	1 (20)
Fatigue	1 (20)	1 (20)
Motor dysfunction*	1 (20)	1 (20)
Muscle rigidity	1 (20)	0 (0)
Neuropathy*^	1 (20)	1 (20)
Neurotoxicity	1 (20)	1 (20)

FDA Group Term	All Grade N (%) N = 5	Grade 3 or higher N (%) N = 5
Paresis [^]	1 (20)	1 (20)
Posture abnormal	1 (20)	0 (0)
Psychomotor retardation	1 (20)	0 (0)
Stereotypy	1 (20)	1 (20)

Source: FDA Analysis of ADAE dataset

^{*}Group term; see FDA Table 27 for list of group and preferred (AEDECOD) terms

[^]Symptoms seen in patient with parkinsonism but unclear if symptoms part of NT with parkinsonism or a distinct neurologic toxicity but likely the latter.

- The symptoms listed in FDA Table 16 above are not inclusive of all symptoms seen in these patients since the ADAE dataset did not reflect all the symptoms in the narrative or symptoms were those encompassed by the term “parkinsonism” as in the ADAE dataset without being specified further by the investigator.
- Certain symptoms such as tremor, etc. were common to both parkinsonism and ICANS. Such symptoms occurring early following cilta-cel administration during the time period of ICANS were not included as symptoms of parkinsonism. Whether such symptoms resulted from two distinct neurological syndromes or reflect a spectrum of the same NT is unclear.
- Of all the terms under the group term of encephalopathy, the following were seen in these patients- memory impairment, mental status changes, confusional state and somnolence. The other AEDECOD terms (group terms in parenthesis) that were reported in the ADAE dataset are: flat affect (depression), gait disturbance (ataxia), muscular weakness (motor dysfunction), personality change (delirium), peroneal nerve palsy (paresis), peripheral motor neuropathy (neuropathy). Although peroneal nerve palsy and peripheral motor neuropathy occurred in a patient with parkinsonism, they represent peripheral nerve involvement as opposed to central nervous system involvement seen with parkinsonism and thus likely represent neurologic toxicity distinct from parkinsonism.
- Symptoms described in the narratives (all 6 patients) but not in any of the terms in FDA Table 16 above or in the bullet above include involuntary movements, loss of spontaneous movements, masked facies, apathy, apraxia, lethargy, loss of consciousness, delayed reflexes, hyperreflexia, difficulty swallowing, bowel incontinence, falls, stooped posture, shuffling gait, muscle wasting, sensory loss, frontal lobe release signs and akinetic mutism. Since the ADAE dataset did not capture the rich detailed description of this syndrome presented in the narratives, these symptoms are listed in the label so that healthcare professionals and patients are appropriately informed of the signs/symptoms, clinical course and possible mitigation strategy of this toxicity from the data available so far.

- Applicant used the term “movement and neurocognitive TEAE” to describe this toxicity. We decided to use the term “parkinsonism” to describe this NT for the following reasons:

i) Many of the movement, posture and personality signs/symptoms of this NT are consistent with parkinsonism. The term parkinsonism refers to a clinical syndrome characterized by any combination of bradykinesia, rest tremor, rigidity and postural instability; parkinsonism may result from Parkinson disease (disorder characterized by progressive neuronal loss in the substantia nigra and associated regions and is responsive to dopaminergic therapy) or from various other etiologies e.g., medications, toxins, repeated head trauma etc.

ii) As opposed to the Applicant’s term, the term “parkinsonism” easily conjures up a clinical picture for the healthcare professional; this may help facilitate the early and easy recognition of this entity. This may also better help in capturing the incidence of this toxicity in the post-marketing setting. Indeed, trial investigators used the AEDECOD term “parkinsonism” to indicate this toxicity without specifically referring to the symptom/sign(s) that prompted this designation. In addition, the pathological findings in the limited sample size from autopsy, suggested that the substantia nigra (a region consistent with Parkinson’s disease) suggesting that the term parkinsonism rather than Parkinson’s disease is more appropriate.

iii) Parkinsonism has been the term used to describe this NT in another product label in the same class.

- There was no pooled analysis of safety for studies CARTITUDE-1 and CARTITUDE-2. Patient in CARTITUDE-2 also had frontal lobe signs/symptoms which are new compared to that reported with patients with similar NT reported in CARTITUDE-1. Hence, information on the symptoms of the 6th patient with NT with parkinsonian features was added in the label and the memo to give the maximum possible information on this new toxicity associated with this product; however this patient was not included in the analysis of number of patients or other analyses e.g., time to onset pertaining to this toxicity in the label given that the 6th patient is in an ongoing trial and it was decided not to include details of AEs for this patient due to the following limitations: i) inadequate follow up ii) denominator i.e. total number of patients in trial is not available iii) data has not been verified by the clinical reviewer.

Narratives of patients with neurologic toxicity with parkinsonism

1. USUBJID (b) (6)

58-year-old male with 3 prior lines of therapy including ASCT and radiation to the spine underwent cilta-cel infusion following lymphodepletion; received bridging therapy with carfilzomib and dexamethasone. Developed Grade 2 CRS, and Grade 1 ICANS days 8-

11; received tocilizumab but no steroids. Onset of Grade 2 Parkinsonism at day 43. Symptoms reported at varying times during clinical course include tremor, apathy, memory loss, decline in cognitive function, micrographia, shuffling gait, monotone speech. Symptoms worsened on day 78 with further worsening of symptoms starting day 100. Now noted to have Grade 3 encephalopathy, decline in personal hygiene, bowel incontinence, hyperreflexia, apathy. CSF analysis (day 109) showed 98% lymphocytes (total WBC count of 24) with CD4+ and CD8+ T cells; MRI (day 128) normal; EEG (day 128) consistent with mild/moderate encephalopathy. Systemic corticosteroids (days 116-140) and chemotherapy (oral Cyclophosphamide days 144-146) started but patient continued to deteriorate- wheelchair bound, difficulty with word finding, swallowing and chewing, involuntary movements of head, decreased movement and motor planning, falls, muscle wasting, severe malnutrition. Placed on hospice care starting day 135; unresponsiveness and hallucinations reported day 246. Patient died of neurologic toxicity with parkinsonian features on day 247 (Grade 5 NT); no autopsy performed; CAR+ CD3+ T cells were noted to be high as of day-128 (2624 cells/uL) and had increased since the day 105 assessment (2464 cells/uL). Myeloma status: sCR as of day 78.

- *Clinical team agreed with Applicant adjudication of Grade 5 NT with parkinsonism*
- *Increased expansion of CAR-T cells at day 128 as compared to day 105 is concerning*

2. USUBJID (b) (6)

58-year-old white male with 6 prior lines of therapy including ASCT x 2 and radiation for extramedullary plasmacytoma who received cilta-cel following lymphodepletion; received bridging therapy with melphalan and steroids; had extramedullary disease at baseline. Had CRS days 9-14-maximum Grade 3 treated with steroids, Anakinra and Tocilizumab; no ICANS; had pneumonia (Grade 4) and febrile neutropenia that resolved (days 51-57). Diagnosed with Parkinsonism on day 101; signs/symptoms included bradykinesia, micrographia, reduced facial expression, resting tremor, delayed reflexes, slow gait, monotone speech, slow alternating movements, fatigue, apraxia and stooped posture. Maximum Grade 2 for parkinsonism symptoms. MRI brain negative (mild chronic changes but no acute findings); DaT scan (Ioflupane I 123 injection, with SPECT imaging on day 155) normal (read as findings not supportive of Parkinson disease or parkinsonism); CSF analysis (x 3) showed no malignancy, autoimmune encephalitis, normal protein and glucose, low WBC count with mature lymphocytes). Treatment included single dose of hydrocortisone IV (day 135 for fatigue), (Anakinra (days 123-137), carbidopa/levodopa (days 135-147), IVIG x 1, 2 doses of IV cyclophosphamide (days 149, 156), 2 doses of intrathecal (IT) steroids and Ara-C (days 149, 156) and plasmapheresis (days 105-106); however, many of the symptoms were noted to be ongoing at time of death. Diagnosed with septic shock on day 161; blood cultures positive for *Serratia marcescens*; chest X-ray with right lower lobe pneumonia. Patient died of septic shock on day 162 despite Rx with multiple antibiotics, oxygen and vasopressor support. Peripheral blood CAR-T cells high on day 100 (562 CAR+CD3+ T-cells/uL) and day 156 (417 CAR+CD3+ T-cells/uL; 80% of all CD3+ cells were CAR-T cells). Myeloma status: best VGPR on day 79.

Autopsy showed focal gliosis of anterior caudate lobe, gliosis of- medial aspect of thalamus, basal ganglia, deep gray matter, white matter, perivascular CD3+ T-cell infiltrate- cerebrum and brainstem, parenchymal CD3+ T-cell infiltration- periventricular region of basal ganglia and subthalamic regions, moderate neuronal loss and gliosis in cerebral cortex. Normal density of pigmented neurons was noted within the substantia nigra and locus ceruleus of the midbrain and pons; no neurofibrillary tangles or neuronal inclusions were noted; there was no hemorrhage, cavitation of inflammation within the cerebral cortex, cerebellum, white or deep gray matter.

- *Clinical team agrees with Applicant adjudication of death from septic shock*
- *Autopsy findings showing preservation of pigmented neurons in substantia nigra is notable since this region is typically involved in Parkinson disease; however, this finding does not exclude the clinical entity of parkinsonism.*

3. USUBJID(b) (6)

62-year-old white male with 9 prior lines of therapy including allogeneic and autologous SCT, prior radiation- to femur, humerus, scapula and clavicle received bridging therapy with daratumumab, pomalidomide and dexamethasone. Had CRS maximum Grade 2 days 7-10 and ICANS (maximum Grade 2) days 8-10; received steroids, Tocilizumab and Levetiracetam. Noted to have micrographia day 15 with Parkinsonism on day 19; worsened to Grade 3 on day 30. Symptoms/signs during clinical course included micrographia, reduced facial expression-“masked facies”, slow speech, decreased arm swing, severe psychomotor retardation, decreased blinking, saccadic eye movements, tongue protrusion (“fly-catcher” tongue) and fasciculations, cogwheel rigidity, bradykinesia, bilateral resting tremors, shuffling gait, hypophonia, decreased upward gaze, difficulty in speech and swallowing, memory impairment, unresponsiveness to noxious stimuli and absence of spontaneous limb movements. Brain imaging (CT, MRI) had various findings at different times- myelomatous calvarial involvement, subacute subdural hematomas, leptomeningeal enhancement; EEG consistent with encephalopathy. CSF showed presence of CAR-T-cells and was negative for autoimmune antibodies, myeloma or infectious agents. Treatment included systemic corticosteroids (dexamethasone days 22-110), Anakinra (days 76-82 and 86-102), dasatinib (days 65-67, 73-107), carbidopa/levodopa (days 37-102), cyclophosphamide IV (day 52), IT steroids and chemotherapy x 2: Ara-C and hydrocortisone (day 53) and methotrexate (day 61). siltuximab (day 57) and levetiracetam (days 64-65). Peripheral blood CAR+CD3+T-cells were 1172/uL on day 102 and patient had ongoing Parkinsonism symptoms at death despite treatment. Other events include bacterial sepsis (day 57; blood cultures positive for pseudomonas and Klebsiella), invasive skin fungal infection, cavitory lung lesion and pneumonia. Patient died day 119 of lung abscess. Autopsy showed right lung abscess with empyema, bone marrow with 80% plasma cells and vertebral lesion with viable myeloma tumor. Brain findings at autopsy include the following-

i) Striatal degeneration of basal ganglia with marked reactive gliosis, focal vacuolization and scattered degenerating cells consistent with neuronal loss
ii) Preserved pigmented neurons in the substantia nigra and locus ceruleus
iii) Rarefaction of white matter of medulla
iv) Normal histology of dura, frontal-, parietal- and occipital lobes
v) Positive beta-amyloid staining (but negative for tau) showing diffuse plaques in frontal and parietal cortex that was not thought to be associated with any clinical symptoms
vi) Perivascular and clustered interstitial T-cell infiltrates in the striatum (gray matter mostly); mostly CD8+ with few CD4+ cells; perivascular T-cells also noted more diffusely-midbrain, pons, frontal, parietal and occipital lobes, hippocampus, cerebellum and medulla.

- *Applicant adjudication of neurologic toxicity with parkinsonism Grade 3 was changed to Grade 4 based on the grade of encephalopathy later in the course of neurologic toxicity with parkinsonism.*
- *Clinical team agrees with Applicant adjudication of death from lung abscess; patient had extensive myeloma at death but without CNS involvement (CSF and autopsy negative for myeloma)*
- *Brain autopsy findings showed preserved pigmented neurons in the substantia nigra and locus ceruleus, regions affected in Parkinson disease; however, findings consistent with parkinsonism include degeneration and neuronal loss in the basal ganglia, and diffuse CAR T-cell infiltration in multiple brain regions including the striatum.*

4. USUBJID (b) (6)

68-year-old white male with 4 prior lines of therapy including ASCT and radiation who received bridging therapy with dexamethasone followed by lymphodepletion and cilta-cel infusion. Had Grade 1 CRS days 7-8 treated with Tocilizumab and grade 1 ICANS days 12-14. Hospitalized on day 108 with Parkinsonism symptoms. Symptoms/signs of NT with parkinsonism included muscular weakness, personality change, lower extremity vibratory sense loss, altered mental status, confusional state, dysgraphia, stereotypy, asthenia and motor dysfunction (weak grasp). Maximum grade of NT with parkinsonism was Grade 3. Other neurologic symptoms that patient had include motor neuropathy and bilateral peroneal nerve palsy. Dysgraphia, mental status changes, motor dysfunction and asthenia did not resolve; peroneal nerve palsy, motor neuropathy also persisted. MRI brain negative except for osseous myeloma lesions. Treated with dexamethasone (days 110-219; varying doses with some gaps in therapy), levetiracetam (days 132-150), IT hydrocortisone and methotrexate (day 135), IV cyclophosphamide (1 gm on day 138). Other clinical events included syncope, atrial fibrillation, pneumocystis pneumonia with respiratory failure, CMV viremia, prolonged Grade 4 thrombocytopenia that required an ASCT (day 220). Peripheral blood CAR+CD3+ T -cells were 115/uL (day 240; CAR-T cells 4% of cCD3+ cells). Myeloma response assessment- sCR (day 80) with no

subsequent progression documented as of data cutoff (day 345). Last know alive day for this patient is day 530.

- *Parkinsonism symptoms include personality change, dysgraphia and stereotypy. The term NT with parkinsonism includes both parkinsonian and non-parkinsonian symptoms. Peroneal nerve palsy and motor neuropathy reported during the same timeframe as parkinsonism may reflect a different subclass of NT i.e., affecting the peripheral nervous system versus CNS as in parkinsonism.*

5. USUBJID (b) (6)

77-year-old white male with 10 prior lines of therapy received bridging therapy with dexamethasone followed by lymphodepletion and cilta-cel infusion. Had CRS (maximum Grade 3) days 6-9 and Grade 1 ICANS days 7-10; treated with tocilizumab, Anakinra and steroids. Onset of NT with parkinsonism was on day 27 (started with tremor). Signs/symptoms included bilateral hand tremor, cogwheel rigidity, bradykinesia, slow gait, micrographia, stooped posture, psychomotor retardation and hyporeflexia; maximum toxicity grade was 3. Patient did not receive any treatment for NT with parkinsonism. Most NT with parkinsonism symptoms resolved except for gait disturbance that remained ongoing at time at clinical data cutoff. CAR+CD3+ T-cells declined rapidly to 7 cells/uL by day 81 and were undetectable by day 101. Patient had length-dependent lower extremity neuropathy that was thought to be out of proportion to that observed with chemotherapy (not recorded in ADAE dataset), Grade 4 neutropenia and Grade 3 thrombocytopenia (till day 100), transaminase elevation that resolved. Myeloma response assessment: VGPR (day 101) with no disease progression reported.

- *Only patient with improvement in some parkinsonism symptoms (had ongoing gait disturbance) without any intervention; only patient with parkinsonism in CARTITUDE-1 to have high grade (Grade 3) CRS.*

6. USUBJID (b) (6) (Study CARTITUDE-2)

44-year-old male who received bridging therapy with bortezomib, doxorubicin and dexamethasone followed by lymphodepletion and cilta-cel infusion. Developed Grade 3 CRS (details not available in MedWatch report) requiring ICU admission that subsequently resolved; no history of ICANS. Subsequently noted by wife to have severe fatigue, “doing thing slowly” and “falling asleep easily”. Symptoms described in MedWatch report include encephalopathy with frontal symptoms, bradykinesia, flat affect, psychomotor retardation, apathy, akinetic mutism, rigidity, parkinsonian gait and stance. Grade 3 bradyphrenia, cognitive disorder, encephalopathy, bradykinesia, gait disturbance and motor dysfunction with onset on day 38 (IR#39) reported. MRI brain showed abnormal, subtle T2-FLAIR hyperintensity of the caudate lobe bilaterally; EEG with bilateral temporal lobe slowing (L>R); CSF negative for infection or paraneoplastic panel. On high-dose steroids, IVIG and plasmapheresis with minimal improvement; toxicity ongoing.

Clinical Reviewer Comments (based on all narratives of patients with parkinsonism)

- Applicant categorized a patient as having parkinsonism if the following criteria were met (IR#19):

i) Reported MedDRA preferred terms in at least 2 of 3 domains that included movement disorder, cognitive impairment and personality changes

ii) Onset of such symptoms occurred after recovery of CRS and ICANS

iii) Investigator flagged symptoms as “other neurotoxicity”

The clinical reviewer looked for all neurologic symptoms that could potentially characterize such toxicity irrespective of the Applicant’s categorization of such events as detailed above. It is difficult to distinguish whether symptoms such as tremor and micrographia noted during ICANS signal the onset of parkinsonism or are less-specific symptoms of ICANS. It is also unclear if symptoms characteristic of parkinsonism e.g., masked facies, cogwheel rigidity, shuffling gait etc. occurring in isolation represent a less severe manifestation of parkinsonism. Two patients with isolated symptoms of ataxia (days 74-211) and impaired cognition (days 28-55) had occurrence of a single symptom in the movement and cognition domain respectively and were not flagged as parkinsonism; we agree with the Applicant’s assessment in these 2 instances. Had the symptoms in these 2 patients been more typical of parkinsonism e.g., rigidity or masked facies, we likely would have classified the patients as having parkinsonism.

- All 5 patients in CARTITUDE-1 with parkinsonism had robust, delayed and/or persistent CAR-T cell expansion (data in narratives above; Applicant response IR#19 in this BLA; response to IR dated 03.04.2020 in IND 18080). Patients (USUBJIDs (b) (6)) ranked 1, 2 and 3 respectively in peripheral blood CAR-T cell expansion data ranked from highest to lowest. However, not all patients with robust, delayed and/or persistent CAR-T expansion had parkinsonism.

- Some patients with parkinsonism experienced later in the time course symptoms/signs e.g., encephalopathy, seen in ICANS. We queried the Applicant as to why these events could not be a 2nd episode of ICANS (IR#19, Question 7). Applicant did not consider such symptoms to be ICANS for the following reasons:

i) onset of parkinsonism occurred later than that described for ICANS in the ASTCT 2019 grading criteria (usually within 4-8 weeks following CAR-T infusion for ICANS); in CARTITUDE-1, onset of ICANS was < 3 weeks

ii) symptoms were unresponsive to steroids and/or other therapy

iii) PK profile with delayed, persistent CAR-T cell expansion as opposed to time to C_{max} of 10-14 days for ICANS

iv) lack of change in ICE scores during parkinsonism versus change in ICE scores seen during ICANS

v) Differences in imaging: MRI/CT unremarkable in parkinsonism versus diffuse white matter changes and cerebral edema in ICANS. FDG-PET with basal ganglia hypometabolism in parkinsonism versus diffuse cortical hypometabolism in ICANS

vi) Differences in autopsy findings: Perivascular and parenchymal T-cell infiltrate, degenerative changes in basal ganglia in parkinsonism versus perivascular T-cell infiltrate and lack of basal ganglia degeneration in ICANS.

We acknowledge that parkinsonism as a toxicity of CAR-T cell therapy needs to be better characterized but for the following reasons we disagree with the Applicant's position stated above:

i) The 2019 ASTCT criteria defined ICANS as "a disorder characterized by a pathologic process involving the central nervous system following any immune therapy that results in the activation or engagement of endogenous or infused T-cells and/or other immune effector cells." By this definition, the entire spectrum of parkinsonism symptoms would be included in ICANS since that toxicity appears to result from T-cell engagement in the CNS.

ii) Parkinsonism as a toxicity was not reported with the approved CAR-T cell therapies at the time of publication of the 2019 ASTCT consensus criteria. As more CAR-T therapies with different antigenic targets and CAR constructs are studied and approved, the spectrum of ICANS may change.

iii) ICANS as currently described in the ASTCT consensus criteria is tied with robust, early CAR-T expansion seen in previous CAR-T product. Similar CAR-T expansion occurring later following CAR-T cell infusion as with cilta-cel could result in the same symptoms since toxicity appears dependent on peak expansion and therefore is irrespective of the timing of such expansion.

iv) Lack of reversibility with steroids or other therapy is not an argument against ICANS since not all ICANS resolves with therapy; ongoing or fatal ICANS has occurred with cilta-cel and has been reported with approved CAR-T therapies to date. Lack of irreversibility following resolution of CAR-T cell expansion may simply reflect irreversible damage to the CNS during peak CAR-T expansion, and thus continuation of symptoms despite decline in CAR-T cell numbers.

v) Imaging differences between ICANS and parkinsonism are difficult to interpret since few patients with parkinsonism had FDG-PET. The observed cases of

parkinsonism appear to involve the basal ganglia in particular, based on limited imaging and autopsy findings. These cases may represent an extended spectrum of ICANS, or a completely different toxicity. Some symptoms attributed to ICANS but deemed not specific e.g., tremor may represent limited toxicity within the spectrum of parkinsonism; patients in the CARTITUDE-1 trial who had multiple parkinsonian symptoms may have experienced greater degree of toxicity.

- Applicant cited prior ICANS, prior CRS and high tumor burden as possible risk factors for parkinsonism. The definition of high, low or intermediate tumor burden was proposed by the Applicant, in the absence of standardized definitions. High tumor burden was defined as any one of the following: i) M-protein \geq 5g/dl ii) serum light chain $>$ 5000mg/L iii) bone marrow plasma cells \geq 80%. Low tumor burden was defined as all of the following: i) bone marrow plasma cells $<$ 50% ii) M-spike $<$ 3g/dl iii) serum free light chains $<$ 3000 mg/L. Patients who did not meet criteria for either low or high tumor burden were classified as having intermediate tumor burden. By these definitions, 4 of 5 patients with parkinsonism in study CARTITUDE-1 had high tumor burden; 1 had intermediate tumor burden. Four of 5 patients had maximum grade 2 CRS while 1 patient had grade 3; 3 of 5 patients had grade 1 ICANS, 1 patient had Grade 2 ICANS while 1 patient had no ICANS. The 6th patient with parkinsonism (CARTITUDE-2) had grade 3 CRS but no ICANS; tumor burden data not available.*
- Based on the above risk factors, Applicant introduced mitigation strategies for parkinsonism including recommendations to aggressively reduce tumor burden with bridging therapy prior to CAR-T cell infusion, early and aggressive treatment of ICANS and CRS, handwriting assessment from pre-infusion to day 196 as a tool for earlier diagnosis of parkinsonism, consideration of longer-duration of antimicrobials per institutional protocols, consideration of CAR-T ablation in the event of high/persistent CAR-T expansion with neurologic toxicity, and CNS evaluation including CSF analysis to rule out viral infection, paraneoplastic syndrome and/or thiamine deficiency and brain imaging to identify abnormalities. Since these strategies were implemented, Applicant reports 1 additional patient with parkinsonism (patient in CARTITUDE-2 study) out of 174 treated patients (IR#34; response to Question#7). Given limited data and follow-up, it is unclear whether the reduced incidence seen thus far is due to the mitigation strategy or due to chance alone. Due to the uncertainty regarding the effectiveness of the mitigation measures in reducing parkinsonism, we decided not to put information regarding the mitigation measures in the REMS material or in the label.*

3. Peripheral Neuropathy

As of September 10, 2021, a total of 13 patients across 3 studies (CARTITUDE-1, CARTITUDE-2 and CARTITUDE-4) of cilta-cel are reported to have new onset

neuropathy including Guillain Barre syndrome (GBS). Six patients in CARTITUDE-1 and 3 patients (excludes patient with GBS who is discussed separately below) in CARTITUDE-2 had peripheral neuropathy as of the 120-day safety update (February 11, 2021, data cutoff) for study CARTITUDE-1 and data cutoff of April 15, 2021, for study CARTITUDE-2. Of the 9 patients, 6 patients had sensory neuropathy and one patient each had motor neuropathy, sensory and motor neuropathy, and polyneuropathy. One patient (with motor neuropathy; USUBJID#(b) (6)) had peroneal nerve palsy listed as AE in addition to motor neuropathy. Maximum toxicity grade was Grade 3 in 3 patients (USUBJID#(b) (6) with motor neuropathy and peroneal nerve palsy, USUBJID#(b) (6) with sensory and motor neuropathy, USUBJID#(b) (6) with polyneuropathy), Grade 2 in 4 patients and Grade 1 in 1 patient. Median time to onset was 66 days (range 4 to 315 days) in all patients; for the 6 patients in CARTITUDE-1, median time to onset was 62 days (range 4 to 136 days). Median duration of peripheral neuropathy in the 6 patients in CARTITUDE-1 including those with ongoing toxicity is 256.5 days (range 2 to 465 days). Only 3 of 9 patients had resolution of peripheral neuropathy; the remaining 6 patients had ongoing toxicity at time of death or last known alive day/data cutoff. Of these 6 patients with ongoing toxicity, maximum grade of ongoing toxicity was Grade 2 in the majority (4 of 6) of patients while 1 patient each had ongoing Grade 3 and Grade 1 toxicity respectively. Treatment was attempted in 3 patients-dexamethasone in USUBJID#(b) (6) , metamizole and opioids in USUBJID#(b) (6) , and duloxetine in USUBJID#(b) (6) but there was no improvement in symptoms (IR#32, response to Question#5).

Three patients in CARTITUDE-4 have been reported to have had neuropathy. These patients were not included in calculations of time to neuropathy, median duration of neuropathy etc. due to lack of availability of detailed, complete data on these patients (CARTITUDE-4 is an ongoing randomized controlled trial). Briefly, USUBJIDs #(b) (6) , respectively had polyradiculoneuritis (grade unspecified), Grade 2 peripheral sensory and motor neuropathy, and sensory neuropathy (grade unspecified) starting 126-, 5- and 31-days after cilta-cel infusion. Two of these 3 patients also had cranial nerve palsies-bilateral, Grade 2 facial paralysis in patient USUBJID (b) (6) that preceded and was ongoing at the time of onset of polyradiculoneuritis and bilateral, partial facial nerve paralysis with onset of sensory neuropathy followed by left, oculomotor nerve paralysis in patient USUBJID (b) (6) . None of the 3 patients with neuropathy in study CARTITUDE-4 have recovered from the toxicity at time of the report (IR#32; September 10, 2021, cutoff)

- *Although peripheral neuropathy, Guillain Barre syndrome (GBS) and cranial nerve palsies are presented separately, GBS involves the peripheral nerves and can present with cranial nerve palsies. So, some cases classified as peripheral neuropathy and cranial nerve palsy could represent typical GBS or a variant. Indeed, in a follow-up IR (IR#44), USUBJID (b) (6) with polyradiculoneuritis and bilateral facial*

nerve palsy was stated to have day 140 EMG (electromyogram)/NCS (nerve conduction study) consistent with GBS; anti-ganglioside antibodies were negative.

- Neuropathy has been reported with previously approved CAR-T products but typically was attributed to chemotherapy; neuropathy with this product may be more common (based on SAE reports submitted to the IND, not a formal comparison). Delayed onset of high-grade (Grade 3) neuropathy e.g., day 315 following CAR-T therapy is what caught our attention, and hence we reviewed this toxicity in detail. Although motor neuropathy is less common in the patients reported so far, it has been Grade 3 in all 3 patients in which it has been reported (including one patient with both sensory and motor neuropathy).*
- Unclear whether the peroneal nerve palsy experienced by patient (USUBJID (b) (6)) with Grade 3 motor neuropathy was accompanied by sensory nerve injury.*
- One patient (USUBJID (b) (6)) was noted to have day 156 EMG/NCS showing length-dependent sensory and motor predominantly axonal neuropathy; unclear if this is a case of Guillain Barre syndrome or peripheral neuropathy from CAR-T therapy not under the umbrella of GBS. Narrative states that the investigator thought that the neuropathy was not in keeping with the clinical picture of chemotherapy-associated neuropathy.*
- Seven of 9 patients had prior history of neuropathy but all except 1 patient did not have ongoing neuropathy between screening and cilta-cel infusion i.e., neuropathy was not an exacerbation of a pre-existing neuropathy in the majority (8/9) of patients (IR#32).*
- Two patients (USUBJIDs (b) (6)) had Grade 1 and Grade 2 peripheral sensory neuropathy attributed by the investigator to bridging therapy. Bridging therapy consisted of carfilzomib, cyclophosphamide and dexamethasone in USUBJID#(b) (6) , and carfilzomib and pomalidomide in USUBJID#(b) (6) (IR#32). However, onset of neuropathy at 86 and 83 days from the last dose of bridging therapy, respectively, in these 2 patients makes it less likely that neuropathy was related to bridging therapy.*
- Data from patients in the CARTITUDE-1 trial only included in the label; data from patients in other ongoing trials not included for the reasons mentioned in section on parkinsonism.*
- Although we had initially analyzed data using group term of peripheral neuropathy to include patients with AE terms like hypoaesthesia that could be indicative of neuropathy, we did not include patients with these signs/symptoms in the label (section 5.2 and 6.1) or in the memo since we did not want patients without a verified diagnosis of neuropathy to “dilute” the data on this toxicity attributed to the product.*

Such patients also had transient symptoms and within a time frame more consistent with neuropathy attributed to chemotherapy.

4. Guillain Barre Syndrome

A single case of GBS has been reported to date-USUBJID (b) (6) in study CARTITUDE-2 (IR#32). However, an additional case (see USUBJID (b) (6) in study CARTITUDE-4 above) is stated to have EMG/NCS findings consistent with GBS (IR#44). Narrative for USUBJID (b) (6) is provided below:

76-year-old male with Grade 3 peripheral motor neuropathy and polyneuropathy during VRd (velcade, bortezomib and low dose dexamethasone) induction therapy that subsequently improved to Grade 2 but was ongoing at time of cilta-cel infusion. Developed diplopia, facial nerve palsy, ataxia and worsening of peripheral neuropathy (grade 4) 17 days after cilta-cel infusion; received treatment with high dose steroids followed by steroids taper with improvement in symptoms to Grade 1 (steroids given although they are not considered to be useful in treatment of GBS). EMG with symmetric, length-dependent, axonal, sensorimotor (predominantly sensory) polyneuropathy; Miller Fisher variant of GBS suspected. Neuropathy worsened following parainfluenza upper respiratory infection after day 69; Grade 4 GBS diagnosed day76 with worsening symptoms and EMG; treated with steroids, IVIG with decrease in toxicity to Grade 3; CSF with albuminocytologic dissociation (CSF protein 76 mg/dl; cell count 8 cells/mm³) consistent with GBS. Approximately 6 weeks later, he was hospitalized again with Grade 4 encephalopathy, frontal type gait disturbance; family had reported increased sleepiness, confusion, slurred speech without worsening weakness prior to hospitalization. However, during hospital stay noted to have increased weakness in hands and feet, mental “slowness” and to be disoriented. MRI with multiple “signal areas” (not infarctions) in gray matter of temporal lobe, midbrain tectum, medial thalamus, hypothalamus and medial temporal lobes. CSF still with albuminocytologic dissociation without specific reports of presence or absence of CAR T cells in the CSF and negative for viral panel and autoimmune encephalitis; EEG- diffuse slowing. Subsequently, developed fever, left hemiparesis and more encephalopathic and finally died after comfort care was initiated. Autopsy pending. Testing for anti-GQ1B, anti-GM1 and antiGD1B antibodies (on day 22) was negative.

- *Cause of death in (b) (6) is likely multifactorial, including a combination of GBS and infection. The patient also may have had NT with parkinsonism though not reported as such. Autopsy results awaited.*
- *Based on EMG/NCS findings provided for some patients (IR#44), it appears that some cases classified as “neuropathy” (especially those with motor or sensorimotor neuropathy) may indeed be GBS or its variants given similar EMG findings in these patients as in those who are labeled as having GBS. e.g., i) (b) (6) (CARTITUDE-2) stated to have had polyneuropathy on day 343 (and subsequently day 368) EMG/NCS with severe acute/subacute, symmetric, length-dependent,*

axonal, sensorimotor polyneuropathy ii) (b) (6) (CARTITUDE-4) with motor and sensory neuropathy is noted to have bilateral, symmetrical, distal, sensory-motor neuropathy on day 34.

5. Cranial Nerve Palsies

Fifteen patients had cranial nerve palsies across 3 studies of cilta-cel in myeloma (IR#19, response to Question#12) for data through August 2, 2021. Three and five patients in CARTITUDE-1 and CARTITUDE-2 had cranial nerve palsies through the 120-day safety update cutoffs for each study (February 11, 2021, for CARTITUDE-1 and April 15, 2021, for CARTITUDE-2). An additional patient was identified in CARTITUDE-2 between the 120-day safety update and August 2, 2021. Six patients in CARTITUDE-4 were diagnosed with cranial nerve palsies as of August 2, 2021 (Applicant blinded to data in ongoing phase 3 study). Data on 8 patients in studies CARTITUDE-1 and CARTITUDE-2 is presented below.

FDA Table 17: FDA - Cranial Nerve Palsies in CARTITUDE-1 and CARTITUDE-2

USUBJID	Involved Cranial Nerve /Max. Grade	Onset Day	End Day**	Intervention
(b) (6)	7 th /2	101	101	Steroids
	7 th /2	26	95	Steroids, Valacyclovir
	7 th , 5 th /3	21	99	Steroids
	7 th /2	28	55	Steroids
	6 th CN/2	38	N/A	None
	7 th /2	22	149	Steroids
	7 th /2	29	79	Steroids
	7 th /2	10	28	None

Source: Applicant response IR#19, IR#32

*Patients in CARTITUDE-1; remainder are in CARTITUDE-2;**End-day includes resolution or improvement of toxicity to a lower grade. Abbreviations: CN- cranial nerve; Max-maximum; Y-Yes; N-No

Median time to onset was 27 days (range 10 to 101 days). Seven of 8 patients had complete resolution of their cranial nerve palsy (IR#52). Median time to resolution of cranial nerve palsy was 51 days (range 1 to 128 days). One of 9 patients did not improve. Six of 9 patients improved/resolved toxicity on steroid therapy while 1 patient improved without steroids (IR#44; Applicant response to Question#7).

All six patients with cranial nerve palsies in CARTITUDE-4 reported as of August 2, 2021, were males with age range of 45-68 years and all had involvement of the 7th (facial) cranial nerve. One patient each had involvement of the 3rd (oculomotor) and 6th (abducens) cranial nerve in addition to the 7th cranial nerve. Onset ranged from as early as 17 days until almost 60 days. Two of six patients had bilateral involvement of the facial nerve; in one patient bilateral enhancement of the 7th cranial nerve was noted on brain imaging although the patient had unilateral facial nerve palsy. CSF analysis was negative for infection in 3 patients in whom such analysis was undertaken; anti-ganglioside antibody was reported negative in 1 patient. One patient had improvement of symptoms followed by recurrence and subsequent occurrence of peripheral neuropathy. Most patients (5/6) were reported to be recovering from the AE at time of the report; 4 of 6 patients received steroids. One patient was also treated with valacyclovir, Bactrim and Diflucan in addition to steroids.

- *The 7th cranial nerve was most frequently affected.*
- *Cranial nerve paralysis was bilateral in some patients. Recurrence of cranial nerve paralysis after improvement was also noted.*
- *Some patients had peripheral neuropathy in conjunction with cranial nerve paralysis. Cranial nerve paralysis can occur in GBS. Thus, patients with cranial nerve paralysis especially in conjunction with neuropathy may have GBS although not labeled as such at this time by investigators/Applicant.*
- *CSF analysis was unremarkable for other causes such as infection in cases where such testing was undertaken.*
- *Steroids were the most common therapeutic agent used to treat cranial nerve palsies with resolution or improvement in most patients. However, dose, route of administration and timing of initiation of therapy were variable.*
- *Cranial nerve palsies in 3 patients in CARTITUDE-1 were included in the label; detailed data on cranial nerve palsies in patients in ongoing studies were not included for the reasons mentioned in other sections of NT.*

Neurologic Toxicity and CRS

All 25 patients with NT had CRS. Neurologic toxicity started before CRS onset, during CRS (including those that started on same day CRS onset or end) or after CRS ended in 3, 16 and 6 patients respectively. For nineteen of 25 patients for whom NT started before or after CRS onset, 14 patients had NT continue after CRS resolution, 3 patients had NT end the same day as CRS while 1 patient had NT resolve prior to CRS resolution. Data on 3, 16 and 3 patients with ICANS onset before CRS onset, during CRS and after CRS resolution is included in the label; data on all 25 patients is not included in the label since only ICANS onset in relationship to CRS has been reported in other labels, and both (ICANS and CRS) occur typically during the early phase of CAR-T expansion.

Management of Neurologic Toxicity

Ten of 22 patients with ICANS received corticosteroids. Four patients received Tocilizumab, 3 patients received Anakinra while 2 patients received Tocilizumab and Anakinra. All 5 patients who received tocilizumab and/or Anakinra had concurrent CRS. A total of 37 patients received levetiracetam -34 as anti-seizure prophylaxis and 3 for non-ICANS neurologic toxicity. Details of management of non-ICANS NT is listed above in the respective sections for these toxicities. None of the 6 patients identified as having ICANS by the clinical reviewer received corticosteroids for ICANS.

Prolonged and Recurrent Cytopenias

Prolonged and recurrent cytopenias were not included as AESI in the CARTITUDE-1 protocol but given their occurrence in CARTITUDE-1 and the implications for monitoring patients for this toxicity and its consequences (risk of infection, bleeding), they have been included under the section on AESI.

Grade 3 or 4 cytopenias were seen in the majority of patients especially neutropenia and lymphopenia. The number of patients with grade 3 or 4 cytopenias and the duration of such cytopenias are shown in FDA Table 18 below.

FDA Table 18: FDA - Grade 3 or 4 Cytopenias in 97 Patients in CARTITUDE-1

	Neutropenia N=97 N (%)	Thrombocytopenia N=97 N (%)	Lymphopenia N=97 N (%)	Anemia N=97 N (%)
Number of Patients n (%)				
Any	95 (98)	61 (63)	96 (99)	69 (71)
One episode	34 (35)	44 (45)	38 (39)	33 (34)
Two episodes	34 (35)	14 (14)	41 (42)	20 (21)
Three or more episodes	27 (28)	3 (3.1)	17 (17.5)	16 (16.5)
Median Time to Recovery in days (range)				
1 st episode	18 (4, 112)	44 (13, 260)	14 (7, 409)	14 (3, 151)

2 nd episode	43 (7, 282)	74.5 (16, 570)	48.5 (15, 215)	28 (7, 123)
3 rd and subsequent episode	44.5 (14,156)	83 (44, 142)	151 (31, 260)	51 (14, 134)

Source: Applicant Analysis IR#32

Grade 3 or 4 cytopenias beyond day 30 (prolonged cytopenias) following cilta-cel infusion were seen in a significant number of patients as outline in FDA Table 19 below. Grade 3/4 cytopenias were defined as follows: i) Neutropenia: ANC < 1000 cell/uL ii) Thrombocytopenia: platelet count (PLC) < 50,000 cells/uL iii) Lymphopenia: Absolute lymphocyte count (ALC) < 500 cells/uL iv) Anemia: Hemoglobin (Hb) < 8 g/dl

FDA Table 19: FDA - Prolonged Initial Grade 3 or 4 Cytopenias in 97 Patients in CARTITUDE-1

	Neutropenia N (%)	Thrombocytopenia N (%)	Lymphopenia N (%)	Anemia N (%)
At day 30	29 (30)	40 (41)	12 (12)	1 (1)
At day 60	10 (10)	25 (26)	8 (8)	1 (1)
At data cutoff*	0	6 (6)	5 (5)	1 (1)

Source: Applicant Response to IR#13, Part 1 * Data cutoff of September 1, 2020

A significant proportion of patients with Grade 3/4 cytopenias required transfusion and/or myeloid, megakaryocytic and erythroid growth factor support as outlined in FDA Table 20 below.

FDA Table 20: FDA - Number of Patients with Transfusion and/or Growth Factor Support for Initial Grade 3/4 Cytopenias

Parameter	Neutropenia N=97 N (%)	Thrombocytopenia N=97 N (%)	Anemia N=97 N (%)
Transfusion beyond day 30	N/A	29 (30)	22 (23)
Transfusion beyond day 60	N/A	15 (15)	13 (13)
Transfusion at data cutoff	N/A	2 (2)	3 (3)
Growth factor support at day 30	41 (42)	7 (7)	3 (3)
Growth factor support at day 60	20 (21)	5 (5)	2 (2)
Growth factor support at data cutoff	5 (5)	2 (2)	0

Source: Applicant Response to IR#13, Part 2

Complications from initial grade 3/4 neutropenia and lymphopenia include infections in 25 patients (21 patients with neutropenia, 15 patients with lymphopenia and 11 patients with both lymphopenia and neutropenia), bleeding in setting of thrombocytopenia in 6 patients and sinus tachycardia related to anemia in 2 patients. Infections included sepsis, febrile neutropenia, pneumonia, influenza A, rhinitis, staphylococcal bacteremia, upper respiratory tract infection (viral and pathogen unspecified), otitis media, peri-rectal abscess, cytomegalovirus (CMV), rhinovirus, enterocolitis, UTI (BK virus and unspecified pathogen), sinusitis, parotitis, gastroenteritis and *C.Difficile* colitis. Four infections

remained unresolved (sepsis, sinusitis, BK virus UTI, rhinitis). Bleeding events included unresolved retinal hemorrhage, Grade 4 pulmonary hemorrhage that resolved and epistaxis (Applicant response to Question#2 IR#13 Part 2 and Question#11 IR#32). A single patient (USUBJID (b) (6)) required autologous stem cell rescue for persistent Grade 4 thrombocytopenia at day 216.

- *Patients who received other anti-myeloma therapy following cilta-cel infusion were excluded from the analysis of patients for any parameter at data cutoff.*
- *Growth factor support included the following: i) Myeloid growth factors-filgrastim, pegfilgrastim, sagramostim ii) Megakaryocytic growth factors- eltrombopag, romiplostim and Amicar (not a growth factor but antifibrinolytic to help with bleeding) iii) Erythroid growth factor- darbepoetin alfa, epoetin alfa.*
- *Another patient (USUBJID (b) (6)) is stated to have received a “stem cell boost” on day 128 but this was clarified as not being an ASCT. Patient was also given multi-agent chemotherapy for progressive disease on the same day as “stem cell boost”; unclear from information provided as to what this stem cell boost was or the purpose of giving it on the same day as chemotherapy.*

Eighty-four (87%; 84/97) patients had recurrence of one or more grade 3/4 cytopenia following recovery to \leq Grade 2 cytopenia from initial episode of grade 3/4 cytopenia with 23 patients having onset any of the recurrent cytopenias 30 days following cilta-cel infusion. Neutropenia, lymphopenia, anemia and thrombocytopenia occurred in 61 (63%, 61/97), 58 (60%, 58/97), 36 (37%, 36/97) and 17 (17.5%, 17/97) patients respectively. One, two, three or all four cytopenias occurred in 27, 32, 19 and 6 patients respectively. In patients with a single cytopenia, lymphopenia was the most common (N=13) followed by neutropenia (n=9). Among 32 patients with bicytopenia, neutropenia and lymphopenia occurred together most commonly (n=21) while amongst 19 patients with 3 cytopenias, anemia, lymphopenia and neutropenia in the same patient was most common (N=12). Eight, twelve, nineteen and twenty patients had onset of recurrent thrombocytopenia, anemia, neutropenia and lymphopenia respectively more than 30 days after cilta-cel infusion. The maximum time to onset for recurrent thrombocytopenia, anemia, neutropenia and lymphopenia was days- 203, 132, 132 and 130 respectively.

Please see FDA Table 21 below for details on onset > 30 days, recovery to grade 2 or less, transfusion and growth factor support and complications of infection, bleeding and heart failure and/or arrhythmias associated with neutropenia and lymphopenia, thrombocytopenia and anemia respectively.

FDA Table 21: FDA - Recurrent Grade 3/4 Cytopenias after recovery from initial episode

Parameter	Neutropenia N=61 N (%)	Lymphopenia N=58 N (%)	Anemia N=36 N (%)	Thrombocytopenia N=17 N (%)
Onset > 30 days	19 (31)	20 (34.5)	12 (33)	8 (47)
Lack of recovery to ≤ Grade 2	2 (3)	14 (24)	2 (5.5)	5 (29)
Transfusion support	N/A	N/A	28 (78)	9 (53)
Growth factor use	35 (57)	N/A	3 (8.3)	0 (0)
Complications	12 (20)	17 (29)	1 (2.7)	0 (0)

Source: Applicant response IR#32; Data based on 120-day Safety Update with February 11, 2021 cutoff

Median time between recovery of cytopenia to ≤ Grade 2 and the onset of the subsequent episode of Grade 3/4 cytopenia is shown in FDA Table 22 below.

FDA Table 22: FDA - Time Interval in Days Between Cytopenia Episodes

	Neutropenia	Thrombocytopenia	Lymphopenia	Anemia
1 st and 2 nd episode	9 (1, 97)	7 (1, 83)	11.5 (2, 78)	5.5 (1, 102)
2 nd and 3 rd episode	7 (1, 182)	14 (5, 22)	21 (3, 55)	6.5 (1, 89)
3 rd and 4 th episode	4.5 (2, 35)	152.5 (12, 293)	24 (24, 24)	6.5 (3, 321)

Source: Applicant Response IR#32; Time interval calculated in days with range in parenthesis

- *The true incidence of prolonged or recurrent cytopenia is likely to be underestimated given that per protocol all patients were required to have hematology laboratory monitoring till day 100 and subsequent monitoring was at investigator's discretion. Approximately 50% of patient has laboratory assessments beyond day 100 with number of patients dwindling to about 15% beyond day 150 (Applicant response IR#32, Question #10).*

Hypersensitivity reactions

Hypersensitivity reactions have occurred in 5% (5/97) of patients following ciltacabtagene autoleucl infusion. All reactions were Grade 1 and symptoms included flushing (n=4), chest discomfort.

- The Applicant did not include information in the Assessment Aid or the label on the occurrence of hypersensitivity reactions in CARTITUDE-1 (information was included in the CSR)
- Details of hypersensitivity reactions in CARTITUDE-1 were added to section 5.8 of the label including information on management of such reactions.

- This section has been added under section on AESI although not specified in the study protocol since it has been an AESI in other CAR-T therapy files.

Serious Infections

Data:

Infections were reported for more than half of subjects (56 subjects [57.7%]) with nearly 20% experiencing (19 subjects [19.6%]) Grade 3 or 4 infections. Three subjects (3.1%) experienced Grade 5 infections including lung abscess, sepsis and septic shock. Neither hepatitis B reactivation nor COVID-19 infection was reported. No single pathogen trends associated with treatment-emergent infections were observed.

The Applicant's Position:

CAR-T therapies are associated with an increased risk of cytopenia and cilta-cel therapy targets BCMA expressing plasma cells, as well as, B-cells, resulting in risk of hypogammaglobulinemia. Due to the risk of cytopenia or hypogammaglobulinemia, administration of cilta-cel may increase the risk of infection. Cilta-cel should not be administered to patients with clinically significant active infection.

While MM patients have an increased risk of infections due to underlying disease causing hypogammaglobulinemia (11.3% of subjects experienced hypogammaglobulinemia) and immunosuppression ([Terpos 2015](#)), the occurrence of infection should be noted and monitored. The cause of infections is multifactorial, there is insufficient evidence to suggest that hypogammaglobulinemia was associated with serious infection. Administration of cilta-cel may increase the risk due to cytopenias or hypogammaglobulinemia.

FDA Assessment

All grade infections excluding febrile neutropenia occurred in 59% (57/97) patients with grade 3 or higher infections occurring in 23% (22/97) patients. FDA Table 23 details infections by broad pathogen class e.g., viral infections. Febrile neutropenia occurred in 10 patients (10%). Sepsis occurred in 10 patients of which 2 were fatal. Overall fatal infections occurred in 4 patients - 2 with sepsis, 1 pneumonia and 1 lung abscess (see narratives under section on deaths).

FDA Table 23: FDA - Infections by pathogen class in 97 MM patients in CARTITUDE-1

Pathogen Class*	Any Grade N (%)	Grade 3 or higher N (%)
Pathogen unspecified	40 (41)	17 (17)
Bacterial infection	8 (8.2)	1 (1)

Pathogen Class*	Any Grade N (%)	Grade 3 or higher N (%)
Viral infection	22 (23)	7 (7.2)
Fungal infection	1 (1)	1 (1)

Source: FDA Analysis of ADAE dataset

* Includes group terms; see FDA Table 27 for preferred terms included in specific group terms

FDA Table 24: FDA - Infection by select sites in 97 MM patients in CARTITUDE-1

Site of Infection*	Any Grade N (%)	Grade 3 or higher N (%)
Upper respiratory tract infection	27 (28)	3
Pneumonia	12 (12)	11 (11)
Urinary tract infection	4 (4)	1 (1)
Gastrointestinal infection	8 (8)	2 (2)

Source: FDA Analysis of ADAE dataset; Analysis may include more than one grouped term

* Includes group terms; see FDA Table 27 for preferred terms included in specific group terms

- The incidence of febrile neutropenia is likely an underestimate since this is based on investigator reported incidence in the ADAE dataset and not a calculation of overlapping period of fever and neutropenia for which the patient received treatment with antimicrobials. Per IR#57, 91 patients (94%) had overlapping of fever and any grade neutropenia of whom 76 patients were deemed to have concurrent CRS. Applicant did not provide information on number of patients with overlapping fever and grade 3 neutropenia (ANC < 1000) which is consistent with definition of febrile neutropenia per CTCAE v. 5.0. The distinction may be less important however since in clinical practice, most patients will be treated concurrently for infection and CRS as it is practically impossible to distinguish between these 2 potentially life-threatening adverse events.
- Cilta-cel has been associated with recurrent and prolonged neutropenia and lymphopenia and thus patients are at risk of late-onset infections. Such infections including those that are fatal have been reported beyond 100 days following cilta-cel infusion

Hypogammaglobulinemia

Data:

Hypogammaglobulinemia was reported as an AE for 11 subjects (11.3%) with 2 subjects experiencing Grade 3 or 4 events. Twenty-three subjects (23.7%) received intravenous immunoglobulin (IVIG) as prophylaxis and 16 subjects (16.5%) were treated with IVIG in response to an AE.

The Applicant's Position:

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. Interpretation of hypogammaglobulinemia is confounded by the presence of MM. As a majority of subjects in Study MMY2001 (58.8%) had IgG myeloma subtype at baseline, we have provided the incidence hypogammaglobulinemia by reported AEs.

The Ig levels should be monitored and treated according to institutional guidelines from the USPI. Monitor Ig levels after treatment, and treat according to standard guidelines, including administration of Ig replacement, antibiotic prophylaxis and monitoring for infection. There is insufficient evidence to suggest hypogammaglobulinemia as a risk factor for serious infection.

FDA Assessment

Ninety-one of 97 patients (94%) had an AE of hypogammaglobulinemia or a laboratory IgG level of < 500mg/dl. Eighty-nine patients (92%; 89/97) had a laboratory IgG level that fell below 500mg/dl after cilta-cel infusion while only 12 of 97 patients (12%) had hypogammaglobulinemia reported as an AE (Applicant response to Question#4 IR#32).

- *Hypogammaglobulinemia is under-reported as an AE. Hence, laboratory data was used to define incidence of hypogammaglobulinemia in CARTITUDE-1.*
- *Both multiple myeloma and cilta-cel infusion targeting plasma cells are risk factors for development of hypogammaglobulinemia.*
- *Monitoring and administration of immunoglobulin either prophylactically or in setting of infection is at discretion of investigator per institutional practice.*

Tumor Lysis Syndrome

Data:

Tumor lysis syndrome (TLS) is a known risk of cilta-cel therapy that can be managed by standard supportive therapy. One subject (1.0%) experienced a Grade 3 increase in blood creatinine and Grade 4 TLS. These events were determined to be very likely related to cilta-cel, and both resolved.

The Applicant's Position:

The observed cases of TLS are within or below expected rates of the target population, the proposed monitoring and management recommendations are deemed enough.

FDA Assessment

FDA agrees with Applicant assessment of TLS above. Tumor lysis syndrome is also an AESI per CARTITUDE-1 study protocol, although not included by the Applicant in this section in this document.

Second Primary Malignancy (SPM)

Data:

As effective therapies improve, the life expectancy of patients with MM has increased, and with that complications due to SPMs are becoming more common ([Landgren 2014](#)). It is also theoretically possible that subjects could develop SPMs following cilta-cel infusion due to the risk of lentiviral insertion ([Bonifant 2016](#)). Nine SPM events were reported for 7 subjects (7.2%) after enrollment in the study; none of these events were assessed by the investigator as related to cilta-cel. Six subjects (6.2%) developed second hematologic malignancies with the most common being myelodysplastic syndrome (MDS) in 5 subjects (5.2%). Two subjects (2.1%) developed acute myeloid leukemia (AML), both resulting in subject death. Basal cell carcinoma was reported in 1 subject (1.1%). All subjects with SPM were RCL negative.

The Applicant's Position:

The most common reported SPM was MDS (1 with subsequent AML) and all had signatures of chemotherapy related MDS, which is expected given heavily pre-treated population.

FDA Assessment

Secondary primary malignancies occurred in 10 patients in CARTITUDE-1 as of the 120-day safety update data cutoff of February 11, 2021; 3 additional patients with secondary malignancy were added to the 7 patients at the time of the original data cutoff of September 1, 2020. Eight of 12 patients had a hematologic malignancy- 3 with AML including 1 patient who had MDS transform to AML and 5 patients with MDS. Three patients had solid tumor malignancies- skin cancer in 3 patients (squamous cell cancer in 2 and basal cell cancer in 2 with 1 patient having both squamous and basal cell cancer). One patient (USUBJID#(b) (6)) had 3 secondary malignancies- squamous cell cancer of the scalp, grade 3 prostate cancer and grade 5 AML. Three patients died of AML (USUBJIDs #(b) (6)).

- *Applicant only included squamous cell cancer in USUBJID #(b) (6) and basal cell cancer in USUBJID #(b) (6) as treatment emergent.*
- *Applicant has not done any analysis on tumor samples from patients with hematologic malignancy for vector integration including the one patient with bi-phenotypic leukemia (IR#19, response to Question#1).*
- *Although all patients with secondary hematologic malignancies were heavily pre-treated with other therapies that carry risk of secondary malignancy including MDS and AML, contribution of CAR-T therapy including the preceding lymphodepleting therapy with fludarabine and cyclophosphamide cannot be ruled out.*
- *Secondary primary malignancies are also an AESI per CARTITUDE-1 protocol, although not included by the Applicant under this section in this document.*

Dropouts and/or Discontinuations Due to Adverse Effects

Data:

Of the 16 subjects who did not receive a cilta-cel infusion, 12 discontinued after apheresis and prior to the start of the conditioning regimen and 4 discontinued after the start of the conditioning regimen and prior to cilta-cel infusion. The most common reason for discontinuation after apheresis and prior to receiving cilta-cel infusion was death and the most common reason for death was progression of disease. No subject was discontinued from the study due to inability to manufacture the cilta-cel drug product.

One subject experienced an AE of thrombocytopenia related to the conditioning regimen that led to withdrawal of study treatment and ultimately discontinuation from the study. A second subject discontinued treatment due to death (cause of death was respiratory failure).

The Applicant's Position:

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Version date: January 2020 (ALL NDA/ BLA reviews)

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.

In Study MMY2001 the incidence of specific TEAEs leading to discontinuation was rare.

FDA Assessment

The Applicant’s assessment of dropouts and discontinuations is acceptable.

Dose Interruption/Reduction Due to Adverse Effects

Data:

Cyclophosphamide and Fludarabine Conditioning

Twenty-three subjects (23.7%) experienced a delay in administration of cyclophosphamide or fludarabine conditioning. These delays were due to AE for 11 subjects (11.3%) and 12 subjects (12.4%) for other reasons (eg, personal reasons, re-apheresis, rapid disease progression, etc).

Cilta-cel Infusion

Cilta-cel infusion was delayed for 1 (1.1%) subject and interrupted for 2 (2.1%) subjects. A summary of the cilta-cel infusion delays, abortion, and interruptions are presented in Table 13.

Table 13: Applicant - Summary of JNJ-68284528 Infusion Delays, Abortion and Interruption; All Treated Analysis Set (Study 68284528MMY2001)

	Phase 1b	Phase 2	Phase 1b + Phase 2
Analysis set: all treated	29	68	97
Subjects with JNJ-68284528 delays	0	1 (1.6%)	1 (1.1%)
Reasons			
No data to report	0	0	0
Other	0	1 (1.5%)	1 (1.0%)
Subject with JNJ-68284528 infusion			
aborted or interrupted	0	2 (2.9%)	2 (2.1%)
Reasons			
Infusion aborted	0	0	0
Infusion interrupted	0	2 (2.9%)	2 (2.1%)
Other	0	2 (2.9%)	2 (2.1%)

[TSIEX05.RTF] [JNJ-68284528\MMY2001\DBR_CSR\RE_CSR\PROD\TSIEX05.SAS] 23OCT2020, 13:22

The Applicant’s Position:

No infusions were delayed, interrupted, or aborted due to AEs.

FDA Assessment

Applicant's assessment is acceptable. See also section on Common Adverse Events.

Significant Adverse Events

Data:

All 97 subjects (100.0%) who received cilta-cel infusion (ie, the All Treated Population) experienced 1 or more Grade 3 or 4 AEs. A complete listing of Grade 3 or 4 TEAEs occurring at a rate of $\geq 5\%$ are presented in Table 14.

Table 14: Applicant - Number of Subjects with Grade 3 or 4 Treatment-emergent Adverse Events with Frequency of at Least 5% in Total by System Organ Class and Preferred Term; All Treated Analysis Set (Study 68284528MMY2001)

	Phase 1b	Phase 2	Phase 1b + Phase 2
Analysis set: all treated	29	68	97
Total number of subjects with Grade 3 or 4 TEAE	29 (100.0%)	68 (100.0%)	97 (100.0%)
MedDRA system organ class/preferred term			
Blood and lymphatic system disorders	29 (100.0%)	67 (98.5%)	96 (99.0%)
Neutropenia	29 (100.0%)	63 (92.6%)	92 (94.8%)
Anaemia	15 (51.7%)	51 (75.0%)	66 (68.0%)
Leukopenia	20 (69.0%)	39 (57.4%)	59 (60.8%)
Thrombocytopenia	20 (69.0%)	38 (55.9%)	58 (59.8%)
Lymphopenia	15 (51.7%)	33 (48.5%)	48 (49.5%)
Febrile neutropenia	1 (3.4%)	8 (11.8%)	9 (9.3%)
Infections and infestations	4 (13.8%)	18 (26.5%)	22 (22.7%)
Pneumonia	2 (6.9%)	6 (8.8%)	8 (8.2%)
Sepsis	1 (3.4%)	4 (5.9%)	5 (5.2%)
Investigations	5 (17.2%)	11 (16.2%)	16 (16.5%)
Gamma-glutamyltransferase increased	1 (3.4%)	5 (7.4%)	6 (6.2%)
Aspartate aminotransferase increased	2 (6.9%)	3 (4.4%)	5 (5.2%)
Metabolism and nutrition disorders	3 (10.3%)	13 (19.1%)	16 (16.5%)
Hypophosphataemia	3 (10.3%)	4 (5.9%)	7 (7.2%)
Vascular disorders	1 (3.4%)	7 (10.3%)	8 (8.2%)
Hypertension	1 (3.4%)	5 (7.4%)	6 (6.2%)
General disorders and administration site conditions	1 (3.4%)	6 (8.8%)	7 (7.2%)
Fatigue	1 (3.4%)	4 (5.9%)	5 (5.2%)

Keys: TEAE=treatment-emergent adverse event.

Note: Adverse events are reported using MedDRA version 23.0.

Note: Percentages are calculated with the number of subjects in the all treated analysis set as denominator.

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The Applicant's Position:

All subjects who received cilta-cel experienced 1 or more TEAEs with a maximum severity of at least Grade 3 or 4. These included most commonly ($\geq 10\%$ subjects): neutropenia (94.8%), anemia (68.0%), leukopenia (60.8%), thrombocytopenia (59.8%), and

lymphopenia (49.5%). Cilta-cel has a safety profile generally consistent with the current understanding of CAR-T therapy and other BCMA CAR-T ide-cel therapy.

FDA Assessment

See section on Common Adverse Events above.

Treatment Emergent Adverse Events and Adverse Reactions

Data:

The Sponsor’s medical experts evaluated safety data using the definition of adverse drug reactions (ADRs) from the ICH guideline entitled, E6: GCP, Consolidated Guideline. The assessment was based on all TEAEs and laboratory abnormalities reported in Study MMY2001 (including 97 subjects in pivotal study and 9 subjects in the Japan Cohort).

The assessment for Study MMY2003 was performed separately since this protocol is a supportive study in multiple different populations of MM, distinct from the target indication and with a small sample size across the 4 enrolling cohorts. The separate assessment was aimed to evaluate if there were any new specific ADRs in earlier lines that were not seen in the pivotal trial (Study MMY2001), and a separate assessment also avoided diluting of any potential signals. No new safety signal was identified as a result of this assessment.

Serious ADRs were reported for 50 subjects (47.2%) in Study MMY2001, most commonly reported ($\geq 5\%$ of subjects) were CRS (19.8%), sepsis (6.6%), encephalopathy (6.6%), and pneumonia (5.7%).

Adverse drug reactions identified for Study MMY2001 are provided in the Summary of Clinical Safety and summarized in Table 15, Table 16, Table 17.

Table 15: Applicant – Pivotal and Japan Cohort: Adverse Reactions ($\geq 10\%$) in Multiple Myeloma Patients Treated with JNJ68284528 in Study MMY2001 (N=106)

System Organ Class	Adverse Reaction	Incidence (%)	
		All Grades	Grade ≥ 3
Infections and infestations	Upper respiratory tract infection ¹	41	3
	Pneumonia ²	10	10
	Sepsis ³	10	7
Blood and lymphatic system disorders	Coagulopathy ⁴	15	1
	Febrile neutropenia	12	11
Immune system disorders	Cytokine release syndrome	94	4

Table 15: Applicant – Pivotal and Japan Cohort: Adverse Reactions ($\geq 10\%$) in Multiple Myeloma Patients Treated with JNJ68284528 in Study MMY2001 (N=106)

System Organ Class	Adverse Reaction	Incidence (%)	
		All Grades	Grade ≥ 3
Metabolism and nutrition disorders	Hypogammaglobulinaemia	10	2
	Hypophosphataemia	28	7
	Decreased appetite	27	1
Psychiatric disorders	Insomnia	12	0
Nervous system disorders	Headache	27	0
	Encephalopathy ⁵	25	6
	Dizziness ⁶	21	1
	Motor dysfunction ⁷	19	6
	Immune effector cell-associated neurotoxicity syndrome	15	2
	Neuropathy peripheral ⁸	10	3
	Tachycardia ⁹	25	1
	Hypotension ¹⁰	46	9
Cardiac disorders	Hypertension	18	6
	Cough ¹¹	36	0
Respiratory, thoracic and mediastinal disorders	Dyspnea ¹²	23	3
	Hypoxia ¹³	12	3
Gastrointestinal disorders	Nausea	31	1
	Diarrhoea	29	1
	Vomiting	21	0
	Constipation	20	0
	Abdominal pain ¹⁴	10	0
	Musculoskeletal pain ¹⁵	45	2
Musculoskeletal and connective tissue disorders			
General disorders and administration site conditions	Pyrexia	95	6
	Fatigue ¹⁶	44	8
	Chills	30	0
	Edema ¹⁷	23	0
	Pain ¹⁸	14	1
Investigations	Blood lactate	11	0
	dehydrogenase increased		

Adverse events are reported using MedDRA version 23.0

¹Upper respiratory tract infection includes Bronchitis, Nasal congestion, Paranasal sinus discomfort, Rhinitis, Rhinorrhoea, Rhinovirus infection, Sinus congestion, Sinusitis, Upper respiratory tract infection, and Viral upper respiratory tract infection.

²Pneumonia includes Atypical pneumonia, Pneumocystis jirovecii pneumonia, Pneumonia, and Pneumonia aspiration.

³Sepsis includes Bacteraemia, Bacterial sepsis, Pseudomonal bacteraemia, Sepsis, Septic shock, and Staphylococcal bacteraemia.

⁴Coagulopathy includes Activated partial thromboplastin time prolonged, Coagulopathy, Disseminated intravascular coagulation, International normalised ratio increased, Prothrombin level increased, and Prothrombin time prolonged.

⁵Encephalopathy includes Amnesia, Bradyphrenia, Confusional state, Depressed level of consciousness, Disturbance in attention, Encephalopathy, Lethargy, Memory impairment, Mental impairment, Mental status changes, Noninfective encephalitis, Psychomotor retardation, Sleep disorder, and Somnolence.

⁶Dizziness includes Dizziness, Presyncope, and Syncope.

⁷Motor dysfunction includes Bradykinesia, Cogwheel rigidity, Dysgraphia, Micrographia, Motor dysfunction, Muscle

Table 15: Applicant – Pivotal and Japan Cohort: Adverse Reactions ($\geq 10\%$) in Multiple Myeloma Patients Treated with JNJ68284528 in Study MMY2001 (N=106)

System Organ Class	Adverse Reaction	Incidence (%)	
		All Grades	Grade ≥ 3
spasms, Muscle tightness, Muscular weakness, Myoclonus, Parkinsonism, Posture abnormal, and Stereotypy.			
⁸ Neuropathy peripheral includes Hypoaesthesia, Neuralgia, Paraesthesia, Peripheral motor neuropathy, Peripheral sensory neuropathy, and Sensory loss.			
⁹ Tachycardia includes Sinus tachycardia, and Tachycardia.			
¹⁰ Hypotension includes Hypotension, and Orthostatic hypotension.			
¹¹ Cough includes Cough, Productive cough, and Upper-airway cough syndrome.			
¹² Dyspnea includes Acute respiratory failure, Dyspnoea, Dyspnoea exertional, Respiratory failure, and Wheezing.			
¹³ Hypoxia includes Hypoxia, and Oxygen consumption decreased.			
¹⁴ Abdominal pain includes Abdominal pain, Abdominal pain upper, and Dyspepsia.			
¹⁵ Musculoskeletal pain includes Arthralgia, Back pain, Bone pain, Musculoskeletal chest pain, Musculoskeletal discomfort, Musculoskeletal pain, Musculoskeletal stiffness, Myalgia, Neck pain, and Pain in extremity.			
¹⁶ Fatigue includes Asthenia, Exercise tolerance decreased, Fatigue, and Malaise.			
¹⁷ Edema includes Face oedema, Fluid retention, Generalised oedema, Joint swelling, Localised oedema, Oedema peripheral, Periorbital oedema, Peripheral swelling, Pulmonary oedema, and Scrotal oedema.			
¹⁸ Pain includes Catheter site pain, Ear pain, Eye pain, Non-cardiac chest pain, Pain, Pain in jaw, Proctalgia, and Toothache.			

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Table 16: Applicant - Pivotal and Japan Cohort: Adverse Reactions ($< 10\%$) in Multiple Myeloma Patients Treated with JNJ-68284528 in Study MMY2001 (N=106)

System Organ Class	Adverse Reaction	Incidence (%)	
		All Grades	Grade ≥ 3
Infections and infestations	Bacterial infection ¹	8	4
	Viral infection ²	8	2
	Cytomegalovirus infection ³	3	3
Immune system disorders	Haemophagocytic lymphohistiocytosis	1	1
Psychiatric disorders	Delirium ⁴	4	0
	Personality changes ⁵	4	1
Nervous system disorders	Aphasia ⁶	8	0
	Ataxia ⁷	8	0
	Tremor	6	0
	Paresis ⁸	4	2
Cardiac disorders	Neurotoxicity	2	2
Cardiac disorders	Cardiac arrhythmias ⁹	8	3
Vascular disorders	Hemorrhage ¹⁰	9	2
Renal and urinary disorders	Renal failure ¹¹	7	4
Investigations	Serum ferritin increased	8	2
	C-reactive protein increased	6	4

Table 16: Applicant - Pivotal and Japan Cohort: Adverse Reactions (<10%) in Multiple Myeloma Patients Treated with JNJ-68284528 in Study MMY2001 (N=106)

System Organ Class	Adverse Reaction	Incidence (%)	
		All Grades	Grade >=3
Adverse events are reported using MedDRA version 23.0			
¹ Bacterial infection includes Abscess limb, Clostridium difficile colitis, Clostridium difficile infection, Folliculitis, Lung abscess, Osteomyelitis, Perirectal abscess, Skin infection, Staphylococcal infection, and Tooth infection.			
² Viral infection includes Adenovirus test positive, Coronavirus infection, Influenza, and Parainfluenzae virus infection.			
³ Cytomegalovirus infection includes Cytomegalovirus syndrome, and Cytomegalovirus viraemia.			
⁴ Delirium includes Agitation, Hallucination, Irritability, and Restlessness.			
⁵ Personality changes includes Flat affect, Personality change, and Reduced facial expression.			
⁶ Aphasia includes Aphasia, Dysarthria, Slow speech, and Speech disorder.			
⁷ Ataxia includes Ataxia, Balance disorder, and Gait disturbance.			
⁸ Paresis includes Cranial nerve paralysis, Facial paralysis, and Peroneal nerve palsy.			
⁹ Cardiac arrhythmias includes Atrial fibrillation, Atrial flutter, Supraventricular tachycardia, Ventricular extrasystoles, and Ventricular tachycardia.			
¹⁰ Hemorrhage includes Conjunctival haemorrhage, Epistaxis, Haemoptysis, Post procedural haemorrhage, Pulmonary haemorrhage, and Retinal haemorrhage.			
¹¹ Renal failure includes Acute kidney injury, Blood creatinine increased, and Chronic kidney disease.			

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Table 17: Applicant - Pivotal and Japan Cohort: Laboratory Abnormalities Following Treatment with JNJ-68284528 Based on CTCAE^a in Study MMY2001 (N=106)

Laboratory Abnormality	Any Grade (%)	Grade 3 or 4 (%)
Anemia	106 (100.0%)	76 (71.7%)
Lymphopenia	106 (100.0%)	105 (99.1%)
Neutropenia	106 (100.0%)	104 (98.1%)
White blood cell decreased	106 (100.0%)	104 (98.1%)
Thrombocytopenia	104 (98.1%)	67 (63.2%)
Fibrinogen decreased	10 (9.4%)	9 (8.5%)
Hypoalbuminemia	94 (88.7%)	6 (5.7%)
Aspartate aminotransferase increased	74 (69.8%)	23 (21.7%)
Alanine aminotransferase increased	73 (68.9%)	10 (9.4%)
Hyponatremia	59 (55.7%)	8 (7.5%)
Hypocalcemia	58 (54.7%)	2 (1.9%)
Gamma Glutamyl Transferase increased	55 (51.9%)	9 (8.5%)
Alkaline phosphatase increased	49 (46.2%)	4 (3.8%)
Hypokalemia	49 (46.2%)	6 (5.7%)
Hypomagnesemia	27 (25.5%)	0
Blood bilirubin increased	14 (13.2%)	2 (1.9%)

^aCTCAE = Common Terminology Criteria for Adverse Events version 5.0

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The data for TEAEs is presented in Section 8.2.4 for common AEs.

The Applicant's Position:

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

FDA Assessment

See section on Common Adverse Events above.

Laboratory Findings

Data:

For the 97 subjects in Study MMY2001:

- Laboratory observations including creatinine clearance, aspartate aminotransferase (AST), ferritin, CRP, and alanine aminotransferase (ALT) show trends of abnormalities reaching maximum impact in the period following infusion (particularly between Days 7 and 14) followed by gradual return to baseline.
- Coagulation lab parameters was assessed at screening and as clinically indicated for subjects with fever or other potential signs of CRS. Fibrinogen was assessed in 19 subjects (19.6%), 9 subjects (47.4%) were within normal limits, 1 subject (5.3%) experienced Grade 2 decrease, 5 subjects (26.3%) experienced Grade 3 decrease, and 4 subjects (21.1%) experienced a Grade 4 decrease. No Grade 5 events were observed.
- Activated partial thromboplastin time was assessed in 18 subjects (18.6%). No Grade 4 or 5 events were observed.
- International Normalization Rate (INR) was assessed in 17 subjects (17.5%). No Grade 3, 4, or 5 increases in INR were observed.
- Immunoglobulin (Ig) data is limited post-infusion for IgD and IgE as only 8 and 6 subjects respectively had measurable values at baselines
- Assessment of clinical laboratory data showed that the majority of Grade 3 or 4 cytopenias with onset after Day 1 (cilta-cel infusion) were transient, with onset and recovery to Grade 2 or better within the first 60 days following cilta-cel infusion. Grade 3 or 4 thrombocytopenia, neutropenia, and lymphopenia with onset after Day 1 did not resolve by Day 60 for 25.8%, 10.3%, and 8.2% of the All Treated Population, respectively.

The Applicant's Position:

Laboratory abnormalities peaked during the period following cilta-cel infusion, however, they gradually returned to baseline by Day 100. The majority of Grade 3 or 4 cytopenias with onset after Day 1 (cilta-cel infusion) were transient, with onset and recovered to Grade 2 or better within the first 60 days following cilta-cel infusion. The safety profile of cilta-cel was consistent with the current understanding of CAR-T therapy.

FDA Assessment

As expected, cytopenias were the most common all grade and grade 3 or 4 laboratory abnormalities following cilta-cel infusion. Although, Grade 3 or 4 aspartate aminotransferase (AST) increase was the only chemistry parameter altered in $\geq 10\%$ of patients, all grade (mainly grade 1/2) laboratory abnormalities were seen in a significant number of patients as shown in FDA Table 25 below.

FDA Table 25: FDA - All grade chemistry laboratory abnormalities in $\geq 10\%$ of patients in CARTITUDE-1

Laboratory Abnormality	All Grade N=97 (%)	Grade 3 or 4 N=97 (%)
Aspartate aminotransferase increased	62 (64)	20 (21)
Alanine aminotransferase increased	60 (62)	8 (8)
Hypoalbuminemia	49 (51)	1 (1)
Hyponatremia	48 (49)	6 (6)
Hypocalcemia	44 (45)	1 (1)
Gamma Glutamyl transferase increased	42 (43)	7 (7)
Alkaline Phosphatase increased	36 (37)	3 (3.1)
Hypokalemia	29 (30)	2 (2.1)
Hypomagnesemia	19 (20)	0 (0)
Creatinine increased	15 (15)	3 (3.1)
Hypernatremia	13 (13)	0 (0)
Creatine kinase increased	11 (11)	0 (0)

Source: FDA Analysis of ADLB, ADSL datasets

The most common Grade 3 or 4 laboratory abnormalities occurring in $\geq 10\%$ of patients following cilta-cel infusion are listed in FDA Table 26 below.

FDA Table 26: FDA- Grade 3 or 4 laboratory abnormalities occurring in ≥ 10% of patients in CARTITUDE-1

Grade 3 or 4 Laboratory Abnormalities	All Treated Patients N=97 (%)
Lymphopenia	96 (99)
Neutropenia	95 (98)
Leukopenia	95 (98)
Anemia	69 (72)
Thrombocytopenia	61 (63)
Aspartate aminotransferase increased	20 (21)

Source: Applicant Analysis of ADLB

Clinical Reviewer Comments

- FDA Table 26 above will be in the label in Section 6.1, Table 4. Percentages represent worst toxicity grade following cilta-cel infusion.
- Fibrinogen, prothrombin time (PT) and partial thromboplastin time (PTT) evaluations at baseline and at least once post cilta-cel were done in 18, 14 and 16 patients respectively. Hypofibrinogenemia was reported in 8 of 18 patients (44% of those tested) with majority (7 of 8 patients) having Grade 3 or 4 decrease. All grade PT and PTT prolongation was seen in 5 of 14 (36%) and 4 of 16 (25%) of tested patients respectively with only 1 patient having grade 3/4 PTT prolongation. Since all patients were not tested, this information will not be in Table 4, Section 6.1 of the label.
- Using the FDA group term of “coagulopathy”, 21 (22%) patients were identified having one or more of the following- hypofibrinogenemia (n=11), PT prolonged (n=3), activated PTT prolonged (n=4), disseminated intravascular coagulation (n=1), international normalized ratio increased (n=9) and coagulopathy (n=1). One patient each had grade 3 DIC and grade 3 hypofibrinogenemia; all other events were grade 1 or 2. Thus, analysis of ADLB identified more patients with grade 3 hypofibrinogenemia.

Vital Signs

Data:

The most common vital sign abnormalities (>30% subjects) included:

- Abnormal temperature (>38 °C and with ≥1 °C increase from prior to cilta-cel infusion): 92 subjects (94.8%)
- Abnormal oxygen saturation (<95%): 52 subjects (53.6%)
- Abnormal pulse rate (>110 bpm and with >20 bpm increases from prior to cilta-cel infusion; or <50 bpm and with >15 bpm decreases from prior to cilta-cel infusion): 31 subjects (32.0%)
- Abnormal respiratory rate (>20 or <7 breaths/minute): 29 subjects (29.9%).

The Applicant's Position:

Mean and median changes in vital signs though evident were not clinically meaningful.

FDA Assessment

Clinical reviewer did not conduct an analysis of the vital signs data. As such, individualized CAR-T therapy is not expected to cause a uniform change in vital signs, and variability in timing of such assessments renders such analyses minimally meaningful. Fever in the majority of patients is consistent with the occurrence of CRS in the majority of patients. Interpretation of other vital signs is most meaningful in the context of individual narrative on a complication e.g., hypoxia to adjudicate grade of CRS; abnormalities of vital signs may be due to other co-morbidities e.g., hypoxia from sleep apnea that have no relation to cilta-cel.

Electrocardiograms (ECGs)

Data:

In Study MMY2001, 12-lead ECGs were performed at baseline and Day 56. Two subjects (2.1%) had unscheduled ECGs at the time of apheresis both resulting in a normal interpretation or abnormal interpretation without clinical significance. Six subjects (6.2%) had unscheduled ECGs during conditioning, 4 of which resulted in a normal interpretation or abnormal without clinical significance. Two subjects had abnormal ECGs during conditioning including 1 subject with prolonged QT interval and a second with atrial fibrillation. Nine subjects (9.3%) had unscheduled ECGs after cilta-cel infusion with 8 subjects having normal interpretations or abnormal interpretation without clinical significance. One subject (1.0%) had an unscheduled ECG at Day 9 with a finding of sinus tachycardia. This was deemed by the investigator to be possibly related to cilta-cel and was reported as resolved at the time of clinical cutoff.

The Applicant's Position:

Based on review of the data, there is no evidence that cilta-cel affects ECG parameters, no subjects had clinically significant ECG interpretations at Day 56.

FDA Assessment

Applicant's assessment is noted. The clinical reviewer did not perform an independent assessment of ECG data and hence cannot comment on the data provided by the Applicant.

Echocardiogram and/or MUGA Scan

Data:

Cardiac function was assessed at screening and upon completion of bridging therapy for subjects who received bridging therapy with known cardiac toxicity and as clinically indicated during the study period using either echocardiogram or MUGA at screening. Twenty subjects (20.6%) had unscheduled echocardiograms and/or MUGA scans at the time of apheresis with 19 of these resulting in a normal interpretation or abnormal interpretation without clinical significance. One subject had a finding of pericardial effusion at this time. Four subjects (4.1%) had unscheduled echocardiograms during conditioning, all with normal results. Five subjects (5.2%) had unscheduled evaluations after cilta-cel infusion with 4 subject having normal interpretations or abnormal interpretation without clinical significance. One subject (1.0%) had an unscheduled echocardiogram at Day 71 with a finding of pericardial effusion. This was deemed to be unrelated to cilta-cel and was reported as resolved at the time of clinical cutoff.

The Applicant's Position:

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

FDA Assessment

Decrease in ejection fraction has been reported in the context of CRS/HLH with cilta-cel in other studies in MM (Applicant response to Question#3 in IR#52; CARTITUDE-1-USUBJID (b) (6)). Decrease in cardiac function with CRS/HLH has been observed with other CAR-T products. Since not all patients with CRS/HLH had a study to evaluate cardiac function, no conclusion can be drawn on the incidence of reduced cardiac function in the context of CRS/HLH following cilta-cel.

Replication Competent Lentivirus (RCL)

Data:

At the time of clinical cutoff, 80, 55, and 15 subjects had evaluable samples for replication competent lentivirus (RCL) analysis at 3-, 6-, and 12-months post cilta-cel infusion, respectively. Evaluable samples were defined as those with a DNA concentration ≥ 10 ng/L. No positive samples for RCL were detected at any of the collection time points.

The Applicant's Position:

Replication competent lentivirus was not detected up to 12 months after cilta-cel infusion.

FDA Assessment

Applicant's assessment is noted.

Immunogenicity

Data:

A review of data regarding immunogenicity, including an assessment of the impact of antibody titer levels on PK parameters, or the clinical efficacy or safety of cilta-cel, is presented and summarized in Section 6.

The Applicant's Position:

The overall incidence of anti-drug (cilta-cel) antibodies (ADA) was 15.5%, and there was no clear evidence of association between ADA and CRS or CAR-T cell neurotoxicity (ICANS and Other Neurotoxicities including movement and neurocognitive TEAEs) as the occurrence rate of these safety endpoints are similar between ADA-negative and ADA-positive subjects based on the data cutoff date of 20 May 2020.

FDA Assessment

Clinical reviewer accepts the Applicant's assessment on the incidence of anti-drug antibodies. The clinical reviewer did not conduct an assessment of the impact of these antibodies on CRS or NT. Therefore, no comments can be made on the impact or lack thereof of these antibodies on CRS and NT. Defer to clinical pharmacology reviewer on this issue.

8.2.4.2 Supportive Safety Data

1 Study MMY2001-Japan Cohort

A country-specific amendment to Study MMY2001 was issued in August 2019 adding a separate cohort of subjects to the Phase 2 portion of the study to evaluate population-

specific safety and efficacy for a Japanese subject population. A description of the study population is presented in Section 8.2.2 and preliminary safety data for 9 subjects treated with cilta-cel in Study MMY2001 in Japan are summarized in this section.

Adverse Events

All 9 subjects treated experienced any grade study drug-related TEAEs. Serious AEs were reported for 1 subject: Grade 4 neutropenia, Grade 3 fatigue, Grade 2 thrombocytopenia, and Grade 1 CRS. All were assessed by the investigator as related to cilta-cel; all but fatigue had resolved. One subject received cilta-cel below the target dose range, and there were no clinically significant safety events.

Deaths

No deaths were reported among subjects treated with cilta-cel.

Adverse Events of Special Interest

The summary of TEAEs of CRS reported in Japan cohort is provided in Appendix 17.3. Eight subjects (88.9%) experienced CRS, all were Grade 1 or 2. The median onset was 7.5 days (range 4 to 11 days), and the median duration was 5 days (range 3 to 6 days). All subjects with CRS recovered. Other AESIs such as ICANS or Other Neurotoxicity, TLS and SPM were not reported in any subject.

Infections

One subject experienced Grade 2 bacteremia beginning on Day 11 with duration of 18 days. The infection was considered not related to cilta-cel by the investigator.

Clinical Laboratory Assessments

Clinical laboratory assessments reported in subject in Japan Cohort were not statistically significant nor clinically relevant.

Dropouts and/or Discontinuations Due to Adverse Effects

As of the 1 September 2020 clinical cutoff date, 13 subjects had been enrolled into Study MMY2001 at Japanese study sites and completed apheresis. Four subjects discontinued the study after apheresis but before starting the conditioning regimen (2 due to progressive disease, 1 withdrawal of subject, and 1 due to AE of cryptococcus test positive).

2 Study 68284528MMY2003

A brief study description and interim safety data for 18 subjects who received cilta-cel infusion in Study MMY2003 are presented below.

Study Description

Study MMY2003 is an ongoing Phase 2, multicohort, open-label, multicenter study to determine whether treatment with cilta-cel (alone or with other treatment regimens) results in MRD negativity in adult subjects with MM. Refer to Table 3 and Section 8.2.2 for the details of the study design and description of the study population.

Adverse Events

Safety information to date across MMY2003 cohorts indicate a similar safety profile with Study MMY2001. At the time of the clinical cutoff date, no subjects in Study MMY2003 experienced neurotoxicities characterized by movement or neurocognitive TEAEs.

Overview of Adverse Events

All 18 subjects (100%) treated with cilta-cel experienced 1 or more TEAEs with a maximum severity of Grade 3 or 4, and 17 subjects (94.4%) experienced AEs considered related to cilta-cel by the investigator.

Deaths

There were no deaths reported among subjects who received cilta-cel in Study MMY2003.

Serious Adverse Events

Serious TEAEs were reported for 4 of 18 subjects (22.2%) and included: CRS (2 subjects [11.1%]), neutropenia (1 subject [5.6%]), COVID-19 pneumonia (1 subject [5.6%]), sepsis (1 subject [5.6%]), ICANS (1 subject [5.6%]), acute kidney injury (1 subject [5.6%]). All serious TEAEs were Grade 3 or 4 severity, except for ICANS, which was assessed as Grade 2 by the investigator.

Common Adverse Events

The most frequently reported TEAEs of any grade (≥20% subjects) for subjects treated with cilta-cel included: neutropenia (16 subjects [88.9%]), thrombocytopenia (13 subjects [72.2%]), CRS (13 subjects [72.2%]), anemia (11 subjects [61.1%]), leukopenia (11 subjects [61.1%]), lymphopenia (10 subjects [55.6%]), hypocalcemia (6 subjects [33.3%]), hypokalemia (5 subjects [27.8%]), hypophosphatemia (5 subjects [27.8%]), diarrhea (5 subjects [27.8%]), and constipation (4 subjects [22.2%]).

Grade 3 or 4 TEAEs

The most frequently reported (≥10% subjects) Grade 3 or 4 TEAEs included: neutropenia (16 subjects [88.9%]), leukopenia (11 subjects [61.1%]), lymphopenia (10 subjects [55.6%]), anemia (7 subjects [38.9%]), thrombocytopenia (7 subjects [38.9%]), CRS (2 subjects [11.1%]), hypocalcemia (2 subjects [11.1%]), hypophosphatemia (2 subjects [11.1%]), hyponatremia (2 subjects [11.1%]), hypotension (2 subjects [11.1%]), and acute kidney injury (2 subjects [11.1%]).

Adverse Events of Special Interest (AESI)

Cytokine Release Syndrome (CRS)

All cases of CRS were assessed using the ASTCT consensus grading system (Lee 2019). CRS of any grade was reported for 13 of 18 subjects (72.2%) who received cilta-cel infusion (See Appendix 17.3). Grade 3 and Grade 4 CRS were each reported for 1 subject, respectively; the remaining 11 subjects experienced Grade 1 or 2 CRS severity. The median time from cilta-cel infusion to CRS onset was 8.0 days (range, 6 to 9 days), and the median duration of CRS was 4.0 days (range, 1 to 11 days); 75% of subjects had CRS duration ≤4 days, and 12 subjects (92.3%) had CRS duration ≤7 days.

Neurotoxicity

Neurotoxicity was evaluated as was done for Study MMY2001 and neurotoxicity of any grade was reported for 4 subjects (22.2%) (See Appendix 17.3).

ICANS (Grade 1) was reported for 2 subjects (11.1%), with disturbance in attention (Grade 1) and hallucination (Grade 1) reported for 1 of the 2 subjects. The median time from cilta-cel infusion to first onset of ICANS was 9.0 days (range, 7 to 11 days), and ICANS duration was 2 days for both subjects. Both subjects had concurrent CRS at the time of ICANS onset.

Other Neurotoxicity not defined as ICANS, as assessed by the investigator either due to symptoms or time of onset, was reported for 2 subjects (11.1%). These other neurotoxicity events included slow speech, facial paralysis, gait disturbance, and pain each reported for 1 subject (5.6%). All Other Neurotoxicity events were Grade 1 or 2 severity, and none were considered serious. The median time to Other Neurotoxicity onset was 20.0 days (range, 11 to 29 days).

Other AESIs such as TLS and SPM were not reported during the study.

Hypogammaglobulinemia

Grade 1 hypogammaglobulinemia was reported for 1 subject (5.6%).

Infections

One subject experienced Grade 3 COVID-19 infection and Grade 3 sepsis. Both TEAEs were considered serious. Hepatitis B reactivation was not reported for any subject. Grade 3 or 4 febrile neutropenia was reported as a symptom of CRS for 2 subjects (11.1%).

Dropouts and/or Discontinuations Due to Adverse Effects

As of the 23 July 2020 clinical cutoff date, 39 subjects had been enrolled into Study MMY2003 and underwent apheresis. Four subjects (10.3%) discontinued the study after apheresis but before starting the conditioning regimen, including 1 subject who died.

FDA Assessment

The clinical reviewer for safety did not independently verify the data reported by the applicant for studies CARTITUDE-1 (Japan cohort) and CARTITUDE-2. No formal assessment of safety data from CARTITUDE-1 (Japan cohort) and CARTITUDE-2 was conducted. Only data requested in the IRs for toxicities like cranial nerve palsies was utilized for writing this memo and in the label (only general statements with no specifics in the label) if applicable.

8.2.5 Analysis of Submission-Specific Safety Issues

Data:

The information on the specific safety issues such as CRS, neurotoxicity, tumor lysis syndrome, and SPM is provided in Section 8.2.4.

The Applicant's Position:

The CRS, neurotoxicity, TLS, and SPM are known risks of CAR-T therapy that can be managed by monitoring and mitigation strategies.

FDA Assessment

Recurrent grade 3 or 4 cytopenia, cranial nerve palsies, peripheral neuropathy including GBS and NT with parkinsonian features were identified as additional AEs related to CARVYKTI in CARTITUDE-1 and/or other studies with cilta-cel. Please see sections on AESI and common adverse events for all the pertinent safety information related to this Application.

8.2.6 Clinical Outcome Assessment (COA) Analyses Informing Safety/Tolerability

Data:

The information of the clinical outcome assessment analyses is provided in Section 8.1.1.

The Applicant's Position:

Please refer to Section 8.1.2 for information on results for COA (PRO) endpoints.

FDA Assessment

Applicant's brief information on PRO in Section 8.1.2 is noted. The clinical reviewer for safety did not perform any assessment to inform safety/tolerability based on COA analyses or PRO endpoints. Safety information based on COA (PRO) endpoints is not included in the label.

8.2.7 Safety Analyses by Demographic Subgroups

Data:

In Study MMY2001, separate analyses of TEAEs are included in this BLA to evaluate potential differences in the safety profile for cilta-cel among subgroups defined by intrinsic factors of age (<65 vs ≥65, <75 vs ≥75), sex (male vs female), race (white vs African American), bone marrow plasma cells (≤30% vs >30%, <60% vs ≥60%), and extrinsic factors of total CAR-Positive Viable T Cells Infused. Safety in special situations is evaluated for the All Treated Safety Population (N=97), for drug interactions, use in pregnancy and lactation, overdose, drug abuse, withdrawal and rebound, effects on ability to drive or operate machinery or impairment of mental ability.

Age: The overall incidence of study drug-related serious AEs for the 3 age groups (<65 years old [n=62], those between 65 and 75 years [n=27], and those >75 years [n=8]) was 40.3%, 44.4%, and 62.5% respectively. The nominally higher rate of serious AEs for subjects >75 years is of uncertain clinical relevance given the relatively small number of subjects enrolled in this subgroup. Grade 3 or 4 AEs also occurred at similar rates between the 3 age groups: 93.5%, 96.3%, and 87.5%, respectively.

Sex: The incidence of AEs was examined separately for male (n=57) and female (n=40) subjects. All subjects, regardless of sex, who received cilta-cel infusion experienced 1 or more AEs. Study drug-related serious TEAEs were reported in 49.1% of male subjects and in 35.0% of female subjects. The incidence of Grade 3 or 4 AEs was also similar between male (91.2%) and female subjects (97.5%).

Race: The incidence of AEs was examined separately for white subjects (n=69), African American subjects (n=17), and subjects of other races (n=11). Given the small size of some subgroups, the overall incidence of study drug-related serious AEs was not clinically meaningful across the 3 racial groups: 46.4%, 47.1%, and 18.2%, respectively. Grade 3 or 4 AEs were occurred at similar rates across the 3 groups: 94.2%, 94.1%, and 90.9%, respectively.

Bone Marrow Plasma Cells at Screening/Baseline: The incidence of AEs was examined separately for subjects who presented with $\leq 30\%$ (n=58), $>30\%$ to $<60\%$ (n=17), and $\geq 60\%$ (n=21) plasma cells (based on the highest value obtained) at baseline. Given the small size of some subgroups, the overall incidence of study drug-related serious AEs was not clinically meaningful across the 3 subgroups: 34.5%, 47.1%, 61.9%, respectively. Incidence of Grade 3 or 4 AEs was also similar across the 3 groups: 94.8%, 100%, and 90.5%, respectively.

Total CAR-Positive Viable T Cells Infused: The incidence of AEs was examined separately for subjects who were infused with less than the median number of CAR-T positive T cells (n=48) and for subjects infused with the median number or more CAR-T positive T cells (n=49). The overall incidence of study drug-related serious AEs was similar between the subgroups: 41.7% and 44.9%, respectively. Incidence of Grade 3 or 4 AEs was also similar: 93.8% and 93.9%, respectively.

The Applicant's Position:

There were no clinically meaningful differences in the cilta-cel AE profile across the subgroups examined for sex, age, race, total CAR-positive viable T cells infused, and bone marrow % plasma cells at baseline.

FDA Assessment

The Applicant's assessment is noted. Clinical reviewer cannot comment on the assessment since this was not independently analyzed. Of the 97 patients in CARTITUDE-1 that received cilta-cel, 28% were 65 to 75 years of age, and 8% were 75 years of age or older. The rate of neurologic toxicity was noted to be higher in patients ≥ 65 years of age compared to those less than 65 years old (in 62 patients less than 65 years of age, all grade and Grade 3 and higher neurologic toxicities occurred in 19% (12/62) and 6% (4/62) respectively while of the 35 patients ≥ 65 years of age, all grade and Grade 3 and higher neurologic toxicities occurred in 37% (13/35) and 20% (7/35) respectively). Given the small number of patients ≥ 65 years of age, no formal conclusions can be drawn, but per the geriatric guidance, the factual information on difference in NT between older and younger patients was placed in section 8.5 of the label.

8.2.8 Specific Safety Studies/Clinical Trials

Data:

Not Applicable.

The Applicant's Position:

[To the Applicant: Insert text here]

FDA Assessment

Not applicable

8.2.9 Additional Safety Explorations

Human Carcinogenicity or Tumor Development

Not Applicable.

FDA Assessment

Not applicable

Human Reproduction and Pregnancy

Not Applicable.

FDA Assessment

Not applicable

Pediatrics and Assessment of Effects on Growth

Not Applicable.

FDA Assessment

Not applicable

Overdose, Drug Abuse Potential, Withdrawal, and Rebound

Not Applicable.

FDA Assessment

Not applicable

8.2.10 Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

Data:

Not applicable as cilta-cel is not yet marketed in any region.

FDA Assessment

Not applicable

Expectations on Safety in the Postmarket Setting

Data:

Not Applicable.

FDA Assessment

Not applicable

8.2.11 Integrated Assessment of Safety

Data:

Cilta-cel has a manageable safety profile generally consistent with the current understanding of CAR-T therapy.

- As expected, CRS was common and reported in 92 subjects (94.8%)

- Most events were mild, with 87 subjects (89.7%) experiencing a Grade 1 or 2 event.
- Median time to onset from cilta-cel infusion was 7 days (range: 1 to 12 days).
- All subjects recovered from CRS, with a median duration of CRS being 4.0 days (range: 1 to 14 days), with the exception of the subject who experienced Grade 5 CRS (97-day duration) complicated by HLH.
- Neurotoxicity is another known risk associated with CAR-T therapies. Twenty subjects (20.6%) reported CAR-T cell neurotoxicity; 9 subjects (9.3%) had a Grade 3 or 4 event, 1 subject (1.0%) had a Grade 5 event. CAR-T cell neurotoxicity was classified as ICANS or other neurotoxicity, occurring after recovery of CRS and/or ICANS. Eight subjects (8.2%) experienced both ICANS and other neurotoxicity events.
 - ICANS: 16 subjects (16.5%) experienced ICANS, most (14 subjects) were Grade 1 or 2 in severity. All 16 subjects recovered from ICANS. Concurrent CRS was noted for 15 out of 16 subjects and no case of ICANS occurred prior to CRS.
 - Other Neurotoxicity: 12 subjects (12.4%) experienced other CAR-T cell neurotoxicity not defined as ICANS. Seven subjects (7.2%) experienced Grade 3 toxicity, 1 subject (1.0%) experienced Grade 4 toxicity, and 1 subject (1.0%) experienced a Grade 5 toxicity.
 - Five of these 12 subjects experienced a similar presentation of a cluster of movement and neurocognitive treatment-emergent adverse events (TEAEs) that were observed in some to progress to an inability to work or care for oneself. These TEAEs appear to be potentially associated with a combination of 2 or more factors including high tumor burden, prior Grade 2 or higher CRS, prior ICANS, and high CAR-T cell expansion and persistence.
- Cytopenia is a common event following lymphodepletion and CAR-T therapy:
 - Cytopenias (neutropenia, anemia, leukopenia, thrombocytopenia, and lymphopenia) were the most common Grade 3 or 4 TEAEs (96 subjects, 99.0%). Most subjects with initial Grade 3 or 4 events recovered to Grade 2 or lower by Day 60.
 - Infections occurred in more than half of all subjects (56 subjects, 57.7%), with nearly 20% (19 subjects) experiencing Grade 3 or 4 infections. Three subjects (3.1%) had Grade 5 infections (lung abscess, sepsis, and septic shock).

Although all 97 subjects who received cilta-cel experienced at least 1 AE, most events were manageable as a majority of subjects recovered from these events.

- Fourteen subjects (14.4%) who received cilta-cel died: 5 (5.2%) due to progressive disease and 9 (9.3%) due to AEs of which 6 were considered related by the investigator (CRS complicated by secondary HLH [1 subject], neurotoxicity

[1 subject], respiratory failure [1 subject], and infection [3 subjects]). All deaths occurred more than 30 days after cilta-cel infusion.

- Serious TEAEs were reported for 53 subjects (54.6%) with Grade 3 or 4 serious TEAEs reported for 29 subjects (29.9%).
- CRS was the most common serious AE, reported in 20 subjects (20.6%).

Additional safety data analyzed from the Japan cohort of Study MMY2001 and Study 68284528MMY2003 were consistent with the safety findings in Study MMY2001. No new safety signals were identified.

The Applicant's Position:

The totality of the data provided in this submission supports a favorable risk/benefit profile in this population of subjects with heavily pre-treated RRMM with an urgent unmet medical need and no further treatment options.

Safety findings for 97 subjects enrolled into the main cohort of Study MMY2001 demonstrate that cilta-cel has a manageable safety profile generally consistent with the current understanding of CAR-T therapy. Safety data for 27 subjects from 2 additional sources (ie, Japan cohort of Study MMY2001 and Study MMY2003) were consistent with this assessment.

FDA Assessment

No integrated safety analyses were performed.

SUMMARY AND CONCLUSIONS

8.3 Statistical Issues

FDA Assessment

There were no major statistical issues that could impact the interpretation of efficacy. However, there was an underrepresentation of minority patients. No statistical inference can be made for efficacy based on the subpopulation of responders. Please see statistical reviewer memo for further details.

8.4 Conclusions and Recommendations

FDA Assessment

In consideration of granting regular approval to CARVYKTI in relapsed/refractory multiple

myeloma patients who have received at least four prior lines of therapy, the clinical team considered the following aspects:

The magnitude of benefit observed with cilta-cel in CARTITUDE-1, specifically the rate of sCR and the median DOR of 21.8 months in all responders, constitutes clinical benefit in this population. Only a small proportion of the patients enrolled (17 patients) had received 3 prior lines of therapy. The recommended indication includes a requirement for receipt of 4 or more lines of therapy for receipt of CARVYKTI and reflects the patient population assessed to support the benefit risk for approval.

Severe and life-threatening adverse reactions of cytokine release syndrome (CRS), HLH/MAS neurologic toxicity (NT) and prolonged and/or recurrent cytopenia have been observed with cilta-cel. Risk mitigation measures and management strategies to mitigate these toxicities are in place. In this patient population with life threatening disease, given the magnitude of benefit observed and the risk mitigation strategies, the overall benefit-risk profile supports the recommendation for regular approval of CARVYKTI for the treatment of adult in patients with relapsed /refractory multiple myeloma after at least 4 or more prior lines of therapy, including a PI, IMiD and an anti-CD-38 monoclonal antibody.

X	X
Primary Clinical Reviewers	Clinical Team Leader

9. Advisory Committee Meeting and Other External Consultations

FDA Assessment

The application was not presented to an Advisory Committee as it did not raise significant efficacy concerns. The safety concerns were addressed with labeling negotiations and REMS. No External Consultations were performed.

10. Pediatrics

The Applicant's Position:

On May 27, 2020, the FDA provided an agreement letter to the Sponsor's initial pediatric study plan (iPSP), which includes a plan to request a waiver for pediatric assessments for cilta-cel for all age groups. A request for a full pediatric waiver consistent with the agreed iPSP is provided in this BLA.

FDA Assessment

Cilta-cel is for use only in adult patients. BCMA is not considered a relevant target in pediatric patients and MM is a rare disease in children. For these reasons, a waiver for pediatric assessments was granted.

11. Labeling Recommendations

Data:

Not Applicable. As this is a new label, all sections are new and therefore unchanged.

The Applicant's Position:

The draft label includes the relevant conclusions to support the indication of cilta-cel for the treatment of adult patients with RRMM, who previously received a PI, an IMiD, and an anti-CD38 antibody.

FDA Assessment

The draft label has been modified to reflect the efficacy and safety data presented in this memo.

The major changes to the draft label pertaining to safety include the following:

i) HLH, Parkinsonism, Guillain Barre syndrome and prolonged and recurrent cytopenias added to the Black Box warnings.

ii) Section 5 Warnings and Precautions:

a) Detailed information on Parkinsonism, cranial nerve palsies, peripheral sensory and motor neuropathy, and GBS added to section 5.2 on NT

b) Detailed information on recurrent cytopenias and need for autologous stem cell rescue added to section 5.4- Prolonged Cytopenias

c) Revised section 5.6 on hypogammaglobulinemia to include information based on analysis of laboratory data

iii) Section 6.1, Clinical Trials Experience- Applicant told to present safety data on 97 patients in CARTITUDE-1 USA cohort. Currently safety analysis based on 106 patients in CARTITUDE-1 that includes the Japan cohort is presented. Applicant was also requested to remove CRS and NT data from this section since this is presented under section 5- Warnings and Precautions.

The main changes pertaining to efficacy in the draft label include the following:

i) Revision of the indication statement to specify prior lines of therapy

ii) Removal of MRD data

iii) Efficacy presented for the leukapheresed population (N=113) and the cilta-cel treated population (N=97), referred to as ciltacabtagene autoleucel in the PI. Seventeen of 97 patients were deemed as having manufacturing failures because drug product did not meet CARVYKTI release specifications, or no data was available to make such a

determination. The non-proprietary name ciltacabtagene autoleucl is used to reference the efficacy and safety data in the label based on the 97 patients in CARTITUDE-1. The proprietary name CARVYKTI is used for the remainder of the information in the label.

- iv) Inclusion of DOR for responders with sCR and responders with VGPR or better.
- v) Removal of time to event endpoints (OS, PFS)

12 Risk Evaluation and Mitigation Strategies (REMS)

FDA Assessment

Because of the risk of CRS and NT, cilta-cel will be approved with a REMS which includes an ETASU. With REMS, hospitals and their associated clinics that dispense cilta-cel must be specially certified, and healthcare providers involved in the prescribing, dispensing or administering of cilta-cel must be trained to recognize and manage CRS and neurologic toxicities.

HLH, neurologic toxicities other than ICANS- Parkinsonism, cranial nerve palsies, peripheral neuropathies and GBS, and prolonged and recurrent cytopenias have been included in the REMS training material.

Please also refer to the REMS memo for additional details on REMS.

- *Negotiations between the OBE review team and the Applicant are ongoing at the time of this review. Refer to OBE review for details of the major REMS modification submissions. Overall, the Applicant has agreed to FDA's edits and recommendations.*
- *OBE review team recommended labeling changes to include daily monitoring for CRS/HLH and early NT for at least 10 days following cilta-cel infusion. This recommendation stems from the fact that daily monitoring (inpatient hospitalization) was mandatory for 14 days for the 1st 6 patients in CARTITUDE-1 followed by a 10-day requirement for the remaining 91 patients. Median duration of hospitalization was 14 days with a minimum of 10 days in CARTITUDE-1 study.*

13. Postmarketing Requirements and Commitment

FDA Assessment

Long-term safety after treatment with CARVYKTI, particularly from the risk of insertional mutagenesis-related secondary malignancies, remains a concern due to limited follow-up

duration. Therefore, the pharmacovigilance plan includes a safety post-marketing requirement (PMR) study under Section 505(o) of the Federal Food, Drug, and Cosmetic Act. The pharmacovigilance plan (PVP) includes a long-term, prospective, non-interventional post-marketing requirement (PMR) registry study in patients treated with cilta-cel. The revised draft protocol 68284528MMY4004 entitled “An observational post-authorization safety study to evaluate the safety of multiple myeloma patients treated with ciltacabtagene autoleucl” was submitted to STN125646/0.43. The applicant agreed to enroll 1500 patients in alignment with post-marketing registry studies being conducted for other CAR T-cell products with 15 years of follow-up.

The proposed milestones for this protocol are as follows:

Final protocol submission: April 30, 2022

Study completion: June 30, 2041

Final report submission: June 30, 2042

12. Chief, Clinical Hematology Branch

X

13. 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

14. Division Director (DCEPT)

X	

15. Appendices

15.1 References

The Applicant's References:

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FDA References

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15.2 Financial Disclosure

The Applicant's Position:

The Applicant has adequately assessed clinical investigators from covered studies 68284528MMY2001 and 68284528MMY2003 for any financial interests/arrangements as defined in 21 CFR Part 54.

One US investigator disclosed significant payments for consulting honoraria exceeding \$25,000 USD. This investigator participated as a Principal Investigator, which screened 6 patients and enrolled/treated 3 patients in Study 68284528MMY2001. Financial certifications and disclosures are provided. [Source: Mod1.3.4].

No disclosable financial interests were found for investigators from Study 68284528MMY2003.

FDA 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):* 68284528MMY2001

Was a list of clinical investigators provided:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request list from Applicant)
Total number of investigators identified: <u>378</u>		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): <u>0</u>		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): <u>1</u>		
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: <u>0</u>		
Significant payments of other sorts: <u>1</u>		
Proprietary interest in the product tested held by investigator: <u>0</u>		
Significant equity interest held by investigator in study: <u>0</u>		
Sponsor of covered study: <u>0</u>		

Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) <u>0</u>		
Is an attachment provided with the reason:	Yes <input type="checkbox"/>	No <input checked="" type="checkbox"/> (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 <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request list from Applicant)
Total number of investigators identified: <u>225</u>		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): <u>0</u>		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): <u>0</u>		
<p>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)):</p> <p>Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: <u>N/A</u></p> <p>Significant payments of other sorts: <u>N/A</u></p> <p>Proprietary interest in the product tested held by investigator: <u>N/A</u></p> <p>Significant equity interest held by investigator in study: <u>N/A</u></p> <p>Sponsor of covered study: <u>N/A</u></p>		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes <input type="checkbox"/>	No <input checked="" type="checkbox"/> (Request details from Applicant) – N/A
Is a description of the steps taken to minimize potential bias provided:	Yes <input type="checkbox"/>	No <input checked="" type="checkbox"/> (Request information from Applicant) – N/A
Number of investigators with certification of due diligence (Form FDA 3454, box 3) <u>0</u>		
Is an attachment provided with the reason:	Yes <input type="checkbox"/>	No <input checked="" type="checkbox"/> (Request explanation from Applicant) – N/A

*The table above should be filled by the applicant and confirmed/edited by the FDA.

15.3 Supportive Safety Data

Study MMY2001 Japan Cohort

Table 18: Applicant - Summary of Treatment-emergent Cytokine Release Syndrome (CRS) Events; Japan Cohort All Treated Analysis Set (Study 68284528MMY2001)

	Total
Analysis set: all treated	9
Number of subjects with CRS	8 (88.9%)
Maximum toxicity grade	
Grade 1	7 (77.8%)
Grade 2	1 (11.1%)
Grade 3	0
Grade 4	0
Grade 5	0
Time from initial infusion of CAR-T cells to first onset of CRS (days)	
N	8
Mean (SD)	7.8 (2.25)
Median	7.5
Range	(4; 11)
Duration of CRS (days)	
N	8
Mean (SD)	4.9 (0.99)
Median	5.0
Range	(3; 6)
Interquartile range	(4.5; 5.5)
Number of subjects with supportive measures to treat CRS ^a	8 (88.9%)
Anti-IL6 receptor Tocilizumab	7 (77.8%)
IL-1 receptor antagonist Anakinra	0
Corticosteroids	3 (33.3%)
IV fluids	0
Vasopressor used	0
Oxygen used	1 (11.1%)
Blow-by	0
Nasal cannula low flow (≤ 6 L/min)	1 (11.1%)
Nasal cannula high flow (> 6 L/min)	0
Face mask	0
Non-Rebreather mask	0
Venturi mask	0
Other	0

Table 18: Applicant - Summary of Treatment-emergent Cytokine Release Syndrome (CRS) Events; Japan Cohort All Treated Analysis Set (Study 68284528MMY2001)

	Total
Positive pressure	0
Analgesics/Antiinflammatory	8 (88.9%)
Antiinfectives	0
Antiepileptics	0
Other	2 (22.2%)
Outcome of CRS	
N	8
Recovered or resolved	8 (100.0%)
Not recovered or not resolved	0
Recovered or resolved with sequelae	0
Recovering or resolving	0
Fatal	0
Unknown	0
Missing	0

Key: ASTCT=American Society for Transplantation and Cellular Therapy; CAR-T=chimeric antigen receptor T (cells); CRS=Cytokine Release Syndrome; IL=interleukin; IV=intravenous; SD=standard deviation.

^a Supportive measures to treat CRS and CRS symptoms are included.

Note: CRS was graded by ASTCT consensus grading system (Lee et al 2019). Toxicity grade by ASTCT is presented in this table.

Note: Time from initial infusion of CAR-T cells to first onset of CRS is calculated as first onset date of CRS - initial infusion date of CAR-T cells +1.

Note: Percentages calculated with the number of subjects in the all treated analysis set as denominator, except for the outcome of CRS for which percentages are calculated with the number of subjects with CRS in the all treated analysis set as denominator.

[TSFAE24JPN.RTF] [JNJ-68284528\MMY2001\DBR SAFETY SUPPORT JAPAN COHORT 2020\RE SAFETY SUPPORT JAPAN COHORT_2020\PROD\TSFAE24JPN.SAS] 23NOV2020, 11:25

Study 68284528MMY2003

Table 19: Applicant - Summary of Treatment-emergent Cytokine Release Syndrome (CRS) Events; All Treated Analysis Set (Study 68284528MMY2003)

	Total
Analysis set: all treated	18
Number of subjects with CRS	13 (72.2%)
Maximum toxicity grade	
Grade 1	7 (38.9%)
Grade 2	4 (22.2%)
Grade 3	1 (5.6%)
Grade 4	1 (5.6%)
Grade 5	0

Table 19: Applicant - Summary of Treatment-emergent Cytokine Release Syndrome (CRS) Events; All Treated Analysis Set (Study 68284528MMY2003)

	Total
Time from initial infusion of JNJ-68284528 to first onset of CRS (days)	
N	13
Mean (SD)	7.8 (1.01)
Median	8.0
Range	(6; 9)
Duration of CRS (days)	
N	13
Mean (SD)	3.9 (2.40)
Median	4.0
Range	(1; 11)
Interquartile range	(3.0; 4.0)
<=7 days	12 (92.3%)
Number of subjects with supportive measures to treat CRS ^a	15 (83.3%)
Anti-IL-6 receptor Tocilizumab	7 (38.9%)
IL-1 receptor antagonist Anakinra	1 (5.6%)
Corticosteroids	3 (16.7%)
IV fluids	6 (33.3%)
Vasopressor used	1 (5.6%)
Oxygen used	2 (11.1%)
Blow-by	0
Nasal cannula low flow (≤ 6 L/min)	1 (5.6%)
Nasal cannula high flow (> 6 L/min)	1 (5.6%)
Face mask	0
Non-Rebreather mask	0
Venturi mask	0
Other	1 (5.6%)
Positive pressure	1 (5.6%)
Continuous Positive Airway Pressure	0
Bilevel Positive Airway Pressure	1 (5.6%)
Intubation/ Mechanical Ventilation	0
Analgesics/Antiinflammatory	11 (61.1%)
Antiinfectives	12 (66.7%)
Antiepileptics	0
Other	5 (27.8%)
Outcome of CRS	
N	13
Recovered or resolved	12 (92.3%)
Not recovered or not resolved	0
Recovered or resolved with sequelae	0

Table 19: Applicant - Summary of Treatment-emergent Cytokine Release Syndrome (CRS) Events; All Treated Analysis Set (Study 68284528MMY2003)

	Total
Recovering or resolving	1 (7.7%)
Fatal	0
Unknown	0
Missing	0

Key: ASTCT=American Society for Transplantation and Cellular Therapy; CRS = Cytokine Release Syndrome; IL= interleukin; IV=intravenous; SD=standard deviation.

^aSupportive measures to treat CRS and CRS symptoms are included.

Note: Percentages calculated with the number of subjects in the all treated analysis set as denominator, except for the outcome of CRS and duration of CRS for which percentages are calculated with the number of subjects with CRS in the all treated analysis set as denominator.

Note: CRS evaluated according to the ASTCT consensus grading system ([Lee et al 2019](#)).

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Table 20: Applicant - Number of Subjects with Neurologic Adverse Event with Onset After JNJ-68284528 Infusion by System Organ Class, High Level Group Term, High Level Term, Preferred Term, and Grade 3 or 4; All Treated Analysis Set (Study 68284528MMY2003)

	Neurologic Adverse Event									
	CAR-T Cell Neurotoxicity									
	Total		Total		ICANS		Other Neurotoxicities		Other Neurologic Adverse Events	
	All Grades	Grade 3 or 4	All Grades	Grade 3 or 4	All Grades	Grade 3 or 4	All Grades	Grade 3 or 4	All Grades	Grade 3 or 4
Analysis set: all treated	18									
Total number of subjects with neurologic AE	8 (44.4%)	1 (5.6%)	4 (22.2%)	0	2 (11.1%)	0	2 (11.1%)	0	5 (27.8%)	1 (5.6%)
MedDRA										
SOC/HLGT/HLT/PT										
Nervous system disorders	8 (44.4%)	0	4 (22.2%)	0	2 (11.1%)	0	2 (11.1%)	0	5 (27.8%)	0
Neurological disorders NEC	4 (22.2%)	0	1 (5.6%)	0	0	0	1 (5.6%)	0	3 (16.7%)	0
Neurological signs and symptoms NEC	2 (11.1%)	0	0	0	0	0	0	0	2 (11.1%)	0
Dizziness	2 (11.1%)	0	0	0	0	0	0	0	2 (11.1%)	0
Cortical dysfunction NEC	1 (5.6%)	0	0	0	0	0	0	0	1 (5.6%)	0
Aphasia	1 (5.6%)	0	0	0	0	0	0	0	1 (5.6%)	0
Dysgraphia	1 (5.6%)	0	0	0	0	0	0	0	1 (5.6%)	0
Disturbances in consciousness NEC	1 (5.6%)	0	0	0	0	0	0	0	1 (5.6%)	0
Depressed level of consciousness	1 (5.6%)	0	0	0	0	0	0	0	1 (5.6%)	0
Lethargy	1 (5.6%)	0	0	0	0	0	0	0	1 (5.6%)	0

Table 20: Applicant - Number of Subjects with Neurologic Adverse Event with Onset After JNJ-68284528 Infusion by System Organ Class, High Level Group Term, High Level Term, Preferred Term, and Grade 3 or 4; All Treated Analysis Set (Study 68284528MMY2003)

	Neurologic Adverse Event									
	CAR-T Cell Neurotoxicity									
	Total		Total		ICANS		Other Neurotoxicities		Other Neurologic Adverse Events	
	All Grades	Grade 3 or 4	All Grades	Grade 3 or 4	All Grades	Grade 3 or 4	All Grades	Grade 3 or 4	All Grades	Grade 3 or 4
Speech and language abnormalities	1 (5.6%)	0	1 (5.6%)	0	0	0	1 (5.6%)	0	0	0
Slow speech	1 (5.6%)	0	1 (5.6%)	0	0	0	1 (5.6%)	0	0	0
Movement disorders (incl parkinsonism)	3 (16.7%)	0	0	0	0	0	0	0	3 (16.7%)	0
Tremor (excl congenital)	2 (11.1%)	0	0	0	0	0	0	0	2 (11.1%)	0
Resting tremor	1 (5.6%)	0	0	0	0	0	0	0	1 (5.6%)	0
Tremor	1 (5.6%)	0	0	0	0	0	0	0	1 (5.6%)	0
Paralysis and paresis (excl cranial nerve)	1 (5.6%)	0	0	0	0	0	0	0	1 (5.6%)	0
Hemiparesis	1 (5.6%)	0	0	0	0	0	0	0	1 (5.6%)	0
Cranial nerve disorders (excl neoplasms)	2 (11.1%)	0	1 (5.6%)	0	0	0	1 (5.6%)	0	1 (5.6%)	0
Facial cranial nerve disorders	2 (11.1%)	0	1 (5.6%)	0	0	0	1 (5.6%)	0	1 (5.6%)	0
Facial paralysis	2 (11.1%)	0	1 (5.6%)	0	0	0	1 (5.6%)	0	1 (5.6%)	0
Encephalopathies	2 (11.1%)	0	2 (11.1%)	0	2 (11.1%)	0	0	0	0	0
Encephalopathies toxic and metabolic	2 (11.1%)	0	2 (11.1%)	0	2 (11.1%)	0	0	0	0	0

Table 20: Applicant - Number of Subjects with Neurologic Adverse Event with Onset After JNJ-68284528 Infusion by System Organ Class, High Level Group Term, High Level Term, Preferred Term, and Grade 3 or 4; All Treated Analysis Set (Study 68284528MMY2003)

	Neurologic Adverse Event									
	CAR-T Cell Neurotoxicity									
	Total		Total		ICANS		Other Neurotoxicities		Other Neurologic Adverse Events	
	All Grades	Grade 3 or 4	All Grades	Grade 3 or 4	All Grades	Grade 3 or 4	All Grades	Grade 3 or 4	All Grades	Grade 3 or 4
Immune effector cell-associated neurotoxicity syndrome	2 (11.1%)	0	2 (11.1%)	0	2 (11.1%)	0	0	0	0	0
Headaches	1 (5.6%)	0	0	0	0	0	0	0	1 (5.6%)	0
Headaches NEC	1 (5.6%)	0	0	0	0	0	0	0	1 (5.6%)	0
Headache	1 (5.6%)	0	0	0	0	0	0	0	1 (5.6%)	0
Mental impairment disorders	1 (5.6%)	0	1 (5.6%)	0	1 (5.6%)	0	0	0	0	0
Mental impairment (excl dementia and memory loss)	1 (5.6%)	0	1 (5.6%)	0	1 (5.6%)	0	0	0	0	0
Disturbance in attention	1 (5.6%)	0	1 (5.6%)	0	1 (5.6%)	0	0	0	0	0
Psychiatric disorders	2 (11.1%)	1 (5.6%)	1 (5.6%)	0	1 (5.6%)	0	0	0	2 (11.1%)	1 (5.6%)
Sleep disorders and disturbances	2 (11.1%)	0	0	0	0	0	0	0	2 (11.1%)	0
Disturbances in initiating and maintaining sleep	2 (11.1%)	0	0	0	0	0	0	0	2 (11.1%)	0
Insomnia	2 (11.1%)	0	0	0	0	0	0	0	2 (11.1%)	0
Anxiety disorders and symptoms	1 (5.6%)	1 (5.6%)	0	0	0	0	0	0	1 (5.6%)	1 (5.6%)
Anxiety symptoms	1 (5.6%)	1 (5.6%)	0	0	0	0	0	0	1 (5.6%)	1 (5.6%)
Agitation	1 (5.6%)	1 (5.6%)	0	0	0	0	0	0	1 (5.6%)	1 (5.6%)
Anxiety	1 (5.6%)	1 (5.6%)	0	0	0	0	0	0	1 (5.6%)	1 (5.6%)
Deliria (incl confusion)	1 (5.6%)	1 (5.6%)	0	0	0	0	0	0	1 (5.6%)	1 (5.6%)

Table 20: Applicant - Number of Subjects with Neurologic Adverse Event with Onset After JNJ-68284528 Infusion by System Organ Class, High Level Group Term, High Level Term, Preferred Term, and Grade 3 or 4; All Treated Analysis Set (Study 68284528MMY2003)

	Neurologic Adverse Event									
	CAR-T Cell Neurotoxicity									
	Total		Total		ICANS		Other Neurotoxicities		Other Neurologic Adverse Events	
	All Grades	Grade 3 or 4	All Grades	Grade 3 or 4	All Grades	Grade 3 or 4	All Grades	Grade 3 or 4	All Grades	Grade 3 or 4
Deliria	1 (5.6%)	1 (5.6%)	0	0	0	0	0	0	1 (5.6%)	1 (5.6%)
Delirium	1 (5.6%)	1 (5.6%)	0	0	0	0	0	0	1 (5.6%)	1 (5.6%)
Depressed mood disorders and disturbances	1 (5.6%)	0	0	0	0	0	0	0	1 (5.6%)	0
Depressive disorders	1 (5.6%)	0	0	0	0	0	0	0	1 (5.6%)	0
Depression	1 (5.6%)	0	0	0	0	0	0	0	1 (5.6%)	0
Disturbances in thinking and perception	1 (5.6%)	0	1 (5.6%)	0	1 (5.6%)	0	0	0	0	0
Hallucinations (excl sleep-related)	1 (5.6%)	0	1 (5.6%)	0	1 (5.6%)	0	0	0	0	0
Hallucination	1 (5.6%)	0	1 (5.6%)	0	1 (5.6%)	0	0	0	0	0
General disorders and administration site conditions	1 (5.6%)	0	1 (5.6%)	0	0	0	1 (5.6%)	0	0	0
General system disorders										
NEC	1 (5.6%)	0	1 (5.6%)	0	0	0	1 (5.6%)	0	0	0
Gait disturbances	1 (5.6%)	0	1 (5.6%)	0	0	0	1 (5.6%)	0	0	0
Gait disturbance	1 (5.6%)	0	1 (5.6%)	0	0	0	1 (5.6%)	0	0	0
Pain and discomfort NEC	1 (5.6%)	0	1 (5.6%)	0	0	0	1 (5.6%)	0	0	0
Pain	1 (5.6%)	0	1 (5.6%)	0	0	0	1 (5.6%)	0	0	0

Table 20: Applicant - Number of Subjects with Neurologic Adverse Event with Onset After JNJ-68284528 Infusion by System Organ Class, High Level Group Term, High Level Term, Preferred Term, and Grade 3 or 4; All Treated Analysis Set (Study 68284528MMY2003)

Neurologic Adverse Event										
CAR-T Cell Neurotoxicity										
Total		Total		ICANS		Other Neurotoxicities		Other Neurologic Adverse Events		
All Grades	Grade 3 or 4	All Grades	Grade 3 or 4	All Grades	Grade 3 or 4	All Grades	Grade 3 or 4	All Grades	Grade 3 or 4	

Keys: AE=adverse event, ICANS=Immune Effector Cell-Associated Neurotoxicity; SOC=system organ class.

Note: ICANS includes ICANS diagnosis and the associated symptoms of ICANS

Note: Other Neurotoxicities includes adverse events reported as chimeric antigen receptor-T (CAR-T) cell neurotoxicity that are neither ICANS nor the associated symptoms of ICANS

Note: Other Neurologic Adverse Events includes adverse events in the Nervous System Disorders SOC or Psychiatric Disorders SOC that are not reported as CAR-T cell neurotoxicity

Note: Percentages are calculated with the number of subjects in the all treated analysis set as denominator.

Note: Adverse events are coded using MedDRA version 23.0.

Note: Adverse events are graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) Version 5.0, with the exception of immune effector cell-associated neurotoxicity (ICANS) and cytokine release syndrome (CRS), which were evaluated according to the American Society for Transplantation and Cellular Therapy (ASTCT) consensus grading system

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15.4 FDA Group and Preferred Terms

Grouped terms that were used for FDA analyses of adverse events are listed in FDA Table 27 below.

FDA Table 27: FDA Group Terms Used for FDA Analyses of Adverse Events

FDA Group Term	AEDECOD/Preferred Terms
Abdominal pain	abdominal pain, abdominal pain upper,
Aphasia	aphasia, dysarthria, speech disorder
Ataxia	ataxia, gait disturbance, balance disorder
Bacterial infection	abscess limb, cholecystitis, cholecystitis active, clostridium difficile infection, clostridium difficile colitis, clostridium difficile infection, enterocolitis bacterial, osteomyelitis, perirectal abscess, soft tissue infection, staphylococcal infection, and tooth infection
Bradycardia	bradycardia, sinus bradycardia
Cardiac Arrhythmias	atrial fibrillation, atrial flutter, supraventricular tachycardia, ventricular extrasystoles, ventricular tachycardia
Chest pain	angina pectoris, chest discomfort, chest discomfort

Coagulopathy	activated partial thromboplastin time prolonged, coagulopathy, disseminated intravascular coagulation, hypofibrinogenemia, international normalised ratio increased, prothrombin time prolonged
Cough	Cough, productive cough, upper-airway cough syndrome
Cytokine release syndrome	Cytokine release syndrome, systemic inflammatory response syndrome
Delirium	Agitation, hallucination, irritability, personality change, restlessness
Depression	Depression, flat affect
Dizziness	Dizziness, dizziness exertional, presyncope, syncope, vertigo
Diarrhea	Colitis, diarrhoea
Dizziness	Dizziness, presyncope, syncope
Dyspnea	Acute respiratory failure, dyspnoea, dyspnoea exertional, respiratory failure, tachypnoea
Edema	face oedema, generalised oedema, localized oedema, oedema peripheral,

	periorbital oedema, peripheral swelling, pulmonary oedema, scrotal oedema
Encephalopathy	Amnesia, bradyphrenia, confusional state, depressed level of consciousness, disturbance in attention, encephalopathy, immune effector cell-associated neurotoxicity syndrome, lethargy, memory impairment, mental impairment, mental status changes, noninfective encephalitis, somnolence
Fatigue	Asthenia, fatigue, malaise
Gastroenteritis	Enterocolitis infectious, gastroenteritis, gastroenteritis cryptosporidial, gastroenteritis salmonella, gastroenteritis viral
Hemorrhage	conjunctival haemorrhage, contusion, ecchymosis, epistaxis, eye contusion, haematochezia, haemoptysis, infusion site haematoma, oral contusion, petechiae, post procedural haemorrhage, retinal haemorrhage, subdural haematoma
Hypotension	hypotension, orthostatic hypotension

Motor dysfunction	motor dysfunction, muscle spasms, muscle tightness, muscular weakness, myoclonus
Musculoskeletal pain	Arthralgia, back pain, bone pain, joint pain, muscle strain, musculoskeletal chest pain, musculoskeletal discomfort, musculoskeletal pain, musculoskeletal stiffness, myalgia, neck pain, non-cardiac chest pain, pain in extremity
Neuropathy	Burning sensation, hypoaesthesia, neuralgia, peripheral motor neuropathy, peripheral sensory neuropathy
Oral Pain	Oral pain, oropharyngeal pain
Paresis	Cranial nerve paralysis, facial paralysis, peroneal nerve palsy
Pneumonia	atypical pneumonia, lung abscess, lung opacity, pneumocystis jirovecii pneumonia, pneumonia aspiration
Rash	erythema, rash, rash maculo-papular, rash pustular
Reflexes abnormal	reflexes abnormal, hyporeflexia
Renal failure	acute kidney injury, blood creatinine increased, chronic kidney disease, renal impairment

Sepsis	bacteraemia, bacterial sepsis, pseudomonal bacteraemia, sepsis, septic shock staphylococcal bacteraemia
Tachycardia Thrombosis	sinus tachycardia, tachycardia deep vein thrombosis, device related thrombosis
Transaminase elevation	alanine aminotransferase increased, aspartate aminotransferase increased
Upper respiratory tract infection	Human rhinovirus test positive, rhinitis, rhinovirus infection, sinusitis, upper respiratory tract infection, viral upper respiratory tract infection
Urinary tract infection	urinary tract infection, urinary tract infection viral
Viral infection	Adenovirus test positive, coronavirus infection, cytomegalovirus infection, enterovirus infection, herpes zoster, herpes zoster disseminated, influenza, influenza like illness, oral herpes, parainfluenzae virus infection
Xerosis	dry eye, dry mouth, dry skin