Summary Basis for Regulatory Action

Date:	February 28, 2022
From:	Zhaohui Ye, PhD, Review Committee Chair, Office of Tissues and Advanced Therapies, Division of Cellular and Gene Therapies
BLA STN:	125746/0
Applicant:	Janssen Biotech, Inc.
Submission Receipt Date:	March 31, 2021
PDUFA Action Due Date:	February 28, 2022
Proper Name:	ciltacabtagene autoleucel
Proprietary Name:	CARVYKTI
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.

Recommended Action: The Review Committee recommends approval of this product.

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Director, Office of Tissues and Advanced Therapies

Discipline Reviews	Reviewer/Consultant, Office/Division
CMC • CMC Product (Product Office and OCBQ/DBSQC) • Facilities review (OCBQ/DMPQ) • Establishment Inspection Report (OCBQ/DMPQ and Product Office) • QC, Test Methods, Product Quality (OCBQ/DBSQC)	Zhaohui Ye, PhD, CBER/OTAT/DCGT Graeme Price, PhD, CBER/OTAT/DCGT Tiffany Lucas, PhD, CBER/OTAT/DCGT Maitreyi Chattopadhyay, PhD, CBER/OTAT/DCGT Karla Garcia, MS, CBER/OCBQ/DBSQC Jing Lin, PhD, CBER/OCBQ/DBSQC Varsha Garnepudi, CBER/OCBQ/DBSQC David Bailey, CBER/OCBQ/DMPQ Nicole Li, CBER/OCBQ/DMPQ Hsiaoling Wang, CBER/OCBQ/DBSQC Jacqueline Diaz-Albertini, ORA/OMPTO/OBPO/BPIS
Clinical • Clinical (Product Office) • Postmarketing safety epidemiological review (OBE/DE) • BIMO	Kavita Natrajan, MD, CBER/OTAT/DCEPT Megha Kaushal, MD, MSc CBER/OTAT/DCEPT Kerry Welsh, MD, PhD, CBER/OBE/DE Haecin Chun, MT(ASAP)SBB, MS, CBER/OCBQ/DIS/BMB Kanaeko Ravenell, MS, SBB (ASCP), CBER/OCBQ/DIS/BMB
Statistical • Clinical data (OBE/DB) • Non-clinical data	Tianjiao Dai, PhD, CBER/OBE/DB
Non-clinical/Pharmacology/Toxicology • Toxicology (Product Office) • Developmental toxicology (Product Office) • Animal pharmacology	Ernesto Moreira, MD, CBER/OTAT/DCEPT
Clinical Pharmacology	Xiaofei Wang, PhD, CBER/OTAT/DCEPT
Labeling • Promotional (OCBQ/APLB)	Dana Jones, CBER/OCBQ/APLB
Other Review(s) not captured above categories, for example: • Consults • Devices • Software • Human Factors • FONSI	Neil Vora, PharmD, MBA, PMP, CDER/OSE/PMS
Advisory Committee Summary	N/A. No Advisory Committee meeting was held.

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1. Introduction

Janssen Biotech, Inc. submitted a Biologics License Application (BLA), STN 125746, for licensure of ciltacabtagene autoleucel (cilta-cel, JNJ-68284528), with the proprietary name of CARVYKTI. CARVYKTI is a B cell maturation antigen (BCMA)-directed genetically modified autologous T cell immunotherapy indicated for the 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.

CARVYKTI is composed of human autologous (b) (4) T cells that are genetically modified by a lentiviral vector (LVV) to target cells expressing BCMA on the

cell surface. The replication-incompetent LVV (b) (4) expresses a chimeric antigen receptor (CAR) consisting of two (b) (4)-derived single domain antibodies (sdAbs), that recognize human BCMA, (b) (4) , 4-1BB intracellular signaling domain, and CD3ζ cytoplasmic domain. Binding of the CAR to BCMA-expressing cells leads to signaling through the CD3ζ and 4-1BB domains, and subsequent CAR+ T cell activation. Antigen-specific activation results in CAR+ T cell proliferation, cytokine secretion, and lysis of BCMA-expressing cells.

This document summarizes the basis for regular approval of CARVYKTI. A single clinical trial, CARTITUDE-1 (Study MMY2001), provides the primary evidence of safety and efficacy for the BLA submission. Our recommendation for approval is based on the overall response rate, complete response rate and duration of response demonstrated in this study. The major risks of CARVYKTI include cytokine release syndrome (CRS), neurologic toxicity- immune effector cell-associated neurotoxicity syndrome (ICANS), parkinsonism, Guillain-Barré syndrome (GBS, hemophagocytic lymphohistiocytosis/macrophage activation syndrome (HLH/MAS), infections and prolonged and recurrent cytopenias, each of which can be disabling or life-threatening.

2. Background

Multiple myeloma is the second most common hematologic malignancy in the US, accounting for 1.8% of all cancers and 17% of all hematologic malignancies. Data from the US Surveillance, Epidemiology, and End Results (SEER) registry estimate approximately 32,270 new cases and 13,000 deaths annually in the US. It constitutes 2% of all cancer-related deaths in the US.

The majority of patients with multiple myeloma will have an initial response to treatment with combination regimens, however, treatment is not curative, and most of these patients ultimately relapse. In addition, some patients do not respond to the initial treatment, which constitutes refractory disease. The introduction of proteasome inhibitors, immunomodulatory agents, monoclonal antibodies and stem cell transplantation has further extended median survival to 5 to 6 years. Myeloma is not considered curable, with a 5-year survival rate of 54% (Cancer stat facts: Myeloma SEER 2010-2016). Patients who are refractory to major classes of available anti-myeloma therapies such as triple class refractory (refractory to a proteasome inhibitor, an immunomodulatory agent, and anti-CD 38 monoclonal antibody) or penta-refractory disease (refractory to 2 proteasome inhibitors, 2 immunomodulatory agents, and anti-CD38 monoclonal antibody) demonstrate low response rates and have poor overall prognosis. Therefore, there is need for new therapies for myeloma that is refractory to standard classes of agents such as anti-CD38 antibody, a proteasome inhibitor, and an immunomodulatory agent.

Available Therapies:
The following are the approved therapies for the overlapping indication of relapsed or refractory (R/R) multiple myeloma who have received four prior lines of therapies, including a proteasome inhibitor (PI), an immunomodulatory (IMiD) agent, and an anti-CD38 monoclonal antibody therapy. These are in addition to the multiple

standard-of-care salvage regimens, which may include re-treatment with one or more of the agents that patients may have previously received.

Regulatory History:

The ciltacabtagene autoleucel regulatory history is summarized below in Table 2:

Table 1. Regulatory History

Regulatory Events / Milestones	Date
IND submission	April 27, 2018
Orphan Drug designation granted	February 1, 2019
Breakthrough Therapy designation granted	December 6, 2019
Pre-BLA meeting	December 8, 2020
BLA submission – final module of rolling BLA received	March 31, 2021
BLA filed	May 25, 2021
Mid-Cycle communication	July 29, 2021
Late-Cycle meeting	September 20, 2021
Major Amendment	October 28, 2021
Action Due Date	February 28, 2022

3. Chemistry Manufacturing and Controls (CMC)

a. Product Quality

Product Description

CARVYKTI is composed of human autologous (b) (4) T cells that are genetically modified by a lentiviral vector (LVV) to target cells expressing B-cell maturation antigen (BCMA) on the cell surface. The replication-incompetent lentivirus vector (b) (4) expresses a chimeric antigen receptor (CAR) consisting of two (b) (4)-derived single domain antibodies (sdAbs) that recognize (b) (4) epitopes on human BCMA, (b) (4) intracellular signaling domain from CD137 (4-1BB), and the cytoplasmic domain of CD3ζ. The CAR gene expression in CARVYKTI is controlled by a (b) (4) promoter. The LVV-transduced and expanded cells are formulated into a suspension and cryopreserved in an infusion bag.

Manufacturing Summary

Patient apheresis material is collected at qualified apheresis centers and is shipped to the Janssen Pharmaceuticals manufacturing facility ((b) (4)), where it is inspected (b) (4) until the initiation of drug product (DP) manufacturing. The (b) (4) manufacturing process starts with apheresis (b) (4), which is followed by (b) (4) T cell enrichment in the (b) (4) system. The enriched cells are (b) (4) and transduced by (b) (4) lentiviral vector in (b) (4). After (b) (4) of culture (b) (4), the cells are harvested, washed, and formulated in (b) (4). The final formulation calculation is performed based on patient weight and target dose using the in-process test results for (b) (4)

(b) (4) . Each dose is then filled into one appropriate size (b) (4) cryopreservation bag. Filled bags are examined for appearance, placed in individual metal cassettes, cryopreserved using a (b) (4) , and stored at ≤-120°C in vapor phase liquid nitrogen until lot release testing is complete. The DP is packaged into a vapor phase liquid nitrogen shipper and shipped to the administration site once patient administration has been scheduled.

The (b) (4) LVV is manufactured at Janssen Vaccines (b) (4)

Manufacturing Controls

COI/COC

The chain of identity (COI) is established at the time of receiving the treating physician's prescription, while the chain of custody (COC) is established at the time of apheresis collection. Both COI and COC are maintained throughout the manufacturing process to administration, by a validated computer-based system with a validated paper-based system as backup, to ensure that the patient receives the correct autologous DP lot.

Material Controls

The CARVYKTI control strategy begins with material qualification that includes source material risk assessment, vendor qualification, confirmation of the certificate of analysis, and material testing. Raw materials and reagents are accepted based on specified quality attributes. Raw materials derived from animals and humans are appropriately controlled to ensure the absence of microbial contaminants and adventitious agents.

Process Controls and Release Testing

Manufacturing process parameters are established for each manufacturing stage based on process characterization, risk assessment and process validation studies. In-process monitoring and controls are implemented throughout the process to support process consistency. Lot release testing is performed on material collected at appropriate stages of the manufacturing process to evaluate product safety and function. Specifically, mycoplasma testing is performed on samples taken at the time of (b) (4) ; replication-competent lentivirus testing on the DP is performed on (b) (4) samples; (b) (4) and CAR identity testing are performed on (b) (4) samples; all other lot release testing (appearance, safety, purity, identity, quantity, dose and potency) is performed on samples taken from the final formulated DP. Lot release test methods are suitably validated or verified, and product specifications are adequate to ensure product quality and consistency.

Impurity Profile

The active ingredient in CARVYKTI is viable CAR+ T cells. Impurities can be classified into product-related and process-related and were evaluated during process characterization and process validation. Product-related impurities include non-viable cells and cellular components derived from the apheresis starting material, including (b) (4)

(b) (4) . T cell viability, T cell purity, (b) (4) and NK cells are measured as part of the DP release specifications to control the impurities. Janssen's clinical manufacturing and process validation data showed that the other product-related impurities were undetectable in DP lots. The CARVYKTI manufacturing process also consistently removed process-related impurities, including LVV-associated impurities, (b) (4) components, to safe levels (levels below the assay quantification limits, and/or within toxicological acceptance limits by a margin of safety determined by impurity risk assessment).

Process Validation
The suitability of the commercial CARVYKTI manufacturing process was assessed at the Janssen Pharmaceuticals manufacturing facility using patient leukapheresis materials and LVV produced by the commercial process. The process validation was assessed against established critical and non-critical process parameters and predefined DP release criteria and was acceptable. All deviations and exceptional conditions during the process validation study were adequately investigated. The manufacturing process validation demonstrated control of process-related impurities, including (b) (4) associated with vector manufacturing. The (b) (4) LVV manufacturing process at Janssen Vaccines (b) (4) was also validated. Shipping was validated for all shipping steps, including shipping (b) (4) , shipping apheresis material to the manufacturing site, and shipping DP to the infusion site from the manufacturing site. In addition, continued process verification (CPV) programs were established to collect, analyze, and respond to trends in process performance and product quality data generated during commercial DP and LVV manufacturing.

Stability
Long-term stability studies, utilizing a combination of DP lots produced from healthy donor and patient apheresis materials, support 9 months of storage for CARVYKTI when stored at ≤ -120°C in vapor phase of liquid nitrogen. In-use stability testing supports a post-thaw expiry of (b) (4) hours, although a decreasing trend in viability was observed at room temperature. Long-term stability studies on (b) (4) support (b) (4) of storage at (b) (4). Acceptable post-approval DP (b) (4) long-term stability protocols, which include collecting (b) (4) potency data, are provided.

CMC Comparability Assessment
There have been several manufacturing changes during the clinical study supporting this application. Studies to demonstrate comparability of DP manufacturing processes at (b) (4) , Janssen (b) (4) , and Janssen (b) (4) (commercial) facilities were performed under IND18080. These studies, together with batch analysis of DP lots manufactured at these sites, demonstrated that the DP manufacturing processes were comparable. Studies to demonstrate comparability of LVV manufactured at the clinical ((b) (4)) and commercial (Janssen Vaccines (b) (4)) manufacturing facilities were also performed. These studies demonstrated that the LVV manufactured at the two facilities were comparable.

Manufacturing risks, potential safety concerns and management
Source Material and Product Mix-up

CARVYKTI is an autologous product manufactured at a central facility using source material collected at apheresis centers and processed at local or central (b) (4) sites; mix-ups at any of the apheresis collection/(b) (4), DP manufacturing, storage, and shipping steps would result in potential risks, including infection, graft versus host disease, and lack of anti-tumor effect. This risk is managed by the validated COI/COC systems that ensure each patient receives the correct autologous lot.

Replication-Competent Lentivirus (RCL)
Generation of RCL is a theoretical concern for the CARVYKTI manufacturing process. The likelihood of RCL generation is reduced by the (b) (4) LVV design: (b) (4) . The final (b) (4) LVV (b) (4) are tested by co-culture in accordance with current FDA guidance prior to release and use in the CAR T cell manufacturing process. To date, no RCL has been detected in clinical trial lots of (b) (4) LVV or CARVYKTI DP.

Insertional Mutagenesis
Vector integration poses a risk for insertional mutagenesis. Activation of proto-oncogenes or disruption of tumor suppressor genes has the potential to cause secondary malignancies. To mitigate the risk of insertional mutagenesis, the vector used for CARVYKTI manufacturing was designed to (b) (4) The insertional mutagenesis risk of CARVYKTI is managed by DP release specifications that (b) (4) to that within the clinical trial experience.

Additional Assays Used in Clinical Studies
Additional assays used in clinical studies include immunoassays, flow cytometry, (b) (4), and (b) (4) assays for determination of minimal residual disease status, measurement of CAR T cells, detection of BCMA expression, assessment of immunogenicity (antibodies against the CAR), quantification of cytokine levels, cytogenetics analysis, and replication-competent lentivirus (RCL) monitoring. The assays used to support study endpoints and for clinical monitoring are adequately described, and are either validated or qualified as fit for purpose.

b. Testing Specifications

The analytical methods and their validations and/or qualifications reviewed for the CARVYKTI drug substance and drug product were found to be adequate for their intended use. The final lot release specifications are shown in Table 3.

Table 2. **CARVYKTI lot release specifications**

Attribute	Test parameter	Test method	Acceptance criteria
General	Appearance of color	Visual examination	(b) (4)
	Appearance of primary container	Visual examination	Each bag is without visible defects or leaks
Safety	Sterility	(b) (4)	No growth
	Endotoxin	(b) (4)	(b) (4)
	Mycoplasma	(b) (4)	Not detected
	Replication-Competent Lentivirus	(b) (4)	(b) (4)
	(b) (4)	Calculation [A]	(b) (4)
Purity	(b) (4) Viability	(b) (4)	(b) (4)
	Phenotype ((b) (4))	(b) (4)	(b) (4)
	Phenotype (% NK)	(b) (4)	(b) (4)
	Phenotype (b) (4) purity)	(b) (4)	(b) (4)
Identity	CAR Identity	(b) (4)	Positive for detection of CAR transgene
Quantity	Viable cell concentration	(b) (4)	(b) (4)
Dose	Number of CAR^+ viable T cells per kg of patient weight of total CAR^+ viable T cells in the final container	Calculation [B]	Patient 100.0 kg or below: 0.5 – 1.0 × 10^6 CAR^+ viable T cells/kg Patient above 100.0 kg: 0.5 – 1.0 × 10^8 CAR^+ viable T cells
Potency/Identity	CAR expression from viable T cells	(b) (4)	(b) (4)
Potency	(b) (4)	(b) (4)	(b) (4)

[A] The calculation is based on results from (b) (4)
[B] The calculation is based on results from (b) (4)

c. CBER Lot Release

An exemption has been granted from CBER Lot Release testing, including no requirement for submission of product samples to CBER. The basis for this decision is that CARVYKTI is an autologous product; as such, each lot will treat a single patient. Failure of a single lot will have a minimal potential impact on public health.

d. Facilities Review / Inspection

Facility information and data provided in the BLA were reviewed by CBER and found to be sufficient and acceptable. The facilities involved in the manufacture of CARVYKTI (ciltacabtagene autoleucel) are listed in the table below. The activities performed and inspectional histories are noted in the table and are further described in the paragraphs that follow.

Table 3. Manufacturing Facilities for CARVYKTI

Name/address	FEI number	DUNS number	Inspection/ waiver	Results/ Justification
Janssen Pharmaceuticals, Inc. (b) (4) *Drug Product* Manufacture, primary and secondary packaging, labeling, and release testing	(b) (4)	(b) (4)	Records request (704(a)(4)) in advance of inspection and Pre-license inspection	Requested documents reviewed and found acceptable CBER Pre-license inspection (b) (4) NAI
Janssen Vaccines (b) (4) *Lentiviral vector* Manufacture	(b) (4)	(b) (4)	Records request (704(a)(4)) in lieu of inspection	Requested documents reviewed and found acceptable
(b) (4) *Drug Product* Release testing	(b) (4)	(b) (4)	Waiver	ORA Surveillance inspection (b) (4) VAI

Name/address	FEI number	DUNS number	Inspection/ waiver	Results/ Justification
Janssen Biotech, Inc. (b) (4) *Drug Product* Release testing	(b) (4)	(b) (4)	Waiver	ORA Surveillance inspection (b) (4) VAI

Abbreviations: CBER = Center for Biologics Evaluation and Research; ORA = Office of Regulatory Affairs; NAI = No Action Indicated; VAI = Voluntary Action Indicated

CBER conducted a records request in advance of an inspection in accordance with Section 704(a)(4) of the Federal Food, Drug and Cosmetic Act (FDCA) for Janssen Pharmaceuticals, Inc., and the requested manufacturing site records appeared acceptable. CBER and ORA also conducted a pre-license inspection of Janssen Pharmaceuticals, Inc. from September (b) (4). No Form FDA 483 was issued, and the inspection was classified as NAI.

Due to the COVID-19 public health emergency, CBER used its authority under FDCA Section 704(a)(4) to request manufacturing site records from Janssen Vaccines (b) (4). The records request was conducted in lieu of performing an on-site inspection. The requested manufacturing site records appeared acceptable.

ORA conducted a surveillance inspection of (b) (4) from (b) (4). All inspectional issues were resolved, and the inspection was classified as VAI.

ORA conducted a surveillance inspection of Janssen Biotech, Inc. from (b) (4). All inspectional issues were resolved, and the inspection was classified as VAI.

e. Container/Closure System

The drug product is filled and cryopreserved ((b) (4)) in (b) (4) cryopreservation bags supplied by (b) (4) located in (b) (4). The cryopreservation bags are 510(k)-cleared for the US market ((b) (4)) and are supplied sterile in two size configurations: (b) (4) ((b) (4) 30 mL) and (b) (4) ((b) (4) 70 mL). The bag and the crimped ports are made of ethyl vinyl acetate (EVA), and the loading tube is made of polyvinyl chloride/EVA co-extrusion. Container closure integrity testing was performed by Janssen Pharmaceuticals, Inc. ((b) (4)), using a validated (b) (4) test method; all acceptance criteria were met. The Janssen Biotech, Inc. facility in (b) (4) serves as a backup testing site for container closure integrity testing using the same validated test method.

f. Environmental Assessment

The BLA includes a request for categorical exclusion from an Environmental Assessment under 21 CFR 25.31(c). The FDA concluded that this request is justified, and no extraordinary circumstances exist that would require an environmental assessment.

4. Nonclinical Pharmacology/Toxicology

CARVYKTI (ciltacabtagene autoleucel; cilta-cel; JNJ-68284528; or LCAR-B38M CAR-T cells) 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 BCMA-targeting domain ((b) (4)) is comprised of two single-domain antibodies, described as (b) (4)

In vitro pharmacology studies characterizing the mechanism of action of CARVYKTI demonstrated tumor cell cytotoxicity and cytokine release following exposure to BCMA-expressing multiple myeloma (MM) cells. On-tumor/on-target specificity of the BCMA-targeting domain to human BCMA was also shown. Although binding between (b) (4) was detected in a (b) (4) , the data suggest that the epitope primarily recognized by (b) (4) is found in BCMA. In addition, specific binding of (b) (4) cilta-cel to healthy donor (HD)-derived myeloid cells that endogenously express native (b) (4) was not observed.

In vivo studies in mice and nonhuman primates (NHPs) did not reveal any adverse findings due to possible off-target binding to (b) (4). These data suggest a low risk of off-target adverse effects in humans. In vivo pharmacology studies showed significant dose-dependent anti-tumor activity and increased survival following administration of LCAR-B38M CAR-T cells in immune-deficient mice engrafted with human MM cells. Following tumor re-challenge, no increase in tumor growth was displayed.

In vitro data indicate that (b) (4) does not significantly bind to recombinant mouse or NHP BCMA expressed on (b) (4) cells. Therefore, animal studies evaluating the safety profile of CARVYKTI were limited due to lack of a pharmacologically relevant animal species.

Traditional genotoxicity assays and carcinogenicity assessments were not conducted. The risk of insertional mutagenesis due to LV transduction, possibly leading to malignant transformation, was evaluated. The resulting data showed that the LV used to manufacture CARVYKTI does not preferentially integrate at or near specific genomic sites of concern for oncogenic transformation. In addition, an (b) (4) assay evaluation of CARVYKTI generated from six patients with MM and three HDs showed no signs of uncontrolled cellular proliferation. These data support the conclusion that any insertional events resulting from LV transduction methods used to generate CARVYKTI have minimal risk for oncogenic transformation.

Animal reproductive and developmental toxicity (DART) studies were not conducted with CARVYKTI, which is acceptable based on the product characteristics and safety profile. In addition, (b) (4) was not detected in human female or male reproductive organs. However, Section 8.1 of the proposed prescribing information describes the potential risks of CARVYKTI to the developing embryo or fetus if the transduced cells cross the placenta following administration in women of childbearing potential.

5. Clinical Pharmacology

The clinical pharmacology section of this BLA is supported by one Phase 1b-2 clinical study that evaluated the safety, efficacy, and pharmacokinetic (PK)/pharmacodynamics of CARVYKTI in subjects with relapsed or refractory multiple myeloma (RRMM) and a population PK study. The proposed CARVYKTI target dose of CARVYKTI is 0.5 – 1.0 x 10^6 CAR-positive viable T cells per kg of body weight, with a maximum dose of 1 x 10^8 CAR-positive viable T cells per single-dose infusion. CARVYKTI is to be administered via intravenous (IV) infusion.

The clinical pharmacology assessments included cellular kinetic/pharmacokinetic (PK) assessment, pharmacodynamic (PD) assessment, immunogenicity assessment and replication-competent lentiviral (RCL) testing.

The pharmacokinetic (PK) samples were measured using both validated (b) (4) assay (transgene levels) and validated flow cytometry methods (CAR+ T cells levels). The PK findings for the CARTITUDE-1 study were primarily based on transgene level data.

The following summarize the important clinical pharmacology findings:

<u>General Cellular Kinetics/Pharmacokinetics</u>

- After a single infusion of CARVYKTI (median dose of 0.709 x 10^6 cells/kg (range: 0.51 x 10^6 to 0.95 x 10^6 cells/kg), CAR transgene levels were below quantification limit until Day 7 or Day 10 post-infusion. The median time to reach peak levels in peripheral blood was 12.7 days post-dose.
- As of the data cut-off date, CARVYKTI's CAR transgene levels were detected in blood up to 703 days post-dose. Levels of CAR transgene were below quantification limit in 65 subjects. Among these 65 subjects, the median time for CAR transgene levels in peripheral blood to return to the pre-dose baseline level (BLQ) was approximately 100 days (range: 28 to 365 days) post-infusion.
- CARVYKTI distributed from systemic circulation to bone marrow after infusion. The highest CARVYKTI CAR transgene levels were observed on Day 28 in bone marrow, and decreased to below limit of quantification by Day 184.
- Population PK analyses were conducted to evaluate potential impacting factors on CARVYKTI PK parameters, including baseline demographic factors, disease factors, baseline biomarkers, and product characteristics. None of the covariates had statistically significant effect.

<u>Drug-Drug Interactions</u>

- Tocilizumab, corticosteroids, and anakinra were used in the management of CRS after treatment with CARVYKTI. Subjects who received tocilizumab, corticosteroids, and/or anakinra for CRS management had higher exposure (Cmax and $AUC_{0\text{-}28d}$) of CARVYKTI, compared to subjects did not receive tocilizumab, corticosteroids, and/or anakinra for CRS management. The observations are in line with the fact that higher CARVYKTI expansion levels are associated with more severe adverse events that

require management with medications. Continued expansion of CARVYKTI was observed in subjects who received tocilizumab, corticosteroids, and/or anakinra.

Exposure-Response Relationship

- No apparent association was observed between the CARVYKTI dose and the incidence of cytokine release syndrome. However, higher CARVYKTI exposure was observed in subjects with Grade 2 or higher CRS. Subjects with Grade 2 or higher CRS (n=43) had 182% and 195% higher median Cmax and $AUC_{0\text{-}28d}$ of CARVYKTI, respectively, compared to subjects with Grade 1 or no CRS (n=54).
- No correlation was observed between the CARVYKTI dose and the incidence of neurotoxicities, although higher exposure of CARVYKTI was observed in subjects who experienced neurotoxicities. Subjects with any grade neurotoxicities (NTs) (n=24) had 175% and 214% higher median Cmax and $AUC_{0\text{-}28d}$ of CARVYKTI, respectively, compared to subjects without any grade NT (n=73). Subjects with severe NT (Grade 3 or higher) (n=10) had 173% and 292% higher median Cmax and $AUC_{0\text{-}28d}$ of CARVYKTI, respectively, compared to subjects who had Grade 2, Grade 1, or no NT (n=87).
- No evident correlations were observed between CARVYKTI dose/exposure and the incidence of prolonged neutropenia and thrombocytopenia.

Pharmacodynamics

- After a single infusion of CARVYKTI, serum soluble BCMA (sBCMA) levels decreased in all treated subjects. Mean serum sBCMA concentrations reached nadir levels around the lower limit of quantification (LLOQ) value (i.e., (b) (4) µg/L) at Day 78 in Phase 1b and Day 100 in Phase 2.
- A positive association was observed between median Cmax and $AUC_{0\text{-}56d}$ of IL-6, IL-10, IFN-γ, and IL-2RA with the incidence of CRS (any grade).
- A positive association was observed between median Cmax and $AUC_{0\text{-}56d}$ of IL-6, IFN-γ, and IL-2Ra with the incidence of immune effector cell-associated neurotoxicity syndrome (ICANS) (any grade). A trend for a positive association was observed between median Cmax and $AUC_{0\text{-}56d}$ of IL-6, IL-10, IFN-γ, and IL-2RA with the incidence of other CAR-T neurotoxicities.

Immunogenicity

- Among all treated subjects (n=97), 19 subjects (19.6%) were observed to be positive for treatment-emergent anti-CARVYKTI antibodies (ADA). Anti-CARVYKTI antibodies started to be detectable around the Day 100 post-infusion for the ADA-positive subjects. There is no clear evidence to draw a conclusion on the association between ADA and CARVYKTI persistence.

Replication-competent Lentivirus (RCL) Testing

- No RCL has been detected in the blood in any treated subjects.

6. Clinical/Statistical

The clinical review team recommends regular approval of CARVYKTI for the 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-CD 38 monoclonal antibody.

a. Clinical Program

CARTITUDE-1 was a single-arm, phase 1b-2 multicenter study of safety and efficacy of CARVYKTI in subjects with relapsed and refractory multiple myeloma who had received at least three prior lines of therapy, including a proteasome inhibitor, an immunomodulatory agent, and an anti-CD 38 monoclonal antibody. The primary endpoint was objective response rate (ORR) defined as rate of stringent complete response (sCR), complete response (CR), very good partial response (VGPR), and partial response (PR), as determined by an Independent Response Committee (IRC) applying the 2016 IMWG (International Myeloma Working Group) Response Criteria.

Complete response rate, defined as rate of sCR plus complete response (CR), was a key secondary endpoint. Other secondary endpoints included duration of response (DOR) and MRD (minimal residual disease) negativity in the bone marrow using ClonoSEQ NGS (next generation sequencing) assay.

For purposes of efficacy and safety assessment, cilta-cel refers to the product that met product specifications for the CARTITUDE-1 study. The product intended for marketing is based on product specifications that were determined during the BLA review on a post-hoc basis and is referred to as CARVYKTI.

Although 113 subjects were enrolled and underwent leukapheresis, 16 subjects did not receive cilta-cel due to death, withdrawal from the study, or disease progression. The product specifications for CARVYKTI were not confirmed for these 16 subjects. Of the 97 subjects who received cilta-cel, 17 subjects (18%) did not receive CARVYKTI either because the cilta-cel product did not meet specifications for CARVYKTI (the marketed product) or because product specifications for CARVYKTI could not be confirmed.

Efficacy Results:

The efficacy evaluable population includes subjects who received cilta-cel who met the protocol-specified criteria for eligibility for cilta-cel infusion and had baseline disease and were followed for at least nine months after their first objective disease response. Bridging therapy was allowed during product manufacturing.

The efficacy data for the efficacy evaluable population (n=97) is summarized below:

The ORR as assessed by the IRC was 97.9% (95% Confidence Interval [CI]: 92.7%, 99.7%) and complete response rate (comprised entirely of stringent CRs) was 78.4%, with a median DOR of 21.8 months (95% CI 21.8, NE).

Efficacy results in CARTITUDE-1 met the study objective that ORR was statistically significantly greater than the pre-specified null hypothesis threshold rate of 30%. Please see the Table below.

Table 4. Efficacy Analysis for CARTITUDE-1

	Ciltacabtagene Autoleucel Treated
Overall Response Rate (sCR[a] + VGPR + PR) n (%)	95 (97.9)
95% CI (%)	(92.7, 99.7)
Stringent complete response (sCR)[a] n (%)	76 (78.4)
Very good partial response (VGPR) n (%)	16 (16.5)
Partial response (PR) n (%)	3 (3.1)
Duration of Response (DOR)	
Number of responders DOR (Months): Median (95% CI)	95 21.8 (21.8, NE)
Number of responders with sCR[a] DOR if best response is sCR[a] (Months): Median (95% CI)	76 NE (21.8, NE)
Number of responders with VGPR or better DOR if best response is VGPR or better (Months): Median (95% CI)	92 21.8 (21.8, NE)

Abbreviations: NE = Not Estimable

MRD data are not included in the prescribing information, because missing data and a higher-than-expected assay failure rate at baseline made the MRD data unreliable.

In summary, CARTITUDE-1 represents an adequate and well-controlled trial that demonstrated high response rates and durability of CR rate. The FDA's conclusion of substantial evidence of effectiveness is based on the durable complete response rate in a disease setting where durable CR rates are dismal with standard-of-care therapies (See Table 1). Overall, the magnitude of benefit with an ORR of 97.9% and a sCR rate of 78.4% with durability of response in an adequate, multi-center trial translates to a meaningful clinical benefit in the 5th line setting for relapsed/refractory myeloma. Hence, the data from this adequate and well controlled single-arm trial in conjunction with supportive evidence from pharmacology/toxicology data support a regular approval for CARVYKTI.

Given that only 17% of the efficacy-evaluable population received only three prior lines of therapy and the majority of the efficacy-evaluable population in CARTITUDE-1 received four or more prior lines, the risk and benefit of this therapy has been established in this latter line population. Therefore, the indication statement in the prescribing information (PI) is restricted to the relapsed/refractory myeloma population that has received at least four prior lines of therapy.

b. Bioresearch Monitoring (BIMO) – Clinical/Statistical/Pharmacovigilance

Bioresearch Monitoring (BIMO) inspections were performed 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 BLA.

c. Pediatrics

This application was granted a full PREA waiver since BCMA is not considered a relevant target in tumors in pediatric subjects, and multiple myeloma is a rare disease in children.

d. Other Special Populations

CARVYKTI has not been studied in any special populations.

7. Safety and Pharmacovigilance

Safety

The primary safety population for the CARTITUDE-1 study is comprised of 97 subjects who were treated with cilta-cel, the product that met clinical study release specification criteria in the dose range of 0.5-1.0 x 10^6 viable CAR-T cells/kg. Treatment-emergent adverse events were defined as those that occurred within and including 100 days after cilta-cel infusion. Supportive safety data from subjects in other clinical trials of cilta-cel (CARTITUDE-2 and CARTITUDE-4) were reviewed for certain adverse events of interest: peripheral neuropathy, cranial nerve palsy, Guillain-Barré syndrome (GBS) and hemophagocytic lymphohistiocytosis (HLH). All 97 subjects had at least one Grade 3 or 4 treatment-emergent adverse event (TEAE) following cilta-cel infusion. Serious adverse events (SAEs) were observed in 53 (55%) subjects, with Grade 3 or higher events in 34 (35%) subjects. Key adverse events observed following administration of cilta-cel are outlined below in Table 6. CRS was graded and reported per the 2019 ASTCT (American Society for Transplantation and Cellular Therapy) consensus grading criteria. Immune effector cell-associated neurologic syndrome (ICANS) was graded by 2019 ASTCT consensus grading criteria but reported using CTCAE v. 5.0 (Common Terminology Criteria for Adverse events version 5) data in the prescribing information due to lack of data elements required for ASTCT consensus grading during the phase 1b portion of the study. All other adverse events including non-ICANS neurologic toxicity were graded using CTCAE v 5.0 criteria. Non-ICANS neurologic toxicity, including features of parkinsonism, peripheral neuropathy, and cranial nerve palsies, were seen in CARTITUDE-1 and other ongoing trials of cilta-cel. Additionally, Guillain-Barré syndrome has been reported in an ongoing trial of cilta-ceI. Recurrence of grade 3 or 4 cytopenias after recovery to ≤ Grade 2 from the initial episode of cytopenia was also reported, in addition to prolonged cytopenias.

Table 5. Key Adverse Events with Cilta-cel in N=97 subjects in CARTITUDE-1

Adverse Event	Any Grade N (%)	≥ Grade 3 N (%)
Cytokine Release Syndrome	92 (95)	5 (5)
Neurologic Toxicity[¶] (ICANS and non-ICANS)	25 (26)	11 (11)
ICANS	22 (23)	5 (5)
Parkinsonism	5 (5)	4 (4.1)
Cranial nerve palsy	3 (3)	1 (1)
Peripheral neuropathy	6 (2)	2 (2)
Prolonged Neutropenia[*]	-	29 (30)
Prolonged thrombocytopenia[*]	-	40 (41)
Recurrent cytopenia[ŧ]	-	84 (87)
Infections	57 (59)	22 (23)
Hypersensitivity reactions	5 (5)	0 (0)
Hemophagocytic lymphohistiocytosis (HLH)/Macrophage Activation Syndrome (MAS)	1 (1)	1 (1)
Hypogammaglobulinemia[**]	91 (94)	2 (2)

Source: FDA analysis of ADAE dataset

[¶]Neurologic toxicity includes all subjects with any type of neurologic toxicity; subtypes of neurologic toxicity-ICANS and non-ICANS described separately in table above

[*] Defined as Grade ≥ 3 cytopenias lasting beyond 30 days following CAR-T infusion; numbers based on Applicant data

[ŧ] Defined as occurrence of one or more episodes of grade 3 or 4 neutropenia, thrombocytopenia, lymphopenia or anemia after recovery to ≤ Grade 2 from one (first) episode of grade 3 or 4 of these cytopenias

[**] Hypogammaglobulinemia (all-grade only) includes incidence based on AE reporting and laboratory testing

Fourteen of 97 subjects treated with cilta-cel in CARTITUDE-1 study had died by the primary data cutoff of September 1, 2020. Five deaths were due to progressive disease; 9 deaths were related (adverse reactions) to cilta-cel and/or preceding lymphodepleting chemotherapy. All deaths occurred more than 30 days after cilta-cel administration. Causes of death from adverse reactions included CRS/HLH (n=1), neurologic toxicity [ICANS (n=2), neurologic toxicity with parkinsonian features (n=1)], infection [pneumonia (n=1), lung abscess (n=1), sepsis (n=2)], and acute myeloid leukemia (n=2). As of the 120-day safety update, an additional 7 subjects died: 5 of progressive disease and 2 of adverse events (n=1, refractory ascites; n=1, acute myeloid leukemia).

CRS: CRS occurred in 92/97 subjects (95%) and Grade ≥3 events occurred in 5/97 (5%). Median time to CRS onset was 7 days (range 1 to 12 days). CRS resolved in 91 of 92 (99%) subjects, with a median time to resolution of 4 days (range 1 to 40 days). One subject had fatal CRS/HLH. The most common manifestations of CRS included fever, hypotension, increased aspartate aminotransferase (AST), chills, increased alanine aminotransferase (ALT) and sinus tachycardia.

HLH/MAS: One of 97 (1%) subjects treated with cilta-cel developed HLH in the setting of worsening CRS and died of CRS/HLH 99 days following cilta-cel infusion. The manifestations of HLH/MAS included respiratory failure, acute kidney injury requiring

dialysis, disseminated intravascular coagulation with pulmonary hemorrhage, sepsis, multiple infections and prolonged grade 4 cytopenias.

Neurologic toxicity (NT): Neurologic toxicity [including immune effector cell-associated neurologic syndrome (ICANS)] and non-ICANS neurologic toxicity occurred in 25/97 (26%) subjects, with Grade ≥3 events reported in 11% (11/97) of the subjects. The median time to onset of all neurologic toxicity was 8 days (range 2 to 101 days). Neurologic toxicity resolved in 15 of 25 (60%) subjects with a median time to resolution of 8 days (range 2 to 208 days). Median duration of NT in all subjects, including those with fatal events and NT ongoing at death or last known alive date was 62 days (range 2 to 926 days). Subtypes of NT are described in the prescribing information and below.

ICANS occurred in 22/97 subjects (23%), with Grade ≥3 events reported in 5% (5/97) of subjects including death from ICANS in 2 subjects. Two patients (n=1, Grade 3; n=1, Grade 1) had ongoing ICANS at last known alive date, while 1 subject had ICANS ongoing at time of death from NT with parkinsonian features. The most common manifestations of ICANS were encephalopathy, aphasia and headache.

Five of 97 subjects (5%) developed NT with parkinsonism that consisted of parkinsonian and non-parkinsonian signs and symptoms, including tremor, micrographia, abnormal posture, bradykinesia, masked facies, depression, stereotypy, psychomotor retardation, and encephalopathy.

Six of 97 (6%) subjects developed peripheral neuropathy. These neuropathies presented as sensory, motor, or sensorimotor neuropathies. Three subjects (3.1%) experienced 7th cranial nerve palsy; one subject had 5th cranial nerve palsy as well. GBS has been included in the Boxed warning for CARVYKTI.

Prolonged and recurrent cytopenia: Thirty percent (29/97) of subjects experienced prolonged (cytopenia not resolved to ≤ Grade 2 by Day 30 following cilta-cel infusion) Grade 3 or 4 neutropenia, and 41% (40/97) of subjects experienced prolonged grade 3 or 4 thrombocytopenia. Eighty-seven percent (84/97) of subjects had one, two, or three or more recurrences of Grade 3 or 4 cytopenias after initial recovery of Grade 3 or 4 cytopenia to Grade 2 or less.

Infections: Iinfections occurred in 59% (57/97) of subjects, with Grade 3 or 4 infections reported in 23% (22/97) of subjects. Four subjects had Grade 5 infections: lung abscess (n=1), sepsis (n=2) and pneumonia (n=1). Grade 3 or 4 infections with an unspecified pathogen were reported in 17%, viral infections in 7%, bacterial infections in 1%, and fungal infections in 1% of subjects.

Hypogammaglobulinemia: Newly diagnosed hypogammaglobulinemia, based either on laboratory value defined as IgG < 500 mg/dL or an adverse event occurred in 94% (91/97) of subjects. Thirty-eight percent of subjects received intravenous immunoglobulin (IVIG) after CARVYKTI for either an adverse reaction or prophylaxis.

Hypersensitivity reactions: Hypersensitivity reactions occurred in 5% (5/97) of subjects, with all reactions reported as Grade 1 in severity. Symptoms included flushing, chest discomfort, tachycardia, wheezing, tremor, and burning sensation.

Secondary malignancies: Seven subjects had secondary malignancies at the time of the original data cut-off, with 3 additional subjects with secondary malignancies reported at the time of the 120-day safety update. Eight of 10 subjects had hematologic malignancy [n=3 acute myeloid leukemia (AML); n=5 with myelodysplastic syndrome (1 subject had MDS transform to AML)] while 3 subjects had solid tumor malignancies (basal and squamous cell skin cancer, prostate cancer). FDA assessed that these malignancies were unlikely to be related to cilta-cel. However, the risk of insertional mutagenesis and secondary malignancy remains a concern.

Laboratory abnormality: Grade 3 or 4 laboratory abnormalities with worsening from baseline occurring in ≥ 10% of subjects included lymphopenia (99%), neutropenia (98%), leukopenia (98%), anemia (72%), thrombocytopenia (63%), and aspartate aminotransferase increased (21%).

Cilta-cel was administered in the inpatient setting in all subjects with a mandatory post-infusion monitoring of 14 days for the 1st 6 subjects followed by a minimum 10-day monitoring period for the remainder of the 91 subjects. To facilitate early diagnosis and management of CRS and neurologic toxicity post-approval, the Risk Evaluation and Mitigation Strategy (REMS) program and labeling call for daily monitoring of patients for at least 10 days in the outpatient setting at a REMS-certified healthcare facility.

The safety database of 97 subjects is sufficient to assess the acute toxicities of cilta-cel, and severity of CRS and neurologic toxicity warrant marketing authorization under the REMS program. The long-term adverse reactions require post-marketing study to evaluate the risks of secondary malignancies, particularly those associated with insertional mutagenesis.

Key Changes made to the prescribing information in reference to safety are outlined below:

1. Boxed Warning was revised to delineate neurologic toxicity as ICANS, and include the risk of parkinsonism and GBS with their attendant life-threatening and/or fatal consequences as a separate entity. HLH/MAS, and prolonged and recurrent cytopenias with risk of infection, bleeding and requirement for hematopoietic stem cell transplantation were added as well.

2. Revision of management tables for CRS and ICANS in section 2.3.

3. Warning and Precaution section was revised extensively to include all the sub-types of neurologic toxicity, include information on recurrent cytopenia in addition to prolonged cytopenia, add a section on HLH/MAS, and revise section on hypersensitivity reactions.

4. Safety information from other studies of cilta-cel included in the PI are Guillain-Barré syndrome, parkinsonism, peripheral neuropathy, cranial nerve palsies and HLH/MAS.

The postmarketing safety monitoring for CARVYKTI includes adverse event reporting in accordance with 21 CFR 600.80; Risk Evaluation and Mitigation Strategy (REMS) program, and a long-term follow-up safety study as a postmarketing requirement (PMR).

Risk Evaluation and Mitigation Strategy (REMS)

FDA determined that a REMS is necessary to ensure that the benefits of CARVYKTI outweigh the serious risks of cytokine release syndrome (CRS) and neurological toxicities.

The goal of the REMS is to mitigate the risks of CRS and neurological toxicities by:

- Ensuring that hospitals and their associated clinics that dispense CARVYKTI are specially certified and have on-site, immediate access to tocilizumab.
- Ensuring that those who prescribe, dispense, or administer CARVYKTI are aware of how to manage the risks of CRS and neurological toxicities.

The REMS program includes the following elements to assure safe use (ETASU):

- Healthcare facilities that dispense CARVYKTI must be specially certified.
- CARVYKTI is dispensed to patients only in certain health care settings.
- The REMS requires that certified healthcare facilities that dispense CARVYKTI must have on-site, immediate access to tocilizumab. Facilities agree to ensure on-site, immediate access to at least two doses of tocilizumab for each patient, for administration within two hours after infusion for the treatment of CRS.
- The REMS materials will provide education on the serious risks for CRS and neurological toxicities, clinical manifestations, timing, monitoring, management of these events, and the need to counsel patients and caregivers about these risks and when to seek immediate medical attention.

Materials provided as part of the CARVYKTI REMS Program include:

- Hospital Enrollment Form
- Patient Wallet Card
- Training Program
- Adverse Reaction Management Guide
- Knowledge Assessment
- REMS Program Website

Post-marketing Requirement (PMR) study

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, a safety post-marketing requirement (PMR) study is warranted under Section 505(o) of the Federal Food, Drug, and Cosmetic Act (FDCA). The applicant is required to conduct a post-marketing, prospective, multi-center, observational study to assess the long-term safety of CARVYKTI and the risk of secondary malignancies occurring after treatment with CARVYKTI. The PMR study will include at least 1500 patients with multiple myeloma who have received at least four prior lines of therapies, including a proteasome inhibitor, an immunomodulatory agent and an anti-CD38 antibody. The primary endpoint will be evaluation for secondary malignancy, which will include the collection and analysis of blood and/or biopsy specimens of certain malignancies for evaluation of insertional mutagenesis. Other important endpoints include CRS, neurologic toxicity including movement and neurocognitive toxicity that clinically resembles Parkinson's Disease, and prolonged or recurrent cytopenia. Patients will be followed for 15 years after CARVYKTI infusion.

The PMR study milestones are as follows:

Final protocol submission: April 30, 2022

Study completion: June 30, 2041

Final report submission: June 30, 2042

8. Labeling

The proposed proprietary name, CARVYKTI, was reviewed by the Advertising and Promotional Labeling Branch (APLB) on May 10, 2021 and was found acceptable. CBER communicated the acceptability of the proprietary name to the applicant on May 25, 2021.

The Advertising and Promotional Labeling Branch (APLB) reviewed the proposed prescribing information, the proposed package and container labels, including the Information for Use and Medication Guide, on July 26, 2021, and found them acceptable from a promotional and comprehension perspective.

9. Advisory Committee Meeting

CARVYKTI is similar to other genetically modified autologous CAR T cell immunotherapies and did not raise new or unique scientific or regulatory issues; as a result, an advisory committee meeting was not deemed necessary.

10. Other Relevant Regulatory Issues

There were no other regulatory issues raised during the review of BLA 125746/0.

11. Recommendations and Benefit/Risk Assessment

a. Recommended Regulatory Action

The review team recommends regular approval of CARVYKTI for the 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.

The recommendation for approval is based on the determination that the applicant has met the statutory standards for substantial evidence of effectiveness and safety based on a single adequate and well-controlled trial and confirmatory evidence in the form of compelling mechanistic evidence from pharmacology/toxicology studies.

b. Benefit/Risk Assessment

CARVYKTI has demonstrated favorable ORR and CR rates and DOR in subjects with relapsed or refractory multiple myeloma after four or more prior lines of

therapy. The safety results demonstrate an acceptable safety profile when implemented with Risk Evaluation and Mitigation Strategies (REMS) with Elements to Assure Safe Use (ETASU) for the management of CRS and neurological toxicities, which represent life-threatening adverse reactions. However, given the life-threatening nature of the disease in the indicated population, these adverse reactions, if managed appropriately, represent toxicities that are acceptable from a benefit-risk perspective. Thus, the overall benefit-risk profile favors regular approval of CARVYKTI in patients with relapsed or refractory multiple myeloma after four or more prior lines of therapy.

c. Recommendation for Postmarketing Activities

Registry study: Marketing approval should include a safety PMR under Section 505(o) of the FDCA that the applicant conduct a multi-center, prospective, observational study to assess the long-term safety of CARVYKTI and the risk of secondary malignancies. The study will use a registry design and will include 1500 adult patients with multiple myeloma who have received at least four prior lines of therapies, including a proteasome inhibitor, an immunomodulatory agent, and an anti-CD38 monoclonal antibody. Patients will be followed for 15 years after their CARVYKTI infusion. This study is observational and focuses on short-term toxicity, documents certain adverse events, and long-term follow-up for evaluation of secondary malignancies, which will include blood and/or tissue work-up for these events. The primary endpoint is long-term safety and risk of secondary malignancies. Other important endpoints include CRS, neurologic toxicity including movement and neurocognitive toxicity that clinically resembles Parkinson’s Disease, and prolonged or recurrent cytopenia.

The PMR study milestones are as follows:

Final protocol submission: April 30, 2022

Study completion: June 30, 2041

Final report submission: June 30, 2042