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| Application Type | Efficacy supplement |
| STN | 125746.74 |
| CBER Received Date | June 06, 2023 |
| PDUFA Goal Date | April 05, 2024 |
| Division / Office | DCEH/OTP |
| Committee Chair | Helkha Peredo-Pinto |
| Clinical Reviewer(s) | Helkha Peredo-Pinto |
| Project Manager | Rachel Blasdell |
| Priority Review | No |
| Reviewer Name(s) | Cong Wang |
| Review Completion Date / Stamped Date | |
| Supervisory Concurrence | Zhenzhen Xu, PhD<br>Team Leader, FDA/CBER/OBPV/DB/TEB1 |
| | Boguang Zhen, PhD<br>Branch Chief, FDA/CBER/OBPV/DB/TEB1 |
| | John Scott, PhD<br>Division Director, FDA/CBER/OBPV/DB |
| Applicant | Janssen Biotech, Inc. |
| Established Name | ciltacabtagene autoleucel (cilta-cel) |
| (Proposed) Trade Name | CARVYKTI |
| Pharmacologic Class | A genetically modified autologous T-cell immunotherapy that binds to B-cell maturation antigen |
| Formulation(s), including Adjuvants, etc | Cell suspension for infusion |
| Dosage Form(s) and Route(s) of Administration | Intravenous infusion |
| Dosing Regimen | Dose range is $0.5\text{-}1.0\times10^{6}$ CAR-positive viable T cells per kg of body weight, with a maximum dose of $1\times10^{8}$ CAR-positive viable T cells per single-dose infusion |
| Indication(s) and Intended Population(s) | For the treatment of adult patients with relapsed or refractory multiple myeloma who have received at least 1 prior line of therapy, including a proteasome inhibitor and an immunomodulatory agent, and are refractory to lenalidomide |

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## GLOSSARY

| Abbreviation | Definition |
|---|---|
| AE | Adverse event |
| AESI | Adverse event of Special Interest |
| BCMA | B-cell maturation antigen |
| BLA | Biologics Licensure Application |
| BOR | Best overall response |
| CAR | Chimeric antigen receptor |
| CAR-T | Chimeric antigen receptor T (cells) |
| CI | Confidence interval |
| Cilta-cel | Ciltacabtagene autoleucel |
| CMH | Cochran-Mantel-Haenszel |
| CR | Complete Response |
| CRS | Cytokine release syndrome |
| CSR | Clinical study report |
| DOR | Duration of response |
| DPd | Daratumumab, pomalidomide, and dexamethasone |
| ECOG | Eastern Cooperative Oncology Group |
| FDA | Food and Drug Administration |
| HR | Hazard ratio |
| ICH | International Conference for Harmonisation |
| IMiD | Immunomodulatory drug |
| IMWG | International Myeloma Working Group |
| IRC | Independent Review Committee |
| ISS | International Staging System |
| ITT | Intent-to-treat |
| KM | Kaplan-Meier |
| MRD | Minimal residual disease |
| NE | Not evaluable |
| NHL | Non-Hodgkin lymphoma |
| NR | Not reached |
| ORR | Overall response rate |
| OS | Overall survival |
| PFS | Progression-free survival |
| PI | Proteasome inhibitor |
| PR | Partial response |
| PVd | Pomalidomide, bortezomib, and dexamethasone |
| R/R | Relapsed or refractory |
| SAE | Serious adverse event |
| SAP | Statistical analysis plan |
| sBLA | Supplemental BLA |
| sCR | Stringent complete response |
| STD | Standard deviation |
| TEAE | Treatment-emergent adverse event |
| US | United States |
| USPI | United States Prescribing Application |
| VGPR | Very good partial response |

# 1. EXECUTIVE SUMMARY

CARVYKTI is a B-cell maturation antigen (BCMA)-directed chimeric antigen receptor T (CAR-T) cell therapy composed of human autologous T cells that are genetically modified by a lentiviral vector to express a BCMA-targeting chimeric antigen receptor (CAR). It was originally approved by the United States (US) Food and Drug Administration (FDA) on February 28, 2022, for the treatment of adult patients with relapsed refractory multiple myeloma after four or more lines of systemic therapy. In this efficacy supplement, the applicant seeks to extend the indication to adult patients with relapsed or refractory multiple myeloma who have received at least 1 prior line of therapy, including a proteasome inhibitor (PI) and an immunomodulatory agent (IMiD), and are refractory to lenalidomide.

The primary source of evidence to support the efficacy and safety of the proposed product comes from Study CARTITUDE-4. CARTITUDE-4 is a Phase 3, randomized, open-label, multicenter study that compared cilta-cel with standard therapy in adults with relapsed and lenalidomide-refractory multiple myeloma after 1 to 3 prior lines of therapy including PI and IMiD. CARTITUDE-4 enrolled 419 patients who were randomized (1:1) to receive cilta-cel or standard-of-care regimens, either pomalidomide, bortezomib, and dexamethasone (PVd) or daratumumab, pomalidomide, and dexamethasone (DPd). The primary endpoint was progression-free survival (PFS) as determined by a blinded independent review committee (IRC) using the International Myeloma Working (IMWG) 2016 criteria. Secondary endpoints included completed response (CR)/stringent complete response (sCR) rate, overall response rate (ORR), minimal residual disease (MRD) negativity rate per blinded central assessment and overall survival (OS).

The median PFS was not reached in the cilta-cel arm (95% confidence interval [CI]: 22.8, not evaluable [NE]), and was 12 months (95% CI: 9.8, 14) in the standard therapy arm. Based on a stratified log-rank test, the stratified hazard ratio for PFS was 0.41 (95% CI: 0.30, 0.56); one-sided p-value < 0.0001. The IRC-assessed CR/sCR rate was statistically significantly higher at 74% (95% CI: 68%, 80%) in the cilta-cel arm compared to 22% (95% CI: 17%, 28%) in the standard therapy arm. Similarly, the ORR was higher at 85% (95% CI: 79%, 89%) in the cilta-cel arm compared to 68% (95% CI: 61%, 74%) in the standard therapy arm, based on the stratified Cochran-Mantel-Haenszel (CMH) test; one-sided p-value < 0.0001. At the time of the efficacy supplement submission with data cut-off date of November 1, 2022, the applicant provided the results of an interim analysis of OS with 34% information fraction. At this interim OS analysis, the OS Kaplan-Meier curves crossed at approximately 10 months, with inferior OS in the cilta-cel arm compared to the standard of care arm prior to 10 months post randomization. The median OS in the cilta-cel arm was not reached and was 26.7 months (95% CI: 22.5, NE) for standard therapy arm.

In conclusion, the CARTITUDE-4 study met its primary endpoint, demonstrating a statistically significant improvement in PFS in patients randomized to the cilta-cel arm compared to patients randomized to the standard therapy arm. Statistically significant improvements were also observed in favor of cilta-cel for key secondary endpoints, ORR

and CR/sCR rate. Although there was observed early OS detriment, this concern appears mitigated by the subsequent long-term benefits. Given the collective statistical evidence, including clinically meaningful improvements in PFS, CRR and ORR in a difficult-to-treat patient population and life-threatening nature of the disease, I recommend approval for cilta-cel of applicant's proposed indication in this BLA efficacy supplement. However, caution is warranted regarding the OS results, and longer follow-up is necessary to further confirm the long-term OS benefit.

# 2. CLINICAL AND REGULATORY BACKGROUND

## 2.1 Disease or Health-Related Condition(s) Studied

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).

The incidence of multiple myeloma is approximately 1.5-fold higher in men than in women (Padala 2021; Turesson 2010). Multiple myeloma incidence and mortality appears highest in Western Europe, the US, Canada, and Australia, with age-standardized incidence rates in these regions ranging from 4.6 to 5.8 per 100,000 persons in 2016 (Cowan 2018). Worldwide, there are an estimated 80,000 deaths annually due to multiple myeloma and approximately 24,300 and 12,800 patients with this disease die annually in Europe and the US, respectively (Ferlay 2013; Cancer.net 2020). The estimated 5-year survival rate for patients with multiple myeloma is approximately 54% (Cancer.net 2020).

## 2.2 Currently Available, Pharmacologically Unrelated Treatment(s)/Intervention(s) for the Proposed Indication(s)

There are several approved triplet regimens for patients with multiple myeloma that has relapsed after 1 to 3 prior lines of therapy; however, these regimens have largely been tested in lenalidomide-naïve or lenalidomide-sensitive patients. More recently, a number of studies evaluated combinations of a monoclonal antibody, with a PI or with pomalidomide. These studies included substantial proportions of lenalidomide-refractory patients: 93% in ICARIA (isatuximab, pomalidomide, dexamethasone; Bringhen 2021), 80% in APOLLO (DPd; Dimopoulos 2021), 70% in OPTIMISMM (PVd; Richardson 2019), 33% in CANDOR (carfilzomib, dexamethasone, and daratumumab; Usmani 2022), and 33% in IKEMA (isatuximab, carfilzomib, and dexamethasone; Moreau 2021).

CAR-T cell-based therapies offer potential advantages over other T-cell redirection therapeutic strategies. The anti-BCMA CAR-T therapy, ide-cel, is indicated for the treatment of adult patients with relapsed or refractory multiple myeloma after 4 or more

prior lines of therapy, including an IMiD, a PI, and an anti-CD38 monoclonal antibody, with a reported ORR of 72% and a median duration of response (DOR) of 11.0 months (ABECMA [idecabtagene vicleucel] USPI 2021). Cilta-cel is a genetically modified autologous T-cell immunotherapy that binds to BCMA. Cilta-cel received FDA approval for the treatment of adult patients with relapsed or refractory multiple myeloma after 4 or more prior lines of therapy, including an IMiD, a PI, and an anti-CD38 monoclonal antibody, with an ORR of 97.9% (CARVYKTI USPI 2023). Refer to clinical review memo for details.

### 2.5 Summary of Pre- and Post-submission Regulatory Activity Related to the Submission

Table 1 summarizes the major pre- and post-submission regulatory activities associated with this supplemental BLA (sBLA).

**Table 1. Summary of major pre- and post-submission regulatory activities**

| Date | Purpose and/or Key FDA Comments |
|---|---|
| Sep 11, 2019 | Type B EOP2 meeting to obtain the FDA's agreement on the Phase 3 registration study (CARTITUDE-4). |
| June 24, 2022 | Type B Meeting to Discuss the Proposed Format and Content for the Planned Ciltacabtagene Autoleucel Supplemental Biologic License Application. |
| Mar 28, 2023 | Type B pre-sBLA meeting to obtain the Agency's review of the topline results from Study CARTITUDE-4 and guidance on sBLA submission plans.<br>FDA reiterated that computerized algorithm remains unvalidated from regulatory perspective and, given the open-label nature of the study, IRC assessment of the primary and secondary endpoints should be conducted and submitted for the initial BLA submission.<br>The efficacy analysis for PFS using the standard, "unweighted," stratified log-rank test will be considered as the primary efficacy analysis for regulatory purposes. |
| Jun 6, 2023 | The Sponsor submitted efficacy supplement based on PFS results from the second interim analysis of CARTITUDE-4, with a cutoff date of November 1, 2022. |
| Aug 5, 2023 | A filing notification was sent to the Applicant of a standard review. The filing letter identified the early potential OS detriment observed in the cilta-cel arm compared to the standard therapy arm in the CARTITUDE-4 as a potential review issue |
| Oct 3, 2023 | The Applicant submitted a 120-day Safety Updated, with a clinical cutoff of April 17, 2023 |
| Dec 8, 2023 | T-con in which FDA communicated its decision to convene an oncology drug advisory committee to obtain committee's input regarding the benefit-risk of ide-cel for the indicated population given the observed early OS detriment with the cilta-cel |
| Jan 7, 2024 | Applicant submitted an exploratory analysis conducted looking the early mortality with cilta-cel |

(Source: Modified from Applicant clinical study report page 32)

## 3. SUBMISSION QUALITY AND GOOD CLINICAL PRACTICES

### 3.1 Submission Quality and Completeness

The submission was adequately organized for conducting an in-depth and complete statistical review without unreasonable difficulty.

# 5. SOURCES OF CLINICAL DATA AND OTHER INFORMATION CONSIDERED IN THE REVIEW

## 5.1 Review Strategy

The primary source of evidence to support the efficacy and the safety of the proposed product comes from Study CARTITUDE-4. This study is the focus of this review memo.

## 5.2 BLA/IND Documents That Serve as the Basis for the Statistical Review

The basis of this statistical memo includes the review of clinical study reports and data sets submitted in modules 2 and 5 of sBLA 125746/74.0

## 5.3 Table of Studies/Clinical Trials

Table 2 summarizes 2 studies relevant to this sBLA submission. Results from Study MMY3002 (CARTITUDE-4) formed the primary evidence of safety and efficacy of cilta-cel for the indicated population. Supportive safety data are provided from Cohorts A and B from Study MMY2003 (CARTITUDE-2).

**Table 2. Studies relevant to this sBLA application**

| Study code | Study population | Study design | # Subjects treated | Data cutoff date |
|---|---|---|---|---|
| CARTITUDE-4 (pivotal) | Adult with relapsed and lenalidomide-refractory multiple myeloma with documented diagnosis according to IMWG diagnostic criteria who have received 1 to 3 prior lines of therapy. | Phase 3 randomized, open-label, multicenter study to compare the efficacy of cilta-cel with standard therapy, investigator's choice of PVd or DPd. | Arm A (standard therapy): 211 randomized, 208 treated; Arm B (cilta-cel): 208 randomized, 188 received conforming product. | November 1, 2022 |
| Cohorts A and B from CARTITUDE-2 | Adult with documented multiple myeloma according to IMWG diagnostic criteria. Participants were not permitted to have received prior therapies targeted to BCMA.<br>Cohort A: 1 to 3 prior lines of therapy including a PI and an IMiD; refractory to lenalidomide;<br>Cohort B: 1 prior line of therapy including a PI and an IMiD and early disease relapse. | Phase 2 multicohort, open-label, multicenter study to evaluate the overall MRD negative rate of participants who receive cilta-cel. | Cohort A: 26 enrolled, 20 received cilta-cel; Cohort B: 21 enrolled, 19 received cilta-cel. | October 08, 2021 (Cohort A); June 01, 2022 (Cohort B) |

(Source: FDA clinical review memo)

## 5.4 Consultations

### 5.4.1 Advisory Committee Meeting

An advisory committee (AC) meeting was held on March 15, 2024. The following voting question was posed to the committee:

Is the risk-benefit assessment for ciltacabtagene-autoleucel (cilta-cel) for the proposed indication, favorable?

All 11 committee members voted "Yes" and 0 members voted "No".

Reviewer Comment #1:

- The AC members unanimously concluded that the risk-benefit assessment for cilta-cel for the proposed indication is favorable. Their justifications included statistically significant improvements in the primary endpoint PFS and key secondary endpoints like CR/sCR rate and ORR. Additionally, observed OS improvement in the long-term follow-up, along with the life-threatening nature of the disease, were factored into the committee's decision.
- Several AC members acknowledged FDA's major concern regarding the observed early OS detriment for ~10 months. They agreed that the OS results should be interpreted with caution and longer follow-up data for OS is warranted to evaluate the long-term OS clinical benefit. However, they considered the benefit of cilta-cel exceeded the risk and therefore voted "Yes".

# 6. Discussion of Individual Studies/Clinical Trials

## 6.1 Study CARTITUDE-4

### 6.1.1 Objectives

Primary:
To compare the efficacy in subjects treated with cilta-cel versus standard therapy defined as PFS.

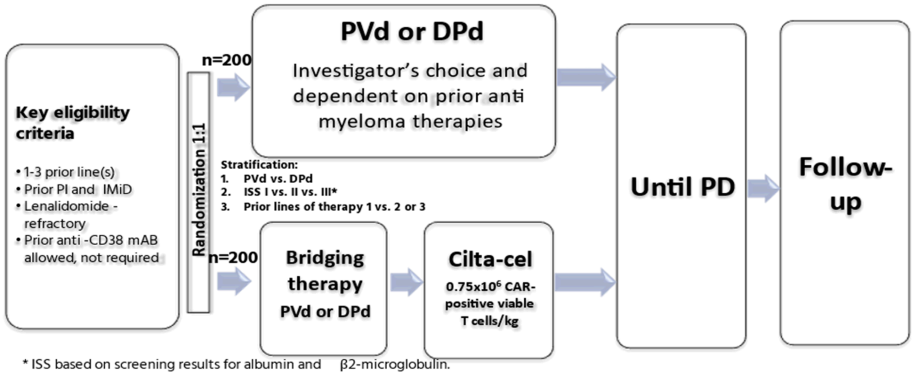
Key secondary:
To compare the efficacy in subjects treated with cilta-cel versus standard therapy defined as ORR, CR/sCR rate, MRD-negativity rate and OS.

### 6.1.2 Design Overview

CARTITUDE-4 study is a randomized (1:1), open-label, multicenter trial comparing cilta-cel with standard therapy in adults with relapsed and lenalidomide-refractory multiple myeloma following treatment with 1 to 3 prior lines of standard therapy including a PI and an IMiD; patients were not required to have previously received an anti-CD38 monoclonal antibody. Patients were randomized to receive a single infusion of

cilta-cel or investigator choice of 2 standard therapies: PVd or DPd. Bridging therapy with PVd or DPd could be administered to patients in the cilta-cel arm at the investigator's discretion during the interval between leukapheresis and lymphodepleting chemotherapy. Study treatment continued until there was documented disease progression, unacceptable toxicity, or the patient or treating physician determined it was not in the patient's best interest to continue. Randomization was stratified by investigator's choice of PVd or DPd for the control arm, International Staging System (ISS) staging (I versus II versus III), and number of prior lines of therapy (1 versus 2 or 3). Cross-over was not allowed in this study when the subjects progressed in the standard therapy arm.

**Figure 1. Study CARTITUDE-4 design schematic**




(Source: Study CARTITUDE-4 CSR Figure 1 - Schematic Overview of the Study)

### 6.1.3 Population

Key elements of eligibility criteria for Study CARTITUDE-4 are listed below.

- had a prior diagnosis of multiple myeloma with documented disease progression by IMWG criteria within 6 months of their last regimen
- required further treatment at time of screening
- had an Eastern Cooperative Oncology Group (ECOG) Performance Status score of 0 or 1
- received 1 to 3 prior lines of therapy, including lenalidomide and a PI and IMiD, and be refractory to both the last line of therapy and to lenalidomide per IMWG consensus guidelines (Rajkumar et al. 2011). Subjects were defined as refractory to lenalidomide by virtue of failure to achieve a PR or better to lenalidomide-containing therapy or progression within 60 days of the last dose of lenalidomide.
- had measurable disease defined as any one of the following: 1) Serum M protein >0.5 g/dL; 2) Urine M-protein level ≥200 mg/24-hour; and 3) serum free light chain >10 mg/dL and abnormal serum kappa to lambda free light chain ratio without measurable disease in the serum or the urine.

### 6.1.4 Study Treatments or Agents Mandated by the Protocol

Subjects randomized to cilta-cel arm underwent leukapheresis. Following apheresis, participants received bridging therapy while product was manufactured. After cilta-cel production and product release, subjects received a lymphodepletion chemotherapy

regimen of fludarabine (30mg/$m^2$) and cyclophosphamide (300mg/$m^2$) intravenously for three consecutive days. A single infusion of cilta-cel was administered 5 to 7 days after the start of the lymphodepletion at a median dose of $0.7\times10^6$ cells/kg.

6.1.6 Sites and Centers

The study was conducted at 81 sites across 16 countries in Europe (61.3% of participants), US (15.3%), and other regions (Australia, Israel, Japan, and Republic of Korea; 23.4%).

6.1.7 Surveillance/Monitoring

An Independent Data Monitoring Committee, consisting of 2 clinicians and 1 statistician, was established to review safety data periodically (approximately every 6 months), and review efficacy and safety results at the planned interim analysis for the primary efficacy endpoint.

6.1.8 Endpoints and Criteria for Study Success

Primary efficacy endpoint: PFS as determined by a blinded IRC according to IMWG 2016 criteria.

Key secondary endpoints:

- ORR based on independent review, defined as best response of sCR, CR, very good partial response (VGPR), and partial response (PR)
- CR/sCR rate
- MRD-negativity rate
- OS

If the null hypothesis was rejected for the primary endpoint PFS, hypothesis testing on ORR (and subsequently on CR/sCR rate, MDR-negativity rate and OS) was to be performed hierarchically. The overall type I error rate was controlled at two-sided 0.05.

6.1.9 Statistical Considerations & Statistical Analysis Plan

Statistical considerations proposed in the study protocol are described in the following:

<u>Statistical hypothesis:</u>
The analysis of the primary efficacy endpoint was performed by testing
$H_0$: HR $\geq$ 1 versus $H_a$: HR < 1, where HR is the PFS hazard ratio of cilta-cel arm versus standard therapy.

<u>Analysis populations:</u>

- *Intention-to-Treat (ITT) Analysis Set* included all subjects randomized to a treatment arm.
- *Safety Analysis Set* included all subjects who received conforming cilta-cel in the investigational arm and subjects who received the study treatment in the standard therapy arm.

Statistical methods:
Efficacy analyses were conducted on the ITT analysis set.

**Primary endpoint**
The primary efficacy endpoint, PFS, was analyzed with a stratified (by randomization stratification factors) log-rank test. In addition, Kaplan-Meier (KM) curves were presented, and KM estimates and 2-sided 95% confidence intervals were calculated.

**Key secondary endpoints**
- ORR, CR/sCR rate and MRD-negativity rate: An exact binomial 2-sided 95% confidence interval was generated for the estimated response rates for each treatment arm. Conditional on demonstrating a statistically significant improvement in PFS, testing the significance of ORR and then CR/sCR rate and MRD-negativity rate was performed with a CMH test stratified by randomization stratification factors for the common odds ratio of response.
- OS: The same analysis methods applied to PFS.

Reviewer Comment #2:
Per the applicant's final statistical analysis plan (SAP), the primary analysis method for PFS is weighted log-rank test where weight 0 was assigned to the events that occurred during the initial 8 weeks post randomization. However, the method used in the sample size and power calculation was a regular, unweighted log-rank test. During the pre-BLA meeting, FDA clearly stated that according to ICH-E9 Guidance, the two analysis methods should be consistent, thus recommend the use of regular log-rank test for the primary analysis of PFS. The FDA statistical review for PFS in this memo was based on the regular log-rank test with stratification.

Censoring rules:
Major censoring rules for PFS are listed below:
- Subjects who have not progressed and are alive by data cutoff date were censored at the last disease assessment.
- Subjects without any post-baseline disease assessment were censored at the date of randomization.
- Subjects who started subsequent anti-myeloma therapies for multiple myeloma without disease progression were censored at the last disease assessment before the start of subsequent therapies.
- Subject who missed two or more consecutive disease evaluations were censored at the date of last disease evaluation prior to the missing assessments.
- Subjects who missed one disease assessment were considered as PFS events with event date at the last disease assessment prior to the missing assessment if progression or death was observed in the next assessment.

Interim analyses:
One interim analysis and one final analysis were planned for PFS. The interim analysis for both futility and efficacy purposes was to be performed when 187 PFS events (~75% information fraction) was observed. The study design employed the Lan-DeMets

spending function with an O'Brien-Fleming-like boundary as the alpha spending function. Three interim analyses and one final analysis were planned for OS. The first interim analysis of OS was to be performed at the time of the planned interim analysis of PFS, and the second interim analysis for OS was to be performed at the time of the final PFS analysis when all 250 PFS events have been observed. The third interim analysis for OS was to be performed when approximately 200 OS events have occurred. The final analysis for OS was to be perform when approximately 250 OS events have been observed.

Sample size and power calculation:
The following assumptions were used to determine the sample size for this study:

- a median PFS of 13 months and 20 months for standard therapy arm and cilta-cel arm, respectively (HR=0.65)
- log-rank test was used
- one-sided alpha level of 0.025
- target power of 90%
- 20-month accrual period and an additional 16-month follow-up
- An annual dropout rate of 5%

Given the assumptions above, 250 PFS events were required. A sample size of 400 subjects was needed to be randomized. Long-term survival follow-up will continue until ~250 deaths have been observed. This study was planned to achieve ~80% power to detect an OS HR=0.7 with a log-rank test (2-sided alpha of 0.05, median OS of 31 months for the standard therapy arm).

Subgroup analyses:
In the ITT analysis set, subgroup analyses were performed based on age, sex, race and a variety of other baseline clinical characteristics.

### 6.1.10 Study Population and Disposition

#### 6.1.10.1 Populations Enrolled/Analyzed

Table 3 summarizes the analysis sets in Study CARTITUE-4. A total of 419 subjects were randomized with allocation ratio of 1:1 to cilta-cel arm and standard therapy arm that constituted the ITT analysis set, and 396 (94.5%) subjects received conforming cilta-cel in the investigational arm or received any study treatment in the standard therapy arm that constituted the safety analysis set.

**Table 3. Analysis sets in Study CARTITUDE-4**

| Analysis set | N |
|---|---|
| ITT (Randomized) | 419 (cilta-cel: 208; standard therapy: 211) |
| Safety | 396 (cilta-cel: 188; standard therapy: 208) |

Note: The data cut-off date is November 1, 2022, when 187 PFS events (i.e., 75% information fraction) were identified
(Source: FDA statistical reviewer's summary)

6.1.10.1.1 Demographics

Table 4 shows the demographic information for subjects in the ITT analysis set. The demographic information was generally balanced between the cilta-cel arm and standard therapy arm.

**Table 4. Subject demographics (ITT analysis set) in Study CARTITUDE-4**

| Characteristic | Cilta-cel N=208 n (%) | Standard Therapy N=211 n (%) | Total N=419 n (%) |
|---|---|---|---|
| Age (years) | - | - | - |
| Median (range) | 61.5 (27-78) | 61(35-80) | 61 (27-80) |
| <65 | 126 (61) | 131 (62) | 257 (61) |
| 65-75 | 78 (37.5) | 76 (36) | 154 (37) |
| >75 | 4 (1.9) | 4 (1.9) | 8 (1.9) |
| Sex | - | - | - |
| Male | 116 (56) | 124 (59) | 240 (57) |
| Female | 92 (44) | 87 (41) | 179 (43) |
| Race | - | - | - |
| Asian | 16 (8) | 20 (10) | 36 (8.6) |
| Black | 6 (3) | 7 (3) | 13 (3) |
| White | 157 (76) | 157 (74) | 314 (75) |
| Other | 1 (0.5) | 1 (0.5) | 2 (0.50) |
| Not reported | 28 (14) | 26 (12) | 54 (13) |
| Hispanic or Latino ethnic group | - | - | - |
| Yes | 18 (9) | 10 (5) | 28 (7) |
| No | 152 (73) | 165 (78) | 317(76) |
| Not reported | 38 (18) | 36 (17) | 80(19) |
| Geographic region | - | - | - |
| Europe | 128 (61.5) | 129 (61) | 257(61) |
| United States | 32 (15.4) | 32 (15) | 64(15) |
| Asia | 27 (13) | 25 (12) | 529(12) |
| Australia | 21 (10) | 25 (12) | 46(11) |

(Source: FDA analysis)

6.1.10.1.2 Medical/Behavioral Characterization of the Enrolled Population

Baseline disease characteristics of subjects enrolled in CARTITUDE-4 study are summarized in Table 5. Overall, these key baseline characteristics were generally balanced between the cilta-cel arm and standard therapy arm.

**Table 5. Baseline characteristics (ITT analysis set) in Study CARTITUDE-4**

| Characteristics | Cilta-cel N=208 | Standard Therapy N=211 | All N=419 |
|---|---|---|---|
| ECOG performance status score % | - | - | - |
| 0/1/2 | 55/44/1 | 57/42/1 | 56/43/1 |
| International Staging System stage % | - | - | - |
| I/II/III | 65/30/6 | 63/30/7 | 64/30/6 |
| Time since diagnosis (years) | - | - | - |
| Median (range) | 3.0 (0.3-18) | 3.4 (0.4-22) | 3.2 (0.3-22) |
| Extramedullary disease n (%) | - | - | - |
| Yes | 44 (21) | 35 (17) | 79 (19) |
| No | 164 (79) | 176 (83) | 340 (81) |

| Characteristics | Cilta-cel N=208 | Standard Therapy N=211 | All N=419 |
|---|---|---|---|
| Bone marrow plasma cells n (%) | - | - | - |
| N | 206 | 208 | 414 |
| ≤30 | 133(65) | 121 (58) | 254 (61) |
| >30-<60 | 31(15) | 44 (21) | 75 (18) |
| ≥60% | 42(20) | 43/208 (21) | 85 (20) |
| Cytogenetic risk n (%) | - | - | - |
| N | 207 | 210 | 417 |
| Standard | 111 (54) | 122 (58) | 233 (55.8) |
| High | 82 (39) | 80 (38) | 162 (39) |
| del(17p) | 49 (24) | 43 (21) | 92 (22) |
| t(4;14) | 30 (15) | 30 (14) | 60 (14) |
| t(14;16) | 3 (2) | 7 (3) | 10 (2) |
| Missing data | 15/207 (7) | 8/210 (4) | 23 (5) |

Abbreviations: ECOG, Eastern Cooperative Oncology Group
(Source: FDA analysis)

6.1.10.1.3 Subject Disposition

At the cutoff date of November 1, 2022, a total of 419 subjects were randomized, 208 in the cilta-cel arm and 211 in the standard therapy arm**.** Thirty-two subjects randomized to the cilta-cel arm (15% of the total number randomized to cilta-cel) had discontinued the study and 51 subjects randomized to the standard therapy arm (24% of the subjects randomized to standard therapy arm) had discontinued in the arm. There were 39 (19%) deaths in the cilta-cel arm and 47 (22%) deaths in the standard therapy arm. Three subjects, all of whom had been randomized to the standard therapy arm, were not treated (0.7% of all subjects randomized to both arms combined). Table 6 below shows reasons for treatment and study discontinuation in the ITT population.

**Table 6. Reasons for Treatment and Study Discontinuation, ITT Population**

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

* Twenty subjects received cilta-cel after disease progression as subsequent therapy and 12 subjects did not receive cilta-cel.
(Source: FDA analysis, data cutoff date November 1, 2022)

6.1.11 Efficacy Analyses

By the data cut-off date on November 1, 2022, 187 PFS events were identified (i.e., 75% information fraction). Therefore, in the efficacy analyses below for Study CARTITUDE-4, the null hypothesis was to be rejected if the one-sided p-value associated with the test was ≤ 0.01 calculated from the O'Brien-Fleming method.

6.1.11.1 Analyses of Primary Endpoint

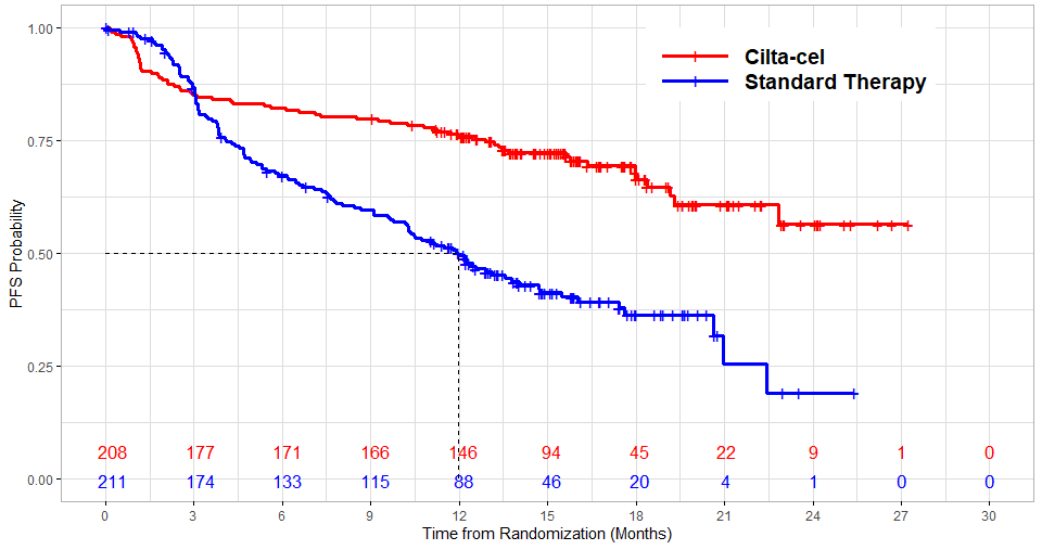
Treatment with cilta-cel in CARTITUDE-4 demonstrated a statistically significant improvement in PFS as assessed by IRC according to IMWG 2016 criteria, compared to the standard therapy: HR 0.41 (95% CI: 0.30, 0.56; p-value <0.0001) based on the stratified log-rank test. Median PFS was not reached for the cilta-cel arm compared to 12 months for the standard therapy arm. Table 7 and Figure 2 below summarize the analysis of PFS.

**Table 7. Progression-Free Survival Per IRC, ITT Population**

| | **Cilta-cel (N=208)** | **Standard Therapy (N=211)** |
|---|---|---|
| Progression-free survival | - | - |
| Number of events, n (%) | 65 (31) | 119 (56.4) |
| Progression, n (%) | 48 (23) | 116 (55) |
| Death, n (%) | 17 (8) | 3 (1.4) |
| Number of censored, n (%) | 143 (69) | 92 (43.6) |
| KM estimate: median, months (95% CI) | NE (22.8, NE) | 12 (9.8, 14) |
| Hazard ratio (95% CI) | 0.41 (0.30, 0.56) | - |
| p-value[1] | <0.0001 | - |

1. One-sided stratified log-rank test.
Median follow-up for PFS is 15.8 (95% CI: 15.4, 16.1) months for the cilta-cel arm and 15.3 (95% CI: 14.3, 16.8) months for the standard therapy arm.
Abbreviations: CI, confidence interval; IA, interim analysis; IRC, Independent Review Committee; KM, Kaplan-Meier
(Source: FDA statistical reviewer's analysis)

**Figure 2. KM curve of PFS (ITT analysis set) in Study CARTITUDE-4**




Abbreviations: IRC, Independent Review Committee; ITT, intent-to-treat; PFS, progression-free survival
(Source: FDA statistical reviewer's analysis)

Reviewer Comment #3:

- Treatment with cilta-cel in CARTITUDE-4 was associated with a statistically significant improvement in PFS as assessed by IRC, compared to the standard therapy with a HR 0.41 (95% CI: 0.30, 0.56; p-value <0.0001). Overall, the observed estimate

of the treatment effect on PFS appears reliable based on balanced prognostic factors across treatment arms, and the blinded independent assessment of the PFS endpoint.

- There is early crossing of PFS curves which is limited to the first 3 months. However, on follow up there is a robust and sustained PFS advantage. The PFS results are mature with 75% information fraction, and the lower PFS is limited to a very short period of time. There are several possible causes of the early PFS detriment, e.g., inadequate bridging therapy or randomness due to very limited number of early events.
- A higher proportion of PFS events in the cilta-cel arm are attributable to deaths compared to the standard therapy arm (cilta-cel arm: 8%, n=17; standard therapy arm 1.4%, n=3). Longer follow-up OS data is warranted to adequately assess whether the overall benefit and risk assessment is favorable.

The analysis of investigator-assessed PFS demonstrated findings similar to the IRC assessment.

6.1.11.2 Analyses of Key Secondary Endpoints

**ORR, CR/sCR rate**

Results of the analysis of the key secondary endpoints, CR/sCR and ORR by IRC are summarized in Table 8. Based on the result from the stratified CMH test, the cilta-cel arm demonstrated a statistically significant improvement in both ORR and CR/sCR rate based on IRC compared to the standard therapy with one-sided p-value < 0.0001.

**Table 8. Rate of CR/sCR and ORR Per IRC, ITT Population**

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

Abbreviations: CI, confidence interval; CR, complete response; IRC, Independent Review Committee; ITT, intent-to-treat; NE, not evaluable; ORR, overall response rate; PR, partial response; sCR, stringent complete response; VGPR, very good partial response
(Source: FDA statistical reviewer's analysis)

**MRD-negativity rate**

Significant issues were noted by FDA regarding the MRD data that had an impact on the strength and validity of the MRD results. Therefore, the MRD data was not considered

robust to support inclusion in the United States Prescribing Application (USPI). Refer to FDA clinical review memo for details.

## OS

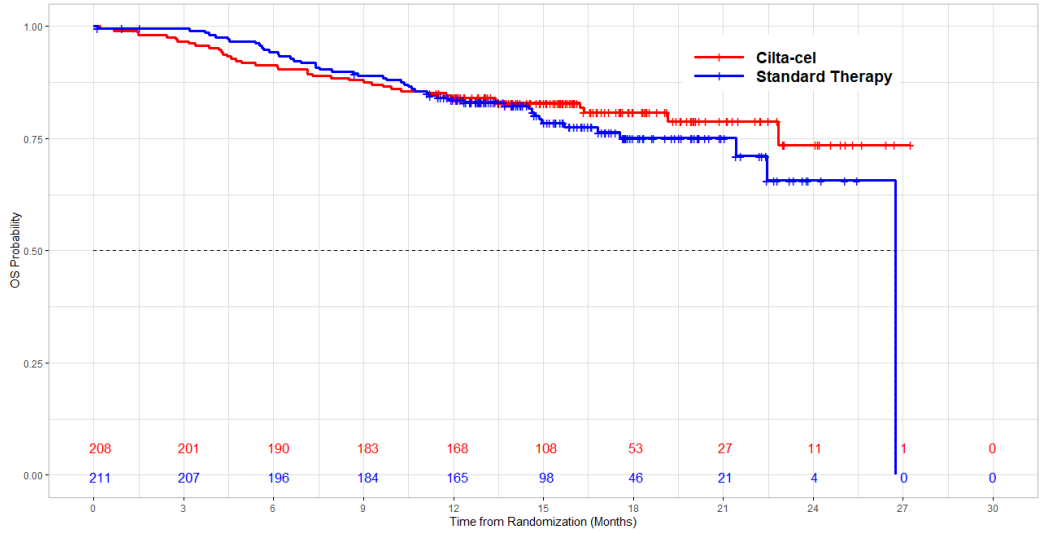
Table 9 and Figure 3 below summarize the analysis of OS.

**Table 9. Overall Survival, Interim Analysis, ITT Population**

| Category | Cilta-cel (N=208) | Standard Therapy (N=211) |
|---|---|---|
| Overall survival | - | - |
| Deaths, n (%) | 39 (19) | 47 (22) |
| Censored, n (%) | 169 (81) | 164 (78) |
| Median, months (95% CI) | NE (NE, NE) | 26.7 (22.5, NE) |
| Hazard ratio (95% CI) | 0.78 (0.51, 1.20) | - |
| p-value[1] | 0.26 | - |

1. The OS curves crossed a~10 months of the study, with greater number of deaths in the cilta-cel arm prior to 10 months and greater number of deaths in the standard therapy arm after 10 months, complicating the interpretation of the overall hazard ratio.
(Source: FDA statistical reviewer's analysis)

**Figure 3. KM curve of OS (ITT analysis set) in Study CARTITUDE-4**




(Source: FDA statistical reviewer's analysis)

Reviewer Comment #4:

- At the interim OS analysis, which was conducted with 34% information fraction, the OS Kaplan-Meier curves crossed at approximately 10 months, with inferior OS in the cilta-cel arm compared to the standard therapy arm prior to 10 months. In the presence of a crossing hazards pattern in survival curves, a single average hazard ratio (HR) across the entire course of a study is unable to accurately capture the entire time-dependent treatment effect profile, making it difficult to interpret and no longer meaningful. Therefore, the FDA explored piecewise HR assessment based on retrospectively selected landmark timepoints to capture the time-dependent treatment effect profile. Table 10 below shows the piecewise HR

estimates based on various data cutoffs. The increased risk of death on the cilta-cel arm goes beyond 3 months after randomization, appears to persist until at least 5 months and possibly up to 10 months. While this analysis may provide information to support a benefit risk assessment, it has inherent limitations- for example, choosing the cutoffs retrospectively based on observed outcomes limits the generalizability of the findings and lacks a biological or clinical rationale, leading to unreliable estimates that are unlikely to be replicated in future studies.

**Table 10. Piecewise Hazard Ratio Assessment**

| Time Interval | Piecewise HR | 95% CI |
|---|---|---|
| **Time interval of 3 months** | | |
| 0-≤3 | 6.24 | (0.75, 51.85) |
| 3-≤6 | 1.07 | (0.46, 2.47) |
| 6-≤9 | 0.65 | (0.25, 1.68) |
| 9-≤12 | 0.72 | (0.29, 1.78) |
| **Time interval of 5 months** | | |
| 0-≤5 | 2.40 | (0.99, 5.85) |
| 5-≤10 | 0.69 | (0.33, 1.42) |
| 10-≤15 | 0.35 | (0.14, 0.90) |
| **Time interval of 10 months** | | |
| 0-≤10 | 1.16 | (0.68, 1.99) |

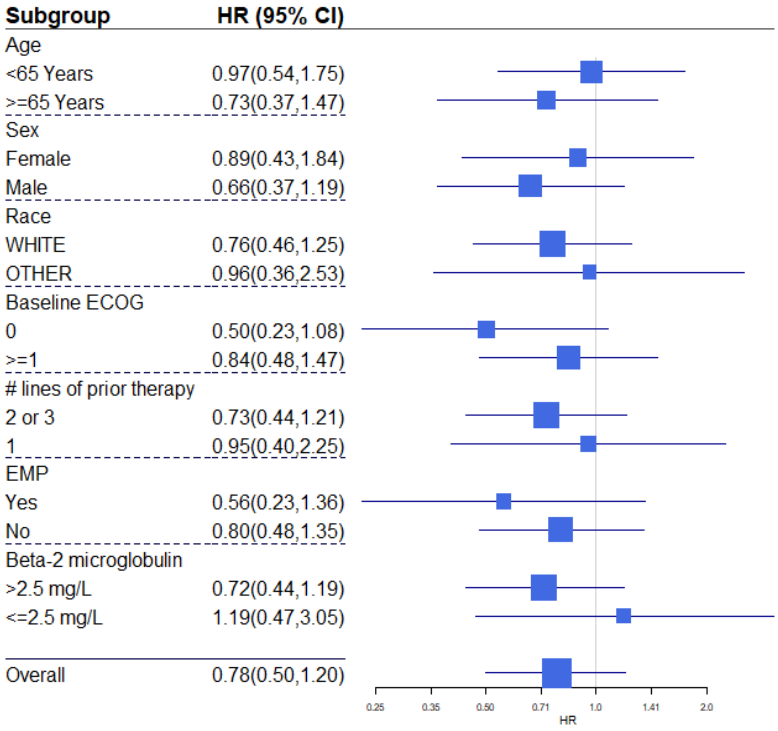
Note: >15 months not reported due to heavy censoring
(Source: FDA Statistical Reviewer's analysis, data cutoff November 1, 2022)

- The median OS estimate of 26.7 (22.5, NE) for the standard therapy arm should be interpreted with caution. The last subject in the at-risk set died at 26.7 months, leading to an immediate OS probability drop from ~65% to 0%. The median OS estimates will become more reliable with longer follow-up OS data.
- The observed early OS detriment of ~10 months is FDA's major concern. FDA evaluated potential causes for the early deaths in the cilta-cel arm. One concern is that, with any subject-specific cell therapy, subjects may suffer morbidity or mortality while waiting for the product to be available. This may have contributed to the early mortality seen on CARTITUDE-4 study in the subjects randomized to cilta-cel arm. It is also possible that there are product-specific toxicities leading to early deaths. There were 32 subjects who experienced progressive disease or died prior to receiving the cilta-cel infusion. Among these 32 subjects, 20 subjects went on to receive cilta-cel as subsequent therapy after progression. Of these 20 subjects, 10 died as of the data cutoff date. It is difficult to determine which deaths had cilta-cel toxicity as a contributing factor, or for which the delayed administration of cilta-cel was the main cause.
- There is heavy censoring after the crossing time point, indicating the OS data is immature.

### 6.1.11.3 Subpopulation Analyses

Figure 4 shows the forest plot of PFS in the ITT analysis set by age group, sex, race and a variety of other baseline clinical characteristics. As the OS plot within each subgroup also demonstrate a crossing hazards pattern or prolonged delayed effect pattern, the single average HR shown in the forest plot should be interpreted with caution.

**Figure 4. Forest plot of PFS result across subgroups in Study CARTITUDE-4**




(Source: FDA statistical reviewer's analysis)

### 6.1.12 Safety Analyses

This section briefly summarizes safety results of Study CARTITUDE-4.

#### 6.1.12.1 Methods

Descriptive statistics were used to summarize safety data for Study CARTITUDE-4. The safety analysis set in this section included a total of 396 subjects who received conforming cilta-cel in the investigational arm (N=188) or any study treatment in the standard therapy arm (N=208).

#### 6.1.12.3 Deaths

Deaths reported in the study are listed in Table 11. Among 188 conforming treated subjects in the cilta-cel arm, 25 (13%) subjects died. Among 208 treated subjects in the standard therapy arm, 46 (22%) subjects died.

**Table 11. Deaths, Study CARTITUDE-4**

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

(Source: FDA clinical review memo)

### 6.1.12.4 Nonfatal Serious Adverse Events

Table 12 summarizes nonfatal serious treatment emergent adverse events that occurred in ≥2% of the safety population.

**Table 12. Nonfatal Serious Treatment Emergent Adverse Events Occurring in ⩾2% of the Safety Population, CARTITUDE-4**

| | Cilta-cel N=188 | | Standard Therapy N=208 | |
|---|---|---|---|---|
| System Organ Class | All Grades (n/%) | Grade 3-4(n/%) | All Grades (n/%) | Grade 3-4 (n/%) |
| **Any nonfatal serious TEAE** | **68 (36)** | **42 (22.3)** | **78 (37.5)** | **67 (32.2)** |
| Infections and infestations | - | - | - | - |
| Pneumoniae (GT) | 10 (5.3) | 9 (4.8) | 24 (11.5) | 22(10.6) |
| Viral infection (GT) | 12 (6.4) | 5 (2.7) | 12 (5.8) | 12 (5.8) |
| Upper respiratory tract infection | 3 (1.6) | 2 (1) | 8 (3.8) | 7 (3.4) |
| Bacterial infection | 3 (1.6) | 3 (1.6) | 7 (3.4) | 7 (3.4) |
| Sepsis | 5 (2.7) | 5 (2.7) | 2 (1) | 0 |
| Blood and lymphatic system disorders | - | - | - | - |
| Febrile neutropenia | 0 | 3 (1.6) | 0 | 5 (2.4) |
| Neutropenia | 4 (2.1) | 4 (2.1) | 1 (0.5) | 1 (0.5) |
| Nervous system disorders | - | - | - | - |
| Encephalopathy | 4 (2.1) | 1 (0.5) | 2 (1) | 2 (1) |
| Cranial nerve palsies | 10 (5.3) | 2 (1) | 1 (0.5) | 0 |
| Gastrointestinal disorders | - | - | - | - |
| Diarrhea | 4 (2.1 | 3(1.6) | 0 | 0 |
| Immune system disorders | - | - | - | - |
| Cytokine release syndrome | 12 (6.4) | 4 (2.1) | 0 | 0 |

Abbreviations: GT, grouped term; SAE, severe adverse event; SOC, system organ class; TEAE, treatment-emergent adverse event
(Source: Applicant's IR response, data cutoff November 1, 2022)

### 6.1.12.5 Adverse Events of Special Interest

Adverse Events of Special Interest (AESIs) are summarized in Table 13.

**Table 13. AESI, Study CARTITUDE-4**

| | Cilta-cel N=188 | | Standard Therapy N=208 | |
|---|---|---|---|---|
| **AESI** | **Any Grade (n/%)** | **Grade ≥3 (n/%)** | **Any Grade (n/%)** | **Grade ≥3 (n/%)** |
| CRS | 146 (77) | 6 (3) | 1(1) | 0 |
| Neurotoxicity | 44 (23) | 8 (4) | 0 | 0 |
| HLH/MAS | 2 (1) | 1(0.5) | 1 (2) | 0 |
| Infections | 107 (57) | 46 (24.5) | 148 (71) | 47 (22.6) |
| Secondary primary malignancy | 8 (4.3) | N/A | 14 (6.7) | N/A |
| Hematologic neoplasm | 3 (1.6) | 1(0.5) | 0 | - |
| Cytopenia | - | - | - | - |
| Neutropenia | 187 (99) | 178 (95) | 203 (98) | 182 (87) |
| Thrombocytopenia | 177 (94) | 82 (44) | 181 (87) | 42 (20) |

Abbreviations: CRS, cytokine release syndrome; HLH/MAS, hemophagocytic lymphohistiocytic syndrome/macrophage activation syndrome
(Source: FDA analysis and Applicant's response to information request, data cutoff November 1, 2022)

# 10. CONCLUSIONS

## 10.1 Statistical Issues and Collective Evidence

The primary source of evidence to support the efficacy and safety of the proposed product comes from Study CARTITUDE-4. CARTITUDE-4 is a Phase 3, randomized, open-label, multicenter study that compared cilta-cel with standard therapy in adults with relapsed and lenalidomide-refractory multiple myeloma after 1 to 3 prior lines of therapy including PI and IMiD. CARTITUDE-4 enrolled 419 patients who were randomized (1:1) to receive cilta-cel or standard-of-care regimens, either PVd or DPd. The primary endpoint was PFS as determined by a blinded IRC using the IMWG 2016 criteria. Secondary endpoints included CR/sCR rate, ORR, MRD-negativity rate and OS.

The median PFS was not reached in the cilta-cel arm (95% CI: 22.8, not evaluable), and was 12 months (95% CI: 9.8, 14) in the standard therapy arm. Based on a stratified log-rank test, the stratified hazard ratio for PFS was 0.41 (95% CI: 0.30, 0.56); one-sided p-value < 0.0001. The IRC-assessed CR/sCR rate was statistically significantly higher at 74% (95% CI: 68%, 80%) in the cilta-cel arm compared to 22% (95% CI: 17%, 28%) in the standard therapy arm. Similarly, the ORR was higher at 85% (95% CI:79%, 89%) in the cilta-cel arm compared to 68% (95% CI: 61%, 74%) in the standard therapy arm, based on the stratified CMH test; one-sided p-value<0.0001. At the time of the efficacy supplement submission, the applicant provided the results of an interim analysis of OS based on a data cut-off date of November 1, 2022. At this interim OS analysis, which was conducted with 34% information fraction, the OS Kaplan-Meier curves crossed at approximately 10 months, with inferior OS in the cilta-cel arm compared to the standard of care arm prior to 10 months. The median OS in the cilta-cel arm was not reached and was 26.7 months (95% CI: 22.5, NE) for standard therapy arm.

## 10.2 Conclusions and Recommendations

The CARTITUDE-4 study met its primary endpoint, demonstrating a statistically significant improvement in PFS in patients randomized to the cilta-cel arm compared to patients randomized to the standard therapy arm. Statistically significant improvements were also observed in favor of cilta-cel for key secondary endpoints, ORR and CR/sCR rate. Although there was observed early OS detriment, this concern appears mitigated by the subsequent long-term benefits. Given the collective statistical evidence, including clinically meaningful improvements in PFS, CRR and ORR in a difficult-to-treat patient population and life-threatening nature of the disease, I recommend approval for cilta-cel of applicant's proposed indication in this BLA efficacy supplement. However, caution is warranted regarding the OS results, and longer follow-up is necessary to further confirm the long-term OS benefit.