



**Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research (CBER)
Division of Epidemiology (DE)**

PHARMACOVIGILANCE ORIGINAL BLA MEMORANDUM

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Subject: Review of Pharmacovigilance Plan

Sponsor: Janssen Biotech

Product: CARVYKTI® (ciltacabtagene autoleucel)

Application Type/Number: BLA/ STN 125746/0

Proposed Indication: Relapsed or refractory multiple myeloma

Submission Date: December 18, 2020

Action Due Date: November 29, 2021

*This product was also referred to as cilta-cel and JNJ-68284528 during clinical development

1 OBJECTIVE

The purpose of this review is to assess the adequacy of the sponsor's pharmacovigilance plan (PVP) submitted under the original BLA 125746/0 based on the safety profile of Carvykti and to determine whether any safety-related studies such as Post-Marketing Requirements (PMRs) and/or Post-Marketing Commitments (PMCs) are warranted, or if Risk Evaluation and Mitigation Strategies (REMS) are required for Carvykti (ciltacabtagene autoleucel), should the product be approved.

2 PRODUCT INFORMATION

2.1 Product Description

Carvykti (ciltacabtagene autoleucel) is a B-cell maturation antigen (BCMA)-directed genetically modified autologous T-cell immunotherapy. Carvykti is prepared from the patient's peripheral blood mononuclear cells, which are obtained via a leukapheresis procedure. The mononuclear cells are enriched for T-cells and genetically modified *ex vivo* by transduction with a replication incompetent lentiviral vector to express a chimeric antigen receptor (CAR) comprising an anti-BCMA targeting domain, which consists of two single domain antibodies linked to 4-1BB costimulatory domain and CD3-zeta signaling domains.

The transduced anti-BCMA CAR T-cells are expanded in cell culture, washed, formulated into a suspension and cryopreserved. The product must pass a sterility test before release for shipping as a frozen suspension in a patient-specific infusion bag. The product is thawed and then infused back into the patient, where the anti-BCMA CAR T-cells can recognize and eliminate BCMA-expressing target cells.

2.2 Proposed Indication

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, who previously received a proteasome inhibitor, an immunomodulatory agent and an anti-CD38 antibody.

3 PERTINENT REGULATORY HISTORY

Feedback on the long term follow-up study and post-marketing registry was provided in IND18080.240.

4 DESCRIPTION OF CARVYKTI SAFETY DATABASE

4.1 Clinical Studies

4.1.1 Study MMY2001

Study MMY2001 is a Phase 1b/2, open-label study in adult subjects with relapsed or refractory multiple myeloma performed at 16 sites in the U.S. The Phase 1b part of the study was intended to confirm the recommended dose level for Phase 2. The Phase 2 part of the study treated additional subjects to evaluate safety and efficacy at the recommended Phase 2 dose.

Study participants underwent apheresis to acquire peripheral blood mononuclear cells (PBMCs). T-cells were selected and used to generate cilta-cel, after which subjects were administered a conditioning regimen of cyclophosphamide and fludarabine. Cilta-cel was given as a single infusion five to seven days after initiation of the conditioning regimen. The post-infusion period of the study was defined as completion of the cilta-cel infusion on Day 1 until Day 100. The study will be considered complete two years after the last subject has received the initial dose of cilta-cel. After study completion, subjects will be enrolled in the long-term follow up study (68284528MMY4002) for up to 15 years. Cilta-cel was administered in a single infusion at a target dose of 0.75×10^6 CAR-positive viable T cells/kg (range: 0.5 to 1.0×10^6 CAR-positive viable T cells/kg).

One hundred and thirteen subjects were enrolled in Study MMY2001, defined as the first apheresis procedure, and 101 subjects received the conditioning regimen. Of these, 97 (85.8%) received a cilta-cel infusion. Short-term treatment with bridging therapy was allowed for subjects waiting for cilta-cel manufacture, which was limited to a treatment the subject previously received and resulted in a response of stable disease or better. Seventy-three subjects (75.3%) received bridging therapy, of which 33 had a decrease in tumor burden. The median follow-up for the 97 subjects was 12.4 months using a data cut-off of September 1, 2020.

4.1.2 Supportive data

Additional supportive safety data are presented for a Japanese cohort of subjects from Study MMY2001 (n = 13 enrolled, n = 9 treated) with a median duration of follow-up of 2.4 months (range 0.9 - 5.2 months) using a data cutoff date of September 1, 2020.

Study MMY2003 / CARTITUDE is a Phase 2, multicohort, open-label, multicenter study to determine the safety and efficacy of cilta-cel in adult subjects with multiple myeloma in various clinical settings. Patients are enrolled in one of five cohorts, receive a conditioning regimen of cyclophosphamide and fludarabine daily for three days, and then receive cilta-cel at a targeted dose of 0.75×10^6 CAR-positive T cells/kg (range 0.5 - 1.0×10^6 cells/kg) 5 - 7 days after starting the conditioning regimen. There were 18 treated subjects (n = 39 enrolled) with a median of 1.58 months follow-up (range 0.1 - 5.2 months) using a data lock point of July 23, 2020.

4.2 Adverse Events

All AEs regardless of relatedness were to be reported from the time of informed consent until 100 days after last study product administration or until the start of subsequent systemic anti-cancer therapy, if earlier. AEs after 100 days considered study drug related are to be reported until study completion. Neurologic AEs and hepatitis B virus laboratory indices are reported during the first year following cilta-cel infusion. All reports of second primary malignancy are also reported regardless of date of onset.

All 97 subjects who received a cilta-cel infusion experienced one or more treatment-emergent adverse events (TEAEs). The most common, defined as $\geq 20\%$ subjects, were neutropenia (n = 93, 95.9%), CRS (n = 92, 94.8%), anemia (n = 79, 81.4%), thrombocytopenia (n = 77, 79.4%), leukopenia (n = 60, 61.9%), lymphopenia (n = 51, 52.6%), fatigue (n = 36, 37.1%), cough (n = 34, 35.1%), hypocalcemia (n = 31, 32.0%),

hypophosphatemia (n = 30, 30.9%), diarrhea (n = 29, 29.9%), decreased appetite (n = 28, 28.9%), aspartate aminotransferase increased (n = 28, 28.9%), hypoalbuminemia (n = 27, 27.8%), nausea (n = 27, 27.8%), alanine aminotransferase increased (n = 24, 24.7%), hyponatremia (n = 22, 22.7%), constipation (n = 21, 21.6%), chills (n = 20, 20.6%), pyrexia (n = 20, 20.6%), and hypokalemia (n = 20, 20.6%).

Hypogammaglobulinemia occurred in 11 (11.3%) subjects, two of which experienced Grade 3 or 4 events. There were 23 (23.7%) subjects who received IVIG as prophylaxis and 16 (16.5%) subjects that were treated with IVIG due to an AE.

Infections were common, occurring in 56 (57.7%) subjects with 19 (19.6%) that had Grade 3 or 4 infections and three (3.1%) subjects with Grade 5 infection (lung abscess, sepsis, and septic shock). Twenty-two (22.7%) infections were viral infections, the most common of which was rhinovirus (n = 6, 6.2%). Eight (8.2%) subjects had bacterial infections, and one subject each had a fungal or protozoal infection. HBV reactivation was not reported.

Hypersensitivity reactions occurred in four (4.1%) subjects, all of which were Grade 1 in severity. The events were flushing (n = 3, 3.1%), chest discomfort (n = 2, 2.1%), tremor (n = 1, 1.0%), tachycardia (n = 1, 1.0%), and wheezing (n = 1, 1.0%). All events resolved on the same day of infusion.

Serious TEAEs were reported for 53 subjects (54.6%), most commonly (defined as \geq 5% subjects) CRS (n = 20, 20.6%), pneumonia (n = 5, 5.2%), sepsis (n = 5, 5.2%), and ICANS (n = 5, 5.2%).

There were 14 subjects who received a cilta-cel infusion and died as of the DLP of September 1, 2021. Five deaths were due to progressive disease and nine deaths were due to AEs. There were six deaths the investigators considered related to cilta-cel (lung abscess, sepsis, septic shock, CRS, neurotoxicity, and respiratory failure). All deaths occurred >30 days (range 45 to 694 days) after cilta-cel infusion. An additional seven deaths were reported in the 120-day Safety Update using a DLP of February 11, 2021 (STN125764.0.24), which were due to progressive disease in five subjects and AEs in two subjects (acute myeloid leukemia on day 718 and ascites on day 445).

At the data lock point, there were 80, 55, 15 subjects with samples evaluable for replication competent lentivirus (RCL) at 3, 6, and 12 months following cilta-cel infusion, respectively. There were no positive RCL samples at any time point.

4.3 Adverse Events of Special Interest (AESI)

Cytokine Release Syndrome (CRS)

CRS occurred in 92 (94.8%) subjects, 87 of which were Grade 1 or 2 events as assessed using the American Society for Transplantation and Cellular Therapy grading system. Three (3.1%) subjects had Grade 3 CRS, 1 (1.0%) subject had Grade 4 CRS, and 1 (1.0%) subject had Grade 5 CRS complicated by secondary HLH. Serious CRS

occurred in 20 (20.6%) subjects. The median onset of CRS from initial infusion of CAR-T cells was seven days (range 1 - 12 days). One fatal event with a duration of 97 days was complicated by HLH. All other subjects recovered from CRS. The median duration of CRS was 4.0 days (range 1 - 14 days, excluding one subject with a 97-day duration with Grade 5 CRS).

The most commonly reported (defined as $\geq 10\%$ of subjects) signs and symptoms of CRS were pyrexia (n = 92, 94.8%), hypotension (n = 40, 41.2%), AST increased (n = 20, 20.6%), chills (n = 14, 14.4%), ALT increased (n = 13, 13.4%), and sinus tachycardia (n = 10, 10.3%).

Of the 92 subjects who developed CRS, 68 received tocilizumab with or without corticosteroids or anakinra. The management of these patients consisted of:

- Sixty-eight (70.1%) received tocilizumab and/or corticosteroids.
- Forty-seven (48.5%) received tocilizumab only.
- Of 68 subjects who received tocilizumab, 49 (72.1%) received one dose and 19 (27.9%) received more than one dose.
- Twenty-one (21.6%) received corticosteroids, none of which received only corticosteroids. Three of the 21 subjects received a single dose of corticosteroids and 18 received more than one dose.
- Eighteen (18.6%) received anakinra, none of which were only treated with anakinra.
- Four (4.1%) received tocilizumab and anakinra only.
- Fourteen (14.4%) received tocilizumab, anakinra, and corticosteroids. There were no subjects who received anakinra and corticosteroids only.

CAR-T Cell Neurotoxicity

CAR-T cell neurotoxicity was categorized as Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS) or Other Neurotoxicity occurring after recovery of CRS and/or ICANS. Twenty (20.6%) of subjects experienced one or more treatment-emergent CAR-T neurotoxicity events, of which 8 (8.2%) subjects had ICANS only, 4 (4.1%) subjects had other neurotoxicity only, and 8 subjects (8.2%) had events in both categories.

Sixteen (16.5%) subjects had an ICANS event. The ICANS occurred concurrent with CRS in 15 subjects, and 4 days after recovery from CRS in 1 subject. The median time to ICANS onset from cilta-cel infusion was 8 days (range 3 - 12 days) with a median duration of four days (range 1 - 12 days). There was one subject each with a Grade 3 and Grade 4 event; the remaining subjects were Grade 1 or 2. All 16 subjects recovered from the ICANS events. The signs and symptoms of ICANS reported in two or more subjects were aphasia (n = 5, 5.2%), confusional state (n = 4, 4.1%), disturbance in attention (n = 2, 2.1%), dysgraphia (n = 2, 2.1%), lethargy (n = 2, 2.1%), somnolence (n = 2, 2.1%), and tremor (n = 2, 2.1%). Other signs and symptoms of note were slow speech, encephalopathy, and depressed level of consciousness. There were 16 (16.5%) subjects that received treatment for ICANS, the most common of which were

dexamethasone (n = 9, 56.6%), tocilizumab (n = 4, 25.0%), and anakinra (n = 3, 18.8%).

There were 12 (12.4%) subjects that experienced other neurotoxicity not defined as ICANS. These events included disturbances in consciousness, coordination and balance disturbances, movement disorders, mental impairment disorders, cranial nerve disorders, and peripheral neuropathies. The median time to onset of other neurotoxicity after cilta-cel infusion was 26.5 days (range 11 - 108 days) with a median time to recovery of 74.5 days (range 2 - 160 days). There were eight (8.2%) subjects that experienced Grade 3 or 4 toxicities and one (1.0%) subject that experienced a Grade 5 toxicity. At the time of the data lock point, six cases have resolved, five cases have not yet resolved, and one case was fatal.

There were 63 (64.9%) subjects who experienced other neurologic AEs not identified by the sponsor as CAR-T cell neurotoxicity. The most common of these, occurring in >5% of subjects, were headache (n = 25, 25.8%), dizziness (n = 20, 20.6%), insomnia (n = 13, 13.4%), confusion state (n = 6, 6.2%), dysgeusia (n = 5, 5.2%), and anosmia (n = 5, 5.2%).

There were five subjects that experienced a similar presentation of movement and neurocognitive TEAEs that clinically resembled Parkinson's disease. These were characterized by movement disorders (e.g., micrographia, tremors), cognitive (e.g., memory loss, disturbance in attention) and personality changes (e.g., reduced facial expression, flat affect). Some of these subjects were unable to work or care for themselves. The five patients were male with a median age of 62 years (range 58 - 77 years). The median onset was 27 days (range 14 - 108 days) after cilta-cel infusion. One subject has recovered, one subject had ongoing symptoms at the time of the data cut-off but was recovering, and three subjects died (neurotoxicity, septic shock, and lung abscess) that had ongoing neurotoxicity at the time of death. The sponsor concluded these movement and neurocognitive TEAEs in these five subjects were possibly associated with high tumor burden, prior Grade 2 or higher CRS, prior ICANS, and high CAR-T cell expansion and persistence. The sponsor introduced additional monitoring and mitigation strategies based on this analysis that included enhanced bridging therapy to reduce baseline tumor burden, early aggressive treatment of CRS and ICANS, handwriting assessments, and extended monitoring for neurotoxicity to ≥ 1 year post-cilta-cel infusion. The sponsor states no additional neurotoxicity events have since been reported after implementation of these measures. A summary of these five cases is as follows:

- Subject ID (b) (6): 58-year-old male experienced Grade 2 CRS (fever, hypotension) and Grade 1 ICANS (hand tremor) on day 7. He was treated with tocilizumab with resolution of events three days later. Grade 1 dizziness was reported on day 28. After day 43, he experienced multiple neurological events including altered mental status, depression, tremors, flat affect, lack of interest, decreased insight and empathy, difficulty with short term memory, balance problems, difficulty walking, and fine motor control. Symptoms gradually deteriorated around day 100. Neurological exam showed intention tremor and

hyperreflexia. Two MRIs were unremarkable. EEG showed generalized slowing without seizures. CSF showed 24 WBCs. He was treated with steroids and cyclophosphamide for persistently elevated CAR-T cells without benefit. He began hospice care on day 135 with difficulty with walking, continence, swallowing solid food, finding words, engaging in conversation, and emotional expression. On day 246, he was hallucinating and in an unresponsive state. He died on day 247 due to neurotoxicity.

- Subject ID (b) (6): 58-year-old male experienced Grade 2 CRS (fever, hypotension) on days 8 – 10, and Grade 3 CRS on days 10 – 12. He was treated with tocilizumab, anakinra, fluids, norepinephrine, and albumin and recovered on day 13. On day 101, he had social withdrawal, delayed motor responses, and significant handwriting changes. Neuro-oncology assessment was mild Parkinsonism (bradykinesia, hypomimia) and short-term memory dysfunction. His symptoms worsened from day 101 – 156. He had stiffness, flat affect, slow response, micrographia, difficulty with ADLs, and difficulty with fine motor control. He was treated with plasmapheresis, anakinra, carbidopa/levodopa, cyclophosphamide x 2, IT cytarabine/hydrocortisone x2, and IT methotrexate. Brain MRI was unremarkable. CSF showed positive CAR-T cells in CSF. DaT scan was negative for features typically associated with Parkinson's disease. Patient presented on day 161 with cough, dyspnea and found to have *Serratia marcescens* bacteria and pneumonia. He died on day 162 of sepsis.
- Subject ID (b) (6): 62-year-old male experienced Grade 2 CRS (fever, hypotension) on day 7 and was treated with tocilizumab. He developed Grade 1 neurotoxicity on day 8 with mild confusion and expressive aphasia that was treated with dexamethasone. He recovered by day 10. Beginning on day 19, he experienced several neurological events including tremors, slow speech, less interactive, flat affect, slow to respond, slow gait, difficulty swallowing, and taking longer with basic tasks. Symptoms became more severe by day 40. Neurological evaluations showed mild hyperreflexia, bradykinesia, tremors, masked facies, severe psychomotor retardation, saccadic eye movements, decreased eye blink, profound rigidity, and positive cogwheel rigidity concerning for a Parkinson-like syndrome. Two MRIs were unremarkable. CSF was positive for CAR-T cells. He was treated with steroids, cyclophosphamide, carbidopa/levodopa, IT cytarabine/hydrocortisone, IT methotrexate and hydrocortisone, and dasatinib with no effect. He continued to worsen with progressive difficulty speaking, swallowing, and required a Dobhoff tube for enteral nutrition. He later developed skin fungal infection, lung infection, *Klebsiella pneumoniae* and *Pseudomonas aeruginosa* bacteremia. He was placed on comfort care and died nine days later.
- Subject ID (b) (6): 68-year-old experienced Grade 2 CRS on days 5 – 8 and Grade 1 ICANS on day 12 – 14 and was treated with tocilizumab. From day 103 – 112, he had several episodes of neurologic and psychiatric events including lower extremity weakness with multiple falls, profound weakness, extreme restlessness, personality changes, flat affect, altered mental status, and anxiety. MRI of brain and spine was unremarkable and there were no nucleated cells in the CSF. The psychiatric manifestations would improve or resolve after steroid administration, but patient remained weak with bilateral foot drop, inability

to get out of bed, and unable to feed himself. He was treated with IT methotrexate and hydrocortisone, and cyclophosphamide that resulted in some improvement in strength.

- Subject ID (b) (6) : 77-year-old with small ischemic cerebrovascular accident on routine screening MRI considered incidental finding experienced Grade 2 CRS and Grade 1 ICANS from days 6 – 9 was treated with tocilizumab, anakinra, and dexamethasone. At day 28, he had slowed motor and psychomotor function with slow gait, shortened stride, increase in axial tone and appendicular tone diffusely with slight cogwheeling in the upper extremities. He also had mild micrographia and was cognitively slowed. No intervention was initiated and he recovered by day 56, with the exception of difficulty getting out of a chair.

Reviewer comment: This cluster of patients with early or delayed onset neurologic toxicity with some features of Parkinson's disease describes a series of AEs not previously seen with other CAR-T products. These subjects all had robust and persistent CAR-T cell expansion; however, other subjects with similar CAR-T cell expansion did not exhibit this toxicity. It is unclear if the mitigations introduced by the sponsor were effective in preventing this syndrome. Additional pharmacovigilance actions and addition of more information on this potential Parkinson-like syndrome to the REMS materials is warranted (please see sections below for further details).

Tumor Lysis Syndrome

One (1.0%) subject had Grade 4 tumor lysis syndrome and a Grade 3 increase in creatinine.

Second Primary Malignancy

There were nine second primary malignancy events in seven (7.2%) subjects after enrollment in the study as of September 1, 2020. Five (5.2%) subjects developed myelodysplastic syndrome, two (2.1%) subjects developed acute myeloid leukemia, one (1.1%) subject developed prostate cancer, and one (1.1%) subject developed basal cell carcinoma. For the two subjects with more than one second primary malignancy, the first subject was diagnosed with prostate cancer on Day 141 followed by acute myeloid leukemia on Day 337; the second subject had myelodysplastic syndrome diagnosed on Day 447 followed by acute myeloid leukemia on Day 569. Second primary malignancies were reported in an additional three subjects in the 120-day Safety Update using a DLP of February 11, 2021 (STN125764.0.24), which were myelodysplastic syndrome in one subject (day 723), acute myeloid leukemia in a second subject (day 712), and basal cell carcinoma (onset not specified) and squamous cell carcinoma (day 421) in a third subject.

Reviewer comment: In a response to an IR sent by OTAT Clinical (STN125746/0.32), the sponsor states that no results have been generated for vector sequence detection or vector integration in subjects with second primary malignancy. The sponsor's justification is that two subjects died before signing an informed consent for the protocol amendment that allows testing of tumor sampling and samples for five subjects are

pending shipment from the site. A sample was received for one subject that is currently being processed.

Prolonged and Recurrent Cytopenias

Prolonged and recurrent Grade 3 or 4 cytopenias were observed in the clinical trials.

Table 1 below shows the numbers of patients who experienced prolonged or recurrent cytopenia. There was one subject that received rescue autologous stem cell transplant for marrow aplasia.

Table 1. Summary of initial and recurrent Grade 3 or 4 cytopenias*

| Grade 3 or 4 cytopenia | Day 30 (%) | Day 60 (%) | At DLP (%) | Recurrence of Grade 3 or 4 cytopenia after recovery (%) |
|------------------------|------------|------------|------------|---|
| Neutropenia | 29 (29.9) | 10 (10.3) | 0 | 61 (62.9) |
| Thrombocytopenia | 40 (41.2) | 25 (25.8) | 6 (6.2) | 17 (17.5) |
| Lymphopenia | 12 (12.4) | 8 (8.2) | 5 (5.2) | 58 (59.8) |
| Anemia | 1 (1.0) | 1 (1.0) | 1 (1.0) | 36 (37.1) |

*Adapted from the Response to 15 July 2021 FDA Clinical Information Request Part 1 and 2 (STN125746/0.21 and STN125746/0.23)

Reviewer comment: Recurrence of cytopenias is novel and not seen with the other CAR-T products. Additional information on recurrent and prolong cytopenias should be added to the REMS Training Materials.

4.4 Supportive Data

Thirteen subjects have been enrolled at Japanese study sites for Study MMY2001 and completed apheresis. Four subjects discontinued after apheresis and before starting the conditioning regimen. The remaining nine subjects received the conditioning regimen and cilta-cel infusion with a median of 2.4 months of follow-up (range 0.9 - 5.2 months). All nine subjects had ≥ 1 TEAEs, and eight subjects (88.9%) had ≥ 1 TEAEs with a maximum severity of Grade 4. One subject experienced SAEs of Grade 4 neutropenia, Grade 3 fatigue, Grade 2 thrombocytopenia, and Grade 1 CRS. No deaths occurred among cilta-cel treated subjects. CRS was reported for 8 (88.9%) subjects, the majority of which were Grade 1 events ($n = 7$, 77.8%) with one (11.1%) subject experiencing a Grade 2 event. The median onset time from cilta-cel infusion to CRS was 7.5 days (range 4 - 11 days) with a median duration of 5.0 days (range 3 - 6 days). Of the 8 Japanese subjects with CRS, seven (77.8%) received tocilizumab and three (33.3%) received corticosteroids. All subjects recovered from CRS. There were no cases of ICANS, other neurotoxicity, tumor lysis syndrome, or second primary malignancy. One subject had Grade 2 bacteremia on day 11.

As of July 23, 2020, 39 subjects have been enrolled into Study MMY2003 and 18 received the conditioning regimen and cilta-cel infusion. The median length of follow-up was 1.6 months (range 0.1 - 5.2 months). All 18 (100%) experienced ≥ 1 TEAEs with a maximum severity of Grade 3 or 4. The most common ($\geq 20\%$) TEAEs were neutropenia ($n = 16$, 88.9%), thrombocytopenia ($n = 13$, 72.2%), CRS ($n = 13$, 72.2%), anemia ($n =$

11, 61.1%), leukopenia (n = 11, 61.1%), lymphopenia (n = 10, 55.6%), hypocalcemia (n = 6, 33.3%), hypokalemia (n = 5, 27.8%), hypophosphatemia (n = 5, 27.8%), diarrhea (n = 5, 27.8%), and constipation (n = 4, 22.2%). SAEs occurred in four (22.2%) subjects, which were CRS (n = 2, 11.1%), neutropenia (n = 1, 5.6%), COVID-19 pneumonia (n = 1, 5.6%), sepsis (n = 1, 5.6%), ICANS (n = 1, 5.6%), and acute kidney injury (n = 1, 5.6%). No deaths were reported. CRS occurred in 13 (72.2%) subjects, 11 of which were Grade 1 or 2, and Grade 3 and 4 for one subject each. The median onset to CRS after cilta-cel infusion was 8.0 days (range 6 - 9 days) with a median duration of 4.0 days (range 1 - 11 days). Fifteen subjects received supportive care for CRS, the most common of which were tocilizumab (n = 7), corticosteroids (n = 3), and supplemental oxygen (n = 2). Grade 1 ICANS was reported for two (11.1%) subjects, both with concurrent CRS. Other neurotoxicity occurred in 2 (11.1%) subjects, which included slow speech, facial paralysis, gait disturbance, and pain. Other neurologic TEAEs occurred in five (27.8%) subjects, which included two (11.1%) subjects with insomnia and one subject each with aphasia, dysgraphia, depressed level of consciousness, lethargy, facial paralysis, tremor, hemiparesis, headache, agitation, anxiety, depression, and delirium. There were no events of tumor lysis syndrome or second primary malignancy. Infections were reported for 2 (11.1%) subjects, which were Grade 3 COVID-19 infection and Grade 3 sepsis. Four (22.2%) of subjects had hypersensitivity reactions of feeling hot (n = 2, 11.1%) and flushing (n = 2, 11.1%).

5 SPONSOR'S PHARMACOVIGILANCE PLAN

A summary of the sponsor's pharmacovigilance plan (PVP) is provided in **Table 2** below which describes the important identified and potential risks, and missing information for ciltacabtagene autoleucel. The sponsor will conduct both passive and active surveillance activities for the safety concerns listed below.

Table 2. Sponsor's pharmacovigilance plan*

| Type of Concern | Safety Concern | Proposed Action |
|-----------------|---|--|
| Identified | Cytokine release syndrome (including HLH) | <ul style="list-style-type: none"> ▪ Routine pharmacovigilance ▪ Study 68284528MMY4004: observational post-marketing safety study ▪ Boxed warning on label |
| Identified | Neurologic toxicities (including ICANS and other neurotoxicities) | <ul style="list-style-type: none"> ▪ Routine pharmacovigilance ▪ Study 68284528MMY4002: Long-term follow-up study of clinical trial subjects ▪ Study 68284528MMY4004: observational post-marketing safety study ▪ Boxed warning on label ▪ Topic of Interest <p>Questionnaire for cases of movement and neurocognitive toxicity</p> |

| | | |
|------------|----------------------------------|---|
| | | <ul style="list-style-type: none"> ▪ Expedited reporting of spontaneous reports of movement and neurocognitive toxicity ▪ Summary and analysis of movement and neurocognitive toxicity in the PAER |
| Identified | Prolonged or recurrent cytopenia | <ul style="list-style-type: none"> ▪ Routine pharmacovigilance ▪ Expedited reporting of spontaneous reports of prolonged or recurrent cytopenia that require stem cell rescue and continued growth factor support and/or transfusion ▪ Summary and analysis of cases of prolonged or recurrent cytopenia that require stem cell rescue and continued growth factor support and/or transfusion in the PAER ▪ Study 68284528MMY4002: Long-term follow-up study of clinical trial subjects ▪ Study 68284528MMY4004: observational post-marketing safety study ▪ Labeling |
| Identified | Serious infections | <ul style="list-style-type: none"> ▪ Routine pharmacovigilance ▪ Study 68284528MMY4002: Long-term follow-up study of clinical trial subjects ▪ Study 68284528MMY4004: observational post-marketing safety study ▪ Labeling |
| Potential | Secondary primary malignancy | <ul style="list-style-type: none"> ▪ Routine pharmacovigilance ▪ Study 68284528MMY4002: Long-term follow-up study of clinical trial subjects ▪ Study 68284528MMY4004: observational post-marketing safety study ▪ Labeling |

| | | |
|-----------|--|--|
| Potential | Decrease in cell viability due to inappropriate handling or preparation of product | <ul style="list-style-type: none"> ▪ Reporting trend analysis of lack of efficacy and relevant Product Quality Complaints from postmarketing safety data per PBRER/PSUR period |
| Missing | Long-term safety | <ul style="list-style-type: none"> ▪ Routine pharmacovigilance ▪ Study 68284528MMY4002: Long-term follow-up study of clinical trial subjects ▪ Study 68284528MMY4004: observational post-marketing safety study |
| Missing | Use in patients who are pregnant or breastfeeding | <ul style="list-style-type: none"> ▪ Routine pharmacovigilance ▪ Study 68284528MMY4002: Long-term follow-up study of clinical trial subjects ▪ Study 68284528MMY4004: observational post-marketing safety study ▪ Labeling |
| Missing | Use in patients with pre-existing autoimmune disease | <ul style="list-style-type: none"> ▪ Routine pharmacovigilance ▪ Study 68284528MMY4002: Long-term follow-up study of clinical trial subjects ▪ Study 68284528MMY4004: observational post-marketing safety study |
| Missing | Use in patients with pre-existing neurodegenerative disorders | <ul style="list-style-type: none"> ▪ Routine pharmacovigilance ▪ Study 68284528MMY4002: Long-term follow-up study of clinical trial subjects ▪ Study 68284528MMY4004: observational post-marketing safety study |
| Missing | Use in patients with active CNS involvement by malignancy | <ul style="list-style-type: none"> ▪ Routine pharmacovigilance ▪ Study 68284528MMY4002: Long-term follow-up study of clinical trial subjects ▪ Study 68284528MMY4004: observational post-marketing safety study ▪ Labeling |
| Missing | Use in patients with chronic controlled HIV and HBV/HCV infection | <ul style="list-style-type: none"> ▪ Routine pharmacovigilance ▪ Study 68284528MMY4002: Long-term follow-up study of clinical trial subjects |

| | | |
|--|--|--|
| | | <ul style="list-style-type: none"> ▪ Study 68284528MMY4004: observational post-marketing safety study ▪ Labeling |
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*Adapted from the Summary of Safety Concerns (Section 4.3), Summary of the Pharmacovigilance Plan (Section 6) in the Pharmacovigilance Plan Document (STN125746/0, Module 1.16)

The sponsor will perform enhanced pharmacovigilance activities for cases of movement and neurocognitive toxicity with features similar to Parkinson's disease. The sponsor has developed a Topic of Interest Questionnaire to collect structured information on cases of movement and neurocognitive toxicity that will be triggered by the occurrence of pre-defined MedDRA terms. The sponsor has also agreed to submit spontaneous reports of movement and neurotoxicity to FAERS as an expedited report and include a summary and analysis of these cases in their Periodic Adverse Experience Report (PAER).

Reviewer comment: The Important Identified Risk of "Neurologic toxicities (including ICANS and other neurotoxicities)" does not specifically mention the movement and neurocognitive toxicity with features similar to Parkinson's Disease; however, this syndrome is encompassed within the Important Identified Risk of Neurologic toxicities. The sponsor includes several enhanced pharmacovigilance activities for cases of movement and neurocognitive toxicity with Parkinson's disease features within the risk of neurologic toxicities.

5.1 Risk Evaluation and Mitigation Strategy (REMS)

The sponsor proposes a REMS program to ensure that the benefits of the drug outweigh the risks. 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 ensure safe use (ETASU) to mitigate the risks for CRS and neurological toxicities:

- Health care settings that dispense Carvykti are specially certified
- Carvykti is dispensed to patients only in certain health care settings

The REMS requirements are detailed in the REMS Document. Certified hospitals and their associated clinics 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. 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. The REMS materials include the Training Program, Adverse Reaction Management Guide, Knowledge Assessment, Hospital Enrollment Form, Patient Wallet Card, and the REMS Program Website.

The REMS includes an implementation system, to monitor and evaluate the implementation of the elements to assure safe use (outlined above). The implementation system also includes an intervention plan to address any findings of non-compliance with elements to assure safe use and to address any findings that suggest an increase in risk to patients. The implementation system includes:

- Carvykti REMS Database. The sponsor will maintain a database of healthcare facilities that are certified to administer Carvykti in the product REMS and maintain records of product distribution to certified healthcare facilities to assess the effectiveness of REMS requirements.
- Audits and Carvykti REMS Non-compliance Action Plan. The sponsor will perform a remote audit for each certified healthcare facility for REMS compliance within 180 calendar days after the facility places its first order of Carvykti to ensure that all processes are in place to support the REMS requirements. Audits will be performed annually thereafter. Onsite audits may be performed if non-compliance issues found in the targeted questionnaire responses could not be resolved by phone, e-mail, or mail.
- Carvykti REMS Coordinating Center and REMS Website. The sponsor will maintain a REMS Coordinating Center which can be contacted by telephone. The sponsor will also implement a REMS Website within 60 days of the REMS approval.
- REMS Healthcare Provider Survey. The sponsor will perform surveys with healthcare providers who received the REMS training and have dispensed or administered Carvykti, or authorized representatives of healthcare facilities that are certified and enrolled in the REMS. The purpose of the surveys is to assess their understanding of Carvykti risks and the REMS requirements. Survey results will be reported every two years starting with year 2 of the Carvykti REMS Assessment Report.
- Adverse Event Monitoring, Analysis, and Reporting. The sponsor will monitor for AEs of special interest, including CRS and neurological toxicities. REMS certified sites are required to report any serious* AEs suggestive of CRS or neurological toxicity to the REMS Program.

* As defined in 21CFR600.80, an adverse experience is "serious" if it results in death, a life-threatening adverse experience, inpatient hospitalization or prolongation of existing hospitalization, persistent or significant disability/incapacity, or a congenital anomaly/birth defect.

The sponsor will submit REMS Assessments to FDA every six months for the first year following approval and then annually thereafter.

Reviewer comment: Section 505-1 of the Federal Food, Drug, and Cosmetic Act (FDCA) authorizes FDA to require the submission of a REMS if FDA determines that such a strategy is necessary to ensure that the benefits of the product outweigh the risks. DE review of the sponsor's proposed REMS incorporated input from the Center for Drug Evaluation and Research (CDER) Division of Risk Management (DRM) and the

Office of the Chief Counsel (OCC). DE presented the REMS program to the CBER Safety Working Group (SWG) on August 12, 2021. It was determined that a REMS with ETASU is necessary to ensure that the benefits of Carvykti outweigh the risks of CRS and neurotoxicity, which can include fatal or life-threatening reactions. The sponsor submitted a REMS with ETASU in the BLA application. An IR was sent to request edits to the REMS Document to maintain consistency and align the REMS program with those of other approved CAR T-cell products. The sponsor revised the REMS Document accordingly, and it is acceptable and was cleared by OCC with minor editorial changes that will be incorporated in final version of the REMS Document. The sponsor submitted a Supporting REMS Document which includes a Carvykti REMS Assessment Plan. The sponsor also submitted an Audit Plan, Audit Questionnaire, Audit Questionnaire Review Form, and a Noncompliance Action Plan. The sponsor will audit all Carvykti REMS facilities no later than 180 calendar days after a facility places its' first order of Carvykti. The sponsor will submit REMS assessment reports to FDA at 6 months, 12 months, and then annually thereafter. IRs was sent to request edits to the REMS Supporting Document to maintain consistency and align the REMS program with those of other approved CAR T-cell products. The sponsor's revised Supporting REMS Document is acceptable.

In addition, the sponsor submitted REMS materials (i.e., Hospital Enrollment Form, REMS Training Program slides, Adverse Reaction Management Guide, Patient Wallet Card, and Knowledge Assessment) which were reviewed. An IR was sent requesting edits to the REMS materials to maintain consistency, and to align the REMS program with those of other approved CAR T-cell products. In addition, FDA requested that the final REMS materials be aligned with the content and language agreed to in the final label.

The sponsor will also conduct knowledge, attitudes, and behavior (KAB) surveys of healthcare providers to assess their understanding of the risks and REMS requirements for Carvykti. The survey instruments will be submitted for FDA review at least 90 days before initial survey administration. The surveys will be reported every two years beginning with the year 2 Carvykti REMS Assessment Report.

5.2 Long-Term Follow-Up Studies

5.2.1 Post-marketing registry study (Study 68284528MMY4004)

The purpose of this study is to document the short and long-term safety of adult patients receiving cilta-cel for multiple myeloma in the post-marketing setting. This study will use data from patients enrolled in the Center for International Blood and Marrow Transplant Research (CIBMTR) registry and other similar registries outside of the United States, including a Janssen owed EU registry and national registries as appropriate. Patients will enroll at the time of cilta-cel infusion administered for multiple myeloma and will be followed for up to 15 years. The study objectives are:

Primary objective

- Evaluate the long-term safety and risk of subsequent malignancy of cilta-cel in adult patients with multiple myeloma

Secondary objectives

- Evaluate the short-term safety of cilta-cel in adult patients with multiple myeloma
- Evaluate the effectiveness in adult patients with multiple myeloma

All eligible patients will be included for data collection in the study. Eligible participants are those who received at least one dose of cilta-cel and signed an informed consent allowing participation in the registry and for pharmaceutical companies to have access to their study data. The data collected will include demographics, diagnosis, and medical history such as disease characteristics, comorbidities, lymphodepleting therapies, ECOG performance status, safety data, and response. Analysis from tumor samples may be performed, when available.

Selected AEs will be collected in this study, as well as SAEs and certain spontaneous reports. The following safety parameters will be collected:

- Subsequent malignancies, including second primary malignancies and recurrent malignancies
- Neurotoxicity including:
 - ICANS
 - Other CAR-T neurotoxicity, including movement and neurocognitive toxicity
- Hematologic disorder using collected laboratory values
- Hypogammaglobulinemia
- Infection
- Organ toxicities (\geq Grade 3)
- CRS, including HLH/MAS
- Tumor lysis syndrome (\geq Grade 3)
- Graft-versus-host disease
- Hepatitis B virus reactivation
- Infusion-related reactions
- Rheumatologic or other autoimmune disorders
- Neurologic disorders other than ICANS and other CAR-T neurotoxicity
- Hematologic disorders, including prolonged or recurrent cytopenias
- Pregnancies and outcomes

Subsequent malignancies should be reported to the sponsor by the treating physicians in an expedited manner, within 72 hours of awareness of diagnosis, to facilitate prompt initiation of obtaining tumor specimens. If clinically feasible, a blood, bone marrow aspirate, or biopsy of the neoplastic tissue or autopsy tissue will be collected in the event of subsequent malignancies and DNA, RNA, or protein analysis may be performed to evaluate the presence of lentiviral elements. Lentiviral integration site analysis will be performed if at least 1% of cells in blood samples are positive for vector sequence. The subject will be closely monitored for occurrence of subsequent malignancies if there is a sign of persistent monoclonality, clonal expansion, or evidence of lentiviral integration site.

Disease evaluations will also be collected. Effectiveness will be based on overall survival, progression-free survival, duration of response, and overall response rate.

Data will be collected on Day 0, Day 100, Month 6, and then annually. The sponsor agreed to enroll up to 1500 subjects to align with the long-term follow-up studies of the other CAR-T cell products.

Reviewer comment: In a response to an IR (STN125746/0.26), the sponsor agreed to add the risk of secondary malignancies to the study objectives. The sponsor also provided clarification on tumor specimen collection including reporting of such cases to the sponsor within 72 hours of awareness, and addition of movement and neurocognitive toxicity (i.e., the Parkinson-like syndrome) as a safety measure of interest. The sponsor also agreed to increase enrollment to 1500 subjects in alignment with other CAR-T products. Recurrent cytopenia was added as a safety endpoint to the revised protocol submitted to STN125746/0.43.

The sponsor proposed the following milestones:

- Final protocol submission: January 31, 2022
- Study completion date: June 30, 2041
- Final report submission: June 30, 2042

Reviewer comment: The sponsor submitted a draft study protocol for the registry study. Carvykti has potential for the serious risk of secondary malignancy due to replication-competent retrovirus or insertional mutagenesis. As required by regulations under Section 901 of the Food and Drug Administration Amendments Act (FDAAA) and as described in CBER SOPP 8415: Procedures for Developing Post-marketing Requirements and Commitments, a Sentinel sufficiency assessment was conducted to determine the sufficiency (i.e., capability) of the CBER Sentinel program to characterize the serious risk of secondary malignancy associated with Carvykti. As outlined in the Sentinel sufficiency memorandum, the CBER Sentinel Team has determined that CBER Sentinel will not be sufficient to characterize the serious risk of secondary malignancy since 15 years of follow-up, and collection of tissue samples are needed; this is not feasible in a claims-based system such as Sentinel.

Sentinel insufficiency serves as a justification for requiring a safety-related post-marketing study under Section 901, Title IX of FDAAA. Therefore, if the product is approved, the sponsor will be required to conduct a PMR safety study under FDAAA Title IX to identify the serious risk of secondary malignancy after treatment with cilta-cel. The PMR will be conducted for up to 15 years in accordance with the FDA Guidance for Industry: Long Term Follow-Up After Administration of Human Gene Therapy Products (January 2020). Similar PMR safety studies have been required for approved CAR T-cell products.

DE presented the PMR to the CBER SWG on August 12, 2021 and the sponsor was notified that the registry study will be a PMR at the late cycle meeting on September 20, 2021.

5.2.2 Long-term follow-up study (Study 68284528MMY4002)

The sponsor proposes a Phase 4 long-term follow-up study of participants previously treated with ciltacabtagene autoleucel in sponsor performed clinical studies. The objectives of the study are:

Primary objective

- To collect long-term follow-up data on delayed adverse events after administration of cilta-cel, and to characterize and understand the long-term safety profile of cilta-cel.

Secondary objective

- To collect additional long-term data on replication competent lentivirus (RCL), product persistence, efficacy, and overall survival.

All subjects who received cilta-cel in the clinical studies performed by the sponsor will be offered enrollment into this study. There are no exclusion criteria. Follow-up for AEs will be performed for each subject up to 15 years after the last dose of cilta-cel. The primary endpoint is the number of subjects with delayed AEs associated with cilta-cel. The following AEs will be collected:

- New malignancies and recurrence of pre-existing malignancy
- New incidence or exacerbation of a pre-existing neurologic disorder
- New incidence or exacerbation of a pre-existing rheumatologic or other autoimmune disorder
- New incidence of Grade ≥ 3 hematologic disorder (for years 6 - 15, only serious hematologic disorder)
- New incidence of Grade ≥ 3 infection (for years 6 - 15, only serious infection)
- All serious adverse events (for years 6 - 15, only related serious AEs assessed by the Investigator)

Secondary endpoints include:

- Number of subjects with measurable RCL in peripheral blood
- Number of subjects with CAR transgene level above the lower limit of quantitation (LLOQ) in peripheral blood cells
- Assessment of the pattern of vector integration sites if $>1\%$ of cells in the blood sample or new malignancy are positive for the vector sequences
- Long term follow-up on CAR-T therapy efficacy if the subject does not have confirmed disease progression or does not initiate subsequent anti-myeloma therapy at the entry of the study and at any time during the study
- Overall survival

Subjects who develop disease progression and initiate subsequent anti-myeloma therapy prior to enrollment will not have AEs of hematologic disorders or infections collected unless the investigator considers the event related to cilta-cel.

There will be two phases of the study: within the first five years following the last dose of cilta-cel, and year 6 - 15 after the last dose. Subjects will have an onsite visit with the Investigator's site at least once per year in the first five years following the final dose of cilta-cel, during which the following will be performed:

- Collection of AEs by the subject for reporting to the investigator
- Physical exam
- Hematology and chemistry laboratory tests
- Blood test for RCL, vector integration site analysis, and CAR-T persistence per protocol indications
- Multiple myeloma disease status if the subject has not had confirmed disease progression prior to entering the study or in previous assessment, and the subject has not initiated anti-myeloma treatment after cilta-cel treatment
- Tests related to disease progression, if applicable.

Subjects in years 6 to 15 after the final dose of cilta-cel will be followed at least once per year via the Investigator or a Direct-to-Patient program. The follow-up could be during a site visit or performed remotely, and by a trained healthcare provider. The following information will be collected:

- Health status
- Most recent hematology and chemistry blood tests, if available
- Multiple myeloma disease status if the subject has not had confirmed disease progression prior to entering the study or in previous assessment, and the subject has not initiated anti-myeloma treatment after cilta-cel treatment
- AEs listed in primary endpoints

Ad hoc visits will be performed if a subject develops a new malignancy or recurrence of pre-existing malignancy, new or exacerbation of pre-existing neurologic disorder, new or exacerbation of prior rheumatologic or other autoimmune disorder, related SAE, or AE suggestive of cilta-cel associated disease.

Testing for CAR-T cell persistence will not be performed in the study if the CAR-T cells are not detectable at enrollment. Peripheral blood samples will be collected at least once per year for patients with detectable transgene, and will not be required again if the transgene becomes undetectable after enrollment. Vector integration site analysis will be conducted if at least 1% of cells in the blood sample are positive for vector sequence. RCL will be tested yearly; however, patients negative for RCL prior to enrollment or at any time during the study will be discontinued from RCL testing. If new malignancies occur, a biopsy of the neoplastic tissue or autopsy material will be collected if feasible for vector integration site analysis for possible insertional mutagenesis.

Reports of pregnancy and the outcome of pregnancy in female subjects or the partners of male subjects will be collected. Abnormal pregnancy outcomes including spontaneous abortion, fetal death, stillbirth, congenital anomalies and ectopic pregnancies are considered SAEs.

The study will report preliminary results in the annual safety update report such as the development safety update report or periodic benefit-risk evaluation report. Study results will be summarized and reported in a periodic clinical study report every three years. A final clinical study report will be issued at the end of the study. Please note that OBE/DE will defer to OTAT clinical team for review of the final study report for study 68284528MMY4002, LTFU for clinical trial subjects.

6 ANALYSIS OF SPONSOR'S PHARMACOVIGILANCE PLAN

6.1 Important Identified Risks

6.1.1 Cytokine Release Syndrome (including HLH)

CRS is a known risk of CAR-T products. It is due to the activation and expansion of CAR-T cells and production of cytokines. The clinical signs and symptoms of CRS include fever, rigors, chills, hypotension, hypoxia, and elevated liver enzymes. Inflammatory markers such as C-reactive protein, ferritin, and interleukin-6 are elevated. Severe CRS may manifest as hemophagocytic lymphohistiocytosis and macrophage activation syndrome. Patients may also have cardiac dysfunction and neurotoxicity. CRS was reported for most clinical trial subjects treated with Carvykti.

The sponsor is implementing a REMS to mitigate the risk of CRS to ensure that only qualified centers that are trained in the management of CRS and have immediate access to tocilizumab will receive the product. The REMS ensures that all healthcare providers who prescribe, dispense, or administer cilta-cel are aware of how to manage the risk of CRS through educational materials. Patients and their caregivers will be provided with a Patient Guide that has a removable Wallet Card that reminds them of the signs and symptoms of CRS that necessitate medical treatment. The label also has a boxed warning on CRS and guidance on the management of CRS.

Reviewer comment: The proposed PVP is appropriate to mitigate the risk of CRS.

6.1.2 Neurologic toxicities (including ICANS and other neurotoxicities)

Neurologic toxicity is associated with CAR-T therapies and may occur concurrently or following resolution of CRS. The cilta-cel clinical trials have reported CAR-T cell neurologic toxicities including both ICANS as well as other neurotoxicity. ICANS was reported for subjects in Study MMY2001 with symptoms that included aphasia, slow speech, dysgraphia, encephalopathy, depressed level of consciousness, and confusional state. Other neurotoxicity not defined as ICANS also occurred in Study MMY2001, with events that included disturbances of consciousness, coordination and balance disturbances, movement disorders, mental impairment disorders, cranial nerve disorders, and peripheral neuropathies.

There were also subjects (n = 5) in Study MMY2001 who presented with a similar presentation of movement and neurocognitive events that resembled Parkinson's disease. These patients presented at a later time than ICANS (median onset 27 days). Symptoms included micrographia, rigidity including cogwheel rigidity, tremors, memory loss, disturbance in attention, reduced facial expression, and flat affect. These events led to inability to work or care for oneself, and one subject died due to neurotoxicity. According to the sponsor, these cases were associated with high tumor burden, prior Grade 2 or higher CRS, prior ICANS, and high CAR-T cell expansion and persistence. However, risks factors cannot be clearly defined given the small number of cases and it is not clear if the mitigations introduced by the sponsor were effective. Per FDA request, the sponsor agreed to add enhanced pharmacovigilance activities including development of a data capture aid to collect structured information on these cases of movement and neurocognitive toxicity that will be triggered by a predefined list of MedDRA Preferred Terms, submission of spontaneous reports of this Parkinson-like syndrome to FAERS as an expedited report, and a discussion and analysis of these cases in the PAER (response to IR and revised PVP submitted to STN125746/0.26). The sponsor also agreed to include this Parkinson-like syndrome as a safety endpoint in the long-term follow-up study.

The sponsor is implementing a REMS to mitigate the risk of neurological toxicities to ensure that only qualified centers that are trained in the management of neurological toxicities will receive the product. The REMS ensures that all healthcare providers who prescribe, dispense, or administer cilta-cel are aware of how to manage neurological toxicities through educational materials. Patients and their caregivers will be provided with a Patient Guide that has a removable Wallet Card that reminds them of the signs and symptoms of neurological toxicities that necessitate medical treatment. The label also has a boxed warning on neurological toxicities and guidance on the management of neurological toxicities.

Reviewer comment: The Healthcare Facility REMS Training slides include a general description of the five cases with a Parkinson-like syndrome. However, additional clinical details and mitigations introduced by the sponsor should be included. Given the small number of cases (n = 5), it is difficult to definitively ascertain the risk factors and if the mitigation strategies were effective. OBE/DE will obtain input from OTAT clinical to provide comments to the sponsor to incorporate information on Parkinson-like syndrome neurotoxicity in the REMS materials (training slides, knowledge assessment, adverse reaction management guide) as applicable. Please see the final version of the REMS materials submitted by the sponsor for the final agreed-upon content and language. The sponsor's revised PVP (STN125746/0.26) that incorporates enhanced pharmacovigilance activities is acceptable to mitigate the risk of neurological toxicity. The sponsor also agreed to include this syndrome as a safety endpoint in the long-term follow-up post-marketing safety study.

6.1.3 Prolonged or recurrent cytopenia

Cytopenia may occur due to the underlying multiple myeloma disease or due to pretreatment with lymphodepleting agents. However, cytopenias have occurred in patients administered CAR-T cells in the absence of conditioning chemotherapy.

Cytopenia occurred in all study subjects in Study MMY2001 and Study MMY2003, including cases of prolonged Grade 3 and 4 cytopenia not resolved by day 30. Some patients have also experienced a recurrence of Grade 3 and 4 cytopenias, including one subject that required autologous stem cell transplant. Severe cytopenia may predispose to infections and bleeding. The risk for prolonged and recurrent cytopenia is included in the product labeling. The sponsor also agreed to enhanced pharmacovigilance for prolonged and recurrent cytopenias including submission of cases that require stem cell rescue and continued growth factor support and/or transfusion to FAERS as an expedited report and a summary and analysis of these cases in the PAER.

Reviewer comment: The revised PVP submitted to STN125746/0.43 is adequate. The sponsor should also add slides describing the occurrence of prolonged and recurrent cytopenias to the REMS Training Materials and include information in the Adverse Event Management Guide. OBE/DE will obtain input from OTAT clinical to provide comments to the sponsor to incorporate information on prolonged or recurrent cytopenia in the REMS materials (training slides, knowledge assessment, adverse reaction management guide) as applicable. Please see the final version of the REMS materials submitted by the sponsor for the final agreed-upon content and language.

6.1.4 Serious infections

Patients with multiple myeloma are at an increased risk of infections due to immunodeficiency from the underlying disease and treatment with corticosteroids, lymphodepleting agents, immunomodulatory agents, and stem cell transplantation. However, as noted above, CAR-T cells may be associated with cytopenias that may increase the risk of infections. Severe infections were reported in the clinical trial subjects administered cilta-cel. The clinical trials excluded patients with active bacterial, viral, uncontrolled systemic infections, and patients with active HBV as defined by positive HBV DNA, antibody or RNA positive or history of HCV, or seropositive for HIV.

The product labeling contains information regarding the risk of infection. A boxed warning states not to give Carvykti to patients with significant active infection.

Reviewer comment: The proposed PVP is adequate to mitigate the risk of infection.

6.2 Important Potential Risks

6.2.1 Second primary malignancy

There is a theoretical risk of second primary malignancy due to DNA integration of the lentiviral vector used to generate cilta-cel cells. Viral insertion to patient cells could disrupt a tumor suppressor gene or activate a proto-oncogene and cause a malignant transformation event. Second primary malignancies were reported for 10 (10.3%) subjects in Study MMY2001. The product labeling notes that patients treated with Carvykti may develop secondary malignancies. The sponsor is conducting a PMR long-term follow-up study for recipients in the post-market setting and a long-term follow-up study for clinical trial subjects.

Reviewer comment: Patients with multiple myeloma may have other risk factors for second primary malignancies such as high-dose alkylating therapy, lenalidomide maintenance therapy, other chemotherapy, radiation treatment, and certain genetic mutations. It is thus difficult to attribute some second primary malignancies to ciltacabtagene autoleucel without analysis for persistence of genetically modified T cells. The long-term follow-up studies in the clinical trial and post-market setting that incorporate testing tumor specimens for vector integration may help better characterize this risk. The sponsor's proposed PVP is appropriate to mitigate the potential risk of secondary malignancy and insertional mutagenesis.

6.2.2 Decrease in cell viability due to inappropriate handling or preparation of product

The cell viability and activity of cilta-cel may be impacted by disruption of controlled temperature conditions or issues with preservation, freezing, or thawing. Issues with the handling of the CAR-T cells may impact their therapeutic success. The sponsor states there were no such cases observed in the clinical trials. The sponsor proposes to perform reporting trend analysis of lack of efficacy and product quality complaints per PBRER/PSUR period.

Reviewer comment: The sponsor's proposed PVP for evaluation of decrease in cell viability due to preparation or handling issues is adequate.

6.3 Important Missing Information

6.3.1 Long-term safety

There are no data on the long-term safety of cilta-cel. It is possible that delayed onset AEs such as second primary malignancies, autoimmune disorders, or neurologic toxicities may occur. The sponsor plans to perform a long-term follow-up study (68284528MMY4002) of patients treated with cilta-cel in the clinical trials. The sponsor will also perform an observational post-marketing safety study (68284528MMY4004) to evaluate the long-term safety in real-world conditions.

Reviewer comment: The sponsor's proposed long-term follow-up studies are adequate to evaluate the long-term safety of the product.

6.3.2 Use in patients who are pregnant or breastfeeding

The clinical studies excluded women who were pregnant or breastfeeding. It is unknown whether cilta-cel has potential to cause fetal toxicity or is excreted in milk. Women treated with cilta-cel may have hypogammaglobulinemia which may impact neonatal immunity. The labeling notes no data are available on the use of Carvykti in pregnant or lactating women. Any reported pregnancies will be included in the long-term follow-up study of clinical trial subjects (68284528MMY4002) and the observational post-marketing safety study (68284528MMY4004).

Reviewer comment: The proposed PVP is appropriate to mitigate the risk of missing information regarding impact on pregnancy and lactation.

6.3.3 Use in patients with pre-existing autoimmune disease

The clinical studies excluded patients with active autoimmune disease or history of autoimmune disease within three years. New incidence or exacerbation of existing autoimmune disorder will be collected in the observational post-marketing safety study (68284528MMY4004) and the long-term follow-up study of clinical trial subjects (68284528MMY4002).

Reviewer comment: The sponsor's plan to collect information on autoimmune disorders in the post-market setting is acceptable.

6.3.4 Use in patients with pre-existing neurodegenerative disorders

The clinical studies excluded participants with clinical evidence of dementia or altered mental status. New incidence or exacerbation of existing neurologic disorders will be collected in the observational post-marketing safety study (68284528MMY4004) and the long-term follow-up study of clinical trial subjects (68284528MMY4002).

Reviewer comment: The sponsor's plan to collect information on neurologic disorders in the post-market setting is acceptable.

6.3.5 Use in patients with active CNS involvement by malignancy

Multiple myeloma patients with active or prior history of CNS involvement or those with signs of meningeal involvement were excluded from the clinical studies. The sponsor plans to collect information on new incidence or exacerbation of existing neurologic disorders in the observational post-marketing safety study (68284528MMY4004) and the long-term follow-up study of clinical trial subjects (68284528MMY4002). The labeling notes that patients with active or prior history of CNS disease may be more vulnerable to AEs.

Reviewer comment: It may be difficult to identify CAR-T associated neurotoxicity and distinguish from underlying disease if patients with CNS involvement are treated. The sponsor's plan to collect additional information on neurologic disorders in the post-market setting and labeling of the potential for increased AEs in patients with CNS disease is acceptable.

6.3.6 Use in patients with chronic controlled HIV and HBV/HCV infection

The clinical studies excluded patients with HIV, HBV, or HCV infection. New incidence of severe infection will be collected in the observational post-marketing safety study (68284528MMY4004) and the long-term follow-up study of clinical trial subjects (68284528MMY4002). The product labeling notes that HBV reactivation can occur in patients with hypogammaglobulinemia and that there is no experience with manufacturing Carvykti for patients with HIV, and active HBV or HCV.

Reviewer comment: The sponsor's PVP regarding use in patients with HIV, HBV, or HCV is acceptable.

7 DE ASSESSMENT

The safety concerns from the clinical trials warrant a REMS Program with ETASU to mitigate the risks of CRS and neurotoxicity and a PMR registry study to assess the serious risk of secondary malignancy. In addition, risks of treatment with Carvykti will be mitigated through risk communication and risk minimization measures as recommended in the USPI, including a Boxed Warning for the risks of CRS and neurotoxicity, and routine and enhanced pharmacovigilance activities. The sponsor will also conduct a long-term follow-up safety study for subjects treated with Carvykti in clinical trials and will test for transgene on all secondary malignancies where tissue is available in the long-term follow-up study. Patients in the long-term follow-up study will be followed for 15 years.

8 DE RECOMMENDATIONS

Should the product be approved, the sponsor's PVP (version 1.2, dated September 7, 2021) for Carvykti, which includes instituting a REMS program with ETASU to ensure that the benefits of the drug outweigh the risks of CRS and neurotoxicity, and conducting a required post-marketing registry long-term follow-up study (safety related PMR under FDAAA Title IX), and routine pharmacovigilance and AE reporting in accordance with 21 CFR 600.80, is adequate for post-market safety monitoring. The REMS program will require hospital sites to be specially certified and have on-site, immediate access to tocilizumab and healthcare provider training about the management of CRS and neurotoxicity. The PMR registry study will further assess the incidence and severity of the serious potential risk of secondary malignancy as well as other selected AEs, in patients treated with Carvykti in the post-market setting and will include 15-year follow-up of patients. The content of the REMS program materials should align with the package insert. Please see the final version of the REMS Document, REMS materials, and package insert submitted by the sponsor for the final agreed-upon content and language.

Appendix A

Table A1. Materials reviewed in support of this assessment

| Date | Source | Document Type | Document(s) Reviewed |
|--------------------|---------------|----------------------|--|
| March 31, 2021 | Sponsor | STN125746/0.2 | Module 1.16.1, Pharmacovigilance Plan |
| March 31, 2021 | Sponsor | STN125746/0.2 | Module 1.16.1, Draft Protocol 68284528MMY4002 |
| March 31, 2021 | Sponsor | STN125746/0.2 | Module 1.16.1, Draft Protocol 68284528MMY4004 |
| March 31, 2021 | Sponsor | STN125746/0.2 | Module 1.16.2.2, Draft REMS |
| March 31, 2021 | Sponsor | STN125746/0.2 | Module 1.14.1.3, Draft Labeling Text |
| February 2, 2021 | Sponsor | STN125746/0.1 | Module 2.5, Clinical Overview |
| February 2, 2021 | Sponsor | STN125746/0.1 | Module 2.7.4, Summary of Clinical Safety |
| July 21, 2021 | Sponsor | STN125746/0.21 | Module 1.11.3, Response to 15 July 2021 FDA Clinical Information Request Part 1 on prolonged and recurrent cytopenia |
| July 27, 2021 | Sponsor | STN125746/0.23 | Response to 15 July 2021 FDA Clinical Information Request Part 2 on prolonged and recurrent cytopenia |
| July 28, 2021 | Sponsor | STN125746/0.24 | Module 5.3.5.3, 120 Day Safety Update |
| July 30, 2021 | Sponsor | STN125746/0.26 | Module 1.11.3, Response to IR on revisions to pharmacovigilance plan and post-marketing registry study; Module 1.16.1, Revised Pharmacovigilance Plan; Module 1.16.1, Revised Draft Protocol 68284528MMY4004 |
| August 2, 2021 | Sponsor | STN125746/0.28 | Module 1.16.2, Revisions to REMS Core Document |
| August 11, 2021 | Sponsor | STN125746/0.32 | Module 1.11.3, Clinical Safety IR |
| August 16, 2021 | Sponsor | STN125746/0.35 | Module 1.16.2.2., Revisions to REMS Core Document |
| September 8, 2021 | Sponsor | STN125746/0.43 | Module 1.11.3, Response to IR on revisions to pharmacovigilance plan and post-marketing registry study; Module 1.16.1, Revised Pharmacovigilance Plan; Module 1.16.1, Revised Draft Protocol 68284528MMY4004 |
| September 20, 2021 | Sponsor | STN125746/0.46 | Module 1.11.3, Response to Clinical Information Request #32 |
| October 6, 2021 | Sponsor | STN125746/0.52 | Module 1.16.2.2, Revisions to REMS Core Document |