European Union Risk Management Plan
ciltacabtagene autoleucel

Data lock point for current RMP	27 Aug 2024	Version number	6.1

Final for Procedure EMEA/H/C/005095/II/0034: 25 April 2025 (CHMP opinion date)

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QPPV Name(s):	Dr. Laurence Oster-Gozet, PharmD, PhD
QPPV Signature:	The MAH QPPV has either reviewed and approved this RMP or approved with an electronic signature appended to this RMP, as applicable.

Details of this RMP Submission	
Version Number	6.1
Rationale for submitting an updated RMP (if applicable)	To consolidate changes related to T-cell malignancies that were submitted in RMP V5.4 with approved RMP V5.6
Summary of significant changes in this RMP:	Addition of important identified risk of "Secondary malignancy of T-cell origin". Change in important potential risk from "Secondary malignancy except secondary malignancy of myeloid origin" to "Secondary malignancies except those of T-cell and myeloid origin". An additional pharmacovigilance activity has been included for testing activity of secondary malignancies of T-cell origin. The additional risk minimization measure of HCP Educational Program has been modified to include the risks of secondary malignancy of T-cell origin and secondary malignancy of myeloid origin.

Other RMP Versions Under Evaluation:

RMP Version Number	Submitted on	Procedure Number
5.2	07 Nov 2024	EMEA/H/C/005095/II/0034
5.4	14 Feb 2024	EMEA/H/C/005095/II/0034

Details of the Currently Approved RMP:

Version number of last agreed RMP:	5.6
Approved within procedure	EMEA/H/C/005095/II/0036 PSUSA/00011000/202408
Date of approval (Competent authority opinion date)	27 March 2025 (CHMP opinion) 13 March 2025 (PRAC recommendation)

TABLE OF CONTENTS

PART I: PRODUCT(S) OVERVIEW

Active substance(s) **(INN or common name)**	JNJ-68284528 ciltacabtagene autoleucel
Pharmacotherapeutic group(s) (ATC Code)	Antineoplastic agents, other antineoplastic agents, ATC code: L01XL05
Marketing Authorization Applicant	Janssen, Inc.
Medicinal products to which the RMP refers	1
Invented name(s) in the European Economic Area (EEA)	CARVYKTI
Marketing authorization procedure	Centralized
Brief description of the product	Chemical class: B cell maturation antigen (BCMA) chimeric antigen receptor T cell (CAR-T) therapy
	Summary of mode of action: Ciltacabtagene autoleucel is a BCMA-directed, genetically modified autologous T-cell immunotherapy, which involves reprogramming a patient's own T cells with a transgene encoding a chimeric antigen receptor (CAR) that identifies and eliminates cells that express BCMA. BCMA is primarily expressed on the surface of malignant multiple myeloma B-lineage cells, as well as late-stage B cells and plasma cells. Upon binding to BCMA expressing cells, the CAR promotes T-cell activation, expansion, and elimination of target cells.
	Important information about its composition: Ciltacabtagene autoleucel is a genetically modified autologous cell-based product containing T cells transduced ex vivo using a replication incompetent lentiviral vector encoding an anti-BCMA CAR.
Reference to the Product Information	Module 1.3.1, Summary of Product Characteristics (SmPC), Labelling and Package Leaflet (PL)
Indication(s) in the EEA	Current: Ciltacabtagene autoleucel is indicated for the treatment of adult patients with relapsed and refractory multiple myeloma, who have received at least 1 prior therapy, including an immunomodulatory agent and a proteasome inhibitor, have demonstrated disease progression on the last therapy, and are refractory to lenalidomide.
	Proposed: Not applicable.

Dosage in the EEA	Current: The target dose is 0.75 x 10^6 CAR-positive viable T cells/kg of body weight (not exceeding 1 x 10^8 CAR-positive viable T cells). Patients 100 kg and below: 0.5 - 1 x 10^6 CAR-positive viable T cells/kg body weight. Patients above 100 kg: 0.5 - 1 x 10^8 CAR-positive viable T cells (non-weight based).	
	Proposed: Not applicable	
Pharmaceutical form(s) and strengths	Current: Ciltacabtagene autoleucel is available as dispersion for infusion. An infusion bag contains 30 mL or 70 mL of dispersion for infusion containing 3.2 x 10^6 to 1 x 10^8 CAR-positive viable T cells.	
	Proposed: Not applicable	
Is/will the product be subject to additional monitoring in the EU?	☑ **Yes**	☐ **No**

PART II: SAFETY SPECIFICATION

Module SI: Epidemiology of the Indication(s) and Target Population(s)

Indication: Multiple Myeloma

Incidence:

Multiple myeloma is a rare disease. Worldwide, an estimated 187,952 incidence cases of multiple myeloma were diagnosed in 2022, with a crude incidence rate of 2.3 cases per 100,000 persons and a world population age-standardized incidence rate of 1.8 cases per 100,000 persons (Ferlay 2024). There was a 126% increase in the global incidence of multiple myeloma between 1990 and 2016 (Cowan 2018). Variation in incidence of multiple myeloma is marked across countries; countries with older populations and greater access to diagnoses have more cases (Cowan 2018). The 3 world regions with the highest incidence rates of multiple myeloma were North America, Western Europe, and Australasia.

Among the 27 European Union (EU) countries, there were 35,333 cases of multiple myeloma estimated in 2022. The 2022 crude incidence rate was 7.9 cases per 100,000 persons, and the European population age-standardized incidence rate was 7.3 cases per 100,000 persons (European Cancer Information System 2024). Crude incidence rates ranged from 3.0 per 100,000 in Bulgaria to 11.3 per 100,000 in Denmark.

Prevalence:

In Europe, the 5-year prevalence of multiple myeloma was 538,948 persons (GLOBOCAN 2022). The 10-year prevalence of multiple myeloma in the 5 most populous countries in the EU – Germany, France, Italy, UK, and Spain – are available through the CancerMpact® Programme of Kantar Health, updated as of June 2022 (CancerMpact 2023). The 10-year prevalence estimates of multiple myeloma projected to 2022 for the 5 most populous EU countries are presented in Table SI.1.

Table SI.1: 10-year Prevalence of Multiple Myeloma in EU Countries

Country	10-year prevalence in 2022 (number)	10-year prevalence per 10,000 persons
France	24,678	3.76
Germany	33,857	4.04
Italy	24,815	4.12
Spain	12,401	2.62
United Kingdom	24,488	3.57
Total	**120,239**	**3.62**

The 10-year prevalence in Nordic countries is available from the NORDCAN project (NORDCAN 2022). The data extracted from the NORDCAN database is updated as of June 2022 and presented in Table SI.2.

Table SI.2: 10-year and Total Prevalence of Multiple Myeloma in Nordic Countries to the End of 2022 from NORDCAN Project

Country	10-year prevalence (number)	10-year prevalence per 10,000 persons	Total prevalence (number)	Total per 10,000 Persons
Denmark	3,298	5.56	3,833	6.47
Finland	1,871	3.36	2,348	4.22
Iceland	169	4.36	201	5.19
Norway	2,824	5.14	3,349	6.10
Sweden	4,581	4.35	5,469	4.35
Nordic countries	**12,743**	**4.57**	**15,200**	**5.45**

Demographics of the Population in the Proposed Indication - Age, Sex, Racial and/or Ethnic Origin and Risk Factors for the Disease

Age:

Myeloma incidence is strongly related to age, with the elderly experiencing the highest incidence rates. The median age at diagnosis is approximately 70 years; 37% of patients are younger than 65 years, 26% are between the ages of 65 and 74 years, and 37% are 75 years of age or older (Palumbo 2011). In the United Kingdom (UK), between 2017 and 2019, more than 4 in 10 new cases (43%) were in people aged 75 and over. Age-specific incidence rates rise from age 35 to 39 more steeply for males than females and drop in the oldest age groups. The highest rates are in the 80 to 84 years age group for females and the 85 to 89 age group for males. The gap is widest at age 90+, when the age-specific incidence rate is 2.1 times lower for females than males (Cancer Research UK 2024). A population-based study that included multiple myeloma data from 4,904 patients during 2008 to 2015 in Sweden observed a median age at diagnosis of 71 years, and 72% of patients were older than 65 years (Blimark 2018).

Sex:

Multiple myeloma is more common in men than women. Globally, the age standardized incidence rate of multiple myeloma was estimated to be 2.1 per 100,000 in men and 1.4 per 100,000 in women in 2018 (Bray 2018). In the UK, 58% of myeloma cases are in men and 42% are in women (Cancer Research UK 2024).

Racial and ethnic origin:

The incidence of multiple myeloma is 2 to 3 times higher in black individuals than in white individuals but is lower in Asian and Hispanic individuals (Kumar 2017). In the UK between 2002 and 2006, age-standardized rates for white men with myeloma ranged from 6.1 to 6.5 per 100,000. Rates for Asian men were similar, ranging from 3.6 to 6.4 per 100,000, whereas the rates for black men were significantly higher, ranging from 10.9 to 18.2 per 100,000. For women there was a similar pattern: the age-standardized rates for white women ranged from 3.9 to 4.2 per 100,000. Rates for Asian women were similar, ranging from 2.3 to 4.4 per 100,000, whereas the rates for black women were significantly higher, ranging from 6.6 to 11.5 per 100,000 (Cancer Research UK 2019). Similarly, in the US, the Surveillance, Epidemiology, and End Results (SEER) Program incidence rates from 2013 to 2021 ranged from 14.0 to 14.6 and from 6.2 to 6.4 per 100,000 person-years for blacks and whites, respectively (SEER 2024).

Risk Factors for the Disease:

Risk factors for developing multiple myeloma include the following: age (the risk of multiple myeloma increases with increasing age); sex (men are slightly more likely to develop multiple myeloma than women); race (multiple myeloma is more than twice as common among blacks compared with whites); radiation (exposure to radiation may increase the risk of multiple myeloma); family history (an individual who has a sibling or parent with multiple myeloma is 4 times more likely to develop the disease than expected, but this represents only a minority of myeloma cases); workplace exposures (some studies have suggested that workers in certain petroleum-related industries may be at a higher risk); obesity (being overweight or obese increases a person's risk of developing myeloma); and other plasma cell diseases (people with monoclonal gammopathy of undetermined significance [MGUS] or solitary plasmacytoma have a higher risk of developing multiple myeloma) (American Cancer Society 2018; Normandin 2018).

Main Existing Treatment Options:

Treatment options for multiple myeloma have substantially improved over time and vary depending on the aggressiveness of the disease, underlying prognostic factors, physical condition of the patient, and existing co-morbidities (Moreau 2017). The introduction of PIs (eg, bortezomib, carfilzomib, and ixazomib), histone deacetylase inhibitors (eg, panobinostat, vorinostat), immunomodulatory agents (eg, thalidomide, lenalidomide, and pomalidomide), and monoclonal antibodies (eg, daratumumab, isatuximab, and elotuzumab) have allowed numerous therapeutic avenues for patients with multiple myeloma. Despite these therapeutic achievements, the disease recurs and remains incurable, thus warranting the need for novel therapeutic approaches (Pinto 2020).

Types of drugs used to treat multiple myeloma often used in varying combinations include the following (American Cancer Society 2020a): chemotherapeutic agents (melphalan, vincristine, cyclophosphamide, etoposide, bendamustine, and doxorubicin); histone deacetylase inhibitors (panobinostat); monoclonal antibodies (daratumumab, isatuximab, and elotuzumab); corticosteroids (dexamethasone and prednisone, among others), an important part of the treatment of multiple myeloma that can be used alone or combined with other drugs, and also help decrease the nausea and vomiting that other chemotherapy agents may cause; IMiDs (thalidomide, lenalidomide, and pomalidomide); PIs (bortezomib, ixazomib, and carfilzomib); nuclear export inhibitor (selinexor); bispecific antibodies (teclistamab, talquetamab, elranatamab); other CAR-T products (idecabtagene vicleucel).

In a multicenter study of 543 patients with triple-class exposed IMiD- and PI-refractory multiple myeloma who also had been treated with an alkylating agent, the median overall survival (OS) was 13 months (95% confidence interval [CI], 11-15 months). In a 2016 retrospective analysis investigating the outcomes in a similar patient population, the OS was poor despite the availability of newer agents, with a median OS of approximately 8 months. Furthermore, a 2018 retrospective analysis demonstrated that patients with multiple myeloma that is penta-refractory to bortezomib, lenalidomide, carfilzomib, pomalidomide, and daratumumab had a median OS of only 5.6 months. Patients relapsed after prior therapy with IMiDs and bortezomib, showing that that the median OS and event-free survival were 9 months and 5 months, respectively. For patients with relapsed or

refractory multiple myeloma, combination regimens have generally been preferred to monotherapy (Mikhael 2020). The only available options in similar populations are the most recently approved. Selinexor, which was approved based on the STORM study (n=122), had a response rate of 26.2%, complete responses (CR) or stringent complete responses (sCR) of 1.6%, very good partial response (VGPR) or better of 6.4%, and median progression-free survival (PFS) of 3.7 months (and 8.9% incidence of fatal adverse events) (Chari 2019).

The 2021 EHA-ESMO guidelines for triple class refractory multiple myeloma suggest using selinexor, a selective inhibitor of XOP1-mediated nuclear export, with dexamethasone as a treatment option (Dimopoulos 2021). This is based on results from the Phase 2 STORM study which showed that selinexor in combination with several standard therapies was more effective than other treatments for relapsed or refractory multiple myeloma. Idecabtagene vicleucel is an anti-BCMA CAR-T therapy indicated for treating relapsed or refractory multiple myeloma in adult patients who have undergone 4 or more prior lines (in EU, after 3 or more prior lines) of therapy, including an IMiD, a PI, and an anti-CD38 monoclonal antibody. It has shown an ORR of 72% and median DOR of 11.0 months. In August 2022, teclistamab received authorization for the treatment of relapsed/refractory multiple myeloma in patients who have received treatment with 3 prior therapies in the EU and 4 prior therapies in the US.

Melphalan flufenamide is authorized in the EU for treating multiple myeloma in adults who have received at least 3 prior therapies, including an IMiD, a PI, and an anti-CD38 antibody and whose disease has worsened since the last treatment. If the cancer relapses after at least 3 years after ASCT, melphalan flufenamide can be used. In 2023, talquetamab and elranatamab were also approved in the EU for treating relapsed and refractory multiple myeloma in adults who have received at least 3 prior therapies, including an IMiD, a PI, and an anti-CD38 antibody and whose disease has worsened since the last treatment.

Natural History of the Indicated Condition in the Untreated Population, Including Mortality and Morbidity:

Multiple myeloma is the 16th most common cause of cancer death in Europe, with approximately 30,860 deaths from multiple myeloma in 2018 (1.7% of total cancer deaths) (Bray 2018). Worldwide, there were 106,105 deaths (1.1% of total cancer deaths) from multiple myeloma reported in 2018. The age standardized mortality rate of multiple myeloma in Europe was estimated to be 2.2 per 100,000 in 2012 (Ferlay 2013). The age-standardized mortality rate worldwide was estimated at 1.0 per 100,000 (Ferlay 2015). In the UK, the 5-year net relative survival for myeloma patients in 2019 was 49.5% (for all ages) and decreases with age, being approximately 61% for 60 to 69 years-old, approximately 43% for 70 to 79 years-old, and approximately 32% among those 80+ years-old (Haematological Malignancy Research Network 2022).

Multiple myeloma is a cytogenetically heterogeneous clonal plasma cell proliferative disorder and is almost always preceded by an asymptomatic premalignant stage termed MGUS. MGUS is present in roughly 3% to 4% of the population over the age of 50 years. The diagnosis of MGUS requires the absence of hypercalcemia, renal failure, anemia, and bone lesions (referred to as

CRAB features) that can be attributed to the underlying plasma cell disorder. The rate of progression of MGUS to multiple myeloma is 0·5–1% per year, but the precise risk is affected by the concentration of the monoclonal protein, type of monoclonal protein, serum free light chain ratio, bone marrow plasmacytosis, proportion of phenotypically clonal plasma cells, and presence of immunoparesis (Rajkumar 2014). Over time, MGUS has the potential to evolve into smoldering (asymptomatic) multiple myeloma (SMM), which then progresses into multiple myeloma (Bird 2019).

Anticipated adverse events in this population as multiple myeloma progresses includes infections, cytopenia, renal failure, osteolytic bone disease, hypercalcemia, and hyper viscosity. Overall, multiple myeloma patients had a 7-fold risk of developing any infection compared to matched controls. The increased risk of developing a bacterial infection was 7-fold (7.1; 6.8-7.4), and for viral infections 10-fold (10.0; 8.9-11.4). The spectrum of micro-organisms isolated during a febrile episode changes in the course of the disease. In early stage myeloma, the most common infections involve the respiratory tract, manifesting as bronchitis and pneumonia. These infections are predominantly caused by Haemophiles influenza or Streptococcus pneumoniae (Blimark 2015). In a population-based study of 9,253 multiple myeloma patients and 34,931 controls in Sweden, multiple myeloma patients had an almost 15-fold (hazard ratio [HR]=14.8; 95% CI: 12.1-18.2) increased risk of Herpes zoster compared to matched controls. Pancytopenia in multiple myeloma may be attributed to several reasons. Most often it is due to the plasma cell proliferation replacing normal hematopoietic cells. Other causes include fas-ligand mediated apoptosis or cytokine-mediated bone marrow failure or even renal failure induced erythropoietin deficiency. A study reported pancytopenia in 9% of multiple myeloma patients; however, they also reported 71% of patients having hemoglobin of <8.5g/dL and thrombocytopenia of <100 x 10^9/L in 16.4% cases (Sridevi 2015).

Symptomatic myeloma causes neutropenia in 6% of patients at diagnosis (Augustson 2005). As a secondary source, a study noted that symptomatic myeloma causes thrombocytopenia in 14% of patients at diagnosis. Thrombocytopenia (<100,000/µL) at presentation was 13% and 5% in 2 reviews of 869 and 1,027 multiple myeloma patients, respectively, from the Mayo Clinic (Kyle 2003). In a study of 3,107 newly diagnosed multiple myeloma patients entered into UK Medical Research Council multiple myeloma studies from 1980 to 2002, 299 patients died within 60 days of study entry (Augustson 2005). Among these 299 patients, 25% had platelets <150 x10^9/L compared with 14% in survivors, and thrombocytopenia was definitely implicated in 3 of the bleeding-related deaths. Anemia is a common feature of myeloma and its treatment and may already be present in most multiple myeloma patients at the time of diagnosis, due to which the exact incidence of anemia among patients with multiple myeloma is unknown. In the European Cancer Anemia Survey that included 704 patients with multiple myeloma, 69.2% of patients were anemic at enrollment, while the proportion who were anemic at any time during the study period, including the time of enrollment, was 85.3% (Birgegård 2006).

A review summarized that renal insufficiency (serum creatinine of >1.3 mg/dL) is found in almost 50% of patients with multiple myeloma at presentation, and severe renal insufficiency (serum creatinine >2.0 to 2.5 mg/dL) is observed in 15% to 20% of cases (Korbet 2006). Since myeloma

patients are mostly elderly and have less muscle mass, the actual prevalence of renal insufficiency may be underestimated with the use of serum creatinine. In a study of 756 newly diagnosed patients with multiple myeloma included in the Greek Myeloma Study Group, 21% of patients presented with renal failure, ie, serum creatinine ≥2 mg/dL at the time of diagnosis (Eleutherakis-Papaiakovou 2007). Multiple myeloma is a disease with the highest incidence of bone involvement among the malignant diseases. A study from Denmark showed that multiple myeloma patients had 2-fold increase in risk of fractures (OR=1.96; 95% CI: 1.50-2.57) compared to controls (Thorsteinsdottir 2020). A review summarized that 13-30% of myeloma patients are affected by hypercalcemia.

Hyper viscosity syndrome is a rare complication of multiple myeloma that occurs most frequently in immunoglobulin G (IgG) myeloma, with a reported incidence of 4.2% (Kistler 2017). Another report summarized that symptomatic hyper viscosity cases are seen in 2% to 6% of patients with multiple myeloma (Coppola 2011). In a review of 1,027 patients with multiple myeloma at the Mayo Clinic, serum viscosity was found to be increased in 76% of the 91 patients in whom it was assessed, and it was 4 centipoises or more in 7%. However, the authors suggested that the true frequency of hyper viscosity is likely to be much lower as patients selected for viscosity measurement were those with high serum M protein values or those who had symptoms suggestive of the hyper viscosity syndrome (Kyle 2003).

The aggressiveness of multiple myeloma depends upon several variables that impact disease biology. Genetic abnormalities seen in the myeloma cells are one of the strongest predictors of tumor aggressiveness. As such, all newly diagnosed multiple myeloma patients are classified as having high, intermediate, or standard risk disease based upon tumor genetics. Approximately 25% of people with multiple myeloma have high-risk disease based on cytogenetic testing. Patients who lack high or intermediate risk genetic abnormalities are considered to have standard risk multiple myeloma. With modern therapy, patients with standard risk multiple myeloma have an estimated median survival of 8 to 10 years (Rajkumar 2018).

The Revised International Staging System ([R-ISS] (Udupa 2020) divides myeloma into 3 stages incorporating cytogenetic abnormalities and lactate dehydrogenase (LDH) in addition to the parameters in ISS. For patients with R-ISS stage I, the median OS was not reached and the median PFS was 66 months, compared with OS and median PFS of 83 months and 42 months, respectively, for patients with R-ISS stage II and OS and median PFS of 43 and 29 months, respectively, for patients with R-ISS stage III (Palumbo 2015).

Important Co-morbidities:

Patients with multiple myeloma tend to be elderly, and therefore, subject to age-related comorbidities. For instance, the elderly population may be at an increased risk of chronic diseases includes ischemic cardiovascular disease, cerebrovascular disease, chronic obstructive pulmonary disease (COPD), diabetes, cancer, degenerative central nervous system (CNS) diseases, and depression.

PART II: SAFETY SPECIFICATION

Module SII: Nonclinical Part of the Safety Specification

Key Safety Findings	Relevance to Human Usage
Toxicity	
Single & repeat-dose toxicity	
No toxicities observed in any measured parameters in a single dose pilot cynomolgus monkey study (n=2). No repeat-dose toxicity studies were conducted.	The potential off-target toxicity of ciltacabtagene autoleucel was assessed in this study. Cynomolgus monkeys are not considered a pharmacologically relevant species. In addition, no assessments were conducted on monkey CAR-T cells after manufacturing or prior to dosing, including no assessment of T cell viability, T cell purity, transduction efficiency, or functionality of the cells. It's possible that a limited number of CAR+ cells were administered since the introduction of the CAR followed human-specific protocols that may not be optimal for cynomolgus monkeys. Therefore, there is limited value in this study.
Reproductive toxicity	
No reproductive toxicity studies were conducted with ciltacabtagene autoleucel because there is no relevant nonclinical species for these assessments. Reproductive toxicity studies (eg, fertility and early embryonic development studies) are generally not applicable to therapies for advanced cancer indications (ICH S9)	Expression of BCMA in reproductive tissues was studied in an examination of 33 tissues for BCMA protein by immunohistochemistry using a commercially available polyclonal antibody. BCMA was not detected in female reproductive organs such as uterus, fallopian tubes, ovary, and placenta, or in male reproductive organs such as prostate and testis (Carpenter 2013). Impact on pregnancy and lactation is considered missing information for the clinical program.
Developmental toxicity	
No developmental toxicity studies were conducted with ciltacabtagene autoleucel. Developmental toxicity studies (pre- and post-natal development studies) are generally not applicable to therapies for advanced cancer indications (ICH S9); however, an assessment of embryo-fetal development toxicity is needed to support marketing applications [ICH S5(R3) and ICH M3(R2)]	Developmental toxicity, including pregnancy and lactation, was not assessed in nonclinical studies; impact on pregnancy and lactation is considered missing information. Although it is not known whether ciltacabtagene autoleucel can traffic from mother to child, T cells can traffic across the placenta (Kinder 2017) and through breastmilk (Moles 2018). However, the role of the relative contribution of maternal and child T cells to immune education in the child is not fully understood (Cosgrove 2019).

Key Safety Findings	Relevance to Human Usage
Genotoxicity	
Routine genotoxicity studies are generally not applicable to biological pharmaceuticals as large proteins cannot diffuse into cells and cannot interact with DNA or chromosomal material (ICH S6). In an Integration Site Analysis (ISA) of pre-infusion ciltacabtagene autoleucel, no lentivirus integration site patterns with preferential insertion near genes of concern were reported.	Ciltacabtagene autoleucel leverages a third-generation self-inactivating lentiviral vector (SIN LVV) packaging system that supports a low risk of generating replication competent lentivirus (RCL) or secondary malignancies. Despite the safety features of the third-generation, SIN LVV system, the use of LVV for gene delivery continues to be a theoretical safety concern because of the potential for generation of RCL and insertional mutagenesis mainly described in autologous hematopoietic stem cell gene therapy with gamma retroviral vectors. With the third generation LVV, there is a small risk that clonal expansions can occur when LVVs integrate within known oncogenes (Maldarelli 2014) and potentially trigger secondary malignancies. In addition, the presence of RCLs could theoretically increase the incidence of insertional mutagenesis in patients through ongoing cycles of viral replication and insertion into the host DNA. Thus far, no RCLs have been detected in any of the GMP LVV batches used in the manufacture of ciltacabtagene autoleucel, indicating that RCLs do not present an additional risk of insertional mutagenesis by ciltacabtagene autoleucel. Insertional mutagenesis was addressed in a lentivirus integration site analysis study where 10 ciltacabtagene autoleucel drug products (7 manufactured from patients, 3 manufactured from healthy donor cells) were analyzed. The results indicate LVV insertional sites within the genome demonstrated a highly polyclonal integration profile and no signs of preferential integration near cancer-associated genes. Based on the nonclinical data, ciltacabtagene autoleucel is not expected to induce clonality or insertional mutagenesis in humans; however, there is a theoretical risk of generation of secondary malignancies and generation of RCL. Based on clinical data, secondary malignancy of T-cell origin and secondary malignancy of myeloid origin are considered important identified risks for ciltacabtagene autoleucel, and secondary malignancy except those of T-cell and myeloid origin is considered an important potential risk.
Carcinogenicity	Ciltacabtagene autoleucel is not expected to be carcinogenic in humans.

Key Safety Findings	Relevance to Human Usage
No standard carcinogenicity studies were conducted with ciltacabtagene autoleucel. Standard carcinogenicity studies are generally not applicable to therapies for advanced cancer indications (ICH S9).	Based on clinical data, secondary malignancy of T-cell origin and secondary malignancy of myeloid origin are important identified risks for ciltacabtagene autoleucel. Secondary malignancies except those of T-cell and myeloid origin is considered an important potential risk. All 3 are being monitored clinically based on the theoretical risk of insertional mutagenesis (see Genotoxicity section).
Other toxicity-related information or data	
In vitro Binding Characterization	
The potential for off-target binding was evaluated in an in vitro plasma membrane protein array (Retrogenix™) screen. A binding interaction between ciltacabtagene autoleucel and BCMA (TNFRSF17) was observed as expected but there was also a binding interaction observed between ciltacabtagene autoleucel and claudin 9 (CLDN9). Orthogonal assays were conducted to determine reproducibility and potential biological significance. The orthogonal assays demonstrated that there was no binding to myeloid cells that endogenously express CLDN9 from healthy donors.	The lack of binding interaction with CLDN9 on primary immune, donor-derived cells with physiological natural expression of CLDN9 suggests a low risk of off-target functional consequences in treated patients.
Cytokine release assay Ciltacabtagene autoleucel was evaluated for potential to stimulate release of cytokines when co-cultured with cell lines that express BCMA and control cell lines that do not express BCMA. Results with ciltacabtagene autoleucel demonstrate IFN-γ was BCMA dependent and no detectable cytokine release on cell lines that do not express BCMA.	Cytokine release is mechanism-based toxicity commonly observed and expected with CAR-T cell therapy and is managed clinically. In vitro data demonstrate BCMA-dependent cytokine release.
In Vitro Cytokine Independent Growth Assay Ciltacabtagene autoleucel was evaluated for the potential to acquire the ability to proliferate in the absence of exogenous IL-2 supplementation and if ciltacabtagene autoleucel acquired enhanced proliferation compared to donor-matched untransduced primary T cells. Ciltacabtagene autoleucel did not acquire the ability to proliferate in the absence of	These results indicate the integration of LVV into the primary T cell genome during transduction does not lead to cytokine independent growth of ciltacabtagene autoleucel.

Key Safety Findings	Relevance to Human Usage
exogenous IL-2 supplementation nor did ciltacabtagene autoleucel exhibit enhanced proliferation compared to donor-matched untransduced primary T cells cultured under similar conditions.	
Replication Competent Lentivirus (RCL) The lentivirus is designed to be replication incompetent however the generation of RCL following infusion of the CAR-T cells remains a theoretical risk and cannot be excluded. Third-generation LVVs have several built-in safety features that minimize the risk of generating replication-competent wild-type human HIV-1 recombinants and increase the incidence of insertional mutagenesis. The LVV used for the transduction of T cells are generated by *trans*-complementation whereby packaging cells are co-transfected with a transfer plasmid, pLLV-LICAR2SINKanR(2), that expresses the CAR with specificity for BCMA, and the packaging and helper plasmids that encode only the proteins essential for LV assembly and function (Mátrai 2010). The helper plasmids include a plasmid encoding lentiviral proteins Gag and Pol, another encoding lentiviral protein Rev, and the third plasmid encoding the VSV-G envelope glycoprotein (Dull 1998). Segregating these proteins across 3 plasmids minimizes the probability of generating RCL by recombination.	RCL can only be formed if there are multiple low-probability recombination events. The presence of RCLs could theoretically increase the incidence of insertional mutagenesis in patients through ongoing cycles of viral replication and insertion into the host DNA. Consequently, there is a risk of generation of RCL and generation of secondary malignancy due to the theoretical risk of insertional mutagenesis. Based on clinical data, secondary malignancy of T-cell origin and secondary malignancy of myeloid origin are considered important identified risks for ciltacabtagene autoleucel. Secondary malignancy except those of T-cell and myeloid origin is considered an important potential risk. In the ongoing and future clinical trials, a VSVG DNA assay is performed as a surrogate for RCL on ciltacabtagene autoleucel and is performed as a safety-related release assay on the drug product.

Summary of Nonclinical Safety Concerns

Important identified risks	Secondary malignancy of T-cell origin
	Secondary malignancy of myeloid origin
Important potential risks	Secondary malignancy except those of T-cell and myeloid origin
	Generation of RCL
Missing information	Impact on pregnancy and lactation

PART II: SAFETY SPECIFICATION

Module SIII: Clinical Trial Exposure

SIII.1. Brief Overview of Development

The safety of ciltacabtagene autoleucel (JNJ-68284528) has been demonstrated in 3 clinical trials. In the initial Marketing Authorization Application for ciltacabtagene autoleucel, 2 clinical trials were used to support the safety of ciltacabtagene autoleucel in patients with multiple myeloma: Trials 68284528MMY2001 and 68284528MMY2003. To provide additional support for the safety of ciltacabtagene autoleucel and to expand the existing indication, additional data are presented from clinical trial 68284528MMY3002. These trials are described below.

The full protocol number for all trials in this Risk Management Plan (RMP) begins with the prefix of "68284528" (the applicant's internal reference number). For brevity, these trials are referred to throughout the RMP without the numeric prefix (eg, Trial 68284528MMY2001 is referred to as Trial MMY2001).

- **Phase 1b/2 Trial MMY2001** (pivotal trial) is an open-label, multicenter trial to evaluate the safety and efficacy of ciltacabtagene autoleucel (autologous CAR-T cells) in adult patients with relapsed/refractory multiple myeloma. Patients had received at least 3 prior lines of therapy or were double refractory to an IMiD and a PI and had received as part of prior therapy an IMiD, a PI, and an anti-CD38 antibody. Patients receive a conditioning regimen of cyclophosphamide 300 mg/m^2 intravenously (IV) daily and fludarabine 30 mg/m^2 IV daily for 3 days, followed by administration of ciltacabtagene autoleucel 5 to 7 days after start of the conditioning regimen. Ciltacabtagene autoleucel is administered as a single infusion at a total targeted dose of 0.75 x 10^6 CAR-positive viable T cells/kg (range: 0.5-1 x 10^6 cells//kg). The RMP dataset for MMY2001 is based on a clinical cutoff date of 11 January 2022 (except where otherwise noted), and includes data from 97 subjects in the US and 9 subjects in Japan.
- **Phase 2 Trial MMY2003** (supportive trial) is an open-label, multicohort, multicenter trial to determine whether treatment with ciltacabtagene autoleucel results in minimal residual disease (MRD) negativity in adult patients with multiple myeloma in multiple-parallel cohorts enrolling patients with unmet medical need. Patients are enrolled into 1 of 6 cohorts based on eligibility criteria. Patients receive a conditioning regimen of cyclophosphamide 300 mg/m^2 IV daily and fludarabine 30 mg/m^2 IV daily for 3 days, followed by administration of ciltacabtagene autoleucel 5 to 7 days after the start of the conditioning regimen. Ciltacabtagene autoleucel is administered as a single infusion at a total targeted dose of 0.75 x 10^6 CAR-positive viable T cells/kg (range: 0.5-1 x 10^6 cells/kg) for all cohorts. The patient populations for the 6 cohorts are described below. The clinical cutoff dates and the numbers of subjects included in the RMP dataset for MMY2003 are as follows: 2 November 2022 for Cohort A (n=43), 1 June 2022 for Cohort B (n=19), and 17 December 2021 (ie, the same cutoff date as prior RMPs) for Cohorts C (n=20), D (n=10), and E (n=2). No subjects have been enrolled into Cohort F as of the 17 December 2021 clinical cutoff date.
  - Cohort A: progressive disease after 1 to 3 prior lines of therapy, including a PI and IMiD either individually or in combination. Patients are required to be refractory to

lenalidomide. Patients who have received prior therapy that is targeted to BCMA are excluded from this cohort.

- Cohort B: one line of previous therapy containing a PI and an IMiD and early relapse defined as disease progression ≤12 months after an autologous stem cell transplantation (ASCT) or ≤12 months after the start of front-line therapy for patients who have not had an ASCT. Patients who have received prior therapy that is targeted to BCMA are excluded from this cohort.
- Cohort C: relapsed or refractory disease in patients previously treated with a PI, an IMiD, an anti-CD38 monoclonal antibody, and a BCMA-directed therapy (excluding cellular immunotherapy).
- Cohort D (ciltacabtagene autoleucel plus lenalidomide): multiple myeloma without complete response after 4 to 8 total cycles of initial therapy, including induction, high-dose chemotherapy, and ASCT with or without consolidation.
- Cohort E (daratumumab, bortezomib, lenalidomide, and dexamethasone induction, then ciltacabtagene autoleucel, then lenalidomide): Patients with high risk, newly diagnosed and untreated multiple myeloma for whom hematopoietic stem cell transplant is not planned as initial therapy.
- Cohort F: newly diagnosed multiple myeloma subjects with standard risk disease and an overall response ≥VGPR after 4 to 8 total cycles of initial therapy.

- **Phase 3 Trial MMY3002** is a Phase 3, randomized, open-label, multicenter trial in patients with relapsed and lenalidomide-refractory multiple myeloma treated with 1 to 3 prior lines of therapy. Patients were randomized to receive PVd or DPd (Arm A; investigator's choice) or to receive ciltacabtagene autoleucel (Arm B). Patients in Arm A received either PVd in 21-day cycles (pomalidomide PO 4 mg/day, bortezomib SC 1.3 mg/m^2, dexamethasone PO 20 mg/day) or DPd in 28-day cycles (daratumumab SC 1800 mg, pomalidomide PO 4 mg/day, dexamethasone PO or IV 40 mg weekly). Patients in Arm B received bridging therapy of PVd or DPd (consistent with administration outlined above for Arm A), conditioning regimen (cyclophosphamide IV 300 mg/m^2 and fludarabine IV 30 mg/m^2), and ciltacabtagene autoleucel (0.75 x 10^6 CAR positive viable T cells/kg). The RMP dataset for MMY3002 is based on a clinical cutoff date of 1 May 2024 (except where otherwise noted) and includes data from 196 subjects who received ciltacabtagene autoleucel, either as study treatment (N=176) or as subsequent therapy (N=20). Risk tables also provide data from the comparator (ie, Arm A; n=208).

SIII.2. Clinical Trial Exposure

Exposure in Randomized Trials

The randomized trials population includes Trial MMY3002. Exposure to ciltacabtagene autoleucel in randomized trials is summarized in Table SIII.1 by age and sex, and in Table SIII.2 by special population (eg, renal impairment at baseline, hepatic impairment at baseline). Exposure by duration and dose are not included, as all subjects received a single infusion of CAR-T cells.

Table SIII.1: Exposure by Age Group and Gender; Randomized Clinical Trials Using Ciltacabtagene Autoleucel - Subjects Treated with Ciltacabtagene Autoleucel

	Men	Women
Age Group	Persons	Persons
Multiple Myeloma		
<30	0	1
30-54 years	35	24
55-64 years	30	28
65-74 years	45	27
75-84 years	2	4
>=85 years	0	0
Total	112	84

Note: The following trials are included: MMY3002 (Arm B, N = 196).

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Table SIII.2: Exposure by Special Populations; Randomized Clinical Trials Using Ciltacabtagene Autoleucel - Subjects Treated with Ciltacabtagene Autoleucel

Population	Persons
Multiple Myeloma	
Renal impairment at baseline	
Normal (CrCl ≥ 90 mL/min)	103
Mild (CrCl 60 to < 90 mL/min)	67
Moderate (CrCl 30 to < 60 mL/min)	26
Severe (CrCl < 30 mL/min)	0
Missing	0
Total	196
Hepatic impairment at baseline[a]	
Normal (Total bilirubin ≤ ULN and AST ≤ ULN)	174
Mild (Total bilirubin ≤ ULN and AST > ULN, or Total bilirubin ULN < Total bilirubin ≤ 1.5 x ULN)	19
Moderate (1.5 x ULN < Total bilirubin ≤ 3 x ULN)	3
Severe (Total bilirubin > 3 x ULN)	0
Missing	0
Total	196
Race	
White	150
Black or African American	6
Asian	15
Other[b]	25
Total	196
Ethnicity	
Hispanic or Latino	17
Not Hispanic or Latino	144
Not Reported	35

Table SIII.2: Exposure by Special Populations; Randomized Clinical Trials Using Ciltacabtagene Autoleucel - Subjects Treated with Ciltacabtagene Autoleucel

Population	Persons
Total	196

Keys: CrCl = creatinine clearance; ULN = upper limit normal; ALT = alanine aminotransferase; AST = aspartate aminotransferase.
[a] Per NCI Organ Dysfunction criteria.
[b] Other includes American Indian or Alaska native, Native Hawaiian or other Pacific islander, and unreported.
Note: Baseline is defined as the last non-missing evaluation prior to ciltacabtagene autoleucel infusion.
Note: The following trials are included: MMY3002 (Arm B, N = 196).
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Exposure in All Clinical Trials

The all clinical trials population includes 3 trials:

- Trial MMY2001
- Trial MMY2003
- Trial MMY3002

Exposure to ciltacabtagene autoleucel in the all clinical trials population is summarized in Tables SIII.3 and SIII.4, respectively, for all subjects by age and sex, and by special population (eg, renal impairment at baseline, hepatic impairment at baseline). Exposure by duration and dose are not included, as all subjects received a single infusion of CAR-T cells and the target dose was the same for all trials.

Table SIII.3: Exposure by Age Group and Gender; All Clinical Trials using Ciltacabtagene Autoleucel – Subjects Treated with Ciltacabtagene Autoleucel

	Men	Women
Age Group	Persons	Persons
Multiple Myeloma		
<30	0	1
30-54 years	72	39
55-64 years	86	57
65-74 years	69	51
75-84 years	9	12
>=85 years	0	0
Total	236	160

Note: The following trials are included: MMY2001 (N=106), MMY2003 (Cohorts A, B, C, D, E) (N=94), and MMY3002 (Arm B, N=196)
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Table SIII.4: Exposure by Special Populations; All Clinical Trials using JNJ-68284528 of Safety Population

Population	Persons
Multiple Myeloma	
Renal impairment at baseline	
Normal (CrCl ≥ 90 mL/min)	229
Mild (CrCl 60 to < 90 mL/min)	120
Moderate (CrCl 30 to < 60 mL/min)	47
Severe (CrCl < 30 mL/min)	0
Missing	0
Total	396
Hepatic impairment at baseline[a]	
Normal (Total bilirubin ≤ ULN and AST ≤ ULN)	352
Mild (Total bilirubin ≤ ULN and AST > ULN, or Total bilirubin ULN < Total bilirubin ≤ 1.5 x ULN)	38
Moderate (1.5 x ULN < Total bilirubin ≤ 3 x ULN)	6
Severe (Total bilirubin > 3 x ULN)	0
Missing	0
Total	396
Race	
White	296
Black or African American	30
Asian	27
Other[b]	43
Total	396
Ethnicity	
Hispanic or Latino	31
Not Hispanic or Latino	316
Not Reported	49
Total	396

[a] Per NCI Organ Dysfunction criteria.
[b] Other includes American Indian or Alaska native, Native Hawaiian or other Pacific islander, and unreported.
Keys: CrCl = creatinine clearance; ULN = upper limit normal; ALT = alanine aminotransferase; AST = aspartate aminotransferase.
Note: Baseline is defined as the last non-missing evaluation prior to ciltacabtagene autoleucel infusion.
Note: The following trials are included: MMY2001 (N=106), MMY2003 (Cohorts A, B, C, D, E) (N=94), and MMY3002 (Arm B, N=196)

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PART II: SAFETY SPECIFICATION

Module SIV: Populations Not Studied in Clinical Trials

SIV.1. Exclusion Criteria in Pivotal Clinical Studies Within the Development Program

Important Exclusion Criteria in Pivotal Clinical Trials Across the Development Program

Criterion 1	**Pregnant or Breastfeeding**
Reason for being an exclusion criterion	Per ICH guidelines, pregnant women should normally be excluded from clinical trials. No reproductive toxicity studies have been conducted in the preclinical setting. Breast-feeding women are usually excluded from clinical trials. It is not known whether ciltacabtagene autoleucel is excreted in human or animal milk or affects milk production.
Considered to be included as missing information: Yes/No	Yes
Rationale (if not included as missing information)	Not applicable
Criterion 2	**Human Immunodeficiency Virus (HIV) infection**
Reason for being an exclusion criterion	It is common clinical practice to exclude subjects with active infections from clinical trials on anticancer therapy because they potentially confound the interpretation of safety. In addition, patients with HIV may have an increased risk of opportunistic infections due to lymphodepletion and CAR-T infusion. Cytopenia, including lymphopenia, is a known risk of CAR-T therapy, which may lead to worsening of HIV disease course. It is for these reasons that patients with HIV have been generally excluded from oncology CAR-T clinical trials.
Considered to be included as missing information: Yes/No	Yes
Rationale (if not included as missing information)	Not applicable

Important Exclusion Criteria in Pivotal Clinical Trials Across the Development Program

Criterion 3	**Serious active viral, bacterial, or uncontrolled systemic fungal infection**
Reason for being an exclusion criterion	It is common clinical practice to exclude subjects with uncontrolled infections from clinical trials on anticancer therapy because they potentially place subjects with these comorbidities at increased risk for severe adverse events and additionally may confound the interpretation of safety data. Also, infection may complicate the course and management of cytokine release syndrome (CRS) associated with CAR-T therapy.
Considered to be included as missing information: Yes/No	No
Rationale (if not included as missing information)	The product label includes a recommendation to delay lymphodepletion therapy as well as ciltacabtagene autoleucel therapy until any active infection has resolved.
Criterion 4	**Hepatitis B Virus (HBV) or Hepatitis C Virus (HCV) infection**
Reason for being an exclusion criterion	It is common clinical practice to exclude subjects with HBV and HCV infections from clinical trials on anticancer therapy because they potentially place subjects with these comorbidities at increased risk for severe adverse events and also may confound the interpretation of safety. In addition, HBV reactivation, in some cases resulting in fulminant hepatitis, hepatic failure, or death, may occur in subjects treated with medicinal products directed against B cells, such as ciltacabtagene autoleucel. Fatal hepatitis reactivation has been reported in patients treated with other CAR-T therapies targeting CD19 and CD22 (Wei 2019).
Considered to be included as missing information: Yes/No	Yes
Rationale (if not included as missing information)	Not applicable
Criterion 5	**Active autoimmune disease or history within 3 years**
Reason for being an exclusion criterion	It is common clinical practice not to include patients with autoimmune diseases in oncology clinical trials because it may potentially place patients at increased risk for immune-related side effects, and additionally may confound the interpretation of safety data.

Important Exclusion Criteria in Pivotal Clinical Trials Across the Development Program

Considered to be included as missing information: Yes/No	Yes
Rationale (if not included as missing information)	Not applicable
Criterion 6	**Overt clinical evidence of dementia or altered mental status**
Reason for being an exclusion criterion	Neurologic toxicities have been reported with other CAR-T therapies. Therefore, inclusion of these subjects may confound analysis of neurotoxicity and may increase risk to subjects with these types of underlying conditions.
Considered to be included as missing information: Yes/No	Yes (pre-existing neurodegenerative disorders)
Rationale (if not included as missing information)	Not applicable
Criterion 7	**Active CNS involvement by malignancy**
Reason for being an exclusion criterion	Neurologic toxicities have been reported with other CAR-T therapies. Therefore, inclusion of patients with known CNS involvement may confound the efficacy and safety results of the trial and may increase risk to subjects with active CNS involvement.
Considered to be included as missing information: Yes/No	Yes
Rationale (if not included as missing information)	Not applicable
Criterion 8	**Cardiac conditions, including 1) New York Heart Association (NYHA) stage III or IV congestive heart failure; 2) Myocardial infarction or coronary artery bypass graft (CABG) ≤6 months prior to enrollment; 3) History of clinically significant ventricular arrhythmia or unexplained syncope, not believed to be vasovagal in nature or due to dehydration; 4) History of severe non-ischemic cardiomyopathy; 5) Impaired cardiac function (left ventricular ejection fraction [LVEF] <45%) as assessed by echocardiogram or multiple-gated acquisition (MUGA) scan (performed ≤8 weeks of apheresis).**

Important Exclusion Criteria in Pivotal Clinical Trials Across the Development Program

Reason for being an exclusion criterion	It is common clinical practice not to include subjects with potentially life-threatening cardiac conditions in trials on anticancer therapy because they potentially place subjects with these comorbidities at increased risk for adverse events and additionally may confound the interpretation of safety data. This is especially true for CAR-T therapy, where hypotension often complicates CRS. Hypotension would be poorly tolerated and potentially fatal for patients with underlying cardiac conditions.
Considered to be included as missing information: Yes/No	No
Rationale (if not included as missing information)	The product label includes a warning indicating that patients with inadequate cardiac function are likely to be more vulnerable to the consequences of adverse reactions observed with ciltacabtagene autoleucel and may require special attention.
Criterion 9	**Any history of Parkinson's disease or other neurodegenerative disorder**
Reason for being an exclusion criterion	Movement and neurocognitive toxicity (MNT) with signs and symptoms of Parkinsonism, under other CAR-T related neurotoxicity, was observed in early clinical trials of ciltacabtagene autoleucel. As a result, patients with any history of Parkinson's disease or other neurogenerative disorders were excluded from subsequent clinical trials.
Considered to be included as missing information: Yes/No	No
Rationale (if not included as missing information)	Neurologic toxicities (including ICANS and other neurotoxicities) is included as an important identified risk for ciltacabtagene autoleucel.

SIV.2. Limitations to Detect Adverse Reactions in Clinical Trial Development Programs

The clinical development program is unlikely to detect certain types of adverse reactions such as rare adverse reactions or adverse reactions with a long latency.

SIV.3. Limitations in Respect to Populations Typically Under-represented in Clinical Trial Development Program(s)

Table SIV.2: Exposure of Special Populations Included or Not in Clinical Trial Development Programs

Type of Special Population	Exposure
Pregnant women	Not included in the clinical development program.
Breastfeeding women	Not included in the clinical development program.
Population with relevant different ethnic origin	Of 396 subjects in the all clinical trials population, 296 (74.7%) subjects were white, 30 (7.6%) subjects were Black or African American, and 27 (6.8%) subjects were Asian. The remaining 43 (10.9%) subjects were either American Indian or Alaska native, Native Hawaiian or other Pacific islander, or data were not reported.
Subpopulations carrying relevant genetic polymorphisms	Not applicable
Patients with relevant comorbidities:	
Patients with hepatic impairment	Subjects must have had alanine transaminase (ALT) and aspartate transaminase (AST) ≤3 x the upper limit of normal (ULN) at screening to be eligible for trial participation. Of the 396 subjects in the all clinical trials population, there were 38 (9.6%) subjects with mild hepatic impairment at baseline (total bilirubin ≤ULN and AST >ULN, or ULN < total bilirubin ≤ 1.5 x ULN; [Ramalingam 2010]), 6 (1.5%) subjects with moderate hepatic impairment at baseline (1.5 x ULN < total bilirubin ≤ 3 x ULN), and no subjects with severe (total bilirubin >3 x ULN) hepatic impairment.
Patients with renal impairment	Subjects must have had creatinine clearance (CrCl) of ≥40 mL/min/1.73 m^2 at screening to be eligible for trial participation. Of the 396 subjects in the all clinical trials population, there were 120 (30.3%) subjects with mild renal impairment at baseline (CrCl <90 mL/min), 47 (11.9%) subjects with moderate renal impairment (CrCl 30 to <60 mL/min), and no subjects with severe renal impairment (CrCl <30 mL/min).
Patients with cardiovascular impairment	Not included in the clinical development program
Patients with a disease severity different from inclusion criteria in clinical trials	Not applicable

Summary of Missing Information Due to Limitations of the Clinical Trial Program

Missing Information	Long-term safety
	Impact on pregnancy and lactation
	Use in patients with pre-existing autoimmune disease
	Use in patients with pre-existing neurodegenerative disorders
	Use in patients with active CNS involvement by malignancy
	Use in patients with chronic controlled HIV and HBV/HCV infection

PART II: SAFETY SPECIFICATION

Module SV: Postauthorization Experience

SV.1. Postauthorization Exposure

SV.1.1. Method used to Calculate Exposure

Patient exposure was estimated by calculation from distribution data. Estimates of exposure are based upon finished and released product. Ciltacabtagene autoleucel is provided as a single dose for infusion containing a suspension of CAR-positive viable T cells. The recommended dose is 0.5-1×10^6 CAR-positive viable T cells per kg of body weight, with a maximum dose of 1×10^8 CAR-positive viable T cells per single infusion. The total number of subjects were counted for calculation of exposure estimation as each subject receives a single infusion of ciltacabtagene autoleucel. Based on clinical experience, 96% of the total number of released doses (assigned unique batch numbers) were then used to calculate estimated postmarketing exposure.

SV.1.2. Exposure

The estimated cumulative exposure to ciltacabtagene autoleucel from launch to 27 August 2024 is provided in the table below.

Cumulative Patient Exposure to Ciltacabtagene Autoleucel (Launch to 27 August 2024)

Country[a]	Number of Patients Receiving Apheresis	Number of Patients Receiving Ciltacabtagene Autoleucel[b]
Austria	[redacted]	[redacted]
Germany	[redacted]	[redacted]
US	[redacted]	[redacted]
Total	[redacted]	[redacted]

Key: US=United States

a: [redacted]

b: [redacted]

[redacted]

PART II: SAFETY SPECIFICATION

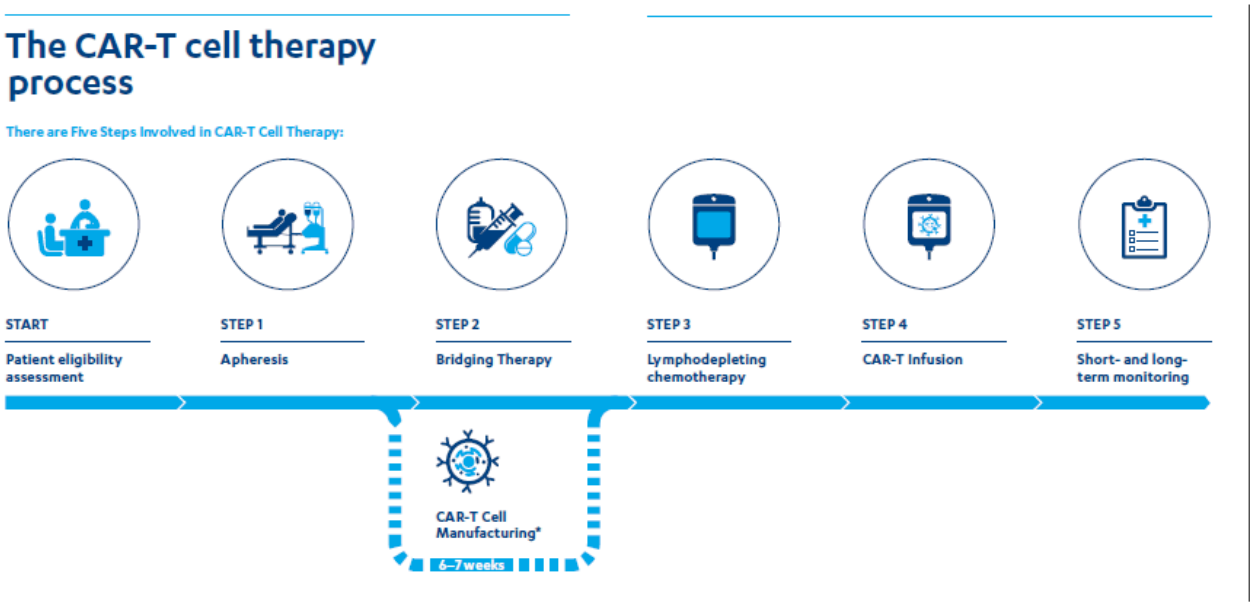
Module SVI: Additional EU Requirements for the Safety Specification

Potential for Misuse for Illegal Purposes

Ciltacabtagene autoleucel will be administered by a healthcare professional and has no abuse potential. Therefore, there is no concern for potential illegal use.

Specific Risks Related to Advanced Therapy Medicinal Products

As detailed in the Committee for Medicinal Products for Human Use (CHMP) Guideline on Safety and Efficacy Follow-up and Risk Management of Advanced Therapy Medicinal Products (ATMP; EMA 2008 and EMA 2018), there may be additional risks related to ciltacabtagene autoleucel based on its status as a novel, complex, and technically advanced therapy. As such, decrease in cell viability due to inappropriate handling or preparation of the product has been identified as an important potential risk and is described in detail in Module SVII.3.1. A flowchart showing the ciltacabtagene autoleucel process is outlined below; ciltacabtagene autoleucel should be transported and stored below -120°C.



PART II: SAFETY SPECIFICATION

Module SVII: Identified and Potential Risks

SVII.1. Identification of Safety Concerns in the Initial RMP Submission

SVII.1.1. Risks Not Considered Important for Inclusion in the List of Safety Concerns in the RMP

Reason for not Including an Identified or Potential Risk in the List of Safety Concerns in the RMP:

Risks not Included in the List of Safety Concerns in the RMP
Risks with minimal clinical impact on patients (in relation to the severity of the indication treated):
Anemia
Adverse reactions with clinical consequences, even serious, but occurring with a low frequency and considered to be acceptable in relation to the severity of the indication treated:
Not applicable
Known risks that require no further characterization and are followed up via routine pharmacovigilance and for which the risk minimization messages in the product information are adhered by prescribers (eg, actions being part of standard clinical practice in each EU Member state where the product is authorized):
Not applicable
Known risks that do not impact the risk-benefit profile:
Hypersensitivity/Infusion-related reactions
Other reasons for considering the risks not important:
Not applicable

SVII.1.2. Risks Considered Important for Inclusion in the List of Safety Concerns in the RMP

Safety Concerns for Inclusion in the RMP	Risk-Benefit Impact
Important identified risks	
Cytokine release syndrome (including hemophagocytic lymphohistiocytosis [HLH])	CRS is a well-known effect of CAR-T products based on their mechanism of action. While CRS can be severe, the events reported for patients in clinical trials of ciltacabtagene autoleucel were mostly low grade and in most cases, symptoms were effectively managed with available treatments. Information on how to manage and mitigate this risk is provided in the SmPC and PL. Additional risk minimization measures to mitigate the risk of CRS include educational materials for Health Care Professionals (HCPs) and patients. Furthermore, ciltacabtagene autoleucel will only be supplied to centers that are qualified and trained in the handling and management of the product (ie, a controlled distribution program). Overall, the risk-benefit balance is positive for the product considering the severity of the disease treated, the lack of other available therapies, and the potential efficacy for patients treated with ciltacabtagene autoleucel.
Neurologic toxicities (including immune effector cell-associated neurotoxicity [ICANS] and other neurotoxicities)	Neurologic toxicity is a well-known effect of CAR-T therapy. Information on how to manage and mitigate this risk is provided in the SmPC and PL. Additional risk minimization measures to mitigate the risk of neurologic toxicities (including ICANS and other neurotoxicities) include educational materials for HCPs and patients, as well as a controlled distribution program. Overall, the risk-benefit balance is positive for the product considering the severity of the disease treated, the lack of other available therapies, and the potential efficacy for patients treated with ciltacabtagene autoleucel.
Prolonged cytopenia (excluding anemia)	Cytopenia is commonly associated with the underlying disease of multiple myeloma as well as a consequence of lymphodepletion therapy. Overall, the risk-benefit balance is positive for the product considering the severity of the disease treated, the lack of other available therapies, and the potential efficacy for patients treated with ciltacabtagene autoleucel.
Serious infections	The SmPC and PL provide information on how to manage the risk of infection. Overall, the risk benefit balance is positive for the product considering the severity of the disease treated, the lack of other available therapies, and the potential efficacy for patients treated with ciltacabtagene autoleucel.

Safety Concerns for Inclusion in the RMP	Risk-Benefit Impact
Hypogammaglobulinemia	Hypogammaglobulinemia is a well-known effect of CAR-T products based on their mechanism of action. Ciltacabtagene autoleucel targets BCMA-expressing B cells, resulting in disruption of normal B-cell maturation to plasma cells, subsequently resulting in hypogammaglobulinemia. Hypogammaglobulinemia was commonly reported for subjects in clinical trials of ciltacabtagene autoleucel, was mostly low grade, and was ameliorated with intravenous gamma globulin infusions. Although there may be many factors associated with infections in patients with multiple myeloma, there were subjects in the ciltacabtagene autoleucel clinical trials with one or more Grade 3 or 4 treatment-emergent infections concurrent with hypogammaglobulinemia. The SmPC and PL provide information on how to manage the risks of both hypogammaglobulinemia and serious infections. Overall, the risk benefit balance is positive for the product considering the severity of the disease treated, the lack of other available therapies, and the potential efficacy for patients treated with ciltacabtagene autoleucel.
Important potential risks	
Second primary malignancy	The risk of second primary malignancy is theoretical due to potential viral insertion (DNA integration) of the lentiviral vector. Second primary malignancies have been reported in clinical trials with ciltacabtagene autoleucel; however, a causal relationship has not been established to date. Data on second primary malignancies will be reported during the duration of the clinical trials, and subsequently will be collected in a long-term follow-up study (68284528MMY4002). In addition, an observational post-authorization safety study (PASS) (68284528MMY4004; which includes 68284528MMY4009 as one of multiple data sources) will also collect second primary malignancy in patients treated with ciltacabtagene autoleucel in the commercial setting. At the time of occurrence of a second primary malignancy, a tumor sample should be collected and DNA, RNA, or protein analysis may be performed to investigate the presence of lentiviral elements in the case of second primary malignancies. Overall, the risk-benefit balance is positive for the product considering the severity of the disease treated, the lack of other available therapies, and the potential efficacy for patients treated with ciltacabtagene autoleucel

Safety Concerns for Inclusion in the RMP	Risk-Benefit Impact
Decrease in cell viability due to inappropriate handling or preparation of the product	Risks of breaking the cold chain or other type of controlled temperature conditions or mishandling the preservation, freezing, or thawing could impact the cell viability and biological activity of ciltacabtagene autoleucel, potentially leading to treatment failure. No cold chain breaks or other product mishandling were reported during clinical trials. Additional risk minimization measures to mitigate this risk include Product Handling training for HCPs and other personnel involved in the transport, storage, thawing, preparation, or handling of ciltacabtagene autoleucel. Overall, the risk-benefit balance is positive for the product considering the severity of the disease treated, the lack of other available therapies, and the potential efficacy for patients treated with ciltacabtagene autoleucel.
Tumor lysis syndrome	While TLS may be a life-threatening condition, the incidence is low in clinical trials of ciltacabtagene autoleucel, reported cases were confounded, and the management of TLS is well known in clinical practice. Patients with high tumor burden or with multiple extramedullary disease sites and/or plasmacytomas are at risk and should be treated prophylactically in accordance with local standards. Data on TLS will be reported during the duration of the clinical trials. An observational PASS (68284528MMY4004; which also includes 68284528MMY4009 as one of multiple data sources) will also collect data on TLS in patients treated with ciltacabtagene autoleucel in the commercial setting. Overall, the risk-benefit balance is positive for the product considering the severity of the disease treated, the lack of other available therapies, and the potential efficacy for patients treated with ciltacabtagene autoleucel.
Aggravation of Graft versus Host Disease	To date, no cases of aggravated or de novo GvHD have been reported in ciltacabtagene autoleucel clinical trials. However, a theoretical risk of aggravation of GvHD may exist in patients receiving allogenic transplant prior to 6 months of ciltacabtagene autoleucel infusion or still receiving immunosuppressants to control a prior event of GvHD after allogenic transplant. Data on GvHD will be reported during the duration of the clinical trials, and subsequently will be collected in a long-term follow-up study (68284528MMY4002). In addition, an observational PASS (68284528MMY4004; which includes 68284528MMY4009 as one of multiple data sources) will also collect data on aggravation of GvHD in patients treated with ciltacabtagene autoleucel in the commercial setting. Overall, the risk-benefit balance is positive for the product considering the severity of the disease treated, the lack of other available therapies, and the potential efficacy for patients treated with ciltacabtagene autoleucel.

Safety Concerns for Inclusion in the RMP	Risk-Benefit Impact
Generation of replication competent lentivirus (RCL)	To date, no cases of RCL have been reported in clinical trials of ciltacabtagene autoleucel. Despite the safety features of the third generation SIN LVV system used for gene delivery in the manufacturing of ciltacabtagene autoleucel, the potential for generation of RCL described in autologous hematopoietic stem cell gene therapy with gamma retroviral vectors remains a theoretical risk. Data on RCL will be collected during the duration of the clinical trials and subsequently in a long-term follow-up study (68284528MMY4002) if any post-treatment samples are positive during the first year or thereafter, as clinically indicated (ie, event-triggered). Data on generation of RCL will also be collected in Study 68284528MMY4009. Overall, the risk-benefit balance is positive for the product considering the severity of the disease treated, the lack of other available therapies, and the potential efficacy for patients treated with ciltacabtagene autoleucel.
Missing information	
Long-term safety	To date, there are no data on the long-term safety of ciltacabtagene autoleucel. A long-term follow-up study (68284528MMY4002) of patients treated with ciltacabtagene autoleucel in clinical trials will be conducted to understand the long-term safety profile of the product. In addition, an observational PASS (68284528MMY4004; which includes 68284528MMY4009 as one of multiple data sources) will be conducted to evaluate the long-term safety of ciltacabtagene autoleucel in adult patients with multiple myeloma under real-world conditions.
Impact on pregnancy and lactation	Pregnant and breastfeeding women were excluded from clinical trials, and both male and female patients were required to practice strict contraception measures. As it is not known whether ciltacabtagene autoleucel has the potential to be transferred to the fetus and cause fetal toxicity, pregnant women should be advised there may be risks to the fetus. Women who are breast-feeding should be advised of the potential risk to the breast-fed infant. Any pregnancies will be reported in all future and ongoing clinical trials, including a long-term follow-up study (68284528MMY4002) and an observational PASS study (68284528MMY4004; which includes 68284528MMY4009 as one of multiple data sources).

Safety Concerns for Inclusion in the RMP	Risk-Benefit Impact
Use in patients with pre-existing autoimmune disease	Patients with active autoimmune disease or a history of autoimmune disease within 3 years were excluded from clinical trials. Any new onset or exacerbation of pre-existing autoimmune disease will be reported an observational PASS study (68284528MMY4004; which includes 68284528MMY4009 as one of multiple data sources). A long-term follow-up study (68284528MMY4002) will also collect any new onset of autoimmune disease.
Use in patients with pre-existing neurodegenerative disorders	Patients with overt clinical evidence of dementia or altered mental status were excluded from clinical trials. Any new onset or exacerbation of pre-existing neurological disorders will be reported in an observational PASS study (68284528MMY4004; which includes 68284528MMY4009 as one of multiple data sources). A long-term follow-up study (68284528MMY4002) will also collect any new onset of neurodegenerative disorders. The product label includes a warning indicating that patients with significant CNS disease are likely to be more vulnerable to the consequences of adverse reactions observed with ciltacabtagene autoleucel and may require special attention.
Use in patients with active CNS involvement by malignancy	Patients with known active or prior history of CNS involvement or those exhibiting signs of meningeal involvement of multiple myeloma were excluded from clinical trials. Any new onset or exacerbation of pre-existing neurological disorders will be reported in an observational PASS study (68284528MMY4004; which includes 68284528MMY4009 as one of multiple data sources). A long-term follow-up study (68284528MMY4002) will also collect any new onset of neurological disorders.
Use in patients with chronic controlled HIV and HBV/HCV infection	There is no experience with manufacturing ciltacabtagene autoleucel for patients with HIV, HBV, or HCV infection, as these patients were excluded from clinical trials. The product information includes that there is currently no experience with ciltacabtagene autoleucel in patients with HIV, active HBV, or active HCV. Screening for HBV, HCV and HIV must be performed in accordance with local guidelines before collection of cells for manufacturing. Severe infections, including any cases of HIV, HBV, or HCV infection, will be reported in a long-term follow-up study (68284528MMY4002) and an observational PASS study (68284528MMY4004; which includes 68284528MMY4009 as one of multiple data sources).

SVII.2. New Safety Concerns and Reclassification with a Submission of an Updated RMP

Based on a signal initiated by PRAC across CAR-T cell products, the Company performed a comprehensive cumulative review of data to assess the signal of T-cell lymphoma. Based on review of the cumulative weight of evidence from all available sources (eg, clinical trials, Global Medical Safety (GMS) global safety database, FAERS/EV data, epidemiology data, literature, EudraVigilance, and responses submitted by the MAHs of other CAR-T cell products), secondary malignancy of T-cell origin has been classified as an important identified risk. The existing important potential risk of "Secondary malignancy except those of myeloid origin" has been updated to "Secondary malignancy except those of T-cell origin and myeloid origin".

SVII.3. Details of Important Identified Risks, Important Potential Risks, and Missing Information

Important identified risks:

1. Cytokine release syndrome (including HLH)
2. Neurologic toxicities (including ICANS and other neurotoxicities)
3. Prolonged or recurrent cytopenia (excluding anemia)
4. Serious infections
5. Hypogammaglobulinemia
6. Secondary malignancy of T-cell origin
7. Secondary malignancy of myeloid origin

Important potential risks:

1. Secondary malignancy except those of T-cell and myeloid origin
2. Decrease in cell viability due to inappropriate handling or preparation of the product
3. Tumor lysis syndrome (TLS)
4. Aggravation of Graft versus Host Disease (GvHD)
5. Generation of replication competent lentivirus (RCL)

Missing Information:

1. Long-term safety
2. Impact on pregnancy and lactation
3. Use in patients with pre-existing autoimmune disease
4. Use in patients with pre-existing neurodegenerative disorders
5. Use in patients with active CNS involvement by malignancy
6. Use in patients with chronic controlled HIV and HBV/HCV infection

Medical Dictionary for Regulatory Activities (MedDRA) version 26.1 (except where noted in risk footnotes) was used to classify the clinical trials adverse event information that is summarized in this section.

SVII.3.1. Presentation of Important Identified Risks and Important Potential Risks

Important Identified Risk – Cytokine Release Syndrome (including HLH)

Potential Mechanisms:

Cytokine release syndrome is shown to be associated with CAR-T therapies and is a systemic response to the activation and expansion of CAR-T cells. It is associated with the elevation of cytokines, namely interferon gamma, interleukin 2 (IL-2) receptor alpha, IL-6, and IL-10. Clinical symptoms are associated with increased inflammatory markers, including C-reactive protein (CRP), ferritin, interferon gamma, and IL-6. Hemophagocytic lymphohistiocytosis (HLH) occurring in the context of CAR-T cell therapies can be a potential manifestation of severe CRS.

Evidence Source(s) and Strength of Evidence:

CRS, including events that were fatal or life-threatening, has been reported in patients treated with ciltacabtagene autoleucel in clinical trials and CRS was identified as an adverse reaction. The risk for CRS and information regarding this adverse reaction are described in the SmPC for ciltacabtagene autoleucel.

CAR-T-related CRS is commonly described in the literature (Barrett 2014), with several published guidelines for toxicity grading and management (Lee 2019; Neelapu 2019). For ciltacabtagene autoleucel clinical trials, CRS was graded using American Society for Transplantation and Cellular Therapy (ASTCT) 2019 criteria as predefined in the trial protocols.

Based on the strength of evidence from the clinical trial data and information from the literature, CRS (including HLH) is considered an important identified risk for ciltacabtagene autoleucel.

Characterization of the Risk:

Treatment-emergent Cytokine Release Syndrome (CRS): Frequency, Seriousness, Outcomes, and Severity; All Clinical Trials Using Ciltacabtagene Autoleucel; Subjects Treated with Ciltacabtagene Autoleucel (Comparator: All Subjects Treated)

	Randomized Clinical Trials		All Clinical Trials
	Ciltacabtagene autoleucel	Comparator	Ciltacabtagene autoleucel
Multiple Myeloma			
Number of subjects treated	196	208	396
Frequency[a]	151 (77.0%)	1 (0.5%)	330 (83.3%)
Seriousness			
Was serious	13 (6.6%)	1 (0.5%)	45 (11.4%)
Outcomes			
Resulted in Death	0	0	1 (0.3%)
Not recovered/Not Resolved	1 (0.7%)	0	3 (0.9%)
Recovered/Resolved	149 (98.7%)	1 (100.0%)	324 (98.2%)
Recovered with sequelae	1 (0.7%)	0	2 (0.6%)
Recovering/Resolving	0	0	0
Unknown	0	0	0
Severity (Toxicity Grade)[b]			
Worst Grade=1	98 (50.0%)	0	197 (49.7%)
Worst Grade=2	46 (23.5%)	1 (0.5%)	117 (29.5%)
Worst Grade=3	5 (2.6%)	0	10 (2.5%)
Worst Grade=4	2 (1.0%)	0	5 (1.3%)
Worst Grade=5	0	0	1 (0.3%)
Missing	0	0	0

[a]The subject is counted only once regardless of the number of events or the number of occurrences.
[b]Note: Study MMY2001 - CRS was originally graded by Lee criteria (Lee et al 2014) in Phase 1b (N=29) and by ASTCT consensus grading system (Lee et al 2019) in Phase 2 (N=77), with conversion of grade in Phase 1b to ASTCT based on data in eCRF. Toxicity grade by ASTCT is presented in this table.
Note: For the purposes of this output, the following AE are used. MMY2001 and MMY2003: treatment-emergent adverse events (TEAE). MMY3002 Arm A: TEAE. MMY3002 Arm B: TEAE on or after ciltacabtagene autoleucel for those who received ciltacabtagene autoleucel as study treatment and ciltacabtagene autoleucel-emergent AE for those who received ciltacabtagene autoleucel as subsequent therapy.
Note: For linked adverse events, outcome is presented for the latest episode of the event. For subjects with more than 1 linked and/or unlinked adverse events, outcome is based on the outcome of the last event.
Note: Percentages are calculated with the number of subjects in the all treated analysis set as denominator, except for the outcome of CRS for which percentages are calculated with the number of subjects with CRS in the all treated analysis set as denominator.
Note: Adverse Events were coded using MedDRA Version 26.1. Search criteria are listed in ANNEX 7.
Note: The following trials are included: All Clinical Trials: MMY2001 (N=106), MMY2003 (Cohorts A, B, C, D, E) (N=94), and MMY3002 (Arm B, N=196); Randomized Clinical Trials: MMY3002.

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Clinical signs and symptoms of CRS may include but are not limited to fever (with or without rigors), chills, hypotension, hypoxia, and elevated liver enzymes. Potentially life-threatening complications of CRS may include cardiac dysfunction, neurologic toxicity, and HLH. Patients who develop HLH may have an increased risk of severe bleeding.

CRS was reported for 83% of subjects treated with ciltacabtagene autoleucel across all clinical trials. For most of these subjects, the worst severity was Grade 1 or 2 (95%; 314 of 330). Grade 3 CRS was reported for 2.5% of subjects and Grade 4 for 1.3% of subjects. One subject (0.3%) died

from Grade 5 CRS complicated by secondary HLH. The median time from ciltacabtagene autoleucel infusion to first onset of CRS was 7 days (range: 1 to 23 days). The median duration of CRS was 4 days, with the duration ranging from 1 to 14 days for all except 1 subject with Grade 5 CRS (duration of 97 days). At the time of clinical cutoff, 98% of subjects with CRS had recovered.

Risk Factors and Risk Groups:

Risk factors for severe CRS include high pre-infusion tumor burden, active infection, and early onset of fever or persistent fever after 24 hours of symptomatic treatment. Active uncontrolled infection was an exclusionary criterion in clinical trials. In Trial MMY3002, 20 subjects discontinued study treatment due to disease progression on bridging therapy and received ciltacabtagene autoleucel as subsequent therapy. These subjects represent a distinct and higher-risk population with poorer safety outcomes compared with the 176 subjects who received ciltacabtagene autoleucel as study treatment. In these subjects, CRS was reported at a higher rate for Grade 3 and 4 events (25%), including events of CRS complicated by HLH (10%) or DIC (10%). Two subjects died due to hemorrhage in the context of HLH or DIC.

Preventability:

Infusion of ciltacabtagene autoleucel should be delayed for any patient with unresolved serious adverse reactions from preceding lymphodepleting or bridging chemotherapies (including cardiac toxicity and pulmonary toxicity), rapid disease progression, or clinically significant active infection, as infection may increase the risk of fatal CRS. For patients with high tumor burden, reducing baseline burden of disease with bridging therapy prior to infusion should be considered. Appropriate prophylactic and therapeutic treatment for infections should be provided, as clinically indicated. Post-infusion, patients should be closely monitored for signs and symptoms of CRS. At the first sign of CRS, patients should be evaluated immediately for hospitalization and treatment. Tocilizumab (or suitable alternative measures if not available and listed in the EMA shortage catalogue) should be available for each patient as outlined in the SmPC. Part V.2 of the RMP outlines additional risk minimization measures to mitigate the risk of CRS, including educational materials for HCPs and patients. The product will only be supplied to centers that are qualified and trained in the management of CRS (ie, controlled distribution program).

Impact on the Risk-benefit Balance of the Product:

CRS is a well-known effect of CAR-T products based on their mechanism of action, and CRS associated with ciltacabtagene autoleucel use is within the expected incidence rate for other CAR-T products. While CRS can be severe, the events reported for subjects in clinical trials of ciltacabtagene autoleucel were mostly low grade and most cases were effectively managed with available treatments. Information on how to manage and mitigate this risk is provided in the SmPC and PL. Additional risk minimization measures to mitigate the risk of CRS include educational materials for HCPs and patients. Furthermore, ciltacabtagene autoleucel will only be supplied to centers that are qualified and trained in the handling and management of the product (ie, a controlled distribution program). Overall, the risk-benefit balance is positive for the product

considering the severity of the disease treated, the paucity of effective therapies, and the potential efficacy for patients treated with ciltacabtagene autoleucel.

Public Health Impact:

All usage will be well controlled by the healthcare professional. No public health impact is anticipated.

Annex 1 MedDRA Term:

Cytokine release syndrome (PT)

Important Identified Risk – Neurologic toxicities (including ICANS and other neurotoxicities)

Potential Mechanisms:

Neurologic toxicity is a risk shown to be associated with CAR-T therapies, concurrently with CRS or after resolution of CRS, in patients with hematologic malignancies. The precise mechanism associated with CAR-T neurologic toxicity is currently unclear.

Evidence Source(s) and Strength of Evidence:

Cases of CAR-T cell neurologic toxicities have been reported for subjects treated with ciltacabtagene autoleucel in clinical trials, and have included both ICANS as well as other neurotoxicity determined by the investigator to be related to CAR-T therapy and occurring after recovery of CRS and/or ICANS. Specific types of neurotoxicity other than ICANS include movement and neurocognitive toxicity with signs and symptoms of Parkinsonism, Guillain-Barré Syndrome (GBS), peripheral neuropathy, and cranial nerve palsies. Note that ICANS and other neurotoxicities are not mutually exclusive as patients can experience both ICANS and other neurotoxicity. Neurologic toxicities (including ICANS and other neurotoxicities) were identified as an adverse reaction. The risk for neurologic toxicities and information regarding this adverse reaction are described in the SmPC for ciltacabtagene autoleucel.

While ICANS and other neurotoxicities (occurring within 8 weeks of infusion) associated with CAR-T therapy are well described in the literature (Neelapu 2019; Santomasso 2019; Brudno 2019), information on late onset of neurological events (ie, onset >8 weeks after CAR-T cell infusion) is still evolving.

Based on the known risk associated with CAR-T therapies, as well as on the strength of evidence from clinical trials of ciltacabtagene autoleucel, neurologic toxicities (including ICANS and other neurotoxicities) is considered an important identified risk.

Characterization of the Risk:

Summary of Neurologic Toxicities (including ICANS and Other Neurotoxicities): Frequency, Seriousness, Outcome, and Severity; All Clinical Trials using Ciltacabtagene Autoleucel, Subjects Treated with Ciltacabtagene Autoleucel (Comparator: All Subjects Treated)

	Randomized Clinical Trials						All Clinical Trials		
	Ciltacabtagene autoleucel			Comparator			Ciltacabtagene autoleucel		
	Total n (%)	ICANS[b] n (%)	Other Neurotoxicities[c] n (%)	Total n (%)	ICANS[b] n (%)	Other Neurotoxicities[c] n (%)	Total n (%)	ICANS[b] n (%)	Other Neurotoxicities[c] n (%)
Multiple Myeloma									
Number of subjects treated	196	196	196	208	208	208	396	396	396
Frequency[a]	46 (23.5%)	15 (7.7%)	37 (18.9%)	0	0	0	90 (22.7%)	45 (11.4%)	61 (15.4%)
Seriousness									
Was serious	17 (8.7%)	4 (2.0%)	14 (7.1%)	0	0	0	43 (10.9%)	14 (3.5%)	31 (7.8%)
Outcomes									
Resulted in Death	0	0	0	0	0	0	3 (3.3%)	1 (2.2%)	2 (3.3%)
Not recovered/Not Resolved	11 (23.9%)	1 (6.7%)	10 (27.0%)	0	0	0	20 (22.2%)	3 (6.7%)	17 (27.9%)
Recovered/Resolved	35 (76.1%)	14 (93.3%)	27 (73.0%)	0	0	0	65 (72.2%)	41 (91.1%)	40 (65.6%)
Recovered with sequelae	0	0	0	0	0	0	0	0	0
Recovering/Resolving	0	0	0	0	0	0	2 (2.2%)	0	2 (3.3%)
Unknown	0	0	0	0	0	0	0	0	0
Severity[b,c]									
Worst Grade=1	17 (8.7%)	10 (5.1%)	11 (5.6%)	0	0	0	29 (7.3%)	27 (6.8%)	13 (3.3%)
Worst Grade=2	22 (11.2%)	3 (1.5%)	19 (9.7%)	0	0	0	36 (9.1%)	9 (2.3%)	29 (7.3%)
Worst Grade=3	6 (3.1%)	2 (1.0%)	6 (3.1%)	0	0	0	17 (4.3%)	6 (1.5%)	14 (3.5%)
Worst Grade=4	1 (0.5%)	0	1 (0.5%)	0	0	0	5 (1.3%)	2 (0.5%)	3 (0.8%)
Worst Grade=5	0	0	0	0	0	0	3 (0.8%)	1 (0.3%)	2 (0.5%)
Missing	0	0	0	0	0	0	0	0	0

[a]The subject is counted only once regardless of the number of events or the number of occurrences.
[b]ICANS evaluated according to the ASTCT consensus grading system (Lee et al 2019) or NCI-CTCAE version 5.0.
[c]Other Neurotoxicities severity were graded according to CTCAEv5.
Note: For linked adverse events, outcome is presented for the latest episode of the event. For subjects with more than 1 linked and/or unlinked adverse events, outcome is based on the last event.
Note: Percentages are calculated with the number of subjects in the all treated analysis set as denominator, except for the outcome of neurologic toxicities for which percentages are calculated with the number of subjects with neurologic toxicities in the all treated analysis set as denominator.
Note: Adverse Events were coded using MedDRA Version 26.1. Search criteria are listed in ANNEX 7.
Note: Total column is not additive of ICANS and Other neurotoxicities since some subjects may have experienced multiple events in more than one category. There are 15 subjects having both ICANS and Other neurotoxicities.
Note: The following trials are included: All Clinical Trials: MMY2001 (N=106), MMY2003 (Cohorts A, B, C, D, E) (N=94), and MMY3002 (Arm B, N=196); Randomized Clinical Trials: MMY3002.

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CAR-T cell neurotoxicity is categorized either as ICANS or as other neurotoxicity determined by the investigator to be related to CAR-T therapy. A subject can have both ICANS and other adverse events categorized as "other neurotoxicity". The incidence of ICANS and other types of neurologic toxicity (ie, movement and neurocognitive toxicity [MNT] with signs and symptoms of Parkinsonism, Guillain-Barré Syndrome [GBS], peripheral neuropathy, and cranial nerve palsies) is discussed below.

ICANS

ICANS was reported for 11% of subjects treated with ciltacabtagene autoleucel across all clinical trials; Grade 3 or 4 events were reported for 2.0% of subjects and Grade 5 for <1% (1 subject). Symptoms included but were not limited to aphasia, slow speech, dysgraphia, encephalopathy, depressed level of consciousness, and confusional state. The median time from ciltacabtagene autoleucel infusion to first onset of ICANS was 8 days (range: 2 to 15 days, except for 1 patient with onset at 26 days). The median duration of ICANS was 3 days (range: 1 to 29 days, except for 1 patient who had a subsequent fatal outcome at 40 days). At the time of data cutoff, 91% of subjects with ICANS had recovered.

MNT with Signs and Symptoms of Parkinsonism

Neurologic toxicity of MNT with signs and symptoms of parkinsonism has been reported in clinical trials. A cluster of symptoms with variable onset spanning more than one symptom domain was observed, including movement (eg, micrographia, tremor, bradykinesia, rigidity, stooped posture, shuffling gait), cognitive (eg, memory loss, disturbance in attention, confusion), and personality change (eg, reduced facial expression, flat affect, masked facies, apathy), often with subtle onset (eg, micrographia, flat affect), that in some patients progressed to an inability to work or care for oneself. Most of these patients presented a combination of 2 or more factors such as high tumor burden at baseline, prior Grade 2 or higher CRS, prior ICANS, and high CAR-T-cell expansion and persistence. Treatment with levodopa/carbidopa was not effective in improving symptomatology in these patients.

Across all clinical trials, 9 male subjects (2.3%) treated with ciltacabtagene autoleucel had signs and symptoms of parkinsonism (distinct from ICANS). The maximum toxicity grades of MNT were Grade 1 for 1 subject, Grade 2 for 2 subjects, and Grade 3 for 6 subjects. One subject died of neurologic toxicity with ongoing Grade 3 parkinsonism 247 days after administration of ciltacabtagene autoleucel, and 2 subjects with ongoing parkinsonism (Grade 2 and 3) died of infectious causes 162 and 119 days after administration of ciltacabtagene autoleucel. One subject recovered. The remaining 5 subjects had symptoms of parkinsonism that are still ongoing (at 309 to 996 days after administration of ciltacabtagene autoleucel). All 9 subjects had a history of prior CRS, while most (67%) of these subjects had prior ICANS. The median onset was 38 days (range: 14 to 914 days) from infusion of ciltacabtagene autoleucel. The median duration was 483 days (range: 62 to 813 days). At the time of data cutoff, 78% of subjects had not recovered.

GBS

One subject was reported to have GBS after treatment with ciltacabtagene autoleucel. Symptoms reported include those consistent with Miller-Fisher variant of GBS, motor weakness, speech

disturbances, and polyradiculoneuritis. Although GBS symptoms improved after receiving treatment with steroids and IVIG, the subject died 139 days after administration of ciltacabtagene autoleucel due to encephalopathy post gastroenteritis with ongoing GBS symptoms.

Peripheral neuropathy

Across all clinical trials, peripheral neuropathy was reported for 7.1% of subjects treated with ciltacabtagene autoleucel, and presented as sensory, motor, or sensorimotor neuropathies. The median time from ciltacabtagene autoleucel infusion to first onset was 58 days (range: 1 to 914 days). The median duration of peripheral neuropathy was 142 days (range: 1 to 1062 days), including those with ongoing neuropathy. Of the subjects with peripheral neuropathy, 18% had Grade 3 or Grade 4 events while the remaining subjects had Grade 1 or 2 events. At the time of data cutoff, 36% of subjects had not recovered.

Cranial nerve palsies

Cranial nerve palsy was reported for 6.8% of subjects treated with ciltacabtagene autoleucel across all clinical trials. Occurrence of 7th, 3rd, 5th, and 6th cranial nerve palsy, some of which were bilateral, worsening of cranial nerve palsy after improvement, and occurrence of peripheral neuropathy in subjects with cranial nerve palsy were reported. The median time to onset was 22 days (range: 17 to 101 days) following infusion of ciltacabtagene autoleucel, and the median duration was 66 days (range: 1 to 822 days). At the time of data cutoff, 19% of subjects had not recovered.

Risk Factors and Risk Groups:

A known risk factor for neurologic toxicity with the use of CAR-T therapy is concurrent or resolved CRS. The cluster of movement and neurocognitive events appears to be potentially associated with a combination of two or more factors such as high tumor burden at baseline (bone marrow plasma cells ≥80% or serum M-spike ≥5 g/dL or serum free light chain ≥5000 mg/L), prior Grade 2 or higher CRS, prior ICANS, and high CAR-T cell expansion and persistence. In Trial MMY3002, 20 subjects discontinued study treatment due to disease progression on bridging therapy and received ciltacabtagene autoleucel as subsequent therapy. These subjects represent a distinct and higher-risk population with poorer safety outcomes compared with the 176 subjects who received ciltacabtagene autoleucel as study treatment. In these subjects, ICANS was reported at a higher rate (35%) and greater severity (Grade 3 for 10%; no Grade 4 events). One subject (5%) was reported to have MNT that was mild in severity.

Preventability:

Patients with overt clinical evidence of dementia or altered mental status at screening were excluded from clinical trials of ciltacabtagene autoleucel, as were patients with active CNS involvement by malignancy. Patients with active or prior history of significant CNS disease may be more vulnerable to the consequences of adverse reactions observed with ciltacabtagene autoleucel and may require special attention. For patients with high tumor burden, reducing baseline burden of disease with bridging therapy prior to infusion should be considered. Patients

should be monitored for signs and symptoms of ICANS for 4 weeks following ciltacabtagene autoleucel infusion. Patients also should be monitored for signs and symptoms of MNTs consistent with parkinsonism, and for signs and symptoms of GBS, peripheral neuropathy, and cranial nerve palsies. After recovery from CRS and/or ICANS, patients should continue to be monitored for signs and symptoms of neurologic toxicities. Patients should be counseled to seek immediate medical attention should signs and symptoms of neurotoxicity occur. At the first sign of CAR-T cell related neurotoxicity, neurology consultation and evaluation should be considered. Consider early and aggressive supportive care including steroids in patients presenting with higher grade CRS or any grade ICANS. Early detection and intervention may be important to prevent neurologic toxicity from worsening. Specific recommendations for treating patients who develop neurotoxicity are provided in the SmPC. Part V.2 of the RMP outlines additional risk minimization measures to mitigate the risk of neurotoxicities (including ICANS), including educational materials for HCPs and patients. The product will only be supplied to centers that are qualified and trained in the management of neurological toxicities (ie, controlled distribution program).

Impact on the Risk-benefit Balance of the Product:

Neurotoxicity is a well-known effect of CAR-T therapy and was observed in clinical trials of ciltacabtagene autoleucel. The overall incidence of CAR-T related neurotoxicity (including ICANS) of 22% was consistent with rates observed for other CAR-T products. Information on how to manage and mitigate this risk is provided in the SmPC and PL. Overall, the risk-benefit balance is positive for the product considering the severity of the disease treated, the paucity of effective therapies, and the potential efficacy for patients treated with ciltacabtagene autoleucel.

Public Health Impact:

All usage will be well controlled by the healthcare professional. No public health impact is anticipated.

Annex 1 MedDRA Term:

ICANs: immune effector cell-associated neurotoxicity syndrome (PT)

Important Identified Risk – Prolonged or recurrent cytopenia (excluding anemia)

Potential Mechanisms:

Cytopenia is a major finding of the underlying disease of multiple myeloma and is expected to occur in the course of the disease. Patients treated with ciltacabtagene autoleucel may have increased cytopenia because they are pretreated with lymphodepleting agents as part of the background therapy. However, patients not receiving conditioning chemotherapy have also had cytopenia following other CAR T-cell therapies, demonstrating that CAR T cells cause myelosuppression by a cytokine-mediated mechanism or some other unknown mechanism.

Evidence Source(s) and Strength of Evidence:

Cytopenia has been identified as one of the most common adverse reactions in subjects after receiving ciltacabtagene autoleucel. Cases of prolonged cytopenia (not resolved by Day 30) have been reported for subjects treated with ciltacabtagene autoleucel in clinical trials and prolonged cytopenia has been identified as an adverse reaction. In addition, cases of cytopenia recurring after 60 days post-infusion have been reported in clinical trials of ciltacabtagene autoleucel. The risk for prolonged or recurrent cytopenia and information regarding this adverse reaction are described in the SmPC for ciltacabtagene autoleucel.

Evidence from clinical data with ciltacabtagene autoleucel suggests a drug association, including temporal association and persistence. Anemia begins to appear after lymphodepleting therapy but typically resolves within approximately 3 weeks post-infusion, and hemoglobin continues to rise thereafter, suggesting that bone marrow hematopoiesis improves following CAR-T therapy. Because of this, anemia is not considered an important risk of ciltacabtagene autoleucel. Some cases of neutropenia, thrombocytopenia, and lymphopenia continued for a longer period of time, with some recurrences of Grade 3 or 4 after Day 60.

Based on the incidence, temporal association, and persistence of the events in clinical trials, prolonged or recurrent cytopenia (excluding anemia) is considered an important identified risk for ciltacabtagene autoleucel.

Characterization of the Risk:

Treatment-emergent Prolonged or Recurrent Cytopenia (Excluding Anemia): Frequency, Seriousness, Outcome, and Severity; All Clinical Trials using Ciltacabtagene Autoleucel, Subjects Treated with Ciltacabtagene Autoleucel (Comparator: All Subjects Treated)

	Randomized Clinical Trials						All Clinical Trials		
	Ciltacabtagene autoleucel			Comparator			Ciltacabtagene autoleucel		
	Neutropenia	Lymphopenia	Thrombocytopenia	Neutropenia	Lymphopenia	Thrombocytopenia	Neutropenia	Lymphopenia	Thrombocytopenia
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Multiple Myeloma									
Number of subjects treated	196	196	196	208	208	208	396	396	396
Laboratory data									
Number of subjects has Grade 3/4 events after Day 1 until Day 100	186 (94.9%)	196 (100.0%)	95 (48.5%)	182 (87.5%)	131 (63.0%)	45 (21.6%)	381 (96.2%)	394 (99.5%)	202 (51.0%)
Total Prolonged (Grade 3/4 not recovered by day 30)[a]	50 (25.5%)	58 (29.6%)	58 (29.6%)	124 (59.6%)	72 (34.6%)	14 (6.7%)	111 (28.0%)	97 (24.5%)	132 (33.3%)
Total Prolonged (Grade 3/4 not recovered by day 60)[a]	20 (10.2%)	22 (11.2%)	29 (14.8%)	8 (3.8%)	34 (16.3%)	5 (2.4%)	44 (11.1%)	45 (11.4%)	76 (19.2%)
Occurrence of Grade 3/4 > day 60 (after initial recovery[a] of Grade 3/4)	67 (34.2%)	48 (24.5%)	13 (6.6%)	92 (44.2%)	36 (17.3%)	7 (3.4%)	116 (29.3%)	116 (29.3%)	21 (5.3%)
Adverse events									
Frequency[b]	168 (85.7%)	47 (24.0%)	101 (51.5%)	179 (86.1%)	29 (13.9%)	67 (32.2%)	358 (90.4%)	156 (39.4%)	248 (62.6%)
Seriousness									
Was serious	6 (3.1%)	0 (0.0%)	0 (0.0%)	7 (3.4%)	0 (0.0%)	0 (0.0%)	24 (6.1%)	0 (0.0%)	7 (1.8%)
Outcomes									
Resulted in Death	0	0	0	0	0	0	0	0	0
Not recovered/Not Resolved	11 (6.5%)	8 (17.0%)	20 (19.8%)	8 (4.5%)	2 (6.9%)	3 (4.5%)	17 (4.7%)	28 (17.9%)	43 (17.3%)
Recovered/Resolved	152 (90.5%)	37 (78.7%)	78 (77.2%)	169 (94.4%)	25 (86.2%)	59 (88.1%)	331 (92.5%)	122 (78.2%)	199 (80.2%)
Recovered with sequelae	1 (0.6%)	0	0	0	0	0	2 (0.6%)	1 (0.6%)	0
Recovering/Resolving	4 (2.4%)	2 (4.3%)	3 (3.0%)	1 (0.6%)	2 (6.9%)	4 (6.0%)	8 (2.2%)	5 (3.2%)	6 (2.4%)
Unknown	0	0	0	1 (0.6%)	0	1 (1.5%)	0	0	0
Severity (Toxicity Grade)[c]									
Worst Grade=1	0 (0.0%)	0 (0.0%)	10 (5.1%)	2 (1.0%)	1 (0.5%)	14 (6.7%)	0 (0.0%)	0 (0.0%)	31 (7.8%)
Worst Grade=2	0 (0.0%)	2 (1.0%)	10 (5.1%)	4 (1.9%)	3 (1.4%)	12 (5.8%)	2 (0.5%)	6 (1.5%)	32 (8.1%)
Worst Grade=3	42 (21.4%)	13 (6.6%)	32 (16.3%)	60 (28.8%)	22 (10.6%)	30 (14.4%)	76 (19.2%)	47 (11.9%)	63 (15.9%)
Worst Grade=4	126 (64.3%)	32 (16.3%)	49 (25.0%)	113 (54.3%)	3 (1.4%)	11 (5.3%)	280 (70.7%)	103 (26.0%)	122 (30.8%)
Worst Grade=5	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

Treatment-emergent Prolonged or Recurrent Cytopenia (Excluding Anemia): Frequency, Seriousness, Outcome, and Severity; All Clinical Trials using Ciltacabtagene Autoleucel, Subjects Treated with Ciltacabtagene Autoleucel (Comparator: All Subjects Treated)

	Randomized Clinical Trials						All Clinical Trials		
	Ciltacabtagene autoleucel			Comparator			Ciltacabtagene autoleucel		
	Neutropenia	Lymphopenia	Thrombocytopenia	Neutropenia	Lymphopenia	Thrombocytopenia	Neutropenia	Lymphopenia	Thrombocytopenia
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)

[a]The lab result with the worst toxicity grade will be used for a calendar day. Recovery definition: must have 2 consecutive Grade <=2 results from separate days if recovery period <=10 days. The lab results assessed after Day 1 until the start of subsequent therapy are included in the analysis.
[b]The subject is counted only once regardless of the number of events or the number of occurrences. Adverse Events after Day 1 until the start of subsequent therapy are included in the analysis.
[c]Graded according to CTCAEv5.
Note: Grade 3/4 thrombocytopenia: Platelets count < 50,000 cells/µL; Grade 3/4 neutropenia: Neutrophil count < 1000 cells/µL; Grade 3/4 Lymphopenia: Lymphocytes count < 0.5×10 9/L; Grade 3 Anemia: hemoglobin count <8g/dL. Grade 4 not defined by laboratory count per NCI-CTCAE v5.
Note: Study day is in reference to the initial administration of ciltacabtagene autoleucel (Day 1) or, for the comparator arm, to the first dose of study therapy.
Note: Percentages are calculated with the number of subjects in the all treated analysis set as denominator, except for the outcome of cytopenia for which percentages are calculated with the number of subjects with cytopenia in the all treated analysis set as denominator.
Note: Adverse Events were coded using MedDRA Version 26.1. Search criteria are listed in ANNEX 7.
Note: For the randomized clinical trial population, total columns are not additive since some subjects may have experienced one or more types of cytopenia. The total number of subjects experiencing any cytopenia adverse events was 178 (90.8%). The total number of subjects experiencing any prolonged cytopenia (based on laboratory data) by Day 30 was 124 (63.3%). The total number of subjects experiencing any prolonged cytopenia by Day 60 was 59 (30.1%). The total number of subjects having recurrence of cytopenia after Day 60 was 93 (47.4%).
Note: Total columns are not additive since some subjects may have experienced one or more types of cytopenia. For the randomized clinical trial population, the total number of subjects experiencing any cytopenia adverse events was 179 (91.3%). The total number of subjects experiencing any prolonged cytopenia (based on laboratory data) by Day 30 was 123 (62.8%). The total number of subjects experiencing any prolonged cytopenia by Day 60 was 58 (29.6%). The total number of subjects having recurrence of cytopenia after Day 60 was 96 (49.0%). For the comparator clinical trial population, The total number of subjects experiencing any cytopenia adverse events was 183 (88.0%). The total number of subjects experiencing any prolonged cytopenia (based on laboratory data) by Day 30 was 149 (71.6%). The total number of subjects experiencing any prolonged cytopenia by Day 60 was 42 (20.2%). The total number of subjects having recurrence of cytopenia after Day 60 was 111 (53.4%). For the All Clinical Trials population the total number of subjects experiencing any cytopenia adverse events was 374 (94.4%). The total number of subjects experiencing any prolonged cytopenia (based on laboratory data) by Day 30 was 245 (61.9%). The total number of subjects experiencing any prolonged cytopenia by Day 60 was 130 (32.8%). The total number of subjects having recurrence of cytopenia after Day 60 was 192 (48.5%).
Note: The following trials are included: All Clinical Trials: MMY2001 (N=106), MMY2003 (Cohorts A, B, C, D, E) (N=94), and MMY3002 (Arm B, N=196); Randomized Clinical Trials: MMY3002.

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Patients may exhibit cytopenias for several weeks following lymphodepleting chemotherapy and ciltacabtagene autoleucel infusion. Severe cytopenia could contribute to susceptibility to infection (neutropenia and lymphopenia) and bleeding (thrombocytopenia).

Cytopenic adverse events were reported for 94% of subjects treated with ciltacabtagene autoleucel across all clinical trials. Neutropenia was reported as serious for 6.1% of subjects, and thrombocytopenia for 1.8% of subjects. Grade 3 or 4 cytopenic events were reported for 94% of subjects; there were no Grade 5 events.

At 30 days and 60 days post-infusion, Grade 3 or 4 thrombocytopenia was ongoing for 33% and 19% of subjects, respectively. At 30 days and 60 days post-infusion, Grade 3 or 4 neutropenia was ongoing for 28% and 11% of subjects respectively, and Grade 3 or 4 lymphopenia was ongoing for 25% and 11% of subjects, respectively. Following resolution of initial Grade 3 or 4 events, Grade 3 or 4 lymphopenia recurred >60 days post-infusion for 23% of subjects, neutropenia for 21% of subjects, and thrombocytopenia for 3.5% of subjects.

Risk Factors and Risk Groups:

Risk factors that may contribute to the development of cytopenia include the type of background therapy, bone marrow function, and disease progression. The use of bridging therapy and lymphodepletion prior to ciltacabtagene autoleucel administration is also a risk factor. Other factors include pre-existing neutropenia, or the concurrent use of antibiotics, corticosteroids, or symptomatic treatment medications. Additionally, age of ≥65 years old and female gender are known risk factors for leukopenia.

Preventability:

Patients should be monitored for hematologic parameters following infusion of ciltacabtagene autoleucel. Supportive care with transfusions should be considered for thrombocytopenia. The use of myeloid growth factors, particularly granulocyte-macrophage colony-stimulating factor (GM-CSF), has the potential to worsen CRS and should be avoided until CRS has resolved.

Impact on the Risk-benefit Balance of the Product:

Cytopenia is commonly associated with the underlying disease of multiple myeloma as well as lymphodepletion therapy. Overall, the risk-benefit balance is positive for the product considering the severity of the disease treated, the paucity of effective therapies, and the potential efficacy for patients treated with ciltacabtagene autoleucel.

Public Health Impact:

All usage will be well controlled by the healthcare professional. No public health impact is anticipated.

Annex 1 MedDRA Term:

Thrombocytopenias (HLT)

Important Identified Risk – Serious Infections

Potential Mechanisms:

In addition to the inherent immunodeficiency from underlying disease, treatment with novel agents, especially immunomodulatory agents and high-dose melphalan with autologous stem cell transplantation, have been shown to increase risk of infections in patients with multiple myeloma. Corticosteroids such as dexamethasone and prednisone, which are an important part of the treatment of multiple myeloma, can suppress the immune system when used for a long time and lead to an increased risk of serious infections. Administration of lymphodepletion therapy as well as ciltacabtagene autoleucel may increase the risk of infection due to potential risks of cytopenia or hypogammaglobulinemia.

Evidence Source(s) and Strength of Evidence:

Serious infections, including life-threatening or fatal infections, have been reported with subjects treated with ciltacabtagene autoleucel in clinical trials and serious infection has been identified as an adverse reaction. The risk for serious infection and information regarding this adverse reaction are described in the SmPC for ciltacabtagene autoleucel.

Based on the strength of evidence from clinical trials, serious infections are considered an important identified risk for ciltacabtagene autoleucel.

Characterization of the Risk:

Treatment-emergent Serious Infections: Frequency, Seriousness, Outcome, and Severity; All Clinical Trials Using Ciltacabtagene Autoleucel, Subjects Treated with Ciltacabtagene Autoleucel (Comparator: All Subjects Treated)

	Randomized Clinical Trials		All Clinical Trials
	Ciltacabtagene autoleucel	Comparator	Ciltacabtagene autoleucel
Multiple Myeloma			
Number of subjects treated	196	208	396
Frequency[a]	115 (58.7%)	159 (76.4%)	213 (53.8%)
Seriousness			
Was serious	46 (23.5%)	64 (30.8%)	84 (21.2%)
Outcomes			
Resulted in Death	12 (10.4%)	7 (4.4%)	17 (8.0%)
Not recovered/Not Resolved	3 (2.6%)	4 (2.5%)	14 (6.6%)
Recovered/Resolved	100 (87.0%)	144 (90.6%)	180 (84.5%)
Recovered with sequelae	0	3 (1.9%)	1 (0.5%)
Recovering/Resolving	0	1 (0.6%)	1 (0.5%)
Unknown	0	0	0
Severity (Toxicity Grade)			
Worst Grade=1	9 (4.6%)	8 (3.8%)	22 (5.6%)
Worst Grade=2	57 (29.1%)	88 (42.3%)	101 (25.5%)
Worst Grade=3	35 (17.9%)	54 (26.0%)	64 (16.2%)
Worst Grade=4	2 (1.0%)	2 (1.0%)	9 (2.3%)
Worst Grade=5	12 (6.1%)	7 (3.4%)	17 (4.3%)
Missing	0	0	0

[a]The subject is counted only once regardless of the number of events or the number of occurrences.
Note: For the purposes of this output, the following AE are used. MMY2001 and MMY2003: treatment-emergent adverse events (TEAE). MMY3002 Arm A: TEAE. MMY3002 Arm B: TEAE on or after cilta-cel for those who received cilta-cel as study treatment and cilta-cel emergent AE for those who received cilta-cel as subsequent therapy.
Note: For linked adverse events, outcome is presented for the latest episode of the event. For subjects with more than 1 linked and/or unlinked adverse events, outcome is based on the outcome of the adverse event with the worst toxicity grade; if there is more than 1 linked and/or unlinked adverse event of the worst toxicity grade, the adverse event with the later onset date will be used.
Note: Percentages are calculated with the number of subjects in the all treated analysis set as denominator, except for the outcome of infections for which percentages are calculated with the number of subjects with infections in the all treated analysis set as denominator.
Note: Adverse Events were coded using MedDRA Version 26.1. Search criteria are listed in ANNEX 7.
Note: The following trials are included: All Clinical Trials: MMY2001 (N=106), MMY2003 (Cohorts A, B, C, D, E) (N=94), and MMY3002 (Arm B, N=196); Randomized Clinical Trials: MMY3002.
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Note: Although the important identified risk is serious infections, all adverse events identified by the system organ class of infections and infestations are captured in the table above, independent of their seriousness.

Early clinical manifestations of infection include fever, chills and sweats, cough, diarrhea, new onset of pain. While patients with multiple myeloma have an increased risk of infections due to chemotherapy-related cytopenia and underlying disease causing hypogammaglobulinemia (11% of patients experienced hypogammaglobulinemia) and immunosuppression (Terpos 2015), the occurrence of infection should be noted and monitored.

Treatment-emergent serious infections were reported for 21% of subjects treated with ciltacabtagene autoleucel across all clinical trials. The most commonly reported serious infections were pneumonia (3.8%), COVID-19 pneumonia (3.3%), and sepsis (2.0%). Fatal infections were reported for 4.3% of ciltacabtagene autoleucel-treated subjects; events included pneumonia, COVID-19 pneumonia, sepsis, septic shock, clostridium difficile colitis, bronchopulmonary aspergillosis, pseudomonal sepsis, neutropenic sepsis, and lung abscess. There was no single pathogen trend associated with treatment-emergent infections.

Patients treated with ciltacabtagene autoleucel may be at an increased risk of severe/fatal COVID-19 infections. Within randomized Trial MMY3002, COVID-19 pneumonia was fatal for 3.6% of patients treated with ciltacabtagene autoleucel compared with 1.0% of subjects treated with the control regimens. Events of COVID-19 will continue to be monitored in ongoing trials to further characterize the important identified risk of serious infections.

Risk Factors and Risk Groups:

Patients with multiple myeloma are at risk of infection due to the overproduction of ineffective monoclonal antibodies from the underlying disease, which causes immune dysfunction. Additionally, the use of chemotherapy (including bridging therapy and lymphodepletion prior to ciltacabtagene autoleucel administration) and immunosuppressive treatments may increase the risk of infection. Multiple myeloma patients have as much as a 15-fold increase in risk of infections, particularly pneumonia. Risk factors for fatal COVID-19 infection include comorbidities associated with severe/fatal COVID-19 such as diabetes and obesity, and concomitant use of immune-suppressant medications. In Trial MMY3002, 20 subjects discontinued study treatment due to disease progression on bridging therapy and received ciltacabtagene autoleucel as subsequent therapy. These subjects represent a distinct and higher-risk population with poorer safety outcomes compared with the 176 subjects who received ciltacabtagene autoleucel as study treatment. In these subjects, there was a higher incidence (3 subjects; 15%) of fatal infections, including bronchopulmonary aspergillosis, pseudomonal sepsis, and sepsis.

Preventability:

Patients with active bacterial, viral, or uncontrolled systemic infections were excluded from participation in clinical trials, as were patients with HBV, HCV, or HIV. Patients should be screened for HBV, HCV, and HIV prior to collection of cells for manufacturing. For immunocompromised patients who are at risk for opportunistic infections, prophylactic use of antibiotics, antivirals, or antifungals should be considered. Patients with clinically significant active infection or inflammatory disorders should not start ciltacabtagene autoleucel infusion until the infection is resolved. Patients should be frequently monitored post-infusion for signs and symptoms of infections. Surveillance testing prior to and during treatment with ciltacabtagene autoleucel should be considered, and patients should be treated appropriately. Patients should be counselled on the importance of COVID-19 prevention measures. Hepatitis B virus (HBV) reactivation, in some cases resulting in fulminant hepatitis, hepatic failure, or death, can occur in patients treated with medicinal products directed against B cells. Screening for HBV, HCV, and

HIV should be performed before collection of cells. Cases of febrile neutropenia should be evaluated and managed appropriately as outlined in the SmPC.

Impact on the Risk-benefit Balance of the Product:

The SmPC and PL provide information on how to manage the risk of infection. Overall, the risk-benefit balance is positive for the product considering the severity of the disease treated, the paucity of effective therapies, and the potential efficacy for patients treated with ciltacabtagene autoleucel.

Public Health Impact:

All usage will be well controlled by the healthcare professional. No public health impact is anticipated.

Annex 1 MedDRA Term:

Infections and infestations (SOC)

Important Identified Risk – Hypogammaglobulinemia

Potential Mechanisms:

Hypogammaglobulinemia is an immune disorder characterized by a reduction in all types of gamma globulins, including antibodies that help fight infection. CAR-T cells target BCMA-expressing B cells, resulting in disruption of normal B-cell maturation to plasma cells, subsequently resulting in hypogammaglobulinemia. However, previous chemotherapy can also contribute to decreased normal B cells and the incidence of hypogammaglobulinemia pre-infusion. Hypogammaglobulinemia is ameliorated with intravenous gamma globulin infusions.

Evidence Source(s) and Strength of Evidence:

Hypogammaglobulinemia has been reported with subjects treated with ciltacabtagene autoleucel in clinical trials and hypogammaglobulinemia has been identified as an adverse reaction. The risk for hypogammaglobulinemia and information regarding this adverse reaction are described in the SmPC for ciltacabtagene autoleucel.

Based on the strength of evidence from clinical trials, including incidence and temporal association, hypogammaglobulinemia is considered an important identified risk for ciltacabtagene autoleucel.

Characterization of the Risk:

Treatment-emergent Hypogammaglobulinemia: Frequency, Seriousness, Outcome, and Severity; All Clinical Trials Using Ciltacabtagene Autoleucel, Subjects Treated with Ciltacabtagene Autoleucel (Comparator: All Subjects Treated)

	Randomized Clinical Trials		All Clinical Trials
	Ciltacabtagene autoleucel	Comparator	Ciltacabtagene autoleucel
Multiple Myeloma			
Number of subjects treated	196	208	396
Laboratory data			
IgG < 500 mg/dL after infusion	182 (92.9%)	147 (70.7%)	360 (90.9%)
Adverse Events			
Frequency[a]	101 (51.5%)	18 (8.7%)	133 (33.6%)
Seriousness			
Was serious	0	0	0
Outcomes			
Resulted in Death	0	0	0
Not recovered/Not Resolved	39 (38.6%)	16 (88.9%)	61 (45.9%)
Recovered/Resolved	61 (60.4%)	2 (11.1%)	70 (52.6%)
Recovered with sequelae	0	0	0
Recovering/Resolving	1 (1.0%)	0	2 (1.5%)
Unknown	0	0	0
Severity (Toxicity Grade)			
Worst Grade=1	7 (3.6%)	2 (1.0%)	13 (3.3%)
Worst Grade=2	77 (39.3%)	14 (6.7%)	101 (25.5%)
Worst Grade=3	17 (8.7%)	2 (1.0%)	19 (4.8%)
Worst Grade=4	0	0	0
Worst Grade=5	0	0	0
Missing	0	0	0
Number of subjects with hypogammaglobulinemia based on laboratory data and/or adverse event data	183 (93.4%)	149 (71.6%)	364 (91.9%)

[a]The subject is counted only once regardless of the number of events or the number of occurrences.
Note: For linked adverse events, outcome is presented for the latest episode of the event. For subjects with more than 1 linked and/or unlinked adverse events, outcome is based on the outcome of the adverse event with the worst toxicity grade; if there is more than 1 linked and/or unlinked adverse event of the worst toxicity grade, the adverse event with the later onset date will be used.
Note: Percentages are calculated with the number of subjects in the all treated analysis set as denominator, except for the outcome of hypogammaglobulinemia for which percentages are calculated with the number of subjects with hypogammaglobulinemia in the all treated analysis set as denominator.
Note: Adverse Events were coded using MedDRA Version 26.1. Search criteria are listed in ANNEX 7.
Note: The following trials are included: All Clinical Trials: MMY2001 (N=106), MMY2003 (Cohorts A, B, C, D, E) (N=94), and MMY3002 (Arm B, N=196); Randomized Clinical Trials: MMY3002.

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Across all clinical trials, 92% of subjects treated with ciltacabtagene autoleucel were reported to have hypogammaglobulinemia based on either laboratory data (ie, IgG <500 mg/dL) or adverse event data. Hypogammaglobulinemia was reported as an adverse event for 34% of subjects; the majority of these subjects had Grade 1 or 2 events. No events were serious. Forty-six percent of subjects with adverse events of hypogammaglobulinemia had not recovered at the time of data

cutoff. Fifty-eight percent of subjects received IVIG after ciltacabtagene autoleucel administration either as prophylaxis or as treatment.

Risk Factors and Risk Groups:

Patients with multiple myeloma are at risk of developing hypogammaglobulinemia and are prone to infection. Hypogammaglobulinemia can be intrinsic to the disease, occurring in 45% to 83% of patients with asymptomatic multiple myeloma (ie, SMM) at some point during the disease course (Patel 2019). The most common infections in these early-stage patients involve the respiratory tract and are predominantly caused by encapsulated bacteria such as H. influenzae or S. pneumonia, and viral reactivation, suggesting a role of hypogammaglobulinemia in their pathogenesis (Compagno 2014). It is also frequently associated with chemo-immunotherapy regimens used to treat the disease, particularly those that either deplete B cells and plasma cells, or inhibit B cell survival, impair activation or interaction with T cells. Multiple prior lines of therapy and low IgG baseline values may increase the risk of developing hypogammaglobulinemia in patients with relapsed multiple myeloma. Finally, patients with co-morbidities, such as chronic lung or heart disease and extra-articular rheumatoid arthritis, have also been reported to have higher instances of hypogammaglobulinemia (Patel 2019).

Preventability:

Studies suggest that patients with IgG levels <400 mg/dL and/or low levels of antibodies against encapsulated organisms with an ongoing history of recurrent bacterial infections that have not responded adequately to prophylactic antibiotics could especially benefit from IVIG. Furthermore, selection of patients should include a wider assessment of comorbidities and innate immunological abnormalities, such as neutropenia as well as demonstrating antibody failure (exposure/test immunization) (Patel 2019). As noted in the SmPC, immunoglobulin levels should be monitored after treatment with ciltacabtagene autoleucel, IVIG should be administered for IgG <400 mg/dL, and patients should be managed according to standard guidelines, including antibiotic or antiviral prophylaxis and monitoring for infection.

Impact on the Risk-benefit Balance of the Product:

Hypogammaglobulinemia is a well-known effect of CAR-T products based on their mechanism of action. Ciltacabtagene autoleucel targets BCMA-expressing B cells, resulting in disruption of normal B-cell maturation to plasma cells, subsequently resulting in hypogammaglobulinemia. Hypogammaglobulinemia was commonly reported for subjects in clinical trials of ciltacabtagene autoleucel, was mostly low grade, and was ameliorated with intravenous gamma globulin infusions. Although there may be many factors associated with infections in patients with multiple myeloma, there were subjects in the ciltacabtagene autoleucel clinical trials with one or more Grade 3 or 4 treatment-emergent infections concurrent with hypogammaglobulinemia. The SmPC and PL provide information on how to manage the risks of both hypogammaglobulinemia and serious infections. Overall, the risk benefit balance is positive for the product considering the severity of the disease treated, the paucity of effective therapies, and the potential efficacy for patients treated with ciltacabtagene autoleucel.

Public Health Impact:

All usage will be well controlled by the healthcare professional. No public health impact is anticipated.

Annex 1 MedDRA Term:

Hypogammaglobulinemia (PT)

Important Identified Risk – Secondary malignancy of T-cell origin

Potential Mechanisms:

Multiple potential intrinsic and/or extrinsic factors may contribute to pathogenesis, including the transduction of T-cells with oncogenic predispositions followed by acquisition of further oncogenic genomic variants. Other potential contributors include germline genomic variation, viral infections, and prior myeloma treatment. The generation of RCL during the manufacturing process of the product is an additional theoretical risk. Contributions of insertional mutagenesis to TCL, via integration of the lentiviral vector into a cellular proto-oncogene or a tumor suppressor gene are currently unclear and cannot be excluded.

Evidence Source(s) and Strength of Evidence:

Secondary malignancies of T-cell origin have been reported in clinical trials with ciltacabtagene autoleucel, and T-cell lymphoma has been identified as an adverse reaction. Based on clinical data, secondary malignancy of T-cell origin is considered an important identified risk. This risk is described in the SmPC for ciltacabtagene autoleucel.

Characterization of the Risk:

Secondary Malignancy of T-cell Origin: Frequency, Seriousness, Outcome, and Severity; All Clinical Trials Using Ciltacabtagene Autoleucel, Subjects Treated with Ciltacabtagene Autoleucel (Comparator: All Subjects Treated)

	Randomized Clinical Trials		All Clinical Trials
	Ciltacabtagene autoleucel	Comparator	Ciltacabtagene autoleucel
Multiple Myeloma			
Number of subjects treated	196	208	396
Frequency[a]	2 (1.0%)	0	2 (0.5%)
Seriousness			
Was serious	2 (1.0%)	0	2 (0.5%)
Outcomes			
Resulted in Death	0	0	0
Not recovered/Not Resolved	2 (100.0%)	0	2 (100.0%)
Recovered/Resolved	0	0	0
Recovered with sequelae	0	0	0
Recovering/Resolving	0	0	0
Unknown	0	0	0
Severity (Toxicity Grade)			
Worst Grade=1	0	0	0
Worst Grade=2	0	0	0
Worst Grade=3	2 (1.0%)	0	2 (0.5%)
Worst Grade=4	0	0	0
Worst Grade=5	0	0	0
Missing	0	0	0

[a]The subject is counted only once regardless of the number of events or the number of occurrences.
Note: For linked adverse events, outcome is presented for the latest episode of the event. For subjects with more than 1 linked and/or unlinked adverse events, outcome is based on the outcome of the adverse event with the worst toxicity grade; if there is more than 1 linked and/or unlinked adverse event of the worst toxicity grade, the adverse event with the later onset date will be used.
Note: Percentages are calculated with the number of subjects in the all treated analysis set as denominator, except for the outcome of TCL for which percentages are calculated with the number of subjects with TCL in the all treated analysis set as denominator.
Note: Adverse Events were coded using MedDRA Version 25.0. Search criteria are listed in ANNEX 7.
Note: The following trials are included: All Clinical Trials: MMY2001 (N=106), MMY2003 (Cohorts A, B, C, D, E) (N=94), and MMY3002 (Arm B, N = 196); Randomized Clinical Trials: MMY3002.

[TSFAE01SPM3A.RTF] [PROD/JNJ-68284528/Z_RMP/DBR_SBLA_2023/RE_SBLA_2023/TSFAE01SPM2A.SAS] 11JUN2024, 09:25

Data presented for this risk are based on a cutoff date of 14 October 2022 for Study MMY2001, a data cutoff date of 31 January 2023 for Study MMY2003 and 27 February 2024 for Study MMY3002.

No cases of T-cell lymphoma were reported in Study MMY2001 or MMY2003. In Study MMY3002, T-cell lymphoma was reported for 0.5% (2/196) of subjects (0.5 events per 100 person-years post ciltacabtagene autoleucel infusion). These patients were diagnosed with peripheral T-cell lymphoma unspecified on Day 159 and Day 688 after ciltacabtagene autoleucel infusion. Presence of the CAR transgene was detected in the tumors.

As of 27 February 2024, no additional cases of T-cell lymphoma have occurred in the long-term follow-up study (Study MMY4002; median follow-up of 31.8 months), representing a cumulative

long-term incidence rate of 0.2 events per 100 person-years post ciltacabtagene autoleucel infusion. Cases of T-cell lymphoma, including CAR-positive T-cell lymphoma, have been reported in the postmarketing setting.

Risk Factors and Risk Groups:

Multiple potential intrinsic and/or extrinsic factors may have contributed to the development of T-cell lymphoma, including pre-existing mutations in driver genes for T-cell lymphoma followed by acquisition of further oncogenic genomic variants. Additional potential but unknown contributors include germline genomic variation, viral infections, prior myeloma treatment. The contributing role of CAR insertion to the development of T-cell lymphoma is not fully understood and therefore cannot be excluded.

Preventability:

Patients with active invasive malignancies other than multiple myeloma were excluded from clinical trial participation. There are no specific recommendations that would prevent the occurrence of secondary malignancies of T-cell origin. The SmPC provides information regarding this risk, including instructions that patients should be monitored life-long for secondary malignancies, and that the sponsor should be contacted to obtain instructions on collection of patient samples. An additional risk minimization measure to increase awareness of this risk is educational materials for HCPs.

Impact on the Risk-benefit Balance of the Product:

Overall, the risk-benefit balance is positive for the product considering the severity of the disease treated, the paucity of effective therapies, and the potential efficacy for patients treated with ciltacabtagene autoleucel.

Public Health Impact:

All usage will be well controlled by the healthcare professional. No public health impact is anticipated.

Annex 1 MedDRA Term:

HLGTs: Lymphomas non-Hodgkin’s T-cell

Important Identified Risk – Secondary malignancy of myeloid origin

Potential Mechanisms:

Expansion of clones with pre-existing MDS/AML malignant potential has been observed in both CD19 and BCMA CAR-T products and is a plausible underlying biological mechanism. Based on previous reports, no new mutations developed after CAR-T cell therapy; rather, the frequency of pre-existing mutations was increased (Vainstein 2023; Zhao 2023).

Evidence Source(s) and Strength of Evidence:

Secondary malignancies of myeloid origin have been reported in clinical trials with ciltacabtagene autoleucel, and MDS and AML have been identified as adverse reactions. Based on clinical data, secondary malignancy of myeloid origin is considered an important identified risk. This risk is described in the SmPC for ciltacabtagene autoleucel.

Characterization of the Risk:

Secondary Malignancy of Myeloid Origin: Frequency, Seriousness, Outcome, and Severity; All Clinical Trials Using Ciltacabtagene Autoleucel, Subjects Treated with Ciltacabtagene Autoleucel (Comparator: All Subjects Treated)

	Randomized Clinical Trials		All Clinical Trials
	Cilta-cel	Comparator	Cilta-cel
Multiple Myeloma			
Number of subjects treated	196	208	396
Frequency[a]	5 (2.6%)	0	16 (4.0%)
Seriousness			
Was serious	5 (2.6%)	0	15 (3.8%)
Outcomes			
Resulted in Death	2 (40.0%)	0	6 (37.5%)
Not recovered/Not Resolved	3 (60.0%)	0	9 (56.3%)
Recovered/Resolved	0	0	1 (6.3%)
Recovered with sequelae	0	0	0
Recovering/Resolving	0	0	0
Unknown	0	0	0
Severity (Toxicity Grade)			
Worst Grade=1	0	0	1 (0.3%)
Worst Grade=2	0	0	0
Worst Grade=3	0	0	3 (0.8%)
Worst Grade=4	3 (1.5%)	0	6 (1.5%)
Worst Grade=5	2 (1.0%)	0	6 (1.5%)
Missing	0	0	0

Keys:AML = acute myeloid leukaemia, Cilta-cel = ciltacabtagene autoleucel, MDS = myelodysplastic syndrome.
[a]The subject is counted only once regardless of the number of events or the number of occurrences.
Note: For linked adverse events, outcome is presented for the latest episode of the event. For subjects with more than 1 linked and/or unlinked adverse events, outcome is based on the outcome of the adverse event with the worst toxicity grade; if there is more than 1 linked and/or unlinked adverse event of the worst toxicity grade, the adverse event with the later onset date will be used.
Note: Percentages are calculated with the number of subjects in the all treated analysis set as denominator, except for the outcome of MDS/AML for which percentages are calculated with the number of subjects with MDS/AML in the all treated analysis set as denominator.
Note: Adverse Events were coded using MedDRA Version 25.0. Search criteria are listed in ANNEX 7.
Note: The following trials are included: All Clinical Trials: MMY2001 (N=106), MMY2003 (Cohorts A, B, C, D, E) (N=94), and MMY3002 (Arm B, N = 196); Randomized Clinical Trials: MMY3002.
[TSFAE01SPM3B.RTF] [PROD/JNJ-68284528/Z_RMP/DBR_SBLA_2023/RE_SBLA_2023/TSFAE01SPM2B.SAS] 05JUL2024, 09:18

Data presented for this risk are based on a cutoff date of 14 October 2022 for Study MMY2001 and 27 February 2024 for Study MMY3002.

In Study MMY2001, myeloid neoplasms were reported for 8.5% (9/106) of subjects as of study close out (median follow-up of 33.0 months). There were 6 cases of MDS, 2 cases of AML, and

1 case of MDS followed by AML. The median time from ciltacabtagene autoleucel infusion to onset was 478 days (range: 162 to 870 days). Seven of the 9 subjects died following the development of myeloid neoplasms; 4 deaths were deemed related to the myeloid neoplasm. Two of the 9 cases occurred after initiation of subsequent antimyeloma therapy. All 9 subjects were heavily pretreated, with a range of 4 to 18 prior therapies, all were previously treated with alkylators, and all previously received ASCT. All subjects had genetic mutations associated with the development of MDS or AML present prior to receiving ciltacabtagene autoleucel.

In Study MMY3002, myeloid neoplasms were reported for 2.6% (5/196) of subjects (1.2 events per 100 person-years post ciltacabtagene autoleucel infusion) as of 27 February 2024 (median follow-up of 28.1 months). There were 2 cases of MDS, 1 case of AML, and 2 cases of MDS followed by AML. The median time from ciltacabtagene autoleucel infusion to onset was 385 days (range: 56 to 758 days). All 5 subjects died following the development of myeloid neoplasms, with all 5 deaths deemed related to the myeloid neoplasm. All subjects were previously treated with alkylators and lenalidomide and the majority of subjects previously received ASCT. Two subjects previously received treatment for other hematologic malignancies. All subjects had genetic mutations associated with the development of MDS or AML present prior to receiving ciltacabtagene autoleucel.

As of 27 February 2024, 3 additional cases of myeloid neoplasms occurred in a long-term follow-up study (Study MMY4002; median follow-up of 31.8 months), representing a cumulative long-term incidence rate of 2 events per 100 person-years post ciltacabtagene autoleucel infusion. The median time to onset of myeloid neoplasm in the long-term follow-up study was 954 days after ciltacabtagene autoleucel infusion. Cases of MDS and AML have also been reported in the postmarketing setting.

Risk Factors and Risk Groups:

Development of MDS and AML is multifactorial. Previous exposure to alkylating agents and/or ASCT has been implicated in the development of MDS/AML leading to the manifestation of MDS/AML mutations in hematopoietic stem cells. Prior exposure to lenalidomide may also be a risk factor for the development of MDS/AML. In addition, immunosuppression caused by lymphodepletion as well as CAR-T therapy may contribute to the risk of MDS/AML.

Preventability:

Patients with active invasive malignancies other than multiple myeloma were excluded from clinical trial participation. There are no specific recommendations that would prevent the occurrence of secondary malignancies of myeloid origin. The SmPC provides information regarding this risk, including instructions that patients should be monitored life-long for secondary malignancies, and that the sponsor should be contacted to obtain instructions on collection of patient samples. An additional risk minimization measure to increase awareness of this risk is educational materials for HCPs.

Impact on the Risk-benefit Balance of the Product:

Overall, the risk-benefit balance is positive for the product considering the severity of the disease treated, the paucity of effective therapies, and the potential efficacy for patients treated with ciltacabtagene autoleucel.

Public Health Impact:

All usage will be well controlled by the healthcare professional. No public health impact is anticipated.

Annex 1 MedDRA Term:

PT: Acute myeloid leukemia (PT)

Important Potential Risk – Secondary malignancy except those of T-cell and myeloid origin

Potential Mechanisms:

The risk of secondary malignancy (except those of T-cell and myeloid origin) is theoretical due to viral insertion (DNA integration) of the lentiviral vector used to make ciltacabtagene autoleucel cells. Integration of the vector into the patient's cells might inadvertently activate a cellular proto-oncogene or disrupt a tumor suppressor gene, leading to malignant transformation events (ie, secondary malignancies). The generation of RCL during the manufacturing process of the product is an additional theoretical safety concern.

Evidence Source(s) and Strength of Evidence:

In addition to secondary malignancies of T-cell and myeloid origin as listed in the important identified risks above, other secondary malignancies are also a theoretical risk from lentiviral vector DNA insertion and RCL.

Characterization of the Risk:

Summary of Secondary Malignancy Except Those of T-cell and Myeloid Origin: Frequency, Seriousness, Outcome, and Severity; All Clinical Trials Using Ciltacabtagene Autoleucel, Subjects Treated with Ciltacabtagene Autoleucel (Comparator: All Subjects Treated)

	Randomized Clinical Trials		All Clinical Trials
	Cilta-cel	Comparator	Cilta-cel
Multiple Myeloma			
Number of subjects treated	196	208	396
Frequency[a]	20 (10.2%)	24 (11.5%)	32 (8.1%)
Seriousness			
Was serious	8 (4.1%)	9 (4.3%)	15 (3.8%)
Outcomes			
Resulted in Death	2 (10.0%)	0	2 (6.3%)
Not recovered/Not Resolved	2 (10.0%)	6 (25.0%)	7 (21.9%)
Recovered/Resolved	16 (80.0%)	18 (75.0%)	23 (71.9%)
Recovered with sequelae	0	0	0
Recovering/Resolving	0	0	0
Unknown	0	0	0
Severity (Toxicity Grade)			
Worst Grade=1	1 (0.5%)	2 (1.0%)	4 (1.0%)
Worst Grade=2	13 (6.6%)	11 (5.3%)	19 (4.8%)
Worst Grade=3	4 (2.0%)	11 (5.3%)	7 (1.8%)
Worst Grade=4	0	0	0
Worst Grade=5	2 (1.0%)	0	2 (0.5%)
Missing	0	0	0

Keys: AML = acute myeloid leukaemia, Cilta-cel = ciltacabtagene autoleucel, MDS = myelodysplastic syndrome, TCL = T-cell lymphomas.
[a]The subject is counted only once regardless of the number of events or the number of occurrences.
Note: For linked adverse events, outcome is presented for the latest episode of the event. For subjects with more than 1 linked and/or unlinked adverse events, outcome is based on the outcome of the adverse event with the worst toxicity grade; if there is more than 1 linked and/or unlinked adverse event of the worst toxicity grade, the adverse event with the later onset date will be used.
Note: Percentages are calculated with the number of subjects in the all treated analysis set as denominator, except for the outcome of secondary malignancies for which percentages are calculated with the number of subjects with secondary malignancies in the all treated analysis set as denominator.
Note: Adverse Events were coded using MedDRA Version 26.1. Search criteria are listed in ANNEX 4.3.
Note: The following trials are included: All Clinical Trials: MMY2001 (N=106), MMY2003 (Cohorts A, B, C, D, E) (N=94), and MMY3002 (Arm B, N = 196); Randomized Clinical Trials: MMY3002.

[TSFAE01SPM2.RTF] [PROD/JNJ-68284528/Z_RMP/DBR_2024/RE_RMP_2024/TSFAE01SPM2.SAS] 06NOV2024, 22:42

Data presented for this risk are based on cutoff dates of 14 October 2022 for Study MMY2001, 27 February 2024 for Study MMY2003, and 1 May 2024 for Study MMY3002.

In the all clinical trials population, secondary malignancy (except those of T-cell and myeloid origin) were reported for 8.1% of subjects treated with ciltacabtagene autoleucel. The time from ciltacabtagene autoleucel infusion to time of diagnosis of these secondary malignancies varied widely, from 6 days (for an event of squamous cell carcinoma) to 994 days (also squamous cell carcinoma). One case of angiosarcoma, which was diagnosed 374 days following ciltacabtagene autoleucel infusion, was fatal.

Risk Factors and Risk Groups:

Secondary malignancy is a theoretical risk of insertional mutagenesis; therefore, all patients who receive ciltacabtagene autoleucel are theoretically at risk. Other risk factors include previous exposure to high-dose alkylating therapy and use of lenalidomide maintenance therapy.

Preventability:

Patients with active invasive malignancies other than multiple myeloma were excluded from clinical trial participation. There are no specific recommendations that would prevent the occurrence of secondary malignancies.

Impact on the Risk-benefit Balance of the Product:

Overall, the risk-benefit balance is positive for the product considering the severity of the disease treated, paucity of effective therapies, and the potential efficacy for patients treated with ciltacabtagene autoleucel.

Public Health Impact:

All usage will be well controlled by the healthcare professional. No public health impact is anticipated.

Annex 1 MedDRA Term:

Angiosarcoma (PT)

Important Potential Risk – Decrease in cell viability due to inappropriate handling or preparation of the product

Potential Mechanisms:

Risks of breaking the cold chain or other type of controlled temperature conditions or mishandling the preservation, freezing, or thawing could impact the cell viability and biological activity of ciltacabtagene autoleucel, potentially leading to treatment failure.

Evidence Source(s) and Strength of Evidence:

While no evidence of decrease in cell viability due to inappropriate handling or preparation has been identified to date from clinical trials of ciltacabtagene autoleucel, this is a potential risk with CAR-T products based on their distinct method of manufacturing and administration.

Characterization of the Risk:

As this is a potential risk with no cases observed in clinical trials, no attributable increased risk with ciltacabtagene autoleucel administration has been established.

Risk Factors and Risk Groups:

The risk factor is lack of strict adherence to the specifications for preparation of ciltacabtagene autoleucel infusion. All patients receiving infusion are potentially at risk.

Preventability:

Ciltacabtagene autoleucel must be prepared, transported, stored, thawed, and administered per strict guidelines to avoid potential risk of decrease in cell viability due to inappropriate handling or preparation of the product. Part V.2 of the RMP outlines additional risk minimization measures to mitigate this risk, including Product Handling Training for HCPs and other personnel involved in the transport, storage, thawing, preparation, or handling of ciltacabtagene autoleucel.

Impact on the Risk-benefit Balance of the Product:

Overall, the risk-benefit balance is positive for the product considering the severity of the disease treated, the paucity of effective therapies, and the potential efficacy for patients treated with ciltacabtagene autoleucel.

Public Health Impact:

All usage will be well controlled by the healthcare professional. No public health impact is anticipated.

Annex 1 MedDRA Term:

Not applicable.

Important Potential Risk – Tumor Lysis Syndrome

Potential Mechanisms:

Tumor lysis syndrome (TLS) is a combination of metabolic derangements caused by the massive and abrupt release of cellular components into the blood after rapid lysis of malignant cells. These metabolites can overwhelm the body's homeostatic mechanisms and cause hyperuricemia, hyperkalemia, hyperphosphatemia, and hypocalcemia. Tumor lysis syndrome can occur spontaneously in patients with tumors of a high proliferative rate, but is more commonly seen following initiation of chemotherapy.

Evidence Source(s) and Strength of Evidence:

The incidence of TLS was low in clinical trials of ciltacabtagene autoleucel, with only 3 cases of TLS reported as of the data cutoff. However, a biological plausibility may exist for risk of developing TLS in multiple myeloma patients with extensive disease burden and/or plasmacytomas, considering the antimyeloma effects of ciltacabtagene autoleucel. Therefore, TLS is considered an important potential risk.

Characterization of the Risk:

Treatment-emergent Tumor Lysis Syndrome: Frequency, Seriousness, Outcome, and Severity; All Clinical Trials using Ciltacabtagene Autoleucel, Subjects Treated with Ciltacabtagene Autoleucel (Comparator: All Subjects Treated)

	Randomized Clinical Trials		All Clinical Trials
	Ciltacabtagene autoleucel	Comparator	Ciltacabtagene autoleucel
Multiple Myeloma			
Number of subjects treated	196	208	396
Frequency[a]	1 (0.5%)	0	3 (0.8%)
Seriousness			
Was serious	0	0	1 (0.3%)
Outcomes			
Resulted in Death	0	0	0
Not recovered/Not Resolved	1 (100.0%)	0	1 (33.3%)
Recovered/Resolved	0	0	2 (66.7%)
Recovered with sequelae	0	0	0
Recovering/Resolving	0	0	0
Unknown	0	0	0
Severity (Toxicity Grade)			
Worst Grade=1	0	0	0
Worst Grade=2	0	0	0
Worst Grade=3	1 (0.5%)	0	2 (0.5%)
Worst Grade=4	0	0	1 (0.3%)
Worst Grade=5	0	0	0
Missing	0	0	0

[a]The subject is counted only once regardless of the number of events or the number of occurrences.
Note: For the purposes of this output, treatment-emergent adverse events (TEAE) in MMY2001 and MMY2003, and TEAE for Arm A in MMY3002 and TEAE on or after ciltacabtagene autoleucel for Arm B in MMY3002 are used.
Note: For linked adverse events, outcome is presented for the latest episode of the event. For subjects with more than 1 linked and/or unlinked adverse events, outcome is based on the outcome of the last event
Note: Percentages are calculated with the number of subjects in the all treated analysis set as denominator, except for the outcome of tumor lysis syndrome for which percentages are calculated with the number of subjects with tumor lysis syndrome in the all treated analysis set as denominator.
Note: Adverse Events were coded using MedDRA Version 26.1. Search criteria are listed in ANNEX 7.
Note: The following trials are included: All Clinical Trials: MMY2001 (N=106), MMY2003 (Cohorts A, B, C, D, E) (N=84), and MMY3002 (Arm B, N = 196); Randomized Clinical Trials: MMY3002.

[TSFAE01TLS1.RTF] [PROD/JNJ-68284528/Z_RMP/DBR_2024/RE_RMP_2024/TSFAE01_SUB.SAS] 03OCT2024, 14:53

Tumor lysis syndrome was reported for 3 subjects (0.8%) treated with ciltacabtagene autoleucel across all clinical trials. One subject had a Grade 4 serious event and the other 2 had Grade 3 non-serious events. As of the clinical cutoff dates, 2 subjects had recovered and 1 subject had not recovered.

Risk Factors and Risk Groups:

Patients at high risk for TLS include those with a high tumor burden (≥60% plasma cell infiltrate on the bone marrow biopsy or aspirate [whichever is higher] or those with multiple extramedullary disease sites and/or plasmacytomas.

Preventability:

Early recognition and monitoring of signs and symptoms of TLS, including identification of abnormal clinical and laboratory values, may lead to successful prevention of the serious clinical complications of the condition. Patients should be monitored closely for symptoms of TLS. Management of TLS, including hyperkalemia, hyperuricemia, hyperphosphatemia, and hypocalcemia, is recommended. High-risk patients should be treated prophylactically in accordance with local standards. As TLS is a common condition, these mitigation measures are well established in clinical practice.

Impact on the Risk-benefit Balance of the Product:

While TLS may be a life-threatening condition, the incidence is low in clinical trials of ciltacabtagene autoleucel, reported cases were confounded, and the management of TLS is well known in clinical practice. Patients with high tumor burden or with multiple extramedullary disease sites and/or plasmacytomas are at risk and should be treated prophylactically in accordance with local standards. Data on TLS will be reported during the duration of the clinical trials. An observational PASS (68284528MMY4004; which includes 68284528MMY4009 as one of multiple data sources) will also collect data on TLS in patients treated with ciltacabtagene autoleucel in the commercial setting. Overall, the risk-benefit balance is positive for the product considering the severity of the disease treated, the paucity of effective therapies, and the potential efficacy for patients treated with ciltacabtagene autoleucel.

Public Health Impact:

All usage will be well controlled by the healthcare professional. No public health impact is anticipated.

Annex 1 MedDRA Term:

Tumor lysis syndrome (PT)

Important Potential Risk – Aggravation of Graft versus Host Disease

Potential Mechanisms:

Graft versus Host Disease occurs when immune cells transplanted from a non-identical donor (the graft) recognize the transplant recipient (the host) as foreign, thereby initiating an immune reaction that causes disease in the transplant recipient. This is the major cause of morbidity and non-relapse mortality in patients after allogeneic HCT. When T cells are obtained and manufactured from the recently allogenic transplanted patient who will receive the infusion, these cells might be genetically identical to the donor of allo-HSCT which may trigger a di novo or aggravate a pre-existing GvHD reaction (Sanber 2021).

Evidence Source(s) and Strength of Evidence:

No cases of aggravated or de novo GvHD have been reported in clinical trials of ciltacabtagene autoleucel to date. However, a biological plausibility may exist for increased risk of aggravation of GvHD, particularly in patients receiving allogenic transplant prior to 6 months of ciltacabtagene autoleucel or still receiving immunosuppressants to control a prior event of GvHD after allogenic transplant who will not be restricted from receiving ciltacabtagene autoleucel. Therefore, aggravation of GvHD is considered a potential risk.

Characterization of the Risk:

As this is a potential risk with no cases observed in clinical trials, no attributable increased risk with ciltacabtagene autoleucel administration has been established.

Risk Factors and Risk Groups:

Risk factors for developing GvHD in multiple myeloma patients after receiving allogenic transplant include the following: higher degree of human leukocyte antigen (HLA) mismatch, older age of the donor or recipient, sex disparity between donor and recipient, prior acute GvHD (aGvHD), a splenectomized recipient, CMV seropositivity in the donor or recipient, donor EBV seropositivity. The probability of developing a subsequent acute or chronic GVHD increases with increasing numbers of risk factors (Hill 2021). Patients receiving allogenic transplant prior to 6 months of ciltacabtagene autoleucel or still receiving immunosuppressants to control a prior event of GvHD after allogenic transplant may be at increased risk for aggravation of GvHD.

Preventability:

Patients are instructed to tell their doctor if they have any signs or symptoms of GvHD prior to treatment, as noted in the PL. Ciltacabtagene autoleucel infusion should be delayed if a patient has active GvHD, as noted in the SmPC.

Impact on the Risk-benefit Balance of the Product:

To date, no cases of aggravated or de novo GvHD have been reported in ciltacabtagene autoleucel clinical trials. However, a theoretical risk of aggravation of GvHD may exist in patients receiving allogenic transplant prior to 6 months of ciltacabtagene autoleucel infusion or still receiving immunosuppressants to control a prior event of GvHD after allogenic transplant. Data on GvHD will be reported during the duration of the clinical trials, and subsequently will be collected in a long-term follow-up study (68284528MMY4002). In addition, an observational PASS (68284528MMY4004; which includes 68284528MMY4009 as one of multiple data sources) will also collect data on GvHD in patients treated with ciltacabtagene autoleucel in the commercial setting. Overall, the risk-benefit balance is positive for the product considering the severity of the disease treated, the paucity of effective therapies, and the potential efficacy for patients treated with ciltacabtagene autoleucel.

Public Health Impact:

All usage will be well controlled by the healthcare professional. No public health impact is anticipated.

Annex 1 MedDRA Term:

Graft versus Host Disease

Important Potential Risk – Generation of Replication Competent Lentivirus (RCL)

Potential Mechanisms:

Ciltacabtagene autoleucel leverages a third-generation SIN LVV packaging system that supports a low risk of generating RCL or secondary malignancies. Despite the safety features of the third generation SIN LVV system (including the removal of non-essential viral accessory genes and segregating the remaining viral genome into separate plasmids), the use of LVV for gene delivery continues to be a theoretical safety concern because of the potential for generation of RCL and insertional mutagenesis mainly described in autologous hematopoietic stem cell gene therapy with gamma retroviral vectors.

Evidence Source(s) and Strength of Evidence:

While no cases of generation of RCL have been reported to date in clinical trials of ciltacabtagene autoleucel, this is a potential risk due to potential viral insertion (DNA integration) of the lentiviral vector.

Characterization of the Risk:

As this is a potential risk with no cases observed in clinical trials, no attributable increased risk with ciltacabtagene autoleucel administration has been established.

Risk Factors and Risk Groups:

All patients who receive ciltacabtagene autoleucel are theoretically at risk.

Preventability:

Although the lentivirus used in ciltacabtagene autoleucel is designed to be replication incompetent, the generation of RCL remains a theoretical risk and cannot be excluded. Third-generation LVVs have several built-in safety features that minimize the risk of generating replication-competent wild-type human HIV-1 recombinants through recombination events and increase the incidence of insertional mutagenesis.

Impact on the Risk-benefit Balance of the Product:

To date, no cases of RCL have been reported in clinical trials of ciltacabtagene autoleucel. Despite the safety features of the third generation SIN LVV system used for gene delivery in the

manufacturing of ciltacabtagene autoleucel, the potential for generation of RCL described in autologous hematopoietic stem cell gene therapy with gamma retroviral vectors remains a theoretical risk. Data on RCL will be collected during the duration of the clinical trials and subsequently in a long-term follow-up study (68284528MMY4002) if any post-treatment samples are positive during the first year or thereafter, as clinically indicated (ie, event-triggered). Data on generation of RCL will also be collected in Study 68284528MMY4009. Overall, the risk-benefit balance is positive for the product considering the severity of the disease treated, the paucity of effective therapies, and the potential efficacy for patients treated with ciltacabtagene autoleucel.

Public Health Impact:

All usage will be well controlled by the healthcare professional. No public health impact is anticipated.

Annex 1 MedDRA Term:

Replication Competent Retrovirus Test Positive (PT)

SVII.3.2. Presentation of the Missing Information

Missing information: Long-term safety
Evidence source: To date, there are no data on the long-term safety of ciltacabtagene autoleucel.
Population in need of further characterization: A risk associated with long-term use cannot be defined based on available evidence. Delayed onset adverse events, including but not limited to neurologic toxicities, autoimmune disorders, secondary malignancy of T-cell origin, secondary malignancy of myeloid origin, and secondary malignancies except those of T-cell and myeloid origin, will be collected as part of the following studies: A long-term follow-up study (68284528MMY4002) of patients treated with ciltacabtagene autoleucel in clinical trials will be conducted to understand the long-term safety profile of the product. An observational PASS study (68284528MMY4004; which includes 68284528MMY4009 as one of multiple data sources) will be conducted to evaluate the long-term safety of ciltacabtagene autoleucel in adult patients with multiple myeloma under real-world conditions.
Missing information: Impact on pregnancy and lactation
Evidence source: Pregnant and breastfeeding women were excluded from clinical trials. There are no available preclinical or clinical data on the use of ciltacabtagene autoleucel during pregnancy. It is unknown whether ciltacabtagene autoleucel has the potential to cause foetal toxicity or is excreted in human milk.
Anticipated risk/consequence of the missing information: It is not known whether ciltacabtagene autoleucel has the potential to be transferred to the fetus and cause fetal toxicity; therefore, pregnant women should be advised there may be risks to the fetus. A risk to the breast-fed infant cannot be excluded. Women who are breast-feeding should be advised of the potential risk to the breast-fed infant. Any pregnancies in ongoing and future clinical trials will be reported, including in a long-term follow up study (68284528MMY4002) and an observational PASS study (68284528MMY4004; which includes 68284528MMY4009 as one of multiple data sources).
Missing information: Use in patients with pre-existing autoimmune disease
Evidence source: Patients with active autoimmune disease or a history of autoimmune disease within 3 years were excluded from clinical trials.
Population in need of further characterization: A risk associated with autoimmune disease cannot be defined based on available evidence. New incidence or exacerbation of a prior rheumatologic or other autoimmune disorder will be reported in an observational PASS study (68284528MMY4004; which includes 68284528MMY4009 as one of multiple data sources). The long-term follow-up study (68284528MMY4002) will also collect any new onset of autoimmune disease.
Missing information: Use in patients with pre-existing neurodegenerative disorders
Evidence source: Patients with overt clinical evidence of dementia or altered mental status were excluded from clinical trials.

Population in need of further characterization: A risk associated with pre-existing neurodegenerative disorders cannot be defined based on available evidence. New incidence or exacerbation of a pre-existing neurologic disorder will be reported in an observational PASS study (68284528MMY4004; which includes 68284528MMY4009 as one of multiple data sources). The long-term follow-up study (68284528MMY4002) will also collect any new onset of neurodegenerative disorders.
Missing information: Use in patients with active CNS involvement by malignancy
Evidence source: Patients with known active or prior history of CNS involvement or those exhibiting signs of meningeal involvement of multiple myeloma were excluded from clinical trials.
Population in need of further characterization: A risk associated with active CNS involvement by malignancy cannot be defined based on available evidence. New incidence or exacerbation of a pre-existing neurologic disorder will be reported in an observational PASS study (68284528MMY4004; which includes 68284528MMY4009 as one of multiple data sources). The long-term follow-up study (68284528MMY4002) will also collect any new onset of neurologic disorders.
Missing information: Use in patients with chronic controlled HIV and HBV/HCV infection
Evidence source: Patients with HIV, HBV, or HCV infection were excluded from clinical trials.
Population in need of further characterization: A risk associated with chronic controlled HIV and HBV/HCV infection cannot be defined based on available evidence. New incidence of severe infection will be reported in both a long-term follow-up study (68284528MMY4002) and an observational PASS study (68284528MMY4004; which includes 68284528MMY4009 as one of multiple data sources).

PART II: SAFETY SPECIFICATION

Module SVIII: Summary of the Safety Concerns

Table SVIII.1: Summary of Safety Concerns

Important Identified Risks	Cytokine release syndrome (including HLH)
	Neurologic toxicities (including ICANS and other neurotoxicities)
	Prolonged or recurrent cytopenia (excluding anemia)
	Serious infections
	Hypogammaglobulinemia
	Secondary malignancy of T-cell origin
	Secondary malignancy of myeloid origin
Important Potential Risks	Secondary malignancy except those of T-cell and myeloid origin
	Decrease in cell viability due to inappropriate handling or preparation of the product
	Tumor lysis syndrome
	Aggravation of Graft versus Host Disease
	Generation of replication competent lentivirus
Missing Information	Long-term safety
	Impact on pregnancy and lactation
	Use in patients with pre-existing autoimmune disease
	Use in patients with pre-existing neurodegenerative disorders
	Use in patients with active CNS involvement by malignancy
	Use in patients with chronic controlled HIV and HBV/HCV infection

PART III: PHARMACOVIGILANCE PLAN (Including Postauthorization Safety Studies)

III.1. Routine Pharmacovigilance Activities Beyond Adverse Reaction Reporting and Signal Detection

Specific Follow-up Questionnaires for Safety Concerns

Safety Concern	Purpose/Description
Neurologic toxicities (including ICANS and other neurotoxicities)	A Topic of Interest Questionnaire (TOIQ) will collect structured information on cases of movement and neurocognitive toxicity that occur in the postmarketing period. A copy of the TOIQ is included in Annex 4.
Secondary malignancy of T-cell origin Secondary malignancy of myeloid origin Secondary malignancy except those of T-cell and myeloid origin	A TOIQ will collect structured information on cases of secondary malignancy. A copy of the TOIQ is included in Annex 4.

Other Forms of Routine Pharmacovigilance Activities

Activity	Objective/Description
Not applicable.	

III.2. Additional Pharmacovigilance Activities

Additional Pharmacovigilance Activities	
Study/Activity	
Study name and title	68284528MMY4002: Long-term Follow-up Study for Participants Previously Treated with Ciltacabtagene Autoleucel
Rationale and study objectives	Rationale: CAR-T therapy, characterized as a cell-based gene therapy, may be associated with delayed adverse events. In order to further characterize the long-term safety and efficacy of CARVYKTI within the indicated relapsed and refractory multiple myeloma population, the MAH shall submit the results of the long-term follow-up study for participants previously treated with ciltacabtagene autoleucel. Primary objective: To collect long-term follow-up data on delayed adverse events after administration of ciltacabtagene autoleucel, and to characterize and understand the long-term safety profile of ciltacabtagene autoleucel. Secondary objectives: To collect additional long-term data on RCL, ciltacabtagene autoleucel persistence, efficacy, and OS.
Safety concern(s) addressed	Neurologic toxicities (including ICANS and other neurotoxicities), prolonged or recurrent cytopenia (excluding anemia), serious infections, hypogammaglobulinemia, secondary malignancy of T-cell origin, secondary malignancy of myeloid origin, secondary malignancy except those of T-cell and myeloid origin, aggravation of GvHD, generation of RCL, long-term safety, impact on pregnancy and lactation, use in patients with chronic controlled HIV and HBV/HCV infection.
Study design	Phase 4, long-term follow-up study. Following completion in a prior company-sponsored interventional study, participants will be enrolled into this study and monitored for up to 15 years after their last dose of ciltacabtagene autoleucel.
Study population	Participants who have received at least one dose of ciltacabtagene autoleucel in a company-sponsored clinical trial and who have provided informed consent.
Milestones	Protocol submission: Q2 2022 First Patient In (FPI): Q1 2022 (US) Interim report: CSRs every 3 years from study start (ie, Q4 2025 and every 3 years thereafter) and routine Periodic Benefit Risk Evaluation Report (PBRER) and Development Safety Update Report (DSUR) reporting Final report: Jun 2043

Additional Pharmacovigilance Activities	
Study	
Study name and title	68284528MMY4004: An Observational Post-authorization Safety Study to Evaluate the Safety of Multiple Myeloma Patients Treated with Ciltacabtagene Autoleucel
Rationale and study objectives	Rationale: CAR-T therapy, characterized as a gene therapy, might be associated with different adverse event profile under real-world conditions than previously known from clinical trials. In order to further characterize the long-term safety of CARVYKTI within the indicated relapsed and refractory multiple myeloma population, the MAH shall conduct and submit the results of an observational post-authorization safety study based on a registry. Primary Objective: To evaluate the short- and long-term safety and risk of subsequent malignancy of ciltacabtagene autoleucel in adult patients with multiple myeloma. Secondary Objectives: To evaluate the effectiveness of ciltacabtagene autoleucel in adult patients with multiple myeloma.
Safety concern(s) addressed	CRS (including HLH), neurologic toxicities (including ICANS and other neurotoxicities), prolonged or recurrent cytopenia (excluding anemia), serious infections, hypogammaglobulinemia, secondary malignancy of T-cell origin, secondary malignancy of myeloid origin, secondary malignancy except those of T-cell and myeloid origin, TLS, aggravation of GvHD, generation of RCL, long-term safety, impact on pregnancy and lactation, use in patients with pre-existing autoimmune disease, use in patients with pre-existing neurodegenerative disorders, use in patients with active CNS involvement by malignancy, use in patients with chronic controlled HIV and HBV/HCV infection
Study design	Prospective, observational, post-authorization safety study (PASS) to collect short-term and long-term safety data (up to 15 years) for multiple myeloma patients exposed to ciltacabtagene autoleucel commercial product in a post-authorization setting. Data sources include Center for International Blood and Marrow Transplant Research (CIBMTR), a company-owned registry (68284528MMY4009), other national registries (as appropriate), analyses from tumor samples, and spontaneous adverse event reporting.
Study population	Patients who received at least 1 dose of ciltacabtagene autoleucel commercial product per the Health Authority approved ciltacabtagene autoleucel information in the respective country/region, and who have signed a participation agreement/informed consent form allowing participation in a registry as applicable.
Milestones	Draft Protocol submission: Feb 2022 Final Protocol submission: Jul 2022 FPI: Q2 2022 Interim report: Q3 2023 and annually thereafter and routine PBRER and DSUR reporting Final report: Q4 2042

Additional Pharmacovigilance Activities	
Study	
Study name and title	68284528MMY4009: A Post-authorization Safety Study to Evaluate the Safety of Multiple Myeloma Patients Treated with Ciltacabtagene autoleucel
Rationale and study objectives	Rationale: The data from this study will be analyzed together with other independent prospective registries and other data sources as part of the global PASS study 68284528MMY4004. To further characterize the long-term safety of CARVYKTI within the indicated relapsed and refractory multiple myeloma population, the MAH shall conduct and submit the results of an observational post-authorization safety study based on patient's data primarily from the EU region. Primary Objective: To evaluate the short- and long-term safety and risk of subsequent malignancy of ciltacabtagene autoleucel in adult patients with multiple myeloma. Secondary Objectives: To evaluate the effectiveness of ciltacabtagene autoleucel in adult patients with multiple myeloma.
Safety concern(s) addressed	CRS (including HLH), neurologic toxicities (including ICANS and other neurotoxicities), prolonged or recurrent cytopenia (excluding anemia), serious infections, hypogammaglobulinemia, secondary malignancy of T-cell origin, secondary malignancy of myeloid origin, secondary malignancy except those of T-cell and myeloid origin, TLS, aggravation of GvHD, generation of RCL, long-term safety, impact on pregnancy and lactation, use in patients with pre-existing autoimmune disease, use in patients with pre-existing neurodegenerative disorders, use in patients with active CNS involvement by malignancy, use in patients with chronic controlled HIV and HBV/HCV infection
Study design	Non-interventional PASS to provide short- and long-term safety data (up to 15 years) of ciltacabtagene autoleucel in the treatment of adult patients with multiple myeloma, primarily in the EU region, with the option to expand to other regions/countries.
Study population	Patients who have undergone apheresis with the purpose of receiving ciltacabtagene autoleucel commercial product per the Health Authority approved ciltacabtagene autoleucel product information in the respective country/region, and who have signed a participation agreement/informed consent form allowing participation in the study.
Milestones	Draft Protocol submission: Feb 2022 Final Protocol submission: Jul 2022 FPI: Q2 2024 Interim report: Q3 2025 and annually thereafter and routine PBRER and DSUR reporting Final report: Q4 2042

Additional Pharmacovigilance Activities	
Study	
Study name and title	Survey to evaluate the effectiveness of the ciltacabtagene autoleucel HCP Educational Program and the Product Handling Training
Rationale and study objectives	Survey to measure the effectiveness of the HCP Educational Program and the Product Handling Training: • Guide for Health Care Professionals, an additional risk minimization measure to advise and increase awareness of the risks of CRS (including HLH), neurologic toxicity (including ICANS and other neurotoxicities), secondary malignancy of T-cell origin, secondary malignancy of myeloid origin, and how to minimize these. • To measure information on awareness of the HCP of the existence of the Patient Alert Card, as well as the intention and time of providing it to the patients. • Product Handling Training, an additional risk minimization measure intended to increase awareness of the potential risk of decrease in cell viability due to inappropriate handling or preparation of the product.
Safety concern(s) addressed	CRS (including HLH) Neurologic toxicity (including ICANS and other neurotoxicities) Secondary malignancy of T-cell origin Secondary malignancy of myeloid origin Decrease in cell viability due to inappropriate handling or preparation of the product
Study design	Analysis of information collected from surveys of sampled HCPs involved in the prescription, dispensing, or administration of ciltacabtagene autoleucel. Analysis of information collected from surveys of sampled HCPs and other personnel involved in the transport, storage, thawing, preparation, or handling of ciltacabtagene autoleucel.
Study population	HCPs (eg, physicians, pharmacists, nurses, ward staff) involved in the prescription, dispensing, or administration of ciltacabtagene autoleucel. HCPs and other personnel involved in the transport, storage, thawing, preparation, or handling of ciltacabtagene autoleucel.
Milestones	Protocol submission: 3 months after EC decision Initiation of survey (wave 1): within 18 months of availability of the approved educational materials in selected countries: Q4 2024 Initiation of survey (wave 2): within 3 years of availability of the approved educational materials in selected countries: Q2 2026 A report on the educational activities undertaken and the results of the survey will be submitted at 24 months and 3.5 years after availability of the approved educational materials. Updates will also be reported in the PBRER/PSUR.

Additional Pharmacovigilance Activities	
Activity	
Activity name and title	Testing Activity of Secondary Malignancies of T-cell Origin
Rationale and objectives	Tumor tissue sample testing from patients who develop a secondary malignancy of T-cell origin after receiving CARVYKTI in the post-marketing setting
Safety concern(s) addressed	Secondary malignancy of T-cell origin
Framework/Process	1. When a patient is prescribed CARVYKTI, they are provided with an ICF that includes information on how their personal information and blood cells will be used in the manufacturing of their CAR-T therapy and they are requested, by signing the form, to confirm their informed consent to the CARVYKTI therapy ("Consent to give Janssen my personal information and blood cells to manufacture my CAR-T therapy"). In this ICF, the patient has the possibility to, optionally, also provide their consent (tick a checkbox) for the collection and testing of available tissue samples, in case a secondary malignancy is diagnosed following administration of CARVYKTI. This ICF is uploaded and kept by CARVYKTI's MAH in their internal system. 2. In case a patient did not initially provide their consent for the collection and testing of tissue samples, they will have another opportunity to provide their consent after a secondary malignancy is diagnosed, by signing a new ICF proposed again by CARVYKTI's MAH. 3. When a secondary malignancy is reported to the MAH and local regulations permit, the MAH will provide instructions for storage and shipping of available samples. Options include samples from a new collection and/or suitable samples already available at the treating center. The MAH will also inform the reporting HCP about the testing assays being for research use only and that patient consent is required. 4. In the event the reporting HCP/treating HCP agrees, the sample is available for testing, and the patient has provided their consent, the MAH will proceed with testing. 5. The MAH has contracted an external central laboratory that coordinates all logistics to collect secondary malignancy samples for testing. 6. The testing of secondary malignancy tissue samples includes screening of lentiviral vector elements in the tumor tissue and lentiviral vector integration site analysis when applicable, as well as testing of RCL. Please refer to the following section "Methodology and Plans for Testing of Malignancies of T-cell Origin" for more information on the "core assays". 7. In the event the testing of secondary malignancy tissue sample ("core assays") is positive for CAR, the MAH will assess whether additional testing is needed to evaluate causality ("extended assays").

Additional Pharmacovigilance Activities	
	8. In case additional testing ("extended assays"), possibly from additional samples (including but not limited to blood, buccal swab, left-over apheresis material, left-over drug product, etc.), is needed, the MAH will contact the reporting HCP/treating HCP to discuss the feasibility of additional consent, sample collection, and research. 9. If feasible based on the discussion with the reporting HCP/treating HCP, the MAH will conduct additional testing ("extended assays") and collection of additional samples.
Population	Any patient who develops a secondary malignancy of T-cell origin following treatment in the postmarketing setting
Milestones	PSURs: Submitted in accordance with the EURD list Interim reports to be submitted after 5, 10, and 15 years

Methodology and Plans for Testing Activity of Malignancies of T-cell Origin

The MAH intends to continue the testing of secondary malignancies of T-cell origin (eg, T-cell lymphoma) with available tumor samples. The MAH will diligently strive to obtain samples from providers reporting secondary malignancies of T-cell origin in patients treated with ciltacabtagene autoleucel in clinical trials or in the commercial setting. Upon reporting, the MAH will provide detailed instructions and kits for sample collection. Depending on the type/location of secondary malignancy, the MAH requests providers to submit tissue samples such as:

- Two entire dedicated formalin-fixed paraffin-embedded (FFPE) blocks from excisional (preferred) or diagnostic blocks. If an entire block is not available, 20-5 μm sections mounted on positively charged slides are desired. The number of slides should be scaled up if the specimen area is smaller than 1 cm x 1 cm and/or the tumor content is less than 60%.
- 4 mL of bone marrow aspirate. Due to logistical difficulties and increased patient burden, the MAH may request a bone marrow aspirate sample for secondary malignancy testing if the treating physician conducts the procedure due to other clinical needs outside of the secondary malignancy.
- 2x 4 mL of blood.

The MAH will review the pathology reports and tumor samples to determine if the tumor sample is sufficiently involved in the reported secondary malignancy before testing.

In the core testing algorithm for post-infusion secondary malignancy assessments, a quantitative approach will be adapted to assess the presence of CAR+ cells and predominant integration site in the tumor sample. The presence of CAR transgene will be assessed by quantitative polymerase chain reaction (qPCR) in a patient's tumor samples. Immunohistochemistry (IHC) will be conducted to assess the presence of anti-camelid+ cells in the tumor FFPE samples, if applicable. If at least 1% of cells in tumor samples are CAR+, next-generation sequencing (NGS)-based lentiviral integration analysis will be conducted to assess the presence of any predominant integration site. Based on sample availability, the MAH may test concurrently across qPCR and IHC assays to complete testing expediently. In case of limited availability of tumor tissue sample, IHC will be prioritized over qPCR to reserve materials for subsequent testing. When qPCR analysis is performed in blood, the obtained number of CAR+ cells will be compared to those observed or predicted at the concerned time after the ciltacabtagene autoleucel infusion, based on the kinetics of CAR+ T cells described during clinical studies.

Because of potential pathogenicity of replication competent lentivirus (RCL), the MAH will also test if RCL is present in the patient from CAR T cell production as part of the core testing algorithm using a qPCR assay against the lentivirus vesicular stomatitis virus-G gene.

The assessment of CAR presence and lentiviral integration pattern will not be sufficient to evaluate the causal relationship of ciltacabtagene autoleucel alone and the development of secondary malignancy of T-cell origin. Listed below are additional assays that could be employed if causality needs to be addressed. And the order reflects the prioritization of testing depending on the sample availability and patient consent.

- Transcriptome analysis: when a predominant integration site is identified in the tumor sample, transcriptome analysis will be conducted to provide direct evidence on the consequences of vector integrations. The MAH will assess the expression modulation of the gene with a predominant CAR insertion by comparing the gene expression in the tumor sample to that from a control cohort of the same diagnosis (eg, T-cell lymphoma) and from the same tissue type in the context of CAR-negative therapies. Of note, the lack of statistical power in such analysis may confound data interpretation.
- Whole exome or whole genome sequencing: the MAH will conduct this analysis to assess the presence of somatic and/or germline mutations if a sample (eg, buccal swab or apheresis materials from the patient) is available to serve as the germline control.
- TCR sequencing: this analysis identifies the malignant clone in the tumor sample and evaluate the evolution of the clone over time. If samples collected prior to ciltacabtagene autoleucel infusion (eg, archived samples, apheresis materials, and/or drug product) are available, the analysis will evaluate the presence of the clone of interest at baseline.

The MAH will carefully allocate samples across the battery of assays delineated above. Analyses will be conducted with available samples to comply with regulatory guidance and perform scientific evaluation of causality.

III.3. Summary Table of Additional Pharmacovigilance Activities

Table Part III.1: Ongoing and Planned Additional Pharmacovigilance Activities

Study/Activity Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorization				
68284528MMY4002: Long-term Follow-up Study for Participants Previously Treated with Ciltacabtagene Autoleucel Ongoing	Primary: To collect long-term follow-up data on delayed adverse events after administration of ciltacabtagene autoleucel, and to characterize and understand the long-term safety profile of ciltacabtagene autoleucel. Secondary: To collect additional long-term data on RCL, ciltacabtagene autoleucel persistence, efficacy, and OS. This study will include subjects who received ciltacabtagene autoleucel in company sponsored clinical trials. Consented subjects will be enrolled in this study once the individual study is completed and will be followed up for 15 years after their last dose of ciltacabtagene autoleucel.	Neurologic toxicities (including ICANS and other neurotoxicities) Prolonged or recurrent cytopenia (excluding anemia) Serious infections Hypogammaglobulinemia Secondary malignancy of T-cell origin Secondary malignancy of myeloid origin Secondary malignancy except those of T-cell and myeloid origin Aggravation of GvHD Generation of RCL Long-term safety Impact on pregnancy and lactation Use in patients with chronic controlled HIV and HBV/HCV infection	Protocol submission FPI Interim report Final report	Q2 2022 Q1 2022 (US) CSRs every 3 years from study start (ie, Q4 2025 and every 3 years thereafter) and routine PBRER and DSUR reporting Jun 2043
68284528MMY4004: An Observational Post-authorization Safety Study to Evaluate the Safety of Multiple Myeloma Patients Treated with Ciltacabtagene Autoleucel Ongoing	Primary: To evaluate the short- and long-term safety and risk of subsequent malignancy of ciltacabtagene autoleucel in adult patients with multiple myeloma. Secondary: To evaluate the effectiveness of ciltacabtagene autoleucel in adult	CRS (including HLH) Neurologic toxicities (including ICANS and other neurotoxicities) Prolonged or recurrent cytopenia (excluding anemia) Serious infections Hypogammaglobulinemia	Draft Protocol Final Protocol FPI Interim report	Feb 2022 Jul 2022 Q2 2022 Q3 2023 and annually thereafter and routine PBRER and DSUR reporting

Study/Activity Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
	patients with multiple myeloma. This study will include data from patients receiving ciltacabtagene autoleucel in the commercial setting, using data from patients consecutively enrolled in a registry as applicable. Other data sources may also include analysis from tumor samples or adverse events spontaneously reported to the MAH, where available.	Secondary malignancy of T-cell origin Secondary malignancy of myeloid origin Secondary malignancy except those of T-cell and myeloid origin TLS Aggravation of GvHD Generation of RCL Long-term safety Impact on pregnancy and lactation Use in patients with pre-existing autoimmune disease Use in patients with pre-existing neurodegenerative disorders Use in patients with active CNS involvement by malignancy Use in patients with chronic controlled HIV and HBV/HCV infection	Final report	Q4 2042

Study/Activity Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
68284528MMY4009: A Post-authorization Safety Study to Evaluate the Safety of Multiple Myeloma Patients Treated with Ciltacabtagene autoleucel Ongoing	Primary: to evaluate the short- and long-term safety and risk of subsequent malignancy of ciltacabtagene autoleucel in adult patients with multiple myeloma. Secondary: To evaluate the effectiveness of ciltacabtagene autoleucel in adult patients with multiple myeloma.	CRS (including HLH) Neurologic toxicities (including ICANS and other neurotoxicities) Prolonged or recurrent cytopenia (excluding anemia) Hypogammaglobulinemia Serious infections TLS Aggravation of GvHD Generation of RCL Secondary malignancy of T-cell origin Secondary malignancy of myeloid origin Secondary malignancy except those of T-cell and myeloid origin Long-term safety Impact on pregnancy and lactation Use in patients with pre-existing autoimmune disease Use in patients with pre-existing neurodegenerative disorders Use in patients with active CNS involvement by malignancy Use in patients with chronic controlled HIV and HBV/HCV infection	Draft Protocol	Feb 2022
			Final Protocol	Jul 2022
			FPI	Q2 2024
			Interim report	Q3 2025 and annually thereafter and routine PBRER and DSUR reporting
			Final report	Q4 2042
Category 2 - Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorization or a marketing authorization under exceptional circumstances				
Category 3 - Required additional pharmacovigilance activities				

Study/Activity Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
Survey to evaluate the effectiveness of the ciltacabtagene autoleucel HCP Educational Program and the Product Handling Training Ongoing	Survey to measure the effectiveness of the HCP Educational Program and the Product Handling Training: Guide for Health Care Professionals, an additional risk minimization measure to advise and increase awareness of the risks of CRS (including HLH), neurologic toxicity (including ICANS and other neurotoxicities), secondary malignancy of T-cell origin, and secondary malignancy of myeloid origin, and how to minimize these. To measure information on awareness of the HCP of the existence of the Patient Alert Card, as well as the intention and time of providing it to the patients. Product Handling Training, an additional risk minimization measure intended to increase awareness of the potential risk of decrease in cell viability due to inappropriate handling or preparation of the product.	CRS (including HLH) Neurologic toxicity (including ICANS and other neurotoxicities) Secondary malignancy of T-cell origin Secondary malignancy of myeloid origin Decrease in cell viability due to inappropriate handling or preparation of the product	Protocol Submission Initiation of survey (wave 1) Initiation of survey (wave 2)	3 months after EC decision within 18 months of availability of the approved educational materials in selected countries: Q4 2024 within 3 years of availability of the approved educational materials in selected countries: Q2 2026
			Reports	24 months and 3.5 years after availability of the approved educational materials. Updates will also be reported in the PBRER and PSUR.
Testing Activity of Secondary Malignancies of T-cell Origin Planned	Tumor tissue sample testing from patients who develop a secondary malignancy of T-cell origin.	Secondary malignancy of T-cell origin	Safety data will be included in PSURs Interim reports:	In accordance with PSUR schedule To be submitted after 5, 10, and 15 years

PART IV: PLANS FOR POSTAUTHORIZATION EFFICACY STUDIES

Table Part IV.1: Planned and Ongoing Postauthorization Efficacy Studies That Are Conditions of the Marketing Authorization or That Are Specific Obligations

Study Status	Summary of Objectives	Efficacy Uncertainties Addressed	Milestones	Due Dates
Efficacy Studies which are conditions of the marketing authorizations				
Not applicable				
Efficacy studies which are Specific Obligations in the context of a conditional marketing authorization or a marketing authorization under exceptional circumstances				
Not applicable				

PART V: RISK MINIMIZATION MEASURES (Including Evaluation of the Effectiveness of Risk Minimization Activities)

Risk Minimization Plan

V.1. Routine Risk Minimization Measures

Table Part V.1: Description of Routine Risk Minimization Measures by Safety Concern

Safety Concern	Routine Risk Minimization Activities
CRS (including HLH)	**Routine risk communication:** • SmPC Section 4.2 • SmPC Section 4.4 • SmPC Section 4.8 • SmPC Section 6.6 • PL Section 2 • PL Section 3 • PL Section 4 **Routine risk minimization activities recommending specific clinical measures to address the risk:** • Requirement to have tocilizumab (or suitable alternative measures if not available and listed in the EMA shortage catalogue) and emergency equipment available prior to infusion and during the recovery period is included in SmPC Sections 4.2, 4.4, and 6.6. • Recommendation for monitoring patients daily for signs and symptoms of CRS for 14 days after dosing and periodically for an addition 2 weeks are included in SmPC Section 4.4. • Recommendation for patients to remain within the proximity of a qualified clinical facility for at least 4 weeks following infusion is provided in SmPC Section 4.4 and in PL Section 3. • Recommendation to counsel patients to seek immediate medical attention if signs and symptoms of CRS occur, and recommendation to evaluate the patient for hospitalization and institute treatment at the first sign of CRS is provided in SmPC Section 4.4. • Recommendation to delay ciltacabtagene autoleucel infusion for patients with unresolved serious adverse reactions from preceding lymphodepleting or bridging chemotherapies (including cardiac toxicity and pulmonary toxicity), rapid disease progression, or clinically significant active infection is provided in SmPC Section 4.4. • Recommendations for the treatment of clinically significant ongoing infections (which may increase the risk of a fatal CRS event) and recommendation to delay ciltacabtagene autoleucel infusion until any infections are resolved, are provided in SmPC Section 4.4.

Safety Concern	Routine Risk Minimization Activities
	• Recommendation for potential early use of tocilizumab in patients with high tumor burden or early or persistent fever is provided in SmPC Section 4.4. • Recommendations for evaluation, treatment, and management of CRS are provided in SmPC Section 4.4. • Recommendations for treating high grade CRS that remains severe following use of tocilizumab and corticosteroids are provided in SmPC Section 4.4. • Recommendation to avoid the use of myeloid growth factors (particularly GM-CSF) during CRS is provided in SmPC Section 4.4. • Recommendation to evaluate for HLH in patients with severe or unresponsive CRS, and a warning that patients who develop HLH may have an increased risk of severe bleeding, is provided in SmPC Section 4.4. • Recommendation for reducing baseline burden of disease with bridging therapy prior to infusion in patients with high tumor burden is provided in SmPC Section 4.4. • Recommendations on treatment for concurrent CRS and neurologic toxicity, including the use of corticosteroids, tocilizumab, and anti-seizure medication, is provided in SmPC Section 4.4. • Information regarding the incidence of CRS and the specific signs and symptoms seen in clinical trials is provided in SmPC Section 4.8. • Patients should inform their doctor or nurse immediately if CRS symptoms occur, as described in PL Section 2, and should seek medical help as described in PL Section 4. **Other routine risk minimization measures beyond the Product Information:** • Use restricted to physicians experienced in the treatment of hematological cancers
Neurologic toxicities (including ICANS and other neurotoxicities)	**Routine risk communication:** • SmPC Section 4.2 • SmPC Section 4.4 • SmPC Section 4.7 • SmPC Section 4.8 • PL Section 2 • PL Section 4 **Routine risk minimization activities recommending specific clinical measures to address the risk:** • Recommendation for monitoring patients daily for signs and symptoms of neurologic events for 14 days after dosing and periodically for an additional 2 weeks are included in SmPC Section 4.4.

Safety Concern	Routine Risk Minimization Activities
	• Recommendation to consider reducing baseline disease burden with bridging therapy prior to infusion in patients with high tumor burden is included in SmPC Section 4.4. • Recommendations on monitoring patients for signs and symptoms of ICANS for 4 weeks after infusion and thereafter for other neurotoxicity are included in SmPC Section 4.4. • Recommendation to continue to monitor patients for signs and symptoms of neurologic toxicity after recovery from CRS and/or ICANS is provided in SmPC Section 4.4. • Recommendation to counsel patients on the signs and symptoms of neurologic toxicities and to seek immediate medical attention if signs and symptoms occur is provided in SmPC Section 4.4. • Recommendations on treating patients with symptoms of neurotoxicity, including intensive care supportive therapy (including steroids) for severe of life-threatening cases, are included in SmPC Section 4.4. • SmPC Section 4.4 provides information on a subset of patients with a cluster of movement and neurocognitive adverse reactions that progressed in some to an inability to work or care for oneself. These events were associated with 2 or more factors at baseline such as high tumor burden, prior Grade 2 or higher CRS, prior ICANS, and high CAR-T cell expansion and persistence. Patients should be monitored for these symptoms and managed with supportive care measures. • Instruction that patients should be monitored for GBS and treatment with intravenous immunoglobulin (IVIG) and plasmapheresis should be considered is included in SmPC Section 4.4. • Instruction that patients should be monitored for signs and symptoms of peripheral neuropathies and cranial nerve palsies, and that management with short-course systemic corticosteroids should be considered, is included in SmPC Section 4.4. • Instructions for treatment of neurotoxicities with early and aggressive supportive care (including steroids) in patients presenting with higher grade CRS or any grade ICANS is included in SmPC Section 4.4. • Recommendations on treatment for concurrent CRS and neurologic toxicity, including the use of corticosteroids, tocilizumab, and anti-seizure medication, is provided in SmPC Section 4.4. • Recommendation to refrain from driving and engaging in hazardous occupations or activities in the 8 weeks following infusion is provided in SmPC Section 4.7. • Information regarding the incidence of neurologic toxicities (including ICANS and other neurotoxicities) and the specific symptoms seen in clinical trials is provided in SmPC Section 4.8.

Safety Concern	Routine Risk Minimization Activities
	● Patients should inform their doctor or nurse immediately if symptoms of ICANS or other neurotoxicities occur, as described in PL Section 2, and should seek medical help for ICANS as described in PL Section 4. **Other routine risk minimization measures beyond the Product Information:** ● Use restricted to physicians experienced in the treatment of hematological cancers
Prolonged or recurrent cytopenia (excluding anemia)	**Routine risk communication:** ● SmPC Section 4.4 ● SmPC Section 4.8 ● PL Section 2 ● PL Section 4 **Routine risk minimization activities recommending specific clinical measures to address the risk:** ● Recommendation to monitor blood counts prior to and after ciltacabtagene autoleucel infusion is provided in SmPC Section 4.4. ● Recommendation to consider supportive care with transfusions for treatment of thrombocytopenia is provided in SmPC Section 4.4. ● Recommendation to avoid the use of myeloid growth factors (particularly GM-CSF) during CRS is provided in SmPC Section 4.4. ● Information regarding the incidence of prolonged or recurrent cytopenia (excluding anemia) is provided in SmPC Section 4.8. ● Patients should inform their doctor right away if they have any symptoms of prolonged or recurrent cytopenia, as described in PL Sections 2 and 4. **Other routine risk minimization measures beyond the Product Information:** ● Use restricted to physicians experienced in the treatment of hematological cancers
Serious infections	**Routine risk communication:** ● SmPC Section 4.2 ● SmPC Section 4.4 ● SmPC Section 4.8 ● PL Section 2 ● PL Section 4 **Routine risk minimization activities recommending specific clinical measures to address the risk:** ● Recommendation to delay lymphodepletion therapy if a patient has clinically significant active infection is provided in Section 4.2.

Safety Concern	Routine Risk Minimization Activities
	• Recommendation that infection prophylaxis should follow local guidelines, and that infections are known to complicate the course and management of concurrent CRS, are provided in SmPC Section 4.4. • Recommendation to delay ciltacabtagene autoleucel infusion until any clinically significant active infection or inflammatory disorder is resolved is provided in SmPC Section 4.4. • Recommendation that patients should be counselled on the importance of prevention measures for COVID-19, as patients treated with ciltacabtagene autoleucel may be at increased risk of severe/fatal COVID-19 infections, is provided in SmPC Section 4.4. • Recommendation on monitoring patients for signs and symptoms of infection is provided in SmPC Section 4.4. • Recommendations for the management and treatment of febrile neutropenia are included in SmPC Section 4.4. • Recommendation to screen for HBV, HCV, and HIV prior to collection of cells for manufacturing is included in SmPC Section 4.4. • Recommendation to monitor immunoglobulin levels after treatment and treat according to standard guidelines, including administration of immunoglobulin replacement, antibiotic prophylaxis and monitoring for infection is included in SmPC Section 4.4. • Information regarding the incidence of serious infections is provided in SmPC Section 4.8. • Ciltacabtagene autoleucel may increase the risk of life-threatening infections that may lead to death. Patients should tell their doctor right away if they have any signs or symptoms of infection, as described in PL Sections 2 and 4. **Other routine risk minimization measures beyond the Product Information:** • Use restricted to physicians experienced in the treatment of hematological cancers
Hypogammaglobulinemia	**Routine risk communication:** • SmPC Section 4.4 • SmPC Section 4.6 • SmPC Section 4.8 **Routine risk minimization activities recommending specific clinical measures to address the risk:** • Recommendation that immunoglobulin levels should be monitored after treatment with ciltacabtagene autoleucel, IVIG should be administered for IgG <400 mg/dL, and patients should be managed according to standard guidelines, including antibiotic or antiviral prophylaxis and monitoring for infection, is described in SmPC Section 4.4.

Safety Concern	Routine Risk Minimization Activities
	• Recommendation that assessment of immunoglobulin levels in newborns of mothers treated with ciltacabtagene autoleucel should be considered is provided in SmPC Section 4.6. • Information regarding the incidence of hypogammaglobulinemia is provided in SmPC Section 4.8. **Other routine risk minimization measures beyond the Product Information:** • Use restricted to physicians experienced in the treatment of hematological cancer
Secondary malignancy of T-cell origin	**Routine risk communication:** • SmPC Section 4.4 • SmPC Section 4.8 • PL Section 2 • PL Section 4 **Routine risk minimization activities recommending specific clinical measures to address the risk:** • Recommendation for life-long monitoring of patients for secondary malignancies is provided in SmPC Section 4.4. • Information regarding the incidence of secondary malignancy of T-cell origin is provided in SmPC Section 4.8. • Patients should tell their doctor or nurse if symptoms of secondary malignancies of T-cell origin occur, as described in PL Section 2 and PL Section 4. • Recommendation to contact the MAH for instructions on collecting patient samples for testing is provided in SmPC Section 4.4. **Other routine risk minimization measures beyond the Product Information:** • Use restricted to physicians experienced in the treatment of hematological cancers
Secondary malignancy of myeloid origin	**Routine risk communication:** • SmPC Section 4.4 • SmPC Section 4.8 • PL Section 2 • PL Section 4 **Routine risk minimization activities recommending specific clinical measures to address the risk:** • Recommendation for life-long monitoring of patients for secondary malignancies is provided in SmPC Section 4.4. • Recommendation to contact the MAH for instructions on collecting patient samples for testing is provided in SmPC Section 4.4.

Safety Concern	Routine Risk Minimization Activities
	• Information regarding the incidence of secondary malignancy of myeloid origin is provided in SmPC Section 4.8. • Patients should tell their doctor or nurse if symptoms of secondary malignancies of myeloid origin occur, as described in PL Section 2 and PL Section 4. **Other routine risk minimization measures beyond the Product Information:** • Use restricted to physicians experienced in the treatment of hematological cancers
Secondary malignancy except those of T-cell and myeloid origin	**Routine risk communication:** • SmPC Section 4.4 **Routine risk minimization activities recommending specific clinical measures to address the risk:** • Recommendation for life-long monitoring of patients for secondary malignancies is provided in SmPC Section 4.4. • Recommendation to contact the MAH for instructions on collecting patient samples for testing is provided in SmPC Section 4.4. **Other routine risk minimization measures beyond the Product Information:** • Use restricted to physicians experienced in the treatment of hematological cancers
Decrease in cell viability due to inappropriate handling or preparation of the product	**Routine risk communication:** • SmPC Section 4.2 • SmPC Section 6.3 • SmPC Section 6.4 • SmPC Section 6.6 **Routine risk minimization activities recommending specific clinical measures to address the risk:** • Instructions for preparation of ciltacabtagene autoleucel, including thawing, are provided in SmPC Sections 4.2 and 6.6. • Shelf life and special precautions for storage of ciltacabtagene autoleucel are provided in SmPC Sections 6.3 and 6.4. • Special precautions for disposal and other handling are provided in SmPC Section 6.6. **Other routine risk minimization measures beyond the Product Information:** • None
TLS	**Routine risk communication:** • None

Safety Concern	Routine Risk Minimization Activities
	Routine risk minimization activities recommending specific clinical measures to address the risk: • None **Other routine risk minimization measures beyond the Product Information:** • Use restricted to physicians experienced in the treatment of hematological cancer
Aggravation of GvHD	**Routine risk communication:** • SmPC Section 4.4 • PL Section 2 **Routine risk minimization activities recommending specific clinical measures to address the risk:** • Instruction that ciltacabtagene autoleucel infusion should be delayed if a patient has active GvHD is provided in SmPC Section 4.4. • Instruction for patients to tell their doctor prior to infusion of ciltacabtagene autoleucel if they have signs or symptoms of GvHD in provided in PL Section 2. **Other routine risk minimization measures beyond the Product Information:** • Use restricted to physicians experienced in the treatment of hematological cancer
Generation of RCL	**Routine risk communication:** • None **Routine risk minimization activities recommending specific clinical measures to address the risk:** • None **Other routine risk minimization measures beyond the Product Information:** • Use restricted to physicians experienced in the treatment of hematological cancer
Long-term safety	**Routine risk communication:** • None **Routine risk minimization activities recommending specific clinical measures to address the risk:** • None **Other routine risk minimization measures beyond the Product Information:** • None

Safety Concern	Routine Risk Minimization Activities
Impact on pregnancy and lactation	**Routine risk communication:** • SmPC Section 4.6 • PL Section 2 **Routine risk minimization activities recommending specific clinical measures to address the risk:** • Recommendations that pregnancy status for females of childbearing age should be verified prior to starting treatment is provide in SmPC Section 4.6. • Recommendation on the need for effective contraception in patients who receive the lymphodepleting chemotherapy according to the corresponding prescribing information is provided in SmPC Section 4.6. • Recommendation to advise pregnant or breastfeeding women that there may be risks to the fetus or breast-fed infant is provided in SmPC Section 4.6. • Recommendation that for any pregnant woman who receives ciltacabtagene autoleucel, assessment of immunoglobulin levels in newborns of mothers should be considered is provided in SmPC Section 4.6. • Patients should notify their doctor immediately if they are pregnant or think they may be pregnant following treatment with ciltacabtagene autoleucel, as described in PL Section 2. **Other routine risk minimization measures beyond the Product Information:** • Use restricted to physicians experienced in the treatment of hematological cancers
Use in patients with pre-existing autoimmune disease	**Routine risk communication:** • None **Routine risk minimization activities recommending specific clinical measures to address the risk:** • None **Other routine risk minimization measures beyond the Product Information:** • Use restricted to physicians experienced in the treatment of hematological cancers
Use in patients with pre-existing neurodegenerative disorders	**Routine risk communication:** • SmPC Section 4.4 • PL Section 2

Safety Concern	Routine Risk Minimization Activities
	Routine risk minimization activities recommending specific clinical measures to address the risk: ● A warning indicating that patients with significant CNS disease are likely to be more vulnerable to the consequences of adverse reactions observed with ciltacabtagene autoleucel and may require special attention is provided in SmPC Section 4.4. ● Patients should tell their doctor before treatment with ciltacabtagene autoleucel if they have current or past nervous system disorders, as described in PL Section 2. **Other routine risk minimization measures beyond the Product Information:** ● Use restricted to physicians experienced in the treatment of hematological cancers
Use in patients with active CNS involvement by malignancy	**Routine risk communication:** ● None **Routine risk minimization activities recommending specific clinical measures to address the risk:** ● None **Other routine risk minimization measures beyond the Product Information:** ● Use restricted to physicians experienced in the treatment of hematological cancers
Use in patients with chronic controlled HIV and HBV/HCV infection	**Routine risk communication:** ● SmPC Section 4.2 ● SmPC Section 4.4 **Routine risk minimization activities recommending specific clinical measures to address the risk:** ● Instructions for screening of HBV, HCV, and HIV are included in SmPC Sections 4.2 and 4.4. **Other routine risk minimization measures beyond the Product Information:** ● Use restricted to physicians experienced in the treatment of hematological cancers

V.2. Additional Risk Minimization Measures

Additional Risk Minimization Activity 1

Additional Risk Minimization Activity 1 Controlled Distribution Program and Availability of Tocilizumab	
Objective(s):	To minimize the important identified risks of CRS (including HLH) and neurotoxicity (including ICANS and other neurotoxicity)
Rationale for the additional risk minimization activity:	To ensure that centers that dispense ciltacabtagene autoleucel are qualified per MAH requirements in accordance with the agreed controlled distribution program. • To ensure that tocilizumab (or suitable alternative measures if not available and listed in the EMA shortage catalogue) is available for each patient on site in order to manage CRS. • To ensure ciltacabtagene autoleucel will only be supplied to centers that are qualified and only if the HCP involved in the treatment of a patient has completed the HCP educational program.
Target audience and planned distribution path:	Centers that dispense ciltacabtagene autoleucel
Plans to evaluate the effectiveness of the interventions and criteria for success:	The effectiveness of the controlled distribution program will be evaluated using a periodic dashboard to enable retrieving relevant information on the performance of the certified centers via systems, including completed certification in order to collect evidence of: • The extent of the completed training of relevant HCPs by all sites for which ciltacabtagene autoleucel was distributed as well as during site qualification • Confirmation that the sites have standard procedures in place during initial certification and that enough doses of tocilizumab per approved SmPC are available for each patient, and when available, confirmation of the extent of compliance based on company audit findings.

Additional Risk Minimization Activity 2

Additional Risk Minimization Activity 2 Health Care Professional (HCP) Educational Program	
Objective(s):	To minimize the important identified risks of CRS (including HLH), neurotoxicity (including ICANS and other neurotoxicity), secondary malignancy of T-cell origin, and secondary malignancy of myeloid origin
Rationale for the additional risk minimization activity:	To increase awareness of CRS (including HLH) and neurotoxicity (including ICANS and other neurotoxicity) and its appropriate monitoring, prevention, and management, including the importance of on-site availability of tocilizumab (or suitable alternative measures if not available and listed in the EMA shortage catalogue) before treating a patient. To facilitate patient counseling relevant information. To provide guidance on reporting these serious adverse reactions associated with ciltacabtagene autoleucel. To increase awareness of secondary malignancies of T-cell origin and secondary malignancies of myeloid origin reported with CAR-T cell therapies.
Target audience and planned distribution path:	HCPs (eg, physicians, pharmacists, nurses, ward staff) who prescribe, dispense, or administer ciltacabtagene autoleucel A DHPC has been distributed to HCPs to inform them of the risk of secondary malignancy of T-cell origin.
Plans to evaluate the effectiveness of the interventions and criteria for success:	HCP Survey: Sampled HCPs involved in the prescription, dispensing, or administration of ciltacabtagene autoleucel will be asked to participate in the survey to assess knowledge and understanding of how to minimize these important identified risks, in accordance with the educational materials. CRS, neurotoxicity, secondary malignancy of T-cell origin, and secondary malignancy of myeloid origin reporting trend analyses from postmarketing safety data per PBRER/PSUR period. Stable reporting trend analysis (after 18 months post-approval) are the criteria for success.

Additional Risk Minimization Activity 3

Additional Risk Minimization Activity 3 Product Handling Training	
Objective(s):	To minimize the important potential risk of decrease in cell viability due to inappropriate handling or preparation of the product
Rationale for the additional risk minimization activity:	To increase awareness of the important potential risk of decrease in cell viability due to inappropriate handling or preparation of the product. To provide guidance on precautions to take before handling or administering ciltacabtagene autoleucel (ie, how to check the product prior to administration, how to thaw, and how to administer).
Target audience and planned distribution path:	HCPs (eg, physicians, pharmacists, nurses, ward staff) and other personnel involved in the transport, storage, thawing, preparation, or handling of ciltacabtagene autoleucel
Plans to evaluate the effectiveness of the interventions and criteria for success:	HCP Survey: Sampled HCPs and other personnel involved in the transport, storage, thawing, preparation, or handling of ciltacabtagene autoleucel will be asked to participate in the survey to assess knowledge and understanding of how to prevent the risk of decrease in cell viability due to inappropriate handling or preparation of the product, in accordance with the educational materials. Reporting trend analyses of lack of efficacy and relevant Product Quality Complaint (PQC) from postmarketing safety data per PBRER/PSUR period. Low and stable reporting trend analysis (after 18 months post-approval) are the criteria for success.

Additional Risk Minimization Activity 4

Additional Risk Minimization Activity 4 Patient Educational Program	
Objective(s):	To minimize the important identified risks of CRS (including HLH) and neurotoxicity (including ICANS and other neurotoxicity)
Rationale for the additional risk minimization activity:	To inform patients of CRS (including HLH) and neurotoxicity (including ICANS and other neurotoxicity) associated with ciltacabtagene autoleucel and increase awareness of symptoms requiring immediate medical attention. To provide a Patient Alert Card that advises patients to carry it at all times and share it with any HCP providing care (including emergency) so the HCP can contact the CAR-T treating HCP.
Target audience and planned distribution path:	Patients who receive treatment with ciltacabtagene autoleucel
Plans to evaluate the effectiveness of the interventions and criteria for success:	The effectiveness of the Patient Educational Program will be evaluated by: • Using a periodic dashboard to enable retrieving relevant information on the performance of the certified centers via systems, including completed certification in order to collect evidence of the extent for which Patient educational materials, including a Patient Alert Card were distributed to patients by HCPs • The survey to evaluate the effectiveness of ciltacabtagene autoleucel HCP educational program will incorporate questions about awareness of the HCP of the existence of Patient Alert Card, as well as the intention and time of providing it to the patients. CRS and neurotoxicity reporting trend analyses from postmarketing safety data per PBRER/PSUR period. Stable reporting trend analysis (after 18 months post-approval) are the criteria for success.

V.2.1. Removal of Additional Risk Minimization Activities

Not applicable

V.3. Summary of Risk Minimization Measures and Pharmacovigilance Activities

Table Part V.3: Summary Table of Risk Minimization Activities and Pharmacovigilance Activities by Safety Concern

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
CRS (including HLH)	**Routine risk minimization measures:** • SmPC Section 4.2 • SmPC Section 4.4 • SmPC Section 4.8 • SmPC Section 6.6 • PL Section 2 • PL Section 3 • PL section 4 • Requirement to have tocilizumab (or suitable alternative measures if not available and listed in the EMA shortage catalogue) and emergency equipment available prior to infusion and during the recovery period is included in SmPC Sections 4.2, 4.4, and 6.6. • Recommendation for monitoring patients daily for signs and symptoms of CRS for 14 days after dosing and periodically for an addition 2 weeks are included in SmPC Section 4.4. • Recommendation for patients to remain within the proximity of a qualified clinical facility for at least 4 weeks following infusion is provided in SmPC Section 4.4 and in PL Section 3. • Recommendation to counsel patients to seek immediate medical attention if signs and symptoms of CRS occur, and recommendation to evaluate the patient for hospitalization and institute treatment at the first sign of CRS is provided in SmPC Section 4.4. • Recommendation to delay ciltacabtagene autoleucel infusion	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** 68284528MMY4004: An Observational Post-authorization Safety Study to Evaluate the Safety of Multiple Myeloma Patients Treated with Ciltacabtagene Autoleucel Final report: Q4 2042 68284528MMY4009: A Post-authorization Safety Study to Evaluate the Safety of Multiple Myeloma Patients Treated with Ciltacabtagene Autoleucel Final report: Q4 2042 Survey to evaluate the effectiveness of the ciltacabtagene autoleucel HCP Educational Program and the Product Handling Training Final report: 3.5 years after the availability of the approved educational materials

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
	for patients with unresolved serious adverse reactions from preceding lymphodepleting or bridging chemotherapies (including cardiac toxicity and pulmonary toxicity), rapid disease progression, or clinically significant active infection is provided in SmPC Section 4.4. • Recommendations for the treatment of ongoing infections (which may increase the risk of a fatal CRS event) and recommendation to delay ciltacabtagene autoleucel infusion until any infections are resolved, are provided in SmPC Section 4.4. • Recommendation for potential early use of tocilizumab in patients with high tumor burden or early or persistent fever is provided in SmPC Section 4.4. • Recommendations for evaluation, treatment, and management of CRS are provided in SmPC Section 4.4. • Recommendations for treating high grade CRS that remains severe following use of tocilizumab and corticosteroids are provided in SmPC Section 4.4. • Recommendation to avoid the use of myeloid growth factors (particularly GM-CSF) during CRS is provided in SmPC Section 4.4. • Recommendation to evaluate for HLH in patients with severe or unresponsive CRS, and a warning that patients who develop HLH may have an increased risk of severe bleeding, is provided in SmPC Section 4.4. • Recommendation for reducing baseline burden of disease with bridging therapy prior to infusion	

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
	in patients with high tumor burden in SmPC Section 4.4. ● Recommendations on treatment for concurrent CRS and neurologic toxicity, including the use of corticosteroids, tocilizumab, and anti-seizure medication, is provided in SmPC Section 4.4. ● Information regarding the incidence of CRS and the specific signs and symptoms seen in clinical trials is provided in SmPC Section 4.8. ● Patients should inform their doctor or nurse immediately if CRS symptoms occur, as described in PL Section 2, and should seek medical help as described in PL Section 4. ● Use restricted to physicians experienced in the treatment of hematological cancers **Additional risk minimization measures:** ● Controlled Distribution Program and Availability of Tocilizumab ● HCP Educational Program ● Patient Educational Program	
Neurologic toxicities (including ICANS and other neurotoxicities)	**Routine risk minimization measures:** ● SmPC Section 4.2 ● SmPC Section 4.4 ● SmPC Section 4.7 ● SmPC Section 4.8 ● PL Section 2 ● PL Section 4 ● Recommendation to consider reducing baseline disease burden with bridging therapy prior to infusion in patients with high tumor burden is included in SmPC Section 4.4.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Topic of Interest Questionnaire (TOIQ) on cases of movement and neurocognitive toxicity **Additional pharmacovigilance activities:** 68284528MMY4002: Long-term Follow-up Study for Participants Previously Treated with Ciltacabtagene Autoleucel Final report: Jun 2043 68284528MMY4004: An Observational Post-authorization Safety Study to Evaluate the Safety of Multiple

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
	• Recommendation for monitoring patients daily for signs and symptoms of neurologic events for 14 days after dosing and periodically for an addition 2 weeks are included in SmPC Section 4.4. • Recommendations on monitoring patients for signs and symptoms of ICANS for 4 weeks after infusion and thereafter for other neurotoxicity are included in SmPC Section 4.4. • Recommendation to continue to monitor patients for signs and symptoms of neurologic toxicity after recovery from CRS and/or ICANS is provided in SmPC Section 4.4. • Recommendation to counsel patients on the signs and symptoms of neurologic toxicities and to seek immediate medical attention if signs and symptoms occur is provided in SmPC Section 4.4. • Recommendations on treating patients with symptoms of neurotoxicity, including intensive care supportive therapy (including steroids) for severe of life-threatening cases, are included in SmPC Section 4.4. • SmPC Section 4.4 provides information on a subset of patients with a cluster of movement and neurocognitive adverse reactions that progressed in some to an inability to work or care for oneself. These events were associated with 2 or more factors at baseline such as higher tumor burden, prior Grade 2 or higher CRS, prior ICANS, and high CAR-T cell expansion and persistence. Patients should be monitored for these symptoms	Myeloma Patients Treated with Ciltacabtagene Autoleucel Final report: Q4 2042 68284528MMY4009: A Post-authorization Safety Study to Evaluate the Safety of Multiple Myeloma Patients Treated with Ciltacabtagene Autoleucel Final report: Q4 2042 Survey to evaluate the effectiveness of the ciltacabtagene autoleucel HCP Educational Program and the Product Handling Training Final report: 3.5 years after availability of the approved educational materials

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
	and managed with supportive care measures. ● Instruction that patients should be monitored for GBS and treatment with intravenous immunoglobulin (IVIG) and plasmapheresis should be considered is included in SmPC Section 4.4. ● Instruction that patients should be monitored for signs and symptoms of peripheral neuropathies and cranial nerve palsies, and that management with short-course systemic corticosteroids should be considered, is included in SmPC Section 4.4. ● Instructions for treatment of neurotoxicities with early and aggressive supportive care (including steroids) in patients presenting with higher grade CRS or any grade ICANS is included in SmPC Section 4.4. ● Recommendations on treatment for concurrent CRS and neurologic toxicity, including the use of corticosteroids, tocilizumab, and anti-seizure medication, is provided in SmPC Section 4.4. ● Recommendation to refrain from driving and engaging in hazardous occupations or activities in the 8 weeks following infusion is provided in SmPC Section 4.7. ● Information regarding the incidence of neurologic toxicities (including ICANS and other neurotoxicities) and the specific symptoms seen in clinical trials is provided in SmPC Section 4.8. ● Patients should inform their doctor or nurse immediately if symptoms of ICANS or other neurotoxicities occur, as described in PL Section 2, and	

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
	should seek medical help for ICANS as described in PL Section 4. ● Use restricted to physicians experienced in the treatment of hematological cancers **Additional risk minimization measures:** ● Controlled Distribution Program and Availability of Tocilizumab ● HCP Educational Program ● Patient Educational Program	
Prolonged or recurrent cytopenia (excluding anemia)	**Routine risk minimization measures:** ● SmPC Section 4.4 ● SmPC Section 4.8 ● PL Section 2 ● PL Section 4 ● Recommendation to monitor blood counts prior to and after ciltacabtagene autoleucel infusion is provided in SmPC Section 4.4. ● Recommendation to consider supportive care with transfusions for treatment of thrombocytopenia is provided in SmPC Section 4.4. ● Recommendation to avoid the use of myeloid growth factors (particularly GM-CSF) during CRS is provided in SmPC Section 4.4. ● Information regarding the incidence of prolonged or recurrent cytopenia (excluding anemia) is provided in SmPC Section 4.8. ● Patients should inform their doctor right away if they have any symptoms of prolonged or recurrent cytopenia, as described in PL Sections 2 and 4.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** 68284528MMY4002: Long-term Follow-up Study for Participants Previously Treated with Ciltacabtagene Autoleucel Final report: Jun 2043 68284528MMY4004: An Observational Post-authorization Safety Study to Evaluate the Safety of Multiple Myeloma Patients Treated with Ciltacabtagene Autoleucel Final report: Q4 2042 68284528MMY4009: A Post-authorization Safety Study to Evaluate the Safety of Multiple Myeloma Patients Treated with Ciltacabtagene Autoleucel Final report: Q4 2042

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
	• Use restricted to physicians experienced in the treatment of hematological cancers **Additional risk minimization measures:** • None	
Serious infections	**Routine risk minimization measures:** • SmPC Section 4.2 • SmPC Section 4.4 • SmPC Section 4.8 • PL Section 2 • PL Section 4 • Recommendation to delay lymphodepletion therapy if a patient has clinically significant active infection is provided in Section 4.2. • Recommendation that infection prophylaxis should follow local guidelines, and that infections are known to complicate the course and management of concurrent CRS, are provided in SmPC Section 4.4. • Recommendation to delay ciltacabtagene autoleucel infusion until any clinically significant active infection or inflammatory disorder is resolved is provided in SmPC Section 4.4. • Recommendation that patients should be counselled on the importance of prevention measures for COVID-19, as patients treated with ciltacabtagene autoleucel may be at increased risk of severe/fatal COVID-19 infections, is provided in SmPC Section 4.4. • Recommendation on monitoring patients for signs and symptoms of infection is provided in SmPC Section 4.4.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** 68284528MMY4002: Long-term Follow-up Study for Participants Previously Treated with Ciltacabtagene Autoleucel Final report: Jun 2043 68284528MMY4004: An Observational Post-authorization Safety Study to Evaluate the Safety of Multiple Myeloma Patients Treated with Ciltacabtagene Autoleucel Final report: Q4 2042 68284528MMY4009: A Post-authorization Safety Study to Evaluate the Safety of Multiple Myeloma Patients Treated with Ciltacabtagene Autoleucel Final report: Q4 2042

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
	● Recommendations for the management and treatment of febrile neutropenia are included in SmPC Section 4.4. ● Recommendation to screen for HBV, HCV, and HIV prior to collection of cells for manufacturing is included in SmPC Section 4.4. ● Recommendation to monitor immunoglobulin levels after treatment and treat according to standard guidelines, including administration of immunoglobulin replacement, antibiotic prophylaxis and monitoring for infection is included in SmPC Section 4.4. ● Information regarding the incidence of serious infections is provided in SmPC Section 4.8. ● Ciltacabtagene autoleucel may increase the risk of life-threatening infections that may lead to death. Patients should tell their doctor right away if they have any signs or symptoms of infection, as described in PL Sections 2 and 4. ● Use restricted to physicians experienced in the treatment of hematological cancers **Additional risk minimization measures:** ● None	
Hypogamma-globulinemia	**Routine risk minimization measures:** ● SmPC Section 4.4 ● SmPC Section 4.6 ● SmPC Section 4.8 ● Recommendation that immunoglobulin levels should be monitored after treatment with ciltacabtagene autoleucel, IVIG should be administered for IgG	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** 68284528MMY4002: Long-term Follow-up Study for Participants Previously Treated with Ciltacabtagene Autoleucel

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
	<400 mg/dL, and patients should be managed according to standard guidelines, including antibiotic or antiviral prophylaxis and monitoring for infection, is described in SmPC Section 4.4. • Recommendation that assessment of immunoglobulin levels in newborns of mothers treated with ciltacabtagene autoleucel should be considered is provided in SmPC Section 4.6. • Information regarding the incidence of hypogammaglobulinemia infections is provided in SmPC Section 4.8. • Use restricted to physicians experienced in the treatment of hematological cancers **Additional risk minimization measures:** • None	Final report: Jun 2043 68284528MMY4004: An Observational Post-authorization Safety Study to Evaluate the Safety of Multiple Myeloma Patients Treated with Ciltacabtagene Autoleucel Final report: Q4 2042 68284528MMY4009: A Post-authorization Safety Study to Evaluate the Safety of Multiple Myeloma Patients Treated with Ciltacabtagene Autoleucel Final report: Q4 2042
Secondary malignancy of T-cell origin	**Routine risk minimization measures:** • SmPC Section 4.4 • SmPC Section 4.8 • PL Section 2 • PL Section 4 • Recommendation for life-long monitoring of patients for secondary malignancies is provided in SmPC Section 4.4. • Information regarding the incidence of secondary malignancy of T-cell origin is provided in SmPC Section 4.8. • Recommendation to contact the MAH for instructions on collecting patient samples for testing is provided in SmPC Section 4.4. • Patients should tell their doctor or nurse if symptoms of secondary malignancies of T-cell origin	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Topic of Interest Questionnaire (TOIQ) on cases of secondary malignancy **Additional pharmacovigilance activities:** 68284528MMY4002: Long-term Follow-up Study for Participants Previously Treated with Ciltacabtagene Autoleucel Final report: Jun 2043 68284528MMY4004: An Observational Post-authorization Safety Study to Evaluate the Safety of Multiple Myeloma Patients Treated with Ciltacabtagene Autoleucel Final report: Q4 2042 68284528MMY4009: A Post-authorization Safety Study to Evaluate the Safety of Multiple

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
	occur, as described in PL Section 2 and PL Section 4. ● Use restricted to physicians experienced in the treatment of hematological cancers **Additional risk minimization measures:** HCP Educational Program	Myeloma Patients Treated with Ciltacabtagene Autoleucel Final report: Q4 2042 Survey to evaluate the effectiveness of the ciltacabtagene autoleucel HCP Educational Program and the Product Handling Training Final report: 3.5 years after availability of the approved educational materials be determined based on results from the initial report Testing activity of secondary malignancies of T-cell origin PSUR reporting intervals; Interim reports to be submitted after 5, 10, and 15 years
Secondary malignancy of myeloid origin	**Routine risk minimization measures:** ● SmPC Section 4.4 ● SmPC Section 4.8 ● PL Section 2 ● PL Section 4 ● Recommendation for life-long monitoring of patients for secondary malignancies is provided in SmPC Section 4.4. ● Recommendation to contact the MAH for instructions on collecting patient samples for testing is provided in SmPC Section 4.4. ● Information regarding the incidence of secondary malignancy of myeloid origin is provided in SmPC Section 4.8. ● Patients should tell their doctor or nurse if symptoms of secondary malignancies of myeloid origin occur, as described in PL Section 2 and PL Section 4. ● Use restricted to physicians experienced in the treatment of hematological cancers	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Topic of Interest Questionnaire (TOIQ) on cases of secondary malignancy **Additional pharmacovigilance activities:** 68284528MMY4002: Long-term Follow-up Study for Participants Previously Treated with Ciltacabtagene Autoleucel Final report: Jun 2043 68284528MMY4004: An Observational Post-authorization Safety Study to Evaluate the Safety of Multiple Myeloma Patients Treated with Ciltacabtagene Autoleucel Final report: Q4 2042 68284528MMY4009: A Post-authorization Safety Study to Evaluate the Safety of Multiple Myeloma Patients Treated with Ciltacabtagene Autoleucel Final report: Q4 2042 Survey to evaluate the effectiveness of the ciltacabtagene autoleucel HCP Educational Program and the Product Handling Training

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
	Additional risk minimization measures: HCP Educational Program	Final report: 3.5 years after availability of the approved educational materials be determined based on results from the initial report
Secondary malignancy except those of T-cell and myeloid origin	**Routine risk minimization measures:** • SmPC Section 4.4 • Recommendation for life-long monitoring of patients for secondary malignancies is provided in SmPC Section 4.4. • Recommendation to contact the MAH for instructions on collecting patient samples for testing is provided in SmPC Section 4.4. • Use restricted to physicians experienced in the treatment of hematological cancers **Additional risk minimization measures:** • None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Topic of Interest Questionnaire (TOIQ) on cases of secondary malignancy **Additional pharmacovigilance activities:** 68284528MMY4002: Long-term Follow-up Study for Participants Previously Treated with Ciltacabtagene Autoleucel Final report: Jun 2043 68284528MMY4004: An Observational Post-authorization Safety Study to Evaluate the Safety of Multiple Myeloma Patients Treated with Ciltacabtagene Autoleucel Final report: Q4 2042 68284528MMY4009: A Post-authorization Safety Study to Evaluate the Safety of Multiple Myeloma Patients Treated with Ciltacabtagene Autoleucel Final report: Q4 2042
Decrease in cell viability due to inappropriate handling or preparation of the product	**Routine risk minimization measures:** • SmPC Section 4.2 • SmPC Section 6.3 • SmPC Section 6.4 • SmPC Section 6.6 • Instructions for preparation of ciltacabtagene autoleucel, including thawing, are provided in SmPC Section 4.2. • Shelf life and special precautions for storage of ciltacabtagene autoleucel are provided in SmPC Sections 6.3 and 6.4.	**Additional pharmacovigilance activities:** Survey to evaluate the effectiveness of the ciltacabtagene autoleucel HCP Educational Program and the Product Handling Training Final report: 3.5 years after availability of the approved educational materials be determined based on results from the initial report

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
	• Special precautions for disposal and other handling are provided in SmPC Section 6.6. **Additional risk minimization measures:** Product Handling Training	
TLS	**Routine risk minimization measures:** • Use restricted to physicians experienced in the treatment of hematological cancer **Additional risk minimization measures:** • None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** 68284528MMY4004: An Observational Post-authorization Safety Study to Evaluate the Safety of Multiple Myeloma Patients Treated with Ciltacabtagene Autoleucel Final report: Q4 2042 68284528MMY4009: A Post-authorization Safety Study to Evaluate the Safety of Multiple Myeloma Patients Treated with Ciltacabtagene Autoleucel Final report: Q4 2042
Aggravation of GvHD	**Routine risk minimization measures:** • SmPC Section 4.4 • PL Section 2 • Instruction that ciltacabtagene autoleucel infusion should be delayed if a patient has active GvHD is provided in SmPC Section 4.4. • Instruction for patients to tell their doctor prior to infusion of ciltacabtagene autoleucel if they have signs or symptoms of GvHD in provided in PL Section 2. • Use restricted to physicians experienced in the treatment of hematological cancer	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** 68284528MMY4002: Long-term Follow-up Study for Participants Previously Treated with Ciltacabtagene Autoleucel Final report: Jun 2043 68284528MMY4004: An Observational Post-authorization Safety Study to Evaluate the Safety of Multiple Myeloma Patients Treated with Ciltacabtagene Autoleucel Final report: Q4 2042 68284528MMY4009: A Post-authorization Safety Study to Evaluate the Safety of Multiple

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
	Additional risk minimization measures: ● None	Myeloma Patients Treated with Ciltacabtagene Autoleucel Final report: Q4 2042
Generation of RCL	**Routine risk minimization measures:** ● Use restricted to physicians experienced in the treatment of hematological cancer **Additional risk minimization measures:** ● None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** 68284528MMY4002: Long-term Follow-up Study for Participants Previously Treated with Ciltacabtagene Autoleucel Final report: Jun 2043 68284528MMY4004: An Observational Post-authorization Safety Study to Evaluate the Safety of Multiple Myeloma Patients Treated with Ciltacabtagene Autoleucel Final report: Q4 2042 68284528MMY4009: A Post-authorization Safety Study to Evaluate the Safety of Multiple Myeloma Patients Treated with Ciltacabtagene Autoleucel Final report: Q4 2042
Long-term safety	**Routine risk minimization measures:** ● None **Additional risk minimization measures:** ● None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** 68284528MMY4002: Long-term Follow-up Study for Participants Previously Treated with Ciltacabtagene Autoleucel Final report: Jun 2043 68284528MMY4004: An Observational Post-authorization Safety Study to Evaluate the Safety of Multiple Myeloma Patients Treated with Ciltacabtagene Autoleucel Final report: Q4 2042

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
		68284528MMY4009: A Post-authorization Safety Study to Evaluate the Safety of Multiple Myeloma Patients Treated with Ciltacabtagene Autoleucel Final report: Q4 2042
Impact on pregnancy and lactation	**Routine risk minimization measures:** • SmPC Section 4.6 • PL Section 2 • Recommendations that pregnancy status for females of childbearing age should be verified prior to starting treatment is provide in SmPC Section 4.6. • Recommendation on the need for effective contraception in patients who receive the lymphodepleting chemotherapy according to the corresponding prescribing information is provided in SmPC Section 4.6. • Recommendation to advise pregnant or breastfeeding women that there may be risks to the fetus or the breast-fed infant is provided in SmPC Section 4.6. • Recommendation that for any pregnant woman who receives ciltacabtagene autoleucel, assessment of immunoglobulin levels in newborns of mothers should be considered is provided in SmPC Section 4.6. • Patients should notify their doctor immediately if they are pregnant or think they may be pregnant following treatment with ciltacabtagene autoleucel, as described in PL Section 2. • Use restricted to physicians experienced in the treatment of hematological cancers	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** 68284528MMY4002: Long-term Follow-up Study for Participants Previously Treated with Ciltacabtagene Autoleucel Final report: Jun 2043 68284528MMY4004: An Observational Post-authorization Safety Study to Evaluate the Safety of Multiple Myeloma Patients Treated with Ciltacabtagene Autoleucel Final report: Q4 2042 68284528MMY4009: A Post-authorization Safety Study to Evaluate the Safety of Multiple Myeloma Patients Treated with Ciltacabtagene Autoleucel Final report: Q4 2042

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
	Additional risk minimization measures: • None	
Use in patients with pre-existing autoimmune disease	**Routine risk minimization measures:** • Use restricted to physicians experienced in the treatment of hematological cancers **Additional risk minimization measures:** • None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** 68284528MMY4004: An Observational Post-authorization Safety Study to Evaluate the Safety of Multiple Myeloma Patients Treated with Ciltacabtagene Autoleucel Final report: Q4 2042 68284528MMY4009: A Post-authorization Safety Study to Evaluate the Safety of Multiple Myeloma Patients Treated with Ciltacabtagene Autoleucel Final report: Q4 2042
Use in patients with pre-existing neurodegenerative disorders	**Routine risk minimization measures:** • SmPC Section 4.4 • PL Section 2 • A warning indicating that patients with significant CNS disease are likely to be more vulnerable to the consequences of adverse reactions observed with ciltacabtagene autoleucel and may require special attention is provided in SmPC Section 4.4. • Patients should tell their doctor before treatment with ciltacabtagene autoleucel if they have current or past nervous system disorders, as described in PL Section 2. • Use restricted to physicians experienced in the treatment of hematological cancers	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** 68284528MMY4004: An Observational Post-authorization Safety Study to Evaluate the Safety of Multiple Myeloma Patients Treated with Ciltacabtagene Autoleucel Final report: Q4 2042 68284528MMY4009: A Post-authorization Safety Study to Evaluate the Safety of Multiple Myeloma Patients Treated with Ciltacabtagene Autoleucel Final report: Q4 2042

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
	Additional risk minimization measures: • None	
Use in patients with active CNS involvement by malignancy	**Routine risk minimization measures:** • Use restricted to physicians experienced in the treatment of hematological cancers **Additional risk minimization measures:** • None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** 68284528MMY4004: An Observational Post-authorization Safety Study to Evaluate the Safety of Multiple Myeloma Patients Treated with Ciltacabtagene Autoleucel Final report: Q4 2042 68284528MMY4009: A Post-authorization Safety Study to Evaluate the Safety of Multiple Myeloma Patients Treated with Ciltacabtagene Autoleucel Final report: Q4 2042
Use in patients with chronic controlled HIV and HBV/HCV infection	**Routine risk minimization measures:** • SmPC Section 4.2 • SmPC Section 4.4 • Instructions for screening of HBV, HCV, and HIV are included in SmPC Sections 4.2 and 4.4. • Use restricted to physicians experienced in the treatment of hematological cancers **Additional risk minimization measures:** • None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** 68284528MMY4002: Long-term Follow-up Study for Participants Previously Treated with Ciltacabtagene Autoleucel Final report: Jun 2043 68284528MMY4004: An Observational Post-authorization Safety Study to Evaluate the Safety of Multiple Myeloma Patients Treated with Ciltacabtagene Autoleucel Final report: Q4 2042 68284528MMY4009: A Post-authorization Safety Study to Evaluate the Safety of Multiple Myeloma Patients Treated with Ciltacabtagene Autoleucel Final report: Q4 2042

PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN

Summary of Risk Management Plan for ciltacabtagene autoleucel

This is a summary of the risk management plan (RMP) for CARVYKTI. The RMP details important risks of CARVYKTI, how these risks can be minimized, and how more information will be obtained about CARVYKTI's risks and uncertainties (missing information).

CARVYKTI's summary of product characteristics (SmPC) and its package leaflet (PL) give essential information to healthcare professionals and patients on how CARVYKTI should be used.

This summary of the RMP for CARVYKTI should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of CARVYKTI's RMP.

I. The Medicine and What it is Used For

CARVYKTI is authorized for the treatment of adult patients with relapsed and refractory multiple myeloma, who have received at least 1 prior therapy, including an immunomodulatory agent (IMiD) and a proteasome inhibitor (PI), have demonstrated disease progression on the last therapy, and are refractory to lenalidomide (see SmPC for the full indication). It contains ciltacabtagene autoleucel as the active substance and is given via intravenous infusion.

Further information about the evaluation of CARVYKTI's benefits can be found in CARVYKTI's EPAR, including in its plain-language summary, available on the European Medicines Agency (EMA) website, under the medicine's webpage:

https://www.ema.europa.eu/en/medicines/human/EPAR/carvykti.

II. Risks Associated with the Medicine and Activities to Minimize or Further Characterize the Risks

Important risks of CARVYKTI, together with measures to minimize such risks and the proposed studies for learning more about CARVYKTI's risks, are outlined below.

Measures to minimize the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorized pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the patient (eg, with or without prescription) can help to minimize its risks.

Together, these measures constitute routine risk minimization measures.

In the case of CARVYKTI, these measures are supplemented with additional risk minimization measures mentioned under relevant important risks, below.

In addition to these measures, information about adverse reactions is collected continuously and regularly analyzed including Periodic Benefit-Risk Evaluation Report/Periodic Safety Update Report assessment so that immediate action can be taken as necessary. These measures constitute routine pharmacovigilance activities.

If important information that may affect the safe use of CARVYKTI is not yet available, it is listed under 'missing information' below.

II.A. List of Important Risks and Missing Information

Important risks of CARVYKTI are risks that need special risk management activities to further investigate or minimize the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of CARVYKTI. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (eg, on the long-term use of the medicine).

List of Important Risks and Missing Information	
Important identified risks	Cytokine release syndrome (CRS) (including hemophagocytic lymphohistiocytosis [HLH]) Neurologic toxicities (including immune effector cell-associated neurotoxicity syndrome [ICANS] and other neurotoxicities) Prolonged or recurrent cytopenia (excluding anemia) Serious infections Hypogammaglobulinemia Secondary malignancy of T-cell origin Secondary malignancy of myeloid origin
Important potential risks	Secondary malignancy except those of T-cell and myeloid origin Decrease in cell viability due to inappropriate handling or preparation of the product Tumor lysis syndrome (TLS) Aggravation of Graft versus Host Disease (GvHD) Generation of replication competent lentivirus (RCL)
Missing information	Long-term safety Impact on pregnancy and lactation Use in patients with pre-existing autoimmune disease Use in patients with pre-existing neurodegenerative disorders

	Use in patients with active central nervous system (CNS) involvement by malignancy Use in patients with chronic controlled human immunodeficiency virus (HIV) and Hepatitis B virus (HBV)/Hepatitis C virus (HCV) infection

II.B. Summary of Important Risks

Important Identified Risk: Cytokine release syndrome (including HLH)	
Evidence for linking the risk to the medicine	CRS, including events that were fatal or life-threatening, has been reported in patients treated with CARVYKTI in clinical trials and CRS was identified as an adverse reaction. The risk for CRS and information regarding this adverse reaction are described in the SmPC for CARVYKTI. CAR-T-related CRS is commonly described in the literature, with several published guidelines for toxicity grading and management. For CARVYKTI clinical trials, CRS was graded using American Society for Transplantation and Cellular Therapy (ASTCT) 2019 criteria as predefined in the trial protocols. Hemophagocytic lymphohistiocytosis (HLH) occurring in the context of CAR-T cell therapies can be a potential manifestation of severe CRS. Based on the strength of evidence from the clinical trial data and information from the literature, CRS (including HLH) is considered an important identified risk for CARVYKTI.
Risk factors and risk groups	Risk factors for severe CRS include high pre-infusion tumor burden, active infection, and early onset of fever or persistent fever after 24 hours of symptomatic treatment. Active uncontrolled infection was an exclusionary criterion in clinical trials.
Risk minimization measures	Routine risk minimization measures • SmPC Section 4.2 • SmPC Section 4.4 • SmPC Section 4.8 • SmPC Section 6.6 • PL Section 2 • PL Section 3 • PL Section 4 • Requirement to have tocilizumab (or suitable alternative measures if not available and listed in the EMA shortage catalogue) and emergency equipment available prior to infusion and during the recovery period is included in SmPC Sections 4.2 and 4.4. • Recommendation for monitoring patients daily for signs and symptoms of CRS for 14 days after dosing and periodically for an addition 2 weeks are included in SmPC Sections 4.4 and 6.6.

	• Recommendation for patients to remain within the proximity of a qualified clinical facility for at least 4 weeks following infusion is provided in SmPC Section 4.4 and in PL Section 3. • Recommendation to counsel patients to seek immediate medical attention if signs and symptoms of CRS occur, and recommendation to evaluate the patient for hospitalization and institute treatment at the first sign of CRS is provided in SmPC Section 4.4. • Recommendation to delay CARVYKTI infusion for patients with unresolved serious adverse reactions from preceding lymphodepleting or bridging chemotherapies (including cardiac toxicity and pulmonary toxicity), rapid disease progression, or clinically significant active infection is provided in SmPC Section 4.4. • Recommendations for the treatment of ongoing infections (which may increase the risk of a fatal CRS event) and recommendation to delay CARVYKTI infusion until any infections are resolved, are provided in SmPC Section 4.4. • Recommendation for potential early use of tocilizumab in patients with high tumor burden or early or persistent fever is provided in SmPC Section 4.4. • Recommendations for evaluation, treatment, and management of CRS are provided in SmPC Section 4.4. • Recommendations for treating high grade CRS that remains severe following use of tocilizumab and corticosteroids are provided in SmPC Section 4.4. • Recommendation to avoid the use of myeloid growth factors (particularly granulocyte-macrophage colony-stimulating factor [GM-CSF]) during CRS is provided in SmPC Section 4.4. • Recommendation to evaluate for HLH in patients with severe or unresponsive CRS, and a warning that patients who develop HLH may have an increased risk of severe bleeding, is provided in SmPC Section 4.4. • Recommendation for reducing baseline burden of disease with bridging therapy prior to infusion in patients with high tumor burden in SmPC Section 4.4. • Recommendations on treatment for concurrent CRS and neurologic toxicity, including the use of corticosteroids, tocilizumab, and anti-seizure medication, is provided in SmPC Section 4.4. • Information regarding the incidence of CRS and the specific signs and symptoms seen in clinical trials is provided in SmPC Section 4.8. • Patients should inform their doctor or nurse immediately if CRS symptoms occur, as described in PL Section 2, and should seek medical help as described in PL Section 4.

	• Use restricted to physicians experienced in the treatment of hematological cancers Additional risk minimization measures • Controlled Distribution Program and Availability of Tocilizumab • HCP Educational Program • Patient Educational Program
Additional pharmacovigilance activities	Additional pharmacovigilance activities: 68284528MMY4004: An Observational Post-authorization Safety Study to Evaluate the Safety of Multiple Myeloma Patients Treated with Ciltacabtagene Autoleucel 68284528MMY4009: A Post-authorization Safety Study to Evaluate the Safety of Multiple Myeloma Patients Treated with Ciltacabtagene Autoleucel Survey to evaluate the effectiveness of the ciltacabtagene autoleucel HCP Educational Program and the Product Handling Training See Section II.C of this summary for an overview of the postauthorization development plan.

Important Identified Risk: Neurologic toxicities (including ICANS and other neurotoxicities)	
Evidence for linking the risk to the medicine	Cases of CAR-T cell neurologic toxicities have been reported for subjects treated with CARVYKTI in clinical trials, and have included both ICANS as well as other neurotoxicity determined by the investigator to be related to CAR-T therapy and occurring after recovery of CRS and/or ICANS. Specific types of neurotoxicity other than ICANS include movement and neurocognitive toxicity with signs and symptoms of Parkinsonism, GBS, peripheral neuropathy, and cranial nerve palsies. Note that ICANS and other neurotoxicities are not mutually exclusive as patients can experience both ICANS and other neurotoxicity. Neurologic toxicities (including ICANS and other neurotoxicities) were identified as an adverse reaction. The risk for neurologic toxicities and information regarding this adverse reaction are described in the SmPC for CARVYKTI. While ICANS and other neurotoxicities (occurring within 8 weeks of infusion) associated with CAR-T therapy are well described in the literature, information on late onset of neurological events (ie, onset >8 weeks after CAR T cell infusion) is still evolving. Based on the known risk associated with CAR-T therapies, as well as on the strength of evidence from clinical trials of CARVYKTI, neurologic toxicities (including ICANS and other neurotoxicities) is considered an important identified risk.
Risk factors and risk groups	A known risk factor for neurologic toxicity with the use of CAR-T therapy is concurrent or resolved CRS. The cluster of movement and neurocognitive events appears to be potentially associated with

	a combination of two or more factors such as high tumor burden, prior Grade 2 or higher CRS, prior ICANS, and high CAR-T cell expansion and persistence.
Risk minimization measures	Routine risk minimization measures • SmPC Section 4.2 • SmPC Section 4.4 • SmPC Section 4.7 • SmPC Section 4.8 • PL Section 2 • PL Section 4 • Recommendation to consider reducing baseline disease burden with bridging therapy prior to infusion in patients with high tumor burden is included in SmPC Section 4.4. • Recommendation for monitoring patients daily for signs and symptoms of neurologic events for 14 days after dosing and periodically for an addition 2 weeks are included in SmPC Section 4.4. • Recommendations on monitoring patients for signs and symptoms of ICANS for 4 weeks after infusion and thereafter for other neurotoxicity are included in SmPC Section 4.4. • Recommendation to counsel patients on the signs and symptoms of neurologic toxicities and to seek immediate medical attention if signs and symptoms occur is provided in SmPC Section 4.4. • Recommendation to continue to monitor patients for signs and symptoms of neurotoxicity after recovery from CRS and/or ICANs and recommendation to consider neurologic evaluation at the first sign of CAR-T cell related neurotoxicity is provided in SmPC Section 4.4. • Recommendations on treating patients with symptoms of neurotoxicity, including intensive care supportive therapy (including steroids) for severe of life-threatening cases, are included in SmPC Section 4.4. • SmPC Section 4.4 provides information on a subset of patients with a cluster of movement and neurocognitive adverse reactions that progressed in some to an inability to work or care for oneself. These events were associated with 2 or more factors at baseline such as higher tumor burden, prior Grade 2 or higher CRS, prior ICANS, and high CAR-T cell expansion and persistence. Patients should be monitored for these symptoms and managed with supportive care measures. • Instruction that patients should be monitored for GBS and treatment with intravenous immunoglobulin (IVIG) and plasmapheresis should be considered is included in SmPC Section 4.4.

	• Instruction that patients should be monitored for signs and symptoms of peripheral neuropathies and cranial nerve palsies, and that management with short-course systemic corticosteroids should be considered, is included in SmPC Section 4.4. • Instructions for treatment of neurotoxicities with early and aggressive supportive care (including steroids) in patients presenting with higher grade CRS or any grade ICANS is included in SmPC Section 4.4. • Recommendations on treatment for concurrent CRS and neurologic toxicity, including the use of corticosteroids, tocilizumab, and anti-seizure medication, is provided in SmPC Section 4.4. • Recommendation to refrain from driving and engaging in hazardous occupations or activities in the 8 weeks following infusion is provided in SmPC Section 4.7. • Information regarding the incidence of neurologic toxicities (including ICANS and other neurotoxicities) and the specific symptoms seen in clinical trials is provided in SmPC Section 4.8. • Patients should inform their doctor or nurse immediately if symptoms of ICANS or other neurotoxicities occur, as described in PL Section 2, and should seek medical help for ICANS as described in PL Section 4. • Use restricted to physicians experienced in the treatment of hematological cancers Additional risk minimization measures • Controlled Distribution Program and Availability of Tocilizumab • HCP Educational Program • Patient Educational Program
Additional pharmacovigilance activities	Additional pharmacovigilance activities: 68284528MMY4002: Long-term Follow-up Study for Participants Previously Treated with Ciltacabtagene Autoleucel 68284528MMY4004: An Observational Post-authorization Safety Study to Evaluate the Safety of Multiple Myeloma Patients Treated with Ciltacabtagene Autoleucel 68284528MMY4009: A Post-authorization Safety Study to Evaluate the Safety of Multiple Myeloma Patients Treated with Ciltacabtagene Autoleucel Survey to evaluate the effectiveness of the ciltacabtagene autoleucel HCP Educational Program and the Product Handling Training See Section II.C of this summary for an overview of the postauthorization development plan.

Important Identified Risk: Prolonged or recurrent cytopenia (excluding anemia)	
Evidence for linking the risk to the medicine	Cytopenia has been identified as one of the most common adverse reactions in patients after receiving CARVYKTI. Cases of prolonged cytopenia (not resolved by Day 30) have been reported for subjects treated with CARVYKTI in clinical trials and prolonged cytopenia has been identified as an adverse reaction. In addition, cases of cytopenia recurring after 60 days post-infusion have been reported in clinical trials of CARVYKTI. The risk for prolonged or recurrent cytopenia and information regarding this adverse reaction are described in the SmPC for CARVYKTI. Evidence from clinical data with CARVYKTI suggests a drug association, including temporal association and persistence. Anemia begins to appear after lymphodepleting therapy but typically resolves within approximately 3 weeks post-infusion, and hemoglobin continues to rise thereafter, suggesting that bone marrow hematopoiesis improves following CAR-T therapy. Because of this, anemia is not considered an important risk of CARVYKTI. Some cases of neutropenia, thrombocytopenia, and lymphopenia continued for a longer period of time, with some recurrences of Grade 3 or 4 after Day 60. Based on the incidence, temporal association, and persistence of the events in clinical trials, prolonged or recurrent cytopenia (excluding anemia) is considered an important identified risk for CARVYKTI.
Risk factors and risk groups	Risk factors that may contribute to the development of cytopenia include the type of background therapy, bone marrow function, and disease progression. The use of bridging therapy and lymphodepletion prior to CARVYKTI administration is also a risk factor. Other factors include pre-existing neutropenia, or the concurrent use of antibiotics, corticosteroids, or symptomatic treatment medications. Additionally, age of ≥65 years old and female gender are known risk factors for leukopenia
Risk minimization measures	Routine risk minimization measures • SmPC Section 4.4 • SmPC Section 4.8 • PL Section 2 • PL Section 4 • Recommendation to monitor blood counts prior to and after CARVYKTI infusion is provided in SmPC Section 4.4. • Recommendation to consider supportive care with transfusions for treatment of thrombocytopenia is provided in SmPC Section 4.4.

	• Recommendation to avoid the use of myeloid growth factors (particularly GM-CSF) during CRS is provided in SmPC Section 4.4. • Information regarding the incidence of prolonged or recurrent cytopenia (excluding anemia) is provided in SmPC Section 4.8. • Patients should inform their doctor right away if they have any symptoms of prolonged or recurrent cytopenia, as described in PL Sections 2 and 4. • Use restricted to physicians experienced in the treatment of hematological cancers Additional risk minimization measures None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: 68284528MMY4002: Long-term Follow-up Study for Participants Previously Treated with Ciltacabtagene Autoleucel 68284528MMY4004: An Observational Post-authorization Safety Study to Evaluate the Safety of Multiple Myeloma Patients Treated with Ciltacabtagene Autoleucel 68284528MMY4009: A Post-authorization Safety Study to Evaluate the Safety of Multiple Myeloma Patients Treated with Ciltacabtagene Autoleucel See section II.C of this summary for an overview of the postauthorization development plan.

Important Identified Risk: Serious infections	
Evidence for linking the risk to the medicine	Serious infections, including life-threatening or fatal infections, have been reported with subjects treated with CARVYKTI in clinical trials and serious infection has been identified as an adverse reaction. The risk for serious infection and information regarding this adverse reaction are described in the SmPC for CARVYKTI. Based on the strength of evidence from clinical trials, serious infections are considered an important identified risk for CARVYKTI.
Risk factors and risk groups	Patients with multiple myeloma are at risk of infection due to the overproduction of ineffective monoclonal antibodies from the underlying disease, which causes immune dysfunction. Additionally, the use of chemotherapy (including bridging therapy and lymphodepletion prior to CARVYKTI administration) and immunosuppressive treatments may increase the risk of infection. Multiple myeloma patients have as much as a 15-fold increase in risk of infections, particularly pneumonia. Risk factors for fatal COVID-19 infection include comorbidities associated with severe/fatal COVID-19 such as diabetes and obesity, and concomitant use of immune-suppressant medications.

Risk minimization measures	Routine risk minimization measures • SmPC Section 4.2 • SmPC Section 4.4 • SmPC Section 4.8 • PL Section 2 • PL Section 4 • Recommendation to delay lymphodepletion therapy if a patient has clinically significant active infection is provided in Section 4.2. • Recommendation that infection prophylaxis should follow local guidelines, and that infections are known to complicate the course and management of concurrent CRS, are provided in SmPC Section 4.4. • Recommendation to delay CARVYKTI infusion until any clinically significant active infection or inflammatory disorder is resolved is provided in SmPC Section 4.4. • Recommendation that patients should be counselled on the importance of prevention measures for COVID-19, as patients treated with ciltacabtagene autoleucel may be at increased risk of severe/fatal COVID-19 infections, is provided in SmPC Section 4.4. • Recommendation on monitoring patients for signs and symptoms of infection is provided in SmPC Section 4.4. • Recommendations for the management and treatment of febrile neutropenia are included in SmPC Section 4.4. • Recommendation to screen for HBV, HCV, and HIV prior to collection of cells for manufacturing is included in SmPC Section 4.4. • Recommendation to monitor immunoglobulin levels after treatment and treat according to standard guidelines, including administration of immunoglobulin replacement, antibiotic prophylaxis and monitoring for infection is included in SmPC Section 4.4. • Information regarding the incidence of serious infections is provided in SmPC Section 4.8. • Ciltacabtagene autoleucel may increase the risk of life-threatening infections that may lead to death. Patients should tell their doctor right away if they have any signs or symptoms of infection, as described in PL Sections 2 and 4. • Use restricted to physicians experienced in the treatment of hematological cancers Additional risk minimization measures None

Additional pharmacovigilance activities	Additional pharmacovigilance activities: 68284528MMY4002: Long-term Follow-up Study for Participants Previously Treated with Ciltacabtagene Autoleucel 68284528MMY4004: An Observational Post-authorization Safety Study to Evaluate the Safety of Multiple Myeloma Patients Treated with Ciltacabtagene Autoleucel 68284528MMY4009: A Post-authorization Safety Study to Evaluate the Safety of Multiple Myeloma Patients Treated with Ciltacabtagene Autoleucel See Section II.C of this summary for an overview of the postauthorization development plan.

Important Identified Risk: Hypogammaglobulinemia	
Evidence for linking the risk to the medicine	Hypogammaglobulinemia has been reported with subjects treated with CARVYKTI in clinical trials and hypogammaglobulinemia has been identified as an adverse reaction. The risk for hypogammaglobulinemia and information regarding this adverse reaction are described in the SmPC for CARVYKTI. Based on the strength of evidence from clinical trials, including incidence and temporal association, hypogammaglobulinemia is considered an important identified risk for CARVYKTI.
Risk factors and risk groups	Patients with multiple myeloma are at risk of developing hypogammaglobulinemia and are prone to infection. Hypogammaglobulinemia can be intrinsic to the disease, occurring in 45% to 83% of patients with asymptomatic multiple myeloma (ie, SMM) at some point during the disease course (Patel 2019). The most common infections in these early-stage patients involve the respiratory tract and are predominantly caused by encapsulated bacteria such as H. influenzae or S. pneumonia, and viral reactivation, suggesting a role of hypogammaglobulinemia in their pathogenesis (Compagno 2014). It is also frequently associated with chemo immunotherapy regimens used to treat the disease, particularly those that either deplete B cells and plasma cells, or inhibit B cell survival, impair activation or interaction with T cells. Multiple prior lines of therapy and low IgG baseline values may increase the risk of developing hypogammaglobulinemia in patients with relapsed multiple myeloma. Finally, patients with co morbidities, such as chronic lung or heart disease and extra-articular rheumatoid arthritis, have also been reported to have higher instances of hypogammaglobulinemia (Patel 2019).
Risk minimization measures	Routine risk minimization measures • SmPC Section 4.4 • SmPC Section 4.6 • SmPC Section 4.8

	• Recommendation that immunoglobulin levels should be monitored after treatment with CARVYKTI, IVIG should be administered for IgG <400 mg/dL, and patients should be managed according to standard guidelines, including antibiotic or antiviral prophylaxis and monitoring for infection, is described in SmPC Section 4.4. • Recommendation that assessment of immunoglobulin levels in newborns of mothers treated with CARVYKTI should be considered is provided in SmPC Section 4.6. • Information regarding the incidence of hypogammaglobulinemia infections is provided in SmPC Section 4.8. • Use restricted to physicians experienced in the treatment of hematological cancers Additional risk minimization measures None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: 68284528MMY4002: Long-term Follow-up Study for Participants Previously Treated with Ciltacabtagene Autoleucel 68284528MMY4004: An Observational Post-authorization Safety Study to Evaluate the Safety of Multiple Myeloma Patients Treated with Ciltacabtagene Autoleucel 68284528MMY4009: A Post-authorization Safety Study to Evaluate the Safety of Multiple Myeloma Patients Treated with Ciltacabtagene Autoleucel See Section II.C of this summary for an overview of the postauthorization development plan.

Important Identified Risk: Secondary malignancy of T-cell origin	
Evidence for linking the risk to the medicine	Secondary malignancies of T-cell origin have been reported in clinical trials with ciltacabtagene autoleucel, and T-cell lymphoma has been identified as an adverse reaction. Based on clinical data, secondary malignancy of T-cell origin is considered an important identified risk.
Risk factors and risk groups	Multiple potential intrinsic and/or extrinsic factors may have contributed to the development of T-cell lymphoma, including pre-existing mutations in driver genes for T-cell lymphoma followed by acquisition of further oncogenic genomic variants. Additional potential but unknown contributors include germline genomic variation, viral infections, prior myeloma treatment. The contributing role of CAR insertion to the development of T-cell lymphoma is not fully understood and therefore cannot be excluded.

Risk minimization measures	Routine risk minimization measures • SmPC Section 4.4 • SmPC Section 4.8 • PL Section 2 • PL Section 4 • Recommendation for life-long monitoring of patients for secondary malignancies is provided in SmPC Section 4.4. • Information regarding the incidence of secondary malignancy of T-cell origin is provided in SmPC Section 4.8. • Patients should tell their doctor or nurse if symptoms of secondary malignancy of T-cell origin occur, as described in PL Section 2 and PL Section 4. • Recommendation to contact the MAH for instructions on collecting patient samples for testing is provided in SmPC Section 4.4. • Use restricted to physicians experienced in the treatment of hematological cancers Additional risk minimization measures • HCP Educational Program
Additional pharmacovigilance activities	Additional pharmacovigilance activities: 68284528MMY4002: Long-term Follow-up Study for Participants Previously Treated with Ciltacabtagene Autoleucel 68284528MMY4004: An Observational Post-authorization Safety Study to Evaluate the Safety of Multiple Myeloma Patients Treated with Ciltacabtagene Autoleucel 68284528MMY4009: A Post-authorization Safety Study to Evaluate the Safety of Multiple Myeloma Patients Treated with Ciltacabtagene Autoleucel Survey to evaluate the effectiveness of the ciltacabtagene autoleucel HCP Educational Program and the Product Handling Training Testing activity of secondary malignancies of T-cell origin See section II.C of this summary for an overview of the postauthorization development plan.

Important Identified Risk: Secondary malignancy of myeloid origin	
Evidence for linking the risk to the medicine	Secondary malignancies of myeloid origin have been reported in clinical trials with ciltacabtagene autoleucel, and MDS and AML have been identified as adverse reactions. Based on clinical data, secondary malignancy of myeloid origin is considered an important identified risk.

Risk factors and risk groups	Development of MDS and AML is multifactorial. Previous exposure to alkylating agents and/or ASCT has been implicated in the development of MDS/AML leading to the manifestation of MDS/AML mutations in hematopoietic stem cells. Prior exposure to lenalidomide may also be a risk factor for the development of MDS/AML. In addition, immunosuppression caused by lymphodepletion as well as CAR-T therapy may contribute to the risk of MDS/AML.
Risk minimization measures	Routine risk minimization measures • SmPC Section 4.4 • SmPC Section 4.8 • PL Section 2 • PL Section 4 • Recommendation for life-long monitoring of patients for secondary malignancies is provided in SmPC Section 4.4. • Recommendation to contact the MAH for instructions on collecting patient samples for testing is provided in SmPC Section 4.4. • Information regarding the incidence of secondary malignancy of myeloid origin is provided in SmPC Section 4.8. • Patients should tell their doctor or nurse if symptoms of secondary malignancy of myeloid origin occur, as described in PL Section 2 and PL Section 4. • Use restricted to physicians experienced in the treatment of hematological cancers Additional risk minimization measures • HCP Educational Program
Additional pharmacovigilance activities	Additional pharmacovigilance activities: 68284528MMY4002: Long-term Follow-up Study for Participants Previously Treated with Ciltacabtagene Autoleucel 68284528MMY4004: An Observational Post-authorization Safety Study to Evaluate the Safety of Multiple Myeloma Patients Treated with Ciltacabtagene Autoleucel 68284528MMY4009: A Post-authorization Safety Study to Evaluate the Safety of Multiple Myeloma Patients Treated with Ciltacabtagene Autoleucel Survey to evaluate the effectiveness of the ciltacabtagene autoleucel HCP Educational Program and the Product Handling Training See section II.C of this summary for an overview of the postauthorization development plan.

Important Potential Risk: Secondary malignancy except those of T-cell and myeloid origin	
Evidence for linking the risk to the medicine	In addition to secondary malignancies of T-cell and myeloid origin as listed in the important identified risks above, other secondary malignancies are also a theoretical risk from lentiviral vector DNA insertion and replication competent lentivirus (RCL).
Risk factors and risk groups	Secondary malignancy is a theoretical risk of insertional mutagenesis; therefore, all patients who receive ciltacabtagene autoleucel are theoretically at risk. Other risk factors include previous exposure to high-dose alkylating therapy and use of lenalidomide maintenance therapy.
Risk minimization measures	Routine risk minimization measures • SmPC Section 4.4 • Recommendation for life-long monitoring of patients for secondary malignancies is provided in SmPC Section 4.4. • Recommendation to contact the MAH for instructions on collecting patient samples for testing is provided in SmPC Section 4.4. • Use restricted to physicians experienced in the treatment of hematological cancers Additional risk minimization measures None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: 68284528MMY4002: Long-term Follow-up Study for Participants Previously Treated with Ciltacabtagene Autoleucel 68284528MMY4004: An Observational Post-authorization Safety Study to Evaluate the Safety of Multiple Myeloma Patients Treated with Ciltacabtagene Autoleucel 68284528MMY4009: A Post-authorization Safety Study to Evaluate the Safety of Multiple Myeloma Patients Treated with Ciltacabtagene Autoleucel See section II.C of this summary for an overview of the postauthorization development plan.

Important Potential Risk: Decrease in cell viability due to inappropriate handling or preparation of the product	
Evidence for linking the risk to the medicine	While no evidence of decrease in cell viability due to inappropriate handling or preparation has been identified to date from Trial MMY2001, this is a potential risk with CAR-T products based on their distinct method of manufacturing and administration.
Risk factors and risk groups	The risk factor is lack of strict adherence to the specifications for preparation of CARVYKTI infusion. All patients receiving infusion are potentially at risk.

Risk minimization measures	Routine risk minimization measures • SmPC Section 4.2 • SmPC Section 6.3 • SmPC Section 6.4 • SmPC Section 6.6 • Instructions for preparation of CARVYKTI, including thawing, are provided in SmPC Section 4.2. • Shelf life and special precautions for storage of CARVYKTI are provided in SmPC Sections 6.3 and 6.4. • Special precautions for disposal and other handling are provided in SmPC Section 6.6. Additional risk minimization measures • Product Handling Training
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Survey to evaluate the effectiveness of the ciltacabtagene autoleucel HCP Educational Program and the Product Handling Training See section II.C of this summary for an overview of the postauthorization development plan.

Important Potential Risk: Tumor Lysis Syndrome	
Evidence for linking the risk to the medicine	The incidence of TLS was low in clinical trials of CARVYKTI, with only 3 cases of TLS reporting as of the data cutoff. However, a biological plausibility may exist for risk of developing TLS in multiple myeloma patients with extensive disease burden and/or plasmacytomas, considering the antimyeloma effects of CARVYKTI. Therefore, TLS is considered an important potential risk.
Risk factors and risk groups	Patients at high risk for TLS include those with a high tumor burden (≥60% plasma cell infiltrate on the bone marrow biopsy or aspirate [whichever is higher] or those with multiple extramedullary disease sites and/or plasmacytomas.
Risk minimization measures	Routine risk minimization measures • Use restricted to physicians experienced in the treatment of hematological cancers Additional risk minimization measures None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: 68284528MMY4004: An Observational Post-authorization Safety Study to Evaluate the Safety of Multiple Myeloma Patients Treated with Ciltacabtagene Autoleucel

	68284528MMY4009: A Post-authorization Safety Study to Evaluate the Safety of Multiple Myeloma Patients Treated with Ciltacabtagene Autoleucel See Section II.C of this summary for an overview of the postauthorization development plan.

Important Potential Risk: Aggravation of Graft versus Host Disease	
Evidence for linking the risk to the medicine	No cases of aggravated or de novo GvHD have been reported in clinical trials of CARVYKTI to date. However, a biological plausibility may exist for increased risk of aggravation of GvHD, particularly in patients receiving allogenic transplant prior to 6 months of CARVYKTI or still receiving immunosuppressants to control a prior event of GvHD after allogenic transplant who will not be restricted from receiving CARVYKTI. Therefore, aggravation of GvHD is considered a potential risk.
Risk factors and risk groups	Risk factors for developing GvHD in multiple myeloma patients after receiving allogenic transplant include the following: higher degree of human leukocyte antigen (HLA) mismatch, older age of the donor or recipient, sex disparity between donor and recipient, prior acute GvHD (aGvHD), a splenectomized recipient, CMV seropositivity in the donor or recipient, donor EBV seropositivity. The probability of developing a subsequent acute or chronic GVHD increases with increasing numbers of risk factors (Hill 2021). Patients receiving allogenic transplant prior to 6 months of CARVYKTI or still receiving immunosuppressants to control a prior event of GvHD after allogenic transplant may be at increased risk for aggravation of GvHD.
Risk minimization measures	Routine risk minimization measures • SmPC Section 4.4 • PL Section 2 • Instruction that CARVYKTI infusion should be delayed if a patient has active GvHD is provided in SmPC Section 4.4. • Instruction for patients to tell their doctor prior to infusion of CARVYKTI if they have signs or symptoms of GvHD in provided in PL Section 2. • Use restricted to physicians experienced in the treatment of hematological cancers Additional risk minimization measures None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: 68284528MMY4002: Long-term Follow-up Study for Participants Previously Treated with Ciltacabtagene Autoleucel

	68284528MMY4004: An Observational Post-authorization Safety Study to Evaluate the Safety of Multiple Myeloma Patients Treated with Ciltacabtagene Autoleucel 68284528MMY4009: A Post-authorization Safety Study to Evaluate the Safety of Multiple Myeloma Patients Treated with Ciltacabtagene Autoleucel See Section II.C of this summary for an overview of the postauthorization development plan.

Important Potential Risk: Generation of Replication Competent Lentivirus	
Evidence for linking the risk to the medicine	While no cases of generation of RCL have been reported to date in clinical trials of CARVYKTI, this is a potential risk due to potential viral insertion (DNA integration) of the lentiviral vector.
Risk factors and risk groups	All patients who receive CARVYKTI are theoretically at risk.
Risk minimization measures	Routine risk minimization measures • Use restricted to physicians experienced in the treatment of hematological cancers Additional risk minimization measures None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: 68284528MMY4002: Long-term Follow-up Study for Participants Previously Treated with Ciltacabtagene Autoleucel 68284528MMY4004: An Observational Post-authorization Safety Study to Evaluate the Safety of Multiple Myeloma Patients Treated with Ciltacabtagene Autoleucel 68284528MMY4009: A Post-authorization Safety Study to Evaluate the Safety of Multiple Myeloma Patients Treated with Ciltacabtagene Autoleucel See Section II.C of this summary for an overview of the postauthorization development plan.

Missing Information: Long-term safety	
Risk minimization measures	No risk minimization measures
Additional pharmacovigilance activities	Additional pharmacovigilance activities: 68284528MMY4002: Long-term Follow-up Study for Participants Previously Treated with Ciltacabtagene Autoleucel 68284528MMY4004: An Observational Post-authorization Safety Study to Evaluate the Safety of Multiple Myeloma Patients Treated with Ciltacabtagene Autoleucel

	68284528MMY4009: A Post-authorization Safety Study to Evaluate the Safety of Multiple Myeloma Patients Treated with Ciltacabtagene Autoleucel See section II.C of this summary for an overview of the postauthorization development plan.

Missing Information: Impact on pregnancy and lactation	
Risk minimization measures	Routine risk minimization measure • SmPC Section 4.6 • PL Section 2 • Recommendations that pregnancy status for females of childbearing age should be verified prior to starting treatment is provide in SmPC Section 4.6. • Recommendation on the need for effective contraception in patients who receive the lymphodepleting chemotherapy according to the corresponding prescribing information is provided in SmPC Section 4.6. • Recommendation to advise pregnant or breastfeeding women that there may be risks to the fetus or the breast-fed infant is provided in SmPC Section 4.6. • Recommendation that for any pregnant woman who receives CARVYKTI, assessment of immunoglobulin levels in newborns of mothers should be considered is provided in SmPC Section 4.6. • Patients should notify their doctor immediately if they are pregnant or think they may be pregnant following treatment with CARVYKTI, as described in PL Section 2. • Use restricted to physicians experienced in the treatment of hematological cancers Additional risk minimization measures None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: 68284528MMY4002: Long-term Follow-up Study for Participants Previously Treated with Ciltacabtagene Autoleucel 68284528MMY4004: An Observational Post-authorization Safety Study to Evaluate the Safety of Multiple Myeloma Patients Treated with Ciltacabtagene Autoleucel 68284528MMY4009: A Post-authorization Safety Study to Evaluate the Safety of Multiple Myeloma Patients Treated with Ciltacabtagene Autoleucel See Section II.C of this summary for an overview of the postauthorization development plan.

Missing Information: Use in patients with pre-existing autoimmune disease	
Risk minimization measures	Routine risk minimization measures Use restricted to physicians experienced in the treatment of hematological cancers Additional risk minimization measures None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: 68284528MMY4004: An Observational Post-authorization Safety Study to Evaluate the Safety of Multiple Myeloma Patients Treated with Ciltacabtagene Autoleucel 68284528MMY4009: A Post-authorization Safety Study to Evaluate the Safety of Multiple Myeloma Patients Treated with Ciltacabtagene Autoleucel See Section II.C of this summary for an overview of the postauthorization development plan.

Missing Information: Use in patients with pre-existing neurodegenerative disorders	
Risk minimization measures	Routine risk minimization measures • SmPC Section 4.4 • PL Section 2 • A warning indicating that patients with significant CNS disease are likely to be more vulnerable to the consequences of adverse reactions observed with CARVYKTI and may require special attention is provided in SmPC Section 4.4. • Patients should tell their doctor before treatment with CARVYKTI if they have current or past nervous system disorders, as described in PL Section 2. • Use restricted to physicians experienced in the treatment of hematological cancers Additional risk minimization measures None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: 68284528MMY4004: An Observational Post-authorization Safety Study to Evaluate the Safety of Multiple Myeloma Patients Treated with Ciltacabtagene Autoleucel 68284528MMY4009: A Post-authorization Safety Study to Evaluate the Safety of Multiple Myeloma Patients Treated with Ciltacabtagene Autoleucel See section II.C of this summary for an overview of the postauthorization development plan.

Missing Information: Use in patients with active CNS involvement by malignancy	
Risk minimization measures	Routine risk minimization measures Use restricted to physicians experienced in the treatment of hematological cancers Additional risk minimization measures None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: 68284528MMY4004: An Observational Post-authorization Safety Study to Evaluate the Safety of Multiple Myeloma Patients Treated with Ciltacabtagene Autoleucel 68284528MMY4009: A Post-authorization Safety Study to Evaluate the Safety of Multiple Myeloma Patients Treated with Ciltacabtagene Autoleucel See section II.C of this summary for an overview of the postauthorization development plan.

Missing Information: Use in patients with chronic controlled HIV and HBV/HCV infection	
Risk minimization measures	Routine risk minimization measures • SmPC Section 4.2 • SmPC Section 4.4 • Instructions for screening of HBV, HCV, and HIV are included in SmPC Sections 4.2 and 4.4. • Use restricted to physicians experienced in the treatment of hematological cancers Additional risk minimization measures None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: 68284528MMY4002: Long-term Follow-up Study for Participants Previously Treated with Ciltacabtagene Autoleucel 68284528MMY4004: An Observational Post-authorization Safety Study to Evaluate the Safety of Multiple Myeloma Patients Treated with Ciltacabtagene Autoleucel 68284528MMY4009: A Post-authorization Safety Study to Evaluate the Safety of Multiple Myeloma Patients Treated with Ciltacabtagene Autoleucel See Section II.C of this summary for an overview of the postauthorization development plan.

II.C. Postauthorization Development Plan

II.C.1. Studies Which are Conditions of the Marketing Authorization

The following studies are conditions of the marketing authorization:

68284528MMY4002: Long-term Follow-up Study for Participants Previously Treated with Ciltacabtagene Autoleucel

Purpose of the study: CAR-T therapy, characterized as a cell-based gene therapy, may be associated with delayed adverse events. The primary objective is to collect long-term follow-up data on delayed adverse events after administration of CARVYKTI, and to characterize and understand the long-term safety profile of CARVYKTI. The secondary objectives are to collect additional long-term data on RCL, CARVYKTI persistence, efficacy, and OS.

68284528MMY4004: An Observational Post-authorization Safety Study to Evaluate the Safety of Multiple Myeloma Patients Treated with Ciltacabtagene Autoleucel

Purpose of the study: CAR-T therapy, characterized as a gene therapy, might be associated with different adverse event profile under real-world conditions than previously known from clinical trials. The primary objective is to evaluate the short- and long-term safety and the risk of subsequent malignancy of CARVYKTI in adult patients with multiple myeloma. The secondary objective is to evaluate the effectiveness of CARVYKTI in adult patients with multiple myeloma.

68284528MMY4009: A Post authorization Safety Study to Evaluate the Safety of Multiple Myeloma Patients Treated with Ciltacabtagene Autoleucel

Purpose of the study: The data from this study will be analyzed together with other independent prospective registries and other data sources as part of the global PASS study 68284528MMY4004. The primary objective is to evaluate the short- and long-term safety and the risk of subsequent malignancy of CARVYKTI in adult patients with multiple myeloma. The secondary objective is to evaluate the effectiveness of CARVYKTI in adult patients with multiple myeloma.

II.C.2. Other Studies in Postauthorization Development Plan

Survey to evaluate the effectiveness of the ciltacabtagene autoleucel HCP Educational Program and the Product Handling Training

Purpose of the study:

- To measure the effectiveness of the HCP Educational Program, an additional risk minimization measure intended to increase awareness about the risks of CRS (including HLH), neurologic toxicity (including ICANS and other neurotoxicities), secondary malignancy of T-cell origin, and secondary malignancy of myeloid origin. There will be a Guide for Health Care Professionals to advise of these risks and how to minimize them.

- To measure information on awareness of the HCP of the existence of Patient Alert Card, as well as the intention and time of providing it to the patients.
- To measure the effectiveness of the Product Handling Training, an additional risk minimization measure intended to increase awareness of the potential risk of decrease in cell viability due to inappropriate handling or preparation of the product

Testing activity of secondary malignancies of T-cell origin

Purpose:

- Tumor tissue sample testing from patients who develop a secondary malignancy of T-cell origin after receiving CARVYKTI in the postmarketing setting

PART VII: ANNEXES

Table of Contents

Annex 4: Specific Adverse Drug Reaction Follow-up Forms

TOIQ for movement and neurocognitive toxicity (MNT), ie Parkinsonism

Ciltacabtagene Autoleucel (CARVYKTI) Topic of Interest Questionnaire (TOIQ) for Movement and Neurocognitive Toxicity (MNT), i.e., Parkinsonism

To the Health Care Provider: *Complete this form as a supplement to the provided Health Care Professional Adverse Event Follow-Up Form.*

Manufacturer Control Number:
Date of Report:
Date of Cilta-Cel Dose:

1. **Patient demographics and medical history:** (check all that apply)
   Gender: ☐ Male ☐ Female ☐ Unknown

   Human Immunodeficiency Virus Infection:
   ☐ Yes, year diagnosed: ☐ No ☐ Unknown

   Pre-existing movement disorder, including Parkinson's disease:
   ☐ Yes, specify type: ☐ No ☐ Unknown

   Pre-existing dementia, including Alzheimer's disease:
   ☐ Yes, specify type: ☐ No ☐ Unknown

   Family history of movement disorder, including Parkinson's disease:
   ☐ Yes, specify type: ☐ No ☐ Unknown

   Family history of dementia, including Alzheimer's disease:
   ☐ Yes, specify type: ☐ No ☐ Unknown

2. **Concomittent medications:** (list all that apply)

   Psychotropics (e.g., antipsychotics, antidepressants, mood stabilizers; illicit "street" drugs if known)
   ☐ Yes, specify: ☐ No ☐ Unknown
   Treatment Dates:

   Interferon alpha
   ☐ Yes, specify: ☐ No ☐ Unknown
   Treatment Dates:

   Calcium channel blocker
   ☐ Yes, specify: ☐ No ☐ Unknown
   Treatment Dates:

   Antiemetic
   ☐ Yes, specify: ☐ No ☐ Unknown
   Treatment Dates:

   Antiepileptic
   ☐ Yes, specify:
   ☐ No ☐ Unknown Treatment Dates:

   If Yes, did symptoms improve if any of the above treatments were reduced or discontinued?
   ☐ Yes, describe:
   ☐ No ☐ Unknown

   Other (specify):
   Treatment Dates:

TV-TFUQ-00185, Version 1.0 Page 1 of 3
Ciltacabtagene Autoleucel (Cilta-Cel) Topic of Interest Questionnaire (TOIQ) for Movement and Neurocognitive Toxicity (MNT), i.e., Parkinsonism

MCN:

3. **Signs and symptoms of Movement and Neurocogntive Toxicity (MNT), i.e. Parkinsonism:**
Is the patient experiencing a cluster of movement and neurocognitive symptoms? ☐ Yes ☐ No

If 'Yes', check all that apply below. Initial symptom:
Date of onset of initial symptom:

Severity of MNT: ☐ Mild ☐ Moderate ☐ Severe ☐ Unknown

Movement Disorder
- ☐ Micrographia
- ☐ Bradykinesia
- ☐ Tremor
  - ☐ Resting
  - ☐ Action
  - ☐ Intention
  - ☐ Bilateral

  Other (specify):
- ☐ Rigidity
  - ☐ Cogwheel Rigidity
  - ☐ Lead-Pipe Rigidity

  Other (specify):
- ☐ Parkinsonian Gait
  - ☐ Shuffling Gait
  - ☐ Festination
  - ☐ Freezing
  - ☐ Reduced Arm Swing
- ☐ Parkinsonian Stance
  - ☐ Stooped Posture
  - ☐ Propulsion
  - ☐ Postural Instability
- ☐ Impaired Balance
- ☐ Impaired Coordination
- ☐ Ataxia
- ☐ Akathisia

Cognitive Impairment
- ☐ Memory Impairment
- ☐ Bradyphrenia
- ☐ Mental Fogginess
- ☐ Increased Forgetfulness
- ☐ Difficulty Word-Finding
- ☐ Dysarthria
- ☐ Aphasia
- ☐ Impaired Attention
- ☐ Impaired Concentration
- ☐ Impaired Problem Solving

Personality Change
- ☐ Flat Affect
- ☐ Masked Facies
- ☐ Reduced Facial Expression
- ☐ Apathy
- ☐ Indifference
- ☐ Less Communicative
- ☐ Loss of Interest in Non-Routine Activities
- ☐ Loss of Initiative in Routine Activities
- ☐ Somnolence
- ☒ Restlessness

Impaired Self-Care
- ☐ Yes
  Onset date:
- ☐ No
- ☐ Unknown

If 'Yes' then:
Requires assistance?
- ☐ Yes
  Specify:
- ☐ No
- ☐ Unknown

Other Symptoms:

List other symptoms not noted above:

4. **Work-up for the adverse event:**

Imaging investigations (provide summary and copy of the results, including date):

Brain MRI performed? ☐ Yes ☐ No ☐ Unknown
Results: Date:

PET scan performed? ☐ Yes ☐ No ☐ Unknown
Results: Date:

Head CT performed? ☐ Yes ☐ No ☐ Unknown
Results: Date:

Dopamine Transporter scan performed? ☐ Yes ☐ No ☐ Unknown
Results: Date:

Other imaging investigations (specify, including date):

Laboratory investigations (provide summary and copy of the results, including date and ranges):

Blood analysis performed? ☐ Yes ☐ No ☐ Unknown

MCN:

Hematology Results: Date:

Infectious Work-Up: Date:

Other Relevant Tests: Date:

CSF analysis performed? ☐ Yes ☐ No ☐ Unknown
Cytology (eg, total and differential cell counts, protein, glucose):
Results: Date:

Flow cytometry, paraneoplastic syndromes, infectious work-up:
Results: Date:

Others laboratory investigations (specify, including date):

Other diagnostic investigations (provide summary copy of the results, including date):

EEG performed? ☐ Yes ☐ No ☐ Unknown
Results: Date:

EMG / Nerve Conduction Studies performed? ☐ Yes ☐ No ☐ Unknown
Results: Date:

Other diagnostic investigations (specify, including date):

Brain autopsy performed? (provide summary and copy of the results):

☐ Yes ☐ No ☐ Unknown Results:

5. **Suspected risk factors for the adverse event:** (check all that apply)

Did the patient have high baseline tumor burden (bone marrow plasma cell ≥80% or serum M-spike ≥5 g/dL or serum free light chain ≥5000 mg/L)?

☐Yes, specify type:
☐No
☐Unknown

Did the patient experience moderate to severe Cytokine Release Syndrome after cilta-cel infusion?

☐Yes, specify date of onset and duration:
☐No
☐Unknown

Did the patient experience Immune Effector Cell Associated Neurotoxicity Syndrome after cilta-cel infusion?

☐Yes, specify date of onset and duration:
☐No
☐Unknown

Please attach additional pages as needed.

TOIQ for Secondary Malignancies for Chimeric Antigen Receptor (CAR) Products

Topic of Interest Questionnaire (TOIQ) for Second Primary Malignancies (SPM) / Subsequent Malignancies for Chimeric Antigen Receptor (CAR) Products

To Health Care Provider: *Please complete this form as a supplement to the provided Health Care Professional Adverse Event Follow-Up Form. Attach additional pages as needed.*

MCN

Manufacturer Control #: Date:
CAR Product Name:
CAR Product Batch #:

Date of CAR Product Dose:
Primary Malignancy for CAR Product Indication:

1. **Second Primary Malignancy / Subsequent Malignancy (Excluding recurrence or metastases of primary malignancy for CAR product indication):**

   Diagnosis: Diagnosis Date:

   Stage of Malignancy:
   Staging System:

   Recurrence of malignancy diagnosed prior to CAR product? ☐Yes ☐ No ☐Unknown

   Was malignancy surgically removed or a biopsy for histopathology performed? ☐Yes ☐ No
   If yes, please attach the histopathology report; if No, is histopathology planned? ☐Yes ☐ No

   Is a biopsy specimen available for lentiviral vector integration site analysis? ☐Yes ☐ No

   If yes, has specimen been sent to Janssen for testing? ☐ Yes ☐ No
   If yes, date sent:

   If no, please contact Janssen to obtain instructions on specimen shipment.

2. **Additional Diagnostic Evaluations Performed:**

   Imaging investigations (provide summary and copy of the results, including date):
   MRI performed? ☐Yes ☐ No ☐Unknown
   Date:
   Results:
   PET scan performed? ☐Yes ☐ No ☐Unknown
   Date:
   Results:
   CT performed? ☐Yes ☐ No ☐Unknown
   Date:
   Results:
   Other imaging investigations (specify, including date):

   Laboratory investigations (provide summary and copy of the results, including date and ranges):
   Cytogenetics performed? ☐Yes ☐ No ☐Unknown
   Date:

MCN#

Results:
Immunophenotype performed? ☐Yes ☐ No ☐Unknown
Date:
Results:
Other laboratory investigations (specify, including date):

Other diagnostic investigations (provide summary and copy of the results, including date): *e.g. prostate-specific antigen test or other biomarker*
Date:
Results:

3. **Risk Factors for Malignancy:**

Cytogenetic abnormalities detected prior to CAR product? ☐Yes ☐ No
If yes, describe:

History of viral infections (check all that apply):
☐ EBV ☐ HPV ☐ HIV ☐ HTLV ☐ HBV ☐ HCV

History of radiation exposure: ☐Yes ☐ No
If yes, describe:
History of excessive sun exposure: ☐Yes ☐ No
If yes, describe:
History of Stem Cell Transplantation: ☐Yes ☐ No
If yes, date(s):

Type(s): ☐ Autologous ☐ Allogenic ☐ Tandem

Family history of malignancy? ☐Yes ☐ No
If yes, describe malignancy and relative:

Previous treatment with other antineoplastic medications, immunosuppressive medications, hormonal therapies, or other drugs that have a risk for malignancy? ☐Yes ☐ No If yes, complete below:

Drug	Indication	Start Date	Stop Date

Other known risk factors for malignancy? ☐Yes ☐ No
If yes, describe:

MCN#

4. **Treatment Received or Planned for Subsequent Malignancy:** ☐ Unknown
If known, complete below:
Systemic Treatment: ☐Yes ☐ No
If yes, Regimen:
Date(s):

Surgery: ☐Yes ☐ No
If yes, Type:
Date(s):

Radiation: ☐Yes ☐ No
If yes, Type:
Date(s):

Stem Cell Transplant: ☐Yes ☐ No
If yes, Type:
Date(s):

Other Treatment: ☐Yes ☐ No
If yes, Type:
Date(s):

No Treatment Planned, or Palliative Care Only? ☐Yes ☐ No

Annex 6: Details of Proposed Additional Risk Minimization Activities

Draft Key Messages of the Additional Risk Minimization Measures

Additional Risk Minimization Measure 1

Controlled Distribution Program and Availability of Tocilizumab

This proposed additional risk minimization measure addresses the important identified risks of "Cytokine release syndrome (including HLH)" and "neurologic toxicities (including ICANS and other neurotoxicities)."

To minimize the risks associated with the treatment of ciltacabtagene autoleucel, the MAH will ensure that in each Member State where ciltacabtagene autoleucel is marketed, all centers that dispense ciltacabtagene autoleucel are qualified per MAH requirements in accordance with the agreed control distribution program.

- The MAH will ensure immediate, on-site access to one dose of tocilizumab per patient prior to ciltacabtagene autoleucel infusion. The treatment center must have access to an additional dose of tocilizumab within 8 hours of each previous dose. In the exceptional case where tocilizumab is not available due to a shortage that is listed in the EMA shortage catalogue, the MAH will ensure that suitable alternative measures to treat CRS instead of tocilizumab are available on site.

- Ciltacabtagene autoleucel will only be supplied to centers that are qualified and only if the HCPs involved in the prescribing, dispensing, or administration of ciltacabtagene autoleucel have completed the educational program for awareness and mitigation of the important identified risks of "cytokine release syndrome (including HLH)" and "neurologic toxicities (including ICANS and other neurotoxicities)."

Additional Risk Minimization Measure 2

Health Care Professional (HCP) Educational Program

This proposed additional risk minimization measure addresses the important identified risks of "cytokine release syndrome (including HLH)," "neurologic toxicities (including ICANS and other neurotoxicities)," "secondary malignancy of T-cell origin," and "secondary malignancy of myeloid origin."

Prior to the launch of ciltacabtagene autoleucel in each Member State, the MAH must agree on the content and format of the educational materials with the National Competent Authority.

The MAH shall ensure that in each Member State where ciltacabtagene autoleucel is marketed, all HCPs (eg, physicians, pharmacists, nurses, ward staff) who are expected to prescribe, dispense, and administer ciltacabtagene autoleucel shall be provided with training for:

- before treating a patient, ensure that tocilizumab is available on site for each patient. In the exceptional case where tocilizumab is not available due to a shortage that is listed in the EMA Agency shortage catalogue, ensure that suitable alternative measures to treat CRS are available on site.
- facilitate identification of CRS (including HLH) and neurologic toxicities (including ICANS and other neurotoxicities)

  Symptoms of CRS:

  - Fever (with or without rigors), chills, hypotension, hypoxia, elevated liver enzymes. Potentially life-threatening complications of CRS may include cardiac dysfunction, neurologic toxicity, and HLH. Patients who develop HLH may have an increased risk of severe bleeding. Evaluation for HLH should be considered in patients with severe or unresponsive CRS.
  - Neurologic signs and symptoms may occur concurrently with CRS, following resolution of CRS or in the absence of CRS.

  Symptoms of Neurologic toxicity:

  - ICANS: aphasia, slow speech, dysgraphia, encephalopathy, depressed level of consciousness and confusional state.
  - Adverse reactions of neurologic toxicity after recovery from CRS and/or ICANS included: disturbances in consciousness, coordination and balance disturbances, movement disorders, mental impairment disorders, cranial nerve disorders, and peripheral neuropathies. Of these, 3% of patients (n=6; all male) experienced a cluster of movement and neurocognitive adverse reactions including movement (eg, micrographia, tremors), cognitive (eg, memory loss, disturbance in attention), and personality change (eg, reduced facial expression, flat affect), often with subtle onset (eg, micrographia, flat affect), that in some patients progressed to an inability to work or care for oneself.

- facilitate awareness of clinical predictors for higher risk of CRS (including HLH) and neurologic toxicities (including ICANS and other neurotoxicities) and recommendations to help prevent or minimize them

  Risk factors of CRS: High pre-infusion tumor burden, active infection and early onset of fever or persistent fever after 24 hours of symptomatic treatment

  Risk factors of other neurotoxicities characterized by movement and neurocognitive adverse reactions: These patients all presented a combination of 2 or more factors such as high tumor burden at baseline (bone marrow plasma cell ≥80% or serum M-spike ≥5 g/dL or serum free light chain ≥5000 mg/L), prior Grade 2 or higher CRS, prior ICANS, and high CAR-T cell expansion and persistence. Reduction of baseline burden of disease with bridging therapy prior to infusion with CARVYKTI in patients with high tumor burden should be considered, which may mitigate the risk of developing neurologic toxicity. Early detection and aggressive treatment of CRS or ICANS may be important to prevent neurologic toxicity from occurring or worsening. At the first sign of ICANS, the patient should be immediately evaluated for hospitalization and treatment.

- facilitate management of CRS (including HLH) and neurologic toxicities (including ICANS and other neurotoxicities)

  Management of CRS:

  - Ensure at least one dose of tocilizumab is available on-site prior to ciltacabtagene autoleucel infusion, with access to an additional dose within 8 hours of each previous dose.
  - At the first sign of CRS, immediately evaluate the patient for hospitalization and institute treatment with supportive care, tocilizumab, or tocilizumab and corticosteroids as indicated in the educational materials.
  - Other monoclonal antibodies targeting cytokines (for example, anti-IL1 and/or anti-TNFα) or therapy directed at reduction and elimination of CAR-T cells may be considered for patients who develop high grade CRS and HLH that remains severe or life-threatening following prior administration of tocilizumab and corticosteroids.
  - For patients with high pre-infusion tumor burden, early onset of fever, or persistent fever after 24 hours, early tocilizumab should be considered.
  - Consider reducing baseline burden of disease with bridging therapy prior to infusion with ciltacabtagene autoleucel in patients with high tumor burden
  - The use of myeloid growth factors, particularly GM-CSF, should be avoided during CRS.
  - Supportive care for CRS (including, but not limited to, anti-pyretic agents, IV fluid support, vasopressors, supplemental oxygen, etc.) should be administered as appropriate. Consider laboratory testing to monitor for disseminated intravascular coagulation, hematology parameters, as well as pulmonary, cardiac, renal and hepatic function.

  Management of Neurologic toxicity:

- At the first sign of ICANS, the patient should be immediately evaluated for hospitalization and treatment instituted with supportive care as indicated in the educational materials.
- At the first sign of neurologic toxicity including ICANS, neurology evaluation should be considered. Rule out other causes of neurologic symptoms.
- Consider reducing baseline burden of disease with bridging therapy prior to infusion with ciltacabtagene autoleucel in patients with high tumor burden, which may mitigate the risk of developing neurologic toxicity. Early detection and aggressive treatment of CRS or ICANS may be important to prevent neurologic toxicity from occurring or worsening.
- Provide intensive care and supportive therapy for severe or life-threatening neurologic toxicities.
- Consider non-sedating, anti-seizure medicines (eg, levetiracetam) for seizure prophylaxis for any grade ICANS.
- It is advisable that outpatients presenting with neurotoxicities are transferred to their CAR-T treatment center. It is important that communication channels are open between the patient's local hospital and the CAR-T treatment center as delayed admission (when the patient's neurotoxicities are Grade 3 or higher) could be associated with worse prognostic outcomes.

- ensure adequate monitoring of CRS (including HLH) and neurologic toxicities (including ICANS and other neurotoxicities)

  Monitoring of CRS:

  - Patients should be monitored daily for 14 days at a qualified clinical facility and then periodically for an additional two weeks following infusion for signs and symptoms of CRS. Frequency of monitoring should be increased if CRS occurs.
  - Monitoring parameters include: temperature, blood pressure, heart rate and oxygen saturation. Patients should be counselled to seek immediate medical attention should signs or symptoms of CRS occur at any time.

  Monitoring of Neurologic toxicity:

  - Monitor patients for signs or symptoms of ICANS for four weeks after infusion. They should also be monitored for signs or symptoms of neurotoxicity occurring after recovery from CRS and/or ICANS.
  - At the first sign of neurologic toxicity including ICANS, neurology evaluation should be considered. Rule out other causes of neurologic symptoms.
  - Counsel patients to seek immediate medical attention should signs and symptoms of neurologic toxicities occur after recovery from CRS and/or ICANS.

- facilitate provision of all relevant information to patients, including the following after approval by relevant National Competent Authority:
  - the "My CAR-T Journey Guide"
  - the Patient Alert Card to be kept with the patient at all times

- ensure that adverse reactions are adequately and appropriately reported
- facilitate awareness of the risk of secondary malignancies of T-cell origin. A DHPC has been distributed to HCPs to inform them of the risk of secondary malignancy of T-cell origin.
- facilitate awareness of the risk of secondary malignancy of myeloid origin.

Additional Risk Minimization Measure 3

Product Handling Training

This proposed additional risk minimization measure addresses the important potential risk of "decrease in cell viability due to inappropriate handling or preparation of the product."

Prior to the launch of ciltacabtagene autoleucel in each Member State, the MAH must agree on the content and format of the educational materials with the National Competent Authority.

The MAH shall ensure that in each Member State where ciltacabtagene autoleucel is marketed, all HCPs (eg, physicians, pharmacists, nurses, ward staff) and other personnel who are involved in the transport, storage, thawing, preparation, or handling of ciltacabtagene autoleucel shall be provided with training to:

- Ensure that detailed instructions are provided about the procedures for transport, storage, thawing, preparation, and handling of ciltacabtagene autoleucel, in order to mitigate the risk of decrease in cell viability of due to inappropriate handling of the product. Specifically, these should include (but are not limited to) the following instructions for product handling and other precautions to take during different steps of the ciltacabtagene autoleucel therapy process:
    - Overview of the CAR-T cell therapy process, aimed to help follow the steps for ordering, receipt, storage, handling, thawing, preparation, and administration of the product;
    - Site instructions at drug product arrival, receipt (including review of packaging shipment), and appropriate on-site storage of ciltacabtagene autoleucel at the infusion center;
    - Instructions for on-site handling of ciltacabtagene autoleucel, including thawing and preparation for infusion of ciltacabtagene autoleucel;
    - Administration steps including clinical assessment prior to lymphodepletion, and ciltacabtagene autoleucel infusion, pre-infusion medications, and detailed administration instructions; and
    - Precautions to be taken for on-site transport and disposal of the medicinal product.
- Ensure that any product quality defects and/or procedure deviations are adequately and appropriately reported:
    - How to report adverse events/product complaints including batch numbers to ensure traceability

Additional Risk Minimization Measure 4

Patient Educational Program

This proposed additional risk minimization measure addresses the important identified risks of "cytokine release syndrome (including HLH)" and "neurologic toxicities (including ICANS and other neurotoxicities)."

The Patient Educational Program is to inform and explain to patients:

- the risks of CRS (including HLH) and neurologic toxicities (including ICANS and other neurotoxicities) associated with ciltacabtagene autoleucel, which may be serious or life-threatening:
  - Cytokine release syndrome (CRS) is a serious immune reaction. Some signs include: Chills, fever (38°C or higher, which can also be a sign of infection), fast heartbeat, difficulty breathing, low blood pressure which can make you feel dizzy or lightheaded.
  - Effects on the nervous system, symptoms of which can occur days or weeks after the infusion, and may initially be subtle; however, close attention should be paid to these and the patient should ask their caregiver to do the same:
    - Immune effector cell-associated neurotoxicity syndrome (ICANS) is a serious immune reaction. Some signs include: feeling confused, less alert, disorientated, anxious, having difficulty speaking or slurred speech, difficulty reading, writing and understanding words.
    - Other effects on the nervous system may include loss of coordination, affecting movement and balance, slower movements, changes in handwriting, memory loss, or personality changes which may include being less talkative, disinterest in activities, and reduced facial expression.
- that symptoms that appear mild may quickly worsen, and in addition, symptoms may be delayed and may occur weeks after ciltacabtagene autoleucel infusion.
- that ciltacabtagene autoleucel is a one-time treatment and that any possible side effects may be an emergency and therefore need to be reported to their treating doctor immediately
- the need to remain within the proximity of a qualified clinical facility for at least 4 weeks following ciltacabtagene autoleucel infusion and that they will be monitored daily at the site for 14 days following ciltacabtagene autoleucel infusion
- to refrain from driving and using tools or machines in the 8 weeks following ciltacabtagene autoleucel infusion
- the need to carry the Patient Alert Card (including signs and symptoms requiring immediate attention and other precautions, date of ciltacabtagene autoleucel dosing, batch numbers, patient and caregiver contact information, and CAR-T center and HCP contact information) at all times
- the "My CAR-T Journey Guide" as educational material after approval by relevant National Competent Authority