Janssen Research & Development*

Non-interventional Post-authorization Safety Study - Protocol

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

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Protocol 68284528MMY4004
Amendment 2

CARVYKTI® (ciltacabtagene autoleucel)

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EU PAS Register Number: EUPAS49218

Status: Approved
Protocol version: 11.0 **Version date:** 4 March 2025
Prepared by: Janssen-Cilag Limited
EDMS number: EDMS-RIM-67663, 16.0
CIBMTR ID number: SC19-09

Compliance: This study will be conducted in compliance with the protocol and applicable regulatory requirements.

1. PASS INFORMATION

Title:	An Observational Post-authorization Safety Study to Evaluate the Safety of Multiple Myeloma Patients Treated with Ciltacabtagene Autoleucel
Protocol version:	11.0
Date of last version of the protocol:	17 February 2023
EU PAS Register No:	EUPAS49218
Active substance (INN common name):	Ciltacabtagene autoleucel
Pharmaco-therapeutic group (ATC Code):	L01XL05
Medicinal product(s):	CARVYKTI
Product reference:	EMEA/H/C/005095
Procedure number:	EMEA/H/C/PSP/S/0100
Name of Marketing Authorization Holder(s)	Janssen-Cilag International NV.
Joint PASS	No
Research question and objectives	This study aims to document the short- and long-term safety of adult patients receiving ciltacabtagene autoleucel (cilta-cel) for multiple myeloma in the post-authorization setting per the health authority approved product information in the respective country/region.
Country(-ies) of study	This study is planned to be conducted in Austria, Brazil, Germany, the United Kingdom, and the United States of America. This list is not considered complete and may be revised as appropriate at a later date.
Author	PPD MD, PPD Janssen Global Services LLC.

2. MARKETING AUTHORIZATION HOLDER(S)

Name of Marketing Authorization Holder:	Janssen-Cilag International NV.
Address:	Turnhoutseweg 30 B-2340 Beerse, Belgium
Contact Details:	PPD Janssen Research and Development 50-100 Holmers Farm Way High Wycombe HP12 4DP UK PPD Janssen R&D US 920 US Highway 202 S Raritan NJ 08869 United States of America (the)
Qualified Person Pharmacovigilance:	
Name:	Dr. Laurence Oster-Gozet, PharmD, PhD
Signature:	Electronic signature appended at the end of the protocol
Date:	

3. RESPONSIBLE PARTIES

Principal Participating Physician:	Denise de Wiest MD, PPD Janssen Global Services LLC
Contact person for this protocol:	PPD
E-mail address or telephone number of contact person:	PPD

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AMENDMENTS AND UPDATES

Neither the participating physician nor the Sponsor will modify this protocol without a formal amendment. All protocol amendments must be issued by the Sponsor, and will follow the review and approval process in accordance with local regulations.

Protocol Version	**Date**
Amendment 2	4 March 2025
Amendment 1	17 February 2023
Original Global Protocol	10 June 2022

Changes made in previous protocol amendments are listed in Annex 3: Protocol Amendment History.

<u>**Amendment 2**</u> (4 March 2025)

The overall reason for the amendment: To address the Food and Drug Administration (FDA) request to increase sample size due to approval of expanded indication, and to align data capture in line with CIBMTR's data delivery practices.

Applicable Section(s).	Description of Change(s).
Rationale: Updated in line with FDA request to increase the sample size by 200 participants, due to approval of expanded indication.	
4. Abstract; 8.2.2. Selection criteria; 8.5. Study size.	Increased the sample size from 1,500 to 1,700 participants.
Rationale: Updated to reflect dates for final protocol and final report submission for both the EU and the US.	
4. Abstract; 5. Milestones.	Updated milestones to reflect dates for final protocol and final report submission for both the EU and the US in the context of this global study, and included provision of those being HA-agreed milestones.
Rationale: Updated to clarify RCL analysis will be performed when the sample quantity and quality is sufficient.	
4. Abstract; Data collection schedule; 7. Research question and objectives; 8.3.2. Evaluation of Safety; 8.3.2.1. Second primary malignancy tumor sampling	Included provision that RCL analysis will be performed in patients who develop second primary malignancies (SPMs) <u>and when samples of adequate quality and in sufficient quantity are available</u>.
Rationale: Updated the RCL testing practices for clarity.	
4. Abstract; 7. Research question and objectives	Updated to "Data on replication competent lentivirus (RCL) testing in patients who develop SPMs will also be collected for each occurrence of SPM during the long-term safety follow up period, where allowed per local regulations in the context of a non-interventional study".

Applicable Section(s).	Description of Change(s).
Rationale: Updated data collection schedule in line with CIBMTR's data delivery practices.	
Data collection schedule.	Updated data collection schedule and footnote c to clarify organ toxicity and tumor lysis syndrome, and other clinically significant adverse events, hematology results and hematologic disorders details will only be collected up to 6 months and 1 year, respectively, following cilta-cel infusion. During the subsequent patient safety follow up period, CIBMTR sites will be trained to report these events to the Sponsor as the spontaneous events, if related to cilta-cel.
Rationale: Updated effectiveness outcomes collection for clarity and to reflect current data practices in CIBMTR.	
4. Abstract; 8.3.3. Evaluation of effectiveness/clinical response.	Clarified in the Effectiveness outcomes that those will apply from the ~~date~~ **day** following cilta-cel infusion. Clarified evidence of progressive disease to calculate duration of response (DOR) will be assessed by the ~~investigator~~ **treating physician/HCP** Updated DOR definition until first documented evidence of progressive disease **or death,** following cilta-cel infusion**, whichever occurs earlier**.
Rationale: Amyloidosis and POEMS syndrome are out of scope for this PASS study. Further, removing it helps to better align with current data capturing practices from registries and applicable cilta-cel label.	
4. Abstract; 7. Research question and objectives; 8.3.3. Evaluation of effectiveness/clinical response.	Removed provision of collection and analysis of cilta-cel effect on myeloma-related comorbidities such as amyloidosis and POEMS syndrome.
Rationale: Removed specific provision of GvHD analysis only in patients with a history of allogenic transplant, due to CIBMTR's ability to also provide GvHD analyses for patients with allogenic transplant during the study as well.	
8.3.2. Evaluation of safety.	Removed specific provision of GvHD analysis only in patients with a history of allogenic transplant.
Rationale: To take out the redundancy and to clarify the hematologic assessment per current data analysis practices.	
4. Abstract; 7. Research question and objectives; 8.3.2. Evaluation of safety.	Clarified hematologic disorders (ie, thrombocytopenia, leukopenia, lymphocytopenia and anemia) will be collected, per collected laboratory values Removed duplication of hematologic disorders as a third bulletpoint under Neurotoxicity.
Rationale: To include an additional source for recruiting patients who received out-of-specification cilta-cel product.	
4. Abstract; 8.3.2 Evaluation of safety.	Included a single patient IND, 68284528MMY4012, as a source of patient receiving out-of-specification cilta-cel product.
Rationale: To ensure clarity on out-of-specification reporting practices with different health authorities.	
4. Abstract; 8.3.2 Evaluation of safety.	Clarified that out-of-specification data will be reported cumulatively to the overall study population within the annual reports (going out to PRAC only). Clarified that the final study report addressed to FDA will only include patients receiving commercial cilta-cel product, and that the final report going out to PRAC will include all patients regardless of conforming or out-of-specification product use.

Applicable Section(s).	Description of Change(s).
Rationale: To update the protocol in line with CIBMTR's data delivery standards.	
Data Collection Schedule; 8.9 Limitations of Research Methods.	Included the provision of longer-term collection of organ toxicity and tumor lysis syndrome, other clinically significant adverse events, hematology results and hematologic disorders; and the associated limitation of data missingness.
Rationale: To describe updates to current process for raising awareness of reporting SPMs.	
10.2. Procedures.	Included provision that HCP guidance on SPM reporting will be disseminated by CIBMTR and other registry owner with Sponsor's feedback and via the prescribing information that is in effect in the country of origin of the patient who has developed the malignancy.
Rationale: To update how MMY4009's reporting will take place..	
10.2. Procedures.	Removed provision that MMY4009's reporting will be made ~~directly~~ to Janssen, as this has been outsourced. Sites will report to a CRO first.
Rationale: To align with current registry data collection practices and better clarify analysis methods for safety and effectiveness parameters.	
4. Abstract; 8.7.1. Main summary measures.	Removed provision cumulative incidence estimates or rates of adverse events reported in person years may be used. Clarified cilta-cel therapy and concomitant medication will be collected where available. Removed provision change from baseline to worst adverse event experienced by a patient during the study will be provided as shift tables. Clarified safety outcomes will be summarized descriptively with counts and percentages, and that time-to-event variables will be analyzed descriptively using the Kaplan-Meier method. Clarified that analysis by prior lines of therapy may be provided if necessary.
Rationale: To clarify the Sponsor will collect the cause of death and number of days when the death occurred post cilta-cel infusion.	
Data collection schedule; 4. Abstract; 8.3. Variables.	Updated wording from "Date and cause of death" to "Cause of death, as well as the number of days after infusion when death occurred post cilta-cel infusion".
Rationale: Updated for consistency across the document and for clarity that data at Year 1 will be collected, and then annually thereafter, where available.	
6.2. Registries and other sources; 8.2.1 Study setting and duration.	Updated wording from "Day 100, Month 6 and annually thereafter" to "Day 100, ***6 Months, 1 Year,*** and then annually***, where available".***
Rationale: Updated for consistency with FDA-preferred language and for consistency within the document.	
Throughout the protocol.	Aligned wording from "secondary malignancy", "subsequent malignancy" and others to "second primary malignancy".
Rationale: Updated for consistency with current preferred nomenclature.	
4 Abstract; Data Collection Schedule; 7. Research questions and objectives; 8.3.2. Evaluation of safety	Updated from "CRS, including HLH/MAS" to separate "CRS" and "MAS/HLH" indications.

Applicable Section(s).	Description of Change(s).
Rationale: Updated in line with newly-available data.	
4. Abstract; 6. Background and rationale.	Updated 5-year survival from "approximately ~~50%~~" to "approximately **61%**", in line with newly available data as overall survival tends to increase over time as new treatments become available.
Rationale: Updated to facilitate enrolment.	
10.2.1 Pregnancy.	Updated wording to remove gender considerations.
Rationale: Updated to for alignment with current CIBMTR and Sponsor processes. This was because of potential delays in real-time reporting coming through CIBMTR due to those being data entry-driven, and data entry delays from sites.	
8.3.2.1 Second Primary Malignancy Tumor Sampling; 10.2 Procedures; 10.2.1 Pregnancy.	Updated wording to include that reporting of SPM cases and pregnancy incidents will be performed via periodic data transfers, which will then be processed for expedited reporting. Sites will also be encouraged to report those directly to Sponsor.
Rationale: Updated for clarification.	
8.3.2.1 Second Primary Malignancy Tumor Sampling.	Included provision for predominant lentiviral integration: "If there is evidence of predominant lentiviral integration within the sample submitted(…)"
Rationale: Updated for alignment with latest available RMP	
4. Abstract; 5. Milestones	Updated timelines per the latest available RMP.
Rationale: Updated in line with latest considerations for long-term reporting.	
8.9 Limitations of Research Methods.	Because reporting of key events on longer timeframes relies on spontaneous reporting channels, data missingness is a consideration be factored in for these events, and included the relevant mitigation strategy by site training at regular schedules.
Rationale: Updated per latest study considerations.	
1. PASS information.	Updated list of countries.
Rationale: Updated the protocol language to include types of tumor samples other than (and including) whole blood for RCL testing.	
Throughout the protocol.	Removed specific consideration of whole blood samples being used for RCL analysis in patients who develop SPMs.
Rationale: Minor errors were noted and administrative updates required.	
Throughout the protocol.	Minor administrative, grammatical, formatting, or spelling changes were made.

4. ABSTRACT

Protocol Title: An Observational Post-authorization Safety Study to Evaluate the Safety of Multiple Myeloma Patients Treated with Ciltacabtagene Autoleucel (11.0, 4 March 2025)

Sponsor's Responsible Medical Officer: PPD MD (Main Author)

NOTE: The term "Sponsor" used throughout this document refers to the entities listed in the Contact Information page(s), which will be provided separately.

Background and Rationale

Multiple myeloma is an incurable, malignant plasma cell disorder that accounts for approximately 10% of hematological malignancies. Worldwide, there were an estimated 80,000 deaths due to multiple myeloma and in Europe approximately 24,300 patients with this disease die annually. The estimated 5-year survival rate for patients with multiple myeloma is approximately 61%. Ciltacabtagene autoleucel (cilta-cel; also known as JNJ-68284528 and LCAR-B38M CAR-T cells) is an autologous chimeric antigen receptor (CAR)-T therapy that targets B-cell maturation antigen (BCMA), a molecule expressed on the surface of mature B-lymphocytes and malignant plasma cells. Cilta-cel is currently under development for treatment of multiple myeloma.

Cilta-cel, characterized as a gene therapy, might be associated with a different adverse event profile under real world conditions than previously known from clinical trials. There is a particular concern for gene therapies for potential delayed adverse events including but not limited to second primary malignancies (SPMs) that may not be readily observed in clinical development trials. This study is a prospective observational post-authorization safety study (PASS) to provide long-term, up to 15 years, follow-up for multiple myeloma patients exposed to cilta-cel commercial product in a post-authorization setting per the health authority approved product information in the respective country/region, to fulfill the requirement set out by health authorities and provide additional data to evaluate the potential short- and long-term safety profile of cilta-cel under real world conditions.

Research Question and Objectives

This study aims to document the short- and long-term safety of adult patients with multiple myeloma receiving cilta-cel in the post-authorization setting per the health authority approved product information in the respective country/region.

The primary objective of the study is to evaluate the short- and long-term safety of cilta-cel including the risk of SPM of cilta-cel in adult patients with multiple myeloma. Data on replication competent lentivirus (RCL) testing in patients who develop SPMs will also be collected for each occurrence of SPM during the long-term safety follow up period, where allowed per local regulations in the context of a non-interventional study.

The secondary objective of the study is to evaluate the effectiveness of cilta-cel in adult patients with multiple myeloma.

Study Design

This study is an observational PASS (68284528MMY4004; referred to throughout as MMY4004 or the "study") to describe the data collection required to define the short- and long-term safety profile of cilta-cel in the treatment of patients with multiple myeloma. This protocol describes the minimum common dataset required to inform the safety profile of cilta-cel across multiple data sources (Center for International Blood and Marrow Transplant Research [CIBMTR], other similar registries outside the US, including a Janssen -sponsored registry [68284528MMY4009; referred to throughout as MMY4009], and other national registries, as required by local regulatory authorities). Other data sources may also include analyses from tumor samples and spontaneously-reported adverse reactions to the Sponsor, where available.

The minimum common dataset for this observational PASS has been modelled based on the existing independent prospective CIBMTR registry. Additional regional and data collection needs, over and above the minimum established common dataset and based on specific requirements from regulatory authorities, shall be described and implemented in separate protocols, such as MMY4009. Study MMY4009 is a non-interventional Janssen-sponsored prospective registry which will enroll patients from select European Union (EU) countries and additional countries outside the EU.

Patients will enroll in this study at the time of receiving cilta-cel infusion and will be followed for a period of up to 15 years. For the purpose of this protocol, the term "study" will be used to refer to this prospective observational PASS (MMY4004) and the term "registry" will be used for registries such as CIBMTR, MMY4009 and national registries, as appropriate. All aspects of treatment decisions and clinical management of patients will be at the discretion of the treating physician and the patient.

A definition of variables for the common dataset collected from the registry for use in this study will be provided as part of the statistical analysis plan of this PASS. All patients included in the registry will give written consent for participation in the registry, and for pharmaceutical companies to have access to study data. The registry will provide data for this study in a non-traceable manner with all patients' identifiable details remaining confidential.

The data collection period will start from the day that cilta-cel therapy is received (baseline), and patients will be followed for up to 15 years, or until withdrawal of consent or the time of death, if applicable. Data will be collected within the registry at the timepoints specified in the DATA COLLECTION SCHEDULE and pooled into the common dataset for this study. Data extracts from the registry will be periodically provided to the Sponsor for analysis. Confidentiality of patient records will be maintained at all times.

Data collection will include pre-infusion demographics, diagnosis and medical history data including previous disease characteristics, treatment information, comorbid conditions and information on lymphodepleting therapies. Post-infusion data collected will include performance status, current multiple myeloma therapies and current disease status. Short-term and long-term safety data will be collected throughout the follow-up period, alongside effectiveness data for response and survival.

The end of the study will be after all consented patients have completed 15 years of follow-up or discontinued from the study.

Setting and Patient Population

The source population for this study will be those patients enrolled in the registry, who are receiving cilta-cel for multiple myeloma and who provided informed consent. Other data sources may also include analysis from tumor samples or spontaneously-reported adverse reactions to the Sponsor, where available.

Each potential participant must satisfy the following criteria to be eligible for data collection in this study: have received at least 1 dose of cilta-cel commercial product per the health authority approved cilta-cel product information in the respective country/region, and who have signed a participation agreement/informed consent form allowing participation within the respective registry, and for pharmaceutical companies to have access to their study data. Patients receiving cilta-cel not meeting pre-specified drug product specifications per label may also be eligible for the study. Enrollment in the study will continue until at least 1,700 patients have been enrolled into the study and received cilta-cel. These will include 1,500 patients with relapsed or refractory multiple myeloma after 4 or more lines of therapy (including a proteasome inhibitor, an immunomodulatory agent, and an anti-CD-38 monoclonal antibody). The remaining 200 patients will include patients with relapsed or refractory multiple myeloma who have received at least 1 and fewer than 4 prior lines of therapy, including a proteasome inhibitor and an immunomodulatory agent, and who are lenalidomide-refractory.

Variables

The documentation of data must be performed according to clinical practice. Only data available from the respective databases for the registry will be collected. Other data sources may also include analysis from tumor samples and spontaneously-reported adverse reactions to the Sponsor, where available.

The following items are to be documented at baseline and/or during the observational period:

- Demographic data
- Diagnosis and medical history
- Performance status
- Comorbid conditions
- History of prior malignancy
- Multiple myeloma disease characteristics
    - Type of myeloma and staging of disease
    - Prior therapies for multiple myeloma
- Cilta-cel therapy
    - Lymphodepleting chemotherapy
    - Dose/number of cells infused
    - Toxicities/complications
    - Treatments for complications
    - Response to cilta-cel therapy
- Relapse/progression of disease
- Subsequent treatments for multiple myeloma, including stem cell transplant or other cellular therapy
- Cause of death, as well as the number of days post cilta-cel infusion when death occurred

Evaluation of Safety

Safety outcomes will be summarized using selected data collected from the registry for patients treated with cilta-cel, including those who receive out-of-specification product through the managed access program 68284528MMY4006 and single patient IND 68284528MMY4012. Patients who receive out-of-specification product will be analyzed and reported to the overall study population within the annual reports (going out to PRAC only).The final study report addressed to FDA will only include patients receiving commercial cilta-cel product. The final report going out to PRAC will include all patients regardless of conforming or out-of-specification product use.

Selected toxicities described below will be collected in the registry and reported in this study. Additionally, any adverse reactions and special situations spontaneously reported to Janssen by the registry participating sites and solicited serious and non-serious adverse events and special situations from Study MMY4009 will be also included in the analysis.

Safety parameters for this study include the following selected adverse events (including latency, frequency, type and severity where available):

- SPMs, defined as a new occurrence of malignancy after cilta-cel administration (including SPMs and recurrent malignancies, other than multiple myeloma).
  - In the event of SPM, a tumor sample should be collected, if clinically feasible and in accordance with the prescribing information that is in effect in the country of origin of the patient who has developed the malignancy, and lentiviral integration site analysis may be performed for possible insertional mutagenesis.
    - Presence of RCL will be tested in patients who develop SPMs, where allowed per local regulations in the context of a non-interventional study, and when samples of adequate quality and in sufficient quantity are available.
- Neurotoxicity, including:
  - Immune effector cell associated neurotoxicity syndrome (ICANS)
  - Other CAR-T cell neurotoxicity, including movement and neurocognitive toxicity
- Hypogammaglobulinemia
- Clinically significant infections, including hepatitis B virus (HBV) reactivation
- Organ toxicities (≥Grade 3)
- CRS
- Macrophage activation syndrome/hemophagocytic lymphohistiocytosis/ (MAS/HLH)
- Tumor lysis syndrome (≥Grade 3)
- Graft-versus-host disease (GvHD)
- Other collected adverse events, including but not limited to:
  - Infusion-related reactions
  - Rheumatologic or other autoimmune disorders
  - Neurological disorders, other than ICANS and other CAR-T cell neurotoxicity
  - Hematologic disorders, including prolonged or recurrent cytopenias (ie, thrombocytopenia, leukopenia, lymphocytopenia and anemia), per collected laboratory values

In addition, all pregnancies and outcomes following exposure to cilta-cel that are documented in the source data will be reported.

Evaluation of Effectiveness/Clinical Response

Disease evaluations will be collected as described using data collected from the registry for patients treated with cilta-cel. Response assessments will be evaluated by the treating physician in the registry per International Myeloma Working Group (IMWG) criteria. Effectiveness will be evaluated based on overall survival (OS), progression-free survival (PFS), duration of response (DOR) and overall response rate (ORR).

Overall survival will be defined as the interval between the day of first cilta-cel infusion and day of death following cilta-cel infusion, reported in the registry, due to any cause.

Progression-free survival will be defined as the interval between the day of first cilta-cel infusion and day of progressive disease according to the judgment of the treating physician following cilta-cel infusion, or death following cilta-cel infusion, whichever occurs earlier.

Duration of response (DOR) will be calculated among responders (with a PR or better response) from the day of initial documentation of a response (PR or better) to the day of first documented evidence of progressive disease (assessed by the treating physician/HCP) or death, following cilta-cel infusion, whichever occurs earlier.

Response to cilta-cel will be captured per IMWG criteria for response assessment in patients with multiple myeloma, ie, as partial response or better (overall response) according to the judgment of the treating physician. Additional response categories will be captured, as available, for example very good partial response (VGPR), complete response (CR), and/or stringent complete response (sCR).

Data Sources

Data Sources From the Externally-Owned CIBMTR Registry and Other National Registries

The data source for this study will be the respective databases for the registry. Additionally, other data sources may also include analysis from tumor samples and spontaneously-reported adverse reactions to the Sponsor, where available. The registry owners will be responsible for data handling and management in their respective databases. Patient level data for patients who meet the selection criteria will be extracted from the registries on a regular data transfer schedule and provided to the Sponsor, or in response to health authority requests. Patient data will be handled in compliance with all applicable privacy laws. CIBMTR sites will be instructed to report serious adverse events (SAEs) directly to Janssen or per institutional policy, as appropriate.

Primary Data Collection Directly From a Janssen-Sponsored Registry (MMY4009)

The primary data source for the MMY4009 study will be the medical record of each patient who has provided a signed informed consent form (ICF). Source documentation should be in patients' records for all data entered into the CRF. The author of any entry in the source documents should be identifiable. Data collection may be conducted through remote patient contacts and review of relevant medical records from the patient's treating physician.

Study Size

Data will be collected from adult patients with multiple myeloma who are treated with the commercial cilta-cel product. The following sample size estimation was calculated for the proposed study design of a single-arm prospective cohort, with potential comparison to a historic or contemporaneous control cohort, for the outcome of SPMs.

Enrollment will continue until at least 1,700 patients have been enrolled into the study and received cilta-cel. These will include 1,500 patients with relapsed or refractory multiple myeloma after 4 or more lines of therapy (including a proteasome inhibitor, an immunomodulatory agent, and an anti-CD-38 monoclonal antibody). The remaining 200 patients will include patients with relapsed or refractory multiple myeloma who have received at least 1 and fewer than 4 prior lines of therapy, including a proteasome inhibitor and an immunomodulatory agent, and who are lenalidomide-refractory.Assuming a conservative background incidence rate for SPM of 4% in heavily treated multiple myeloma patients, which reflects the lower bound confidence interval of the most conservative estimate that has been reported in previous studies of patients treated with lenalidomide and other therapies, an alpha of 0.05, will provide at least 90% power, for a minimally detectable increased relative risk among cilta-cel exposed patients of 1.5.

These sample size estimates assume the rate of new malignancies is constant over time. However, the estimate is based on a conservative cumulative background rate observed at a median of 3 years follow-up.

The rate of malignancy and SPM increase with age and over time, so considerations for increases in background rate at later time points would only increase the statistical power. This estimate serves as a guide for study planning purposes, pending finalization of the statistical analysis plan (SAP).

Data Analysis

Statistical analyses will be performed by or under the authority of the Sponsor. A general description of the planned statistical methods to be used to analyze the data collected in this study is presented in the following subsections. Additional details will be provided in the SAP.

The analysis set will include all patients who meet the selection criteria in all relevant data sources, including (but not limited to) CIBMTR and MMY4009.

Only selected toxicities will be collected in the registry and reported in this study. Additionally, any adverse reactions and special situations spontaneously reported to Janssen by the sites and solicited serious and non-serious adverse events and special situations from Study MMY4009 will also be included in the analysis. Adverse event reporting within the registries will be calendar driven, with events information collected at patient visits conducted within clinical practice. A common harmonized dataset including adverse events from all registries will be detailed within the SAP. Other data sources for this study may also include analyses from tumor samples of patients from both registries.

The safety outcomes will be summarized descriptively with counts and percentages. Where appropriate, additional summaries, listings, datasets, or narratives may be provided, as appropriate.

The time-to-event variables (PFS, OS and DOR) will be analyzed descriptively using the Kaplan-Meier method.

Milestones

Milestone	Planned date
Final protocol submission (US)	April 2022
Final protocol submission (EU)	July 2022
Start of data collection	Quarter 2 2022
End of data collection	Up to 15 years after last patient has been enrolled
Study completion date	30 June 2041
Final report submission (US)	30 June 2042
Final report submission (EU)	Quarter 4 2042

Note: Data will be regularly extracted from start of data collection and analysis will be performed annually with results summarized in interim reports. Milestones included in this protocol have been agreed upon with the relevant health authorities.

DATA COLLECTION SCHEDULE WITHIN THE REGISTRIES

	Baseline Day 0[a]	Day 100	Month 6	Month 12	Every 12 Months	End of Study
Patient information						
Patient consent[b]	X					
Selection criteria	X					
Demographics	X					
Medical history	X					
Performance status	X					
Disease characteristics						
Disease history	X					
Disease burden at cilta-cel treatment	X					
Current disease status	X					
Comorbid conditions	X					
Multiple myeloma therapy						
Previous multiple myeloma therapy	X					
Current multiple myeloma therapy	X	X	X	X	X	X
Ongoing patient review						
Adverse events[c]	X	X	X	X	X	X
Second primary malignancies (SPMs)	Continuous from the time of enrollment, where possible in clinical practice, appropriate samples depending on the tumor type will be collected for SPMs in accordance with the prescribing information that is in effect in the country of origin of the patient who has developed the malignancy (eg, whole blood, bone marrow, tissue biopsy in FFPE blocks/slides) and vector integration site analysis may be performed for possible insertional mutagenesis, and when samples of adequate quality and in sufficient quantity are available					
Replication competent lentivirus	Only in patients with SPMs in accordance with the prescribing information that is in effect in the country of origin of the patient who has developed the malignancy and when samples of adequate quality and in sufficient quantity are available.[h]					
Concomitant therapy[d]	X	X	X	X	X	X
Hematology results[e]	X[f]	X	X	X		
Clinical response assessments						
Survival status[g]		X	X	X	X	X
Myeloma and comorbid conditions response to cilta-cel		X	X	X	X	X
Disease progression		X	X	X	X	X

[a] The CIBMTR registry collects Day 0 data before cellular therapy is administered.

[b] Before the start of data collection in the registries, all patients must sign a participation agreement/informed consent form (ICF) allowing consent for participation in the respective registries, and for pharmaceutical companies to have access to their data; the participation agreement/ICF may be obtained at or before baseline.

[c] The rate of the following selected adverse events will be collected: SPMs, neurotoxicity including ICANS and other CAR-T cell neurotoxicity, CRS, MAS/HLH, TLS, GvHD, infusion-related reactions, hypogammaglobulinemia, clinically significant infection including hepatitis B reactivation, organ toxicities, hematologic disorders including prolonged or recurrent cytopenias, rheumatologic or other autoimmune disorders, and neurological disorders other than ICANS and other CAR-T cell neurotoxicity including movement and neurocognitive toxicity, other clinically significant adverse events, and pregnancy and pregnancy outcomes. Additionally, any adverse reactions and special situations should be spontaneously reported during the study. Organ toxicities and tumor lysis syndrome will be collected for up to 6 months following the cilta-cel infusion. Similarly, other clinically

significant adverse events and hematologic disorders will be collected for up to 1 year following cilta-cel infusion. During the subsequent patient safety follow up period, CIBMTR sites will be trained to report these events to the Sponsor as the spontaneous events, if related to cilta-cel.

[d] Either subsequent antimyeloma therapy or concomitant therapy for treatment of selected adverse events. Adverse reactions spontaneously reported during the study only.

[e] Collected where available within clinical practice.

[f] Pre-cilta-cel infusion.

[g] Cause of death, as well as the number of days after infusion when death occurred post cilta cel infusion.

[h] Where allowed per local regulations in the context of a non-interventional study.

5. MILESTONES

The initial planned dates for key milestones in this study are outlined below.

Milestone:	**Planned Date:**
Final protocol submission (US)	April 2022
Final protocol submission (EU)	July 2022
Start of data collection	Quarter 2 2022
End of data collection	Up to 15 years after last patient has been enrolled
Registration in the EU PAS register	24 October 2022
Interim report	Quarter 3 2023, and annually thereafter and routine PBRER and DSUR reporting
Study completion date	30 June 2041
Final report submission (US)	30 June 2042
Final report submission (EU)	Quarter 4 2042

Note: Data will be regularly extracted from start of data collection and analysis will be performed annually with results summarized in interim reports. Milestones included in this protocol have been agreed upon with the relevant health authorities.

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviations

ADR	adverse drug reaction
ATC	Anatomic Therapeutic Chemical
BCMA	B-cell maturation antigen
CAR	chimeric antigen receptor
CD3ζ	CD3 zeta cytoplasmic domain
CD8α hinge+TM	CD8 alpha hinge and transmembrane domain
CD8α SP	CD8 alpha signal peptide
CIBMTR	Center for International Blood and Marrow Transplant Research
CR	complete response
CRF	case report form
CRO	contract research organization
CRS	cytokine release syndrome
DOR	duration of response
DSUR	development safety update report
eDC	electronic data capture
EMA	European Medicines Agency
EU	European Union
FDA	Food and Drug Administration
FFPE	Formalin-Fixed Paraffin-Embedded
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation
GvHD	Graft versus Host Disease
HBV	Hepatitis B Virus
HCP	health care provider
hEF1α promoter	human elongation factor 1 alpha promoter
HIPAA	Health Insurance Portability and Accountability Act
HLH	hemophagocytic lymphohistiocytosis
HSCT	hematopoietic stem cell transplantation
ICANS	immune effector cell associated neurotoxicity
ICD	International Classification of Diseases
ICF	informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IMiD	immunomodulatory agent
IMWG	International Myeloma Working Group
IRB	Institutional Review Board
LV	lentiviral vector
MAS	macrophage activation syndrome
MedDRA	Medical Dictionary for Regulatory Activities
ORR	overall response rate
OS	overall survival
PASS	post-authorization safety study
PBRER	Periodic benefit-risk evaluation report
PFS	progression-free survival
PI	proteasome inhibitor
RCL	replication competent lentivirus
SAE	serious adverse event
SAP	Statistical Analysis Plan
sCR	stringent complete response
SPM	second primary malignancy
VGPR	very good partial response
WHO	World Health Organization

Definition of Term(s)

Registry	The term “registry” will be used for registries such as CIBMTR, MMY4009, and national registries, as appropriate. A registry is an organized system that uses observational study methods to collect uniform data (clinical and other) to evaluate specified outcomes for a population defined by a particular disease, condition, or exposure, and that serves one or more predetermined scientific, clinical, or policy purposes.
Study	The term “study” refers to this prospective observational PASS (MMY4004). The use of this term in no way implies that any interventional treatments or procedures, planned or otherwise, have been provided or performed.
Prospective study	A study in which the outcome of interest occurs after the research begins.
Post-Authorization Safety Study (PASS)	Any study relating to an authorized medicinal product conducted with the aim of identifying, characterizing or quantifying a safety hazard, confirming the safety profile of the medicinal product, or of measuring the effectiveness of risk management measures.

6. BACKGROUND AND RATIONALE

Multiple myeloma is an incurable, malignant plasma cell disorder that accounts for approximately 10% of hematological malignancies.[13,14] Multiple myeloma is characterized by the proliferation of neoplastic clones of plasma cells derived from B-lymphocytes. These neoplastic clones grow in the bone marrow, frequently invade adjacent bone, disrupt both bone homeostasis and hematopoiesis, and cause multifocal destructive lesions throughout the skeleton that result in bone pain and fracture.[2] Common clinical presentations of multiple myeloma are hypercalcemia, renal insufficiency, anemia, bony lesions, bacterial infections, hyperviscosity, and secondary amyloidosis.[11]

Worldwide, there were an estimated 80,000 deaths due to multiple myeloma and in Europe, approximately 24,300 patients with this disease die annually.[6] The estimated 5-year survival rate for patients with multiple myeloma is approximately 61%.[1] Despite multiple therapeutic options, the disease most often recurs and remains incurable. With each successive relapse, symptoms return, quality of life worsens, and the chance and duration of response typically decreases. Therefore, there remains a significant and critical unmet need for new therapeutic options directed at alternative mechanisms of action that can better control the disease, provide deeper, more sustained responses, and better long-term outcomes including maintenance of health-related quality of life.[17]

6.1. Current Treatments

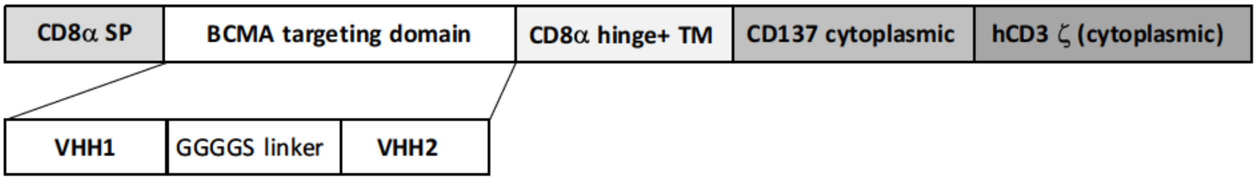
Until 2000, the standard therapies for multiple myeloma were melphalan- or doxorubicin-based regimens with corticosteroids.[2] Since then, the introduction of proteasome inhibitors (PI) (eg, bortezomib, carfilzomib, and ixazomib), histone deacetylase inhibitors (eg, panobinostat), immunomodulatory agents (IMiD) (eg, thalidomide, lenalidomide, and pomalidomide), and monoclonal antibodies (daratumumab [anti-CD38] and elotuzumab [anti-CS1/SLAMF7]) have provided numerous therapeutic avenues for patients with multiple myeloma.

The vast majority, if not all patients with this disease eventually relapse and become refractory to existing treatments. Median overall survival in patients who have received at least 3 prior lines of therapy and are refractory to both an IMiD and a PI is only 13 months.[8] The reported overall response rate (ORR) for approved therapies for the population of heavily pre-treated and refractory patients with multiple myeloma, is approximately 20% to 30%.[7,9,16]

In the last 2 to 3 years, chimeric antigen receptor (CAR)-T cells therapies targeting B-cell maturation antigen (BCMA) have emerged as a highly promising therapy for patients with advanced multiple myeloma who have exhausted available therapies such as PI, IMiD, and CD38 monoclonal antibody. Early data indicate that BCMA CAR-T therapy could lead to an ORR of 80% or more, a complete response (CR) rate of 40% to 70% and median progression-free survival (PFS) of 12 months or more.[12]

Ciltacabtagene autoleucel or cilta-cel (also known as JNJ-68284528 and LCAR-B38M CAR-T cells) consists of autologous T cells genetically modified to express a CAR utilizing a lentiviral vector (LV). The target antigen of the CAR is BCMA, which is expressed on malignant plasma cells. The LV coding sequence is comprised of a human CD8 alpha signal peptide (CD8α SP), BCMA targeting domains (VHH1 and VHH2), human CD8 alpha hinge and transmembrane domain (CD8α hinge+TM), human CD137 cytoplasmic domain (4-1BB), and a human CD3 zeta cytoplasmic domain (CD3ζ) (Figure 1). The expression of the LV is driven/controlled by a human elongation factor 1 alpha promoter (hEF1α promoter). The novel design of the CAR includes 2 targeting domains to BCMA and enables tight binding of the modified CAR-expressing T cells to BCMA-expressing cells.

Figure 1: Lentiviral Vector Coding Region



BCMA = B-cell maturation antigen; hCD3ζ = a human CD3 zeta cytoplasmic domain; CD8α SP = CD8 alpha signal peptide; CD8α hinge + TM = CD8 alpha hinge and transmembrane domain; GGGGS = 4 glycines and 1 serine; VHH = variable fragments of heavy chain antibodies (clone A37353 as VHH1 and clone A37917 as VHH2).

6.2. Registries and Other Sources

This protocol is an analysis of data collected in the externally-owned independent Center for International Blood and Marrow Transplant Research (CIBMTR) registry and other registries, such as the Janssen-sponsored registry (68284528MMY4009; referred to throughout as MMY4009) for the European Union (EU) and other regions. During the course of the study, other similar registries may be added, as required by local regulatory authorities. Additionally, other data sources may also include analysis from tumor samples and spontaneously-reported adverse reactions to the Sponsor, where available.

The CIBMTR registry comprises an international network of more than 420 centers and across more than 30 countries to collect hematopoietic stem cell transplantation (HSCT) and cellular therapy data from patients and donors. The CIBMTR collaborates with centers from around the world to collect clinical data from allogeneic and autologous transplants performed worldwide, including nearly all allogeneic transplants and approximately 80% of the autologous transplants performed in the US (250 centers in the US including pediatric centers or 180 centers including adult patients only).

FormsNET3 “FN3” is a web-based data collection system that is compliant with the US database security requirements established by the Health Resources and Services Administration Office of Information Technology and with the Food and Drug Administration (FDA) 21 Code of Federal Regulations (CFR) 11. Sites need to be registered as a CIBMTR member and sign a Master Healthcare Data Agreement and a Sample Submission Agreement to allow the transfer of data between organizations (CIBMTR and Site). Upon Master Healthcare Data Agreement completion, site staff are provided access to FN3 and are provided trainings on the CIBMTR data collection processes including the use of the FN3 system. Sites initiate patient reporting through the FN3 generation of a CIBMTR Research Identification number, which is unique to every patient. The Therapy Indication Form will identify that the patient is a recipient of a cilta-cel therapy and trigger a series of forms appropriate for the indication. With the CIBMTR Research Identification number, the patient's record can be tracked over time as well as multiple indications. In addition, data are managed through a role-based security model and the CIBMTR data collection, data storage and data sharing systems are externally audited every year.

The CIBMTR collects data before cellular therapy is administered and at Day 100, 6 Months, 1 Year and annually where available. All patients provide Institutional Review Board (IRB)-approved consent to participate in the database and have their data included in observational studies.[3]

The Janssen-sponsored registry (MMY4009) for the EU and other regions will follow a similar time and events schedule and collect similar data points as the CIBMTR registry, as well as additional data based on specific regulatory requirements. Other potential national registries and data sources will follow similar data extraction routines to ensure consistent collection of data and pooled analysis for this study.

6.3. Overall Rationale for the Study

Cilta-cel is an autologous CAR-T therapy that targets BCMA, a molecule expressed on the surface of mature B-lymphocytes and malignant plasma cells. Cilta-cel is currently under development for treatment of multiple myeloma.

Cilta-cel, characterized as a gene therapy, might be associated with a different adverse event profile under real world conditions than previously known from clinical trials. There is a particular concern for gene therapies for potential delayed adverse events, including but not limited to second primary malignancies (SPMs) that may not be readily observed in clinical development trials. Those events could be due to several potential or theoretical risks outlined below:

- The integration activity of CAR gene: the biological activity of CAR-T therapy depends on integration of CAR into the T-cell genome. However, this integration is random and is not directed to specific sites in the human genome, which raises the potential for disruption of critical host genes (tumor suppressing gene) or activation of proto-oncogenes, resulting in potential tumorigenesis. There could also be an off-target effect on the genomes which may product undesirable changes of host genomes, and impair gene function, resulting in risk of malignancy.
- Prolonged expression: Although prolonged expression of CAR in the T-cell could have beneficial effects on anti-tumor activities, the prolonged expression could also introduce the risk for autoimmune-like reactions to self-antigens.
- Latency and potential persistent infection: Although the risk for reactivation and replication of competent lentivirus is very low or only theoretical, the potential risk of delayed adverse events due to viral reactivation or competent viral replication caused symptomatic infection or persistent infection is present, especially in immunocompromised patients.

This study is a prospective observational post-authorization safety study (PASS) to provide long-term, up to 15 years, follow-up for multiple myeloma patients exposed to cilta-cel commercial product in a post-authorization setting per the health authority approved product information in the respective country/region, to fulfill the requirement set out by health authorities and provide additional data to evaluate the potential short- and long-term safety profile of cilta-cel under real-world conditions. Patients will be consecutively enrolled in the registry. Other data sources may also include analysis from tumor samples and spontaneously-reported adverse reactions to the Sponsor, where available. The data collected from these sources will be used in this study to characterize the short- and long-term safety profile of cilta-cel.

7. RESEARCH QUESTION AND OBJECTIVES

Research Question

This study aims to document the short- and long-term safety of adult patients with multiple myeloma receiving cilta-cel in the post-authorization setting per the health authority approved product information in the respective country/region.

Objective(s)

The primary objective of the study is to evaluate the short- and long-term safety of cilta-cel including the risk of SPM of cilta-cel in adult patients with multiple myeloma. Data on replication competent lentivirus (RCL) testing in patients who develop SPMs will also be collected for each occurrence of SPM during the long-term safety follow up period, where allowed per local regulations in the context of a non-interventional study.

The secondary objective of the study is to evaluate the effectiveness of cilta-cel in adult patients with multiple myeloma.

Measure(s) of Interest

The safety of cilta-cel will be measured through the rate of the following selected adverse events associated with patients receiving administration of cilta-cel (including latency, frequency, type and severity when available):

- SPMs, including:
  - RCL in patients who develop SPMs and when samples of adequate quality and in sufficient quantity are available
- Neurotoxicity, including:
  - immune effector cell associated neurotoxicity syndrome (ICANS)
  - other CAR-T cell neurotoxicity, including movement and neurocognitive toxicity
- Hypogammaglobulinemia
- Clinically significant infections, including hepatitis B virus (HBV) reactivation
- Organ toxicities (≥Grade 3)
- CRS
- Macrophage activation syndrome (MAS)/ hemophagocytic lymphohistiocytosis (HLH)

- Tumor lysis syndrome (≥Grade 3)
- Graft-versus-host disease (GvHD)
- Other collected adverse events, including but not limited to:
  - Infusion-related reactions
  - Rheumatologic or other autoimmune disorders
  - Neurological disorders, other than ICANS and other CAR-T cell neurotoxicity
  - Hematologic disorders, including prolonged or recurrent cytopenias (ie, thrombocytopenia, leukopenia, lymphocytopenia and anemia), per collected laboratory values
- Pregnancy and pregnancy outcomes

The effectiveness of cilta-cel measured through the following parameters:

- Overall response rate (ORR)
- Duration of response (DOR)
- Progression-free survival
- Overall survival (OS)

Refer to Section 8.7 for statistical aspects of measures of interest.

8. RESEARCH METHODS

8.1. Study Design

8.1.1. Overview of Study Design

This study is an observational PASS (68284528MMY4004; referred to throughout as MMY4004 or the "study") to describe the data collection required to define the short- and long-term safety profile of cilta-cel in the treatment of patients with multiple myeloma. This protocol describes the minimum common dataset required to inform the safety profile of cilta-cel across multiple data sources (Center for International Blood and Marrow Transplant Research [CIBMTR], other similar registries outside the US, including a Janssen-sponsored registry [MMY4009], and other national registries, as required by local regulatory authorities). Other data sources may also include analyses from tumor samples and spontaneously-reported adverse reactions to the Sponsor, where available.

The minimum common dataset for this observational PASS has been modelled based on the existing independent prospective CIBMTR registry. Additional regional and data collection needs, over and above the minimum established common dataset and based on specific requirements from regulatory authorities, shall be described and implemented in separate protocols, such as MMY4009. Study MMY4009 is a non-interventional Janssen-sponsored prospective registry, which will enroll patients from select EU countries and additional countries outside the EU.

Patients will enroll at the time of receiving cilta-cel infusion and will be followed for a period of up to 15 years from cilta-cel infusion. For the purpose of this protocol, the term "study" will be used to refer to this prospective observational PASS (MMY4004) and the term “registry” will be used for registries, such as CIBMTR, MMY4009, and national registries, as required by local regulatory authorities. All aspects of treatment decisions and clinical management of patients will be at the discretion of the treating physician and the patient.

A definition of variables for the common dataset collected from the registry for use in this study will be provided as part of the statistical analysis plan of this PASS. All patients included in the registry will give written consent for participation in the respective registries, and for pharmaceutical companies to have access to study data. The registry will provide data for this study in a non-traceable manner with all patients’ identifiable details remaining confidential.

The data collection period will start from the day that cilta-cel therapy is received (baseline), and patients will be followed for up to 15 years, or until withdrawal of consent or the time of death, if applicable. Throughout the data collection period, data will be collected within the registry at the timepoints specified in the DATA COLLECTION SCHEDULE and pooled into the common dataset for this study. Data extracts from the registry will be periodically provided to the Sponsor for analysis. Confidentiality of patient records will be maintained at all times.

Data collection will include pre-infusion demographics, diagnosis and medical history data including previous disease characteristics, treatment information, comorbid conditions and information on lymphodepleting therapies. Post-infusion data collected at baseline will include performance status, current multiple myeloma therapies and current disease status. Short-term and long-term safety data will be collected throughout the follow-up period, alongside effectiveness data for response and survival. Section 10 provides further details of safety data collection and reporting procedures.

The end of the study will be after all consented patients have completed 15 years of follow-up or discontinued from the study.

8.1.2. Rationale for Study Design Elements

The prospective observational design facilitates collection of a sufficient quantity of defined variables, where available in clinical practice, to address the study objectives.

To avoid potential bias in patient selection, each participating physician should enroll eligible patients in a consecutive manner (ie, in the order in which they are assessed for eligibility) in the registry. All patients who meet the selection criteria should be offered participation in the study.

A registry source is chosen to provide data for this study as registry-based evaluations can extend and add to findings from randomized trials and in situations where randomized trials are not feasible, eg, rare adverse reactions or long-term safety evaluation. In 2015, an EU report observed that these data will allow authorities to not only monitor and ensure safety, quality and functionality of novel therapies but also to justify public investments to ensure availability of tissue and cell therapies.[4] The CIBMTR registry comprises an international network of more than 420 centers and across more than 30 countries to collect HSCT and cellular therapy data from patients and donors. A Janssen-sponsored registry and national registries as appropriate, alongside the CIBMTR registry, and analysis from tumor samples or spontaneously-reported adverse reactions to the Sponsor, will be pooled to collect data from multiple regions, allowing analysis of the patient population across regions and meeting the planned target sample size.

The safety and effectiveness measures collected in this study will provide detailed characterization of the short- and long-term safety profile of cilta-cel. The data collected in this study are in line with the recommended crucial core data elements to be collected per health authority guidance in the short- and long-term follow-up of CAR-T cell products in a real world setting per the health authority approved product information in the respective country/region and enable the generation of meaningful efficacy and safety data using haemato-oncological registries.[5] Additional regional and global data collection needs, over and above the minimum established common dataset and based on specific requirements from regulatory authorities, shall be described and implemented in separate protocols, such as MMY4009 for the EU and other regions.

8.2. Setting and Patient Population

8.2.1. Study Setting and Duration

This is an observational PASS to evaluate the short- and long-term safety, and risk of SPM, of patients treated with cilta-cel. The source population will be those patients enrolled in the registry, who are receiving cilta-cel for multiple myeloma and who provided informed consent. Other data sources may also include analysis from tumor samples or spontaneously-reported adverse reactions to the Sponsor, where available.

During the data collection period, data will be collected on Day 0 (cilta-cel infusion), Day 100, 6 Months, 1 Year and then annually, where available. A patient will be considered to have completed the study if data collection up to the agreed follow-up period, for a maximum of 15 years after the last administration of cilta-cel has been completed within the registry, and captured in this study.

A patient will be withdrawn from further documentation in this study for any of the following reasons:

- Withdrawal of consent for participation in the registry
- Lost to follow-up
- Death

All treatment decisions will be made at the discretion of the treating physician. Starting or stopping therapies for multiple myeloma during the observation period will not impact data collection for this study.

Due to the duration of registry and length of time between data collection time points, lost to follow-up is a potential concern. To reduce chances of a patient being deemed lost to follow-up, contact information from each patient and that of a back-up contact (eg, caregiver or family member) should be obtained at enrollment into the registry and reconfirmed throughout the study.

If a patient is not reachable, reasonable effort should be made by the registry in accordance with routine care and the external registry protocol to contact the patient or their back-up contact. Reasonable effort may include telephone calls, e-mails, and/or letter to the patient's last known mailing address. Locator agencies may also be used as local regulations permit. The measures taken to follow-up should be documented.

Further details of study completion and termination procedures are presented in Annex 1.9.

8.2.2. Selection Criteria

The eligibility of patients for data collection in this study will be based on the selection criteria described below. To avoid potential selection bias, all eligible patients should be included for data collection in the study. Enrollment in the study will continue until at least 1,700 patients have been enrolled into the study and received cilta-cel. These will include 1,500 patients with relapsed or refractory multiple myeloma after 4 or more lines of therapy (including a proteasome inhibitor, an immunomodulatory agent, and an anti-CD-38 monoclonal antibody). The remaining 200 patients will include patients with relapsed or refractory multiple myeloma who have received at least 1 and fewer than 4 prior lines of therapy, including a proteasome inhibitor and an immunomodulatory agent, and who are lenalidomide-refractory.

Each potential participant must satisfy the following criteria to be eligible for data collection in the treatment cohort within this study:

1. Patient who received at least 1 dose of cilta-cel commercial product per the health authority approved cilta-cel product information in the respective country/region. Patients receiving cilta-cel not meeting pre-specified drug product specifications per label may also be eligible for the study.
2. Patient must sign a participation agreement/informed consent form (ICF) allowing participation within the respective registry, as applicable, and for pharmaceutical companies to have access to their study data.

Because this is a non-interventional, secondary data analysis of databases of patients enrolled into the registry, therapy decisions will be made at the discretion of the treating physician, prior to enrollment into this study. Janssen will not provide guidance on any aspect of therapy, or patient clinical management. Recommended clinical follow-up in the form of particular laboratory and clinical investigations for patients treated with cilta-cel will be described in the Summary of Product Characteristics, United States Prescribing Information or other local labels, as appropriate. It is expected that treating physicians will take into account the product label recommendations and existing general guidelines for clinical follow-up of relapsed-refractory multiple myeloma patients treated with CAR-T cell therapies.

8.3. Variables

The DATA COLLECTION SCHEDULE that follows the abstract summarizes the frequency and timing of data collection in this non-interventional study. The documentation of data must be performed according to clinical practice. Only data available from the respective databases for the registry will be collected. Other data sources may also include analysis from tumor samples or spontaneously-reported adverse reactions to the Sponsor, where available.

The following items are to be documented at baseline and/or during the observational period:

- Demographic data
- Diagnosis and medical history
- Performance status
- Comorbid conditions
- History of prior malignancy
- Multiple myeloma disease characteristics
  - Type of myeloma and staging of disease
  - Prior therapies for multiple myeloma
- Cilta-cel therapy
  - Lymphodepleting chemotherapy
  - Dose/number of cells infused
  - Toxicities/complications (see Section 8.3.2)
  - Treatments for complications (see Section 8.3.1)
  - Response to cilta-cel therapy (see Section 8.3.3)
- Relapse/progression of disease (see Section 8.3.3)
- Subsequent treatments for multiple myeloma, including stem cell transplant or other cellular therapy (see Section 8.3.2).
- Cause of death, as well as the number of days after infusion when death occurred post cilta-cel infusion

8.3.1. Exposures

The main exposure of interest is treatment with cilta-cel. This study will collect data from patients enrolled in the registry who are treated with cilta-cel in a post-authorization setting, per the health authority approved product information in the respective country/region.

In addition, the following retrospective data will be documented at baseline:

- Multiple myeloma therapies administered since diagnosis

The following data (including product information, dosing information, batch number, where available) will be documented during the prospective observational period:

- Treatments for selected adverse events (CRS and neurotoxicities) or others (where available)
- Subsequent treatments (type) for multiple myeloma, including stem cell transplant or other cellular therapy
- Lymphodepleting chemotherapy

8.3.2. Evaluation of Safety

Safety outcomes will be summarized using selected data collected from the registry for patients treated with cilta-cel, including those who receive out-of-specification product through the managed access program 68284528MMY4006 and single patient IND 68284528MMY4012. Patients who receive out-of-specification product will be analyzed and reported to the overall study population within the annual reports (going out to PRAC only). The final study report addressed to FDA will only include patients receiving commercial cilta-cel product. The final report going out to PRAC will include all patients regardless of conforming or out-of-specification product use.

Selected toxicities described below will be collected in the registry and reported in this study. Additionally, any adverse reactions and special situations spontaneously reported to Janssen by the registry participating sites and solicited serious and non-serious adverse events and special situations from Study MMY4009 will also be included in the analysis.

Section 10.2 provides further details of safety data collection and reporting procedures.

Safety Variables

Data for the following key clinically important study variables will be reported by the treating physician in the registry, and will be collected for this study.

Safety parameters for this study include the following selected adverse events (including latency, frequency, type and severity where available):

- SPMs, defined as a new occurrence of malignancy after cilta-cel administration (including SPMs and recurrent malignancies, other than multiple myeloma)
  - In the event of SPM in accordance with the prescribing information that is in effect in the country of origin of the patient who has developed the malignancy, a tumor sample should be collected, if clinically feasible, and lentiviral integration site analysis may be performed for possible insertional mutagenesis (see Section 8.3.2.1)
    - Samples should be collected to test the presence of RCL in patients who develop SPMs, where allowed per local regulations in the context of a non-interventional study and when samples of adequate quality and in sufficient quantity are available.
- Neurotoxicity, including:
  - Immune effector cell associated neurotoxicity syndrome (ICANS)
  - Other CAR-T cell neurotoxicity, including movement and neurocognitive toxicity
- Hypogammaglobulinemia
- Clinically significant infections, including HBV reactivation
- Organ toxicities (≥Grade 3)
- CRS
- Macrophage activation syndrome/hemophagocytic lymphohistiocytosis (MAS/HLH)
- Tumor lysis syndrome (≥Grade 3)

- Graft-versus-host disease (GvHD)
- Other collected adverse events, including but not limited to:
    - Infusion-related reactions
    - Rheumatologic or other autoimmune disorders
    - Neurological disorders, other than ICANS and other CAR-T cell neurotoxicity
    - Hematologic disorders, including prolonged or recurrent cytopenias (ie, thrombocytopenia, leukopenia, lymphocytopenia and anemia), per collected laboratory values

In addition, all pregnancies and outcomes following exposure to cilta-cel that are documented in the source data will be reported.

8.3.2.1. Second Primary Malignancy Tumor Sampling

For patients who receive commercial cilta-cel post-authorization and develop SPMs in accordance with the prescribing information that is in effect in the country of origin of the patient who has developed the malignancy, the Sponsor plans to offer, if and as allowed by clinical practices and local regulation, a transgene assay service allowing their treating physicians to voluntarily request and submit tumor samples for insertional mutagenesis analysis. Analyses from tumor samples of patients from the registry obtained through this post-marketing service may also be included as other data sources for this study.

In the event of SPMs, and depending on the type of malignancy in accordance with the prescribing information that is in effect in the country of origin of the patient who has developed the malignancy, a blood, bone marrow or biopsy sample of the neoplastic tissue will be collected, where possible within clinical practice, and DNA, RNA, or protein analysis may be performed in a central laboratory to investigate the presence of lentiviral elements. Lentiviral integration site analysis should be conducted if at least 1% of cells in the sample are positive for vector sequence. The Sponsor will take a systematic approach to investigate whether lentiviral vector integration could have played a role for the adverse event. If there is evidence of predominant lentiviral integration within the sample submitted, the Sponsor will follow adverse events reporting in the subject closely to determine the occurrence of additional SPMs.

SPMs from the externally-owned CIBMTR registry and other national registries should be reported to the Sponsor in periodic data transfers. For SPMs in accordance with the prescribing information that is in effect in the country of origin of the patient who has developed the malignancy, this process will also facilitate prompt initiation of the process to obtain tumor specimens.

Details on tissue requirements and sample collection will be provided as part of the laboratory manual for specimen collection.

Presence of RCL will be tested in patients who develop SPMs, where allowed per local regulations in the context of a non-interventional study and when samples of adequate quality and in sufficient quantity are available.

8.3.3. Evaluation of Effectiveness/Clinical Response

Disease evaluations will be collected as described using data collected from the registry for patients treated with cilta-cel. Response assessments will be evaluated by the treating physician in the registry per International Myeloma Working Group (IMWG) criteria. Effectiveness will be evaluated based on OS, PFS, DOR and ORR.

- Overall survival will be defined as the interval between the day of first cilta-cel infusion and day of death following cilta-cel infusion, reported in the registry, due to any cause
- Progression-free survival will be defined as the interval between the day of first cilta-cel infusion and day of progressive disease according to the judgment of the treating physician following cilta-cel infusion, or death following cilta-cel infusion, whichever occurs earlier
- Duration of response (DOR) will be calculated among responders (with a PR or better response) from the day of initial documentation of a response (PR or better) to the day of first documented evidence of progressive disease (assessed by the treating physician/HCP) or death, following cilta-cel infusion, whichever occurs earlier.
- Response to cilta-cel will be captured per IMWG criteria for response assessment in patients with multiple myeloma, ie, as partial response or better (overall response) according to the judgment of the treating physician. Additional response categories will be captured, as available, for example very good partial response (VGPR), complete response (CR), and/or stringent complete response (sCR)

8.4. Data Sources

Data Sources From the Externally-Owned CIBMTR Registry and Other National Registries

The data source for this study will be the respective databases for registry. Additionally, other data sources may also include analysis from tumor samples and spontaneously-reported adverse reactions to the Sponsor, where available. The registry owners will be responsible for data handling and management in their respective databases. Patient level data for patients who meet the selection criteria will be extracted from the registries on a regular data transfer schedule and provided to the Sponsor, or in response to health authority requests. Patient data will be handled in compliance with all applicable privacy laws. CIBMTR sites will be instructed to report serious adverse events (SAEs) directly to Janssen, or per institutional policy, as appropriate. Section 10.2 provides further details of reporting procedures.

Primary Data Collection Directly From a Janssen-Sponsored Registry (MMY4009)

The primary data source for the MMY4009 study will be the medical record of each patient who has provided a signed ICF. The author of any entry in the source documents should be identifiable. Data collection may be conducted through remote patient contacts and review of relevant medical records from the patient's treating physician.

The type and level of detail of source data available for a patient should be consistent with that commonly recorded at the participating site as a basis for standard medical care.

8.5. Study Size

Data will be collected from adult patients with multiple myeloma who are treated with the commercial cilta-cel product. The following sample size estimation[15] was calculated for the proposed study design of a single-arm prospective cohort, with potential comparison to a historic or contemporaneous control cohort, for the outcome of SPMs and modified following health authority review.

Enrollment will continue until at least 1,700 patients have been enrolled into the study and received cilta-cel. These will include 1,500 patients with relapsed or refractory multiple myeloma after 4 or more lines of therapy (including a proteasome inhibitor, an immunomodulatory agent, and an anti-CD-38 monoclonal antibody). The remaining 200 patients will include patients with relapsed or refractory multiple myeloma who have received at least 1 and fewer than 4 prior lines of therapy, including a proteasome inhibitor and an immunomodulatory agent, and who are lenalidomide-refractory. Assuming a conservative background incidence rate for second primary malignancy of 4% in heavily treated multiple myeloma patients, which reflects the lower bound confidence interval of the most conservative estimate that has been reported in previous studies of patients treated with lenalidomide and other therapies,[10] an alpha of 0.05, will provide at least 90% power, for a minimally detectable increased relative risk among cilta-cel exposed patients of 1.5.

These sample size estimates assume the rate of SPMs is constant over time. However, it is estimated based on a conservative cumulative background rate observed at a median of 3 years follow-up. The rate of malignancy and SPM increase with age and over time, so considerations for increases in background rate at later time points would only increase the statistical power. This estimate serves as a guide for study planning purposes, pending finalization of the statistical analysis plan (SAP).

8.6. Data Management

The data source for this study will be the registries and may also include analysis from tumor samples or spontaneously-reported adverse reactions to the Sponsor, where available. Further details are provided in Section 8.4.

8.7. Data Analysis

Statistical analyses will be performed by or under the authority of the Sponsor. A general description of the planned statistical methods to be used to analyze the data collected in this study is presented in the following subsections. Additional details will be provided in the SAP.

The analysis set will include all patients who meet the selection criteria in all relevant data sources, including (but not limited to) CIBMTR and MMY4009.

8.7.1. Main Summary Measures

The verbatim terms used by physicians to document adverse events in the respective databases for the registry will be coded using the Medical Dictionary for Regulatory Affairs (MedDRA). All selected adverse events will be included in the analysis. For each adverse event, the percentage of patients who experience at least 1 occurrence of the given event will be summarized. Further detail will be included in the SAP.

Patient demographics, medical history and disease history (including history of prior and current malignancies), current disease status, concomitant medications and any previous therapies for multiple myeloma will be collected at baseline. Cilta-cel therapy data and concomitant medication, where available, will be collected for each patient throughout the study.

Only selected toxicities will be collected in the registry and reported in this study. Additionally, any adverse reactions and special situations spontaneously reported to Janssen by the sites and solicited serious and non-serious adverse events and special situations from Study MMY4009 will be also included in the analysis. Adverse event reporting within the registries will be calendar driven, with events information collected at patient visits conducted within clinical practice. A common harmonized dataset including adverse events from all registries will be detailed within the SAP. Other data sources for this study may also include analyses from tumor samples of patients from all registries.

The safety outcomes will be summarized descriptively with counts and percentages. Where appropriate, additional summaries, listings, datasets, or narratives may be provided, as appropriate.

Parameters with predefined toxicity grades will be summarized.

The exploratory analysis may be performed for detection and characterization of other known and potentially unknown safety signals. Where possible, administered dose of cilta-cel will be collected and exploratory analyses of the association between dose and safety profile may be performed.

The time-to-event variables (PFS, OS, DOR) will be analyzed descriptelively using the Kaplan-Meier method.

Analysis by prior lines of therapy may be provided if necessary. Further details will be provided in the SAP.

8.7.2. Interim Analysis

The study will have analysis performed annually and results will be summarized in interim reports.

8.8. Quality Control

Quality Control for the Externally-Owned CIBMTR Registry and Other National Registries, as Required by Local Regulatory Authorities

Overall, the registry owners will be solely responsible for data quality and integrity.

For the CIBMTR, the CIBMTR will ensure quality of study data through the quality assurance process involving the standard procedures for data management of clinical outcomes research study cycle.

The CIBMTR data collection process has integrated data auditing process to offer optimum quality assurance for the data collected from all participating transplant and cell therapy centers. The auditing process verifies the accuracy of collected data in CIBMTR registry with the source document at each transplant center. This offers an additional level of scrutiny for catching data errors as opposed to online validation built into the data entry program. The CIBMTR auditing team will routinely share a summary of the auditing process with the Sponsor to support the data quality initiatives.

The CIBMTR employs a query-based resolution system for occurrences of missing, discrepant or possibly incorrect data. Queries issued by CIBMTR operations staff in the registry will prompt the site data manager to review and to correct the data. The CIBMTR will also routinely share a summary of query status report with the Sponsor to provide assessment on accuracy and completeness of the data.

CIBMTR will comply with the regulatory agencies requirements of maintaining source documentation and study data hosting in their registry.

Quality Control for the Janssen-Sponsored Registry (MMY4009)

Procedures to ensure the accuracy and reliability of data will include the selection of qualified physicians and appropriate participating sites, and review of data collection procedures with the participating physician and site personnel before the study. Written instructions for the handling, storage, and shipments of samples obtained in clinical practice will be provided where appropriate.

Guidelines for CRF completion will be provided and reviewed with the participating site personnel before the start of the study (see Annex 1.7). The Sponsor will review CRFs for accuracy and completeness after transmission to the Sponsor; any discrepancies will be resolved with the participating physician or designee, as appropriate. After upload of the data into the study database, they will be verified for accuracy and consistency with the data sources.

The participating physician and/or site will maintain all CRFs and source documentation that support the data collected for each patient, as well as all study documents specified by the applicable regulatory requirement(s) (see Annex 1.2). The participating physician and/or site will take measures to prevent accidental or premature destruction of these documents. Essential documents must be retained for at least 5 years after the completion of the final study report, but will be retained for a longer period if required by applicable regulatory requirements or by an agreement with the Sponsor. It is the responsibility of the Sponsor to inform the participating physician and/or site as to when these documents no longer need to be retained. Further details of record retention policies are provided in Annex 1.8.

Representatives of the Sponsor may visit the participating site at any time during or after completion of the study to conduct an audit of the study in compliance with regulatory guidelines and/or company policy. Similar procedures may also be conducted by a regulatory body.

Further details of on-site audit policies can be found in the 68284528MMY4009 study protocol.

8.9. Limitations of the Research Methods

A limitation of the research method is recognized within this study as the sample size of patients included in the study will be dependent on the number of patients enrolled in the registry, and who meet the selection criteria listed in this study (see Section 8.2.2).

This study is an observational secondary data analysis using data collected in the externally-owned independent CIBMTR and other registries. Therefore, the actual frequency of clinical follow-up will depend on practice patterns in the usual care setting; however, sites will be strongly encouraged to enter data in a timely fashion, ie, within 30 days of visit or patient status change. This could lead to incomplete data collection, which may not be under the control of the Sponsor. Additionally, limited recall of adverse events at the patient visits conducted within clinical practice may lead to incomplete information or under reporting of some adverse events or bias. Finally, data collected is limited to the information documented within the respective databases of the independently external registry. As a result, there may be missing data, including the potential for underreporting of spontaneous adverse reactions. To account for this in part, the central dataset will encompass other data sources, including analysis from tumor samples and spontaneously-reported adverse reactions to the Sponsor, as they become available.

Finally, because reporting of key safety events (including but not limited to hematological toxicity, organ toxicity and lab reports) on longer timeframes relies on spontaneous reporting channels, data missingness is a consideration be factored in for these events. To mitigate the risk of data missingness, site training at regular intervals will take place.

9. PROTECTION OF HUMAN SUBJECTS

Personal data collected from patients enrolled in any applicable registry will be limited to those data that are necessary to fulfill the objectives of the study, and must be collected and processed with adequate precautions to ensure confidentiality and compliance with applicable data privacy protection laws and regulations (see Annex 1.6).

Protection of Human Subjects in the Externally-Owned CIBMTR Registry and Other National Registries, as Required by Local Regulatory Authorities

This portion of the study will use data collected from patients already participating in the externally-owned registries; therefore no patients will participate directly in the study.

In accordance with the laws and regulations applicable to each country, the respective registry owner will be responsible for obtaining approval of their respective protocols and amendments, ICF, recruitment procedures and any other relevant documents in connection with the registry, from the relevant Independent Ethics Committee (IEC)/Institutional Review Board (IRB), prior to commencement of the registries.

Registry owners will be responsible for ensuring that an ICF is signed by or on behalf of each human subject prior to the first registry related procedure within their respective registries. The registries ICF should include provisions allowing for pharmaceutical companies to have access to their study data.

Protection of Human Subjects in the Janssen-Sponsored Registry (MMY4009)

Where appropriate, as required by local regulations, this study will be undertaken only after the Independent Ethics Committee (IEC)/Institutional Review Board (IRB) has given full approval of the final protocol, any applicable amendments, and the participation agreement/ICF, and the Sponsor has received a copy of this approval (see Annex 1.3).

Prior to data collection, all patients (and/or a legally acceptable representative where applicable) must sign an ICF allowing source data verification in accordance with local requirements and Sponsor policy (see Annex 1.4). Potential participants will be told that their consent to allow collection of information within the context of this non-interventional study is entirely voluntary and may be withdrawn at any time. Patients will be informed of the observational nature of the study, that the Sponsor only intends to collect information and follow the course of treatment in the clinical practice setting, however in case of a new malignancy a blood sample may be collected if local regulations allow. Only patients who are fully able to understand the nature of the study and provide their consent voluntarily will be enrolled.

10. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

Timely, accurate, and complete reporting and analysis of safety information from clinical studies are crucial for the protection of patients, physicians, and the Sponsor, and are mandated by regulatory agencies worldwide. All studies conducted by the Sponsor or its affiliates will be conducted in accordance with established procedures and regulatory requirements worldwide to ensure appropriate reporting of safety information. All safety data collected for this study will be recorded and summarized in the interim safety analysis and in the final study report.

10.1. Definitions and Classifications

10.1.1. Adverse Event Definitions

Adverse Event

An adverse event is any untoward medical occurrence in a patient administered a medicinal (investigational or non-investigational) product. An adverse event does not necessarily have a causal relationship with the treatment. An adverse event can be any unfavorable and unintended sign (including an abnormal finding or lack of expected pharmacological action), symptom, or disease temporally associated with the use of a medicinal (investigational or non-investigational) product, whether or not related to that medicinal (investigational or non-investigational) product.

(Definition based on International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use [ICH]).

This includes any occurrence that is new in onset or aggravated in severity from the baseline condition, or abnormal results of any diagnostic procedures that are conducted per clinical practice.

Adverse Drug Reaction

An adverse drug reaction (ADR) is defined as a response to a medicinal (investigational or non-investigational) product that is noxious and unintended. The phrase "response to a medicinal product" means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility. The phrase "a reasonable possibility" means that there are facts, evidence, or arguments to support a causal association with the medicinal product.

An ADR, in contrast to an adverse event, is characterized by the fact that a causal relationship between the medicinal product and the occurrence is suspected. All adverse events judged by either the reporting physician or the Sponsor as having a reasonable causal relationship to a medicinal product qualify as ADRs.

Serious Adverse Event

A serious adverse event, based on ICH and EU Guidelines on Pharmacovigilance for Medicinal Products for Human Use, is any untoward medical occurrence that at any dose:

- Results in death
- Is life threatening
  (the patient was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe)
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Is a suspected transmission of any infectious agent via a medicinal product
- Is medically important*

* Medical and scientific judgment should be exercised in deciding whether other situations should be considered serious, such as important medical events that might not be immediately life threatening or result in death or hospitalization but might jeopardize the patient or might require intervention to prevent one of the other outcomes listed above.

Unlisted (Unexpected) Adverse Event

An adverse event is considered unlisted if the nature or severity is not consistent with the applicable product reference safety information. The expectedness of an adverse event will be determined by whether or not it is listed in the applicable reference safety information.

NOTE: Unlistedness of an event is only relevant for the Sponsor's reporting obligations, but is not determining reporting requirements of the participating physician to the Sponsor or Marketing Authorization Holder.

Product Quality Complaint

A product quality complaint is any complaint that indicates a potential quality issue during manufacturing, packaging, release testing, stability monitoring, dose preparation, storage or distribution of the product or drug delivery system.

10.1.2. Attribution Definitions

Assessment of Causality

The causal relationship to treatment is not collected in the CIBMTR CRF. However, events spontaneously reported by registry participant sites to Janssen will be evaluated for causality by the Sponsor.

For solicited events reported to Janssen under the MMY4009 protocol, the causal relationship to treatment is determined by a physician at the participating site and should be assessed for all adverse events. For the MMY4009 protocol, the causal relationship can be one of the following:

Related

There is a reasonable causal relationship between administration of the medicinal product [or the product under study] and the adverse event.

Not Related

There is not a reasonable causal relationship between administration of the medicinal product [or the product under study] and the adverse event.

The term "reasonable causal relationship" means there is evidence to support a causal relationship.

10.1.3. Severity Criteria

The participating physician should use clinical judgment in assessing the severity of events.

10.2. Procedures

This study encompasses the following sources of safety data collection:

Safety Data Extracted From the Externally-Owned CIBMTR Registry and Other National Registries, as Required by Local Regulatory Authorities

During the conduct of the study, participating centers will collect and report selected adverse events (see Section 8.3.2, Safety Variables) including SPMs for each of their respective cilta-cel-treated patients, using the external registries' standard CRF specifications and in accordance with the registry procedures. Data extracts from the external registries databases will be periodically provided to the Sponsor as individual patient level data.

In some instances, due to the nature of these registries, the information on toxicity collected by the external registry holders may not include event characteristics, such as seriousness, causality (suspected or non-suspected), severity, start and end dates, action taken, and outcome. Specifically, the CIBMTR standard CRF does not collect a treating physician's/HCP's assessment of causality or seriousness. Therefore, with the exception of the selected events described further below, expedited reporting of individual case safety reports from participating centers to external registries or from external registries to Janssen will not occur.

SPMs from the externally-owned CIBMTR registry and other national registries should be reported to the Sponsor in periodic data transfer.

On receipt of patient level data on a periodic basis from CIBMTR registry and other national registries, all fatal events that are not reported as considered due to disease progression, and SPMs will be processed for expedited reporting by the Sponsor. For SPMs, this process will also facilitate initiation of the process to obtain tumor specimens in accordance with the prescribing information that is in effect in the country of origin of the patient who has developed the malignancy (see Section 8.3.2.1, Second Primary Malignancy Tumor Sampling).

To ensure that all safety information is received and evaluated on an ongoing manner, sites participating in the CIBMTR registry will be trained to report SPMs, adverse reactions and special situations to the Sponsor through standard spontaneous adverse event-reporting channels. Training on HCP responsibilities regarding reporting of adverse reactions, will be provided by the Sponsor during the site certification process and will be communicated to the external registry owners. For this study, HCP guidance on SPM reporting will be disseminated by CIBMTR and other registry owners with Sponsor's feedback and via the prescribing information that is in effect in the country of origin of the patient who has developed the malignancy.

Primary Data Collection Directly From a Janssen-Sponsored Registry (MMY4009)

During the conduct of the study, participating physicians will complete the Janssen specific registry CRF for each of their respective patients, according to the Janssen registry specifications, and will report all solicited serious and non-serious adverse events and special situations (as defined in the protocol) to Janssen. All safety data will be processed, managed, and reported according to local regulations and Janssen procedures.

Other Data Sources - Tumor Samples and Replication Competent Lentivirus Results

Results from tumor samples of patients from the registry obtained through a post-marketing transgene assay service and RCL results from these patients may also be included as other data sources for this study, if and as allowed by clinical practices and local regulations. As applicable, the Sponsor will submit summaries of medically important individual tumor analysis results, with Sponsor assessment, as follow-up information of individual case safety reports of SPMs previously reported.

10.2.1. Pregnancy

All reports of pregnancy in participants of childbearing potential or in partners of participants of childbearing potential following exposure to cilta-cel within the registries are to be documented. Data will be extracted for all reports of pregnancy occurring in temporal association with the administration of cilta-cel and pregnancy outcomes within the registry in the planned data extracts, for submission at the milestones listed in Section 5.

All reports of pregnancy from the externally-owned CIBMTR registry and other national registries will be reported to the Sponsor in periodic data transfer, which will be processed for expedited reporting by the Sponsor. To ensure that all safety information is received and evaluated on an ongoing manner, sites participating in the CIBMTR registry will be trained to report pregnancy, adverse reactions and special situations to the Sponsor through standard spontaneous adverse event-reporting channels.

11. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

The results of the study will be reported in a clinical study report generated by the Sponsor, which will contain data collected from the registry. The Sponsor will register and/or disclose the existence of and the results of clinical studies as required by law.

Patient identifiers will not be used in the publication of results. Any work created in connection with performance of the study and contained in the data that can benefit from copyright protection (except any publication by the participating physician) shall be the property of the Sponsor as author and owner of copyright in such work.

Further details of publication policies and practices are provided in Annex 1.10.

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ANNEX 1: STAND-ALONE DOCUMENTS AND ADDITIONAL INFORMATION

Annex 1.1: List of Stand-alone Documents

Title	Reference No	Date
Not applicable	-	-

Annex 1.2: Regulatory Documentation

This protocol and any amendment(s) must be submitted to the appropriate regulatory authorities in each respective country, where applicable. A study may not be initiated until any applicable local regulatory requirements are met.

Annex 1.3: Ethics Compliance

In accordance with the laws and regulations in each applicable country, the respective registry owner (including, but not limited to, Janssen for MMY4009 and CIBMTR) will be responsible for obtaining approval of any registry-specific protocols and amendments, informed consent forms, recruitment procedures, and any other relevant documents in connection with the respective registries, from the applicable IEC/IRB prior to commencement of enrolling patients into the registries.

Additional details on ethics compliance for MMY4009 can be found in the 68284568MMY4009 study protocol.

Annex 1.4: Patient Consent

The respective registry owner (including, but not limited to, Janssen for MMY4009 and CIBMTR) will be responsible for ensuring that the ICF is signed by or on behalf of each human subject before the registry related procedure. This ICF shall be the document approved by each of the respective registry's study sites' related IECs/IRBs and for allowing pharmaceutical companies to have access to their study data, prior to the subject's participation in the study. If requested, the registry owner will provide Janssen with a copy of the positive opinion letter from each IEC/IRB, the approved ICF and any relevant communications with each IEC, which includes but is not limited to information which may affect the conduct of the respective registry.

Additional details on patient consent for MMY4009 can be found in the 68284568MMY4009 study protocol.

Annex 1.5: Patient Identification and Enrollment

The study will be conducted using data collected from patients who will be enrolled in registry. All patient identification and enrollment will be the responsibility of the respective registry owner (including, but not limited to, Janssen for MMY4009 and CIBMTR), as applicable to that patient.

For MMY4009, the participating physician agrees to complete a patient identification and enrollment log to permit easy identification of each patient during and after the study. This document will be reviewed by the Sponsor and participating site contact for completeness. The patient identification and enrollment log will be treated as confidential and will be filed by the participating physician in the study file.

Additional details on patient identification and enrollment for MMY4009 can be found in the 68284568MMY4009 study protocol.

Annex 1.6: Patient Data Protection

The respective registry owner (including, but not limited to, Janssen for MMY4009 and CIBMTR) will be responsible for maintenance of all records and data for the study, in compliance with all applicable legal and regulatory requirements, as well as with generally accepted conventions such as the Declaration of Helsinki and ICH-GCP.

Collection, processing and disclosure of personal data, such as patient health and medical information is subject to compliance with applicable data protection and security laws and regulations. When collecting and processing personal data, the respective registry owner, agrees to take appropriate measures to safeguard those data, maintain confidentiality of patient health and medical information, to properly inform the concerned data subjects about the collection and processingof their personal data, to grant data subjects reasonable access to their personal data and to prevent access by unauthorized persons.

Patient Data Protection in Externally-Owned Registry CIBMTR

CIBMTR will protect the data and information received from centers and patients, and will be committed to the ethical conduct of research. CIBMTR will obey the United States Health Insurance Portability and Accountability Act (HIPAA) and the European Union's General Data Protection Regulation (GDPR). CIBMTR's data systems follow the Federal Information Systems Management Act of 2002 and the recommendations of the National Institute of Standards and Technology. Our Institutional Review Board (IRB) is fully accredited by the Association for the Accreditation of Human Research Protection Programs.

Patient Data Protection in a Janssen-Sponsored Registry (MMY4009)

The collection and processing of personal data from patients enrolled in this study will be limited to those data that are necessary to fulfill the objectives of the study, which must be collected and processed with adequate precautions to ensure confidentiality and compliance with applicable data privacy protection laws and regulations. Appropriate technical and organizational measures to protect the personal data against unauthorized disclosures or access, accidental or unlawful destruction, or accidental loss or alteration must be put in place. Sponsor personnel whose responsibilities require access to personal data agree to keep the identity of patients confidential.

The participation agreement/ICF obtained from the patient (or his/her legally acceptable representative) includes explicit consent for the processing of personal data and for the participating physician and/or site to allow direct access to his/her original medical records (source data/documents) for study-related monitoring, audit, IEC/IRB review, and regulatory inspection as appropriate. This consent also addresses the transfer of the data to other entities and other countries.

The patient has the right to request through the participating physician access to his/her personal data and the right to request rectification of any data that are not correct or complete. Reasonable steps will be taken to respond to such a request, taking into consideration the nature of the request, the conditions of the study, and the applicable laws and regulations.

Annex 1.7: Case Report Form Completion

The data source for this study will be the databases for the registry. The respective registry owner (including, but not limited to, Janssen for MMY4009 and CIBMTR) will be responsible for data handling and management within their respective registries.

For MMY4009, case report forms are provided for each patient in electronic format. Electronic Data Capture (eDC) will be used. The study data will be transcribed from the source documents onto an electronic CRF by personnel at each participating site, and transmitted in a secure manner to the Sponsor within the timeframe agreed upon between the Sponsor and the site. The electronic file will be considered to be the CRF. Further the participating physician must verify all data entries in the CRFs are accurate and correct.

Additional details on case report form completion for MMY4009 are discussed in the 68284568MMY4009 study protocol.

Annex 1.8: Record Retention

Record retention will be the responsibility of the respective registry owners (including, but not limited to, Janssen for MMY4009 and CIBMTR).

If at any point in time a relevant patient withdraws (part of) his or her consent and/or requests for (partial) deletion of his or her personal data, the Sponsor agrees, except when impossible and where such data is stored for safety reporting and signal detection, to delete the data from its files after such request was made by the registry owner. In such case, the Sponsor shall no longer use this part of the data in the context of the PASS.

For MMY4009, if the responsible participating physician retires, relocates, or for other reasons withdraws from the responsibility of keeping the study records, custody must be transferred to a person who will accept the responsibility. The Sponsor must be notified in writing of the name and address of the new custodian. Under no circumstance shall the participating physician relocate or dispose of any study documents before having obtained written approval from the Sponsor.

Additional details on record retention for MMY4009 are discussed in the 68284568MMY4009 study protocol.

Annex 1.9: Study Completion/Termination

The final data from the registries will be sent to the Sponsor (or designee) after completion of the final data collection time point in either of the registries.

Additional details on study completion/termination for MMY4009 are discussed in the 68284568MMY4009 study protocol.

Annex 1.10: Use of Information and Publication

All data (including without limitation, case report forms, written, printed, graphic, video and audio material, and information contained in any computer database or computer readable form) created or developed during the course of the registry will be the property of respective registry owners (including, but not limited to, Janssen for MMY4009 and CIBMTR), and which they may utilize in any way they deem fit, subject to and in accordance with applicable privacy laws and the terms of respective contractual agreements on this PASS.

All information concerning cilta-cel or Janssen's or its affiliates' operations, such as patent applications, formulas, manufacturing processes, basic scientific data, prior clinical data and formulation information supplied by Janssen or its affiliates to the registry owners and not previously published are considered confidential and shall remain the sole property of the Sponsor. The registry owners agree to maintain this information in confidence, to use this information only to accomplish this study, and not to use it for other purposes without the Sponsor's prior written consent.

Additional details on use of information and publication for MMY4009 are discussed in the 68284568MMY4009 study protocol.

ANNEX 2: ENCEPP CHECKLIST FOR STUDY PROTOCOLS

Section 1: Milestones	**Yes**	**No**	**N/A**	**Section Number**
1.1 Does the protocol specify timelines for				
1.1.1 Start of data collection[a]	☒	☐	☐	5
1.1.2 End of data collection[b]	☒	☐	☐	5
1.1.3 Progress report(s)	☐	☒	☐	
1.1.4 Interim report(s)	☒	☐	☐	5
1.1.5 Registration in the EU PAS Register®	☒	☐	☐	5
1.1.6 Final report of study results.	☒	☐	☐	5

Comments:

Section 2: Research question	**Yes**	**No**	**N/A**	**Section Number**
2.1 Does the formulation of the research question and objectives clearly explain:	☒	☐	☐	7
2.1.1 Why the study is conducted? (e.g. to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue)	☒	☐	☐	6.3
2.1.2 The objective(s) of the study?	☒	☐	☐	7
2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	8.2
2.1.4 Which hypothesis(-es) is (are) to be tested?	☐	☐	☒	
2.1.5 If applicable, that there is no *a priori* hypothesis?	☒	☐	☐	8.1.1

Comments:

No formal statistical hypothesis is defined in the study, and no statistical testing is planned for this study.

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[a] Date from which information on the first study is first recorded in the study dataset or, in the case of secondary use of data, the date from which data extraction starts.

[b] Date from which the analytical dataset is completely available.

Section 3: Study design	**Yes**	**No**	**N/A**	**Section Number**
3.1 Is the study design described? (e.g. cohort, case-control, cross-sectional, other design)	☒	☐	☐	8.1.1
3.2 Does the protocol specify whether the study is based on primary, secondary or combined data collection?	☒	☐	☐	8.9
3.3 Does the protocol specify measures of occurrence? (e.g., rate, risk, prevalence)	☒	☐	☐	8.5
3.4 Does the protocol specify measure(s) of association? (e.g. risk, odds ratio, excess risk, rate ratio, hazard ratio, risk/rate difference, number needed to harm (NNH))	☒	☐	☐	8.5
3.5 Does the protocol describe the approach for the collection and reporting of adverse events/adverse reactions? (e.g. adverse events that will not be collected in case of primary data collection)	☒	☐	☐	10

Comments:

Section 4: Source and study populations	**Yes**	**No**	**N/A**	**Section Number**
4.1 Is the source population described?	☒	☐	☐	8.2
4.2 Is the planned study population defined in terms of:				
4.2.1 Study time period	☒	☐	☐	8.2.1
4.2.2 Age and sex	☐	☐	☒	
4.2.3 Country of origin	☒	☐	☐	8.1
4.2.4 Disease/indication	☒	☐	☐	8.2
4.2.5 Duration of follow-up	☒	☐	☐	8.2
4.3 Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☒	☐	☐	8.2

Comments:

Patients will be enrolled based on received at least 1 dose of cilta-cel commercial product per the health authority approved cilta-cel product information in the respective country/region, and who have signed a participation agreement/informed consent form allowing participation within the respective registry, and for pharmaceutical companies to have access to their study data. No selection will be performed based on age or gender.

<u>Section 5: Exposure definition and measurement</u>	**Yes**	**No**	**N/A**	**Section Number**
5.1 Does the protocol describe how the study exposure is defined and measured? (e.g. operational details for defining and categorising exposure, measurement of dose and duration of drug exposure)	☐	☐	☒	
5.2 Does the protocol address the validity of the exposure measurement? (e.g. precision, accuracy, use of validation sub-study)	☐	☐	☒	
5.3 Is exposure categorised according to time windows?	☐	☐	☒	
5.4 Is intensity of exposure addressed? (e.g. dose, duration)	☐	☐	☒	
5.5 Is exposure categorised based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☐	☐	☒	
5.6 Is (are) (an) appropriate comparator(s) identified?	☐	☐	☒	

Comments:

Exposure definition and measurement are not characterized in the protocol due to cilta cel being administered as single infusion within at a target dose.

A comparator is not identified due to the single-arm nature of the study and lack of available prospective comparator population; however, a potential comparison with historical control will be attempted.

<u>Section 6: Outcome definition and measurement</u>	**Yes**	**No**	**N/A**	**Section Number**
6.1 Does the protocol specify the primary and secondary (if applicable) outcome(s) to be investigated?	☒	☐	☐	7
6.2 Does the protocol describe how the outcomes are defined and measured?	☒	☐	☐	8.7.1
6.3 Does the protocol address the validity of outcome measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, use of validation sub-study)	☐	☐	☒	
6.4 Does the protocol describe specific outcomes relevant for Health Technology Assessment? (e.g. HRQoL, QALYs, DALYS, health care services utilisation, burden of disease or treatment, compliance, disease management)	☐	☒	☐	

Comments:

The primary objective of the study is to collect safety outcomes for patients treated with cilta cel.

The post approval safety study is observational and not primarily intended to inform health technology assessments.

Section 7: Bias	**Yes**	**No**	**N/A**	**Section Number**
7.1 Does the protocol address ways to measure confounding? (e.g. confounding by indication)	☐	☐	☒	
7.2 Does the protocol address selection bias? (e.g. healthy user/adherer bias)	☒	☐	☐	8.2.2
7.3 Does the protocol address information bias? (e.g. misclassification of exposure and outcomes, time-related bias)	☐	☐	☒	

Comments:

Only patients treated with cilta cel according to the licensed indication in the respective country are eligible for the study.

Section 8: Effect measure modification	**Yes**	**No**	**N/A**	**Section Number**
8.1 Does the protocol address effect modifiers? (e.g. collection of data on known effect modifiers, sub-group analyses, anticipated direction of effect)	☐	☐	☒	

Comments:

No subgroup of patients is expected to be subject to safety effect modifier.

Section 9: Data sources	**Yes**	**No**	**N/A**	**Section Number**
9.1 Does the protocol describe the data source(s) used in the study for the ascertainment of:				
9.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview)	☒	☐	☐	8.4
9.1.2 Outcomes? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics)	☒	☐	☐	8.4
9.1.3 Covariates and other characteristics?	☒	☐	☐	8.4
9.2 Does the protocol describe the information available from the data source(s) on:				
9.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☒	☐	☐	8.4
9.2.2 Outcomes? (e.g. date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	8.4

Section 9: Data sources	**Yes**	**No**	**N/A**	**Section Number**
9.2.3 Covariates and other characteristics? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, lifestyle)	☒	☐	☐	8.4
9.3 Is a coding system described for:				
9.3.1 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System)	☐	☐	☒	
9.3.2 Outcomes? (e.g. International Classification of Diseases (ICD), Medical Dictionary for Regulatory Activities (MedDRA))	☒	☐	☐	8.7.1
9.3.3 Covariates and other characteristics?	☐	☒	☐	
9.4 Is a linkage method between data sources described? (e.g. based on a unique identifier or other)	☐	☐	☒	

Comments:

The data source for this study will be the respective databases for registry.

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Section Number**
10.1 Are the statistical methods and the reason for their choice described?	☒	☐	☐	8.7
10.2 Is study size and/or statistical precision estimated?	☒	☐	☐	8.5
10.3 Are descriptive analyses included?	☒	☐	☐	8.7
10.4 Are stratified analyses included?	☐	☐	☒	
10.5 Does the plan describe methods for analytic control of confounding?	☐	☒	☐	
10.6 Does the plan describe methods for analytic control of outcome misclassification?	☐	☒	☐	
10.7 Does the plan describe methods for handling missing data?	☐	☒	☐	
10.8 Are relevant sensitivity analyses described?	☐	☒	☐	

Comments:

Stratification not applicable to the main objective of the study.

Section 11: Data management and quality control	**Yes**	**No**	**N/A**	**Section Number**
11.1 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	☒	☐	☐	6.2
11.2 Are methods of quality assurance described?	☒	☐	☐	6.2
11.3 Is there a system in place for independent review of study results?	☐	☒	☐	

Comments:

Independent review of study results not deemed necessary due to the safety evaluation nature of the data collection

Section 12: Limitations	**Yes**	**No**	**N/A**	**Section Number**
12.1 Does the protocol discuss the impact on the study results of:				
12.1.1 Selection bias?	☒	☐	☐	8.9
12.1.2 Information bias?	☒	☐	☐	8.9
12.1.3 Residual/unmeasured confounding? (e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods).	☐	☒	☐	
12.2 Does the protocol discuss study feasibility? (e.g. study size, anticipated exposure uptake, duration of follow-up in a cohort study, patient recruitment, precision of the estimates)	☒	☐	☐	8.9

Comments:

Section 13: Ethical/data protection issues	**Yes**	**No**	**N/A**	**Section Number**
13.1 Have requirements of Ethics Committee/ Institutional Review Board been described?	☒	☐	☐	9
13.2 Has any outcome of an ethical review procedure been addressed?	☒	☐	☐	Annex 1.3
13.3 Have data protection requirements been described?	☒	☐	☐	Annex 1.6

Comments:

Section 14: Amendments and deviations	**Yes**	**No**	**N/A**	**Section Number**
14.1 Does the protocol include a section to document amendments and deviations?	☒	☐	☐	Page 6

Comments:

Section 15: Plans for communication of study results	**Yes**	**No**	**N/A**	**Section Number**
15.1 Are plans described for communicating study results (e.g. to regulatory authorities)?	☒	☐	☐	11
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	11

Comments:

Publications plans are being discussed and will be implemented based on data availability

ANNEX 3: PROTOCOL AMENDMENT HISTORY

The Protocol Amendment Summary of Changes Table for the current amendment is located directly before the Abstract.

Amendment 1 (17 February 2023)

The overall reason for the amendment: To address the Food and Drug Administration (FDA) requests to clarify the nature of subsequent malignancies that will be tested for lentiviral integration analysis and replication competent lentivirus, and clarify reason for why causality and seriousness assessment of adverse events will not be included in periodic safety reports; as well as to address EMA requests included in the EMA endorsement letter received on 29 September 2022..

Applicable Section(s)	Description of Change(s).
Rationale: To clarify that testing of tumor samples will only occur in patients who develop subsequent malignancies in accordance with the prescribing information that is in effect in the country of origin of the patient who has developed the malignancy.	
4. Abstract; Data Collection Schedule Within the Registries; 7. Research Question and Objectives; 8.3.2. Evaluation of Safety; 8.3.2.1. Subsequent Malignancy Tumor Sampling; 10.2. Procedures	Included that tumor samples will be tested in patients who develop subsequent malignancies based on the respective product information relevant to the country participating in the registry.
Rationale: To clarify procedures related to collection of safety data.	
4. Abstract; 8.1.1. Overview of Study Design; 8.3.2. Evaluation of Safety; 10.2. Procedures	Clarified procedures related to collection of safety data extracted from the externally-owned Center for International Blood and Marrow Transplant Research (CIBMTR) Registry and other national registries, as required by local regulatory authorities; a Janssen-sponsored registry (MMY4009) and other data sources – tumor samples and replication competent lentivirus results.
10.1.2. Attribution Definitions	Defined causality assessments performed during the study on event relationship to treatment.
10.2.1. Pregnancy	Included procedures for real-time notification of pregnancy data.
4. Abstract; 8.3.2. Evaluation of Safety	Specified that safety outcomes will be summarized for data collected from the registry for patients treated with cilta-cel, including those who receive out-of-specification product through the managed access program.
8.7.1 Main Summary Measures	Specified an exploratory analysis may be performed for the detection and characterization of known and potentially unknown safety signals. Specified how association between adverse events (AEs) collected in the study and specific dose will be captured.
Throughout the protocol	Specified that adverse reactions will be collected within this study.
Rationale: To clarify data protection for CIBMTR, other national registries and MMY4009	

Applicable Section(s)	Description of Change(s).
9 Protection of Human Subjects; Annex 1.6 Patient Data Protection	Updated to more accurately describe data protection for CIBMTR and other national registries, as well as the Janssen-sponsored registry MMY4009.
Rationale: To clarify data sources for CIBMTR, other national registries and MMY4009.	
4. Abstract; 8.4 Data Sources	Updated to more accurately describe data sources for CIBMTR and other national registries, as well as the Janssen-sponsored registry MMY4009.
Rationale: To clarify collection of cilta-cel dose	
8.7.1 Main Summary Measures	Specified that when possible, administered dose of cilta-cel will be collected.
Rationale: To clarify data merging/pooling from different sources	
4. Abstract; 8.7 Data Analysis	Described data merging/pooling from different sources for all patients who meet the selection criteria in all relevant data sources.
Rationale: To clarify mechanisms of quality control for CIBMTR and MMY4009.	
8.8 Quality Control	Specified mechanisms of quality control for the CIBMTR and MMY4009 registries.
Rationale: To clarify registry owners included in this study.	
Annex 1 Stand-Alone Documents and Additional Information	Specified registry owners include, but is not limited to, Janssen for MMY4009 and CIBMTR.
Rationale: To clarify further details for MMY4009.	
Annex 1 Stand-Alone Documents and Additional Information	Included further information regarding MMY4009's patient identification and enrollment, case form completion and record retention. Specified that further details for MMY4009 can be found in the 68284568MMY4009 study protocol.
Rationale: Minor errors were noted and administrative updates required.	
8.3.2.1. Subsequent Malignancy Tumor Sampling	Specified bone marrow samples will be collected, not bone marrow aspirate.
8.3.2.1, Subsequent Malignancy Tumor Sampling	Specified that analysis may be performed in a central laboratory.
5. Milestones	Updated planned milestones dates for the study.
Throughout the protocol	Minor administrative, grammatical, formatting, or spelling changes were made.

PARTICIPATING PHYSICIAN AGREEMENT

I have read this protocol and agree that it contains all necessary details for carrying out this study. I will conduct the study as outlined herein and will complete the study within the time designated.

I will provide copies of the protocol and all pertinent information to all individuals responsible to me who assist in the conduct of this study. I will discuss this material with them to ensure that they are fully informed regarding the conduct of the study and the obligations of confidentiality.

Sponsor's Responsible Medical Officer (Main Author):

Name (typed or printed): PPD, MD

Institution: Medical Director US Medical Affairs CAR-T, Janssen Global Services LLC

Signature: eSignature has been applied on the next page. Date: ______________
(Day Month Year)

Note: If the address or telephone number of the participating physician changes during the course of the study, written notification will be provided to the Sponsor; a protocol amendment will not be required.

Signature

User	Date	Reason
PPD	05-Jun-2025 18:06:22 (GMT)	Document Approval
PPD	06-Jun-2025 07:04:52 (GMT)	Document Approval