Janssen Research & Development*

Non-interventional Post-authorization Safety Study - Protocol

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

Protocol 68284528MMY4009

CARVYKTI (ciltacabtagene autoleucel)

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Protocol version:	2.0	**Version date:**	22 April 2022
Prepared by:	Janssen-Cilag Limited		
EDMS number:	EDMS-RIM-588202, 4.0		

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

1. PASS INFORMATION

Title:	**A Post-authorization Safety Study to Evaluate the Safety of Multiple Myeloma Patients Treated with Ciltacabtagene Autoleucel**
Protocol version:	2.0
Date of last version of the protocol:	14 February 2022
EU PAS Register No:	Study not registered
Active substance (INN common name):	Autologous Human T Cells Genetically Modified Ex-Vivo with a Lentiviral Vector Encoding a Chimeric Antigen Receptor for B-Cell Maturation Antigen
Pharmaco-therapeutic group (ATC Code):	Not yet assigned
Medicinal product(s):	EMEA/H/SA/4228/1/FU/2/2020/PA/ADT/PR/II
Product reference:	H0005095
Procedure number:	N/A (product not yet authorized)
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 with multiple myeloma receiving ciltacabtagene autoleucel (cilta-cel) in the postauthorization 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, Belgium, Czech Republic, Denmark, Finland, France, Germany, Greece, Hungary, Ireland, Israel, Italy, Netherlands, Norway, Poland, Portugal, Brazil, Romania, Russia, Saudi Arabia, Spain, Sweden, Switzerland, and the United Kingdom. This list is not considered complete and may be revised as appropriate at a later date.
Author	PPD

2. MARKETING AUTHORIZATION HOLDER(S)

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Date:	

3. RESPONSIBLE PARTIES

Principal Participating Physician:	PPD
Contact person for this protocol:	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.

There are no amendments for this protocol.

1. ABSTRACT

Protocol Title: A Post-authorization Safety Study to Evaluate the Safety of Multiple Myeloma Patients Treated with Ciltacabtagene Autoleucel (2.0, 22 April 2022)

Sponsor's Responsible Medical Officer: PPD

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 50%. 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 cell 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 subsequent malignancies that may not be readily observed in clinical development trials. This study is a prospective, non-interventional 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 fulfil 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 postauthorization setting per the health authority approved product information in the respective country/region.

The primary objective of the study is to evaluate the short-term and long-term safety including the risk of subsequent malignancy, of cilta-cel in adult patients with multiple myeloma. Long-term data on replication competent lentivirus (RCL) will also be collected in patients who develop subsequent malignancies, where allowed per local regulations in the context of a non-interventional study.

The secondary objectives of the study are to:

- evaluate the effectiveness of cilta-cel in adult patients with multiple myeloma.
- explore the potential association between cytopenia events, patient baseline and demographics characteristics.

Study Design

This is a non-interventional PASS (68284528MMY4009; referred to throughout as MMY4009) to describe the safety profile of cilta-cel in the treatment of adult patients with multiple myeloma, primarily in the European Union (EU) region, with the option to expand to other regions/countries. This study will contribute to a common dataset (observational PASS 68284528MMY4004 evaluating the short- and long-term safety profile of cilta-cel under real world conditions) to inform the safety profile of cilta-cel across primary data sources and collect additional data requested by regulatory authorities.

Patients will be enrolled in the study at the time of apheresis, and will be followed for a period of up to 15 years from the day of cilta-cel infusion. All patients included in the study will provide written consent for participation and data collection. All aspects of treatment decisions and clinical management of patients will be at the discretion of the treating physician and the patient.

The data collection period will start from the day of apheresis, and patients will be followed for up to 15 years from the day of cilta-cel infusion, withdrawal of consent or until the time of death, if applicable. Patients who are apheresed but do not receive cilta-cel will only be followed-up until the time of decision not to infuse cilta-cel. Data will be collected within the registry at the timepoints specified in the DATA COLLECTION SCHEDULE. The data for this study will then be periodically extracted from the registry for analysis. Confidentiality of patient records will be maintained at all times.

Data collection will include baseline demographics, diagnosis and medical history data including previous disease characteristics, treatment, comorbid conditions and information on lymphodepleting therapies. Post-infusion data collected will include Eastern Cooperative Oncology Group (ECOG) 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.

Patients will be permitted to enroll no later than at Day 0 (cilta-cel infusion), in the event that they were not enrolled at the time of apheresis. A patient's baseline data will be collected, where available, upon enrollment into the study. The end of the study will be after all consented patients have completed 15 years of follow-up from the day of cilta-cel infusion, or discontinued from the study or died (whichever occurs earlier).

Setting and Patient Population

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 adverse events spontaneously reported to the sponsor, where available.

Each potential participant must satisfy the following criteria to be eligible for data collection in this study: have undergone apheresis with the purpose of receiving 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.

Variables

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

- Demographic data
- Diagnosis and medical history

  Including history or serology of hepatitis B virus (HBV), and history of human T-lymphotropic virus (HTLV)-related T-cell leukemia/lymphoma and demyelinating disease (in Brazilian patients only)
- ECOG 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

  Apheresis date and any adverse event related to this procedure

  Lymphodepleting chemotherapy

  Bridging therapy

  Dates and reasons for discontinuation for patients who are apheresed but do not receive cilta-cel

  Dose/number of cells infused

  Toxicities/complications including those occurring between apheresis and Day 0 of CAR-T administration (please refer the Evaluation of Safety section below)

  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
- Date and cause of death

Evaluation of Safety

All adverse events (with the exception noted below) and special situations regardless of causality to cilta-cel beginning from product administration on Day 0 until Day 100 following CAR-T infusion will be recorded in the electronic case report form (eCRF). Thereafter, only non-serious AEs related to cilta-cel except the safety variables defined below, and all SAEs regardless of causality up to End of Study will be recorded in the eCRF.

In addition, events of HBV reactivations and HTLV-related T-cell leukemia/lymphoma and demyelinating disease (in Brazilian patients only) regardless of seriousness or causality from product administration on Day 0 until one year following CAR-T infusion will be recorded in the eCRF.

Safety parameters for this study include the rate of the following selected adverse events (including latency, frequency, type and severity when available) regardless of causality and seriousness:

- Subsequent malignancies, defined as a new occurrence of malignancy after cilta-cel administration (including subsequent malignancies and recurrent malignancies, other than multiple myeloma).

  In the event of subsequent malignancy, a tumor sample should be collected, if clinically feasible, and lentiviral integration site analysis may be performed for possible insertional mutagenesis.

  - Presence of RCL will be tested in patients who develop subsequent malignancies (where allowed per local regulations in the context of a non-interventional study).

- Neurotoxicity, including:

  Immune effector cell-associated neurotoxicity syndrome (ICANS)

  Other CAR-T cell neurotoxicity, including movement and neurocognitive toxicity (i.e., Parkinsonism)

- Hematologic disorders, per collected laboratory values, and their relation to patients' demographics and baseline characteristics
- Hypogammaglobulinemia
- Clinically significant infections
- Organ toxicities
- Cytokine release syndrome (CRS), including hemophagocytic lymphohistiocytosis/macrophage activation syndrome (HLH/MAS)
- Tumor lysis syndrome
- 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

    HBV reactivation

    HTLV-related T-cell leukemia/lymphoma and demyelinating disease (in Brazilian patients only)

    Hematologic disorders, including prolonged or recurrent cytopenias (ie, thrombocytopenia, leukopenia, lymphocytopenia and anemia)

In addition, all pregnancies and outcomes following exposure to cilta-cel will be reported.

Evaluation of Effectiveness/Clinical Response

Response assessments will be evaluated by the treating physician in the study 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). In addition, the effect of cilta-cel on myeloma-related comorbidities (amyloidosis and POEMS syndrome, if present) will be collected and analyzed.

- Overall Survival, reported in the study, will be collected and will be defined as the interval between the date of first cilta-cel infusion and date of death due to any cause.
- Progression-free survival will be defined as the interval between the date of cilta-cel infusion and date of progressive disease according to the judgment of the treating physician, or death, whichever occurs earlier.
- Duration of response will be calculated among responders (with a partial response [PR] or better response) from the date of initial documentation of a response (PR or better) to the date of first documented evidence of progressive disease. Response to cilta-cel will be captured per IMWG criteria for response assessment in patients with multiple myeloma, ie, as PR 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

The primary data source for this study will be the medical records 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 electronic case report form (eCRF). 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.

Study Size

The sample size estimation was calculated for the global PASS (MMY4004), with potential comparison to historic control, for the outcome of subsequent malignancy (secondary primary malignancy). For the current study (MMY4009) it is estimated that around 300 patients will contribute to the overall enrollment target for the global PASS. Once enrollment is complete within the global PASS, which aims to enroll a total of 1500 patients across the target regions, enrollment will be considered complete for this study. Enrollment is competitive between participating prospective registries/studies.

Assuming a conservative background incidence rate for subsequent 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, 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 secondary malignancy 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 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. Additional details will be provided in the SAP. In addition, the data from this study will be pooled and analyzed together with other independent prospective registries and other data sources as part of the global PASS study (MMY4004).

The verbatim terms used to identify adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). All documented 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. Additionally, cumulative incidence estimates or rates of adverse events reported in person-years may be used. Further detail will be included in the SAP.

The analysis set will include all patients who meet the selection criteria.

Patient demographics, medical history and disease history (including history of prior and current malignancies), current disease status and any previous therapies for multiple myeloma will be collected at baseline.

All adverse events regardless of causality to cilta-cel beginning from product administration on Day 0 until Day 100 following CAR-T infusion will be collected and included in the analysis. Thereafter, only non-serious AEs related to cilta-cel (except the safety variables defined above) and all SAEs regardless of causality up to End of Study will be collected and analyzed. Other data sources for this study may also include analyses from tumor samples of patients developing second primary malignancies.

Rates of adverse events collected within the study will be estimated. Where appropriate, additional summaries, listings, datasets, or narratives may be provided, as appropriate.

Parameters with predefined National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) toxicity grades will be summarized. Changes from baseline to the worst adverse event grade experienced by a patient during the study will be provided as shift tables.

The survival analysis will be performed for time-to-event variables (i.e., PFS, OS).

The study will have analysis performed annually and results will be summarized in interim reports. The scope of the analysis will be documented in the SAP.

Milestones

Milestone	**Planned date**
Final protocol submission	30 April 2022
Start of data collection	Quarter 2 2023
End of data collection	Up to 15 years after last patient has been enrolled
Study completion date	30 June 2041
Final report submission	30 June 2042

Note: Data will be regularly extracted from start of data collection and analysis will be performed annually with results summarized in interim reports.

DATA COLLECTION SCHEDULE

	Apheresis (Enrollment)	Bridging Period	Cilta-cel Infusion Day 0[a]	Day 100	Month 6	Month 12	Every 12 Months	End of Study[b]
Patient information								
Patient consent[c]	X							
Selection criteria	X							
Demographics	X							
Medical history	X							
ECOG performance status			X	X	X	X	X	X
Disease characteristics								
Disease history	X							
Disease burden of cilta-cel			X					
Current disease status			X					
Comorbid conditions	X		X	X	X	X	X	X
Multiple myeloma therapy								
Previous multiple myeloma therapy			X					
Current multiple myeloma therapy[d]			X	X	X	X	X	X
Bridging therapy		X						
Ongoing patient review								
Physical and neurological examination[e]	X		X	X	X	X	X	X
Adverse events[f]	X	X	X	X	X	X	X	X
Subsequent malignancy			Continuous from the time of enrollment, if clinically feasible, appropriate samples depending on the tumor type (eg, whole blood, bone marrow aspirate, tissue biopsy in formalin-fixed, paraffin-embedded blocs/slides) will be collected. If at least 1% of cells in new malignancy samples are positive for vector sequences, the sample will be analyzed for lentiviral integration site					
Replication competent lentivirus[g]			In patients with subsequent malignancies, in case of a positive result, subsequent RCL testing will be conducted at all protocol follow-up visits until the test is negative or end of study, whichever comes first.					
Concomitant therapy[h]			X	X	X	X	X	X

	Apheresis (Enrollment)	Bridging Period	Cilta-cel Infusion Day 0[a]	Day 100	Month 6	Month 12	Every 12 Months	End of Study[b]
Clinical response assessments								
Survival status[i]				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
Disease assessment			Collect physician's determination of response on an ongoing basis, per local clinical practice					

[a] The study will collect Day 0 data before cellular therapy is administered.

[b] Date and reason for discontinuation will be captured in the eCRF at the time of discontinuation.

[c] Before the start of data collection in the study, all patients must sign a participation agreement/informed consent form (ICF) allowing consent for participation in the respective registries.

[d] Including cilta-cel therapy.

[e] Only abnormal findings (i.e., adverse events per Section 6.3.1.1 and comorbidities) will be recorded in the eCRFs.

[f] All adverse events regardless of causality to cilta-cel beginning from product administration on Day 0 until Day 100 following CAR-T infusion will be recorded in the CRF. Thereafter, only non-serious AEs related to cilta-cel except safety variables defined in Section 4.3.2, and all SAEs regardless of causality up to End of Study will be recorded in the CRF. For the collection of Adverse Events occurring prior to cilta-cel infusion and related to administration procedures (from Apheresis to Day 0), please refer to Section 6.3.1.1.

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

[h] Either subsequent antimyeloma therapy or concomitant therapy for treatment of selected adverse events.

[i] Including date and cause of death.

1. MILESTONES

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

Milestone:	**Planned Date:**
Final protocol submission	30 April 2022
Start of data collection	Quarter 2 2023
End of data collection	Up to 15 years after last patient has been enrolled
Registration in the EU PAS register	TBC
Interim Report 1	Quarter 1 2023
Final report of study results	30 June 2042

Note: Data will be regularly extracted from start of data collection and analysis will be performed annually with results summarized in interim reports.

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviations

ADL	Activities of daily living
ADR	Adverse Drug Reaction
AE	Adverse Event
AESI	Adverse Events of Special Interests
ASTCT	American Society for Transplantation and Cellular Therapy
BCMA	B-cell maturation antigen
CAR	Chimeric antigen receptor
CR	Complete response
CRS	Cytokine release syndrome
DOR	Duration of response
DRB	Designated Regulatory Body
eCRF	Electronic Case Report Form
eDC	electronic data capture
EU	European Union
GVHD	Graft-versus-host disease
HBV	Hepatitis B virus
HLH	hemophagocytic lymphohistiocytosis
HTLV	Human T-lymphotropic virus
ICANS	Immune effector cell-associated neurotoxicity syndrome
ICE	Immune Effector Cell-Associated Encephalopathy
ICF	Informed consent form
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IMWG	International Myeloma Working Group
IRB	Institutional Review Board
LV	Lentiviral vector
MAS	Macrophage activation syndrome
MedDRA	Medical Dictionary for Regulatory Activities
MRU	medical resource utilization
NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
ORR	Overall response rate
OS	Overall survival
PASS	Postauthorization Safety Study
PFS	Progression-free survival
PQC	Product Quality Complaint
PR	Partial Response
RCL	Replication competent lentivirus
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SmPC	Summary of Product Characterisitcs
VGPR	Very good partial response
WHO	World Health Organization

Definition of Term(s)

Registry	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” indicates the collection of data for research purposes only. 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.
Postauthorization 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.

2. BACKGROUND AND RATIONALE

2.1. Background

Multiple myeloma is an incurable, malignant plasma cell disorder that accounts for approximately 10% of hematological malignancies (Rodriguez-Abreu 2007; Rajkumar 2011). 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 (Chung 2017). Common clinical presentations of multiple myeloma are hypercalcemia, renal insufficiency, anemia, bony lesions, bacterial infections, hyperviscosity, and secondary amyloidosis (Orlowski 2013).

Worldwide, there were an estimated 80,000 deaths due to multiple myeloma and in Europe, approximately 24,300 patients with this disease die annually (Ferlay 2013). The estimated 5-year survival rate for patients with multiple myeloma is approximately 50% (Multiple Myeloma Statistics, Cancer.Net, August 2021). 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 (DOR) 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 (Usmani 2015).

2.2. Current Treatments

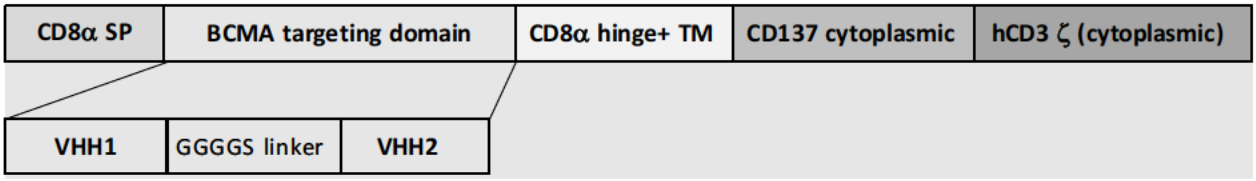
Until 2000, the standard therapies for multiple myeloma were melphalan- or doxorubicin-based regimens with corticosteroids (Chung 2017). Since then, the introduction of proteasome inhibitors (eg, bortezomib, carfilzomib, and ixazomib), histone deacetylase inhibitors (eg, panobinostat), immunomodulatory 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 (OS) 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 (Kumar 2017; Gandhi 2019). 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% (San Miguel 2013; Lonial 2016; Hajek 2017).

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 (Raje 2019).

Ciltacabtagene autoleucel (also known as cilta-cel, 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 cilta-cel 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).

2.3. 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 cell 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 subsequent malignancies 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 non-interventional postauthorization safety study (PASS) in patients exposed to cilta-cel in a post-authorization setting per the health authority approved product information in the respective country/region, to fulfil the requirement set out by health authorities.. The study will constitute primary data collection. Patients will be consecutively enrolled in this non-interventional study to serve as a registry to analyze the potential short- and long-term (up to 15 years follow-up) safety profile observed in patients receiving cilta-cel.

3. 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 postauthorization setting per the health authority approved product information in the respective country/region.

Objectives

The primary objective of the study is to evaluate the short-term and long-term safety including the risk of subsequent malignancy, of cilta-cel in adult patients with multiple myeloma. Long-term data on replication competent lentivirus (RCL) will also be collected in patients who develop subsequent malignancies, where allowed per local regulations in the context of a non-interventional study.

The secondary objectives of the study are to:

- evaluate the effectiveness of cilta-cel in adult patients with multiple myeloma.
- explore the potential association between cytopenia events, patient baseline and demographics characteristics.

Measures 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) regardless of causality and seriousness:

- Subsequent malignancies, including:

  RCL (in patients with subsequent malignancies)
- Neurotoxicity, including:

  immune effector cell-associated neurotoxicity syndrome (ICANS)

  other CAR-T cell neurotoxicity, including movement and neurocognitive toxicity
- Hematologic disorders, per collected laboratory values, and their relation to patients' demographics and baseline characteristics
- Hypogammaglobulinemia

- Clinically significant infections
- Organ toxicities
- Cytokine release syndrome (CRS), including hemophagocytic lymphohistiocytosis/macrophage activation syndrome (HLH/MAS)
- Tumor lysis syndrome
- 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

  Hepatitis B virus (HBV) reactivation

  Human T-lymphotropic virus (HTLV)-related T-cell leukemia/lymphoma and demyelinating disease (in Brazilian patients only)

  Hematologic disorders, including prolonged or recurrent cytopenias
- Pregnancy and pregnancy outcomes

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

- Overall survival (OS)
- Progression-free survival (PFS)
- Duration of response (DOR)
- Overall response rate (ORR)
- Cilta-cel's effect on myeloma-related comorbidities (amyloidosis and POEMS syndrome, if present)

Please refer to Section 4.3.2 for a summary of the safety outcomes, and Section 4.3.3 for the parameters of clinical response for the study. Refer to Section 4.7 for statistical aspects of measures of interest.

4. RESEARCH METHODS

4.1. Study Design

4.1.1. Overview of Study Design

This is a non-interventional PASS (68284528MMY4009; referred to throughout as MMY4009) to describe the safety profile of cilta-cel in the treatment of adult patients with multiple myeloma, primarily in the European Union (EU) region, with the option to expand to other regions/countries. This study will contribute to a common dataset (observational PASS 68284528MMY4004 evaluating the short- and long-term safety profile of cilta-cel under real world conditions) to inform the safety profile of cilta-cel across primary data sources and collect additional data requested by

regulatory authorities. For the purposes of the current protocol, the current PASS is referred to as "study".

Patients will be enrolled in the study at the time of apheresis, and will be followed for a period of up to 15 years from the day of cilta-cel infusion. All patients included in the study will provide written consent for participation and data collection. All aspects of treatment decisions and clinical management of patients will be at the discretion of the treating physician and the patient.

The data collection period will start from the day of apheresis, and patients will be followed for up to 15 years from the day of cilta-cel infusion, withdrawal of consent or until the time of death, if applicable. Patients who are apheresed but do not receive cilta-cel will only be followed-up until the time of decision not to infuse cilta-cel. For these patients, dates and reasons for discontinuation will be captured in the eCRF at the time of discontinuation. Data will be collected within the registry at the timepoints specified in the DATA COLLECTION SCHEDULE. The data for this study will then be periodically extracted from the registry for analysis. Confidentiality of patient records will be maintained at all times.

Data collection will include baseline demographics, diagnosis and medical history data including previous disease characteristics, treatment, comorbid conditions and information on lymphodepleting therapies. Post-infusion data collected will include Eastern Cooperative Oncology Group (ECOG) 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.

Patients will be permitted to enroll no later than at Day 0 (cilta-cel infusion), in the event that they were not enrolled at the time of apheresis. A patient's baseline data will be collected, where available, upon enrollment into the study. The end of the study will be after all consented patients have completed 15 years of follow-up from the day of cilta-cel infusion, or discontinued from the study or died (whichever occurs earlier).

A definition of variables for the common dataset collected from study will be provided as part of the statistical analysis plan (SAP) for the study.

4.1.2. Rationale for Study Design Elements

Study Design

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). All patients who meet the selection criteria should be offered enrollment in the study.

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 (EMA 2020).

This Janssen owned registry and national registries as appropriate, will be pooled to collect data from EU/European Economic Area, US and other regions, allowing analysis of the patient population across regions and meeting the planned target sample size in the global PASS study, protocol number 68284528MMY4004.

4.2. Setting and Patient Population

4.2.1. Study Setting and Duration

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 adverse events spontaneously reported to the sponsor, where available.

The data collection period will start from the time of apheresis, and patients will be followed for up to 15 years, up to discontinuation from the study or until the time of death, if applicable. During the data collection period, data will be collected upon enrollment on Day 0, Day 100, Month 6, Month 12, Month 18 and then annually, where available. A patient will be considered to have completed the study if data collection for a maximum of 15 years after the last administration of cilta-cel has been completed, 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
- Patients who are apheresed but do not receive cilta-cel
- Lost to follow-up
- Death

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

Due to the duration of study and length of time between data collection time points, loss 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, family member or referral physician) should be obtained at enrollment into the study and reconfirmed throughout the study.

If a patient is not reachable, reasonable effort should be made in accordance with routine care 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 4.12.

4.2.2. 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.

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

1. Has undergone apheresis with the purpose of receiving 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.

Therapy decisions will be made at the discretion of the participating 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 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.

4.3. Variables

The DATA COLLECTION SCHEDULE that follows the abstract summarizes the frequency and timing of data collection in this non-interventional study. Where available, the following items are to be documented at baseline and/or during the observational period:

- Demographic data
- Diagnosis and medical history

  Including history or serology of HBV, and history of Human T-lymphotropic virus (HTLV)-related T-cell leukemia/lymphoma and demyelinating disease (in Brazilian patients only)
- ECOG 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
  - Apheresis date and any adverse event related to this procedure
  - Lymphodepleting chemotherapy
  - Bridging therapy
  - Dates and reasons for discontinuation for patients who are apheresed but do not receive cilta-cel (these patients will only be followed-up until the time of decision not to infuse cilta-cel)
  - Dose/number of cells infused
  - Toxicities/complications (see Section 4.3.2 and Section 6.3) including those occurring between apheresis and Day 0 of CAR-T administration (see Section 6.3.1.1)
  - Treatments for complications (see Section 4.3.1)
  - Response to cilta-cel therapy (see Section 4.3.3)
- Relapse/progression of disease
- Subsequent treatments for multiple myeloma, including stem cell transplant or other cellular therapy
- Date and cause of death

4.3.1. Exposures

The main exposure of interest is treatment with cilta-cel. This study will collect data from patients enrolled in the study who are treated with cilta-cel per the health authority approved cilta-cel Summary of Product Characteristics (SmPC) in the respective country/region, or who have received cilta-cel not meeting pre-specified drug product specifications per label.

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

- Multiple myeloma therapies administered since diagnosis.
- Start/stop dates and of multiple myeloma therapies.
- Response to prior multiple myeloma therapies (complete remission, partial remission [>50%], no response [<50%], relapse/progression).

The following data will be documented during the prospective observational period:

- Treatments for adverse drug reactions.
- Date of initiation of the first subsequent antimyeloma therapy.
- Subsequent treatments (type) for malignancy including stem cell transplant or cellular therapy.

- Treatments for comorbidities.
- Lymphodepleting chemotherapy.

4.3.2. Evaluation of Safety

Safety outcomes will be summarized using selected data collected from the study for patients treated with cilta-cel.

Selected toxicities described below, any serious adverse events, other non-serious events and special reporting situations as described in Section 6.3 will be collected in the study and reported in the global PASS.

Safety Variables

Safety parameters for this study include the rate of the following selected adverse events (including latency, frequency, type and severity when available), regardless of causality and seriousness:

- Subsequent malignancies, defined as a new occurrence of malignancy after cilta-cel administration (including subsequent malignancies and recurrent malignancies, other than multiple myeloma)

  In the event of subsequent malignancy, a tumor sample should be collected, if clinically feasible, and lentiviral integration site analysis may be performed for possible insertional mutagenesis (see Section 4.3.2.1)

  - Presence of RCL will be tested in patients who develop subsequent malignancies (where allowed per local regulations in the context of a non-interventional study).
- Neurotoxicity, including:

  ICANS

  Other CAR-T cell neurotoxicity, including movement and neurocognitive toxicity (i.e., Parkinsonism)
- Hematologic disorders, per collected laboratory values, and their relation to patients' demographics and baseline characteristics
- Hypogammaglobulinemia
- Clinically significant infections
- Organ toxicities
- CRS, including HLH/MAS
- Tumor lysis syndrome
- 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

HBV reactivation

HTLV-related T-cell leukemia/lymphoma and demyelinating disease (in Brazilian patients only)

Hematologic disorders, including prolonged or recurrent cytopenias (ie, thrombocytopenia, leukopenia, lymphocytopenia and anemia)

In addition, all pregnancies and outcomes following exposure to cilta-cel will be reported. In patients with subsequent neoplasms, tumor specimen will be collected if available for analysis of the presence of lentiviral sequences and insertion of the virus in the tumor cell genome.

4.3.2.1. Subsequent Malignancy Tumor Sampling

For patients who will receive commercial cilta-cel post-authorization and develop second primary malignancies, 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 subsequent malignancy, and depending on the type of malignancy, a blood, bone marrow aspirate or biopsy sample of the neoplastic tissue will be collected, where possible within clinical practice, and DNA, RNA, or protein analysis may be performed 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 LV integration could have played a role for the adverse event. If there is evidence of lentiviral integration within the sample submitted, the Sponsor will follow adverse events reporting in the subject closely to determine the occurrence of additional subsequent malignancies.

Subsequent malignancies should be reported to the sponsor by treating physicians in an expedited manner (eg, within 24 hours of awareness of diagnosis) to 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.

4.3.3. Evaluation of Effectiveness/Clinical Response

Effectiveness/Clinical Response

Disease evaluations will be collected as described using data collected from the study for patients treated with cilta-cel. Response assessments will be evaluated by the treating physician in the study per International Myeloma Working Group (IMWG) criteria. Effectiveness will be evaluated based on OS, PFS, DOR and ORR. In addition, the effect of cilta-cel on myeloma-related comorbidities (amyloidosis and POEMS syndrome, if present) will be collected and analyzed.

- Overall Survival, reported in the study, will be collected and will be defined as the interval between the date of first cilta-cel infusion and date of death due to any cause.
- Progression-free survival will be defined as the interval between the date of first cilta-cel infusion and date of progressive disease according to the judgment of the treating physician, or death, whichever occurs earlier.
- Duration of response (DOR) will be calculated among responders (with a partial response [PR] or better response) from the date of initial documentation of a response (PR or better) to the date of first documented evidence of progressive disease. Response to cilta-cel will be captured per IMWG criteria for response assessment in patients with multiple myeloma, ie, as PR 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), CR, and/or stringent complete response (sCR).

4.4. Data Sources

The primary data source for this study will be the medical record of each patient who has provided a signed ICF. Source documentation should be in patients' records for all data entered into the CRF. In addition, source documentation should be available for the following to confirm data collected in the CRF for this study: patient identification, eligibility and study identification; date of signed ICF; date of study completion and reason for early discontinuation of treatment or withdrawal from the study (if applicable). 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 according to the DATA COLLECTION SCHEDULE.

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. Specific details required as source data for the study will be reviewed with the participating physician before the study.

4.5. Study Size

Data for the global PASS (MMY4004) dataset 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 global PASS, with potential comparison to historic control, for the outcome of subsequent malignancy (secondary primary malignancy). For the current study (MMY4009) it is estimated that around 300 patients will contribute to the overall enrollment target

for the global PASS. Enrollment in the global PASS is competitive between participating prospective registries/studies. Once enrollment is complete within the global PASS, which aims to enroll a total of 1500 patients across the target regions, enrollment will be considered complete for this study.

Assuming a conservative background incidence rate for subsequent 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, 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 secondary malignancy 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 SAP.

4.6. Data Management

The primary data source for this study will be the medical record of each patient who has provided a signed ICF. The data source for the global PASS study will be the registries and may also include analysis from tumor samples or adverse events spontaneously reported to the sponsor, where available. Patient data will be handled in compliance with all applicable privacy laws. Further detail is provided in Section 4.4.

4.7. Data Analysis

Statistical analyses will be performed 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. Additional details will be provided in the SAP. In addition, the data from this study will be pooled and analyzed together with other independent prospective registries and other data sources as part of the global PASS study (MMY4004).

The analysis set will include all patients who meet the selection criteria.

4.7.1. Main Summary Measures

The verbatim terms used to identify adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). All documented adverse events will be included in the analysis. For each adverse event, the count and percentage of patients who experience at least 1 occurrence of the given event will be summarized. Additionally, cumulative incidence estimates or rates of adverse events reported in person-years may be used. Further detail will be included in the SAP.

Patient demographics, medical history and disease history (including history of prior and current malignancies) will be collected at apheresis (enrollment).

All adverse events regardless of causality to cilta-cel beginning from product administration on Day 0 until Day 100 following CAR-T infusion will be collected and included in the analysis. Thereafter, only non-serious AEs related to cilta-cel (except the safety variables defined in Section 4.3.2) and all SAEs regardless of causality up to End of Study will be collected and analyzed. Other data sources for this study may also include analyses from tumor samples of patients developing second primary malignancies.

Rates of adverse events collected within the study will be estimated. Where appropriate, additional summaries, listings, or narratives may be provided, as appropriate.

Toxicity grades will be summarized per predefined National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE; version 5.0) except for CRS and CAR-T cell-related neurotoxicity (ie, ICANS). Cytokine release syndrome will be evaluated and summarized according to the American Society for Transplantation and Cellular Therapy (ASTCT) consensus grading (Annex 1) (Lee 2019). Neurotoxicity that is not temporally associated with CRS, or any other neurologic AEs that do not qualify as ICANS, will be graded and summarized by CTCAE criteria.

The survival analysis will be performed for time-to-event variables (such as PFS, OS).

4.7.2. Interim Analysis

The study will have analysis performed annually and results will be summarized in interim reports. The scope of the analysis will be documented in the SAP.

4.8. Quality Control

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 (see Section 4.6). 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 4.8). 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 4.3). 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 4.11.

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 are presented in Annex 4.10.

4.9. Limitations of the Research Methods

This study is an observational primary data analysis using data collected from the patients' medical records at 6- and 12-monthly intervals. However, sites will be strongly encouraged to enter data in a timely fashion, ie, within 30 days of visit or patient status change, to limit discrepancies in data collection. In addition, limited recall of adverse events at the patient visits may lead to incomplete information or under reporting of some adverse events or bias.

5. PROTECTION OF HUMAN SUBJECTS

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 4.4).

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 4.5). 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, and that their participation in the study does not involve invasive procedures outside of the recommendations in the local label. Only patients who are fully able to understand the nature of the study and provide their consent voluntarily will be enrolled.

Personal data collected from patients enrolled in this study will be limited to those data that are necessary to fulfil 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 4.7).

6. 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.

6.1. Definitions and Classifications

6.1.1. 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 Conference on Harmonization [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.

6.1.2. Attribution Definitions

Assessment of Causality

The causal relationship to treatment is determined by a physician and should be used to assess all adverse events. 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.

6.1.3. Severity Criteria

Where applicable, an assessment of severity grade will be made by the participating physician according to the NCI-CTCAE version 5.0, except for CRS and CAR-T cell-related neurotoxicity (ie, ICANS). Cytokine release syndrome should be evaluated according to the ASTCT consensus grading (Annex 1). Immune Effector Cell-associated Neurotoxicity Syndrome should be graded using the ASTCT consensus grading (Annex 2). Neurotoxicity that is not temporally associated with CRS, or any other neurologic AEs that do not qualify as ICANS, will be graded and summarized by CTCAE criteria. Any AEs or an SAEs not listed in the NCI-CTCAE version 5.0 should be evaluated for severity/intensity by using the following general categorical descriptors:

Grade 1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
Grade 2	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living (ADL)*.
Grade 3	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL**.
Grade 4	Life-threatening consequences; urgent intervention indicated.
Grade 5	Death related to adverse event.

Activities of Daily Living (ADL):

* Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

** Self-care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

The participating physician should use clinical judgment in assessing the severity of events not directly experienced by the patient (eg, laboratory abnormalities).

6.2. Special Situations

Safety events of interest for a Janssen product under study that require reporting and/or safety evaluation by Janssen include, but are not limited to:

- Overdose of a product
- Exposure to a product from breastfeeding
- Suspected abuse/misuse of a product
- Inadvertent or accidental exposure to a product
- Any failure of expected pharmacological action (ie, lack of effect) of a product
- Unexpected therapeutic or clinical benefit from use of a product

- Medication error, intercepted medication error, or potential medication error involving a Janssen medicinal product (with or without patient exposure to the Janssen medicinal product, eg, product name confusion, product label confusion, intercepted prescribing or dispensing errors)

These safety events may not meet the definition of an adverse event; however, from a policy perspective, they are treated in the same manner as adverse events.

Special situations for a Janssen product under study should be recorded in the CRF. Any special situation that meets the criteria of a serious adverse event should be recorded on a Serious Adverse Event Report Form and reported to the local sponsor within 24 hours of them becoming aware of the event.

6.3. Procedures

In this non-interventional study, cilta-cel is the Janssen product(s) under study.

The sponsor will provide appropriate pharmacovigilance training to the participating site personnel. The sponsor assumes responsibility for appropriate reporting of (serious) adverse events and significant safety information originating from the data collected for Janssen medicinal products to the regulatory authorities (see country-specific attachments). All collected adverse events will be summarized in the final study report.

The names (and corresponding telephone numbers) of the individuals who should be contacted regarding product safety issues and/or quality issues are listed on the contact information page(s), which is/are provided separately.

6.3.1. Prospective Study Period

6.3.1.1. All Adverse Events

Adverse Events Systematically Collected (Solicited Adverse Events)

All AEs (with the exceptions noted below) and special situations regardless of causality to cilta-cel beginning from product administration on Day 0 until Day 100 following CAR-T infusion will be recorded in the CRF. Thereafter, only non-serious AEs related to cilta-cel except safety variables defined below and in Section 4.3.2, or SAEs regardless of causality up to End of Study will be recorded in the CRF.

Events of HBV reactivations and HTLV-related T-cell leukemia/lymphoma and demyelinating disease (in Brazilian patients only) regardless of seriousness or causality from product administration on Day 0 until one year following CAR-T infusion will be recorded in the CRF.

Additionally, the following adverse events must be collected from Day 0 and for the duration of study regardless of causality and seriousness (see Section 4.3.2: Evaluation of Safety - Safety Variables):

- Subsequent malignancies, defined as a new occurrence of malignancy after cilta-cel administration (including subsequent malignancies and recurrent malignancies, other than multiple myeloma)

  In the event of subsequent malignancy, a tumor sample should be collected, if clinically feasible, and lentiviral integration site analysis may be performed for possible insertional mutagenesis (see Section 4.3.2.1)

- Neurotoxicity, including:

  ICANS

  Other CAR-T cell neurotoxicity, including movement and neurocognitive toxicity (i.e., Parkinsonism)

- Hematologic disorders, per collected laboratory values, and their relation to patients' demographics and baseline characteristics
- Hypogammaglobulinemia
- Clinically significant infections
- Organ toxicities
- CRS, including HLH/MAS
- Tumor lysis syndrome
- 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

  HBV reactivation

  HTLV-related T-cell leukemia/lymphoma and demyelinating disease (in Brazilian patients only)

  Hematologic disorders, including prolonged or recurrent cytopenias (ie, thrombocytopenia, leukopenia, lymphocytopenia and anemia)

All AEs should be recorded in the CRF.Any event that meets the definition of a serious adverse event (see Section 6.1.1) should be reported as a serious adverse event according to the requirements in Section 6.3.1.2.

All adverse events following exposure cilta-cel should be assessed by the participating physician to document their opinion concerning the relationship of the event to a product under study; the causal relationship of the adverse event must be recorded in the CRF. An adverse event will be considered as an ADR if there is at least a reasonable possibility of a causal relationship (see Section 6.1.1). Where necessary, the sponsor and/or participating physician, as applicable will report non-serious ADRs to the local health authorities following applicable requirements.

All adverse events should be followed-up- in accordance with clinical practice, regardless of seriousness. This follow-up should be recorded in the patients' source records and documented according to sponsor instructions.

Non-serious Adverse Events Requiring Expedited Reporting

For cilta-cel, the following medical concepts require further follow-up to meet regulatory reporting requirements, regardless of causality or seriousness:

- ≥Grade 3 CRS
- ≥Grade 3 neurotoxicity (including ICANS and other CAR-T cell neurotoxicities)
- Any grade movement and neurocognitive toxicity (ie, Parkinson-like syndrome)
- Any grade subsequent malignancy defined as new occurrence of malignancy after cilta-cel administration (including subsequent malignancies and recurrent malignancies) with the exception of multiple myeloma

All adverse events for cilta-cel that fall under these medical concepts should be recorded in the CRF and reported to the sponsor's designee within 24 hours according to the process for serious adverse event reporting (Section 6.3.1.2), regardless of causality or whether it meets serious criteria.

Adverse Events Occurring Prior to Infusion and Related to Administration Procedures (From Apheresis to Day 0)

For the purpose of this study, adverse events will be collected for patients intended to receive CAR-T from the day of apheresis until Day 0 of CAR-T administration. This includes any untoward medical occurrence in a patient prior to CAR-T administration related to administration procedures (eg, apheresis, bridging therapy and lymphodepletion therapy). These events will be collected in the electronic CRF and be described in the clinical study report.

All adverse events for Janssen products related to bridging therapy should be reported to the sponsor's designee within 24 hours according to the process for serious adverse event reporting (Section 6.3.1.2), regardless of causality or whether it meets serious criteria.

Adverse Events Not Systematically Collected (Spontaneous Adverse Events)

For adverse events and special situations that are not systematically collected (eg, for a medicinal product other than the product(s) under study, or for adverse events excluded from systematic data collection within the study) and where the participating physician considers there is at least a reasonable possibility of a causal relationship to a medicinal product (ie, spontaneous ADRs), the participating physician is requested to notify the manufacturer of the medicinal product or the appropriate regulatory/competent authority through the national spontaneous reporting system as soon as possible.

For ADRs and special situations related to non-studied Janssen products, it is requested to report the event directly to the local sponsor (see country-specific attachments).

Where available, reports of spontaneous ADRs will be summarized in the clinical study report.

6.3.1.2. Serious Adverse Events

All serious adverse events following exposure to a Janssen product under study should be reported directly by the participating physician, within 24 hours of them becoming aware, to the local sponsor (see country-specific attachments) using a Serious Adverse Event Report Form (or local equivalent).

For SAEs following exposure to the non-Janssen products under study, the participating physician should notify the manufacturer of the medicinal product or the appropriate regulatory/competent authority through the national spontaneous reporting system as soon as possible. These events should be recorded in the CRF.

For reports of hospitalization, it is the sign, symptom or diagnosis which led to hospitalization that is the serious event for which details must be provided.

Any event requiring hospitalization (or prolongation of hospitalization) that occurs during the study must be reported as a serious adverse event, except hospitalizations for the following:

- Hospitalizations not intended to treat an acute illness or adverse event (eg, social reasons such as pending placement in long-term care facility).
- Surgery or procedure(s) planned before entry into the study (should be documented in the CRF). Note: Hospitalizations that were planned before the start of data collection, and where the underlying condition for which the hospitalization was planned has not worsened, will not be considered serious adverse events. Any adverse event that results in a prolongation of the originally planned hospitalization is to be reported as a new serious adverse event.

The cause of death of a patient in a study whether or not the event is expected or associated with the product under study, is considered a serious adverse event.

Disease progression should not be recorded as an adverse event or SAE term; instead, signs or symptoms of clinical sequelae resulting from disease progression will be reported in the CRF if it fulfils the serious adverse event definition.

6.3.1.3. Pregnancy

All reports of pregnancy occurring in temporal association with the administration of a Janssen product under study must be reported to the sponsor by the participating site personnel within 24 hours of their knowledge of the event using the appropriate pregnancy notification form. Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered serious adverse events and must be reported using a Serious Adverse Event Form.

As this is an observational study, it is recommended that participating physicians follow the guidance in the approved local product labels for cilta-cel regarding contraception and discontinuation of therapy in patients who become pregnant during the study. If a patient becomes pregnant during the study, data specified in the Data Collection Schedule that is collected as part

of the patient's standard-of-care will continue to be recorded in the CRF for the applicable time points.

Because the effect of the Janssen product under study on sperm is unknown, pregnancies in partners of male patients exposed to a Janssen product under study will be reported by the participating site personnel within 24 hours of their knowledge of the event using the appropriate pregnancy notification form. Depending on local legislation this may require prior consent of the partner.

Follow-up information regarding the outcome of the pregnancy and any postnatal sequelae in the infant should be obtained where possible.

6.3.2. Product Quality Complaints

A PQC may have an impact on the safety and effectiveness of the product. Timely, accurate, and complete reporting and analysis of PQC information from studies are crucial for the protection of patients, physicians, and the sponsor, and are mandated by regulatory agencies worldwide. The sponsor has established procedures in conformity with regulatory requirements worldwide to ensure appropriate reporting of PQC information; all studies conducted by the sponsor or its affiliates will be conducted in accordance with those procedures.

All initial PQCs involving a Janssen product must be reported to the local sponsor by the participating site personnel within 24 hours after being made aware of the event. The names (and corresponding telephone numbers) of the individuals who should be contacted regarding PQCs for a Janssen product are listed on the contact information page(s), which is/are provided separately.

If the defect for a Janssen product is combined with a serious adverse event, the study-site personnel must report both the SAE and the PQC to the local sponsor according to the serious adverse event reporting timelines. A sample of the suspected product should be maintained for further investigation if requested by the sponsor.

7. 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 all study sites that participated in the study. 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 4.13.

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ANNEX 1: CYTOKINE RELEASE SYNDROME ASTCT CONSENSUS GRADING SYSTEM

Grade	Toxicity
Grade 1	Fever[a] (Temperature ≥38°C)
Grade 2	Fever[a] (Temperature ≥38°C) with either: • Hypotension not requiring vasopressors • And/or[c] hypoxia requiring low-flow nasal cannula[b] or blow-by.
Grade 3	Fever[a] (Temperature ≥38°C) with either: • Hypotension requiring a vasopressor with or without vasopressin, • And/or[c] hypoxia requiring high-flow nasal cannula[b], facemask, nonrebreather mask, or Venturi mask.
Grade 4	Fever[a] (Temperature ≥38°C) with either: • Hypotension requiring multiple vasopressors (excluding vasopressin), • And/or[c] hypoxia requiring positive pressure (eg, CPAP, BiPAP, intubation and mechanical ventilation).
Grade 5	Death

Abbreviations: BiPAP=bilevel positive airway pressure; CPAP=continuous positive airway pressure, CRS=cytokine release syndrome; NCI-CTCAE=National Cancer Institute Common Terminology Criteria for Adverse Events.

a Fever not attributable to any other cause. In patients who have CRS then receive antipyretics or anticytokine therapy such as tocilizumab or steroids, fever is no longer required to grade subsequent CRS severity. In this case, CRS grading is driven by hypotension and/or hypoxia.

b Low-flow nasal cannula is defined as oxygen delivered at ≤6 L/minute or blow-by oxygen delivery. High-flow nasal cannula is defined as oxygen delivered at >6 L/minute.

c CRS grade is determined by the more severe event: hypotension or hypoxia not attributable to any other cause.

Note: Organ toxicities associated with CRS may be graded according to NCI-CTCAE (version 5.0) but they do not influence CRS grading.

Source: Lee 2019

ANNEX 2: IMMUNE EFFECTOR CELL-ASSOCIATED NEUROTOXICITY SYNDROME (ICANS) ASTCT CONSENSUS GRADING SYSTEM[A,B]

Neurotoxicity Domain	Grade 1	Grade 2	Grade 3	Grade 4
ICE Score	7-9	3-6	0-2	0 (patient is unarousable and unable to perform ICE).
Depressed Level of Consciousness	Awakens spontaneously.	Awakens to voice.	Awakens only to tactile stimulus.	Patient is unarousable or requires vigorous or repetitive tactile stimuli to arouse. Stupor or coma.
Seizure	N/A	N/A	Any clinical seizure, focal or generalized, that resolves rapidly; or Non-convulsive seizures on EEG that resolve with intervention.	Life-threatening prolonged seizure (>5 min); or Repetitive clinical or electrical seizures without return to baseline in between.
Motor Findings	N/A	N/A	N/A	Deep focal motor weakness such as hemiparesis or paraparesis.
Raised Intracranial Pressure/Cerebral Edema	N/A	N/A	Focal/local edema on neuroimaging.	Diffuse cerebral edema on neuroimaging; or Decerebrate or decorticate posturing; or Cranial nerve VI palsy; or Papilledema; or Cushing's triad.

Abbreviations: EEG=electroencephalogram; ICANS=Immune Effector Cell-associated Neurotoxicity Syndrome ICE=Immune Effector Cell-associated encephalopathy; ICP=intracranial pressure; N/A=not applicable; NCI CTCAE=National Cancer Institute Common Terminology Criteria for Adverse Events.

a Toxicity grading according to Lee 2019.

b ICANS grade is determined by the most severe event (ICE score [Annex 3], level of consciousness, seizure, motor findings, raised ICP/cerebral edema) not attributable to any other cause.

Note: all other neurological adverse events (not associated with ICANS) should continue to be graded with NCI CTCAE version 5.0 during both phases of the study.

ANNEX 3: : IMMUNE EFFECTOR CELL-ASSOCIATED ENCEPHALOPATHY (ICE) TOOL

Immune Effector Cell-Associated Encephalopathy (ICE) Tool[a]
Orientation: Orientation to year, month, city, hospital: • **4 points** **Naming**: Name 3 objects (eg, point to clock, pen, button): • **3 points** **Following commands**: (eg, Show me 2 fingers or Close your eyes and stick out your tongue): • **1 point** **Writing**: Ability to write a standard sentence (eg, Our national bird is the bald eagle): • **1 point** **Attention**: Count backwards from 100 by 10: • **1 point**
a: ICE-Tool Scoring: • Score 10: No impairment • Score 7-9: Grade 1 ICANS • Score 3-6: Grade 2 ICANS • Score 0-2: Grade 3 ICANS • Score 0 due to patient unarousable and unable to perform ICE assessment: Grade 4 ICANS

Abbreviations: ICANS=Immune Effector Cell-associated Neurotoxicity Syndrome ICE=Immune Effector Cell-associated encephalopathy.

ANNEX 4: STANDALONE DOCUMENTS AND ADDITIONAL INFORMATION

Annex 4.1: List of Standalone Documents

Title	Reference No	Date

Annex 4.2: Information to be Provided to Participating Physicians

The participating physician will be provided with the following supplies:

- SmPC, if required by local regulations
- NCI-CTCAE Version 5. 0
- eDC Manual
- Sample participation agreement/ICF

Annex 4.3: Regulatory Documentation

Regulatory Approval/Notification

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.

Required Prestudy Documentation

The following documents must be provided to the sponsor before starting the study:

- Protocol and amendment(s), if any, signed and dated by the participating physician
- Where appropriate, as required by local regulations, a copy of the dated and signed written IEC/IRB approval of the protocol, amendments, participation agreement/ICF, and any recruiting materials
- Where appropriate, as required by local regulations, a copy of the dated and signed written Designated Regulatory Body (DRB) approval of the protocol, protocol amendments, participation agreement/ICF, and any other recruiting materials. This approval must clearly identify the specific protocol by title and number and must be signed by the chairman or authorized designee
- Where appropriate, as required by local regulations, the name and address of the DRB (with a statement that it is organized and operates according to applicable laws and regulations). If a participating physician or a member of the participating site personnel is a member of the DRB, documentation must be obtained to state that this person did not participate in the deliberations or in the vote or opinion of the study
- Regulatory authority approval or notification, if applicable

- Documentation of the qualifications (eg, curriculum vitae) of the participating physician, where appropriate
- Any other documentation required by local regulations

The following documents must be provided to the sponsor before enrollment of the first patient:

- Signed and dated clinical trial agreement, which includes the financial agreement

Annex 4.4: Ethics Compliance

Independent Ethics Committee or Institutional Review Board

Before the start of data collection, the participating physician (or sponsor where required) will provide the IEC/IRB with current and complete copies of the following documents (as required by local regulations):

- Final protocol and, if applicable, protocol amendments
- Sponsor-approved participation agreement/ICF (and any other written materials to be provided to the patients)
- Participating physician's curriculum vitae or equivalent information (unless not required, as documented by the IEC/IRB)
- Information regarding name of the sponsor, institutional affiliations, other potential conflicts of interest
- Any other documents that the IEC/IRB requests to fulfil its obligation

Where appropriate, as required by local regulations, this study will be undertaken only after the IEC/IRB has given full approval of the final protocol, amendments (if any, excluding those that are purely administrative, with no consequences for data collection), and the participation agreement/ICF, and the sponsor has received a copy of this approval. This approval letter must be dated and must clearly identify the IEC/IRB and the documents being approved.

During the study the participating physician (or sponsor where required) will send the following documents and updates to the IEC/IRB for their review and approval, where appropriate:

- Protocol amendments (excluding those that are purely administrative, with no consequences for data collection)
- Revision(s) to the participation agreement/ICF and any other written materials to be provided to patients
- If applicable, new or revised patient recruiting materials approved by the sponsor
- Summaries of the status of the study at intervals stipulated in guidelines of the IEC/IRB
- Reports of adverse events that are serious, unlisted/unexpected, and temporally associated with the product under study
- New information that may adversely affect the safety of the patients or the conduct of the study

- Report of deaths of patients under the participating physician's care
- Notification if a new physician is responsible at the participating site
- Any other requirements of the IEC/IRB

For all protocol amendments (excluding those that are purely administrative, with no consequences for data collection), the amendment and applicable revisions to the participation agreement/ICF must be submitted promptly to the IEC/IRB for review and approval before implementation of the change(s).

At the end of the study, where required by local regulations, the participating physician (or sponsor where required) will notify the IEC/IRB about the study completion [(if applicable, the study completion notification will be submitted through the head of the participating site)].

Annex 4.5: Patient Consent

The participation agreement/ICF [and assent form] that is/are used must be reviewed and approved in accordance with local regulations, applicable regulatory requirements and sponsor policy, and must be in a language that the patient can read and understand. The participation agreement/ICF must be signed before collection of any patient data.

Before enrollment in the study, the participating physician or an authorized member of the participating site personnel must explain to potential participants [and/or their legally acceptable representatives] their involvement in the study and data protection. Patients will be informed that their participation is entirely voluntary and that they may withdraw consent for data collection at any time. They will also be informed that choosing not to participate in this study will not affect the standard-of-care the patient will receive. Finally, they will be told that the participating physician will maintain a patient identification register for the purposes of long-term follow-up if needed and that their records may be accessed by health authorities and authorized sponsor personnel without violating the confidentiality of the patient, to the extent permitted by the applicable law(s) or regulations. By signing the participation agreement/ICF the patient [and/or legally acceptable representative] is authorizing such access, including permission to obtain information about his/her survival status, and agrees to allow the participating physician to re-contact the patient to obtain information about his/her survival status.

The patient [or legally acceptable representative] will be given sufficient time to read the participation agreement/ICF and will be given the opportunity to ask questions. After this explanation and before entry into the study, consent should be appropriately recorded by means of [either] the patient's [or his/her legally acceptable representative's personally dated signature. After having obtained the consent, a copy of the participation agreement/ICF must be provided to the patient.

If the patient [or legally acceptable representative] is unable to read or write, an impartial witness should be present for the entire informed consent process (which includes reading and explaining all written information) and should personally date and sign the participation agreement/ICF after the oral consent of the patient or legally acceptable representative is obtained.

Before enrollment in the study, the participating physician or an authorized member of the participating site personnel must explain to potential participants (as appropriate for age and per local regulations) as well as the legally acceptable representatives of potential participants, their involvement in the study and data protection (see Annex 4.7). They will also be informed that their participation is voluntary and that they may withdraw consent for data collection at any time. They will also be informed that choosing not to participate will not affect the care the patient will receive.

Finally, they will be told that the participating physician will maintain a patient identification register for the purposes of long-term follow-up if needed and that their records may be accessed by health authorities and authorized sponsor personnel without violating the confidentiality of the patient, to the extent permitted by the applicable law(s) or regulations. By signing the participation agreement/ICF the patient [and/or legally acceptable representative] is authorizing such access [, including permission to obtain information about his/her survival status,] [and agrees to allow the participating physician to re-contact the patient to obtain information about his/her survival status].

If the patient, if appropriate, or legal guardian are unable to read or write, an impartial witness should be present for the entire informed consent and assent process (which includes reading and explaining all written information) and should personally date and sign the participation agreement/ICF after the oral consent of the patient, if appropriate, and legal guardian is obtained.

When prior assent of the patient, if appropriate, and consent of the legal guardian are not possible, enrollment procedures should be described in the protocol with documented approval/favorable opinion by the IEC/IRB to protect the rights of the patient and to ensure compliance with applicable regulatory requirements. The patient, if appropriate, and legal guardian must be informed about the study as soon as possible and give assent/consent to continue.

The patient's medical record must include a statement that the consent signed by the legal guardian and the assent signed by the patient (if appropriate) were obtained before the patient was enrolled in the study as well as the date the written consent was obtained. The authorized person obtaining the informed consent and assent must also sign the ICF and assent forms.

Annex 4.6: Patient Identification and Enrollment

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. To ensure patient confidentiality, no copy will be made. All reports and communications relating to the study will identify patients by patient identification and age at initial informed consent. In cases where the patient is not enrolled for data collection in the study, the date seen and age at initial informed consent will be used.

Where applicable, the participating physician should also complete a patient screening log, which documents all patients who were seen to determine eligibility for data collection in the study.

Annex 4.7: Patient Data Protection

The collection and processing of personal data from patients enrolled in this study will be limited to those data that are necessary to fulfil 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 4.8: Case Report Form Completion

Case report forms are provided for each patient in electronic format.

Electronic Data Capture (eDC) will be used for this study. 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.

Worksheets may be used for the capture of some data to facilitate completion of the CRF. Any such worksheets will become part of the patient's source documentation. All data relating to the study must be recorded in CRFs prepared by the sponsor. Data must be entered into CRFs in English. Designated site personnel must complete the CRF as soon as possible after a patient visit.

The participating physician must verify that all data entries in the CRFs are accurate and correct. All CRF entries, corrections, and alterations must be made by the participating physician or other authorized participating site personnel. If necessary, queries will be generated in the eDC tool.

If corrections to a CRF are needed after the initial entry into the CRF, this can be done in 3 different ways:

- Personnel at each participating site can make corrections in the eDC tool at their own initiative or as a response to an auto query (generated by the eDC tool).
- The manager of the participating site can generate a query for resolution by the personnel at that site.

- Clinical data manager can generate a query for resolution by the participating site personnel.

Annex 4.9: Monitoring

- At the first post-initiation visit, the monitor will compare the data entered into the CRFs with the source documents. The nature and location of all source documents will be identified to ensure that all sources of original data required to complete the CRF are known to the sponsor and participating site personnel and are accessible for verification by the sponsor/participating site contact. If electronic records are maintained at the participating site, the method of verification must be discussed with the site personnel.
- Direct access to source documentation must be allowed for the purpose of verifying that the data recorded in the CRF are consistent with the original source data. Findings from this review of CRFs and source documents will be discussed with the participating site personnel. The sponsor expects that, during monitoring visits, the relevant participating site personnel will be available, the source documentation will be accessible, and a suitable environment will be provided for review of study-related documents. The monitor will meet with the participating physician on a regular basis during the study to provide feedback on the study conduct.

Annex 4.10: On-Site Audits

- Any audits conducted by the sponsor at a participating site will require access to all study records, including source documents, for inspection and comparison with the CRFs. Patient privacy must, however, be respected. The participating physician and participating site personnel are responsible for being present and available for consultation during routinely scheduled site audit visits conducted by the sponsor or its designees.

Annex 4.11: Record Retention

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.

If it becomes necessary for the sponsor or the appropriate regulatory authority to review any documentation relating to this study, the participating physician and/or site must permit access to such reports.

Annex 4.12: Study Completion/Termination

The final data from the participating site will be sent to the sponsor (or designee) after completion of the final data collection time point at that site.

The sponsor reserves the right to close a participating site for data collection or to terminate the study at any time for any reason at the sole discretion of the sponsor.

A participating site is considered closed when all required documents and study-specific supplies have been collected and a site closure assessment has been performed.

The participating physician may initiate site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a participating site by the sponsor or participating physician may include but are not limited to:

- Failure of the participating physician to comply with the protocol, requirements of the local health authorities, or the sponsor's procedures
- Inadequate recruitment of patients by the participating physician

The participating physician should immediately notify the sponsor if they have been contacted by a regulatory agency concerning an upcoming inspection.

Annex 4.13: Use of Information and Publication

All information, including but not limited to information regarding cilta-cel or the sponsor's operations (eg, patent applications, formulas, manufacturing processes, basic scientific data, prior clinical data, formulation information) supplied by the sponsor to the participating physician and not previously published, and any data generated as a result of this study, are considered confidential and remain the sole property of the sponsor. The participating physician agrees 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.

The participating physician understands that the information obtained in the study will be used by the sponsor in connection with the continued development of cilta-cel, and thus may be disclosed as required to other clinical investigators or regulatory agencies. To permit the information obtained to be used, the participating physician is obligated to provide the sponsor with all data obtained in the study.

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 as provided for below) shall be the property of the sponsor as author and owner of copyright in such work.

Consistent with Good Publication Practices and International Committee of Medical Journal Editors guidelines, the sponsor shall have the right to publish the primary (multicenter) data and information without approval from the participating physician. The participating physician has the right to publish data specific to the associated participating site after the primary data are published. If a participating physician wishes to publish information from the study, a copy of the manuscript must be provided to the sponsor for review at least 60 days before submission for publication or presentation. Expedited reviews will be arranged for abstracts, poster presentations, or other materials. If requested by the sponsor in writing, the participating physician will withhold such publication for up to an additional 60 days to allow for filing of a patent application. In the event that issues arise regarding scientific integrity or regulatory compliance, the sponsor will review these issues with the participating physician. The sponsor will not mandate modifications to scientific content and does not have the right to suppress information. For multicenter study

designs and substudy approaches, secondary results generally should not be published before the primary endpoints of a study have been published. Similarly, participating physicians will recognize the integrity of a multicenter study by not submitting for publication data derived from the individual site until the combined results from the completed study have been submitted for publication, within 12 months of the availability of the final data (tables, listings, graphs), or the sponsor confirms there will be no multicenter study publication. Authorship of publications resulting from this study will be based on the guidelines on authorship, such as those described in the Uniform Requirements for Manuscripts Submitted to Biomedical Journals, which state that the named authors must have made a significant contribution to the design of the study or analysis and interpretation of the data, provided critical review of the paper, and given final approval of the final version.

ANNEX 5: ENCEPP CHECKLIST FOR STUDY PROTOCOLS

Doc.Ref. EMA/540136/2009

European Network of Centres for Pharmacoepidemiology and Pharmacovigilance

ENCePP Checklist for Study Protocols (Revision 4)

Adopted by the ENCePP Steering Group on 15/10/2018

The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) welcomes innovative designs and new methods of research. This Checklist has been developed by ENCePP to stimulate consideration of important principles when designing and writing a pharmacoepidemiological or pharmacovigilance study protocol. The Checklist is intended to promote the quality of such studies, not their uniformity. The user is also referred to the ENCePP Guide on Methodological Standards in Pharmacoepidemiology, which reviews and gives direct electronic access to guidance for research in pharmacoepidemiology and pharmacovigilance.

For each question of the Checklist, the investigator should indicate whether or not it has been addressed in the study protocol. If the answer is "Yes", the section number of the protocol where this issue has been discussed should be specified. It is possible that some questions do not apply to a particular study (for example, in the case of an innovative study design). In this case, the answer 'N/A' (Not Applicable) can be checked and the "Comments" field included for each section should be used to explain why. The "Comments" field can also be used to elaborate on a "No" answer.

This Checklist should be included as an Annex by marketing authorisation holders when submitting the protocol of a non-interventional post-authorisation safety study (PASS) to a regulatory authority (see the Guidance on the format and content of the protocol of non-interventional post-authorisation safety studies). The Checklist is a supporting document and does not replace the format of the protocol for PASS presented in the Guidance and Module VIII of the Good pharmacovigilance practices (GVP).

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

EU PAS Register® number: Study Not Yet Registered
Study reference number (if applicable):

Section 1: Milestones	**Yes**	**No**	**N/A**	**Section Number**
1.1 Does the protocol specify timelines for				
1.1.1 Start of data collection[1]	☒	☐	☐	1
1.1.2 End of data collection[2]	☒	☐	☐	1
1.1.3 Progress report(s)	☐	☒	☐	
1.1.4 Interim report(s)	☒	☐	☐	1
1.1.5 Registration in the EU PAS Register®	☒	☐	☐	1
1.1.6 Final report of study results.	☒	☐	☐	1

[1] 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.
[2] Date from which the analytical dataset is completely available.

Comments:

Registration to EU PASS register pending

Section 2: Research question	**Yes**	**No**	**N/A**	**Section Number**
2.1 Does the formulation of the research question and objectives clearly explain:	☒	☐	☐	3
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)	☒	☐	☐	2.3
2.1.2 The objective(s) of the study?	☒	☐	☐	3
2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	4.2
2.1.4 Which hypothesis(-es) is (are) to be tested?	☐	☐	☒	
2.1.5 If applicable, that there is no *a priori* hypothesis?	☒	☐	☐	4.1.1

Comments:

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

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)	☒	☐	☐	4.1.1
3.2 Does the protocol specify whether the study is based on primary, secondary or combined data collection?	☒	☐	☐	4.9
3.3 Does the protocol specify measures of occurrence? (e.g., rate, risk, prevalence)	☒	☐	☐	4.5
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))	☒	☐	☐	4.5
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)	☒	☐	☐	6

Comments:

Section 4: Source and study populations	**Yes**	**No**	**N/A**	**Section Number**
4.1 Is the source population described?	☒	☐	☐	4.2
4.2 Is the planned study population defined in terms of:				
4.2.1 Study time period	☒	☐	☐	4.2.1
4.2.2 Age and sex	☐	☐	☒	
4.2.3 Country of origin	☒	☐	☐	4.1

Section 4: Source and study populations	**Yes**	**No**	**N/A**	**Section Number**
4.2.4 Disease/indication	☒	☐	☐	4.2
4.2.5 Duration of follow-up	☒	☐	☐	4.2
4.3 Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☒	☐	☐	4.2

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.

Section 5: Exposure definition and measurement	**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.

Section 6: Outcome definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
6.1 Does the protocol specify the primary and secondary (if applicable) outcome(s) to be investigated?	☒	☐	☐	3
6.2 Does the protocol describe how the outcomes are defined and measured?	☒	☐	☐	4.7.1

Section 6: Outcome definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
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)	☒	☐	☐	4.2.2
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)	☒	☐	☐	4.4
9.1.2 Outcomes? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics)	☒	☐	☐	4.4
9.1.3 Covariates and other characteristics?	☒	☐	☐	4.4
9.2 Does the protocol describe the information available from the data source(s) on:				

Section 9: Data sources	**Yes**	**No**	**N/A**	**Section Number**
9.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☒	☐	☐	4.4
9.2.2 Outcomes? (e.g. date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	4.4
9.2.3 Covariates and other characteristics? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, lifestyle)	☒	☐	☐	4.4
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))	☒	☐	☐	4.7.1
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 study will collect data from patient medical records.

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Section Number**
10.1 Are the statistical methods and the reason for their choice described?	☒	☐	☐	4.7
10.2 Is study size and/or statistical precision estimated?	☒	☐	☐	4.5
10.3 Are descriptive analyses included?	☒	☐	☐	4.7
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)	☒	☐	☐	Annex 4.8
11.2 Are methods of quality assurance described?	☒	☐	☐	4.8
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?	☒	☐	☐	4.9
12.1.2 Information bias?	☒	☐	☐	4.9
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)	☒	☐	☐	4.9

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?	☒	☐	☐	5
13.2 Has any outcome of an ethical review procedure been addressed?	☒	☐	☐	Annex 4.4
13.3 Have data protection requirements been described?	☒	☐	☐	Annex 4.7

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)?	☒	☐	☐	7
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	7

Comments:

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

Name of the main author of the protocol: PPD

Date: 29/July/2022

Signature: PPD

PARTICIPATING PHYSICIAN AGREEMENT

CARVYKTI (ciltacabtagene autoleucel)

Protocol 68284528MMY4009

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.

Coordinating Physician:

Name (typed or printed): _____

Institution and Address: _____

_____

_____

_____

Signature: _____ Date: _____

(Day Month Year)

Principal Participating Physician:

Name (typed or printed): _____

Institution and Address: _____

_____

_____

_____

Telephone Number: _____

Signature: _____ Date: _____

(Day Month Year)

Sponsor's Responsible Medical Officer (Main Author):

Name (typed or printed): PPD

Institution: Janssen-Cilag Italy

Signature: PPD PPD Date: 2022.10.14 11:19:09 +02'00' Versione di Adobe Acrobat Reader: 2020.013.20064 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.

Status: Approved CONFIDENTIAL - FOIA Exemptions Apply in U.S. 59

Protocol version: 2.0, Version date: 22 April 2022

Signature

User	Date	Reason
Oster-Gozet Laurence 155007523	14-Oct-2022 15:27:35 (GMT)	Document Approval