Janssen-Cilag International NV

Non-interventional Postauthorization Safety Study - Protocol

Postauthorization Safety Study Survey to Evaluate the Effectiveness of the Ciltacabtagene Autoleucel HCP Educational Program and the Product Handling Training

Protocol PCSONCA0014
Amendment 1

CARVYKTI® (ciltacabtagene autoleucel)

EU PAS Register Number: EUPAS1000000047

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Prepared by:	Janssen-Cilag Limited		
EDMS number:	EDMS-RIM-563838, 8.0		

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

Confidentiality Statement

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PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY	
Document	**Date**
Amendment 1	4 November 2024
Original Protocol	16 June 2023

Amendment 1 (4 November 2024)

Overall Rationale for the Amendment: The main rationale for this amendment is to align the protocol with the EU SmPC, and align milestones with those notified to and agreed with PRAC.

Section Number and Name	Description of Change	Brief Rationale
4. Abstract; 5. Milestones; 8.1. Study Design; 8.1.4. Recruitment and Eligibility Criteria; 8.2. Settings and Participant Population; 8.7. Data Analysis.	Updated milestones in line with PRAC agreement.	To bring the milestones in line with agreed timelines.
5. Milestones.	Included footnote explaining that during Wave 2, the study will continue in Wave 1 countries where new sites have been activated.	Due to the challenges for recruitment in this study, the MAH will continue the study in Wave 1 countries where new sites have been activated.
4. Abstract; 6.3. Ciltacabtagene Autoleucel.	Updated considerations on ciltacabtagene autoleucel from "it is being developed for multiple myeloma treatment" to "has been approved" for relapsed and refractory multiple myeloma treatment, per approved SmPC considerations.	Due to ciltacabtagene autoleucel approval in the EU.
6.3. Ciltacabtagene Autoleucel.	Included reference to CARTITUDE-4 regarding the use of ciltacabtagene autoleucel in less heavily pretreated patients.	Due to ciltacabtagene autoleucel approval for patients with 1 previous line of therapy.
6.3.1. Risk Minimization Measures.	Updated details for monitoring patients for signs and symptoms of neurologic events.	Updated per latest SmPC (September 2024).
1. PASS Information; 4. Abstract; 6.3. Ciltacabtagene Autoleucel; 6.3.1. Risk Minimization Measures; 6.3.2. Educational Materials and Overall Rationale for the Study; 7. Research Question and Objectives; Annex 3: Key Messages.	As per SmPC updates, "Secondary malignancy of T-cell origin" has been added as a new important identified risk.	Secondary malignancy of T-cell origin has been confirmed as an important identified risk with the use of CAR-T therapies such as ciltacabtagene autoleucel.
8.1.2. Target Participant Group Identification.	Removed reference to random sampling as a strategy to minimize bias.	Due to the challenges for recruitment in this study, the MAH will encourage all centers to join.
	Included footnote explaining the rationale for the MAH to encourage all centers to join the study.	Due to the limited number of sites utilizing CAR-T and the staggered activation of sites across countries.

	Added provision to include the Sponsor's local medical teams may circulate and/or follow up to increase survey engagement from local participants, while making sure to preserve the anonymity of survey takers and survey results.	To facilitate recruitment for this study.
8.1.4. Recruitment and Eligibility Criteria.	Removed provision that relevant consents will be sought prior to commencing the survey.	As the survey itself is already covered by the privacy notice in the contract, there is no need for a separated ICF.
8.2. Settings and Participant Population	Updated list of countries, now including (but not limited to) Germany, Austria, Switzerland, and the UK.	As ciltacabtagene autoleucel is already available or will shortly be available in those countries.
8.5 Study Size	Removed provision of survey completion period of approximately 4 to 5 months from the start of data collection in each market.	Due to phased launch approach across countries, the MAH is adding new sites to each country on an ongoing basis, hence the provision would hinder enrollment.
4. Abstract; 8.7. Data Analysis	Removed specific list of countries for the first wave of countries in which ciltacabtagene autoleucel is launched.	Due to dynamic timelines regarding ciltacabtagene autoleucel launch across countries.
Annex 3: Key Messages.	Per the last SmPC, key messages were updated.	Due to updated considerations available in the final SmPC (September 2024).
Throughout the protocol.	Updated "HCP" to "participant" or "individual".	For more accurate description of the study population, which may include participants who are not HCPs.
Throughout the protocol.	Minor changes (eg, formatting, or spelling) were made.	Minor errors were noted.

1. PASS INFORMATION

Title:	Postauthorization Safety Study Survey to Evaluate the Effectiveness of the Ciltacabtagene Autoleucel HCP Educational Program and the Product Handling Training
Protocol version:	5.0
Date of last version of the protocol:	16 June 2023
EU PAS Register No:	EUPAS1000000047
Active substance (INN common name):	Ciltacabtagene autoleucel
Pharmaco-therapeutic group (ATC Code):	L01XL05
Medicinal product(s):	CARVYKTI®
Product reference:	EMEA/H/C/005095
Procedure number:	EMEA/H/C/005095 MEA 007
Name of Marketing Authorization Holder(s)	Janssen-Cilag International NV
Joint PASS	No
Research question and objectives	To measure the effectiveness of the healthcare professional (HCP) Educational Program, an additional risk minimization measure intended to increase awareness about the risks of cytokine release syndrome (CRS) (including hemophagocytic lymphohistiocytosis), neurologic toxicity (including immune effector cell-associated neurotoxicity syndrome and other neurotoxicities), the risk of secondary malignancies of T-cell origin; as well as the potential risk of cell viability due to inappropriate handling or preparation of the product, and the HCP awareness of the need to provide patients of a patient CAR-T Journey Guide with its enclosed Patient Alert Card to improve their understanding of the risks associated with CAR-T therapy and how to better manage them
Countries of study	The survey is proposed to be conducted in selected countries where CARVYKTI® (ciltacabtagene autoleucel) has been approved and is commercially available, including the EU.
Author	Natalia Martín Suñé, MD

2. MARKETING AUTHORIZATION HOLDER(S)

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3. RESPONSIBLE PARTIES

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AMENDMENTS AND UPDATES

The Protocol Amendment Summary of Changes Table for the current amendment is located directly before Section 1 PASS Information.

4. ABSTRACT

Protocol Title: Postauthorization Safety Study Survey to Evaluate the Effectiveness of the Ciltacabtagene Autoleucel HCP Educational Program and the Product Handling Training (5.0, 4 November 2024)

Main Author: Natalia Martín Suñé, MD

Background and Rationale: Ciltacabtagene autoleucel employs chimeric antigen receptor (CAR) technology to genetically engineer autologous peripheral blood T-cells to identify and eliminate cells that express B-cell maturation antigen (BCMA), which is primarily expressed on late-stage B-cells, plasma cells, and malignant B-lineage cells. Ciltacabtagene autoleucel has been approved for the treatment of relapsed and refractory multiple myeloma for patients who have received at least one prior therapy, including an immunomodulatory agent and a proteasome inhibitor, have demonstrated disease progression on the last therapy, and are refractory to lenalidomide.

Due to risks inherently associated with CAR-T therapies such as cytokine release syndrome (CRS), neurologic toxicity, and secondary malignancy of T-cell origin; as well as the potential risk of decrease in cell viability due to inappropriate handling or preparation of the product, a healthcare professional (HCP) educational program was put in place to ensure healthcare professionals would be aware of these risks and how to minimize them. To evaluate the effectiveness of this HCP educational program, a survey is to be carried out to assess the awareness of the risks.

Research Question and Objectives: To measure the effectiveness of the HCP Educational Program, an additional risk minimization measure intended to increase awareness about the risks of CRS (including hemophagocytic lymphohistiocytosis [HLH]), neurologic toxicity (including immune effector cell-associated neurotoxicity syndrome [ICANS] and other neurotoxicities), and secondary malignancy of T-cell origin; the potential risk of cell viability due to inappropriate handling or preparation of the product; and the HCP awareness of the need to provide patients of a patient CAR-T Journey Guide with its enclosed Patient Alert Card to improve their understanding of the risks associated with CAR-T therapy and how to better manage them.

Study Design: A survey will be completed independently by ciltacabtagene autoleucel center participants to measure the effectiveness of the educational materials relating to safe and effective use of ciltacabtagene autoleucel.

Participants will be asked to participate in the survey to assess knowledge and understanding of important identified and important potential risks of ciltacabtagene autoleucel treatment, in accordance with the educational materials. Participants can include physicians, pharmacists, nurses and ward staff. These include participants from CAR-T centers certified by the sponsor for ciltacabtagene autoleucel treatment and involved in prescribing, dispensing, administering, transporting, storing, thawing, preparing or handling of ciltacabtagene autoleucel, or managing ciltacabtagene autoleucel treated patients.

Setting and Participant Population: The main survey will be conducted in selected countries within 24 months of availability of the approved educational materials and where there will be an adequate projected number of participants. The following participants from the CAR-T centers certified by the sponsor for ciltacabtagene autoleucel treatment will be invited to participate in the survey:

- Participants involved in the prescription and management (ie, dispensing or administration) of ciltacabtagene autoleucel treatment.
- Participants involved in the transport, storage, thawing, preparation, or handling of ciltacabtagene autoleucel.

All participants will be independently recruited through a third-party vendor. Participation in this survey will be completely voluntary. No patients will participate in the survey.

Variables: The key messages to be tested by the survey include but are not limited to messages about prescription and management of ciltacabtagene autoleucel will carry a heavier weight for the results for participants involved in these processes (ie, physicians and nurses). For CRS management, participants will be referred to the CRS management table in the SmPC. Additionally, key messages about transport, storage, thawing, preparation, or handling of ciltacabtagene autoleucel will carry a heavier weight for the results for participants involved in these processes (ie, pharmacists and ward staff).

Data Sources: The data source for this survey will be the online questionnaire used to survey participants involved in the prescription, management, transport, storage, thawing, preparation, or handling of ciltacabtagene autoleucel treatment.

Study Size: The proposed sample is designed to be representative of ciltacabtagene autoleucel prescribers and handlers in selected countries, including in the EU. The number of required completed surveys has been estimated based on the assumption that eligible CAR-T centers certified by the sponsor will be limited during the first years. Within those centers, the sponsor will provide relevant details of the eligible participants who received appropriate training and the educational materials.

The goal for the survey is to obtain a total target of 220 completed surveys across the selected countries. This sample has been determined based on a number of criteria including:

- Ability to reflect a representative view across participants involved in prescribing and management of patients with ciltacabtagene autoleucel in the markets in scope
- Feasibility of survey completion within a reasonable time period (approximately 4 to 5 months from the start of data collection in each market), and in light of the limited number of centers certified for CAR-T treatment by the sponsor
- Acceptable statistical confidence to support the intended analysis

From the total sample of 220 completed surveys, the target will be to achieve a minimum of 100 in each of the two major sub-categories of participants (those involved in prescription and

management, and those involved in the transport, storage, thawing, preparation, or handling of ciltacabtagene autoleucel). Achievement of this stratification will be dependent on having sufficient eligible participants within each sub-category; the sample stratification may need to be adjusted once the total number of eligible participants in each sub-category is known. Additional analysis by participant role (physicians, nurses, pharmacists) will also be conducted with a minimum enrolment of 30 participants in each role to allow valid statistical analysis.

Data Analysis: A minimum total score of ≥80% across all survey questions will be considered indicative of satisfactory effectiveness. This threshold represents the 'vast majority' of correct responses and is consistent with the threshold in previous surveys of risk minimization measures conducted by the sponsor in selected countries, including in the EU. The criteria for success will differ if the responders are involved in prescribing/administering or in thawing/handling ciltacabtagene autoleucel, giving more weight to questions relevant to each specialty.

Upon completion of the survey by the required number of sample respondents, responses will be aggregated and tabulated. Summary results for the overall achievement of a satisfactory effectiveness score and 95% Clopper-Pearson (exact) CI will be presented for absolute numbers of respondents and percentages of the total sample. For each question, the proportion of respondents answering it correctly will also be presented. The first wave of countries in which ciltacabtagene autoleucel is launched, will provide an interim analysis 30 months after the availability of the approved educational materials. The final analysis will be available 4 years after the availability of the approved educational materials.

5. MILESTONES

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

Milestone:	Planned Date:
Protocol submission	3 months after EC decision
Initiation of survey (Wave 1)	Within 24 months of availability of the approved educational materials in selected countries
Initial report	30 months after availability of the approved educational materials. Updates will also be reported in the PBRER/PSUR
Initiation of survey (Wave 2)[a]	Within 3.5 years of availability of the approved educational materials in selected countries
Final report of study results	4 years after availability of the approved educational materials. Updates will also be reported in the PBRER/PSUR

[a] During Wave 2, the study will continue in Wave 1 countries where new sites have been activated.

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviations

ADR	adverse drug reaction
AML	acute myeloid leukemia
BCMA	B-cell maturation antigen
CAR	chimeric antigen receptor
CI	confidence interval
CNS	central nervous system
CRS	cytokine release syndrome
EMA	European Medicines Agency
EV	EudraVigilance
FAERS	FDA adverse event reporting system
FDA	Food and Drug Administration
GVP	Good Pharmacovigilance Practices
HCP	healthcare professional
HLH	hemophagocytic lymphohistiocytosis
ICANS	immune effector cell-associated neurotoxicity syndrome
ICE	Immune Effector Cell-Associated Encephalopathy
Igs	immunoglobulins
IMiDs	immunomodulatory agents
LN2	liquid nitrogen
MAH	Marketing Authorization Holder
MDS	myelodysplastic syndrome
MedDRA	Medical Dictionary for Regulatory Activities
NNH	number needed to harm
PRAC	Pharmacovigilance Risk Assessment Committee
RMP	risk management plan
SmPC	Summary of Product Characteristics
WHO	World Health Organization

Definition of Term(s)

Post Authorization Safety Study (PASS)	Any study relating to an authorized medicinal product conducted with the aim of identifying, characterizing or quantifying a safety hazard, confirming the safety profile of the medicinal product, or of measuring the effectiveness of risk management measures

6. BACKGROUND AND RATIONALE

6.1. Multiple Myeloma

Multiple myeloma is a malignant plasma cell disorder that accounts for approximately 10% of all hematologic cancers (Kyle 2008). Multiple myeloma is characterized by production of monoclonal proteins composed of pathological immunoglobulins (Igs) or fragments of such, which have lost their function (Kyle 2009; Palumbo 2011). The proliferation of multiple myeloma cells leads to subsequent displacement of normal bone marrow hematopoietic precursors and overproduction of monoclonal proteins. Characteristic hallmarks of multiple myeloma include osteolytic lesions, anemia, increased susceptibility to infections, hypercalcemia, renal insufficiency or failure, and neurological complications (Korde 2011; Palumbo 2011).

Multiple myeloma is the sixteenth most common cause of cancer death in Europe, with approximately 30,860 deaths from multiple myeloma in 2018 (1.7% of total cancer deaths) (Bray 2018).

6.2. Treatment Options

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

6.3. Ciltacabtagene Autoleucel

CARVYKTI® (ciltacabtagene autoleucel, also known as JNJ-68284528, and LCAR-B38M CAR-T cells) is a genetically modified autologous T-cell immunotherapy that binds to B-cell maturation antigen (BCMA). Ciltacabtagene autoleucel employs chimeric antigen receptor (CAR) technology to genetically engineer autologous peripheral blood T-cells to identify and eliminate cells that express BCMA, which is primarily expressed on late-stage B-cells, plasma cells, and malignant B-lineage cells. Ciltacabtagene autoleucel has been approved for the treatment of relapsed and refractory multiple myeloma for patients who have received at least one prior therapy, including an immunomodulatory agent and a proteasome inhibitor, have demonstrated disease progression on the last therapy, and are refractory to lenalidomide (CARVYKTI® SmPC 2024).

Treatment with ciltacabtagene autoleucel led to early, deep, and durable responses in heavily pretreated patients with multiple myeloma with a manageable safety profile in the CARTITUDE 1 study (Berdeja 2021) and CARTITUDE-4 study in less heavily pretreated patients (San-Miguel 2023). Due to risks inherently associated with CAR-T therapies such as cytokine release syndrome (CRS), neurologic toxicity (Brudno 2016), and secondary malignancy of T-cell origin (CARVYKTI® SmPC 2024); as well as the important potential risk of cell viability decrease due to inappropriate handling or preparation of the product, a healthcare professional (HCP)

educational program was put in place to ensure healthcare professionals would be aware of these risks and how to minimize them. To evaluate the effectiveness of this HCP educational program, a survey is to be carried out to assess the awareness of the risks.

6.3.1. Risk Minimization Measures

A key risk of ciltacabtagene autoleucel is the induction of CRS (including hemophagocytic lymphohistiocytosis [HLH]) due to cytokines released as a result of the effects from the infused CAR-T cells (Brudno 2016). This can be mitigated, among others, by patient monitoring and tocilizumab treatment. Relevant HCPs should have tocilizumab (or a suitable alternative measure, in the exceptional case where tocilizumab is not available due to a shortage listed in the European Medicines Agency [EMA] shortage catalogue) and emergency equipment available prior to infusion and during the recovery period. Patients should be monitored daily for signs and symptoms of CRS for 14 days at a qualified clinical facility after ciltacabtagene autoleucel dose and periodically for an additional 2 weeks after infusion, for signs and symptoms of CRS, neurologic events and other toxicities (please refer to the "Ciltacabtagene autoleucel Information for CAR-T Centre Healthcare Providers" mentioned below and the Summary of Product Characteristics [CARVYKTI® SmPC 2024]).

Additionally, based on review of the cumulative weight of evidence from available sources, it became apparent that patients treated with ciltacabtagene autoleucel may develop secondary malignancies. T-cell malignancies have been reported following treatment of hematological malignancies with a BCMA- or CD19- directed CAR-T-cell therapy, including ciltacabtagene autoleucel. T-cell malignancies, including CAR-positive malignancies, have been reported within weeks and up to several years following administration of a CD19- or BMCA-, directed CAR-T-cell therapy. As such, patients treated with ciltacabtagene autoleucel should be monitored life-long for secondary malignancies. In the event a secondary malignancy occurs, the company should be contacted to obtain instructions on patient samples to collect for testing (CARVYKTI® SmPC 2024). The SmPC provides information regarding this risk, including instructions that patients should be monitored life-long for secondary malignancies, and that the sponsor should be contacted to obtain instructions on collection of patient samples (CARVYKTI® SmPC 2024).

There is also a risk of ciltacabtagene autoleucel inducing neurologic toxicities (including immune effector cell-associated neurotoxicity syndrome [ICANS] and other neurotoxicities), whose pathophysiology is unclear (Belin 2020), and can be mitigated by reducing the tumor burden with bridging therapy and monitoring. Key recommendations to reduce this risk include reducing baseline disease burden with bridging therapy prior to infusion in patients with high tumor burden and monitoring patients daily for signs and symptoms of neurologic events for 14 days after ciltacabtagene autoleucel infusion at a qualified clinical facility, and then periodically for an additional 2 weeks after ciltacabtagene autoleucel infusion (CARVYKTI® SmPC 2024). Following this period, patients will be asked to enrol in a registry for at least 15 years in order to better understand the long-term effects of ciltacabtagene autoleucel.

Finally, in terms of logistics, a risk of decrease in cell viability due to inappropriate handling or preparation of ciltacabtagene autoleucel exists. This may be minimized by following the instructions indicated in the Summary of Product Characteristics.

In light of this, the Marketing Authorization Holder (MAH) (Janssen-Cilag International N.V., Belgium; hereafter referred to as 'Sponsor') developed educational materials for all HCPs involved in prescribing, dispensing and administering ciltacabtagene autoleucel to patients, as well as HCPs involved in the transport, storage, thawing, preparation, or handling of ciltacabtagene autoleucel.

6.3.2. Educational Materials and Overall Rationale for the Study

To increase understanding of the effective and safe use of ciltacabtagene autoleucel, the sponsor shall ensure that all HCPs who are expected to prescribe, dispense, transport, store, thaw, prepare or handle ciltacabtagene autoleucel will have access to/will be provided with the educational materials below:

- Ciltacabtagene autoleucel Information for CAR-T Centre Healthcare Providers: Guide for HCPs to advise of the risks of CRS (including HLH) and neurologic toxicity (including ICANS and other neurotoxicities) and how to minimize these.

  This material is created for HCPs to increase awareness of CRS (including HLH), neurotoxicity (including ICANS and other neurotoxicity) and secondary malignancy of T-cell origin; and their appropriate monitoring, prevention, and management, including the importance of on-site availability of tocilizumab before treating a patient. It should facilitate patient counseling using relevant information and provide guidance on reporting these serious adverse reactions associated with ciltacabtagene autoleucel.

- Ciltacabtagene autoleucel Handling Guide: Guide for HCPs to advise of the risk of a decrease in cell viability due to inappropriate handling or preparation of ciltacabtagene autoleucel, and how to avoid this risk.

  This material is created for HCPs to increase awareness of the important potential risk of a decrease in cell viability due to inappropriate handling or preparation of ciltacabtagene autoleucel, and to provide guidance on precautions to take before handling or administering ciltacabtagene autoleucel (ie, how to check ciltacabtagene autoleucel prior to administration, how to thaw, and how to administer).

- My CAR-T Journey Guide: Guide for patients containing relevant information about the ciltacabtagene autoleucel treatment journey, from cell harvesting to infusion and monitoring.

  This material is created to provide patients with additional information to help patients improve their understanding of some of the risks involved with CAR-T cell therapy and help them manage these risks better. HCPs will provide patients with this document, which includes a Patient Alert Card; HCPs will be evaluated on their awareness of the existence of the Patient Alert Card, as well as the intention and time of providing it to the patients

7. RESEARCH QUESTION AND OBJECTIVES

To measure the effectiveness of the HCP Educational Program, an additional risk minimization measure intended to increase awareness about the risks of CRS (including HLH), neurologic toxicity (including ICANS and other neurotoxicities) and secondary malignancy of T-cell origin; the potential risk of cell viability decrease due to inappropriate handling or preparation of the product; and the HCP awareness of the need to provide patients of a patient CAR-T Journey Guide with its enclosed Patient Alert Card to improve their understanding of the risks associated with CAR-T therapy and how to better manage them.

8. RESEARCH METHODS

8.1. Study Design

A survey will be completed independently by ciltacabtagene autoleucel center participants to measure the effectiveness of the educational materials relating to the safe and effective use of ciltacabtagene autoleucel. For more information on the educational materials, refer to Section 6.3.2.

Participants will be asked to take part in the survey to assess knowledge and understanding of important identified and important potential risks of ciltacabtagene autoleucel treatment, in accordance with the educational materials. Participants can include physicians, pharmacists, nurses and ward staff. These include HCPs from CAR-T centers certified by the sponsor for ciltacabtagene autoleucel treatment and involved in prescribing, dispensing, administering, transporting, storing, thawing, preparing or handling of ciltacabtagene autoleucel, or managing ciltacabtagene autoleucel treated patients.

The main survey will be conducted in selected countries where the approved ciltacabtagene autoleucel educational materials have been available within 24 months, as described in Section 8.2.

Prior to commencing the main survey a small pilot test of the questionnaire will be performed in the first launch market to validate the questionnaire. In the pilot test, 2 separate HCPs will complete the online survey with a trained moderator observing via a screen sharing platform, to identify any questions that may need additional clarity or further instruction, and to check the survey programming and logic is working correctly and capturing the required data. Feedback received from the pilot test will be used to ensure that the main online quantitative survey will provide data relevant to meeting the survey objectives.

8.1.1. Suitable Methodology

An external third-party vendor experienced in conducting multi-country effectiveness surveys will be contracted by the sponsor to conduct the survey. The contract organization, Adelphi Research, is responsible for the operational conduct of the survey including recruiting of the participants, facilitating data collection and ensuring adherence to local regulations including data privacy. In addition, the contract organization, Adelphi Research, will draft the study documents, perform analysis and produce planned interim and final study reports. The survey will be conducted in

accordance with the EU Good Pharmacovigilance Practices (GVP) VIII guidelines and GVP Module XVI Guidelines.

The main online quantitative phase, referred to as the survey, will be conducted in selected countries and CAR-T sites certified by the sponsor for ciltacabtagene autoleucel treatment, and where commercial ciltacabtagene autoleucel has been used. Country selection will be based on whether there will be an adequate projected number of participants who have received ciltacabtagene autoleucel educational materials.

The most effective design for this survey involves an online quantitative approach to provide representative numbers of participants involved in treatment with ciltacabtagene autoleucel. An online methodology has a number of associated advantages including covering a wide geographical spread and flexibility for participants to complete the survey at a convenient time, in addition to allowing participants to be completely honest without feeling like they are being questioned or judged by an interviewer. A quantitative online survey is considered the most suitable methodology over a qualitative method, as the latter would not allow for robust sample sizes and therefore results would only be of an indicative/directional nature.

8.1.2. Target Participant Group Identification

The survey will include participants from CAR-T centers certified by the sponsor who have received ciltacabtagene autoleucel educational materials, as described in Section 8.1.

All participants will be independently recruited through a third party. The participants chosen will remain anonymous and will be checked for eligibility criteria (as described in Section 8.1.4). The participants included in the survey will be those involved in prescribing, dispensing, administering, transporting, storing, thawing, preparing or handling ciltacabtagene autoleucel, or managing ciltacabtagene autoleucel treated patients.

Where available, and in line with data privacy regulations, lists of trained participants from the certified centers will be provided to the recruitment provider by the Marketing Authorization Holder. To minimize sample bias, all trained HCPs within the selected centers will be invited to participate.[a] All identified individuals within a certified center will be invited to participate in the survey, with no additional selection criteria applied, to ensure a balanced and representative sample of those involved in prescribing, managing, dispensing, administering transporting, storing, thawing, preparing or handling ciltacebtagene autoleucel.

For all participants, the survey introduction will capture all required consents from the participant and there will be screening questions to confirm their eligibility to participate. All those who meet the inclusion criteria will be invited to complete the main questionnaire (until the required sample size is achieved) to avoid introducing any sample bias. Up to 3 reminder emails (1 per week) will be sent to any participants who have been invited to participate but have not yet completed the full

[a] Due to the limited number of sites utilizing CAR-T and the staggered activation of sites across countries, the Marketing Authorization Holder is encouraging all centers to join in the study.

questionnaire. The Sponsor's local medical teams may circulate and/or follow up to increase survey engagement from local participants, while making sure to preserve the anonymity of survey takers and survey results. Following this, the survey will remain accessible to them until the required sample size is achieved.

8.1.3. Questionnaire Design

The questionnaire will be developed to assess participants' knowledge and understanding of the important identified and important potential risks of ciltacabtagene autoleucel treatment outlined in the educational materials mentioned on Section 6.3.2. Patients' knowledge and understanding of the ciltacabtagene autoleucel important identified and important potential risks included in the CAR-T Journey Guide will be assessed by surveying participants.

The questionnaires will consist of closed and/or multiple-choice questions. The survey will be programmed so that the participants can only progress forward through the questions and will not be able to go back to revise previously given answers. The participant is therefore unable to alter answers once responses have been given. Every question must be answered for the participant to progress forward through the survey. The survey will be presented in the local language. Questions will be translated from English to the local language and then thoroughly checked by native language speakers to ensure the translator correctly understood the questions.

8.1.4. Recruitment and Eligibility Criteria

An external third-party vendor will be responsible for the following activities for the study:

- Contacting participants involved in the prescription, patient management and product handling of ciltacabtagene autoleucel in patients with multiple myeloma and inviting them to participate in the survey. Participants will include physicians, pharmacists, nurses and ward staff across identified markets within 24 months of availability of the approved educational materials
- Securing informed consent for participation. All individual-level data will be protected by confidentiality measures and reported in aggregate form only

The survey will capture the following classification information:

- Country/region of participant
- Type of participant: physicians, nurses, ward staff and pharmacists (when applicable)
- Role in the prescription, management or handling of ciltacabtagene autoleucel

A screening questionnaire will be used to assess whether an individual meets the participation criteria and can proceed to the main questionnaire.

8.2. Setting and Participant Population

The main survey will be conducted in selected countries within 24 months of availability of the approved educational materials and where there will be an adequate projected number of participants, including (but not limited to) Germany, Austria, Switzerland, and the UK.

The following participants from the CAR-T centers certified by the sponsor for ciltacabtagene autoleucel treatment will be invited to participate in the survey:

- Participants involved in the prescription and management (ie, dispensing or administration) of ciltacabtagene autoleucel treatment.
- Participants involved in the transport, storage, thawing, preparation, or handling of ciltacabtagene autoleucel.

All participants will be independently recruited through a third-party vendor. Participation in this survey will be completely voluntary. No patients will participate in the survey.

8.3. Variables

The key messages to be tested by the survey include but are not limited to, those listed in ANNEX 3.

8.4. Data Sources

The data source for this survey will be the online questionnaire used to survey participants involved in the prescription, management, transport, storage, thawing, preparation, or handling of ciltacabtagene autoleucel treatment.

8.5. Study Size

The proposed sample is designed to be representative of ciltacabtagene autoleucel prescribers and handlers in selected countries, including in the EU.

The number of required completed surveys has been estimated based on the assumption that eligible CAR-T centers certified by the Sponsor will be limited during the first years. Within those centers, the sponsor will provide relevant details of the eligible participants who received appropriate training and the educational materials.

Satisfactory effectiveness of the survey is defined as a minimum of 80% of respondents achieving a satisfactory effectiveness score across all survey questions. Applying an 80% threshold, the exact 95% Clopper-Pearson (exact) confidence intervals (CI) will be as follows for the sample size of 30, 50, 100 and 220 participants:

Table 1: Clopper-Pearson (Exact) Confidence Intervals For Varying Sample Sizes

Sample size	Proportion of sample achieving satisfactory effectiveness score	Number of surveys achieving satisfactory effectiveness score	Exact 95% CIs
30	80%	24	61.4 – 92.3
50	80%	40	66.3 – 90.0
100	80%	80	70.8 - 87.3
220	80%	176	74.1–85.1

Clopper-Pearson (exact) 2-sided CIs are used to indicate that for an estimated comprehension level (ie, proportion achieving a satisfactory effectiveness score) the true population level of

comprehension is at least as high as the lower limit of the 95% CI and may be as high as the upper limit of the 95% CI.

As such, the goal for the survey is to obtain a total target of 220 completed surveys across the selected countries. This sample has been determined based on a number of criteria including:

- Ability to reflect a representative view across participants involved in prescribing and management of patients with ciltacabtagene autoleucel in the markets in scope
- Feasibility of survey completion within a reasonable time period, and in light of the limited number of centers certified for CAR-T treatment by the sponsor
- Acceptable statistical confidence to support the intended analysis

From the total sample of 220 completed surveys, the target will be to achieve a minimum of 100 in each of the two major sub-categories of participants (those involved in prescription and management, and those involved in the transport, storage, thawing, preparation, or handling of ciltacabtagene autoleucel). This will be achieved by allowing a maximum of 120 completed surveys from each sub-category, with the survey programmed to prevent access to additional participants once that threshold is reached. Achievement of this stratification will be dependent on having sufficient eligible participants within each sub-category; the sample stratification may need to be adjusted once the total number of eligible participants in each sub-category is known.

Additional analysis by participant role (physicians, nurses, pharmacists) will also be conducted with a minimum enrolment of 30 participants in each role to allow valid statistical analysis.

Clopper-Pearson (exact) CIs for these sample sizes are included in Table 1.

8.6. Data Management

An external third-party vendor will perform rigorous ‘real-time’ checks to ensure that the data collected are valid and of a high quality. These checks will involve:

- Reviewing the length of time participants take to complete sections of the survey, as well as total survey length
- Looking at patterned responses to questions

8.7. Data Analysis

A minimum total score of ≥80% across all survey questions will be considered indicative of satisfactory effectiveness. This threshold represents the ‘vast majority’ of correct responses and is consistent with the threshold in previous surveys of risk minimization measures conducted by the sponsor in selected countries, including in the EU. The criteria for success will differ if the responders are involved in prescribing/administering or in thawing/handling ciltacabtagene autoleucel, giving more weight to questions relevant to each specialty. Individual survey questions will have different weightings applied according to participant role, to reflect the importance and relevance of questions to specific roles. For example, questions relating to storage and thawing will have a higher weight for pharmacists than for nurses or prescribing specialists. However, the

total achievable score for each HCP role will be consistent so that the overall criteria for success remains as individuals achieving a total survey score of ≥80%. The delay from any survey being sent until collection of the survey results will be captured when possible to investigate any potential bias due to the time passed between training completion and survey submission.

Upon completion of the survey by the required number of respondents, responses will be aggregated and tabulated. Summary results for the overall achievement of a satisfactory effectiveness score and 95% Clopper-Pearson (exact) CI will be presented for absolute numbers of respondents and percentages of the total sample. For each question, the proportion of respondents answering correctly it will also be presented. Separate effectiveness analysis will also be conducted on each of the major sub-categories of participants (those involved in prescription and management, and those involved in the transport, storage, thawing, preparation, or handling). Should the proportion of participants in each sub-category in the sample differ significantly from the proportion in the total eligible HCP population, weighting can be applied to the sample to align the proportions with the latter.

The first wave of countries in which ciltacabtagene autoleucel is launched, will provide an interim analysis 30 months after the availability of the approved educational materials. The final analysis will be available 4 years after availability of the approved educational materials.

8.8. Quality Control

A unique online survey link will be generated when each participant is invited to take part in the survey. This link can only be accessed and completed once by the participant, preventing multiple survey completions from one participant.

To accurately assess participants' knowledge, care will be taken in drafting survey questions to avoid raising any implication that affirmative guesses would probably be 'correct', which is sometimes observed when a series of yes/no agreement questions are posed to survey participants. The most practical and least intrusive method for achieving this is to provide multiple-choice questions where the participant may choose a number of possible answers from a list. In addition, participants will be offered the opportunity to select 'I don't know' as a response.

As an additional quality control measure, where multiple answers are offered, the order of presentation will be rotated. Routing and logic checks within the questionnaires will ensure that answers will be logical and correct, thereby enhancing data accuracy and minimizing the risk of missing data.

8.9. Limitations of the Research Methods

A quantitative limitation of the research methods is recognized within this study as the number of evaluated participants is representative of the whole, ie, it is not feasible to survey every single participant involved in ciltacabtagene autoleucel prescription and treatment management across each country in the study.

The potential for selection bias of participating respondents in a survey is an inherent bias/limitation to any study based on volunteer participation. To quantify any selection bias, the distribution of each eligibility criterion of respondents (country/region, specialty [when applicable] and role [in prescription, management or handling of ciltacabtagene autoleucel]) will be compared between invited participants who responded and those who did not. The collection of data on non-respondents is not always possible due to absence of response.

9. PROTECTION OF HUMAN SUBJECTS

This survey will be provided to participants involved in the prescription, management or handling of ciltacabtagene autoleucel only. No patients will participate in this survey.

The collection and processing of personal data from survey respondents will be limited to those data that are necessary to fulfill the objectives of the study. Respondents will be anonymized, retaining professional group (ie, physicians, pharmacists, nurses or ward staff), setting and country.

The external third party vendor conducting the survey will at all times comply with the European Data Protection Directive.

10. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

No adverse events will be collected or reported within this study. No patients will participate in the survey and no open text responses will be available to respondents for reporting other information.

However in case of any adverse event related to any Janssen product being reported by the HCP participating in this survey to the third party vendor overseeing and administering the survey, the third party vendor is obliged to report the event directly to the sponsor in accordance with agreed timelines

11. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

The results of the study will be reported in a report generated by the sponsor. The report will contain data collected from all participants in the study and will be submitted to EMA according to the agreed timelines. The sponsor will register and/or disclose the existence of and the results of clinical studies as required by law. All information, including but not limited to information regarding ciltacabtagene autoleucel or the sponsor's operations, and any data generated as a result of this study are considered confidential and remain the sole property of the sponsor.

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ANNEX 1: STAND-ALONE DOCUMENTS AND ADDITIONAL INFORMATION

Annex 1.1: List of Standalone Documents

Title	Reference No	Date
Survey questionnaire	EDMS-RIM-822131	

ANNEX 2: ENCEPP CHECKLIST FOR STUDY PROTOCOLS

Section 1: Research question	Yes	No	N/A	Page Number(s)
1.1 Does the formulation of the research question clearly explain:				
1.1.1 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)	☐	☐	☒	
1.1.2 The objectives of the study?	☐	☐	☒	
1.2 Does the formulation of the research question specify:				
1.2.1 The target population? (i.e. population or subgroup to whom the study results are intended to be generalized)	☐	☐	☒	
1.2.2 Which formal hypothesis(-es) is (are) to be tested?	☐	☐	☒	
1.2.3 if applicable, that there is no a priori hypothesis?	☐	☐	☒	

Comments:

Section 2: Source and study populations	Yes	No	N/A	Page Number(s)
2.1 Is the source population described?	☐	☐	☒	
2.2 Is the planned study population defined in terms of:				
2.2.1 Study time period?	☐	☐	☒	
2.2.2 Age and sex?	☐	☐	☒	
2.2.3 Country of origin?	☐	☐	☒	
2.2.4 Disease/indication?	☐	☐	☒	
2.2.5 Co-morbidity?	☐	☐	☒	
2.2.6 Seasonality?	☐	☐	☒	
2.3 Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☐	☐	☒	

Comments:

Section 3: Study design	Yes	No	N/A	Page Number(s)
3.1 Does the protocol specify the primary and secondary (if applicable) endpoint(s) to be investigated?	☐	☐	☒	
3.2 Is the study design described? (e.g. cohort, case-control, randomized controlled trial, new or alternative design)	☐	☐	☒	
3.3 Does the protocol describe the measure(s) of effect? (e.g. relative risk, odds ratio, deaths per 1000 person-years, absolute risk, excess risk, incidence rate ratio, hazard ratio, number needed to harm (NNH) per year)	☐	☐	☒	
3.4 Is sample size considered?	☐	☐	☒	
3.5 Is statistical power calculated?	☐	☐	☒	

Comments:

Section 4: Data sources	Yes	No	N/A	Page Number(s)
4.1 Does the protocol describe the data source(s) used in the study for the ascertainment of:				
4.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview, etc)	☐	☐	☒	
4.1.2 Endpoints? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics, etc)	☐	☐	☒	
4.1.3 Covariates?	☐	☐	☒	
4.2 Does the protocol describe the information available from the data source(s) on:				
4.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☐	☐	☒	
4.2.2 Endpoints? (e.g. date of occurrence, multiple event, severity measures related to event)	☐	☐	☒	
4.2.3 Covariates? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, life style, etc.)	☐	☐	☒	
4.3 Is the coding system described for:				
4.3.1 Diseases? (e.g. International Classification of Diseases (ICD)-10)	☐	☐	☒	
4.3.2 Endpoints? (e.g. Medical Dictionary for Regulatory Activities (MedDRA) for adverse events)	☐	☐	☒	
4.3.3 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC)Classification System)	☐	☐	☒	
4.4 Is the linkage method between data sources described? (e.g. based on a unique identifier or other)	☐	☐	☒	

Comments:

Section 5: Exposure definition and measurement	Yes	No	N/A	Page Number(s)
5.1 Does the protocol describe how exposure is defined and measured? (e.g. operational details for defining and categorising exposure)	☐	☐	☒	
5.2 Does the protocol discuss the validity of exposure measurement? (e.g. precision, accuracy, prospective ascertainment, exposure information recorded before the outcome occurred, use of validation sub-study)	☐	☐	☒	
5.3 Is exposure classified according to time windows? (e.g. current user, former user, non-use)	☐	☐	☒	
5.4 Is exposure classified based on biological mechanism of action?	☐	☐	☒	
5.5 Does the protocol specify whether a dose-dependent or duration-dependent response is measured?	☐	☐	☒	

Comments:

Section 6: Endpoint definition and measurement	Yes	No	N/A	Page Number(s)
6.1 Does the protocol describe how the endpoints are defined and measured?	☐	☐	☒	
6.2 Does the protocol discuss the validity of endpoint measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, prospective or retrospective ascertainment, use of validation sub-study)	☐	☐	☒	

Comments:

Section 7: Biases and Effect modifiers	Yes	No	N/A	Page Number(s)
7.1 Does the protocol address: 7.1.1 Selection biases?	☐	☐	☒	
7.1.2 Information biases? (e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods)	☐	☐	☒	
7.2 Does the protocol address known confounders? (e.g. collection of data on known confounders, methods of controlling for known confounders)	☐	☐	☒	
7.3 Does the protocol address known effect modifiers? (e.g. collection of data on known effect modifiers, anticipated direction of effect)	☐	☐	☒	
7.4 Does the protocol address other limitations?	☐	☐	☒	

Comments:

Section 8: Analysis plan	Yes	No	N/A	Page Number(s)
8.1 Does the plan include measurement of absolute effects?	☐	☐	☒	
8.2 Is the choice of statistical techniques described?	☐	☐	☒	
8.3 Are descriptive analyses included?	☐	☐	☒	
8.4 Are stratified analyses included?	☐	☐	☒	
8.5 Does the plan describe the methods for identifying: 8.5.1 Confounders?	☐	☐	☒	
8.5.2 Effect modifiers?	☐	☐	☒	
8.6 Does the plan describe how the analysis will address: 8.6.1 Confounding?	☐	☐	☒	
8.6.2 Effect modification?	☐	☐	☒	

Comments:

Section 9: Quality assurance, feasibility and reporting	Yes	No	N/A	Page Number(s)
9.1 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	☐	☐	☒	
9.2 Are methods of quality assurance described?	☐	☐	☒	
9.3 Does the protocol describe quality issues related to the data source(s)?	☐	☐	☒	
9.4 Does the protocol discuss study feasibility? (e.g. sample size, anticipated exposure, duration of follow-up in a cohort study, patient recruitment)	☐	☐	☒	
9.5 Does the protocol specify timelines for				
9.5.1 Start of data collection?	☐	☐	☒	
9.5.2 Any progress report?	☐	☐	☒	
9.5.3 End of data collection?	☐	☐	☒	
9.5.4 Reporting? (i.e. interim reports, final study report)	☐	☐	☒	
9.6 Does the protocol include a section to document future amendments and deviations?	☐	☐	☒	
9.7 Are communication methods to disseminate results described?	☐	☐	☒	
9.8 Is there a system in place for independent review of study results?	☐	☐	☒	

Comments:

Section 10: Ethical issues	Yes	No	N/A	Page Number(s)
10.1 Have requirements of Ethics Committee/Institutional Review Board approval been described?	☐	☐	☒	
10.2 Has any outcome of an ethical review procedure been addressed?	☐	☐	☒	
10.3 Have data protection requirements been described?	☐	☐	☒	

Comments:

ANNEX 3: KEY MESSAGES

Awareness and understanding of the following ciltacabtagene autoleucel key messages are proposed to be tested by the effectiveness survey, with answers relating to key messages relevant to specific functions carrying a more important weight for the overall scoring.

As such, key messages about prescription and management of ciltacabtagene autoleucel will carry a heavier weight for the results for HCPs involved in these processes (ie, physicians and nurses), and are described in Table 2. For CRS management, participants will be referred to the CRS management table in the SmPC. Additionally, key messages about transport, storage, thawing, preparation, or handling of ciltacabtagene autoleucel will carry a heavier weight for the results for HCPs involved in these processes (ie, pharmacists and ward staff), and are described in Table 3.

Table 2: Key Messages to be Tested for Participants Involved in Prescription and Management of Ciltacabtagene Autoleucel

Key Message:	Supporting Material(s):
Patients treated with ciltacabtagene autoleucel may develop secondary malignancies. T-cell malignancies have been reported following treatment of haematological malignancies with a BCMA- or CD19- directed CAR-T-cell therapy, including ciltacabtagene autoleucel. T-cell malignancies, including CAR-positive malignancies, have been reported within weeks and up to several years following administration of a CD19- or BMCA-, directed CAR-T-cell therapy. There have been fatal outcomes.	Ciltacabtagene autoleucel Information for CAR-T Centre Healthcare Providers
Patients should be monitored life-long for secondary malignancies. In the event a secondary malignancy occurs, the company should be contacted to obtain instructions on patient samples to collect for testing.	Ciltacabtagene autoleucel Information for CAR-T Centre Healthcare Providers
Ensure at least 1 dose of tocilizumab is available on-site prior to ciltacabtagene autoleucel infusion, with access to an additional dose within 8 hours of each previous dose. In the exceptional case where tocilizumab is not available due to a shortage that is listed in the European Medicines Agency shortage catalogue, suitable alternative measures to treat CRS instead of tocilizumab must be available prior to infusion.	Ciltacabtagene autoleucel Information for CAR-T Centre Healthcare Providers
Patients with active or prior history of significant central nervous system (CNS) disease or inadequate renal, hepatic, pulmonary, or cardiac function are likely to be more vulnerable to the consequences of adverse reactions and require special attention. There is no experience of use of ciltacabtagene autoleucel in patients with CNS involvement of myeloma or other pre-existing, clinically relevant CNS illnesses.	Ciltacabtagene autoleucel Information for CAR-T Centre Healthcare Providers
Appropriate prophylactic and therapeutic treatment for infections should be provided, and complete resolution of any active infections should be ensured prior to ciltacabtagene autoleucel infusion. Infections may also occur concurrently with CRS and may increase the risk of a fatal event.	Ciltacabtagene autoleucel Information for CAR-T Centre Healthcare Providers
Ciltacabtagene autoleucel infusion should be delayed if a patient has any of the following conditions: • Clinically significant active infection or inflammatory disorders. • Grade ≥3 non-hematologic toxicities of cyclophosphamide and fludarabine conditioning except for Grade 3 nausea, vomiting, diarrhea, or constipation. Ciltacabtagene autoleucel infusion should be delayed until resolution of these events to Grade ≤1.	Ciltacabtagene autoleucel Information for CAR-T Centre Healthcare Providers

Table 2: Key Messages to be Tested for Participants Involved in Prescription and Management of Ciltacabtagene Autoleucel

Key Message:	Supporting Material(s):
• Active graft versus host disease.	
Nearly all patients experienced CRS after ciltacabtagene autoleucel infusion, with majority of these being Grade 1 or Grade 2.	Ciltacabtagene autoleucel Information for CAR-T Centre Healthcare Providers
The median time from ciltacabtagene autoleucel infusion (Day 1) to onset of CRS was 7 days (range: 1 to 23 days). Approximately 83% of patients experienced CRS onset after Day 3 of receiving the ciltacabtagene autoleucel infusion. In almost all cases, duration of CRS ranged from 1 to 18 days (median duration, 4 days). 89% of patients had a CRS duration of ≤7 days.	Ciltacabtagene autoleucel Information for CAR-T Centre Healthcare Providers
Clinical signs and symptoms of CRS may include, but are not limited to, fever (with or without rigors), chills, hypotension, hypoxia and elevated liver enzymes. Potentially life-threatening complications of CRS may include cardiac dysfunction, neurologic toxicity and hemophagocytic lymphohistiocytosis (HLH).	Ciltacabtagene autoleucel Information for CAR-T Centre Healthcare Providers
Patients should be closely monitored for signs or symptoms of these events, including fever. Risk factors for severe CRS include high pre-infusion tumor burden, active infection and early onset of fever or persistent fever after 24 hours of symptomatic treatment.	Ciltacabtagene autoleucel Information for CAR-T Centre Healthcare Providers
Patients should be counselled to seek immediate medical attention should signs or symptoms of CRS occur at any time.	Ciltacabtagene autoleucel Information for CAR-T Centre Healthcare Providers
At the first sign of CRS, the patient should be immediately evaluated for hospitalization and treatment with supportive care, tocilizumab, or tocilizumab and corticosteroids should be instituted as indicated in Table 1 of the SmPC (CRS grading and management guidance).	Ciltacabtagene autoleucel Information for CAR-T Centre Healthcare Providers
Supportive care for CRS (including but not limited to anti-pyretic agents, IV fluid support, vasopressors, supplemental oxygen, etc.) should be administered as appropriate.	Ciltacabtagene autoleucel Information for CAR-T Centre Healthcare Providers
Laboratory testing to monitor for disseminated intravascular coagulation, hematology parameters, as well as pulmonary, cardiac, renal, and hepatic function should be considered.	Ciltacabtagene autoleucel Information for CAR-T Centre Healthcare Providers
Other monoclonal antibodies targeting cytokines (for example, anti-IL1 and/or anti-TNFα), or therapy directed at reduction and elimination of CAR-T cells, may be considered for patients who develop high grade CRS and HLH that remain severe or life-threatening following prior administration of tocilizumab and corticosteroids.	Ciltacabtagene autoleucel Information for CAR-T Centre Healthcare Providers
The onset of neurologic toxicity can be concurrent with CRS, following resolution of CRS or in the absence of CRS.	Ciltacabtagene autoleucel Information for CAR-T Centre Healthcare Providers
ICANS symptoms included aphasia, slow speech, dysgraphia, encephalopathy, depressed level of consciousness and confusional state.. The median time from ciltacabtagene autoleucel infusion to first onset of ICANS was 8 days (range: 2 to 15 days, except for 1 patient with onset at 26 days) and the median duration was 3 days (range: 1 to 29 days, except for 1 patient how had a subsequent fatal outcome at 40 days).	Ciltacabtagene autoleucel Information for CAR-T Centre Healthcare Providers

Table 2: Key Messages to be Tested for Participants Involved in Prescription and Management of Ciltacabtagene Autoleucel

Key Message:	Supporting Material(s):
Nine male patients had neurologic toxicity with several signs and symptoms of parkinsonism, distinct from ICANS.	Ciltacabtagene autoleucel Information for CAR-T Centre Healthcare Providers
Consider reducing baseline burden of disease with bridging therapy prior to infusion with ciltacabtagene autoleucel in patients with high tumor burden.	Ciltacabtagene autoleucel Information for CAR-T Centre Healthcare Providers
Patients should be monitored daily for 14 days after the ciltacabtagene autoleucel infusion at a qualified clinical facility and then periodically for an additional 2 weeks after ciltacabtagene autoleucel infusion for signs and symptoms of CRS, neurologic events and other toxicities.	Ciltacabtagene autoleucel Information for CAR-T Centre Healthcare Providers
At the first sign of neurologic toxicity including ICANS, neurology evaluation should be considered. Rule out other causes of neurologic symptoms. Provide intensive care and supportive therapy for severe or life-threatening neurologic toxicities.	Ciltacabtagene autoleucel Information for CAR-T Centre Healthcare Providers
ICANS severity assessment according to Table 3 of the SmPC (Immune Effector Cell-Associated Encephalopathy (ICE) Assessment).	Ciltacabtagene autoleucel Information for CAR-T Centre Healthcare Providers
At the first sign of ICANS, the patient should be immediately evaluated for hospitalization and treatment instituted with supportive care as indicated in Table 2 of the SmPC (Guideline for management of ICANS).	Ciltacabtagene autoleucel Information for CAR-T Centre Healthcare Providers
Early detection and aggressive treatment of CRS or ICANS may be important to prevent neurologic toxicity from occurring or worsening. Continue to monitor patients for signs and symptoms of neurologic toxicities after recovery from CRS and/or ICANS.	Ciltacabtagene autoleucel Information for CAR-T Centre Healthcare Providers
Patients should be instructed to remain within proximity of the qualified clinical facility for at least 4 weeks following infusion. Following this period, patients are asked to enrol and will be followed in a registry for at least 15 years in order to monitor their health and better understand the long-term effects of ciltacabtagene autoleucel.	Ciltacabtagene autoleucel Information for CAR-T Centre Healthcare Providers

Table 3: Key Messages to be Tested for Participants Involved in Transport, Storage, Thawing, Preparation or Handling of Ciltacabtagene Autoleucel

Key message:	Supporting material(s):
The traceability requirements of cell-based advanced therapy medicinal products must apply. To ensure traceability, the name of the product, the batch number and the name of the treated patient should be kept for a period of 30 years after the expiry date of the product.	Ciltacabtagene autoleucel Handling Guide
Ciltacabtagene autoleucel is intended solely for autologous use and must not under any circumstances be administered to other patients. Ciltacabtagene autoleucel must not be infused if the information on the product labels and Lot Information Sheet does not match the patient's identity.	Ciltacabtagene autoleucel Handling Guide
Ciltacabtagene autoleucel should not be irradiated as irradiation could inactivate the medicinal product.	Ciltacabtagene autoleucel Handling Guide

Table 3: Key Messages to be Tested for Participants Involved in Transport, Storage, Thawing, Preparation or Handling of Ciltacabtagene Autoleucel

Key message:	Supporting material(s):
This medicinal product contains human blood cells. Healthcare professionals handling ciltacabtagene autoleucel should take appropriate precautions (wearing gloves, protective clothing and eye protection) to avoid potential transmission of infectious diseases.	Ciltacabtagene autoleucel Handling Guide
Ciltacabtagene autoleucel must be stored and transported in the vapour phase of liquid nitrogen (≤120°C) and must remain frozen until the patient is ready for treatment to ensure viable cells are available for patient administration: • Temperature conditions during on-site storage of ciltacabtagene autoleucel must be monitored and recorded. • If a temperature out-of-range event happens at any time during storage then immediately quarantine ciltacabtagene autoleucel according to the manufacturing requirements (eg, LN2). • The shelf life of ciltacabtagene autoleucel is 9 months.	Ciltacabtagene autoleucel Handling Guide
Ciltacabtagene autoleucel should be transported within the facility in closed, break-proof and leak-proof containers.	Ciltacabtagene autoleucel Handling Guide
Ciltacabtagene autoleucel must not be thawed until it is ready to be used. The timing of ciltacabtagene autoleucel thaw and infusion should be coordinated; the infusion time should be confirmed in advance, and the start time for thaw must be adjusted so that ciltacabtagene autoleucel is available for infusion when the patient is ready. Ciltacabtagene autoleucel should be administered immediately after thawing and the infusion should be completed within 2.5 hours of thawing.	Ciltacabtagene autoleucel Handling Guide
The ciltacabtagene autoleucel infusion bag should not be removed from the cryo cassette if the information on the patient-specific label does not match the intended patient.	Ciltacabtagene autoleucel Handling Guide
Once patient identification is confirmed, the ciltacabtagene autoleucel infusion bag should be removed from the cryo cassette.	Ciltacabtagene autoleucel Handling Guide
The infusion bag should be inspected for any breaches of container integrity such as breaks or cracks before thawing. Do not administer if the bag is compromised and contact Janssen-Cilag International NV.	Ciltacabtagene autoleucel Handling Guide
Thawing: • The infusion bag should be placed inside a sealable plastic bag prior to thawing. • Ciltacabtagene autoleucel should be thawed at 37°C±2°C using either a water bath or dry thaw device until there is no visible ice in the infusion bag. Total time from start of thaw until completion of thawing should be no more than 15 minutes. – The infusion bag should be removed from the sealable plastic bag and wiped dry. – The contents of the infusion bag should be gently mixed to disperse clumps of cellular material. If visible cell clumps remain, the contents of the bag should continue to be gently mixed. – Small clumps of cellular material should disperse with gentle manual mixing. Ciltacabtagene autoleucel must not be pre-	Ciltacabtagene autoleucel Handling Guide

Table 3: Key Messages to be Tested for Participants Involved in Transport, Storage, Thawing, Preparation or Handling of Ciltacabtagene Autoleucel

Key message:	Supporting material(s):
filtered into a different container, washed, spun down, and/or resuspended in new media prior to infusion. – Once thawed, the medicinal product should not be re-frozen or refrigerated.	
Once thawed, the entire contents of the ciltacabtagene autoleucel bag should be administered by intravenous infusion within 2.5 hours at room temperature (20°C to 25°C), using infusion sets fitted with an in-line filter. The infusion usually takes less than 60 minutes.	Ciltacabtagene autoleucel Handling Guide
Do NOT use a leukodepleting filter.	Ciltacabtagene autoleucel Handling Guide
Gently mix the contents of the bag during ciltacabtagene autoleucel infusion to disperse cell clumps.	Ciltacabtagene autoleucel Handling Guide
After the entire content of the product bag is infused, flush the administration line, inclusive of the in-line filter, with sodium chloride 9 mg/mL (0.9%) solution for injection to ensure all medicinal product is delivered.	Ciltacabtagene autoleucel Handling Guide
Unused medicinal product and all material that has been in contact with ciltacabtagene autoleucel (solid and liquid waste) should be handled and disposed of as potentially infectious waste in accordance with local guidelines on handling of human-derived material.	Ciltacabtagene autoleucel Handling Guide
In case of accidental exposure local guidelines on handling of human-derived material should be followed. Work surfaces and materials which have potentially been in contact with ciltacabtagene autoleucel must be decontaminated with appropriate disinfectant.	Ciltacabtagene autoleucel Handling Guide

PARTICIPATING PHYSICIAN AGREEMENT

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

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

Sponsor's Responsible Party (Main Author):

Name (typed or printed): Natalia Martín Suñé, MD

Institution: Janssen-Cilag Limited

Signature: eSignature has been applied on the next page. Date: _____

(Day Month Year)

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

Signature

User	Date	Reason
MARTIN SUÑE NATALIA 152977194	05-Feb-2025 05:50:07 (GMT)	Document Approval
Oster-Gozet Laurence 155007523	05-Feb-2025 16:01:35 (GMT)	Document Approval