

Novartis Research and Development

Non-Interventional Study Protocol (PASS)

Redacted Protocol

CCTL019B2402

Title	A Non-Interventional Study (NIS) PASS to characterize secondary malignancies of T-cell origin following tisagenlecleucel therapy
Protocol version number	V02 (Clean)
Content final date	15-Dec-2025
EU PAS register number	Study not registered
NIS Type	NIS with Primary Data Collection and Secondary Use of Data
Active substance	Tisagenlecleucel, ATC code: L01XL04
Medicinal product	Kymriah®
Product reference	EU/1/18/1297/001
Procedure number	EMA/H/C/004090
Name of Marketing authorization holder(s)	Novartis Pharma AG
Joint PASS	No
Research question and objectives	The overall objective of this non-interventional study is to investigate whether tisagenlecleucel may contribute to the oncogenesis of secondary malignancies of T-cell origin by providing a procedural framework and process guidance to support and facilitate collection of existing participant samples to analyze, as a first step, the potential presence of muCAR19 transgene using qPCR analysis and/or RCL. In

cases where tumor tissue specimen is muCAR19 qPCR/Vector Copy Number (VCN) positive, other testing may include Lentiviral Integration Site Analysis, analysis of the T-cell receptor repertoire, transcriptomics and whole gene sequencing, as appropriate.

Countries of study Global

Author PPD [redacted]
[redacted]

PPD [redacted]

PPD [redacted]

Property of Novartis
Restricted
May not be used, divulged, published or otherwise disclosed
without the consent of Novartis

NIS Protocol Template Secondary Use of Data Version 4.0 dated 15-Dec-2023

Table of contents

Table of contents	3
List of tables	4
List of figures	4
List of abbreviations	6
1 Responsible parties	8
2 Abstract/Study Summary	9
3 Amendments and updates	13
4 Milestones	14
5 Rationale and background	15
5.1 Rationale	15
5.2 Background	15
5.3 Research question(s)	17
5.4 Study Objectives	17
6 Research methods	18
6.1 Study design	18
6.2 Primary data collection and secondary use of data components	21
6.3 Setting and study population	22
6.3.1 Inclusion criteria	24
6.3.2 Exclusion criteria	25
6.4 Variables	25
6.4.1 Context and rationale for exposure(s) of interest	25
6.5 Data sources	25
6.5.1 Early study termination by the Sponsor	28
6.6 Study size	29
6.7 Data management	29
6.8 Data analysis	29
6.8.1 Context and rationale for analysis plan	29
6.8.2 Sensitivity analyses – rationale, strengths and limitations	30
6.9 Quality control	30
6.9.1 Data quality management	30
6.9.2 Data recording and document retention	30
6.9.3 Site monitoring	30
6.10 Limitations of the research methods	30
7 Protection of human subjects	31
8 Management and reporting of adverse events/adverse reactions	32

9	Plans of disseminating and communicating study results	33
10	References	34
11	Annexes	37
11.1	Annex 1 – List of stand-alone documents	37
11.2	Annex 2 – ENCePP checklist for study protocols	38

List of tables

Table 1-1	Responsible parties.....	8
Table 2-1	Planned dates of study milestones.....	11
Table 3-1	Study protocol amendments and updates	13
Table 3-2	Study protocol amendments and updates	13
Table 4-1	Planned dates of study milestones.....	14
Table 6-1	Data Collection.....	27

List of figures

Figure 6-1	Study design diagram.....	20
Figure 6-2	Testing algorithm for Cohort 1 and Cohort 2.....	20
Figure 6-3	Secondary Malignancy of T-cell Origin Additional Analyses Flowchart.....	21
Figure 6-4	Participant identification journey	23

Marketing authorization holder(s)

Marketing authorization holder(s) Novartis Pharma AG, Lichtstrasse 35, CH-4056 Basel, Switzerland
MAH contact person PPD

List of abbreviations

ALL	Acute Lymphoblastic Leukemia
ATC	Anatomical Therapeutic Chemical
CAR	Chimeric antigen receptor
CIBMTR	Center for International Blood and Marrow Transplant Research
COSMIS	Catalogue of Somatic Mutations in Cancer
CRF	Case Report/Record Form
CTL019	Tisagenlecleucel
DLBCL	Diffuse large B-cell lymphoma
DNA	Deoxyribonucleic acid
EBMT	European Society for Blood and Marrow Transplantation
EMA	European Medicines Agency
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
EU	European Union
FACS	Fluorescence activated cell sorting
FDA	Food & Drug Administration
FFPE	Formalin-fixed paraffin-embedded
FISH	Fluorescence in situ hybridization
FL	Follicular lymphoma
GPP	Good Pharmacoepidemiology Practices
GRACE	Good Research for Comparative Effectiveness
GVP	Good Pharmacovigilance Practices
HA	Health Authority
HIV	Human immunodeficiency virus
HSCT	Hematopoietic stem cell transplantation
ICF	Informed Consent Form
ICH	International Conference on Harmonization
ICMJE	International Committee of Medical Journal Editors
IEC	Independent Ethics Committee
IHC	Immunohistochemistry
IIT	Investigator initiated trial
IRB	Institutional Review Board
ISH	In situ hybridization
ISPE	International Society for Pharmacoepidemiology
LD	Lymphodepleting chemotherapy
LISA	Lentiviral Integration Site Analysis
LK	Leukapheresis
LPLV	Last Participant Last visit
LSSS	Large Simple Safety Study
LTFU	Long term follow-up
MAH	Marketing Authorization Holder
MAP	Managed access program
MedDRA	Medical Dictionary for Regulatory Activities
MSL	Medical safety lead
MTA	Material transfer agreement

muCAR	Murine CAR19
NHL	Non-Hodgkin's lymphoma
NI	Non-Interventional
NIS	Non-Interventional Study
OSS	Out of Specification
PASS	Post-Authorization Safety Study
PBMC	Peripheral blood
Ped-Ya	Pediatric-young adult
PK	Pharmacokinetics
PRAC	Pharmacovigilance and Risk Assessment Committee
qPCR	Quantitative polymerase chain reaction
RCL	Replication competent lentivirus
REB	Regulatory Ethics Board
r/r	Relapsed/refractory
RTPCR	Reverse transcription polymerase chain reaction
STROBE	Strengthening the Reporting of Observational Studies in Epidemiology
TCR	T-cell receptor
T-ALL	T-acute lymphoblastic leukemia
TLGL	T-cell large granular lymphatic leukemia
VCN	Vector copy number
WGS	Whole genome sequencing
WHO	World Health Organization

1 Responsible parties

Table 1-1 Responsible parties

Role	Person
Main protocol author	PPD [REDACTED], Novartis Pharma
Principal investigator (PI)	N/A
MAH contact person	PPD [REDACTED] Novartis Pharma AG

2 Abstract/Study Summary

This section contains a summary of the study information. Additional details can be found in each subsequent section of the protocol.

Title

A Non-interventional Study (NIS) and Post-Authorization Safety Study (PASS) to characterize secondary malignancies of T-cell origin following tisagenlecleucel therapy

Protocol version and release date

V02, 15-Dec-2025

Name and affiliation of main author

PPD

Novartis Pharma

Rationale and background

Tisagenlecleucel belongs to a class of therapies known as chimeric antigen receptor (CAR)-T-cell therapy, involving genetic modification of autologous T-cells. Tisagenlecleucel is approved under the tradename Kymriah® for the treatment of certain patients with pediatric-young adult (Ped-YA) relapsed/refractory (r/r) B-cell acute lymphoblastic leukemia (B-ALL), adult large B-cell lymphoma including diffuse large B-cell lymphoma (DLBCL), and adult r/r follicular lymphoma (FL). Patients treated with tisagenlecleucel may develop secondary malignancies or recurrence of their cancer. The Prescribing Information recommends that patients should be monitored life-long for secondary malignancies. In the event that a secondary malignancy occurs, Novartis should be contacted to obtain instructions on patient samples to collect for testing. In 2024 FDA, EMA and several other health authorities recommended safety label changes for any commercially approved CAR-T therapies for B-cell malignancies directed at CD19, to warn on the risk of secondary malignancies of T-cell origin as an identified risk for this class of therapies.

This NIS PASS protocol CCTL019B2402 aims to provide an adequate procedural framework and process guidance to support and facilitate collection of existing participant samples for testing to address the risk for secondary malignancy of T-cell origin. Formal testing of existing tumor tissue, bone marrow aspirate/biopsy and/or blood or DNA from blood or bone marrow aspirate, using samples where the malignant T cells are documented, will assess a potential role of tisagenlecleucel in the development/oncogenesis of secondary malignancies of T-cell origin. The data generated from this study may help determine whether there is a true safety signal associated with tisagenlecleucel in the emergence of secondary T-cell malignancies in the current approved indications. The participant population will include individuals who have been treated either in the post-marketing/commercial setting (Cohort 2) or in the clinical trial setting (Cohort 1) but discontinued from the primary interventional study trials, did not move to the LTFU study, or discontinued from the long-term follow-up (LTFU) clinical trial CCTL019A2205B and have a confirmed secondary malignancy of T-cell origin.

Research question and objectives

The objective of this non-interventional study is to investigate whether tisagenlecleucel may contribute to the oncogenesis of secondary malignancies of T-cell origin. The study aims to

provide an adequate procedural framework to support and facilitate collection of existing participant samples and their testing to investigate a potential contribution of insertional oncogenesis in the emergence of secondary malignancy of T-cell origin after tisagenlecleucel (a lentiviral-generated CAR-T therapy) in the approved B-cell malignancy indications.

Study design

Participants who have received tisagenlecleucel either from prior interventional clinical trial, but are no longer actively followed on that trial, nor yet transitioned to the LTFU study (Cohort 1) or in a post-marketing/commercial setting (Cohort 2) with confirmed secondary malignancy of T-cell origin will be approached for participation into the study. Once enrolled, existing participant samples will be collected and tested for muCAR19 transgene and RCL (replication competent lentivirus) by qPCR (quantitative polymerase chain reaction). Further testing, such as LISA (Lentiviral Integration Site Analysis), of samples may occur for cases where VCN (vector copy number) values are higher than 0.1 viral copies/cell.

Setting and study population

While recruitment will not be limited it is anticipated that the study will enroll approximately 30 participants (Cohort 1 and 2 combined) with confirmed cases of secondary T-cell malignancies for analysis. The study population may include both pediatric and adult participants who have previously received tisagenlecleucel and have a confirmed secondary malignancy of T-cell origin. The study will remain open for the enrollment of participants from Cohort 1 and Cohort 2 for up to approximately 15 years from the last indication approved for tisagenlecleucel. An interim analysis is planned approximately every 5 years from start of data collection.

Cohort 1 includes participants who received tisagenlecleucel in Novartis CTL019 interventional clinical trials, but who are no longer followed in the interventional clinical trial nor in the LTFU study (CCTL019A2205B). Cases of secondary malignancy of T-cell origin after tisagenlecleucel therapy may be reported after a participant has completed an interventional CTL019 study and/or the LTFU, or has withdrawn consent for study follow-up, or is lost to follow-up, or has completed the initial study but has not yet transitioned to the LTFU study, but reported a secondary malignancy of T-cell origin through the Novartis Pharmacovigilance system, medical literature or to HA who then may report to Novartis.

Cohort 2 includes participants who received tisagenlecleucel in the post-marketing/commercial setting, including patients who received out of specification (OOS) product, or patients enrolled into a MAP (Managed Access Program) or IIT (Investigator Initiated Trial). Cases of secondary malignancy of T-cell origin following tisagenlecleucel infusion in the post-marketing/commercial setting may be reported directly to Novartis by HAs, physicians, health care providers or patients through the Novartis Pharmacovigilance system. Cases may also be reported to Novartis via the NIS PASS CCTL019B2401 study where data is shared from CIBMTR or EBMT to Novartis and subsequent efforts are made to determine whether the reported secondary malignancy of T-cell origin is confirmed by the clinician. Cases may also be reported in medical literature or scientific congresses. Regardless of the initial method for reporting, the participants will be identified from cases documented in the Novartis pharmacovigilance system as a confirmed secondary malignancy of T-cell origin.

Variables

DNA extracted from tumor tissue, bone marrow aspirate and/or blood will be tested to quantify muCAR19 transgene by qPCR to calculate VCN. muCAR19 levels will be reported as either “detectable” or as “non-detectable”, in which case the level is below the limit of detection. Reports are generated for each participant, one report for VCN and one for RCL, separately. For cases where there is insufficient DNA for qPCR measurement, or when tissue contains bone that may interfere with DNA extraction, IHC will be considered. All cases where tumor tissue, bone marrow aspirate and/or blood containing malignant T cells, are positive for qPCR muCAR19 transgene and/or positive for muCAR19 will be discussed for additional analyses with careful consideration of VCN. VCN is a critical determinant for a decision to proceed with additional testing such as LISA. The percentage of malignant T-cells in the tissue/bone marrow aspirate and/or blood is also taken into consideration. VCN threshold to consider additional testing such as LISA, is a minimum of 0.1 viral copies/cell. Generally, the next step to prioritize is LISA, but the testing decision is dependent on availability (or lack thereof) of tumor and/or blood samples. These results are descriptive in nature and require a higher level of interpretation by a cross-functional internal Novartis team, usually with the treating clinician as well.

Data sources

Medical record for participant information will be used as source data for entry into the specific case report forms (CRFs). Data captured outside of the CRF includes qPCR, IHC testing, LISA and other additional testing for cases of positive muCAR19 transgene such as transcriptomics, TCR, and WGS.

Study size

While recruitment will not be limited, the expected sample size is approximately 30 participants over approximately 15 years from the last indication approved for tisagenlecleucel. This estimation is based on 10 participants identified with secondary malignancy of T-cell origin over a period of 7 years, at the data lock point of the latest PSUR (12-Aug-2024), at the time of preparation of this protocol.

Data analysis

All analyses will be performed by Novartis. Results will be listed and descriptively summarized by age group, indication for tisagenlecleucel and type of T-cell malignancy (NHL, leukemia, other). No statistical testing will be applied.

Milestones

Table 2-1 **Planned dates of study milestones**

Milestone	Planned date
HMA-ERA-RWD catalogue number	2026
Start of data collection	2026
End of data collection	2039
Interim report 1 (Year 5)	2031
Interim report 2 (Year 10)	2036
Submission of study progress reports with annual PSURs	2026

Milestone	Planned date
Final report of study results	2039

3 Amendments and updates

Version date: 15-Dec-2025

Version number: 02

The protocol is being amended as per the Health Authority request.

Table 3-1 Study protocol amendments and updates

Version date	Version number	Section of protocol	Substantial Amendment or update	Reason
15 Dec 2025		Section 2	Update	Clarification added for the source of samples where the malignant T cells are documented
		Section 3	Update	Added amendment information.
		Section 4	Update	Updated planned dates
		Section 5	Update	Updated information available for two cases of secondary T cell malignancy.
		Section 6	Update	Updated information for sample origin, minimal volume availability for further testing, and storage of samples. In Table 6-1, editorial change made. Editorial changes made in Section 6.3.1 and Section 6.4.
		Various	Update/edits	Editorial changes made.

Version date: 09-Jul-2025

Version number: 01

Table 3-2 Study protocol amendments and updates

Version date	Version number	Section of protocol	Substantial Amendment or update	Reason
DD July 2025	01	Section 2	Update	Updated abstract and summary to reflect summary of protocol changes as outlined in sections below.
		Section 3	Update	Added amendment information.
		Table 4-1 ; Section 6.8	Substantial	Interim reports should be submitted in five-year intervals following approval of the last indication. A second interim report has been added at Year 10.
		Section 5.2	Update	Updated with additional background information.
		Section 5.4	Substantial	Primary objectives expanded to include vector copy number.

Version date	Version number	Section of protocol	Substantial Amendment or update	Reason
		Section 6.1	Substantial	The study design has been updated to include additional collection of data and samples as well as results communication. Secondary malignancy additional analyses flowchart, testing algorithm and timeline of testing have been added for clarity.
		Section 6.2	Substantial	Removed the requirement of at least 20% tumor involvement for testing to allow for as many cases as possible to be included in the evaluation.
		Section 6.3.1	Substantial	Inclusion criterion expanded to include examples of sample types.
		Section 6.4	Substantial	Additional sample analysis for the causality assessment have been added as variables regardless of the classification of the genes (cancer-associated or not) in which the integration site(s) has/have been identified.
		Section 6.5, Table 6-1	Update	Added clarification on the data to be captured in study CRFs.
		Section 6.7	Update	Added clarification on data collection for initial qPCR analyses and further testing.
		Section 7	Update	Updated wording on regulatory and IRB/EC approvals.
		Section 9	Update	Removed the need for internal interpretation prior to communication of testing results.
		Section 10	Update	Added additional references.

4 Milestones

Table 4-1 Planned dates of study milestones

Milestone	Planned date
HMA-ERA-RWD catalogue number	2026
Start of data collection	2026
End of data collection	2039
Interim report 1 (Year 5)	2031
Interim report 2 (Year 10)	2036
Submission of study progress reports with annual PSURs	2026
Final report of study results	2039

5 Rationale and background

5.1 Rationale

Tisagenlecleucel belongs to a class of therapies known as chimeric antigen receptor (CAR)-T-cell therapy, involving genetic modification of autologous T-cells. Tisagenlecleucel is approved under the tradename Kymriah® for the treatment of certain patients with Ped-YA relapsed/refractory (r/r) B-cell acute lymphoblastic leukemia (B-ALL), adult large B-cell lymphoma including diffuse large B-cell lymphoma (DLBCL), and adult r/r follicular lymphoma (FL) (Maude et al 2018, Fowler et al 2021, Schuster et al 2021). Approved indications may vary by country.

Tisagenlecleucel is a CD19-directed CAR-T therapy based on autologous T-cells, engineered to stably integrate genetic information to express the muCAR19. The potential for oncogenesis caused by lentiviral genomic integration or other mechanisms was an early safety concern linked to CAR-T therapy and long-term monitoring for the emergence of secondary malignancies, including secondary malignancies of T-cell origin, after CAR-T therapy was recommended in CAR-T therapies labels including Kymriah® (SmPC, USPI).

In January 2024, the FDA determined there is a class effect for secondary T-cell malignancies following treatment with CD19-directed CAR-T-cell therapies and requested a safety label change for all CAR-T therapies. In June 2024, EMA PRAC also recommended for all commercially approved CAR-T therapies in EU a safety label change to warn on the risk of secondary malignancies of T-cell origin, as well as Risk Management Plan update to add the risk of secondary malignancies of T-cell origin as an identified risk for this class of therapies (EMA 2024). Several other health authorities mandated similar actions in 2024

This NIS, PASS protocol CCTL019B2402 aims to provide an adequate procedural framework to support and facilitate collection of existing participant samples from patients who were diagnosed with secondary malignancy of T-cell origin any time after tisagenlecleucel treatment for testing of muCAR19 transgene and RCL, as well as additional analyses as warranted. Formal testing of existing tumor tissue and/or blood DNA will assess a potential role of tisagenlecleucel in the development/oncogenesis of secondary malignancy of T-cell origin. The data generated from this study may help determine whether there is a true safety risk associated with tisagenlecleucel in the emergence of secondary T-cell malignancies in the current approved indications. The participant population will include individuals treated either in post-marketing/commercial setting (Cohort 2) or in clinical trial setting (Cohort 1) but who are no longer enrolled in the clinical trial where tisagenlecleucel was administered nor in the LTFU clinical study CCTL019A2205B and have a confirmed secondary malignancy of T-cell origin.

5.2 Background

In 2022, there were initial reports of secondary malignancy of T-cell origin observed in patients treated for B-cell malignancy and multiple myeloma indications with tisagenlecleucel and other commercial CAR-T products from other sponsors (EMA 2024, Patel et al 2024). Secondary malignancies may be related to potential insertional oncogenesis of the CAR expressing lentiviral vector (Harrison et al 2023, Ghilardi et al 2024, Levine et al 2024, Verdun and Marks 2024), though there have been no documented cases confirming this to date (Patel et al 2024).

Insertional oncogenesis was an early safety concern theoretically linked to CAR-T therapy and life-long monitoring for the emergence of secondary malignancies after CAR-T therapy was implemented.

The risk for potential therapy-related secondary cancer exists independent of tisagenlecleucel infusion. It is known that secondary cancers can arise in patients who received prior lines of therapies such as chemotherapy, immunotherapy and/or radiation. Indeed, patients with B-cell Non-Hodgkin's Lymphoma (NHL) have a five-fold higher incidence of second primary T-cell lymphomas compared to the general population ([Chihara et al 2021](#), [Verdun and Marks 2024](#)).

Importantly, cancer patients, irrespective of therapy used to treat, are at increased risk of developing secondary malignancies due to a panel of risk factors such as older age of the patient ([Haycock et al 2017](#)), tobacco ([Hect and Hatsukami 2022](#)) and alcohol use ([Rumgay et al 2021](#)), obesity ([Friedenreich et al 2021](#)), genetic and family cancer predisposition, prior radiation, immuno-therapy, and/or chemotherapy for the indication for tisagenlecleucel, ([Milligan et al 1999](#), [Lowe et al 2007](#), [Patel et al 2024](#), [Cordeiro et al 2024](#)). In a recent analysis, the cumulative incidence of subsequent malignancies is 6.5% at 3 years ([Hamilton et al 2024](#)). The fludarabine and cyclophosphamide doses for lymphodepleting (LD) chemotherapy prior to tisagenlecleucel are relatively low and with very limited contribution to the overall cumulative dose per patient. However, in theory, the LD chemo may also contribute towards oncogenesis for any secondary malignancy of T-cell origin ([Van Besien 2006](#), [Carney et al 2010](#)).

Immune dysregulation may also contribute towards the development of secondary malignancies of T-cell origin ([Ballow et al 2022](#), [NCCN 2023](#), [Patel et al 2024](#), [NCCN 2025](#)). Patients with HIV or congenital causes of immunodeficiency present with infection, immune dysregulation, and an increased risk of malignancy ([Pai et al 2021](#)). NHL is the most common cancer amongst patients with HIV.

To date, all but one of the rare cases of secondary malignancies of T-cell origin reported to Novartis have been in patients receiving commercial tisagenlecleucel for the DLBCL or FL indication. There have been more cases of secondary T-cell NHL than cases of secondary T-ALL (or T-cell large granular lymphatic leukemia, TLGL), with the majority of the cases reported in older adult patients with DLBCL. To date, only one case was reported for a patient treated in the clinical trial setting. The patient received treatment in the pivotal study CCTL019E2202 with the r/r FL indication and then enrolled in the LTFU study CCTL019A2205. This patient's peripheral blood was tested upon patient's transition in the LTFU study and neither muCAR19 transgene nor RCL was detected.

As of June 2025, 2 of the reported cases of secondary malignancy of T-cell origin after tisagenlecleucel treatment have had a positive muCAR19 transgene and sufficiently positive VCN result (≥ 0.1 viral copies/cell) for the tumor. One of the 2 cases was reported as secondary T-cell NHL, with peripheral blood containing the circulating malignant T-cells post tisagenlecleucel. Testing of DNA extracted from this blood by qPCR demonstrated positive muCAR19 transgene and positive VCN. This prompted further Novartis investigative tests, including LISA. The dominant muCAR19 positive clone presented pathogenic mutations in TET2 and DNMT3A, a vector copy number of ~ 3 and lentiviral integration in the genes DPF2, NPLOC4 and RAB11FIP3. As DPF2, NPLOC4 and RAB11FIP3 are not classified as cancer genes, insertional oncogenesis was excluded, however the possibility that the manufacturing

process and/or the in vivo stimulation by CD19 engagement accelerated the outgrowth of the pre-existing TET2/DNMT3A mutated malignant clone cannot be excluded (Kobbe et al 2024).

The second case where muCAR19 PCR and VCN was sufficiently positive to proceed with LISA and other studies was recently published (Bezerra et al 2025). This was an adult patient with the DLBCL indication for tisagenlecleucel in the commercial setting. He developed secondary malignancy of T cell NHL of the palate with an isolated lesion. There was no direct causality for tisagenlecleucel for the T cell NHL through insertional oncogenesis.

Research question(s) and objectives

5.3 Research question(s)

The objective of this non-interventional study is to investigate whether tisagenlecleucel may contribute to the oncogenesis of secondary malignancy of T-cell origin.

5.4 Study Objectives

This study aims to provide an adequate procedural framework to support and facilitate collection of existing participant samples and their testing to investigate a potential contribution to insertional oncogenesis in the emergence of secondary malignancy of T-cell origin occurring after tisagenlecleucel (a lentiviral-generated CAR-T therapy) in the approved B-cell malignancy indications.

Primary Objective:

- Test specific participant samples using qPCR for muCAR19 transgene/VCN to determine whether the tumor is positive for the muCAR19 transgene with sufficiently positive VCN (≥ 0.1 viral copies/cell). In cases where there is insufficient DNA to perform qPCR, or when the tumor tissue contains bone (such as bone marrow biopsy), IHC will be performed when feasible. The presence of bone in the sample precludes isolation of DNA of appropriate quality to perform qPCR. In cases where muCAR19 transgene copies are not detectable per qPCR, and/or IHC for muCAR19 is negative, no further testing is performed.
- A percentage of muCAR19 qPCR and VCN positive tumors tested in the total number of patients enrolled in the study will be calculated and reported at the 5 and 10-year interim CSR.
- To estimate the average vector copy number (VCN) and replication competent lentivirus (RCL) among confirmed secondary primary malignancy tumors from patients exposed to tisagenlecleucel.
- To determine whether there is any evidence for a contribution from tisagenlecleucel in the oncogenesis of the secondary malignancy of T-cell origin.
 - For any case where VCN value in the tumor tissue is sufficiently positive with a muCAR19-positive tumor, or positive muCAR19 IHC, perform Lentiviral Integration Site Analysis (LISA).
 - Determine whether LISA demonstrates any evidence for insertional oncogenesis.

Based on LISA findings and hypothesis driven investigation, further analyses including but not limited to T-cell receptor (TCR) repertoire, transcriptomics and whole genome sequencing (WGS) may follow. This additional testing will be determined by a cross functional Novartis team in collaboration with the treating clinician. This testing is dependent on availability of samples from the participant and may include existing blood and/or bone marrow aspirate and/or DNA from blood and/or bone marrow aspirate tumor tissue (including bone marrow aspirate or biopsy) in the form of FFPE block or unstained slides. For a complete investigation, if available, retained vial(s) from the leukapheresis (LK) cells collected and stored at Novartis prior to manufacture of tisagenlecleucel, and retained vial(s) from the final manufactured product should be analyzed as well.

6 Research methods

6.1 Study design

This is a non-interventional PASS, that involves the following steps : (Figure 6-1 and Figure 6-2):

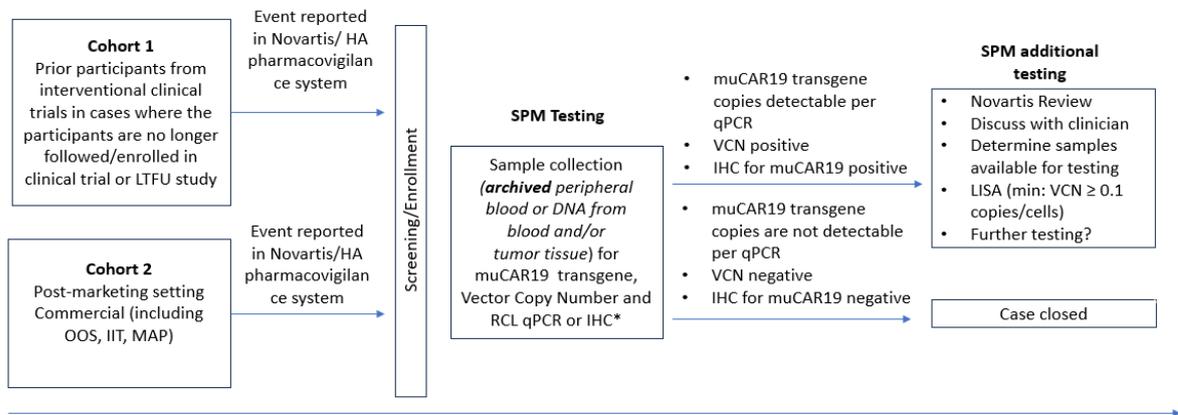
1. Participants are identified as outlined in Figure 6-1.
2. Clinician/PI discussion with Novartis Clinical/Medical team to determine if patient is alive or able to obtain consent from prior tissue bank ICF or patient representative as well as confirm whether samples exist for testing.
3. For eligibility, the diagnosis of the secondary malignancy of T-cell origin must be confirmed. This includes Novartis's review of the redacted pathology report along with any ancillary analyses used to diagnose secondary T-cell malignancy as well as direct communication with the treating clinician and pathologist for more complex cases.
4. Novartis to send the protocol package to the clinical site.
5. Site to obtain IRB/EC approval.
6. Site to document ICF process and participant enrolled in the study.
7. Novartis to send laboratory kit(s) to the clinical site (takes approximately 2 weeks).
8. Site to complete CRFs for demographics of the participant, indication for tisagenlecleucel, cytogenetics, tumor immunophenotype for participants with indicated B-ALL, tumor location and stage for B NHL, prior lines of therapy, prior allogeneic vs autologous HSCT yes/no, other medical history, date and dose administered for tisagenlecleucel infusion (Dose Administration Record), clinical response to tisagenlecleucel, , any anti-neoplastic treatment post infusion of tisagenlecleucel, but prior to the diagnosis of secondary malignancy of T-cell origin, date of diagnosis of secondary malignancy of T-cell origin and confirmation of pathology report review/clinical review, immunophenotype for T-ALL (and TCR receptor rearrangement assays if performed), IHC and cytogenetics of T-NHL, as well as any therapy given for the secondary malignancy of T cell origin.
9. Documentation in CRF for sample type available of tumor tissue/specimen with the secondary malignancy of T cell origin (this may include blood, bone marrow aspirate, bone marrow biopsy and/or cerebral spinal fluid if secondary malignancy is present) vs blood vs DNA from blood and/or bone marrow aspirate and date the sample(s) were obtained previously as well as method stored. The percentage of malignant T cells in the

samples is documented clearly. This is used when calculating the VCN. Each participant may have different samples available for testing. For example, only existing blood or DNA from blood may be available for some participants, only existing tumor tissue may be available for some participants, and some participants may have both tumor tissue and blood/DNA from blood available. Limitations of samples available are carefully taken into consideration when making decisions regarding testing prioritization.

10. Samples to be packaged as per instructions in the central lab manual and shipped to central laboratory for analysis (approximately 2 weeks). FFPE tissue block and/or unstained slides are sent at ambient temperature. Bone marrow aspirate, blood or DNA from blood or bone marrow must be previously stored as frozen and is sent as frozen. Please refer to the lab manual for details on the requested ideal volume of blood and/or bone marrow aspirate in EDTA, number of unstained slides and/or FFPE tissue block requirements. Any remaining sample not analyzed is reviewed with the PI/clinician with formal arrangements made to return this remaining sample when this is requested/indicated.
11. Testing by qPCR for muCAR19 transgene and RCL on available, existing tumor sample(s) and/or existing blood or DNA from blood or bone marrow aspirate, or blood and bone marrow sample from routine clinical practice (approximately 2-3 weeks). In cases where muCAR19 transgene copies are not detectable per qPCR or IHC result is negative when qPCR cannot be done, the case is closed, results are communicated to the clinician and documented in the Novartis data capture system as well as Novartis Argus safety data system, and no further testing is performed. If there are any remaining samples at Novartis, we will offer to the clinician/PI to return these.
12. For cases where the qPCR for muCART19 is positive in the tumor tissue, blood and/or bone marrow and the calculated VCN would suggest the presence of a muCAR19 positive malignant T cells, or for positive muCAR19 IHC, LISA will be performed if adequate existing sample is available. Additional analyses will be performed based on LISA results and is dependent on sample availability (Figure 6-3 and Section 6.3). Anticipated timelines for sample analysis:
 - Samples availability to be determined for LISA and/or other testing may take up to 2-4 weeks. In some cases, Novartis will already have these additional samples, but in others, sites may provide only the sample(s) needed for the additional muCAR19 and RCL PCR
 - MTA and/or additional ICF and visit for countries needing extra protection of patient samples for genetic testing: 1-3 months
 - Samples shipped for testing to appropriate Novartis designated laboratory: 2- 8 weeks
 - Samples tested and results generated, reviewed and shared 1-2 months

The study will remain open for enrollment of participants from Cohort 1 and Cohort 2 for up to approximately 15 years from the last indication approved for tisagenlecleucel in EU. While recruitment will not be limited, it is anticipated that the study will enroll approximately 30 participants (Cohort 1 and 2 combined) with confirmed cases of secondary T-cell malignancies for analysis. The duration of the study is defined by the lifetime of the EU Risk Management Plan commitment. The duration of an individual participant will depend on which tests are performed and the speed at which results can be obtained.

Figure 6-1 Study design diagram

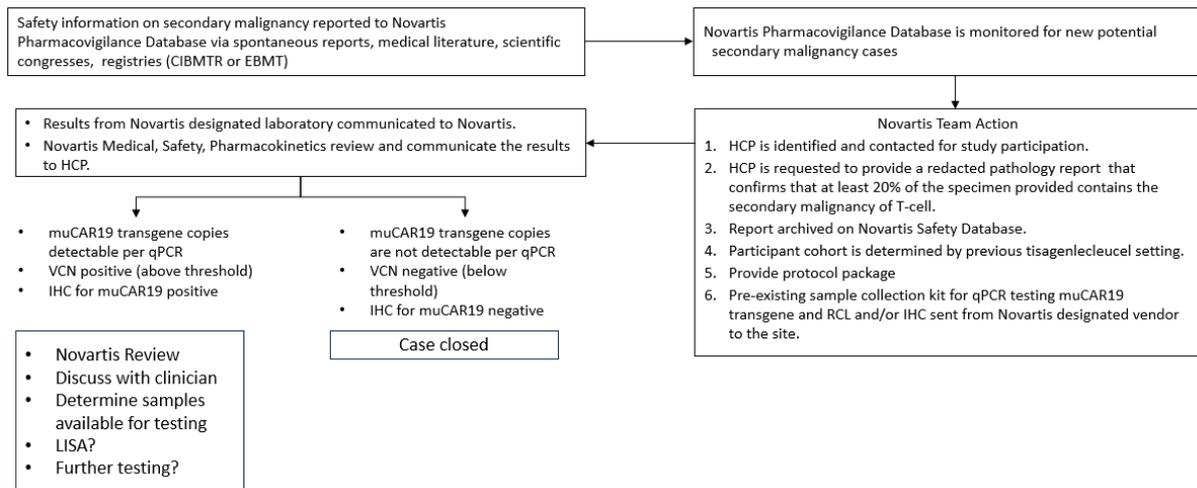


Duration includes screening, enrollment and testing only. Once results are available and communicated to clinician, the participant leaves the study
For all cases where the blood muCAR19 transgene is positive:

- For Cohort 1: the prior levels obtained on study for the participant will be reviewed and compared to average for that study.
- For Cohort 2: level for the participant will be compared to the appropriate clinical trial average

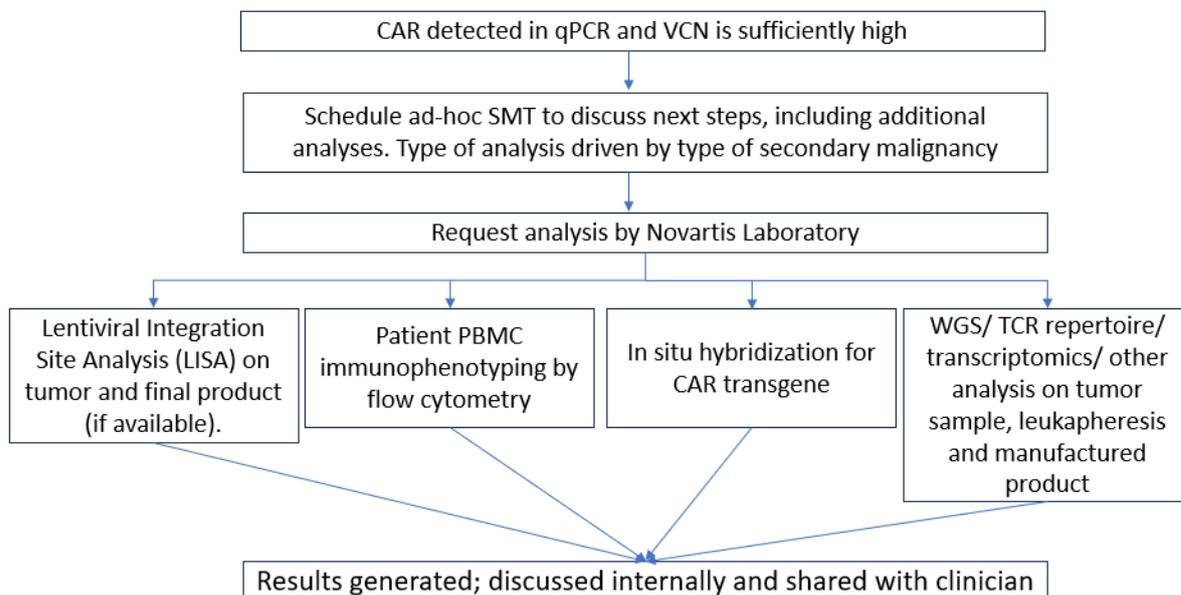
* In cases where there is insufficient DNA to perform qPCR, or when the tumor tissue contains bone (such as bone marrow biopsy), IHC will be performed when feasible.

Figure 6-2 Testing algorithm for Cohort 1 and Cohort 2



Results will be transferred as described in the designated Data Transfer Plan.
Results and decisions are archived in Novartis Safety Database. External and internal communication of results align with Novartis SOP on Global Safety Communication.

Figure 6-3 Secondary Malignancy of T-cell Origin Additional Analyses Flowchart



6.2 Primary data collection and secondary use of data components

Central laboratory review by the designated Novartis pathologist is required prior to performing any of the tests, including the initial qPCR testing for muCAR19 transgene and RCL. For pathology review ideally there is confirmation that at least 20% of the specimen provided contains the secondary malignancy of T-cell origin. However, specimens between 5 and 20% tumor involved are still considered for testing. The percentage of tumor in the specimen is used to calculate a corrected VCN value, that should be higher than 0.5 viral copies/tumor cell to trigger LISA. Corrected VCN is calculated by dividing VCN by the percentage of tumor cells in the tissue section, e.g. if VCN is 0.1 viral copies/cell and the percentage of tumor in the tissue is 20%, the corrected VCN is 0.5 viral copies/tumor cell.

For participants who discontinued from prior CTL019 clinical studies, including the LTFU study (Cohort 1), the cellular kinetics of tisagenlecleucel may have been captured from peripheral blood and/or bone marrow aspirate, as measured by two assays: (i) qPCR that measures muCAR19 transgene and (ii) flow cytometry assay that quantifies the relative number of muCAR19 positive T-cells. Based on the clinical trial experience, qPCR data were observed to be more robust and more sensitive than the flow cytometry data. Therefore, as a first step, the transgene levels will be quantified using the qPCR method. These bioanalytical data will be generated by the assigned Novartis-designated laboratory, as the first step with review of any prior muCAR19 PK data available for prior clinical trial participants.

The duration of this study and total number of participants with secondary malignancy of T-cell origin will be defined by the lifetime of Risk Management Plan commitment. Current plans are to include but not limited to approximately 30 participants over approximately 15 years based on estimation of using the number of cases reported per year (as of 12-Aug-2024, ten cases were reported over 7 years (10 cases/7 years = 1.4 cases per year).

In this study, samples will be tested for muCAR19 transgene (for VCN) and RCL using qPCR assay. In cases where muCAR19 transgene is detected in peripheral blood and/or bone marrow aspirate DNA and/or secondary malignancy tissue, the levels will be compared to the average VCN levels observed in peripheral blood and/or bone marrow in the pivotal CTL019 clinical studies at a corresponding time point or visit with the objective to estimate the fold-change in transgene presence. Of note, the trafficking of CAR T-cells in lymph nodes or other tissues outside blood and bone marrow is not yet well characterized. All cases of positive muCAR19 qPCR in blood, bone marrow and/or tumor will be reviewed. All cases of positive muCAR19 qPCR with sufficiently positive VCN are eligible for further exploration.

In cases where insufficient DNA from tumor tissue occurs, or for cases where the tumor specimen contains bone, IHC will be considered on tumor, or immunophenotype on existing blood or bone marrow PBMC (peripheral blood mononuclear cells) for cases where T-cell malignant cells are in peripheral blood and/or bone marrow aspirate.

Additional testing will be performed to determine potential causality for muCAR19 in the oncogenesis of secondary malignancies of T-cell origin for all cases where the muCAR19 transgene qPCR is positive in tumor tissue. In case of a CAR-driven secondary malignancy, all secondary malignancy cells are expected to contain the CAR transgene, and therefore the muCAR19 qPCR signal would be expected to be very strong and significantly above average blood levels at that time point post tisagenlecleucel infusion.

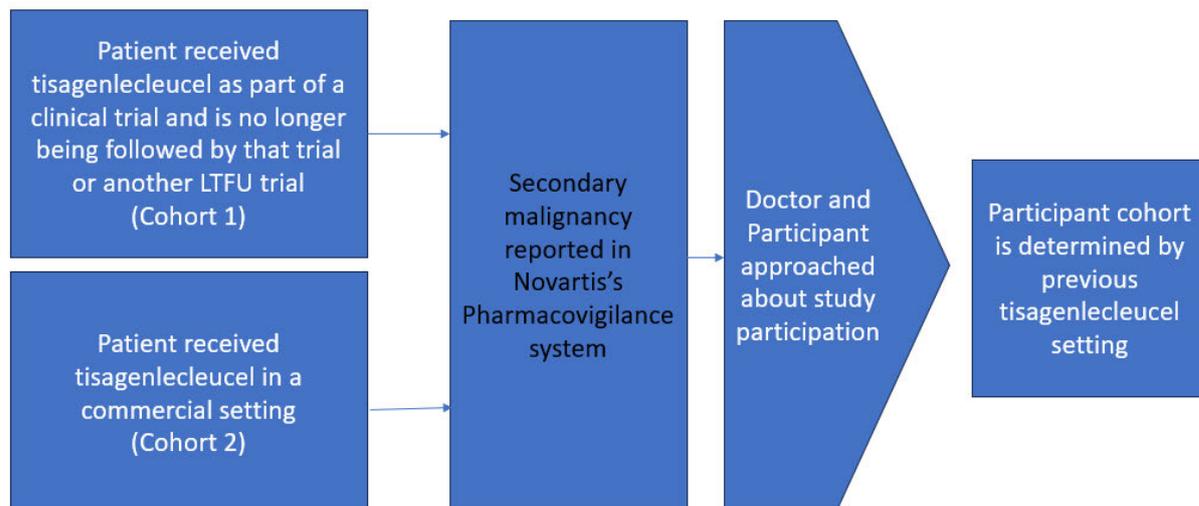
Based on any positive results for muCAR19 transgene in the malignancy of T cell origin sample and/or RCL, a decision will be taken, in alignment with the clinician and with consideration of samples available, regarding the additional analyses as described in the methods section. For cases where there is a positive qPCR muCAR19 transgene result from the secondary malignancy of T cell origin, additional analyses may include immunophenotyping, IHC analysis, in situ hybridization (ISH), or LISA. If samples are limited the priority analysis is LISA. Additional testing may also be considered using retained vials from leukapheresis prior to manufacture of tisagenlecleucel and/or final manufactured product characterization for all cases where the PCR is positive from the secondary malignancy of T-cell origin specimen and/or in cases where IHC results are positive for CAR T-cells (supported by appropriate positive and negative control).

Although there are currently no reported cases of secondary malignancy of T-cell origin reported for the Ped-YA ALL indication, there is still a possibility that this may occur. Therefore, pediatric patients/participants are included in this protocol.

6.3 Setting and study population

The patient identification journey is presented in [Figure 6-4](#).

Figure 6-4 Participant identification journey



Historic muCAR transgene levels will be available for participants in Cohort 1 from their previous enrollment in CTL019 interventional clinical trials.

Cohort 1

Cohort 1 includes participants who received tisagenlecleucel in Novartis CTL019 interventional clinical trials, and discontinued from the interventional clinical trial and/or the LTFU study (CCTL019A2205B). Cases of secondary malignancy of T-cell origin after tisagenlecleucel therapy may be reported after a participant has completed an interventional CTL019 study and/or the LTFU, or has withdrawn consent for study follow-up, or is lost to follow-up, or has completed the initial study but has not yet transitioned to the LTFU study, but reported a secondary malignancy of T-cell origin through the Novartis Pharmacovigilance system, medical literature or to HA who then may report to Novartis.

Cohort 2

Cohort 2 includes participants who received tisagenlecleucel in the post-marketing/commercial setting, including patients who received OOS product, or patients enrolled into a MAP or IIT. Cases of secondary malignancy of T-cell origin following tisagenlecleucel infusion in the post-marketing/commercial setting may be reported directly to Novartis by HAs, physicians, health care providers or patients through the Novartis Pharmacovigilance system. Cases may also be reported to Novartis via the NIS PASS CCTL019B2401 study where data is shared from CIBMTR or EBMT to Novartis and subsequent efforts are made to determine whether the reported secondary malignancy of T-cell origin is confirmed by the clinician. Cases may also be reported directly to the HA or in the medical literature or scientific congresses. Regardless of the initial method for reporting, the cases will be identified as those documented in the Novartis pharmacovigilance system as confirmed secondary malignancy of T-cell origin.

6.3.1 Inclusion criteria

Study participants eligible for inclusion in this study must meet all of the following criteria:

1. Prior use of tisagenlecleucel treatment in CTL019 clinical trial setting or post-marketing/commercial tisagenlecleucel setting as outlined for Cohort 1 and Cohort 2
2. Confirmed diagnosis of secondary malignancy of T-cell origin via redacted pathology report and/or clinical confirmation by the Principal Investigator/clinician responsible for enrolling the participant. Clinical judgement may be required in cases where the diagnosis is not clearly confirmed in the redacted pathology report. There also may be cases in certain site/countries, where sharing the redacted pathology reports is not allowed, hence the clinical diagnosis will be allowed for eligibility.
3. Availability of existing secondary malignancy of T cell origin specimen(s) from tissue, and/or bone marrow aspirate sample(s) and/or blood or DNA extracted from blood (with confirmed T-cell malignancy diagnosis in the sample provided) collected during routine standard of care during the secondary malignancy of T-cell origin diagnosis. Often, only a limited amount of the appropriate sample(s) may be available. For the testing process, a specimen containing the malignant T-cells for the secondary malignancy of T-cell origin must be present. The type of specimen/sample for testing is determined based on the location of the secondary malignancy of T-cell origin. For example, bone marrow aspirate and/or blood and/or bone marrow biopsy may be needed for analysis for a secondary malignancy of T cell origin when the malignant T cells are present in blood and/or bone marrow, and tissue such as a lymph node location or cutaneous or other location is needed when this is the region of the body affected by the secondary malignancy of T-cell origin. Blood, (even if NOT involved with the T cell malignant cells) when available, may also be used for comparison to the tissue/bone marrow used for the analysis. Novartis has established ranges of CAR transgene level in blood for all 3 pivotal trial indications at specific time points. This is used for comparison.

See laboratory manual for detailed instructions. The following types of samples are recommended for collection if available/pre-existing:

- a. Tumor tissue (FFPE block (ambient temp), unstained slides (ambient temp), or bone marrow aspirate in EDTA or blood in EDTA and frozen, if malignant T-cells present)
 - b. Peripheral blood EDTA frozen- to be used when available and either not involved with T-cell malignancy for comparison to the tumor sample provided and/or if peripheral blood has circulating malignant T cells for analysis.
 - c. Bone marrow aspirate EDTA frozen if involved with secondary malignancy of T-cell origin.
 - d. DNA extracted from blood or bone marrow aspirate stored frozen
 - e. Bone marrow biopsy if malignant T-cells are present (FFPE block, unstained slides, ambient temperature)
4. Signed informed consent. For participants who have died, it is acceptable for clinical/academic sites to use a previous biospecimen research consent, or to have an appropriate family member or designated representative to provide consent on behalf of the participant as per local regulations.

6.3.2 Exclusion criteria

Study participants meeting any of the following criteria are not eligible for inclusion in this study:

1. Ongoing enrollment on Novartis sponsored CTL019 interventional or LTFU clinical trial
2. Cases where there is no existing available specimens that include the secondary malignancy of T cell origin (tumor tissue and/or existing blood and/or bone marrow and/or DNA from blood for testing)
3. Cases where informed consent is not possible.

6.4 Variables

1. DNA extracted from tumor tissue, bone marrow aspirate and/or blood will be tested to quantify muCAR19 transgene by qPCR to calculate VCN. muCAR19 levels will be reported as either “detectable” or non-detectable, in which case the level is below the qPCR limit of detection. Reports are generated for each participant, one report for VCN and one for RCL separately. For cases where there is insufficient DNA for qPCR measurement, or when tissue contains bone that may interfere with DNA extraction, IHC will be considered. For cases where DNA from blood and/or bone marrow is provided from the site, DNA extraction step is not necessary.
2. All cases where tumor tissue is positive for qPCR muCAR19 transgene will be discussed for additional analyses with careful consideration of VCN. VCN is a critical determinant for a decision to proceed with additional testing such as LISA. The percentage of malignant T-cells in the tissue/bone marrow aspirate and/or blood is also taken into consideration. VCN threshold to consider additional testing such as LISA, is a minimum of 0.1 viral copies/cell as outlined in [Section 5.4](#). Generally, the next step to prioritize is LISA, but the testing decision is dependent on availability (or lack thereof) of tumor and/or blood samples. These results are descriptive in nature and require a higher level of interpretation by a cross-functional internal team, usually with the treating clinician involved as well.

6.4.1 Context and rationale for exposure(s) of interest

Only participants with documented exposure to tisagenlecleucel are included in this study.

With the recent update of the prescribing information enhancing the awareness of the potential of secondary T-cell malignancies, and relevant publications from 2023 to 2024, reporting of T-cell malignancies after CAR-T therapies may increase and 2-3 cases/patients per year are estimated.

6.5 Data sources

Medical records for participant information will be used as source data for entry into the specific CRFs. Refer to [Table 6-1](#) for specific CRF data collection.

Data captured outside of the CRF includes:

- muCAR19 transgene and RCL qPCR and/or IHC testing laboratory (Novartis). Results from the qPCR assays are provided in official results report format. IHC results are provided in a non-formal report, but in images with positive and negative controls.

muCAR19 transgene qPCR with VCN and RCL outputs only, will also be transferred directly via outputs from the Novartis-designated laboratory. The results will be reported to Novartis safety database and shared with the PI and HA.

- LISA and other additional testing for cases of positive muCAR19 qPCR or IHC (if qPCR cannot be done) in the tumor tissue. LISA is performed to identify the genomic location(s) of viral integration(s). Genes in which viral integration sites are identified are further classified as cancer-genes or non cancer-genes according to COSMIC. If one (or few) dominant integrations are identified regardless of its occurrence in cancer genes, the possibility of insertional oncogenesis must be further investigated. In this scenario, transcriptomics (or similar analysis) is required to evaluate if viral integration has affected the expression of the gene or cancer gene(s) in which the integration occurred. Genome sequencing is required to evaluate genetic background of the participant and the presence of pre-existing predisposing mutations.
- Transcriptomics evaluates gene expression by RNA Sequencing. Particular attention should be paid to aberrant fusion transcripts between vector and host genome that are often linked to insertional oncogenesis.
- TCR repertoire analysis may be performed to establish clonality of the secondary malignancy of T-cell origin
- WGS may be performed to identify the mutations/chromosomal aberrations that characterize the tumor. WGS or, if required, more sensitive methods (e.g. error corrected Next Generation Sequencing) on leukapheresis and manufacturing samples should be performed to evaluate if identified mutations were pre-existing CAR T-cell manufacturing.

Prior and post tisagenlecleucel anti-neoplastic therapy (including chemotherapy, immune therapy, radiation therapy, surgery+ HSCT when applicable) entered into the database will be coded using the World Health Organization (WHO) Drug Reference List. Medical history/current medical conditions and adverse events will be coded using the medical dictionary for regulatory activities (MedDRA) terminology.

Data collection schedule

This is a non-interventional study and does not impose a therapy protocol, diagnostic/therapeutic procedure, or a visit schedule. Participants were treated according to the local prescribing information (Cohort 2), and routine medical practice in terms of visit frequency and types of assessments performed or according to the respective treatment trial protocol (Cohort 1) and only these data will be collected as part of the study. Only existing samples are collected for testing and no additional sampling is required or will be requested, given the scope of this non-interventional trial. The treating physician is asked to complete the appropriate CRF in a timely manner.

Table 6-1 Data Collection

Variable/outcome	Screening	Sample collection
Informed Consent	X	
Demography	X	
Medical History	X	
Status of participant alive Y/N	X	
If participant not alive, is ICF possible by prior consent and/or designated person to provide consent on behalf of participant?		
Date and dose of treatment with tisagenlecleucel (incl. batch ID and for Cohort 1 participants, the prior clinical trial code and participant ID)	X	
Diagnosis and extent of primary B-cell malignancy as indication for tisagenlecleucel and current status by response to tisagenlecleucel	X	
Cytogenetics/FISH/RTPCR/other	X	
Tumor immunophenotype for primary B-ALL indication when applicable (repeat CRF to be used if T-ALL is the secondary malignancy of T-cell origin reported)	X	
Immunohistochemistry staining for primary B-NHL or B-ALL (from bone marrow biopsy rarely) when applicable. Repeat CRF for secondary T-cell NHL IHC when applicable	X	
Diagnosis of T-cell malignancy (date, type, confirmation of diagnosis by pathology and/or clinical). Captured in this secondary malignancy CRF which includes documentation of tumor tissue sample availability. If immunophenotype is done, a repeat tumor immunophenotype CRF is used (this applies only to cases where T-cell malignant lymphoblasts are present in peripheral blood and/or bone marrow aspirate)	X	X
Antineoplastic therapies (prior to tisagenlecleucel and after tisagenlecleucel but prior to diagnosis of secondary malignancy of T-cell origin). HSCT+/- and type auto vs allo HSCT and agents used for conditioning (pre and post tisagenlecleucel when appropriate). All therapies are to be listed including date and route of administration	X	

Variable/outcome	Screening	Sample collection
Date of blood sample or DNA from blood sample, storage conditions, amount available for analysis (repeat CRFs to be added for cases where muCAR19 and VCN are sufficiently positive to warrant consideration for LISA and/or additional testing. Testing decisions dependent on availability of samples from the patient)	X	X
Date of biopsy, FFPE vs unstained slides vs bone marrow aspirate vs bone marrow biopsy and amount available for analysis (repeat CRFs to be added for cases where muCAR19 and VCN are sufficiently positive to warrant consideration for LISA and/or additional testing. Testing decisions are dependent on availability of samples from the patient).	X	X
Date of LK retained vial sample and whether available and number of vials available- only when applicable as related to cases with positive muCAR19 qPCR for transgene AND sufficient level of VCN to proceed with LISA and additional testing consideration		X*
Date of final manufactured tisagenlecleucel product retained vials and whether available and number of vials available- only when applicable as related to cases with positive muCAR19 qPCR for transgene AND sufficient level of VCN to proceed with LISA and additional testing consideration		X*
LISA and/or additional testing performed for cases of positive muCAR19 qPCR in tumor tissue- date for testing and testing to be performed. To include samples to be used for each test indicated- dependent on availability of sample(s) as well as potential additional ICF and/or MTA for genetic testing (required in most sites/countries)		X*
Unscheduled visit(s)		

*Initial existing samples are sent for qPCR analysis and VCN and/or IHC. If the tumor tests positive for muCAR19 transgene and VCN at appropriate level based on % tumor present (minimum >0.1 copies/cell), additional tests to be conducted for further analysis.

Note: No additional sampling is required during this study.

6.5.1 Early study termination by the Sponsor

The study can be terminated by Novartis at any time with agreement from HA.

6.6 Study size

While recruitment will not be limited it is anticipated that the expected sample size is approximately 30 participants over approximately 15 years from the most recent indication approved for tisagenlecleucel. This estimation is based on 10 cases identified with secondary malignancy of T-cell origin over a period of 7 years, at the data lock point of the latest PSUR (12-Aug-2024), at the time of preparation of this protocol.

6.7 Data management

Data Collection will be performed using Rave EDC for the initial qPCR analyses. Further testing indicated based on positive PCR with confirmed positive VCN will be added to PVI or CRF for appropriate cases where VCN is positive above the threshold level outlined.

Designated investigator staff will enter the data required by the protocol into the electronic CRF. The eCRFs have been built using fully validated secure web-enabled software that conforms to 21 CFR Part 11 requirements. Investigator site staff will not be given access to the EDC system until they have been trained. Automatic validation programs check for data discrepancies in the eCRFs, allow modification and/or verification of the entered data by the investigator staff.

The investigator/designee is responsible for assuring that the data (recorded on CRFs) is complete, accurate, and that entry and updates are performed in a timely manner. The Investigator must certify that the data entered are complete and accurate. After final database lock, the investigator will receive copies of the participant data for archiving at the investigational site.

All data should be recorded, handled, and stored in a way that allows its accurate reporting, interpretation, and verification.

6.8 Data analysis

All analyses will be performed by Novartis. Results will be listed and descriptively summarized by age group, tisagenlecleucel indication (B NHL or B-ALL) and type of T-cell secondary malignancy (NHL, leukemia, other). No statistical testing will be applied. An interim analysis is planned at approximately 5 years and 10 years from start of data collection. Data for all reported secondary malignancies of T cell origin is also reviewed annually and reported in the annual PSUR.

6.8.1 Context and rationale for analysis plan

This study provides a procedural framework to ensure case summaries and testing performed with results reviewed as outlined, on existing/existing samples from the participants. The percentage of secondary malignancy of T cell origin muCAR19 transgene positive cases will be determined. For the cases of positive muCAR19 transgene or muCAR19 IHC, LISA will analyze for insertional oncogenesis. This information, combined with the additional testing outlined in [Section 6](#) will be used to evaluate a potential causal contribution of tisagenlecleucel in the oncogenesis of secondary malignancy of T-cell origin. A descriptive analysis for each participant will be provided. Therefore, no statistical endpoint is being evaluated, and no hypothesis testing is being conducted.

6.8.2 Sensitivity analyses – rationale, strengths and limitations

Not applicable.

6.9 Quality control

The study will be conducted according to the guidelines for Good Pharmacoepidemiology Practice (GPP) ([International Society for Pharmacoepidemiology 2016](#)) and according to the ENCePP code of conduct ([European Medicines Agency 2016](#)). All database partners have experience in conducting pharmacoepidemiological research and research is done by researchers trained in pharmacoepidemiology.

6.9.1 Data quality management

Novartis Data Management will assure database quality processes are followed including review of the data entered into the CRFs by investigational staff for completeness and accuracy, and in accordance with the data validation plan.

In case of audit or inspections, Novartis Data Management will assure that access to the required/requested study related documents is provided.

6.9.2 Data recording and document retention

The CRFs for individual participants will be provided by the study Sponsor. In all scenarios, the physician must maintain source documents which provides evidence for the existence and substantiate the integrity of the data collected for each participant in the study, consisting of case and visit notes (hospital or clinic medical records) containing demographic and medical information, and the results of any other tests or assessments. All information entered in the CRF must be traceable to these source documents in the participant's file. Any discrepancies between the source documents and the CRF must be explained. The study related records and documents, including signed ICFs, pertaining to the conduct of the study will be kept for 15 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of Novartis. No records may be transferred to another location or party without written notification to Novartis.

The physician must give Novartis (or designee), IRB/IEC and competent authorities access to all relevant source documents to confirm their consistency with the CRF entries.

6.9.3 Site monitoring

Formal site monitoring will be performed as described in the NIS Monitoring Plan for this study. Novartis Data Management will ensure compliance monitoring.

6.10 Limitations of the research methods

The ability to perform protocol testing is dependent on the availability of existing tumor and/or blood samples for the participants. Each assay has a risk of generating potential false positive or false negative results, however, all of the assays have been intensively validated and routinely

performed under strict quality standards. In case of ambiguous results, if material is available, a finding identified with a method should be corroborated by a different approach. For example:

- VCN by qPCR could be confirmed by IHC/ISH against the CAR transgene/vector on FFPE slides and/or by FACS analysis of CAR expression on blood samples
- Integration Site identified by LISA may be confirmed via WGS and/or targeted sequencing
- TCR repertoire analysis performed via multiplex PCR may be confirmed by WGS or targeted sequencing
- Genetic mutations and chromosomal aberrations identified via WGS may be confirmed/measured using targeted sequencing or via qPCR with appropriate TaqMan assays

7 Protection of human subjects

Any participant records or datasets that are transferred to Novartis will contain the participant's identifier only, including any data provided in aggregate form; participant names or any information which would make the participant directly identifiable will not be transferred.

The participant must be informed that his/her personal study-related data will be used by Novartis in accordance with local data protection law. The level of disclosure must also be explained to the participant who will be required to give consent for their data to be used as described in the informed consent.

The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by Novartis, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

Novartis has appropriate processes and policies in place to handle personal data breaches according to applicable privacy laws.

Regulatory and ethical compliance

Compliance with Novartis and regulatory standards provides assurance that the rights, safety, and well-being of participants participating in non-interventional studies are protected (consistent with the principles that have their origin in the Declaration of Helsinki) and that the study data are credible and responsibly reported.

This study was designed and shall be implemented and reported in accordance with the GPP of the International Society for Pharmacoepidemiology ([ISPE 2016](#)), the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines ([Vandenbroucke et al 2007](#)), and with the ethical principles laid down in the Declaration of Helsinki.

This study fulfills the criteria of a 'European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) study' and follows the 'ENCePP Code of Conduct' ([European Medicines Agency 2016 References](#)).

The protocol and any proposed informed consent form must be reviewed and approved by a properly constituted Institutional Review Board/Independent Ethics Committee/Research Ethics Board (IRB/EC/REB) before study start. Prior to study start, the investigator is required

to sign a protocol signature page confirming his/her agreement to conduct the study in accordance with these documents and all the instructions and procedures found in this protocol and to give access to all relevant data and records to Novartis monitors, auditors, Novartis Clinical Quality Assurance representatives, designated agents of Novartis, IRBs/IECs/REBs and regulatory authorities as required.

Informed consent procedures

The protocol and the proposed informed consent form must be reviewed and approved by a properly constituted IRB/IEC/REB or before start. The physician or his/her representative will explain the nature of the study, including the risk and benefits to the participant or their legally authorized representative and answer all questions regarding the study. Participants must be informed that their participation is voluntary, but also that they can leave the study at any time. If withdrawal of consent occurs before analysis of samples is performed, no analysis will be performed. No further study-related activities will be performed and no new information will be collected once a participant informs the Study Doctor about their decision to stop participation.

For participants that have died prior to enrolling in the study, ICF may be provided by the site either in the form of a prior biobank ICF and/or consent provided by family member or other designated representative.

The physician must keep the original informed consent form signed by the participant (a signed copy is given to the participant).

Eligible participants may only be included in the study after providing written (witnessed, where required by law or regulation), IRB/EC-approved informed consent, or, if incapable of doing so, after such consent has been provided by a legally acceptable representative of the participant. In cases where the participant's representative gives consent, the participant should be informed about the study to the extent possible given his/her understanding. If the participant is capable of doing so, he/she should assent by personally signing and dating the written informed consent document or a separate assent form. In case of children (7-11 years old) and adolescent (12-17 years old) participants, the appropriate assent forms should be signed by the child/adolescent and by the parent/guardian. If during the study, a minor reaches adult age per local regulations, the minor must be consented as an adult with an adult informed consent form (ICF) and all other corresponding ICFs before continuing in the study. Informed consent must be obtained before any data are collected. The process of obtaining informed consent should be documented in the participant source documents.

Novartis will provide to treating physicians or other involved medical professionals in a separate document a proposed informed consent form that complies with the Declaration of Helsinki principle and regulatory requirements and is considered appropriate for this study.

8 Management and reporting of adverse events/adverse reactions

Collection of events of secondary malignancy of T-cell origin occurs outside of this study, and is documented in the Novartis pharmacovigilance system, as per applicable laws, regulations

and guidelines. Therefore, no solicited safety data capture is expected in this study, in relation to secondary malignancy of T-cell origin following tisagenlecleucel use.

However, if during the course of the study an adverse reaction (i.e. an adverse event suspected to be associated with the use of a drug) is identified in a participant receiving a Novartis product, it must be reported to Novartis as a spontaneous report or to the local Health Authority if required by national requirement for individual case safety reporting. Adverse reactions identified for non-Novartis products should be reported to the local Health Authority in accordance with national regulatory requirements for individual case safety reporting or the Marketing Authorization Holder.

9 Plans of disseminating and communicating study results

Participant level testing results will be communicated with the treating clinician in real-time as they become available. In parallel, the Novartis pharmacovigilance system will be updated to reflect the results of testing.

Upon completion and finalization of the study report, the results of this non-interventional study may be either submitted for publication and/or posted in a publicly accessible database of results. Publications will comply with internal Novartis standards and the International Committee of Medical Journal Editors (ICMJE) guidelines.

For applicable non-interventional PASS (in the EU or mandated by an EU Health Authority outside the EU), the final manuscript will be submitted to EMA and the competent authorities of the Member States in which the product is authorized within two weeks after first acceptance for publication.

10 References

- Ballow M, Sanchez-Ramon S, Walter J.(2022) Secondary Immune Deficiency and primary immune deficiency crossovers: Hematological Malignancies and Autoimmune diseases. *Front Immunol.* 13:928062. doi: 10.3389/fimmu.2022.928062.
- Bezerra E, Lulu L, Lima M et al (2025) Isolated oral CD30+/CD4+ CAR+ T cell lymphoma in long-term remission after radiotherapy. *Molecular Therapy Vol. 33 No 12* 6033-6040 doi.org/10.1016/j.ymthe.2025.0
- Carney DA, Westerman DA, Tam CS, et al. (2010) Therapy-related myelodysplastic syndrome and acute myeloid leukemia following fludarabine combination chemotherapy. *Leukemia* 24:2056-62.
- Chihara D, Dores GM, Flowers CR, et al (2021) The bidirectional increased risk of B-cell lymphoma and T-cell lymphoma. *Blood*; 138 (9):785-9.
- Corderio A C, Durisek G, Batista M V, et al. (2024) Late events after anti-CD-19 CAR T-cell therapy for relapsed/refractory B-cell non-Hodgkin lymphoma. *Front. Oncol.* 14:1404351. Doi:10.3389/fonc.2024.1404351.
- European Medicines Agency (2016) The ENCePP Code of Conduct – for Scientific Independence and Transparency in the Conduct of Pharmacoepidemiological and Pharmacovigilance Studies. Available from: encepp.eu/code_of_conduct/documents/ENCePPCodeofConduct_Rev3amend.pdf (Accessed 11 August 2016).
- European Medicines Agency. (2017) Guideline on good pharmacovigilance practices (GVP) EMA/873138/2011 rev. 2.
- European Medicines Agency. (2024) Pharmacovigilance Risk Assessment Committee minutes for the meeting on 10-13 June 2024. Available from [://.ema.europa.eu/en/documents/prac-recommendation/prac-recommendations-signals-adopted-10-13-june-2024-prac-meeting_en.pdf](http://.ema.europa.eu/en/documents/prac-recommendation/prac-recommendations-signals-adopted-10-13-june-2024-prac-meeting_en.pdf).
- Fowler N H, Dickinson M, Dreyling M, et al. (2021) Tisagenlecleucel in adult relapsed or refractory follicular lymphoma: the phase 2 ELARA trial. *Nat Med.*;28:325-32.
- Friedenreich C M, Ryder-Burbidge C, McNeil J (2021) Physical activity, obesity and sedentary behavior in cancer etiology: epidemiologic evidence and biologic mechanisms. *Mol Oncol*;15:790-800.
- Ghilardi G., Fraietta J A, Gerson, J N. et al. (2024) T cell lymphoma and secondary primary malignancy risk after commercial CAR T cell therapy. *Nat Med.*; 30:984–9.
- Govindarajan R, Jagannath S, Flick J T, et al. (1996) Preceding standard therapy is the likely cause of MDS after autotransplants for multiple myeloma. *Br J Haematol.* 95:349-53.
- Hamilton MP, Sugio T, Noordenbos T, et al. (2024) Risk of second tumors and T-cell lymphoma after CAR T-cell therapy. *N Engl J Med* ;390(22):2047-2060.
- Harrison SJ, Nguyen T, Rahman M, et al. (2023) CAR+ T cell lymphoma post ciltacabtagene autoleucel therapy for relapsed refractory multiple myeloma. *Blood.* 142 (1):6939-40.

Haycock P, Burgess S, Nounu A, et al. (2017) Association Between Telomere Length and Risk of Cancer and Non-Neoplastic Diseases: A Mendelian Randomization Study. *Jama Oncol.* 3(5):636-651.

Hect S S, Hatsukami D K (2022) Smokeless Tobacco and Cigarette Smoking: Chemical Mechanisms and Cancer Prevention. *Nat Rev Cancer* 22(3):143-55.

International Society for Pharmacoepidemiology (2016) Guidelines for good pharmacoepidemiology practices (GPP). *Pharmacoepidemiol Drug Saf*; 25:2-10.

Kobbe G, Bruggermann M, Baermann B N, et al. (2024) Aggressive Lymphoma after CD19 CAR T-Cell Therapy. *N Eng J Med.* 391:1217-26. doi:10.1056/NEJMoa2402730.

Kymriah (tisagenlecleucel) Summary of Product Characteristics (SmPC), 2020

Kymriah US prescribing information:

pharma.us.novartis.com/sites/pharma.us.novartis.com/files/kymriah.pdf, accessed May 10, 2018.

Levine B L, Pasquini MC, Connolly J E. et al. (2024) Unanswered questions following reports of secondary malignancies after CAR-T cell therapy. *Nature Med.*30(2):338-341.

Lowe T, Bhatia S, Somlo G (2007) Second Malignancies after Allogeneic Hematopoietic Cell Transplantation. *Biol Blood Marrow Transplant.* 13:1121-34.

Maude SL, Laetsch T W, Buechner J, et al. (2018) Tisagenlecleucel in Children and Young Adults with B-cell Lymphoblastic Leukemia. *N Engl J Med.* 378:439-48.

Milligan D, Ruiz De Elvira M C, Kolb H-J, et al (1999) Secondary leukaemia and myelodysplasia after autografting for lymphoma: results from the EBMIT. *Br J Haematol.*; 106:1020-6.

National Comprehensive Cancer Network (NCCN) (2023). NCCN Clinical Practice Guideline in Oncology. Pediatric Acute Lymphoblastic Leukemia Version 2.2023; National Comprehensive Cancer Network.

National Comprehensive Cancer Network (NCCN) (2025). NCCN Clinical Practice Guideline in Oncology. T-Cell Lymphomas Version 2.2025; National Comprehensive Cancer Network.

Pai S-Y, Lurain K, Yarchoan R. (2021) How immunodeficiency can lead to malignancy. *Am Soc Hematol Educ.* 1:287-95.

Patel S A, Spiegel J Y, Dahiya S (2024) Second Primary Cancer After Chimeric Antigen Receptor-T-Cell Therapy A review. *JAMA Oncol.* doi:10.1001/jamaoncol.2024.5412.

Rumgay H, Murphy N, Ferrari P et al (2021) Alcohol and Cancer: Epidemiology and Biological Mechanisms. *Nutrients.* 13(3173):1-13.

Schuster S J, Tan C S, Borchmann P, et al (2021) Long-term clinical outcomes of tisagenlecleucel in patients with relapsed or refractory aggressive B-cell lymphomas (JULIET): a multicentre, open-label, single-arm, phase 2 study. *Lancet Oncol.*; 22(10):1403-15.

Van Besien K (2006) The evolving role of autologous and allogeneic stem cell transplantation in follicular lymphoma. *Blood Rev.* 20:235-44.

Vandenbroucke JP, von Elm E, Altman DG, et al (2007) Strengthening the Reporting of Observational Studies in Epidemiology (STROBE): explanation and elaboration. *Ann Intern Med*; 147(8):W163-94.

Verdun N, Marks P. (2024) Secondary cancers after chimeric antigen receptor T- cell therapy. *N Eng J Med*. 390:584-6. doi:10.1056/NEJMp2400209.

11 Annexes

11.1 Annex 1 – List of stand-alone documents

None.

11.2 Annex 2 – ENCePP checklist for study protocols

Study title: A Non-Interventional Study (NIS) and Pot-Authorization Safety Study (PASS) to characterize secondary malignancies of T-cell origin following tisagenlecleucel therapy

EU PAS Register® number: Study not registered
Study reference number (if applicable): EU/1/18/1297/001

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	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	4
1.1.2 End of data collection ²	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	4
1.1.3 Progress report(s)	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
1.1.4 Interim report(s)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	4
1.1.5 Registration in the EU PAS Register®	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
1.1.6 Final report of study results.	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	4

Comments:

Section 2: Research question	Yes	No	N/A	Section Number
2.1 Does the formulation of the research question and objectives clearly explain:	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	6
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)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	5
2.1.2 The objective(s) of the study?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	6.2
2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	7.3
2.1.4 Which hypothesis(-es) is (are) to be tested?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
2.1.5 If applicable, that there is no <i>a priori</i> hypothesis?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	

Comments:

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.

<u>Section 3: Study design</u>		Yes	No	N/A	Section Number
3.1	Is the study design described? (e.g. cohort, case-control, cross-sectional, other design)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	7.1
3.2	Does the protocol specify whether the study is based on primary, secondary or combined data collection?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	7.2
3.3	Does the protocol specify measures of occurrence? (e.g., rate, risk, prevalence)	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
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))	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
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)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	9

Comments:

--

<u>Section 4: Source and study populations</u>		Yes	No	N/A	Section Number
4.1	Is the source population described?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	7.3
4.2	Is the planned study population defined in terms of:				
	4.2.1 Study time period	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
	4.2.2 Age and sex	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
	4.2.3 Country of origin	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
	4.2.4 Disease/indication	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	7.3
	4.2.5 Duration of follow-up	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
4.3	Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	7.3

Comments:

--

<u>Section 5: Exposure definition and measurement</u>		Yes	No	N/A	Section Number
5.1	Does the protocol describe how the study exposure is defined and measured? (e.g. operational details for defining and categorising exposure, measurement of dose and duration of drug exposure)	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	

<u>Section 5: Exposure definition and measurement</u>	Yes	No	N/A	Section Number
5.2 Does the protocol address the validity of the exposure measurement? (e.g. precision, accuracy, use of validation sub-study)	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
5.3 Is exposure categorised according to time windows?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
5.4 Is intensity of exposure addressed? (e.g. dose, duration)	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
5.5 Is exposure categorised based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
5.6 Is (are) (an) appropriate comparator(s) identified?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	

Comments:

No drug is administered in this study.

<u>Section 6: Outcome definition and measurement</u>	Yes	No	N/A	Section Number
6.1 Does the protocol specify the primary and secondary (if applicable) outcome(s) to be investigated?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	6.2
6.2 Does the protocol describe how the outcomes are defined and measured?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	7.8
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)	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
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)	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	

Comments:

--

<u>Section 7: Bias</u>	Yes	No	N/A	Section Number
7.1 Does the protocol address ways to measure confounding? (e.g. confounding by indication)	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
7.2 Does the protocol address selection bias? (e.g. healthy user/adherer bias)	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	

<u>Section 7: Bias</u>	Yes	No	N/A	Section Number
7.3 Does the protocol address information bias? (e.g. misclassification of exposure and outcomes, time-related bias)	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	

Comments:

--

<u>Section 8: Effect measure modification</u>	Yes	No	N/A	Section Number
8.1 Does the protocol address effect modifiers? (e.g. collection of data on known effect modifiers, subgroup analyses, anticipated direction of effect)	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	

Comments:

--

<u>Section 9: Data sources</u>	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)	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
9.1.2 Outcomes? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	7.5
9.1.3 Covariates and other characteristics?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	7.5
9.2 Does the protocol describe the information available from the data source(s) on:				
9.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
9.2.2 Outcomes? (e.g. date of occurrence, multiple event, severity measures related to event)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	7.5
9.2.3 Covariates and other characteristics? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, lifestyle)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	7.5
9.3 Is a coding system described for:				
9.3.1 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System)	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
9.3.2 Outcomes? (e.g. International Classification of Diseases (ICD), Medical Dictionary for Regulatory Activities (MedDRA))	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
9.3.3 Covariates and other characteristics?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	

<u>Section 9: Data sources</u>	Yes	No	N/A	Section Number
9.4 Is a linkage method between data sources described? (e.g. based on a unique identifier or other)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	7.9.1

Comments:

--

<u>Section 10: Analysis plan</u>	Yes	No	N/A	Section Number
10.1 Are the statistical methods and the reason for their choice described?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	7.8
10.2 Is study size and/or statistical precision estimated?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	7.6
10.3 Are descriptive analyses included?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	7.8
10.4 Are stratified analyses included?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
10.5 Does the plan describe methods for analytic control of confounding?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
10.6 Does the plan describe methods for analytic control of outcome misclassification?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
10.7 Does the plan describe methods for handling missing data?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
10.8 Are relevant sensitivity analyses described?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	

Comments:

--

<u>Section 11: Data management and quality control</u>	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)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	7.7
11.2 Are methods of quality assurance described?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	7.9
11.3 Is there a system in place for independent review of study results?	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	

Comments:

--

<u>Section 12: Limitations</u>	Yes	No	N/A	Section Number
12.1 Does the protocol discuss the impact on the study results of: 12.1.1 Selection bias?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	

<u>Section 12: Limitations</u>	Yes	No	N/A	Section Number
12.1.2 Information bias?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	7.10
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).	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	7.10
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)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	7.6

Comments:

--

<u>Section 13: Ethical/data protection issues</u>	Yes	No	N/A	Section Number
13.1 Have requirements of Ethics Committee/ Institutional Review Board been described?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	8
13.2 Has any outcome of an ethical review procedure been addressed?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	8
13.3 Have data protection requirements been described?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	8

Comments:

--

<u>Section 14: Amendments and deviations</u>	Yes	No	N/A	Section Number
14.1 Does the protocol include a section to document amendments and deviations?	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	

Comments:

Protocol amendment 2

<u>Section 15: Plans for communication of study results</u>	Yes	No	N/A	Section Number
15.1 Are plans described for communicating study results (e.g. to regulatory authorities)?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	8
15.2 Are plans described for disseminating study results externally, including publication?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	8

Comments:

--