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Novartis Research and Development

Non-Interventional Study Protocol (PASS) with secondary use of data

REDACTED PROTOCOL

CCTL019B2401

Title	Registry study to assess the long-term safety of patients with B lymphocyte malignancies treated with tisagenlecleucel
Protocol version identifier	V07 (Clean)
Date of last version of protocol	08-Feb-2023
EU PAS register number	EUPAS 32497
Active substance	Tisagenlecleucel
Medicinal product	Tisagenlecleucel
Product reference	Not available
Procedure number	EMEA/H/C/4090 and Section 505 (o)
Name of Marketing authorization holder(s)	Novartis Pharma AG
Joint PASS	No

Research question and objectives	The primary objective is to evaluate the long-term safety and the risk of secondary malignancies in patients with B lymphocyte malignancies treated with tisagenlecleucel in a real-world setting as measured by type and frequency of AEs.
Countries of study	North America and the European Union. Additional countries may be added upon commercialization.
Authors	[redacted], MD, [redacted]; [redacted], MD, [redacted] [redacted] MD, [redacted]

Table of contents

List of tables

List of figures

List of abbreviations

AE	Adverse Event
B-ALL	B-cell Acute lymphoblastic leukemia
BOR	Best Overall Response
CAPA	Corrective and Preventive Actions
CAR	Chimeric Antigen Receptor
CAR-T	Chimeric Antigen Receptors T cell
CFR	Code of Federal Regulations
CI	Confidence Interval
CIBMTR	The Center for International Blood and Marrow Transplant Research
CR	Complete remission/ response
CRi	Complete remission with incomplete blood count recovery
CRR	Complete Response Rate
CRS	Cytokine release syndrome
DLBCL	Diffuse large B-cell lymphoma
DOR	Duration of response
EBMT	The European Society for Blood and Marrow Transplantation
EC	Ethics Committee
EMA	European Medicines Agency
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
EU	European Union
FACT	Foundation for the Accreditation of Cellular Therapy
FDA	Food and Drug Administration
FL	Follicular lymphoma
GPP	Good Pharmacoepidemiology Practices
GVP	Good Pharmacovigilance Practice
HA	Health Authority
HCP	Health Care Provider
ICF	Informed Consent Form
ICSR	Individual Case Safety Reports
IRC	Independent Review Committee
KM	Kaplan-Meier
LPFV	Last patient first visit
LPLV	Last patient last visit
MAH	Marketing Authorization Holder
MAP	Managed Access Program
MedDRA	Medical Dictionary for Regulatory Activities
MHRA	The Medicines and Healthcare products Regulatory Agency
NIS	Non-Interventional Study
OOS	Out of Specification
ORR	Overall response/ remission rate
OS	Overall Survival
PASS	Post-Authorization Safety Study
PR	Partial response
r/r	Relapsed or refractory

RCL	Replication Competent Lentivirus
RMP	Risk Management Plan
SAP	Statistical Analysis Plan
SCT	Stem cell transplantation
SNAR	Serious neurological adverse reaction
STROBE	Strengthening the Reporting of Observational Studies in Epidemiology
USA	United States of America
WBC	White Blood Cell
WHO	World Health Organization

1 Responsible parties

Table 1-1 Responsible parties

Role	Person
Main protocol author(s)	[redacted] MD, [redacted] MD, [redacted] MD, [redacted]
Principal investigator (PI)	Not applicable
MAH contact person	[redacted], MD, [redacted]

2 Abstract

Title: Registry study to assess the long-term safety of patients with B lymphocyte malignancies treated with tisagenlecleucel.

Version and date: v07, 08-Feb-2023

Name and affiliation of main author:

[redacted], MD, [redacted]

Rationale and background:

Tisagenlecleucel is a genetically modified autologous immunocellular cancer therapy, approved under the tradename Kymriah® for the treatment of certain patients with relapsed/refractory (r/r) B-cell acute lymphoblastic leukemia (B-ALL), large B-cell lymphoma including diffuse large B-cell lymphoma (DLBCL), and r/r follicular lymphoma (FL). Approved indications may vary by countries.

CAR-T (Chimeric Antigen Receptors T cell) therapies, like tisagenlecleucel, are a novel class of therapy involving genetic modification of T cells. The assessment of long-term outcomes in large patient populations is of interest due to limited data availability and is a post-approval commitment for the FDA and EMA.

This protocol plans to collect long-term, real-world safety and effectiveness data from patients treated with tisagenlecleucel [redacted] in compliance with Health Authority guidelines for gene therapy (FDA) and advanced therapy medicinal products (EMA).

Research question and objectives: This study will inform on long-term real-world safety and effectiveness of tisagenlecleucel. The primary objective is to evaluate the long-term safety and the risk of secondary malignancies in patients with B lymphocyte malignancies treated with tisagenlecleucel in a real-world setting. The main secondary objective is to evaluate the long-term effectiveness of tisagenlecleucel.

Study design: This post-authorization safety study (PASS) is a global, non-interventional, multi-database study that will obtain data on patients treated with marketed tisagenlecleucel in an authorized indication. Patient data will be retrieved from established Registries conducted by the following groups:

- The European Society for Blood and Marrow Transplantation (EBMT) and

- The Center for International Blood and Marrow Transplant Research (CIBMTR)

The study consists of 2 cohorts:

- in cohort 1, a 5-year enrollment period is planned to enroll approximately 2,500 patients with either r/r pediatric/young adult B-cell ALL (at least 1,000 patients) or with r/r large B-cell lymphoma (at least 1,500 patients).
- in cohort 2, a 3-year enrollment is planned to enroll approximately 300 patients with r/r follicular lymphoma.

Cohort 1 (data retrieved from CIBMTR and EBMT) and cohort 2 (data retrieved from CIBMTR only) patients will be followed for safety and overall survival (OS) for up to 15 years after tisagenlecleucel infusion. Cohort 1 and cohort 2 patients will be followed for effectiveness (other than overall survival) up to 15 and 5 years, respectively. The total study duration will therefore be approximately 23 years.

Setting and study population: The study population will include patients who received tisagenlecleucel infusion in the commercial setting. This study will also include patients who received tisagenlecleucel under a managed access program or other pathway, [redacted]

Variables: Adverse events (AE). This includes secondary malignancies, [redacted]. The study also collects data on frequency and outcome of pregnancy for female patients and for partners of male patients, overall response rate, minimal residual disease (MRD) for B-ALL patients, duration of response, relapse-free survival, event-free survival (B-ALL patients), progression-free survival (lymphoma patients), and overall survival.

Data sources: Data for this study will be retrieved from ongoing Registry holders: CIBMTR and/or EBMT. CIBMTR and EBMT will be responsible and accountable for the accuracy and completeness of the data entered in their databases. For secondary malignancies, follow up for additional information and/or testing of tissue and/or blood as outlined, is performed separately from this study.

Study size: The sample size calculation for this study is not based on statistical considerations but reflective of request by health authorities. [redacted]

Data analysis: Safety data will be summarized and listed by approved indication in interim reports up until the end of the study. The final Clinical Study Report will be prepared including all planned effectiveness and safety analyses at the end of the study.

Milestones:

- Start date of data collection
  Cohort 1:
  Cohort 2:
- End date of data collection:
  Cohort 1:
  Cohort 2:

Safety reports will be submitted periodically in accordance with local regulatory requirements and the tisagenlecleucel EU Risk Management Plan (RMP) for the duration of the study:

Reports based on EBMT registry only

For cohort 1, intermediate quarterly report will be submitted to applicable Health Authorities in the instance of a newly occurring safety concern (including a new risk or safety signal) or in case the safety profile becomes more unfavorable.

3 Amendments and updates

Table 3-1 Study protocol amendments and updates

Number	Date	Section of study protocol	Amendment or update	Reason
1	28 Aug 2018	Refer to Amendment 1 section	Adapted all relevant sections for secondary use of data with data owners CIBMTR and EBMT	Study design was modified from a non-interventional study with primary data collection to a non-interventional study with secondary use of data
2	10 Oct 2019	Refer to Amendment 2 section	Refer to Amendment 2 section	Further clarify the frequency, type and content of the safety reports to be submitted to the HAs, describe the data source for the PASS, and the quality of data collection.
3	14 Oct 2021	Refer to Amendment 3 section	Refer to Amendment 3 section	Stop entry of individual safety data, transferred from the Registry holder(s), into the Novartis global safety database (Argus)
4	24 Jan 2022	Refer to Amendment 4 section	Refer to Amendment 4 section	Corrected wrong cutoff date for study CCTL019B2202 (ELIANA) in Section 3 Amendment 3 Updated Abstract version and date in Section 2
5	04 Aug 2022	Refer to Amendment 5 section	Refer to Amendment 5 section	Adding a cohort of 300 r/r Follicular lymphoma patients for 15 years follow up. Clarified that the primary objective includes the evaluation of the risk of secondary malignancies and updated the primary endpoint to include the identification of patients with secondary malignancies (formerly an exploratory endpoint)..
6	18 Oct 2022	Refer to Amendment 6 section	Refer to Amendment 6 section	Removal of semi-annual reports based on EBMT registry
7	08-Feb-2023	Refer to Amendment 7 section	Refer to Amendment 7 section	Adding Cohort 1 intermediate quarterly reports based on EBMT registry

Amendment 07 (08-Feb-2023)

Amendment 07 rationale

The purpose of this amendment is to add the provision of an intermediate quarterly report based solely on EBMT registry [redacted]

- Abbreviation list: updated.
- Abstract: version and date updated.

  Paragraph starting with "Cohort 1 and cohort 2 patients will be followed..." was modified by adding more details. i.e. "Cohort 1 (data retrieved from CIBMTR and EBMT) and cohort 2 (data retrieved from CIBMTR only)".

  Paragraph with the heading title: "Reports based on EBMT registry only" was added to the section.
- Section 3: table 3-1 was updated with protocol amendment 7.
- Section 4: paragraph with heading title: "Intermediate quarterly reports" was added under Table 4-1.
- Section 7.8.1: was corrected and aligned with other sections of the protocol.
- Section 10: wording was aligned with other sections of the protocol.
- Sub-section 10.2: paragraph with heading title: "Intermediate quarterly reports based on EBMT registry" was added and subsequent sub-sections' numbering was updated accordingly.
- Reference list: Lee at al 2014 reference was removed as it is no longer cited in the protocol.
- Editorial changes including minor deletions and additions were made within this protocol amendment.

Amendment 06 (18-Oct-2022)

Amendment 06 rationale

The purpose of this amendment is to remove the provision of semi-annual reports that are based solely on EBMT registry data. [redacted] Therefore, Novartis proposed the removal of the semi-annual reports in this protocol amendment.

- Abstract: version and date updated.
  From the title "Reports based on CIBMT and EBMT registries" the wording "For both cohorts" was removed.
  Semi-annual reporting was removed from the section.
- Section 3: section is updated with protocol amendment 6
- Table 3-1: table is updated with protocol amendment 6
- Table 4-1: semi-annual reporting was removed
- Section 7.7.5: semi-annual reporting was removed
- Section 7.8.1.1 wording was aligned with other sections of the protocol
- Section 9.1: wording was corrected and aligned with other sections of the protocol
- Section 10.2: the entire section describing semi-annual reports based on EBMT registry was deleted

Amendment 05 (04-Aug-2022)

Amendment 05 rationale

The purpose of this amendment is to introduce a new cohort for the evaluation of long-term safety of patients treated with tisagenlecleucel for the approved follicular lymphoma (FL) indication. Moreover, in response to a request from the FDA, it was clarified that the primary objective includes the evaluation of the risk of secondary malignancies. The primary endpoint was updated to include the identification of patients with secondary malignancies for further analyses (formerly an exploratory endpoint).

- Authors change indicated in the cover pages (page 2)
- List of abbreviations: BOR (Best Overall Response), CAR (Chimeric Antigen Receptor), CAR-T (Chimeric Antigen Receptors T cell), CI (Confidence Interval), CRR (Complete Response Rate), IRC (Independent Review Committee), Follicular lymphoma (FL), last patient first visit (LPFV), SNAR (Serious neurological adverse reaction) and WBC (White Blood Cell) added.
- Table 1-1: main authors' changes indicated in the table
- Abstract: name of the main author changed
- Abstract: Follicular lymphoma added as approved indication in a new cohort and text is aligned with other section of the protocol
- Section 2: Follicular lymphoma added as approved indication in a new cohort and figure 2.1 added. Number of treated patients in the study updated from 2,500 to 2,800. The total study duration updated to 23 years.
- Section 2 and section 7.1 aligned: Addition of the cohort for FL for 15 years safety follow-up and for at least 5 years efficacy follow up
- Section 2: "For secondary malignancies, follow up for additional information and/or testing of tissue and/or blood as outlined, is performed separately from this study. "added for process clarification and aligned as per section 7.3.1.2.
- Section 4: Milestones updated and aligned as per section 2.
- Section 5 updated with the approved tisagenlecleucel indication for the treatment of patients with follicular lymphoma.
- Section 5.3 added for the description of "Tisagenlecleucel for adults with relapsed/refractory follicular lymphoma".
- Section 6: In Table 6-1: Primary objective updated by adding the risk of secondary malignancy and primary endpoint updated by adding "The identification of patients with secondary malignancy for detection of CAR transgene and/ or CAR surface expression and presence of replication-competent lentivirus". For the secondary objective: Complete response rate added for FL and 5 years duration for efficacy follow up for FL. Due to the modification of the primary objective and endpoint, the exploratory objective and endpoint have been deleted.
  Footnote text was updated accordingly.

- Section 7.1: Patients follow up for safety and OS added and aligned with other section of the protocol
- Section 7.2: evaluation of the FL recruitment period in over a 3-year enrollment period and alignment with section 7.5.
- Section 7.3.1.2: For Secondary malignancy, update for treating physicians/healthcare providers who should contact Novartis directly within 72 hours of diagnosis of a secondary malignancy. To clarify the limitation of the follow up of secondary malignancy cases, the sentence "Novartis will perform due diligence when contacting the treating physicians/ HCPs for potential cases of secondary malignancies and will strongly recommend analysis of relevant samples if the secondary malignancy is confirmed." is updated; sentence "In these cases, Novartis provides kits for this testing to the treating clinician and results of this testing are communicated to the treating clinician via a formal follow up document, and recorded into the appropriate data base(s)." added for operational details; Figure 7-2 is updated as the results are communicated to the HCPs.
- Section 7.4.1: In the sentence: "Long-term safety and effectiveness data will be collected such that the observational follow-up for each patient will be 15 years from last infusion or until patient is lost to follow-up, death, early discontinuation or completion of the study", "early discontinued" added and "All patients will be followed-up for safety, effectiveness and survival until LPLV is achieved" deleted in section 7.1 for consistency.
- Table 7-1: "Secondary malignancy sample collection (the work-up of this endpoint will be performed outside of PASS B2401)" - (the work-up of this endpoint will be performed outside of PASS B2401) added also in section 6 for clarification of the process.
- Section 7.4.3.3: Survival period clarified as until 15 years after infusion".
- Section 7.5: Study size updated and aligned as per section 2.
- Section 7.6 updated for EBMT systems clarifications
- Section 7.7.4.2 added for the definition of the Complete response rate applicable to FL patients.
- Section 7.7.5: "Safety reports" updated to "Reports" as title of the section and clarification was added to describe the required reports for the study which are not limited to safety only.
- Section 7.7.6: section updated to align with other section of the protocol (section 2 and 10.4)
- Section 8: Title changed from patients to human subjects
- Section 10.1: updated as annual reports are applicable for both cohorts, aligned with section 2. Clarification added as these reports will contain an evaluation of adverse events of special interest including important identified risk.
- Section 10.2: cohort 1 description added to align with section 2
- Section 10.3: Milestones aligned with section 2.

- Section 10.4: added for the Final report for cohort 1.
- Section 10.5: clarification added as the Clinical study report is applicable “for the complete study patient population”
- Editorial changes including minor deletions and additions are also made within this protocol amendment.
- Section 11 for References section updated

Amendment 04 (24-Jan-2022)

Amendment 04 rationale

This amendment is prepared to update two incorrect dates reported in Protocol amendment 3 and requested for modification by the European Medicines Agency (EMA).

Changes to the protocol

- A summary of the changes includes the following: Updated Authors on the cover page of the protocol
- Updated Table 1-1 for Responsible parties
- Section 2 Abstract: Updated version and date of abstract for alignment with current version of protocol: v04, 24-Jan-2022
- Updated Table 3-1 for Amendment 4
- Section 3 Amendments and updates: Updated the incorrect cutoff date of 01-Jul-2021 given in the section “Amendment 03 - Changes to the protocol” to the correct date of 01-Jul-2019 to align the date correctly to Section 5.1 of the protocol

Amendment 03 (14-Oct-2021)

Amendment 03 rationale

This amendment is prepared to address a finding by the Medicines and Healthcare products Regulatory Agency (MHRA) regarding safety reporting.

The purpose is to stop entry of individual safety data, transferred from the Registry holder(s), into the Novartis Safety Database and creation of individual case safety reports (ICSRs) from secondary data. This is in accordance with EMA Good Pharmacovigilance Practice (GVP) Module VI Revision 2 (2017), Section VI.C.1.2.1.2 (page 30), entitled 'Non-interventional post-authorization studies with a design based on secondary use of data'. Accordingly, information on pharmacovigilance safety data management has been updated. This amendment is in line with the Novartis Corrective and Preventive Actions (CAPA) commitment to address a finding issued by The MHRA following a GVP inspection conducted in May 2021. Safety relevant results will continue to be analyzed and presented in periodic study reports as outlined in Section 10 of the study protocol.

Changes to the protocol

A summary of the major changes includes the following:

- Updated Table 1-1 for Responsible parties
- Section 2: For alignment with section 5, country status updated; for alignment with section 7.2, "for an authorized indication in participating countries" removed. For alignment with Table 6-1, variables for exploratory analyses detailed.
- Updated Section 5 for approvals in additional countries: "Tisagenlecleucel is approved in the United States, European Union, Canada, Switzerland and Australia" replaced by ". Tisagenlecleucel is approved in 42 countries/regions worldwide including in the United States, the European Union and Japan, and is marketed under the proprietary name tradename Kymriah®."
- Updated Section 5.1 to reflect CCTL019B2202 (ELIANA) data based on most recent cutoff date (01-Jul-2019) with updated number of patients from 75 to 79.
- Updated Section 5.2 to reflect CCTL019C2202 (JULIET) data based on most recent cutoff date (20 February 2020) with updated number of patients from 92 to 115.
- Updated Section 7.3.1.1: Potential risk of secondary malignancies added
- Updated Section 7.3.1.1: "and additional details are provided in Section 9.1.1." deleted.
- Section 7.3.1.2 and Table 6-1: RCL testing added to evaluate secondary malignancy samples and clarified language in Section 7.3.1.2.
- Updated Section 7.6: data management system updated for EBMT part from "MACRO" to "CASTOR". The sentence "The EBMT, in cooperation with the participating centers, has the primary responsibility for data completeness and accuracy." removed as present in Section 7.8.1.1.
- Updated Section 7.8.1.1: data management system updated for EBMT part from "MACRO" to "CASTOR" and "21 CFR part 11 adherent" removed as not relevant.

- Updated Section 8: Clarified language and the sentence "In addition, as per the EMA guidance "Guideline on safety and efficacy follow-up and risk management of Advanced Therapy Medicinal Products" (draft dated 25 January 2018), the MAH (Novartis) must ensure procedures are in place for follow-up of reported adverse reactions which allows identification of the batch number linked to the reported adverse reactions in place (traceability)." removed.
- Updated and restructured Section 9:
  - New information added on safety reporting based on secondary use of data.
  - Sentence "The Novartis Patient Safety department will enter all AEs into the Novartis safety database and process them as post-marketing clinical trial cases as per pharmacovigilance standard operating procedures, including reporting of ICSRs to Health Authorities." removed.
  - Sentence "Respective AE cases will be included in the review and analysis provided in PSUR Section 16." removed.
  - Section 9.1.2 for Pregnancy deleted since status is already stated in the Section 9.1.
- References: "Testing of Retroviral Vector-Based Human Gene Therapy Products for Replication Competent Retrovirus During Product Manufacture and Patient Follow-up, Guidance for Industry" and "Guideline on good pharmacovigilance practices (GVP) EMA/873138/2011 rev. 2. (2017)" are added.
- Website [redacted] has been updated to [redacted]
- Sentence added to clarify that a process for consent and collection of samples will occur outside of the study.

Amendment 02 (10-Oct-2019)

Amendment 02 rationale

The purpose of this amendment is to further clarify the frequency, type and content of the safety reports to be submitted to the HAs, describe the data source for the PASS, and the quality of data collection. As a result, changes were made to the following:

- Data quality and auditing/monitoring measures performed by the Registry holder was added.
- Additional information on spontaneous reporting of adverse reactions by physicians was also added.
- Interim reporting frequency and schedule was updated as per Health Authority recommendation.
- Clarification added that enrollment will continue until minimum patient population is reached for each indication.

Changes to the protocol

Changes to specific Sections of the protocol are shown in track changes version of the protocol using red font and red strike through. Majority of the revisions were clarifications, updates and corrections throughout the protocol. A summary of the major changes include the following:

- Updated Section 2, Section 5, Section 7.1, Section 7.2 and Section 7.7 to clarify the OOS batches
- Revised Table 4-1 on safety and interim report frequency
- Revised table 6-1 with administrative changes, clarification and removed repetition.
- Updated Section 7.1 with administrative changes
- Updated Section 7.2.1
  - Inclusion 2: Added clarification with target population and inclusion criterion
- Updated Section 7.2.2
  - Exclusion: Clarified target excluded population
- Updated Section 7.3.1.1 trimmed repetition and added clarification about adverse event of special interest (AESI)
- Updated Section 7.3.1.2 Added language on handling of sample collection
- Added figure 7.2 Added diagram on sample collection
- Updated figure 7-3 to show connection of sample collection with treating physicians
- Updated Section 7.4 to delete the GVP module 4 reference as not applicable for the European registry holder i.e., EBMT
- Updated Section 7.4.1 to clarify data collection
- Updated Section 7.6 added information on electronic data collection mechanism and data transfers details
- Updated the safety set in Section 7.7.1
- Updated Section 7.7.3 to clarify primary analysis
- Updated Section 7.7.4.1 to clarify the OS

- Updated Section 7.7.4.4 to clarify the RFS
- Updated Section 7.7.4.5 to correct definition of study day 1
- Updated data quality assurance in Section 7.8
- Added Section 7.8.1.1 with EBMT quality measures performed
- Added Section 7.8.1.2 with CIBMTR quality and auditing measures performed
- Updated Section 8.1.1 Informed Consent procedures clarified ICF template use in case of secondary malignancy sample collection and analysis
- Updated Section 9 clarified the reporting of adverse event from CIBMTR and EBMT and encourage physicians to spontaneously report them to Novartis/local HA
- Updated Section 10 to clarify the frequency, type and content of the safety reports to be submitted to the HAs

Amendment 01 (28-Aug-2018)

Amendment 01 rationale

[redacted]

- The study design was modified from a non-interventional study with primary data collection to a non-interventional study with secondary use of data. Data will be owned by CIBMTR and EBMT and will be transferred to Novartis periodically at pre-specified time points. CIBMTR and EBMT will maintain data quality and direct interaction with study centre(s). Novartis will not be responsible for auditing or monitoring sites that participate in the Registry.
- The amended protocol is in line with the recommendation from the EMA CAR-T Registry workshop dated 09 February 2018.
- [redacted]

4 Milestones

Table 4-1 Planned dates of study milestones

Milestone	Planned date
Start of data collection cohort 1 B-ALL/DLBCL (1st CIBMTR data transfer to Novartis) Start of data collection cohort 2 FL	[redacted]
Annual Reports	**Annual reports based on CIBMTR and EBMT registries** [redacted]
Interim Reports	[redacted]
Final report for completion of the PASS (for B-ALL and DLBCL only)	[redacted]
End of data collection	[redacted]
Registration in the EU PAS register	
Study completion date	[redacted]
Final Clinical Study Report	

Intermediate quarterly reports

Intermediate quarterly reports based upon data obtained from the EBMT registry for r/r B-ALL and r/r DLBCL indications will be submitted to applicable Health Authorities in the instance of a newly occurring safety concern (including a new risk or safety signal) or in case the safety profile becomes more unfavorable.

5 Rationale and background

Tisagenlecleucel is a genetically modified autologous immunocellular cancer therapy approved under the tradename Kymriah® for the treatment of patients with relapsed/refractory (r/r) B-cell acute lymphoblastic leukemia (B-ALL), large B-cell lymphoma including diffuse large B-cell lymphoma (DLBCL), and r/r follicular lymphoma. Approved indications may vary by countries.

The product involves reprogramming a patient's own T-cells with a transgene encoding a chimeric antigen receptor (CAR) to identify and eliminate CD19 expressing cells. The CAR is comprised of a murine single chain antibody fragment, which recognizes CD19, fused to intracellular signaling domains from 4-1BB (CD137) and CD3 zeta. The CD3 zeta component is critical for initiating T-cell activation and antitumor activity, while 4-1BB enhances the expansion and persistence of tisagenlecleucel cells. Upon binding to CD19 expressing cells, the CAR transmits a signal to promote T-cell expansion, activation, target cell elimination and persistence of the tisagenlecleucel cells.

This protocol plans to collect long-term safety and effectiveness data from patients treated with the CAR-T therapy tisagenlecleucel [redacted] per Health Authority guidelines for gene therapy (FDA) and advanced therapy medicinal products (EMA).

This study is designed as non-interventional study with secondary use of data. Data for this study will be retrieved from databases of two large Registry holders [The European Group Society for Bone Blood and Marrow Transplantation (EBMT) and the United-States based Center for International Blood and Marrow Transplant Research (CIBMTR)]. These Registry holders will collect data from patients who received tisagenlecleucel infusion in the commercial setting, under a managed access program or other pathway, [redacted]

Data collected by the Registry holders will reflect real-world safety and effectiveness of tisagenlecleucel [redacted] further support the benefit-risk assessment of tisagenlecleucel in the approved indications. The study may also allow for detection of new safety signals and provide further guidance on the management of safety risks associated with tisagenlecleucel to patients, health care providers (HCPs) and treating physicians, who use tisagenlecleucel in both the post marketing and clinical trial setting.

Details about each of the Registry holders, data collection methods and analysis, as well as patient protection and quality control measures are provided in Section 7.

5.1 Tisagenlecleucel for children and young adults with relapsed/refractory B-cell precursor acute lymphoblastic leukemia

The efficacy and safety of tisagenlecleucel in r/r B-cell ALL patients up to 25 years of age were demonstrated in a multi-center, global phase 2 study (CCTL019B2202; ELIANA). As of 01-Jul-2019, 79 children and young adults with relapsed/refractory B-cell ALL received an infusion of tisagenlecleucel. At enrollment, patients had a median age of 11 years (range, 3 to 24), a median of 3 previous therapies (range, 1 to 8), and a median marrow blast percentage of 74% (range, 5 to 99); 48 patients (60.8%) had undergone previous allogeneic hematopoietic stem-cell transplantation.

The overall remission rate (best overall response of CR/CRi during 3 months) was 82.3%; 49 patients (62%) had complete remission (CR), and 16 (20.3%) had complete remission with incomplete hematologic recovery (CRi). A total of 64 out of the 65 patients who had a best overall response of complete remission with or without complete hematologic recovery during 3 months were negative for minimal residual disease (for one patient, MRD data was not available).

The rate of relapse-free survival among the 66 patients with a response to treatment at any time (including 65 patients with a response during the first three months) was 80.8% at 6 months and 67.4% at 12 months. Among the 66 patients with remission, 24 (36.4%) had a relapse or died due to the underlying cancer.

The rate of event-free survival was 49.3% at 24 months and 44.4% at 39 months. The rate of overall survival was 67.7% at 24 months after infusion and 62.8% at 48 months after infusion.

All patients had at least one adverse event during the study; 75 of 79 patients (94.9%) had an adverse event that was suspected by the investigators to be related to tisagenlecleucel. The most common adverse events of any grade at any time after infusion were cytokine-release syndrome (77.2%), pyrexia (43.0%), hypogammaglobulinemia (40.5%), decreased appetite (38.0%), febrile neutropenia (34.2%) and headache (34.2%).

AEs indicative of the risk 'serious neurological adverse reactions'(SNAR) occurred in 31 of 79 patients (39.2%) within 8 weeks after infusion. Ten patients (12.7%) had grade 3 neurologic events; no grade 4 events or cerebral edema were reported. The most common neurologic events of any grade were encephalopathy (10.1%), confusional state (8.9%), delirium (8.9%), tremor (7.6%), agitation (6.3%), and somnolence (6.3%); 2 patients (2.5%) had seizures of any grade (one patient with grade 3). The majority of neurologic events occurred during the CRS or shortly after its resolution. Twenty-eight deaths occurred after tisagenlecleucel infusion, the majority (21 deaths) related to progressive B-cell ALL (Maude, et al 2018).

Tisagenlecleucel resulted in high remission rates and durable remissions without the need for additional therapy in high-risk pediatric and young adult patients with relapsed and refractory B-cell ALL. The risks were substantial but were mitigated in most patients with supportive care and cytokine blockade.

5.2 Tisagenlecleucel for adults with relapsed/refractory diffuse large B-cell lymphoma

A global, multicenter trial demonstrated the efficacy and safety of tisagenlecleucel in patients with DLBCL. In the JULIET (CCTL019C2201) phase 2 study (cutoff date 20-Feb-2020), 115 patients (aged 18 years or older and had previously received ≥ two lines of therapy) with relapsed/refractory DLBCL were infused with tisagenlecleucel. Patients had either relapsed after autologous HSCT or were ineligible for autologous HSCT. Patients with DLBCL transformed from follicular lymphoma and high-grade double-hit lymphoma were included. Patients were excluded if they received prior CD19-directed therapy, had primary mediastinal DLBCL, had prior allogeneic HSCT, or had active central nervous system (CNS) involvement.

Prior to infusion, 89.6% of patients received bridging therapy, including combinations of rituximab (53%), gemcitabine (34.8%), platinum compounds (35.7%), dexamethasone (22.6%),

etoposide (22.6%), and cytarabine (18.3%), as well as agents such as ibrutinib (8.7%) and lenalidomide (7%).

Efficacy was established on the basis of complete response (CR) rate and duration of response (DOR), as determined by an independent review committee. The overall response rate (ORR) was 53%, with 39.1% CR and 13.9% partial response (PR). The median duration of response was not reached. Response durations were longer in patients who achieved CR, as compared to patients with a best response of partial response (PR). Median OS among all infused patients was 11.1 months.

Any time post-infusion, regardless of study drug relationship, the most frequently reported AEs in ≥25% of patients were CRS (57.4%), anemia (47.8%), WBC count decreased and pyrexia (35.7% each), neutrophil count decreased (34.8%), platelet count decreased (33.9%), diarrhea (31.3%), nausea (28.7%), fatigue (26.1%), and hypotension (25.2%).

Twenty-three patients (20%) had AEs indicative of the risk SNAR within 8 weeks post-tisagenlecleucel infusion. Eight patients (7%) had grade 3, and five patients (4.3%) had grade 4 AEs indicative of the risk SNAR. The most commonly occurring grade 4 event was encephalopathy, which occurred in four patients. In these four patients, encephalopathy occurred during a CRS episode. The high rate of durable responses sustained at 6 and 9 months with tisagenlecleucel infusion in the JULIET trial were promising. Adverse events, such as CRS can be severe and life threatening, yet were manageable. Patients with r/r DLBCL who are not eligible for auto-HSCT or for whom auto-HSCT was not successful have very few treatment options. Within this population, tisagenlecleucel is an effective therapy.

5.3 Tisagenlecleucel for adults with relapsed/refractory follicular lymphoma

A global, multicenter trial demonstrated the efficacy and safety of tisagenlecleucel in patients with follicular lymphoma (FL). In the ELARA phase 2 trial (CCTL019E2202), 97 FL patients (aged ≥ 18 years) had been infused with tisagenlecleucel. The study included patients who were refractory to a second or later line of systemic therapy, relapsed within 6 months after completion of a second or later line of systemic therapy, relapsed during anti-CD20 maintenance or within 6 months after its completion, or relapsed after autologous HSCT. The primary objective was to evaluate the efficacy of tisagenlecleucel as measured by complete response rate (CRR) determined by independent review committee (IRC).

Of the 97 patients infused, 44 patients (45.4%) received optional antineoplastic bridging therapy prior to tisagenlecleucel infusion for stabilization of disease. The most commonly used agents (in ≥ 5% of patients) were rituximab (21.6%), dexamethasone (11.3%), gemcitabine (10.3%), oxaliplatin (7.2%), prednisolone (7.2%), etoposide (6.2%), cyclophosphamide (5.2%), and vincristine (5.2%). In 5% patients, only corticosteroids were administered as bridging therapy. Furthermore, two patients (%) received bridging radiotherapy – one patient received only radiotherapy and the other patient received radiotherapy and corticosteroids.

The primary endpoint was complete response rate (CRR) as determined by an independent review committee in the efficacy analysis set (n=94). The overall response rate (ORR) was 86.2%, with 69.1% CR and 17% partial response (PR). The median duration of response was not reached and the estimated probability at 12 months for duration of response was 71.6% (95%

CI: 58.9, 80.9), whereas the estimated probability at 12 months for progression-free survival was 67% (95% CI: 56.0, 75.8). Median OS was not reached, and the estimated probability of overall survival was 95.3% (95% CI: 88.0, 98.2) at Month 12 and 91.6% (95% CI: 81.7, 96.2) at Month 15. The treatment was tolerable with a favorable safety profile, the most common AEs reported in ≥ 20% of the patients were CRS, neutropenia, anemia, headache, diarrhea, and decreased WBC count. The most common grade ≥ 3 AEs reported in ≥ 10% of patients any time post-infusion were neutropenia (42.3%), neutrophil decreased (17.5%), WBC decreased (17.5%), anemia (16.5%), febrile neutropenia (12.4%), and thrombocytopenia (11.3%). Adverse events were reported primarily within 8 weeks post-tisagenlecleucel infusion (96.9%) and between > 8 weeks to 1 year post-infusion (83.3%). The incidence of AEs decreased considerably 1 year after infusion (26.8%, 19/71 patients).

CRS was identified in 49.5% of patients, and only 1% were Grade ≥ 3. Thirteen events of SNARs (including both non-serious and serious AEs) were reported in 11 patients (11.3%).

6 Research question and objectives

This study is not designed to test a formal hypothesis but has been initiated to analyze long-term safety data in patients treated with tisagenlecleucel in line with Health authority requirements.

The objectives and related endpoints of the study are presented in Table 6-1. Definitions and details of analyses are provided in Section 7.7.

Table 6-1 Objectives and related endpoints

Objectives	Endpoint
Primary	
Evaluate the long-term safety and the risk of secondary malignancies in patients with B lymphocyte malignancies treated with tisagenlecleucel in a real-world setting	The type and frequency of AEs (including secondary malignancies) The identification of patients with secondary malignancies[1] for detection of CAR transgene and/ or CAR surface expression and presence of replication-competent lentivirus[2]
Secondary	
Evaluate the long-term effectiveness of tisagenlecleucel by approved indication The efficacy endpoints for FL are followed at least 5 years after LPFV (except for OS which will be followed for 15 years).	Overall response rate (ORR) (i.e., B-ALL: CR + CRi; and lymphoma: CR + PR) • Complete response rate (CRR) for follicular lymphoma • MRD status in bone marrow in B-ALL patients who achieve a best overall response (BOR) of CR or CRi • Duration of response (DOR) • Relapse-free survival (RFS) • Event-free survival (EFS) for B-ALL patients • Progression free survival (PFS) for lymphoma patients • Overall survival (OS)
Evaluate any pregnancy occurring in women of child-bearing potential or female partners of males after infusion with tisagenlecleucel	• Frequency and outcome of pregnancy
CR=complete remission/response, CRi=complete remission with incomplete blood count recovery, PR=partial response	

Objectives	Endpoint
[1]Identification of patients with secondary malignancies will be performed for patients whose batch numbers are transferred from the registry holders to Novartis [2]The collection and analysis of samples will be performed outside of PASS Study B2401 (please refer to Section 7.3.1.2)	

7 Research methods

7.1 Study design

This PASS is a global, non-interventional, multi-database study that will obtain long-term data on the safety and effectiveness of tisagenlecleucel (in the commercial setting, or under a managed access program or other pathway, [redacted] as defined by the study objectives in Section 6. This is a non-interventional study (NIS) based on secondary use of data; therefore, no study assessments will be mandated and no (study) drug administration will occur within this study. The study will consist of a baseline ("Pre-infusion") and a "Post infusion follow-up period" [redacted] as depicted in Figure 7-1.

This data collection follows Health Authority guidance for monitoring patients with respect to type and frequency of assessments, [redacted] The specific number of visits completed by the patient will depend upon sites' medical practice and the time since infusion with tisagenlecleucel. Annual or more frequent reporting of data for relevant events is planned for submission to Health Authorities in line with local regulatory requirements. Ongoing updates to Health Authority guidance on gene and cellular therapies and the experience from CAR T-cell therapies may impact the length and type of follow-up required in the study.

The study will retrieve data from the following Registry holders as part of secondary use of data:

- The CIBMTR and
- The EBMT

The Registry holders will collect data using data collection forms from each of the participating centers. Outside the scope of this non-interventional study, Novartis or designee will facilitate collection of samples in the event secondary malignancies are diagnosed.

For the purposes of the PASS study, "pre-infusion" and "post infusion follow-up" phases are defined and shown in Figure 7-1.

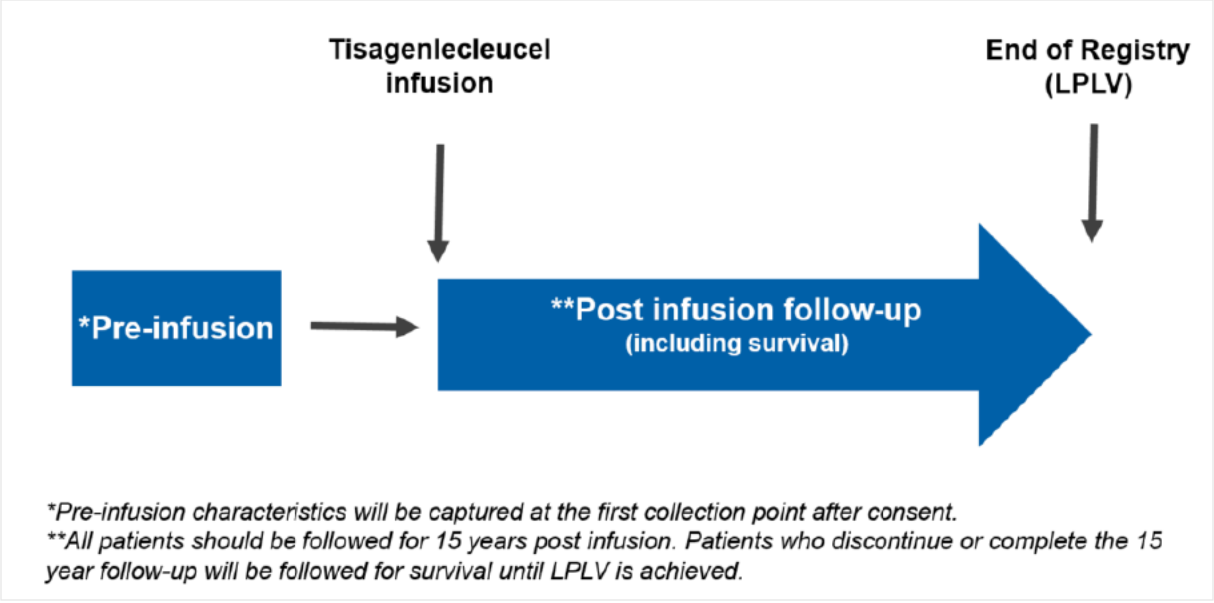
- "Pre-infusion" will consist of the patient's information from the time of diagnosis until just prior to infusion with tisagenlecleucel.
- "Post infusion Follow-up" information will comprise of any information from infusion of tisagenlecleucel onwards.

Patients with r/r DLBCL, ped B-ALL and r/r FL will be followed for safety and overall survival for up to 15 years after tisagenlecleucel infusion. Cohort 1 (r/r DLBCL, pediatric and young adult r/r B-ALL) and cohort 2 (FL) patients will be followed for other effectiveness endpoints

up to 15 and 5 years, respectively (refer to Table 6-1). The total study duration will therefore be approximately 23 years.

In the case a patient receives multiple tisagenlecleucel infusions, [redacted] Although patients may receive other anti-cancer therapies post tisagenlecleucel, these patients will also be followed in the study to collect experience after tisagenlecleucel treatment.

Figure 7-1 Registry Study Diagram



**Pre-infusion characteristics will be captured at the first collection point after consent.*
***All patients should be followed for 15 years post infusion. Patients who discontinue or complete the 15 year follow-up will be followed for survival until LPLV is achieved.*

7.2 Setting and study population

The study population includes patients who received tisagenlecleucel infusion either in the commercial setting or under a managed access program or other pathway, [redacted]

Data for this study will come from well-established Registry holders: CIBMTR and EBMT. [redacted]

Every effort will be made by CIBMTR and EBMT, in accordance with their respective practice and policies, to offer participation in the respective Registry to all patients meeting the inclusion criteria.

For patients who enter the Registry after their tisagenlecleucel infusion, historical safety and effectiveness data will be collected retrospectively. Thereafter, safety and effectiveness follow-up data will be collected routinely through the end of the patient follow-up period.

7.2.1 Inclusion

1. Patients who receive tisagenlecleucel infusion in the commercial setting, treated under a managed access program or other pathway, [redacted]
2. Consented to data collection.

7.2.2 Exclusion

1. Patients who are enrolled or will be enrolled in the Novartis long term follow-up protocol CCTL019A2205B.

7.3 Variables

7.3.1 Primary variable

The primary variable comprises AEs reported by physicians to Registry holders post tisagenlecleucel infusion.

7.3.1.1 Safety

The study will evaluate AEs that occur [redacted], as reported by the treating physician. The collection of AEs follows the case report forms and the data collection plans designed, owned and implemented by the Registry holders (CIBMTR, EBMT). [redacted]

7.3.1.2 Secondary malignancies

[redacted]

Independently of the reporting to the Registry holders, treating physicians/healthcare providers should contact Novartis directly within 72 hours of diagnosis of a secondary malignancy.

[redacted]

7.3.2 Secondary Variables

Refer to Table 6-1 for details on secondary variables.

7.4 Data sources

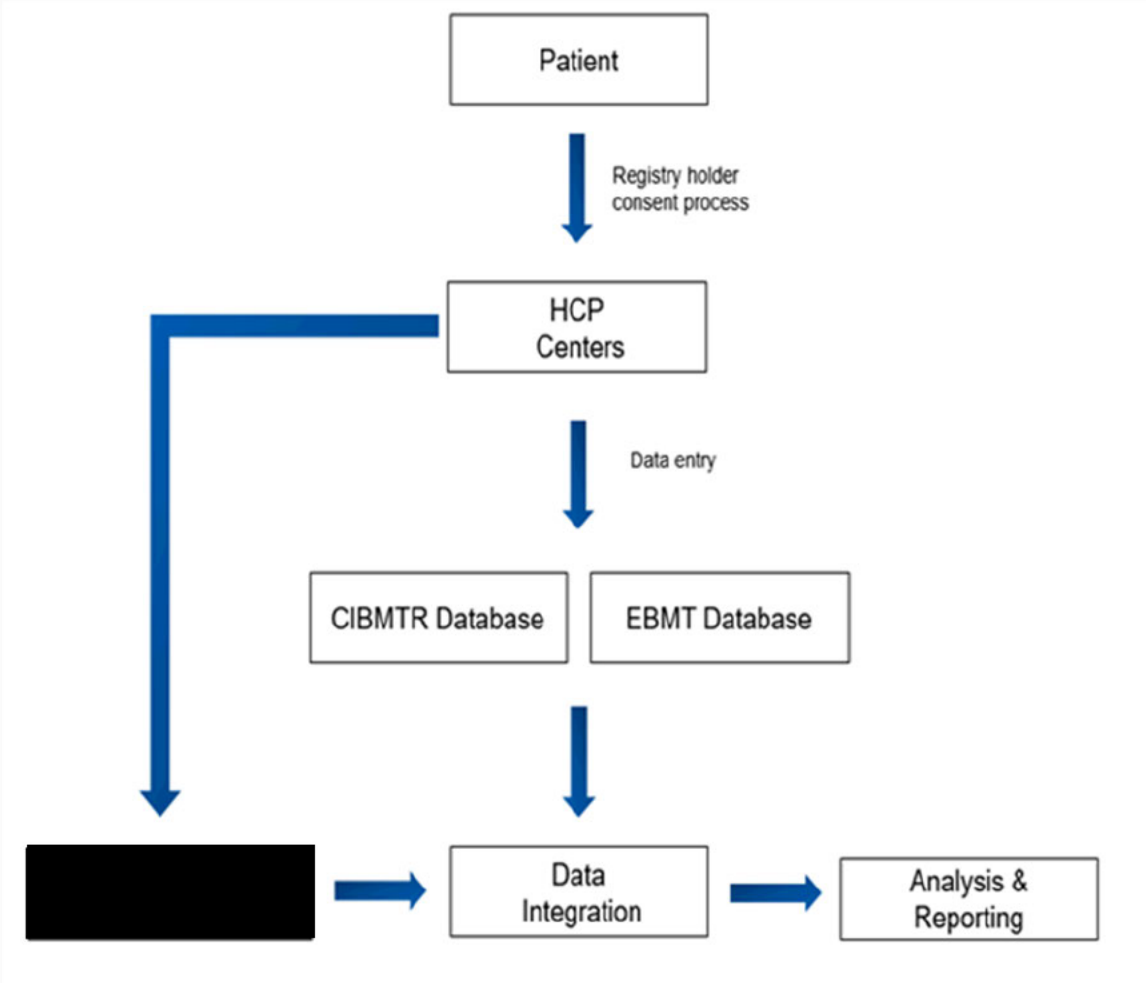
Clinical data for this study will be retrieved from the databases of the Registry holders (CIBMTR, EBMT). These Registries have been selected in alignment with Health Authority recommendations. Real-time data collection is not expected due to the nature of these Registries. The data collection forms used by the Registries, CIBMTR or EBMT, include details about the [redacted] The treating physician and/or designee at each center will be responsible for the accuracy and completeness of the data entered in the ongoing Registries. Novartis or a designee will integrate secondary malignancy sample data results (at the time of analysis) with the data received from the Registry holders.

CIBMTR and EBMT will be responsible for collecting, storing, monitoring and checking the accuracy of the data in accordance with local Health Authority requirements. CIBMTR and EBMT will follow data management practices based on Good Pharmacovigilance Practice (GVP) Module VIII (post-authorization safety studies), EMA's Guideline on safety and efficacy follow-up and risk management for advanced therapy medicinal products (draft dated 25 January 2018) and from the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance Code of Conduct (ENCePP Code of Conduct). The Registry holders will be responsible and accountable for ensuring that data quality measures have been conducted,

which includes checking the data for completeness and accuracy. CIBMTR and EBMT will also train participating centers on the use of their electronic data collection forms and create appropriate data entry manuals.

At regular intervals (e.g., quarterly), the Registry holders (i.e., CIBMTR and EBMT) will transfer data to Novartis or designee through a secure system. A diagram of the data flow is presented in Figure 7-3.

Figure 7-3 General flow of data Registry holders



7.4.1 Data collection schedule

This is a non-interventional study and does not impose a therapy, diagnostic/therapeutic procedures, or a visit schedule. Patients are expected to be treated according to the local standard of care and routine medical practice in terms of visit frequency and the types of assessments performed for disease evaluation, and only these data will be collected as part of the study.

The treating centers are asked to enter data directly into the appropriate electronic cell therapy forms for each respective patient using a pre-selected data entry schedule, where possible. [redacted] All data since the patient's previous visit will be recorded at the next scheduled data entry visit. Long-term safety and effectiveness data will be collected such that the observational follow-up for each patient will be [redacted] from last infusion or until patient is lost to follow-up, death, early discontinuation or completion of the study. For patients who enter the Registry after their tisagenlecleucel infusion, historical safety and effectiveness data will be collected retrospectively. Thereafter, safety and effectiveness follow-up data will be collected routinely through the end of the patient follow-up period.

Table 7-1 reflects how data collection is expected, based on the information captured by the Registry holders.

Patients may receive other anti-cancer therapies after tisagenlecleucel but will remain in this study to collect AE data.

Table 7-1 Data collection schedule

Phase	[redacted]
Time of evaluation	
Inclusion/ Exclusion criteria	
Demographics	
Medical history (pre-infusion)	
Disease characteristics	
Tisagenlecleucel product information	
Weight and height at time of infusion	
Performance status	
Adverse events	
Secondary malignancy sample collection (the work-up will be performed outside of PASS B2401)	
Pregnancies and outcome	

Phase	[redacted]
Time of evaluation	
Selected concomitant medications (e.g., tocilizumab, IVIG)	
Selected laboratory parameters (e.g., complete blood count)	
Current status of primary B-cell malignancy	
Antineoplastic therapies	
Survival status	

7.4.2 Pre-infusion collection

Pre-infusion information from the time of diagnosis until just prior to start of treatment with tisagenlecleucel will be captured, as available.

- Demographic information and other background (i.e., age at diagnosis, sex, extent of disease)
- Disease characteristics (i.e., date of diagnosis of primary malignancy)
- Relevant medical history and concomitant disease
- Relevant prior lines of therapy
- Any history of malignancy (hematologic or non-melanoma skin cancer) other than the primary disease treated with tisagenlecleucel (yes/no)
- Lymphodepleting therapies
- Tisagenlecleucel product information

Cellular product information (including batch number) and cellular dose will be collected from the respective Registry holders for infused product.

7.4.3 Follow-up (post-infusion) collection

Post infusion information will be captured from the time of infusion with tisagenlecleucel until date of death, lost to follow-up or end of study, as available.

7.4.3.1 Safety

7.4.3.1.1 Adverse events

Adverse events will be collected as outlined in Section 7.3.1.1 and Section 9.1 Refer to the CIBMTR and EBMT data collection forms for additional details.

7.4.3.1.2 Concomitant medications

Selected concomitant medications will be collected, such as tocilizumab and/or corticosteroids for patients who suffer from CRS, intravenous immunoglobulin (IVIG), and new anti-cancer therapies post tisagenlecleucel infusion (including hematopoietic stem cell transplant). The selected concomitant medications are referring to all medications captured by the registry holders according to the CIBMTR and EBMT data collection plan.

Refer to the CIBMTR and EBMT data collection forms on their respective public website for additional details.

7.4.3.1.3 Pregnancy

Refer to Section 9.1.

7.4.3.1.4 Laboratory parameters

Sites may perform selected local laboratory tests as medically indicated for management of patient safety issues.

7.4.3.2 Effectiveness assessment

Effectiveness assessments will be determined by recording the status of the primary malignancy as collected by medical history or records. Antineoplastic therapies administered post tisagenlecleucel infusion will also be captured.

7.4.3.3 Survival

Survival status will be collected on all patients at a minimum [redacted]

7.5 Study size/power calculation

The sample size for this study is not based on statistical considerations but on Health Authority recommendation. [redacted]

7.6 Data management

Data collection will be performed using the relevant electronic system in use at the CIBMTR or EBMT.

[redacted]

[redacted]

Data transfer plan and the processes for receipt, loading and processing of data from external sources will be performed in accordance with Novartis procedures for secure file exchange with external partners.

CIBMTR and EBMT will upload their data into a restricted access repository and upon each data transfer Novartis will merge the data, including data from internal sources, into a single data file for analysis.

Novartis in collaboration with the registry holder(s) will be responsible for proactive planning and delivering of all milestones, including data snapshots and interim/final analyses.

7.7 Data analysis

Safety and effectiveness data will be summarized and listed by indication in interim reports until the final database lock. The final Clinical Study Report will be prepared including all planned safety and effectiveness analyses by indication at the end of the study. Patients who received treatment under a managed access program or other pathway, [redacted]

7.7.1 Analysis sets

[redacted]

7.7.2 Patient demographics/ other baseline characteristics

Demographics and other baseline data and disease characteristics will be summarized descriptively using the Safety set. Categorical data will be presented as frequencies and percentages. For continuous data, summary statistics will be presented (i.e., mean, median, standard deviation, minimum,).

7.7.3 Primary Analysis

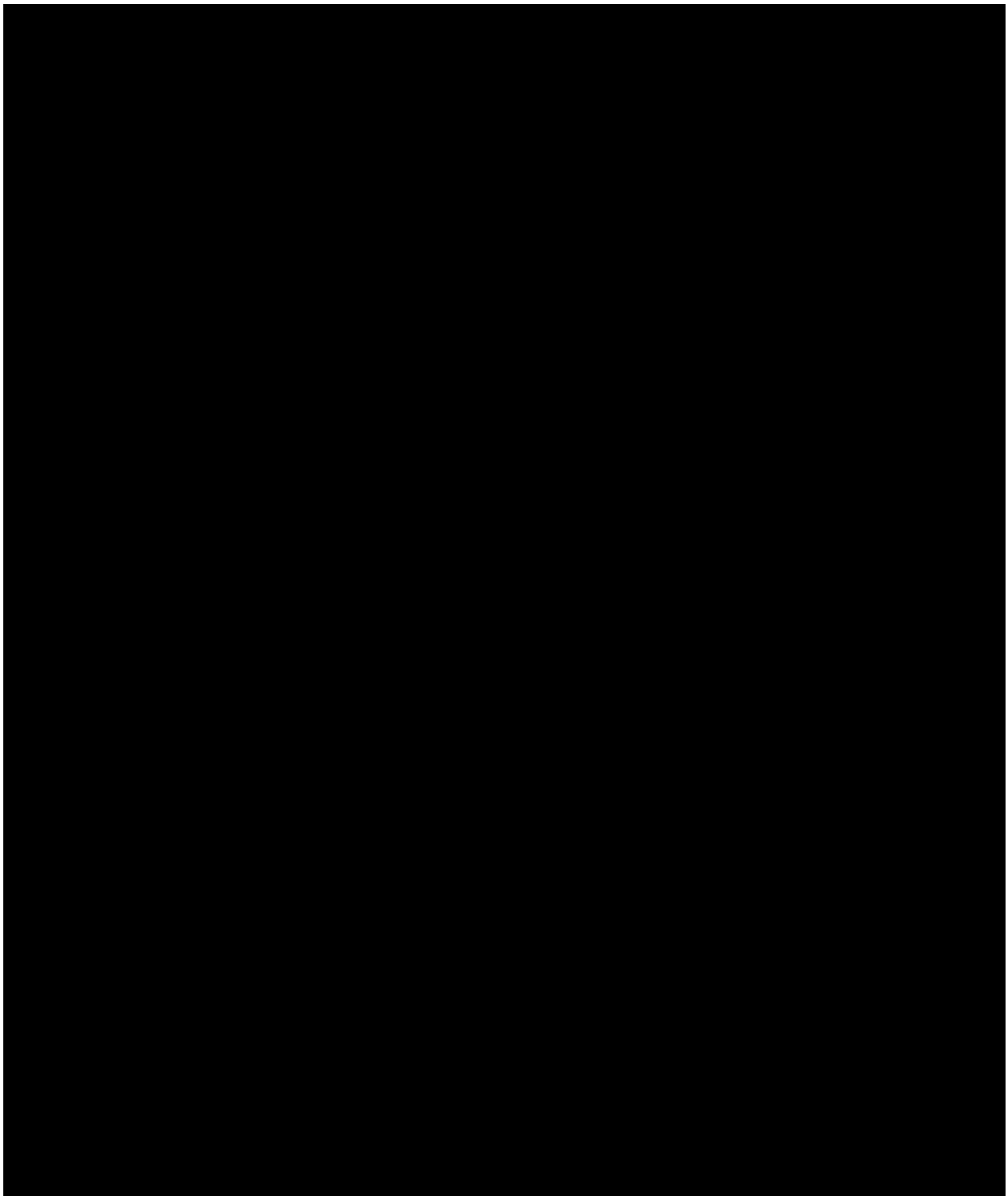
[redacted]

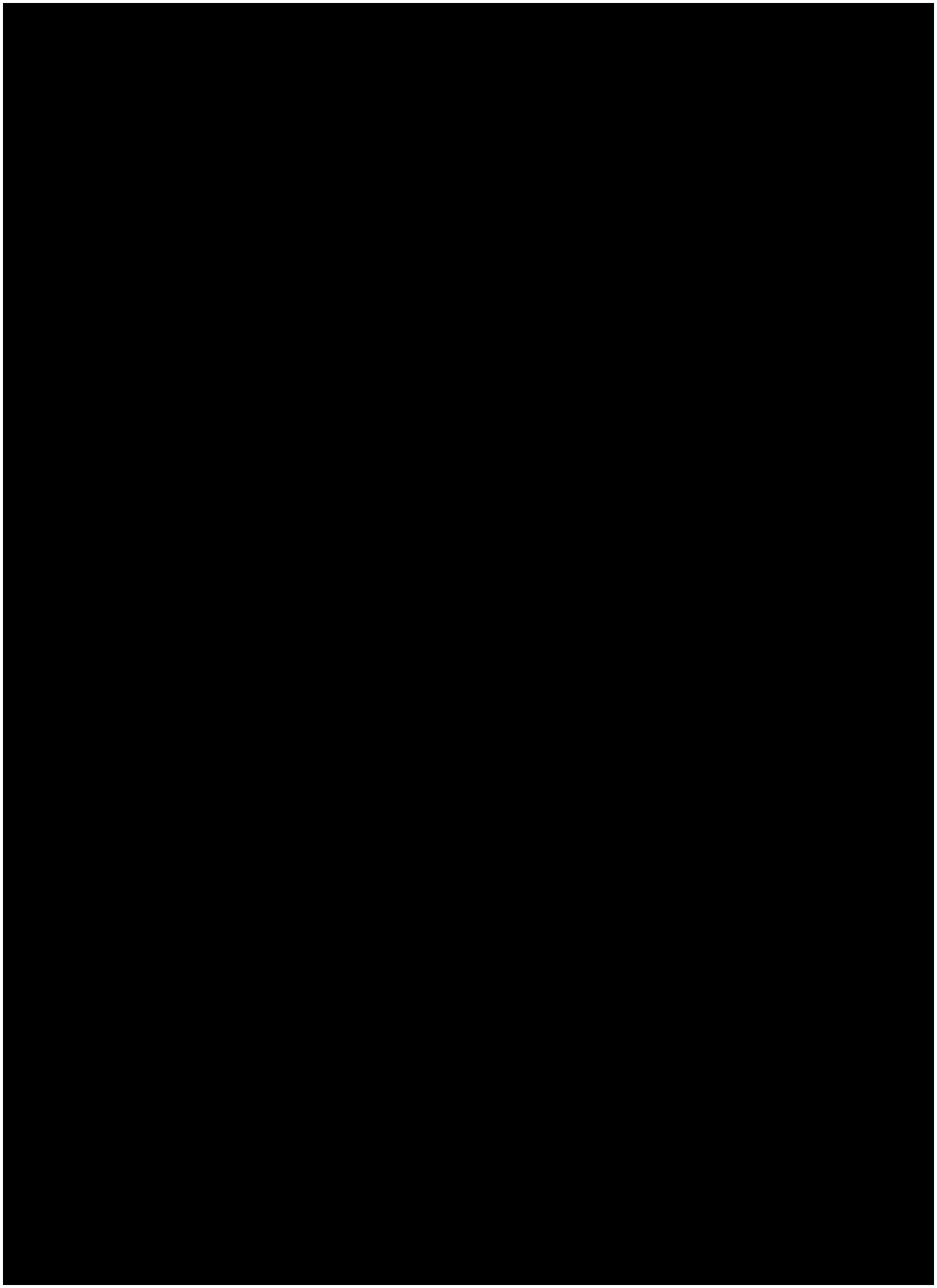
Additionally, data regarding the clinical management of CRS (e.g., use of anti-cytokine therapies, etc.) will be summarized, as reported by the registry holders. Details of neurotoxicity (e.g., degree of consciousness, dysphasia, seizures, etc.), as well as the specific therapy given

(e.g., anti-epileptics, corticosteroids, etc.) will also be provided, as reported by the registry holders.

The frequency and type of secondary malignancies (as shown per data from the Registry Holders) will be summarized. The incidence rates per patient-year will also be provided.

7.7.4 Secondary analysis





[redacted]

7.7.5 Reports

[redacted]

7.7.6 Interim reports

[redacted]

7.8 Quality control

7.8.1 Data quality assurances

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 2011). All database partners have experience in conducting pharmacoepidemiological research and research is done by researchers trained in pharmacoepidemiology.

7.8.1.1 EBMT

[redacted]

[redacted]

7.8.1.2 CIBMTR

[redacted]

[redacted]

7.8.2 Site monitoring

Novartis will not be responsible for site monitoring. The Registry holders will perform any monitoring or auditing activities as per Registry holder processes for a Registry study.

7.9 Limitations of the research methods

Potential limitations of the present study are due to its non-interventional nature.

[redacted]

There are differences in timing of data updates in the various databases (medical records are continuously updated, administrative databases are updated only once per year in most instances). However, as data-extraction will be repeated during the course of the study, this should allow for "up-to-date data" at study end.

[redacted]

8 Protection of human subjects

For this study, all of the Registry holder databases are currently already used for pharmaco-epidemiological research and have a well-developed mechanism to ensure that local regulations dealing with ethical use of the data and adequate privacy control are adhered to.

The treating physician must ensure anonymity of the patients; patients must not be identified by names in any documents submitted to Novartis.

[redacted]

[redacted]

8.1 Regulatory and ethical compliance

Compliance with Novartis and regulatory standards provides assurance that the rights, safety, and well-being of patients participating in non-interventional studies are protected (consistent with the principles that have their origin in the Declaration of Helsinki), the personal information are handled securely (as reflected in the European Economic Area (EEA) General Data Protection Regulation (GDPR) requirements), and that the study data are credible and responsibly reported.

This study was designed and shall be implemented and reported in accordance with the Guidelines for Good Pharmacoepidemiology Practices (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 is fulfilling 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).

8.1.1 Informed Consent procedures

There will be no Novartis-specific study informed consent form (ICF) for standard data collection. CIBMTR and EBMT will develop and implement ICFs for data collection within each individual registry database.

[redacted]

9 Management and reporting of adverse events/adverse reactions

9.1 Reporting of adverse events and pregnancy data based on CIBMTR and EBMT registries

As this is a study based on secondary use of data, submission of suspected adverse reactions in the form of ICSRs to Health Authorities is not required as outlined in EMA Good Pharmacovigilance Practice (GVP) Module VI Revision 2 (2017), Section VI.C.1.2.1.2 (page

30), entitled 'Non-interventional post-authorization studies with a design based on secondary use of data'. Accordingly, Novartis Patient Safety will not enter safety events, such as AEs or pregnancy, in the global safety database (Argus).

In studies based on secondary use of data with a safety relevant result, reports of AEs/adverse reactions will be summarized in the periodic study reports, i.e., the overall association between an exposure and an outcome will be presented. For milestones of issuing study reports refer to Table 4-1. Relevant findings from the study report will be included in the periodic aggregated regulatory reports submitted to Health Authorities.

The scope of AE and pregnancy data evaluation will be contingent on the data collection plans owned by the Registry holders CIBMTR and EBMT. The Registry holders will transmit all AE and pregnancy data that are reported for patients infused with tisagenlecleucel to Novartis at regular intervals (e.g., quarterly).

The information on AEs collected by the Registry holders is descriptive and may not include event characteristics such as seriousness, causality (suspected or non-suspected), severity, start and end dates, action taken and outcome.

Due to the study design, no follow-up of AEs will be feasible except for AEs of secondary malignancies (refer to Section 7.3.1.2), for which Novartis will attempt to contact the treating physician outside of Study B2401 for additional information and bio-sampling.

Spontaneous reporting of adverse reactions

Novartis and Health Authorities emphasize the importance of timely, spontaneous reporting of adverse reactions following tisagenlecleucel infusion administered in the post marketing setting.

Healthcare providers are encouraged to report adverse reactions of Kymriah [redacted] or call the phone number listed in the local Kymriah prescriber information, or report to the local Health Authorities. The Novartis Patient Safety department will enter all spontaneous AE reports from the post-marketing setting into the Novartis safety database and process those as per pharmacovigilance standard operating procedures, including reporting to Health Authorities as required by regulations.

10 Plans of disseminating and communicating study results

Data obtained from both the CIBMTR (for cohort 1 and 2) and EBMT (for cohort 1) registries will be analyzed and reports issued in line with the milestones presented in Table 4-1.

10.1 Annual reports based on CIBMTR and EBMT registries

[redacted]

10.2 Intermediate quarterly reports based on EBMT registry

[redacted]

10.3 Interim reports based on CIBMTR and EBMT registries

[redacted]

10.4 Final report for completion of the PASS

The final report for cohort 1 will be prepared including all planned effectiveness and safety analyses at the end of the [redacted] follow-up period for B-ALL and DLBCL patients.

10.5 Clinical study report

The final CSR will be prepared including all planned effectiveness and safety analyses at the end of the study for the complete study patient population.

10.6 Publications

Upon study 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.

[redacted]

11 References

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12 Annex 2- ENCePP checklist for study protocol

European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
Doc.Ref. EMA/540136/2009

ENCePP Checklist for Study Protocols (Revision 3)

Adopted by the ENCePP Steering Group on 01/07/2016

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

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

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

Study title:

Registry study to assess the long term safety of patients with B lymphocyte malignancies treated with tisagenlecleucel

Study reference number:

CCTL019B2401

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]	☒	☐	☐	Section 4
1.1.2 End of data collection[2]	☒	☐	☐	
1.1.3 Study progress report(s)	☒	☐	☐	
1.1.4 Interim progress report(s)	☒	☐	☐	
1.1.5 Registration in the EU PAS register	☒	☐	☐	
1.1.6 Final report of study results.	☒	☐	☐	
	☒	☐	☐	

Comments:

Section 2: Research question	Yes	No	N/A	Section Number
2.1 Does the formulation of the research question and objectives clearly explain:				
• 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)	☒	☐	☐	Section 6
• 2.1.2 The objective(s) of the study?	☒	☐	☐	Section 6
2.1.3 The target population? (i.e., population or subgroup to whom the study results are intended to be generalized)	☒	☐	☐	Section 7.2
2.1.4 Which hypothesis(-es) is (are) to be tested?	☐	☐	☒	
2.1.5 If applicable, that there is no *a priori* hypothesis?	☐	☐	☒	

Comments:

Section 3: Study design	Yes	No	N/A	Section Number
3.1 Is the study design described? (e.g., cohort, case-control, cross-sectional, new or alternative design)	☒	☐	☐	Section 7.1
3.2 Does the protocol specify whether the study is based on primary, secondary or combined data collection?	☒	☐	☐	Section 7.1
3.3 Does the protocol specify measures of occurrence? (e.g., incidence rate, absolute risk)	☐	☒	☐	

3.4 Does the protocol specify measure(s) of association? (e.g., relative risk, odds ratio, excess risk, incidence rate ratio, hazard ratio, number needed to harm (NNH) per year)	☐	☒	☐	
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)	☒	☐	☐	Section 7.4.3.1.1 Section 9

Comments:

Section 4: Source and study populations	**Yes**	**No**	**N/A**	**Section Number**
4.1 Is the source population described?	☒	☐	☐	Section 7.1 Section 7.2 Section 7.4
4.2 Is the planned study population defined in terms of: 4.2.1 Study time period? 4.2.2 Age and sex? 4.2.3 Country of origin? 4.2.4 Disease/indication 4.2.4 Duration of follow-up?	☒ ☒ ☒ ☒	☐ ☐ ☐ ☐ ☐ ☐	☐ ☐ ☐ ☐ ☐ ☐	Section 7.1 Section 7.2 Section 7.2 Section 7.2.1 Section 7.2 Section 7.1
Section 4: Source and study populations	**Yes**	**No**	**N/A**	**Section Number**
4.2.4 Disease/indication? 4.2.5 Duration of follow-up?	☒ ☒	☐ ☐	☐ ☐	Section 7.2.1 Section 7.2 Section 7.1
4.3 Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☒	☐	☐	Section 7.2.1 Section 7.2.2

Comments:

Section 5: Exposure definition and measurement	Yes	No	N/A	Section Number
5.1 Does the protocol describe how the study exposure is defined and measured? (e.g., operational details for defining and categorizing exposure, measurement of dose and duration of drug exposure)	☐	☒	☐	
5.2 Does the protocol address the validity of the exposure measurement? (e.g., precision, accuracy, use of validation sub-study)	☐	☐	☒	
5.3 Is exposure classified according to time windows? (e.g., current user, former user, non-use)	☐	☐	☒	
5.4 Is exposure classified based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☐	☐	☒	

Comments:

Section 6: Outcome definition and measurement	Yes	No	N/A	Section Number
6.1 Does the protocol specify the primary and secondary (if applicable) outcome(s) to be investigated?	☒	☐	☐	Table 6-1
6.2 Does the protocol describe how the outcomes are defined and measured?	☒	☐	☐	Table 6-1
6.3 Does the protocol address the validity of outcome measurement? (e.g., precision, accuracy, sensitivity, specificity, positive predictive value, prospective or retrospective ascertainment, use of validation sub-study)	☐	☐	☒	Table 6-1
6.4 Does the protocol describe specific endpoints relevant for Health Technology Assessment? (e.g. HRQoL, QALYs, DALYS, health care services utilization, burden of disease, disease management)	☐	☐	☒	

Comments:

Section 7: Bias	Yes	No	N/A	Section Number
7.1 Does the protocol describe how confounding will be addressed in the study?	☐	☐	☒	
7.1.1. Does the protocol address confounding by indication if applicable?	☐	☐	☒	

7.2 Does the protocol address: 7.2.1. Selection biases (e.g., healthy user bias) 7.2.2. Information biases (e.g., misclassification of exposure and endpoints, time-related bias)	☒ ☒	☐ ☐	☐ ☐	Section 7.9 Section 7.9
7.3 Does the protocol address the validity of the study covariates?	☐	☐	☒	

Comments:

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

Comments:

Section 9: Data sources	Yes	No	N/A	Section Number
9.1 Does the protocol describe the data source(s) used in the study for the ascertainment of: 9.1.1 Exposure? (e.g., pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview, etc.) 9.1.2 Outcomes? (e.g., clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics, etc.) 9.1.3 Covariates?	 ☒ ☒ ☐	 ☐ ☐ ☐	 ☐ ☐ ☒	 Section 7.4 Section 7.4
9.2 Does the protocol describe the information available from the data source(s) on: 8.2.1 Exposure? (e.g., date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber) 8.2.2 Outcomes? (e.g., date of occurrence, multiple event, severity measures related to event) 8.2.3 Covariates? (e.g., age, sex, clinical and drug use history, co-morbidity, co-medications, life style, etc.)	 ☒ ☒ ☐	 ☐ ☐ ☐	 ☐ ☐ ☒	 Section 7.4 Section 7.4
9.3 Is a coding system described for: 9.3.3 Exposure? (e.g., WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC)Classification System) 9.3.2 Outcomes? (e.g., International Classification of Diseases (ICD)-10, Medical Dictionary for Regulatory Activities (MedDRA)) 9.3.3 Covariates?	 ☒ ☒ ☐	 ☐ ☐ ☐	 ☐ ☐ ☒	 Section 7.4 Section 7.4 Section7.7.3
9.4 Is a linkage method between data sources described? (e.g., based on a unique identifier or other)	☒	☐	☐	Section 7.4

Section 10: Analysis plan	Yes	No	N/A	Section Number
10.1 Is the choice of statistical techniques described?	☒	☐	☐	Section 7.7
10.2 Are descriptive analyses included?	☒	☐	☐	Section 7.7
10.3 Are stratified analyses included?	☐	☒	☒	Section 7.7
10.4 Does the plan describe methods for adjusting for confounding?	☐	☐	☒	
10.5 Does the plan describe methods for handling missing data?	☐	☐	☒	
10.6 Is sample size and/or statistical power estimated?	☐	☒	☐	Section 7.5

Comments

Section 11: Data management and quality control	Yes	No	N/A	Section Number
11.1 Does the protocol provide information on data storage? (e.g., software and IT environment, database maintenance and anti-fraud protection, archiving)	☒	☐	☐	Section 7.4 and Section 7.6
11.2 Are methods of quality assurance described?	☒	☐	☐	Section 7.4 and Section 7.8.1
11.3 Is there a system in place for independent review of study results?	☐	☐	☒	

Comments:

Section 12: Limitations	Yes	No	N/A	Section Number
12.1 Does the protocol discuss the impact on the study results of: 12.1.1 Selection bias? 12.1.2 Information bias? 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)	 ☒ ☒ ☐	 ☐ ☐ ☐	 ☐ ☐ ☒	 Section 7.9 Section 7.9
12.2 Does the protocol discuss study feasibility? (e.g. study size, anticipated exposure, duration of follow-up in a cohort study, patient recruitment)	☐	☐	☒	

Comments:

Section 13: Ethical issues	Yes	No	N/A	Section Number
13.1 Have requirements of Ethics Committee Institutional Review Board been described?	☐	☐	☒	
Section 13: Ethical issues	**Yes**	**No**	**N/A**	**Section Number**
13.2 Has any outcome of an ethical review procedure been addressed?	☐	☐	☒	
13.3 Have data protection requirements been described?	☒	☐	☐	Section 8

Comments:

EC/IRB oversight is held by registry holder.

Section 14: Amendments and deviations	Yes	No	N/A	Section Number
14.1 Does the protocol include a section to document amendments and deviations?	☒	☐	☐	Section 3

Comments:

Section 15: Plans for communication of study results	Yes	No	N/A	Section Number
15.1 Are plans described for communicating study results (e.g., to regulatory authorities)?	☒	☐	☐	Section 7.7.5 Section 10
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	Section 10

Comments:

Name of the main author of the protocol: [redacted], MD

Date: / /

Signature: _____