PROSPECTIVE, INTERNATIONAL, NON-INTERVENTIONAL STUDY TO ASSESS SHORT- AND LONG-TERM SAFETY AND EFFECTIVENESS OF ADULT PATIENTS WITH RELAPSED OR REFRACTORY B CELL ACUTE LYMPHOBLASTIC LEUKEMIA RECEIVING AUCATZYL® TREATMENT

AUTOLUS PROTOCOL AUTO1-LT2

Protocol Version Identifier	AUTO1-LT2 Version 1.4, 17-Feb-2026
Date of Last Version of Protocol	1.3 09-Apr-2025
EU PAS Register Number	Study not registered
Active Substance	Obecabtagene autoleucel (Obe-cel)
Medicinal Product	Aucatzyl
EMA Product Reference	EMEA/H/C/005907
EMA Procedure Number	EMA/PASS/0000300590
Marketing Authorization Holder(s)	Autolus Inc./Autolus Ltd./Autolus GmbH
Joint PASS	No
Research Question and Objectives	This is a prospective, international, non-interventional study to evaluate the safety (including secondary malignancies) and effectiveness of adult patients with r/r B ALL receiving Aucatzyl® (obecabtagene autoleucel; obe-cel) treatment in the post-marketing setting. <u>Primary objective:</u> To characterize the short- and long-term safety of Aucatzyl in treatment of r/r B ALL, specifically to evaluate the rate and severity (where applicable) of the following AEs:

- CRS, including HLH/MAS
- ICANS
- Prolonged cytopenia
- Hypogammaglobulinemia
- Clinically significant infections
- Secondary malignancies
- Other neurologic toxicities
- TLS
- Immunogenicity, defined as hypersensitivity reactions
- Aggravation of GvHD
- New occurrence of an autoimmune disorder
- Overdose
- Other safety concerns not yet identified in the clinical program
- To evaluate pregnancy outcomes

Secondary objectives:

The secondary objectives of this study are to describe the effectiveness of Aucatzyl as well as further characterizing safety in the real-world setting.

Effectiveness:

- To evaluate the effectiveness of Aucatzyl in terms of ORR.
- To determine the DOR post-Aucatzyl administration.
- To determine the rwPFS post-Aucatzyl treatment.
- To determine the rwEFS post-Aucatzyl treatment.
- To determine the OS post-Aucatzyl treatment.
- To determine rate and outcomes after subsequent allogeneic HCT.

Safety:

- To determine the causes of death after Aucatzyl administration and mortality rate.
- To characterize B cell aplasia.

Exploratory objective:

- To determine MRD negativity status in patients in remission

	All objectives will be assessed separately for data from EBMT and CIBMTR registries, dependent on data interoperability a pooled analysis will be performed if feasible. Furthermore, results for patients who receive out-of-specification product will be analyzed separately.
Country(-ies) of Study	In countries where Aucatzyl will be authorized. Countries and regions currently foreseen for inclusion are the United States and Europe. The study will enroll patients throughout European countries as reimbursement becomes available.
Study Director	[redacted]
Author	[redacted]
EU-Qualified Person Responsible for Pharmacovigilance	[redacted]

Marketing Authorization Holder(s)

Marketing Authorization Holder(s)	Autolus Inc. 15810 Gaither Drive Suite 230 Gaithersburg, MD 20877 USA Autolus Ltd The Mediaworks 191 Wood Lane White City London W12 7FP United Kingdom Autolus GmbH Im Schwarzenbach 4, 79576 Weil am Rhein Germany
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2. LIST OF ABBREVIATIONS

Abbreviation	Expansion
AE	Adverse event
ALL	Acute lymphoblastic leukemia
ANC	Absolute neutrophil count
ASTCT	American Society for Transplantation and Cellular Therapy
B ALL	B cell acute lymphoblastic leukemia
CAR	Chimeric antigen receptor
CAR T	Chimeric antigen receptor T cell
CD	Cluster of differentiation
CI	Confidence interval
CIBMTR	Center for International Blood and Marrow Transplant Research
CR	Complete remission
CRi	Complete remission with incomplete blood count recovery
CRID	CIBMTR Recipient ID
CRS	Cytokine release syndrome
CTED	Cellular Therapy Essential Data Form
DOR	Duration of response
EBMT	European Society for Blood and Marrow Transplantation
EC	European Commission
EEA	European Economic Area
EFS	Event-free survival
EMA	European Medicines Agency
ENCePP	European Network of Centers for Pharmacoepidemiology and Pharmacovigilance
EU	European Union
FDA	Food and Drug Administration
GDPR	General Data Protection Regulation
GvHD	Graft versus host disease
HCT	Hematopoietic cell transplantation
HLH	Hemophagocytic lymphohistiocytosis
ICANS	Immune effector cell-associated neurotoxicity syndrome
ICF	Informed consent form
ID	Identification
Ig	Immunoglobulin

Abbreviation	Expansion
KM	Kaplan-Meier
MAS	Macrophage activation syndrome
MRD	Measurable residual disease
MHRA	Medicines and Healthcare products Regulatory Agency
NMDP	National Marrow Donor Program
OOS	Out-of-specification
ORR	Overall remission rate
OS	Overall survival
PASS	Post-authorization safety study
r/r	Relapsed and/or refractory
RWD	Real-world data
rwEFS	Real-world event-free survival
rwPFS	Real-world progression-free survival
SAP	Statistical analysis plan
TLS	Tumor lysis syndrome
US	United States

3. RESPONSIBLE PARTIES

Center for International Blood and Marrow Transplant Research	[redacted]
European Society for Blood and Marrow Transplantation	[redacted]rg
Autolus	[redacted]
	[redacted]
	[redacted]

	[redacted]
	[redacted]

4. ABSTRACT

Title: Prospective, international, non-interventional study to assess the short- and long-term safety and effectiveness of adult patients with relapsed or refractory B cell acute lymphoblastic leukemia receiving Aucatzyl® treatment

Version and date: 1.4, 17-Feb-2026

Main author: [redacted]

Rationale and background: The purpose of this study is to characterize the short- and long-term safety profile of Aucatzyl® (obecabtagene autoleucel; obe-cel) in the post-marketing setting, including the important identified risks and potential risks associated with this product. Aucatzyl is a cell-based therapy product consisting of autologous enriched T cells that are transduced with a lentiviral vector to express an anti-CD19 (CAT) CAR. This study will make secondary use of data collected from patients included in the EBMT and the CIBMTR cellular therapy registries.

Research question and objectives: This is a prospective international, non-interventional study to evaluate the safety (including secondary malignancies) and effectiveness of adult patients with r/r B ALL receiving Aucatzyl treatment in the post-marketing setting.

Primary objective:

To characterize the short- and long-term safety of Aucatzyl in treatment of r/r B ALL, specifically to evaluate the rate and severity (where applicable) of the following AEs:

- CRS, including HLH/MAS.
- ICANS.
- Prolonged cytopenia.
- Hypogammaglobulinemia.
- Clinically significant infections.
- Secondary malignancies.
- Other neurologic toxicities.
- TLS.
- Immunogenicity, defined as hypersensitivity reactions.
- Aggravation of GvHD.
- New occurrence of an autoimmune disorder.
- Overdose.
- Other safety concerns not yet identified in the clinical program.
- To evaluate pregnancy outcomes.

Secondary objectives:

The secondary objectives of this study are to describe the effectiveness of Aucatzyl as well as further characterizing safety in the real-world setting.

Effectiveness:

- To evaluate the effectiveness of Aucatzyl in terms of ORR.
- To determine the DOR post-Aucatzyl administration.
- To determine the rwPFS post-Aucatzyl treatment.
- To determine the rwEFS post-Aucatzyl treatment.
- To determine the OS post-Aucatzyl treatment.
- To determine rate and outcomes after subsequent allogeneic HCT.

Safety:

- To determine the causes of death after Aucatzyl administration and mortality rate.
- To characterize B cell aplasia.

Exploratory objective:

- To determine MRD negativity status in patients in remission.

All objectives will be assessed separately for data from EBMT and CIBMTR registries, dependent on data interoperability a pooled analysis will be performed if feasible. Furthermore, results for patients who receive OOS product will be analyzed separately.

Study design: This is a non-interventional, prospective cohort study, using secondary data captured in the EBMT and the CIBMTR cellular therapy registries. This study will include data from patients with r/r B ALL who have been treated with Aucatzyl in the post-approval setting and who consented to share the data with Autolus (the Marketing Authorization Holder). Participating treatment centers will enter data into the registry databases following registry-specific procedures and requirements. The treatment centers will complete the data collection forms per the defined registry schedules. Patients must consent to have their data reported to the registries and to submit pseudonymized data to Autolus. As this study is making secondary use of data, reporting individual AEs and adverse reactions will follow the standard spontaneous reporting system per local regulations, agreements and timelines for patients treated in the post-marketing setting. Participating treatment centers will report any suspected adverse reactions directly to Autolus or respective health authorities. If any secondary malignancy is suspected, and independently of the reporting to the registry holders, the treatment center must contact Autolus within 72 hours of becoming aware of the diagnosis to obtain instructions on collection and transfer of tumor tissue sample for testing. As this study will make secondary use of data collected in registries, expedited reporting of individual case safety reports will be duplicative and so will not occur.

Data from a total of 500 patients treated with Aucatzyl with at least 1 post-infusion follow-up will be collected until death, lost to follow-up, or withdrawal of consent, or up to 15 years,

whichever occurs first. This study is expected to require up to 4 years to recruit the planned number of patients.

Population: Adult patients diagnosed with r/r B ALL who have been treated with Aucatzyl in the post-marketing setting, independent of whether the product was within approved product specifications or OOS but released at physician request. Eligible patients include adult patients (≥ 18 years old) with r/r B ALL treated with Aucatzyl in the post-marketing setting who have consented to have data reported to the registries and shared with Autolus and are documented within the independent registries participating in this study.

Variables: This study makes secondary use of data captured in the CIBMTR and EBMT registries. The domains and non-exhaustive list of variables captured in this study are described below. As both registries have slight differences in the data they collect, the resolution, derivation and classification of variables will be completed individually for each data source. Further details will be provided in the SAP.

Domain	Variables	Baseline	Follow-up
Patient variables	Age	x	
	Sex	x	
	Performance Status	x	
	Ethnicity and race (where data are available)	x	
	Country where infusion was performed	x	
	Height/weight at the time of lymphodepleting chemotherapy	x	
Disease variables	Disease status at the time of cellular therapy	x	
	MRD status in patients in remission	x	
	Prior lines of treatment	x	
	Disease characteristics or other known molecular markers (presence of Philadelphia chromosome t(9;22) or other known molecular markers, Philadelphia-like ALL)	x	
	Interval from diagnosis to cellular therapy	x	
	Prior HCT: autologous or allogeneic	x	
	If prior allogeneic-HCT, GvHD status/grade	x	
	Bone marrow blast cells percentage (%) prior to lymphodepleting chemotherapy	x	
	Extramedullary disease, including central nervous system disease	x	
Cell therapy-related variables	Leukapheresis	x	
	Type of lymphodepleting chemotherapy	x	
	Lot number	x	

Domain	Variables	Baseline	Follow-up
	Cell dose infused	x	
	Aucatzyl infusion dates	x	
	Route of administration	x	
	Whether Aucatzyl was released at physician's request because the manufactured product was out-of-specification	x	
Variables collected to derive endpoints	CRS (severity, date of onset, resolution status, date of resolution, treatment where available)		x
	HLH/ MAS (date of onset, resolution status, date of resolution)		x
	ICANS (severity, date of onset, resolution status, date of resolution, treatment where available)		x
	Prolonged cytopenia (date of neutropenia recovery, date of platelet reconstitution, resolution status)		x
	Hypogammaglobulinemia (date of onset, resolution status, date of resolution, treatment [where available])		x
	Clinically significant infections (type, pathogen, location, resolution)		x
	Incidence of other neurologic toxicities such as parkinsonism, Guillain-Barré syndrome, immune mediated myelitis, peripheral neuropathies, cranial nerve palsies, etc. (type, severity, date of onset, resolution status, date of resolution)		x
	TLS (severity, date of onset, resolution status, date of resolution)		x
	Immunogenicity, defined as hypersensitivity reactions (incidence)		x
	Aggravation of GvHD. Incidence and severity		x
	New occurrence of an existing autoimmune disorder (type, date of onset)		x
	Secondary malignancy, including secondary malignancies of T cell origin, other hematological secondary malignancies (excluding T cell origin), and solid tumor malignancies (type, location, date of onset) at any point after Aucatzyl administration		x

Domain	Variables	Baseline	Follow-up
	Overdose (incidence)	x	
	Other safety concerns (type, date of onset, resolution status, date of resolution)		x
	Pregnancy outcomes (status of pregnancy, year, and month of birth)		x
	Out-of-specification product	x	
	Overall complete remission and date response evaluated		x
	Date and primary cause of death or last day known being alive		x
	Date of treatment failure or first relapse after Aucatzyl infusion		x
	Date of first relapse or progression or significant worsening of the disease after Aucatzyl administration		x
	Date of subsequent treatments		x

Abbreviations: ALL=acute lymphoblastic leukemia; CRS=cytokine release syndrome; GvHD=graft versus host disease; HCT=hematopoietic cell transplantation; HLH=hemophagocytic lymphohistiocytosis; ICANS=immune effector cell-associated neurotoxicity syndrome; MAS=macrophage activation syndrome; MRD=measurable residual disease; TLS=tumor lysis syndrome.

Data sources: For this protocol: patient data, as available within the EBMT and CIBMTR registries.

Study size: 500 patients with at least 1 post-infusion follow-up.

Data analysis:

A general description of the planned statistical methods to be used to analyze the data collected in this study is presented.

The data from EBMT and from CIBMTR will be analyzed separately and combined as appropriate.

Categorical data will be summarized by the number and percentage of subjects. Continuous data will be summarized using sample size, mean, standard deviation, median, Q1, Q3, minimum, and maximum.

For each AE, the number and percentage of patients who experience at least 1 occurrence of the given event will be summarized.

Time to event data will be summarized using KM estimators.

A detailed SAP will be finalized before the first analysis.

5. AMENDMENTS AND UPDATES

Number	Date	Section of study protocol	Amendment or update	Reason
1.4	17-Feb-2026	Multiple	Update	To address the comments of the PRAC Request for a Revised PASS protocol in the PRAC PASS protocol assessment report and to implement the respective changes.

6. MILESTONES

The registries will provide yearly safety and effectiveness data to Autolus.

Table 1: Protocol Milestones

Milestones	Planned date
FDA	
Final protocol submission	16-Dec-2024
Start of data collection in US	30-Jun-2025
Annual Progress Report	Annually within 60 days of approval anniversary
Study completion	30-Jun-2044
Final study report	30-Jun-2045
EMA	
Final protocol submission EU	Within 3 months of approval
Registration in the EU PASS register	Within 2 weeks of protocol approval
Start of data collection in EU	Pending[a]
End of data collection	30-Jun-2043
Interim study report	31-Jul-2030
Study completion	30-Jun-2044
Final study report	30-Jun-2045
MHRA	
Final protocol submission MHRA	Following the approval of the protocol by EMA
Start of data collection in UK	Pending
End of data collection	30-Jun-2043
Study completion	30-Jun-2044
Final study report	30-Jun-2045

Abbreviations: EBMT=European Society for Blood and Marrow Transplantation; EMA=European Medicines Agency; EU=European Union; FDA=Food and Drug Administration; MHRA=Medicines and Healthcare products Regulatory Agency; PASS=Post-authorization safety study; UK=United Kingdom; US=United States.

a. As the data collection in the EBMT Registry is independent of this study (secondary use of data), the start of data collection is the date from which data extraction starts in the respective geographies, after this protocol approval and the commercial launch of Aucatzyl in the EU and/or UK.

This study will be conducted in accordance with the guidelines of Good Pharmacoepidemiology Practices and Heads of Medicines Agencies Good Pharmacovigilance Practices including archiving and retention of essential documents.

7. RATIONALE AND BACKGROUND

B ALL is a severe malignant disease marked by the proliferation of non-functional B-precursor cells in the bone marrow, resulting in excessive lymphoblasts and impaired normal blood cell production. This weakens immune function, causing infections, bleeding, and anemia. The spread of lymphoblasts to organs complicates treatment and worsens prognosis. Without intervention, B ALL progresses quickly and is usually fatal. Despite therapeutic advances, many patients with r/r B ALL remain incurable and often exhaust available treatment options. While CAR T cell therapies have shown remarkable efficacy, they are associated with significant risks such as severe CRS and neurotoxicity.

Aucatzyl was designed to improve the safety profile of the CAR T therapy using a CD19 antigen recognition domain that has fast off-rate binding kinetics. The FELIX study (AUTO1-AL1) was a Phase 1b/2 registrational study to evaluate safety, efficacy, and scalability of obe-cel in adults with r/r B ALL. In the 94 participants with morphological disease at enrolment who received at least 1 dose of Aucatzyl, the CR/CRi rate was 77%, with a CR rate of 55%. At a median follow-up of 20.3 months, the median DOR was 14.1 months and the median EFS was 9.0 months. Grade ≥ 3 events of CRS and ICANS were reported in 3 (3.2%) and 6 (6.4%) of the 94 infused participants, respectively. Other serious treatment-emergent AEs (all grades, over 5%) for these patients included febrile neutropenia (13.8%), pyrexia (7.4%), and hyperferritinemia (6.4%).

Based on the FELIX study data demonstrating promising safety and efficacy, Aucatzyl was approved by the US FDA on 08-Nov-2024 and received a conditional marketing authorization from MHRA on 25-Apr-2025 for the treatment of r/r B ALL in adults aged 18 and above. Aucatzyl received a conditional marketing authorization from the EC on 17-Jul-2025 for the treatment of r/r B ALL in adults aged 26 and above. The safety profile is characterized by several important identified or potential class risks listed in the Risk Management Plan, including CRS, ICANS, prolonged cytopenia, hypogammaglobulinemia, severe infections, secondary malignancies of T cell origin or other hematological origin, aggravation of GvHD, TLS, antigenicity and immunogenicity, and overdose/medication error. These risks are managed through pharmacovigilance routine and additional risk minimization measures for Aucatzyl, such as close monitoring and restricted use in Autolus qualified centers.

Further data collection and analyses are required for the assessment of the long-term safety profile of Aucatzyl, particularly regarding the incidence and management of potential late onset AEs, secondary malignancies, and outcomes in special populations (e.g., pregnant or breastfeeding women, those with autoimmune disorders). Published data from the pivotal FELIX study and post-authorization experience highlight the frequency and seriousness of acute toxicities but are limited by relatively short follow-up and underrepresentation of certain patient groups. Previous epidemiological studies and registry data on CAR T therapies confirm the class risks and underscore the need for extended surveillance.

As part of the approval for Aucatzyl, this study is an imposed PASS designed to confirm effectiveness and safety and to further characterize the short- and long-term safety and effectiveness of Aucatzyl in adult patients with r/r B ALL. This study is designed to address the abovementioned knowledge gaps by systematically collecting safety and effectiveness data in

real-world settings using the CIBMTR and EBMT registries as data sources. The study will provide critical insights into the incidence, severity, and outcomes of key safety concerns, and contribute to the evolving understanding of CAR T cell therapy safety in adult B ALL. The findings are expected to complement existing evidence, support regulatory decision-making, and optimize patient care.

8. RESEARCH QUESTION AND OBJECTIVES

This is a non-interventional, descriptive, prospective cohort study that utilizes data captured in the CIBMTR and EBMT cellular therapy registries. This study aims to investigate the incidence rate and severity (where applicable) of events of special interest (including CRS and ICANS) in patients treated with Aucatzyl in the real-world setting. No formal hypothesis will be evaluated in this study.

8.1. Objectives

8.1.1. Primary Objective

To characterize the short- and long-term safety of Aucatzyl (in the treatment of r/r B ALL). Specifically, the rates and severity (where applicable) of the following AEs:

- CRS, including HLH/MAS.
- ICANS.
- Prolonged cytopenia.
- Hypogammaglobulinemia.
- Clinically significant infections.
- Secondary malignancies.
- Other neurologic toxicities.
- TLS.
- Immunogenicity, defined as hypersensitivity reactions.
- Aggravation of GvHD.
- New occurrence of an autoimmune disorder.
- Overdose.
- Other safety concerns not yet identified in the clinical program.
- To evaluate pregnancy outcomes.

8.1.2. Secondary Objectives

The secondary objectives of this study are to describe the effectiveness of Aucatzyl as well as further characterizing safety in the real-world setting.

Effectiveness:

- To evaluate the effectiveness of Aucatzyl in terms of ORR.
- To determine the DOR post-Aucatzyl administration.
- To determine the rwPFS post-Aucatzyl treatment.

- To determine the rwEFS post-Aucatzyl treatment.
- To determine the OS post-Aucatzyl treatment.
- To determine rate and outcomes after subsequent allogeneic HCT.

Safety:

- To determine the causes of death after Aucatzyl administration and mortality rate.
- To characterize B cell aplasia.

8.1.3. Exploratory Objective

- To determine MRD negativity status in patients in remission.

All objectives will be assessed separately for data from EBMT and CIBMTR registries. A feasibility assessment to assess the interoperability between the EBMT and CIBMTR registries was performed across all relevant endpoints to determine if such an analysis is scientifically robust. Dependent on data interoperability, a pooled analysis will be performed, if feasible. Details of the conventions for any appropriate merging of data between EBMT and CIBMTR will be provided in the SAP. Furthermore, results for patients who receive OOS product will be analyzed separately.

9. RESEARCH METHODS

9.1. Study Design

This is a prospective, international, non-interventional study to describe the short- and long-term safety and effectiveness of adult patients with r/r B ALL who have been treated with Aucatzyl in the real-world setting.

This study will use secondary data from the EBMT and CIBMTR cellular therapies registry-based on the feasibility assessment and rationale described in Section 9.4.

This study will include data from patients who have been treated with Aucatzyl in the post-approval setting and who consented to share the data with Autolus. This study will follow patients for up to 15 years following Aucatzyl infusion.

Participating centers will enter data directly into the CIBMTR and EBMT databases using electronic case report forms and will follow registry-specific procedures and requirements. The treatment centers will complete the data collection forms per the defined registry schedules. Patients must consent to have their data reported in the registry and to submit pseudonymized data (patient-level data) to Autolus. As this is a non-interventional study, no specific visit schedule is mandated.

All study data will be obtained from clinical, laboratory, and diagnostic assessments conducted during routine medical practice. Information collected from the registries on patients who are suspected of developing a secondary malignancy (including solid tumors, T cell origin and hematologic malignancies [except of T cell origin]) will be included as part of this non-interventional study. In addition, the treating centers will be instructed to contact Autolus within 72 hours of the diagnosis of a secondary malignancy to obtain instructions on collection and transfer of tumor tissue sample for testing, per the algorithm for post-marketing testing of insertional mutagenesis outlined in Section 14.4.

9.1.1. Study Design Definitions

9.1.1.1. Baseline Period

The baseline period is defined as the period immediately prior to a patient receiving Aucatzyl therapy. The baseline period will encompass a look-back period where information related to patient demographics, previous disease and treatment history are derived. The baseline period is used to accurately capture the patients' relevant medical histories to enable characterization and contextualization of outcomes.

9.1.1.2. Exposure

The exposure for the purposes of this study is defined as a patient receiving at least 1 dose of Aucatzyl therapy. Exposure to therapy will form the only basis for inclusion in the study.

9.1.1.3. Index Date

The index date is defined as the date on which the exposure occurs. The index date will be used as the reference point for the derivation of all outcomes.

9.1.1.4. Follow-up Period

The follow-up period will be defined as the difference in time between the index date, death, lost to follow-up or 15 years from the index date, whichever comes first. The follow-up period will be utilized to derive all outcomes for this study.

9.1.1.5. Justification for the Study Design

This study employs a registry-based design utilizing the extensive datasets of the EBMT and CIBMTR registries to evaluate the safety and effectiveness of Aucatzyl in a real-world setting. The design was selected to capture comprehensive patient-level data across diverse clinical and geographic settings, ensuring broad external validity. By leveraging existing registries with extensive geographic representation, including those currently used in PASS contexts by other sponsors, the study benefits from large sample sizes, long-term follow-up, and the capacity to analyze real-world outcomes with robust patient heterogeneity that reflect diverse clinical practices and population-level treatment patterns. Additionally, the use of standardized data collection methods and harmonized response criteria within the registries ensures high data quality, while stratified analyses address potential biases and confounding inherent in observational research.

9.2. Setting

This study will make secondary use of data captured in the EBMT or CIBMTR cellular therapy registries that includes the majority of the centers registered and authorized to administer Aucatzyl. These registries comprise broad geographic and demographic representation. All participating centers have been approved to administer Aucatzyl and contribute data to the registry, which provides a robust foundation for capturing real-world outcomes associated with the therapy.

The EBMT and CIBMTR collect in their registries a defined data set as specified in the EBMT or CIBMTR forms and publicly available data dictionaries. Available data within the EBMT or CIBMTR registries will be pooled and analyzed for this study at defined time points whenever possible (see Section 9.4).

9.2.1. Inclusion Criteria

- Patients aged 18 and over, diagnosed with r/r B ALL who have been treated with Aucatzyl at participating centers who have consented to share their pseudonymized data with Autolus.

9.2.2. Exclusion Criteria

- Not applicable

9.2.3. Enrollment

All patients scheduled to receive their Aucatzyl infusion at participating centers will be eligible for the study (see Sections 9.2.1 and 9.2.2 for eligibility criteria). Data from 500 patients (CIBMTR and EBMT) with at least 1 post-infusion follow-up will be collected. Enrollment requires signed informed consent by the patient or a legal guardian to allow data to be provided to CIBMTR or EBMT. The informed consent document will include information about sharing data with CIBMTR or EBMT. Tissue sample collection due to secondary malignancies will occur outside the registry.

9.3. Variables

This study makes secondary use of data captured in the CIBMTR and EBMT registries. The domains and non-exhaustive list of variables captured in this study are described in Table 2. As both registries have slight differences in the data they collect, the resolution, derivation and classification of variables will be completed individually for each data source. Further details will be provided in the SAP.

Table 2: Summary of Variables Used in the Study

Domain	Variables	Baseline	Follow-up
Patient variables	Age	x	
	Sex	x	
	Performance Status	x	
	Ethnicity and race (where data are available)	x	
	Country where infusion was performed	x	
	Height/weight at the time of lymphodepleting chemotherapy	x	
Disease variables	Disease status at the time of cellular therapy	x	
	MRD status in patients in remission	x	
	Prior lines of treatment	x	
	Disease characteristics or other known molecular markers (presence of Philadelphia chromosome t(9;22) or other known molecular markers, Philadelphia-like ALL)	x	
	Interval from diagnosis to cellular therapy	x	
	Prior HCT: autologous or allogeneic	x	
	If prior allogeneic-HCT, GvHD status/grade	x	
	Bone marrow blast cells percentage (%) prior to lymphodepleting chemotherapy	x	

Domain	Variables	Baseline	Follow-up
	Extramedullary disease, including central nervous system disease	x	
Cell therapy-related variables	Leukapheresis	x	
	Type of lymphodepleting chemotherapy	x	
	Lot number	x	
	Cell dose infused	x	
	Aucatzyl infusion dates	x	
	Route of administration	x	
	Whether Aucatzyl was released at physician's request because the manufactured product was out-of-specification	x	
Variables collected to derive endpoints	CRS (severity, date of onset, resolution status, date of resolution, treatment where available)		x
	HLH/MAS (date of onset, resolution status, date of resolution)		x
	ICANS (severity, date of onset, resolution status, date of resolution, treatment where available)		x
	Prolonged cytopenia (date of neutropenia recovery, date of platelet reconstitution, resolution status)		x
	Hypogammaglobulinemia (date of onset, resolution status, date of resolution, treatment [where available])		x
	Clinically significant infections (type, pathogen, location, resolution)		x
	Incidence of other neurologic toxicities such as parkinsonism, Guillain-Barré syndrome, immune mediated myelitis, peripheral neuropathies, cranial nerve palsies, etc. (type, severity, date of onset, resolution status, date of resolution)		x
	TLS (severity, date of onset, resolution status, date of resolution)		x
	Immunogenicity, defined as hypersensitivity reactions (incidence)		x
	Aggravation of GvHD. Incidence and severity		x

Domain	Variables	Baseline	Follow-up
	New occurrence of an autoimmune disorder (type, date of onset)		x
	Secondary malignancy, including secondary malignancies of T cell origin, other hematological secondary malignancies (excluding T cell origin), and solid tumor malignancies (type, location, date of onset) at any point after Aucatzyl administration		x
	Overdose (incidence)	x	
	Other safety concerns (type, date of onset, resolution status, date of resolution)		x
	Pregnancy outcomes (status of pregnancy, year, and month of birth)		x
	Out-of-specification product	x	
	Overall complete remission and date response evaluated		x
	Date and primary cause of death or last day known being alive		x
	Date of treatment failure or first relapse after Aucatzyl infusion		x
	Date of first relapse or progression or significant worsening of the disease after Aucatzyl administration		x
	Date of subsequent treatments		x

Abbreviations: ALL=acute lymphoblastic leukemia; CRS=cytokine release syndrome; GvHD=graft versus host disease; HCT=hematopoietic cell transplantation; HLH=hemophagocytic lymphohistiocytosis ; ICANS=immune effector cell-associated neurotoxicity syndrome; MAS=macrophage activation syndrome; MRD=measurable residual disease; TLS=tumor lysis syndrome.

The compatibility of the Data Collection Forms for the variables and outcomes of interest in CIBMTR and EBMT is reviewed and included in Section 14.5.

Derivations of variables for registry-specific contexts will be provided in detail in the SAP.

9.3.1. Definition of Endpoints

The endpoints for this study are defined in the following sections.

9.3.1.1. Primary Endpoints Definitions

The primary endpoint for this study is to describe and characterize all relevant safety events. Namely, that the rates and severity (where applicable) of the following events post-Aucatzyl will be summarized:

- CRS, including HLH/MAS

CRS is a disorder characterized by symptoms such as fever, rapid breathing (tachypnea), headache, rapid heart rate (tachycardia), low blood pressure (hypotension), rash, and/or low oxygen levels (hypoxia) due to the release of cytokines. It can occur after the administration of a cellular therapy product, which triggers an immune response leading to the rapid release of several inflammatory cytokines.

HLH is defined as a rare disorder characterized by the accumulation of histiocytes and lymphocytes in organs such as the skin, spleen, and liver, resulting in the destruction of other blood cells. HLH can be inherited (primary HLH) or triggered by various conditions or diseases (secondary HLH), including infections, immunodeficiency (the body's inability to combat infections), cancer, and the infusion of gene therapy products (NCI, 2025). MAS, a subset of secondary HLH, is associated with autoimmune diseases (Lerkvaleekul and Vilaiyuk, 2018).

- ICANS

ICANS is defined by the emergence of various neurological signs and symptoms following the administration of a cellular therapy product. These manifestations can range from fine tremors and difficulties in word-finding to seizures and loss of consciousness. ICANS may occur independently of other signs of CRS.

- Prolonged cytopenia

Prolonged cytopenia is defined as the failure of ANC or platelet count recovery following the first Aucatzyl infusion (e.g., not resolved between Month 1 and 3). ANC recovery is defined as $\geq 500/mm^3$ sustained across 3 laboratory values (CIBMTR), or the first of 3 consecutive values after 7 days without transfusion containing neutrophils (EBMT). For platelet recovery to $\geq 20 \times 10^9/L$, CIBMTR uses the first of 3 consecutive platelet counts $\geq 20 \times 10^9/L$ obtained on separate days, whereas the EBMT requires the first of 3 consecutive counts following a 7-day period without platelet transfusions.

- Hypogammaglobulinemia

Hypogammaglobulinemia is characterized by low levels of circulating gamma-globulins, or immunoglobulins, in the blood, typically determined by quantitative measurements of IgG, IgA, and IgM, or most commonly IgG alone. Levels of circulating IgG below 600 mg/dL indicate hypogammaglobulinemia.

- Clinically significant infections

Infection is characterized by the invasion of a patient's body tissues by microorganisms, including bacteria, viruses, parasites, and fungi, which are not typically present within the body, followed by their subsequent multiplication. Clinically significant infections are considered those that require treatment.

- Secondary malignancies.

The occurrence of any secondary malignancy is defined as the diagnosis of a new or secondary malignancy, including lymphoproliferative or myeloproliferative disorders, which is not a recurrence, or transformation of the primary disease for which the cellular therapy was administered, following the initial Aucatzyl infusion. New malignancies, lymphoproliferative disorders, myelodysplastic, and myeloproliferative disorders include, but are not limited to, skin cancers (basal cell carcinoma, squamous cell carcinoma, melanoma), new leukemia, new myelodysplasia, solid tumors, and post-transplant lymphoproliferative disorder reported as lymphoma or lymphoproliferative disease (Working Group Report, 2005).

- Other neurologic toxicities.

Neurologic toxicity is defined as the development of different neurologic signs and symptoms (excluding ICANS) after the administration of cellular therapy such as Parkinsonism, Guillain-Barré syndrome, immune-mediated myelitis, peripheral neuropathies, cranial nerve palsies, etc.

- TLS.

TLS constitutes a spectrum of metabolic disorders and clinical symptoms arising from the release of substantial intracellular substances and metabolites into the bloodstream, subsequent to either spontaneous or therapy-induced cytolysis of a significant number of tumor cells. The metabolic abnormalities associated with TLS include hyperkalemia, hyperphosphatemia, hyperuricemia, and hypocalcemia (Miao et al, 2021).

- Immunogenicity.

Immunogenicity is defined as hypersensitivity reactions occurring after the index date focusing on anaphylaxis, angioedema, urticaria and allergic reactions.

- Aggravation of GvHD.

GvHD may occur after an allogeneic transplant when donor T cells attack the recipient's healthy cells. GvHD is categorized as acute or chronic, each affecting different organs and tissues with distinct symptoms. Patients may experience one, both, or neither type. Chronic GvHD can be mild, moderate, or severe. Acute GvHD is characterized as Stage 1, 2, 3, or 4. Aggravated GvHD refers to the increased risk of GvHD due to CAR T cells, especially if derived from donor cells. Any new onset after Aucatzyl infusion or aggravation of pre-existing GvHD in patients who have undergone prior allogeneic stem cell transplantation prior to Aucatzyl infusion will be considered aggravation of GvHD.

- Autoimmune disorders.

Autoimmune disorders are defined as any new diagnosis of an autoimmune condition post-index date.

- Overdose.

Drug overdose is the accidental or intentional use of Aucatzyl at a dose higher than > 25% of the recommended Day 1 dose according to the bone marrow blast percentage at lymphodepletion, or a dose > 25% of the recommended total dose of 410×10^6 viable CD19 CAR T cells.

- Other safety concerns.

Other AEs are defined as any unforeseen event not previously identified in the clinical development program for Aucatzyl. These safety concerns may include any newly observed AEs or unexpected clinical conditions, as documented in the registry during the study.

- Pregnancy outcomes.

Evaluation of pregnancy outcomes include female patients and female partners of male patients who become pregnant.

9.3.1.2. Secondary Endpoints Definitions

The secondary effectiveness endpoints are defined as follows:

- The first effectiveness endpoint is defined as the ORR, including the proportion of patients in each ORR category (e.g., CR and CRi) among all patients treated with Aucatzyl. All responses are according to physician assessments.
- The second effectiveness endpoint is defined as the DOR in all patients treated with Aucatzyl. For the purposes of this study DOR shall be defined as the difference in time from the date of the first documented remission (CR or CRi) after the index date, to the date of the first documented relapse or death, whichever occurs first.
- The third effectiveness endpoint is defined as the rwPFS in all patients treated with Aucatzyl. For the purposes of this study rwPFS shall be defined as the difference in time between the index date and the date of relapse/progression of disease according to the judgment of the treating physician or death, whichever occurs first.
- The fourth effectiveness endpoint is defined as the rwEFS in all patients treated with Aucatzyl. For the purposes of this study rwEFS shall be defined as the difference in time between the index date and the date of treatment failure, relapsed disease according to the judgment of the treating physician or death, whichever occurs first.

  Treatment failure is defined as not achieving CR/CRi or death due to underlying disease within 100 days of Aucatzyl infusion.
- The fifth effectiveness endpoint is defined as the OS in all patients treated with Aucatzyl. For the purposes of this study OS is defined as the difference in time between the index date and the date of death.

- The sixth effectiveness endpoint is defined as the description of allogeneic HCT after Aucatzyl treatment. For the purposes of this study all HCTs occurring after the index will be summarized.

The secondary safety endpoints are defined as follows:

- The first secondary safety endpoint is defined as the characterization and description of the causes of death in patients treated with Aucatzyl. The incidence rate of specific causes of death will be described for all patients after the index date.
- The final secondary safety endpoint is defined as the characterization and description of the incidence of B cell aplasia in patients treated with Aucatzyl.

Exploratory endpoint:

- The first exploratory endpoint is described as the determination of MRD negativity status in patients who achieve remission after the index date. The percentage of patients who achieve MRD negativity will be described for all patients achieving remission after the index date.

All endpoints will be derived separately for patients who receive OOS product as well as separately for each registry. Details of the operationalization and derivation of these endpoints will be provided in the SAP.

9.4. Data Sources

Autolus conducted a pragmatic review and feasibility study to identify which existing data sources would be appropriate to use for the conduct of a prospective cohort study with the objective of characterizing both the short- and long-term safety and effectiveness of Aucatzyl.

The criteria for a data source to be considered suitable for this study are summarized in Table 3.

Table 3: Summary of Pragmatic Review and Feasibility Assessment of Data Sources

Criteria	Description	Rationale
The data source must represent patients and practices across multiple treatment centers.	The data source should include diverse patient populations and reflect real-world practices across various locations. Furthermore, the data source should have a high likelihood of capturing Aucatzyl-treated patients.	The data source must enable a study that is able to adequately assess both the long- and short-term safety of Aucatzyl. An essential component of this is to capture information from a broad range of treating centers as well as sufficient patient numbers.
The data source must be able to accurately capture information related to treatment with Aucatzyl.	The data source should be able to capture detailed treatment information related to Aucatzyl.	The study requires detailed information to be captured related to the administration of Aucatzyl inclusive of specifications. The data source must capture such information with sufficient resolution.

Criteria	Description	Rationale
The data source must be able to accurately capture information related to specific safety-related events in patients treated with Aucatzyl.	The data source should be able to capture detailed information about specific safety-related events related to patients treated with Aucatzyl. The specific events were CRS, including HLH/MAS, ICANS, prolonged cytopenia, hypogammaglobulinemia, clinically significant infections, secondary malignancies, other neurologic toxicities, TLS, immunogenicity, defined as hypersensitivity reactions, aggravation of GvHD, new occurrence of an autoimmune disorder, overdose, pregnancy outcomes and other safety concerns not yet identified in the clinical program.	The objective of the study is to characterize the rates and severity (where applicable and including CRS and ICANS) of specific events in patients treated with Aucatzyl. Data sources must be able to capture events of interest with high resolution, including both start and end dates.
The data source must adhere to rigorous quality control standards.	The data source must adhere to rigorous quality control standards inclusive of source data verification.	The veracity and validity of the data captured must be verifiable.
The data source must have been previously used in regulatory submissions.	The data source should have a track record of acceptance by regulatory authorities, particularly in PASS studies.	The study is intended for a regulatory submission, data providers and sources that have been previously used in this context are likely to adhere to regulatory standards and expectations.

Abbreviations: CRS=cytokine release syndrome; GvHD=graft versus host disease; HLH=hemophagocytic lymphohistiocytosis; ICANS=immune effector cell-associated neurotoxicity syndrome; MAS=macrophage activation syndrome; PASS=post-authorization safety study; TLS=tumor lysis syndrome.

The pragmatic feasibility assessment identified the CIBMTR and EBMT cellular therapy registries as the most suitable data sources for this study. Both registries have a demonstrated history of providing high-quality, reliable data for cellular therapy research, supported by robust data collection frameworks and standardized reporting practices. They encompass diverse patient populations and treatment centers across both the US and Europe, ensuring a high likelihood of capturing sufficient patients treated with Aucatzyl and generalizability of study findings to these geographic contexts.

Alternative data sources identified during the feasibility assessment were predominantly reliant on International Classification of Diseases (10^{th} Revision) and the Healthcare Common Procedure Coding System. These ontologies lack the specificity necessary to capture events of interest with adequate detail. For example, critical events such as CRS, ICANS, and other complex AEs are challenging to accurately identify and classify due to the inherent limitations of these coding systems. The absence of granularity in such ontologies compromises the ability to distinguish between clinically distinct conditions or capture nuanced characteristics such as

severity, timing, and resolution, potentially leading to under-reporting or misclassification of safety outcomes.

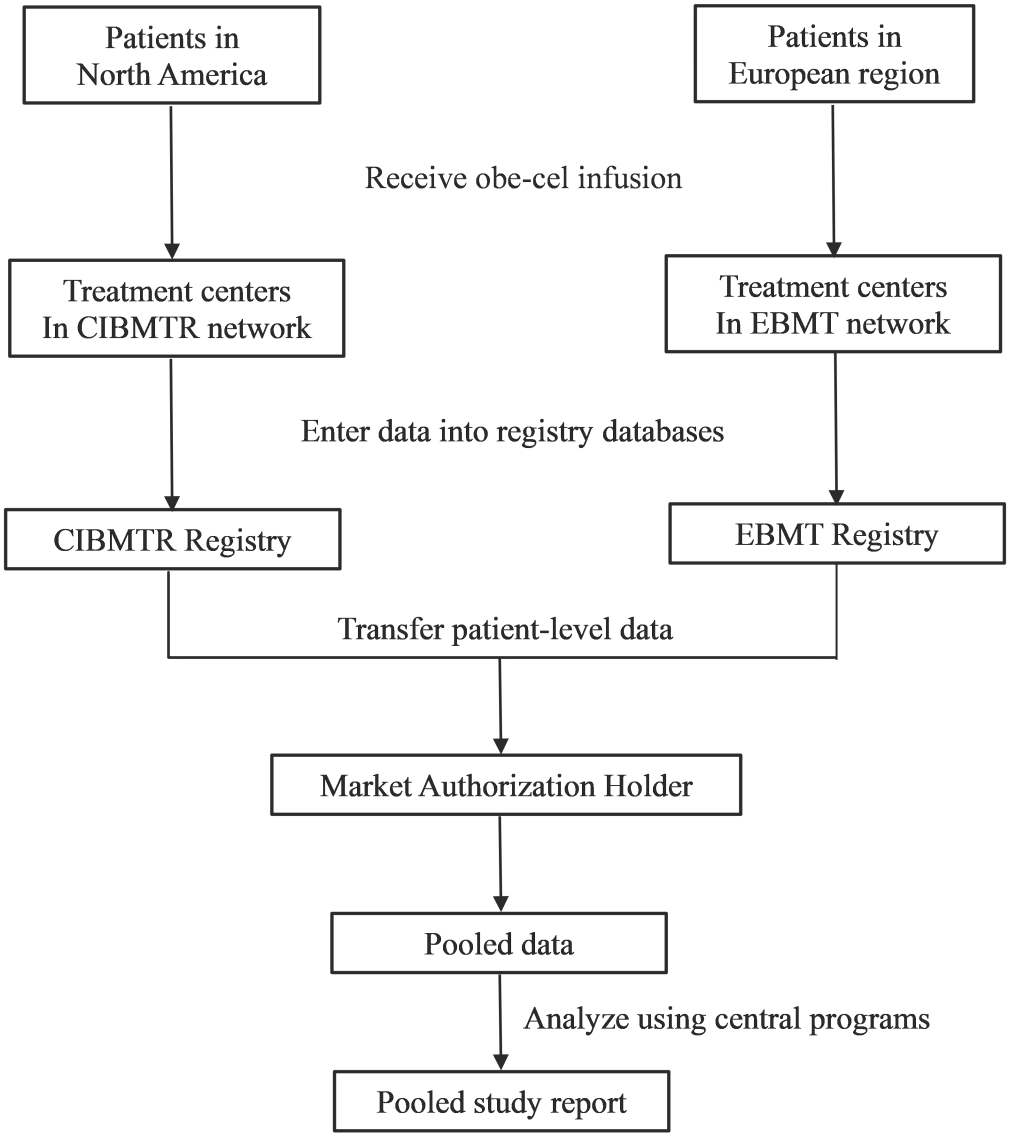
In contrast, the CIBMTR and EBMT registries utilize detailed and structured data collection mechanisms specifically designed for cellular therapy studies. These include event-specific data collection forms and physician-adjudicated AE reporting, ensuring precise and comprehensive documentation. This level of detail is critical for the accurate characterization of both the short- and long-term safety profile of Aucatzyl.

Furthermore, both the CIBMTR and EBMT registries adopt rigorous quality assurance frameworks as part of their standard operating procedures that have been utilized in prior regulatory submissions in the PASS context, which lends credence to the validity and veracity of the data collected.

At regular intervals, the registries will provide pseudonymized patient-level datasets to the Marketing Authorization Holder through a secure file transfer protocol. These datasets will include baseline characteristics, outcome variables, and other covariates. Data dictionaries will also be prepared to describe all variables included in the datasets.

Since the 2 registry databases are similar in content, the patient-level data will be integrated into pooled analysis datasets to allow consistent and periodic reporting, where possible. A diagram of data collection, transfer, and integration is provided in Figure 1.

Figure 1: Flow Diagram of Data Collection, Transfer, and Integration



Abbreviations: CIBMTR=Center for International Blood and Marrow Transplant Research; EBMT=European Society for Blood and Marrow Transplantation.

9.4.1. Data Sources/Measurements

The study will use secondary data from 2 blood and marrow transplant registries (CIBMTR and EBMT). A two-stage feasibility assessment was completed by IQVIA to inform the selection of these disease-specific registers. In Stage 1, a data landscaping approach utilizing IQVIA's Global Health Data Catalogue, the EMA RWD Catalogue, and desktop research was completed using "cancer registry", "ALL", and "CAR T" search terms. Twenty-eight data sources that include patients in 25 countries across Europe, United Kingdom, and the US were identified. Next, IQVIA shortlisted the data sources based on ALL patient populations and ability to contribute

prospective secondary data for a PASS. Eight data sources that include data from patients across 23 countries were identified from this process, and a Stage 1 data source screening tool was completed for each data source. The tool evaluated data governance, population (sample size and representativeness by country), and availability of key study variables. Results from Stage 1 concluded that CIBMTR and EBMT were potentially fit for purpose for this study. In Stage 2, IQVIA developed a detailed questionnaire to assess data provenance, relevance, and reliability elements and sub-dimensions of each study variable, as well as quality management systems and processes, to confirm the fit for purpose of CIBMTR and EBMT.

Clinical data for this study will be retrieved from the databases of the registry holders (CIBMTR and EBMT). Data collection forms include details about the primary disease, patient health status, prior treatments, cell therapy information, and treatment response including complications and AEs. The participating sites are responsible for notifying Autolus of AEs per spontaneous reporting procedures. The treating physician and/or designee at each center is responsible for the accuracy and completeness of the data entered into the ongoing registries.

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 Module VIII (post-authorization safety studies), EMA's guideline on safety and efficacy follow-up and risk management for advanced therapy medicinal products (EMEA/149995/2008 rev.1 2018) and from the 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.

EBMT and CIBMTR will transfer data to Autolus through a secure system.

9.4.1.1. The CIBMTR Research Database

CIBMTR is a research collaboration of the Medical College of Wisconsin and NMDP. CIBMTR collaborates with scientists around the globe to study cellular therapies and cure life-threatening diseases, many of which are rare.

More than 350 medical centers worldwide submit clinical data to CIBMTR about HCT and other cellular therapies, such as CAR T. These therapies treat malignant and non-malignant hematologic conditions and some other disorders. By analyzing these data, CIBMTR identifies the best treatments to help people live longer and enjoy better quality of life.

CIBMTR also collects and analyzes participant-reported outcomes and quality-of-life data.

CIBMTR maintains one of the world's largest observational databases of clinical information on HCT and other cellular therapies. Data are collected, stored and shared under terms of the *Protocol for a Research Database for Hematopoietic Cell Transplantation, Other Cellular Therapies and Marrow Toxic Injuries* and its accompanying consent forms (CIBMTR, 2021; CIBMTR, 2022; CIBMTR, 2023; CIBMTR, 2025a; CIBMTR, 2025b). At the time of treatment, patients consent for their data to be entered into the Research Database and used to support a

broad research agenda. Currently, CIBMTR's Research Database includes long-term clinical data from more than 675,000 patients.

The database includes:

- Almost 100% of allogeneic transplants in the US.
- More than 85% of autologous transplants in the US.
- About 22,000 patients who received other cellular therapies.

CIBMTR holds the contract for the Stem Cell Therapeutic Outcomes Database, awarded by the Health Resources and Services Administration of the US Department of Health and Human Services. As the contract holder, CIBMTR is charged with collecting data on all allogeneic (related and unrelated) HCTs performed in the US. All US transplant centers are required to report data to CIBMTR.

CIBMTR also maintains a biorepository with tissue samples (CIBMTR, 2021). CIBMTR's unique staff of physicians, biostatisticians, research coordinators, data management staff and Information Technology teams conduct both observational research and clinical trials.

9.4.1.2. The EBMT Research Database

The EBMT is a non-profit organization registered in the Netherlands, first established in 1974. The EBMT Registry holds data on patients given an HCT or cellular therapy infusion procedure. As of 2024, the registry holds data on more than 850,000 patients who received a transplant procedure, as well as data on approximately 10,000 patients who received a CAR T cell therapy. The registry receives data from approximately 80% of European transplant centers and is the principal source of data in the field for clinical research for retrospective clinical studies, epidemiological trends and feasibility studies for prospective clinical studies.

In recent years, the EBMT Registry has been used for regulatory purposes and represents a valuable research tool for future long-term studies of outcomes among recipients of cell and gene therapies requiring an autologous HCT procedure.

The EBMT full membership requires that clinical transplant centers commit to submitting a minimum set of data on all patients treated in their center on an annual basis. Their duty is to report all consecutive HCT and other cellular therapies and follow-up data.

In August 2023, EBMT moved to a new platform for data collection called EBMT Registry. EBMT standard data collection forms can be divided into the Core Dataset Forms and the Extended Dataset Forms:

1. **Core Dataset Forms**: These forms collect the minimum essential data that must be provided by all member centers for their consenting patients.
2. **Extended Dataset Forms**: These forms collect additional information that can be provided by centers to keep more details on a patient's medical history. They include items with more detailed questions that are relevant to CAR T or other advanced therapy medicinal products treatments. Data from the extended dataset are collected through several standard additional forms and can only be entered in addition to the core dataset.

9.4.1.3. Cellular Therapy Data

Both the CIBMTR and EBMT's infrastructure for collecting cellular therapy data are intentionally designed to be flexible and so are adaptable to a wide range of cell sources and treatment indications.

Transplant and infusion centers voluntarily submit cellular therapy data to their respective platforms, CTED forms (CIBMTR) and EBMT Registry Data Editor (EBMT). Data are submitted at baseline (before infusion) and then during regular follow-up periods at 100 days, 6 months, and yearly through 15 years during the therapy of the patient. All data since the patient's previous form is recorded at the next scheduled data entry.

9.4.1.4. Data Pooling

Across CIBMTR and EBMT, alignment is ongoing and spans shared definitions and revised forms, building an international consensus on key HCT endpoints and corresponding updates to both registries' data capture (Sureda et al, 2024). Review of the current forms indicates a high degree of consistency in the variables of interest across data sources, thus allowing pooled analyses (see Section 14.5). Notably, data for AEs such as CRS, including HLH/MAS, and ICANS are compatible and can be pooled given the data forms available. Details of data harmonization conventions and any appropriate merging of data will be provided in the SAP. For outcomes/fields that are not fully harmonized, analyses will be conducted per registry, with results combined where appropriate.

9.5. Study Size

Data from 500 patients (CIBMTR and EBMT) with at least 1 follow-up visit will be collected until death, lost to follow-up, or withdrawal of consent, or up to 15 years, whichever occurs first. The enrolment schedule is provided in Section 6.

This is a single-arm non-interventional study and therefore no statistical hypothesis testing and no formal powered sample size calculation is possible.

The sample size indicated above will provide a 99% probability of detecting an event with an underlying cumulative incidence of 1%. This sample size will also provide a high probability (92%) of identifying rare events with an underlying cumulative incidence of 0.5% (Table 4).

Table 4: Sample Size Probabilities

Underlying cumulative incidence	Probability of observing at least 1 case with 500 patients
> 2%	> 99%
1%	99%
0.5%	92%
0.2%	63%
0.1%	39%

In the FELIX study, Grade ≥ 3 CRS, ICANS, and hypogammaglobulinemia were reported in 2.4% (3/127), 7.1% (9/127), and 0.8% (1/127) of patients, respectively.

Considering the expected incidence of the primary endpoints of this study (Table 5), a sample size of 500 patients with at least 1 post-infusion follow-up will provide sufficient probability to observe the safety events of interest listed above.

Table 5: Observed Incidence of the Key Important Identified and Potential Risks of Aucatzyl

Safety Endpoints	Patients	Observed Incidence	Cumulative Incidence Proportion*
CRS			
Any grade	127	87	69
Grade ≥ 3	127	3	2
HLH/MAS			
Grade ≥ 3	127	2	2
ICANS			
Any grade	127	29	23
Grade ≥ 3	127	9	7
Prolonged cytopenia not resolved at Month 1	127	87	68
Neutropenia Grade ≥ 3	127	73	58
Thrombocytopenia Grade ≥ 3	127	66	52
Hypogammaglobulinemia			
Any grade	127	10	9
Grade ≥ 3	127	1	2
Clinically significant infections			
Grade ≥ 3	127	66	52
Second primary malignancies (Tix et al, 2024)#	5517	326	6

Abbreviations: CAR=chimeric antigen receptor; CRS=cytokine release syndrome; HLH=hemophagocytic lymphohistiocytosis; ICANS=immune effector cell-associated neurotoxicity syndrome; MAS=macrophage activation syndrome.
*According with Summary of Product Characteristics, unless indicated otherwise.
#Secondary primary malignancy of CAR T per literature review in hematological malignancies.

Precision estimates for cumulative incidence under different sample size assumptions using the Clopper-Pearson are displayed in Table 6.

Table 6: Clopper-Pearson Precision Estimates

Sample size	Cumulative Incidence 2%	Cumulative Incidence 1%	Cumulative Incidence 0.50%	Cumulative Incidence 0.20%
n=100	(0.24, 7.04)	(0.03, 5.45)	(0, 3.62)	(0, 3.62)
n=200	(0.55, 5.04)	(0.12, 3.57)	(0.01, 2.75)	(0, 1.83)
n=300	(0.74, 4.3)	(0.21, 2.89)	(0.08, 2.39)	(0.01, 1.84)
n=400	(0.87, 3.9)	(0.27, 2.54)	(0.06, 1.79)	(0.01, 1.38)

Sample size	Cumulative Incidence 2%	Cumulative Incidence 1%	Cumulative Incidence 0.50%	Cumulative Incidence 0.20%
n=500	(0.96, 3.65)	(0.33, 2.32)	(0.05, 1.44)	(0.01, 1.11)

9.6. Data Management of CIBMTR and EBMT Data

CTED forms are captured by the CIBMTR proprietary FormsNet web-based software. Centers initiate the report through generation of a CRID Assignment Form and Indication for CRID Assignment Form, which trigger a series of forms due. Baseline CTED forms include the Pre-CTED, Pre-Cellular Therapy Baseline, Disease Classification, Cellular Therapy Product, Cellular Therapy Infusion, and baseline ALL disease-specific forms. Follow-up forms include the Post-CTED, Post-Cellular Therapy Follow-up and follow-up ALL forms. Forms will be completed on a calendar-driven basis, except for forms for subsequent neoplasm and death, which will require expedited reporting. Centers will be instructed that, in the event of development of a subsequent neoplasm, reporting to CIBMTR should be event-driven (on demand) instead of calendar-driven.

EBMT has utilized the new EBMT Registry as a clinical data management system. This new registry contains the core and extended forms for CAR T data collection. The EBMT Registry is a web-based secure application for collecting clinical data and facilitates data collection, data querying, data monitoring, and reporting. It offers real-time validations and control of data entry flow. Participating centers will be able to record their patients' data directly into the Cellular Therapy forms when logging in to the EBMT Registry selecting the CAR T form.

CIBMTR and EBMT will upload data into a restricted-access repository and upon each data transfer, Autolus will merge the data, including data from internal sources, into a single data file for analysis. Autolus, in collaboration with the registry holders, will be responsible for proactive planning and delivery of all milestones, including data snapshots and interim/final analyses.

9.6.1. EBMT

The EBMT Registry is a flexible data entry web application, connected to a fast and responsive live application database, enabling users to enter and retrieve data. The application database is then connected to the analytical database where all the data are restructured and organized according to the Observational Medical Outcomes Partnership Common Data Model (https://ohdsi.github.io/CommonDataModel/).

To ensure the data entered into the database are complete, correct, accurate, allowable, valid, and consistent, the following data quality edit checks will be implemented where applicable:

- EBMT Registry system-generated edit checks.
- Automated (programmed) edit checks.
- Manual edit checks by EBMT statisticians, data managers, clinical study coordinators, monitors, or any applicable user.
- Medical review by the EBMT medical officer.

Retrieval of study data is a verified process carried out by qualified data managers and enabled by qualified information technology specialists. After data are extracted, the datasets undergo an analyses dataset preparation process, which includes:

- Data verification by qualified and experienced data managers and monitors at the EBMT Clinical Study Unit; and
- Study data file preparation: analyses datasets by qualified and experienced statisticians and medical experts at the EBMT.

The study data file preparation takes place in order to enable data analytics on the EBMT Registry collected data, study statistical analyses, site management, and study management.

9.7. Data Analysis

The analysis will be performed for all patients who received at least 1 Aucatzyl infusion in this study. The data from EBMT and from CIBMTR will be analyzed separately and combined as appropriate. Categorical data will be summarized by the number and percentage of patients. Continuous data will be summarized using sample size, mean, standard deviation, median, Q1, Q3, minimum, and maximum.

Time to event data will be summarized using KM estimators.

The extent of missing data in the study will be described and tabulated. When possible, the number of missing data will be reduced by retrieving the data or imputing the correct value, if it can be derived from other information already collected.

A detailed SAP will be finalized before the first analysis to include scope of each milestone analysis, sensitivity analysis, subgroup analysis, and missing data handling.

9.7.1. Analysis of the Primary Objective: Safety Endpoints

For the primary endpoints, the number and percentage of patients who experience at least 1 occurrence of the given event will be summarized for each risk defined in the primary endpoints. The severity will be summarized where applicable, including CRS, ICANS, TLS, and GvHD. Furthermore, annual incidence rates adjusted for follow-up duration will be calculated with the appropriate time periods and methods for relevant risks requiring long-term follow-up (e.g., secondary malignancies).

Time to onset of an AE will be summarized using appropriate methods. Time to onset of long-term risks (e.g., any secondary malignancy) will be analyzed using competing risk method with death before experiencing an AE treated as competing event. Competing risk analysis will be performed for secondary malignancies, aggravation of GvHD, and autoimmune disorders.

The analyses of the primary endpoints will be pooled between CIBMTR and EBMT where feasible.

Subgroup analyses may be considered to explore the potential risk factors, including:

- Age categories: ≤ 25 versus 26-54 versus ≥ 55.
- Age category: ≥ 26.

- Patients who receive OOS product.

9.7.1.1. CRS

The overall rate and severity of CRS, according to the ASTCT consensus grading, will be described using frequency distributions (Lee et al, 2019). Summary statistics will be provided for the time from infusion to CRS onset, defined as the date when the earliest symptom of CRS is observed.

Resolution status of CRS will also be described. Summary statistics will be provided for the time from CRS onset to resolution. Therapies administered will be described where available (not collected in the EBMT registry).

9.7.1.2. MAS/HLH

Descriptive statistics will be described by frequency distributions (count and percentage). Summary statistics will be provided on time to onset, resolution status, and time to resolution.

9.7.1.3. ICANS

The overall incidence and severity of ICANS, according to ASTCT consensus grading, both in general and by specific type, will be described using frequency distributions (Lee et al, 2019). Summary statistics will be provided for the interval from the initial Aucatzyl infusion to the onset of ICANS, with the onset defined as the date when the earliest symptom of ICANS is observed. Resolution status, time to resolution, and therapy given if available (e.g., not collected in the EBMT registry).

9.7.1.4. Prolonged Cytopenia

Summary statistics will be provided for resolution status and time to resolution.

The proportion of patients in the safety dataset who did not recover normal counts of neutrophils and platelets following the first Aucatzyl infusion will be described (e.g., not resolved between Month 1 and 3), along with a 95% CI calculated using the exact binomial method. Resolution status and time to resolution will be provided.

9.7.1.5. Hypogammaglobulinemia

The overall incidence of hypogammaglobulinemia during the follow-up period will be described. Summary statistics will be provided for the interval from the first Aucatzyl infusion to the onset of hypogammaglobulinemia, resolution status, time to resolution, and therapy given where available (not collected in the EBMT registry).

Among those who develop hypogammaglobulinemia, the use of Ig replacement therapy and resolution will be described using frequency distributions.

9.7.1.6. Clinically Significant Infections

The type, organism (e.g., bacterial, viral, fungal), location (where available), and timing of the first reported clinically significant infection following the initial Aucatzyl infusion will be

described. A clinically significant infection is defined as a bacterial, viral, or fungal infection that is diagnosed by a physician and requires treatment, consistent with CIBMTR infection reporting criteria, and considered clinically meaningful according to EBMT Registry practice, irrespective of culture confirmation, provided there is clinical or microbiologic evidence supporting infection. The pathogen category (bacterial, viral, or fungal), causative organism (if identified), location (where available), and date of diagnosis will be recorded.

The number of patients with events (overall and by infection types) within 100 days and beyond 100 days will be reported.

9.7.1.7. Secondary Malignancies

Descriptive summaries of secondary malignancies by type, location, time to onset, and whether the new secondary malignancy is derived from the cell product will be provided. Incidence rates will be calculated as number of events per 1000 person-years. Exact 95% Poisson CIs will be computed for incidence rates. The incidence rate of solid tumors, secondary malignancies of T cell origin and hematological secondary malignancies (excluding T cell origin) will be summarized separately.

The cumulative incidence of secondary malignancies will be estimated using competing risk method with death before experiencing a secondary malignancy as competing event. Other competing risks and censoring events will be detailed in the SAP.

9.7.1.8. Other Neurologic Toxicity (Excluding ICANS)

The rate and severity (where available) of neurologic toxicity other than ICANS (Lee et al, 2019), both overall and by type, will be described using frequencies.

Summary statistics will also be provided for time from infusion to neurological toxicity onset.

Among those who develop neurological toxicity by Day 100, frequencies of treatments and resolution will also be described. Summary statistics will be provided for time from neurological toxicity onset to resolution and resolution status.

9.7.1.9. TLS

TLS will be identified and classified according to physician assessment based on laboratory findings and clinical symptoms. The classification of TLS events is as follows:

- Grade 3: Present.
- Grade 4: Life-threatening consequences; urgent intervention indicated.
- Grade 5: Death.

The proportion of patients (count and percentage) experiencing TLS following the initial infusion will be summarized descriptively, along with the maximum toxicity grading. Time to onset, resolution status, and time to resolution will be provided.

9.7.1.10. Immunogenicity

Descriptive statistics will be described by frequency distributions (count and percentage).

9.7.1.11. Aggravation of GvHD

This analysis will be performed in patients having undergone allogeneic HCT prior to Aucatzyl infusion.

The development of aggravated GvHD following Aucatzyl infusion will be described for both the short-term (first 100 days) and long-term (first 100 days; 101 days to ≤ 6 months, > 6 months to ≤ 1 year, 1 year to ≤ 2 years, and annually thereafter) as well as overall. This includes the maximum grade of acute GvHD (Przepiorka et al, 1995) and the severity of chronic GvHD observed since the Aucatzyl infusion.

The cumulative incidence of aggravated GvHD will be estimated using competing risk method. Acute and chronic GvHD will be analyzed separately.

9.7.1.12. Autoimmune Disorders

Descriptive summaries of autoimmune disorders by type will be provided.

The cumulative incidence of autoimmune disorders will be estimated using competing risk method. The frequency distributions (count and percentage) will be summarized for patients with events, competing risks, and censored data. Point-wise estimates for the cumulative incidences of autoimmune disorders and their corresponding 95% CIs will be provided at 1, 2, 5, 10, and 15 years.

9.7.1.13. Overdose

Descriptive statistics will be described by frequency distributions (count and percentage).

9.7.2. Other Safety Concerns

Descriptive statistics will be described by frequency distributions (count and percentage).

9.7.2.1. Pregnancy and Pregnancy Outcomes

Female patients and female partners of male patients who become pregnant, and the pregnancy outcome, will be described by frequency distributions.

9.7.3. Analysis of the Secondary Objectives

Deaths: Deaths within 30 days, within 3 months and anytime post-obe-cel infusion and cause of death will be summarized.

B cell aplasia: B cell aplasia will be identified per physician’s assessment. Time to B cell recovery will be summarized.

9.7.4. Effectiveness Endpoints

For ORR, the 95% Clopper-Pearson CIs will be provided.

KM curves will be used to illustrate OS, rwPFS, rwEFS, and DOR; and the median, as well as probabilities at specified time points post-infusion, will be estimated using the KM estimator. The associated 2-sided 95% CIs of all point estimates will be calculated; also, the number of

individuals at risk, the total number of patients included in the analysis, the number of censored and the number of events will be given. The median follow-up will be calculated using the reverse KM method.

9.8. Quality Control

9.8.1. CIBMTR

CIBMTR operates a series of automated and manual quality checks. CIBMTR data operations teams work directly with centers to maintain both consistency and quality of data collected. In addition, CIBMTR performs on-site source data audits, and each member center is audited in a 4-year cycle. These validations and verifications produce high-quality data. If a center fails to meet data quality standards, its data are removed (embargoed) from research studies.

9.8.2. EBMT

EBMT's quality control system relies primarily upon electronic data entry control triggers that promote consistency of the data and data quality / completion reports provided to the individual transplant centers. Data quality and completion reports may include information on percent of patients with annual reporting as well as individual missing data and statistical assessments for outlying data points. EBMT provides assistance (e.g., completion guidelines per data collection form, training modules, help desk support) for form completion. Although there is no external audit system of the EBMT Registry, in the present study the contractual agreement with the EBMT Registry will include the remote and/or on-site monitoring and source data verification of 10% of all patients enrolled in the study with the costs charged to the Marketing Authorization Holder.

Data collection for this study implies ethics committee procedures to have Informed Consent Forms in place with the option to share the data with the Marketing Authorization Holder.

With study-specific funding to the EBMT, processes to ensure higher data quality and completeness will be implemented. Additional site personnel training will be applied by the EBMT with dedicated Clinical Study Unit personnel. Furthermore, to facilitate the completeness of the data in the present study, a documentation fee will be provided to the participating centers, which will be reduced when the data provided are significantly incomplete or of poor quality.

Data from EBMT subjects will be stored within the EBMT Registry. Participating centers will enter the data directly into the electronic data collection forms. Each center typically has one or more designated staff who enter data. Registry data are maintained in the central database, and it is the EBMT and the center's responsibility to ensure that the data are accurate.

EBMT Quality Assurance Unit periodically performs quality checks on the Study Master File on an established frequency of 6 months. With this process, it is ensured that all essential study documentation is present, up-to-date and correctly saved in the proper folder of the Study Master File.

For sponsored studies, EBMT is planning to have a general third-party audit every 2 to 3 years. Additionally, the Clinical Study Unit is audited internally by the EBMT Quality Assurance Unit on a yearly basis.

9.9. Limitations of the Research Methods

While several safeguards have been built into the design of this registry-based study, including a prespecified protocol, utilization of validated data capture mechanisms, and data quality verification, the inherent nature of observational research means that the risks of bias cannot be fully eliminated. Below is a summary of potential biases that may affect the study and the steps taken to mitigate them.

9.9.1. Misclassification Bias

Despite using high-quality patient-level data from the EBMT and CIBMTR registries, as well as standardized definitions for outcomes and responses, there remains a risk of misclassification bias. Misclassifying eligible patients as ineligible or incorrectly recording response assessments could significantly limit the validity of inferences drawn from the study. To mitigate this risk, the following strategies have been implemented:

- **Automated Data Quality Checks**: Built-in validation rules within the registries' data collection systems help identify inconsistencies or potential errors in the data.
- **Medical Data Review**: Centralized medical review teams assess the data, and queries are sent to sites if potential misclassifications or inconsistencies are detected.
- **Training**: Registry staff and contributing site personnel are trained on eligibility criteria, response assessments, and data entry processes to ensure high-quality data abstraction.

9.9.2. Information Bias

Since this study involves multiple countries and centers, variations in the interpretation of patient outcomes (e.g., disease staging or response criteria) could result in information bias and limit generalizability. To address this:

- **Harmonized Definitions**: All outcomes, dispositions, and staging criteria are standardized based on international guidelines and indices, such as the Hematopoietic Cell Transplantation Comorbidity Index.
- **Response Guidelines**: Both the EBMT and CIBMTR registries provide response guidelines to participating sites.

9.9.3. Selection Bias

Selection bias could arise from over- or under-recruitment by specific centers or regions, particularly if these centers have distinct clinical practices or patient populations. To mitigate this:

- **Stratification by Recruitment Country and Center**: Country of recruitment and center characteristics will be defined as stratification factors in the analysis to account for any systematic differences.

Selection bias could also arise from selective patient consent or selective loss to follow-up. Loss to follow-up may compromise the precision of the estimates, particularly for secondary malignancy events where follow-up completeness is critical.

9.9.4. Confounding

Although stratification factors and registry metadata enable detailed descriptive analysis, confounding remains a concern, particularly when comparing patient groups.

To address this:

- **Avoidance of Formal Group Comparisons**: The study will not perform direct intergroup comparisons without appropriate multivariate adjustments. Further details will be provided in the SAP.
- **Contextualized Findings**: Results will be interpreted within the broader evidence base for the disease, leveraging existing literature to minimize confounding.

9.9.5. Missing Data

Incomplete data may arise due to several reasons, including the following:

- Patients may receive care across multiple sites or from multidisciplinary teams, leading to incomplete data capture.
- Specific data points may not be consistently available across registry reporting periods.
- Details on treatment interruptions, reasons for discontinuation, or transitions to new therapies may be underreported.
- In some regions, data on deceased patients may be inaccessible due to regulatory or privacy constraints.

To mitigate the impact of missing data:

- **Data Querying**: Registries employ robust query processes to request missing or incomplete data from reporting centers where feasible.
- **Sensitivity Analyses**: Sensitivity analyses will be performed to assess the robustness of findings under different assumptions about the nature of missing data. Further details will be provided in the SAP.

9.9.6. External Validity of the Study

This study seeks to emulate the rigor of a prospective trial while leveraging the extensive RWD collected by the EBMT and CIBMTR registries. By recruiting patients across diverse geographic and clinical settings, the study aims to capture a broad and representative sample of treatment

practices and patient outcomes. Endpoint definitions and response harmonization ensure alignment with prospective trial standards, enhancing the study's generalizability and relevance to clinical practice.

10. PROTECTION OF HUMAN SUBJECTS

For this study, all of the registry holder databases are 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.

CIBMTR protects the privacy and human rights of participants (CIBMTR, 2025c). CIBMTR obeys international laws and ethical guidelines, including the United States Health Insurance Portability and Accountability Act and the EU's GDPR. The NMDP Institutional Review Board, which is fully accredited by the Association for the Accreditation of Human Research Protection Programs, reviews CIBMTR's research. Patients and/or guardian(s) give informed consent for research.

The treating physician must ensure anonymity of the patients; patients must not be identified by name in any documents submitted to Autolus. Patient data will be transferred to Autolus on an individual, pseudo-anonymized individual patient-level together with the Aucatzyl batch number in compliance with the Regulation (EC) 1394/2007, Article 15, traceability for advanced therapy medicinal products (EUR-Lex, 2007). The treating physician and the registry holders (CIBMTR and EBMT) will be able to link the Patient Number to the patient's identity. Due to the nature of the Aucatzyl product and this guidance, selected Autolus employees will have access to patient identifier information, such as the manufacturing facility. Other Autolus teams will have access to the batch ID and manufactured product details but will not be privy to patient names.

For analysis and publication purposes, data will be presented only in an anonymized manner, unless required for analysis of specific manufactured product characteristics.

Following the GDPR, and to ensure the maximum accordance with the law in all EU/EEA nations, personal data of patients residing in EU member countries shall only be used for research through the EBMT when appropriate informed consent is ensured. This has been common practice for many years. The informed consent is collected by the individual centers or donor registries submitting data to the EBMT to make sure that the respective national laws are followed. The EBMT makes patient consent a prerequisite for submitting the data and provides all necessary information about usage of the data, to ensure appropriate consent is obtained in all cases. Post-authorization study ICF templates are provided to all countries. Copies have been/will be submitted to Competent Authorities and ethics committees where applicable for approval.

10.1. Regulatory and Ethical Compliance

Compliance with Autolus 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 EEA 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 of the International Society for Pharmacoepidemiology (EMA, 2018), the Strengthening the Reporting of Observational Studies

in Epidemiology guidelines (Vandenbroucke et al, 2014), and with the ethical principles laid down in the Declaration of Helsinki.

This study is fulfilling the criteria of an "ENCePP study" and follows the "ENCePP Code of Conduct" (EMA, 2018).

10.2. Informed Consent Procedures

There will be no Autolus-specific study ICF for standard data collection. CIBMTR and EBMT will develop and implement ICFs for data collection within each individual registry database.

11. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

This post-authorization study protocol is a non-interventional research based on secondary use of data (i.e., utilizing data from patients' medical records that was previously collected for another purpose and included into the CIBMTR and EBMT registries; and where the AEs have already occurred and will not be reported in expedited manner) as outlined in Good Pharmacovigilance Practices Module VI.

Data collection for this non-interventional study is calendar-driven and not designed to detect and report individual AEs quickly. Reporting of individual AEs will follow the standard spontaneous AE reporting system per the local regulations, and sites are advised to report any suspected adverse reactions to Autolus (safety email) or directly to the FDA (www.fda.gov/medwatch) in the US or the applicable competent authority in other countries. The center and the Marketing Authorization Holder are responsible for up-to-date AE reporting. Consequently, there is no general requirement for the registries for AE reporting except for tabulations of the primary and secondary outcomes in study reports.

An exception will be reporting on the development of subsequent neoplasms. Centers will be asked to submit the subsequent neoplasm form to the CIBMTR or EBMT within 72 hours of knowledge of diagnosis and, if possible, before institution of therapy, so that informed consent for collection of patient samples, and collection of those samples can be obtained.

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.

12. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

The registries will provide yearly safety and effectiveness data to Autolus at least until the planned interim analysis, and thereafter, for the final study report.

12.1. Annual and Interim Reports

CIBMTR and EBMT will upload data into a restricted-access repository. Pooling of data between CIBMTR and EBMT will be performed as required when feasible.

Autolus, in collaboration with the registry holders, will be responsible for proactive planning and delivering of all milestones, including data snapshots and interim/final analyses.

Autolus will submit reports to regulatory agencies in accordance with any prespecified agreements/commitments as outlined in Section 6. A final report will be provided after 15 years of follow-up, or when the last patient finishes follow-up in the registry, whichever occurs earlier.

12.2. Final Report

The final report will be prepared including all planned effectiveness and safety analyses at the end of the 15-year follow-up period.

13. REFERENCES

CIBMTR. (2025a). Data Collection Forms. https://cibmtr.org/CIBMTR/Data-Operations/Data-Collection-Forms. Accessed on 15-Dec-2025.

CIBMTR. (2023). 2023 Annual Report. https://cibmtr.org/Files/Administrative-Reports/Annual-Reports/2023-Annual-Report.pdf. Accessed on 15-Dec-2025.

CIBMTR. (2025b). Protocols & Consent Forms. https://cibmtr.org/CIBMTR/Data-Operations/Protocols-Consent-Forms. Accessed on 15-Dec-2025.

CIBMTR. (2022). Protocol For a Research Database for Hematopoietic Cell Transplantation, Other Cellular Therapies and Marrow Toxic Injuries, version 9.1 2022. https://cibmtr.org/Files/Protocols-and-Consent-Forms/Research-Database/PTC-00002-Protocol-for-a-Research-Database-for-HCT-Other-Cell-Therapies-and-Marrow-Toxic-Injuries-Legacy-T00006.pdf. Accessed on 15-Dec-2025.

CIBMTR. (2021). Protocol for a Research Sample Repository for Hematopoietic Cell Transplantation, Other Cellular Therapies and Marrow Toxic Injuries, version 13.0. https://cibmtr.org/Files/Protocols-and-Consent-Forms/Research-Sample-Repository/PTC-00003-Protocol-for-a-Research-Sample-Repository-for-HCT-Other-Cell-Therapies-and-Marrow-Toxic-Injuries--Legacy-T00007.pdf. Accessed on 15-Dec-2025.

CIBMTR. (2025c). Data Protection & Privacy. Last updated: 20-Oct-2025. https://cibmtr.org/CIBMTR/About/Data-Protection-Privacy. Accessed on 15-Dec-2025.

CIBMTR. (2025d). Data Collection Forms. https://cibmtr.org/CIBMTR/Data-Operations/Data-Collection-Forms. Accessed on Apr-2025.

EBMT. (2025). Data Collection Forms. https://www.ebmt.org/registry/ebmt-data-collection. Accessed on Apr-2025.

EMA. (2018). The ENCePP Code of Conduct For Scientific Independence and Transparency in the Conduct of Pharmacoepidemiological and Pharmacovigilance Studies (EMA/929209/2011). https://encepp.europa.eu/document/download/e504e741-1813-4327-85d5-0f7ac8214ca1_en?filename=ENCePPCodeofConduct.pdf. Accessed on 15-Dec-2025.

EUR-Lex. (2007). Regulation (EC) No 1394/2007 of the European Parliament and of the Council of 13 November 2007 on advanced therapy medicinal products and amending Directive 2001/83/EC and Regulation (EC) No 726/2004. https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32007R1394. Accessed on 15-Dec-2025.

Lee DW, Santomasso BD, Locke FL, et al. (2019). ASTCT Consensus Grading for Cytokine Release Syndrome and Neurologic Toxicity Associated with Immune Effector Cells. Biol Blood Marrow Transplant. 25(4):625–38. DOI: 10.1016/j.bbmt.2018.12.758.

Lerkvaleekul B, Vilaiyuk S. (2018). Macrophage activation syndrome: early diagnosis is key. Open Access Rheumatol. 10:117–28. DOI: 10.2147/OARRR.S151013.

Miao L, Zhang Z, Ren Z, Li Y. (2021). Reactions Related to CAR-T Cell Therapy. Front Immunol. 12:663201. DOI: 10.3389/fimmu.2021.663201.

NCI. (2025). National Cancer Institute Definitions of Cancer Terms. Definition of HLH. https://www.cancer.gov/publications/dictionaries/cancer-terms/def/hlh. Accessed on 15-Dec-2025.

Przepiorka D, Weisdorf D, Martin P, et al. (1995). 1994 Consensus Conference on Acute GVHD Grading. Bone Marrow Transplantation. 15(6):825–8.

Sureda A, Carpenter PA, Bacigalupo A, et al. (2024). Harmonizing definitions for hematopoietic recovery, graft rejection, graft failure, poor graft function, and donor chimerism in allogeneic hematopoietic cell transplantation: a report on behalf of the EBMT, ASTCT, CIBMTR, and APBMT. Bone Marrow Transplantation. 59(6):832–7. DOI: 10.1038/s41409-024-02251-0.

Tix T, Alhomoud M, Shouval R, et al. (2024). Second Primary Malignancies after CAR T-Cell Therapy: A Systematic Review and Meta-analysis of 5,517 Lymphoma and Myeloma Patients. Clin Cancer Res. 30(20):4690–700. DOI: 10.1158/1078-0432.CCR-24-1798.

Vandenbroucke JP, von Elm E, Altman DG, et al. (2014). Strengthening the Reporting of Observational Studies in Epidemiology (STROBE): Explanation and elaboration. International Journal of Surgery. 12(12):1500–24. DOI: 10.1016/j.ijsu.2014.07.014.

Working Group Report. (2005). International rules for multiple primary cancers (ICD-0 third edition). Eur J Cancer Prev. 14(4):307–8. DOI: 10.1097/00008469-200508000-00002.

14. APPENDICES

14.1. Annex 1: List of Stand-alone Documents

Number	Document reference number	Date	Title
2	NA	15-Apr-2024	American Society for Transplantation and Cellular Therapy CRS Consensus Grading
3	NA	15-Apr-2024	Immune Effector Cell-Associated Neurotoxicity Syndrome Consensus Grading for Adults
4	NA	16-Jan-2025	Post-Marketing Secondary Malignancy Testing Algorithm
5	NA	Apr-2025	Data Collection Forms for the Variables and Outcomes of Interest
6	NA	09-Dec-2024	ENCePP Checklist

Abbreviations: CRS=cytokine release syndrome; ENCePP=European Network of Centers for Pharmacoepidemiology and Pharmacovigilance; NA=not applicable.

14.2. Annex 2: American Society for Transplantation and Cellular Therapy CRS Consensus Grading

CRS Parameter	Grade 1	Grade 2	Grade 3	Grade 4
Fever*	Temperature ≥38°C	Temperature ≥38°C	Temperature ≥38°C	Temperature ≥38°C
		With		
Hypotension	None	Not requiring vasopressors	Requiring a vasopressor with or without vasopressin	Requiring multiple vasopressors (excluding vasopressin)
		And/or†		
Hypoxia	None	Requiring low-flow nasal cannula‡ or blow-by	Requiring high-flow nasal cannula‡, facemask, nonrebreather mask, or Venturi mask	Requiring positive pressure (eg, CPAP, BiPAP, intubation and mechanical ventilation)

Organ toxicities associated with CRS may be graded according to CTCAE v5.0 but they do not influence CRS grading.

* Fever is defined as temperature ≥38°C not attributable to any other cause. In patients who have CRS then receive antipyretic or anticytokine therapy such as tocilizumab or steroids, fever is no longer required to grade subsequent CRS severity. In this case, CRS grading is driven by hypotension and/or hypoxia.

† CRS grade is determined by the more severe event: hypotension or hypoxia not attributable to any other cause. For example, a patient with temperature of 39.5°C, hypotension requiring 1 vasopressor, and hypoxia requiring low-flow nasal cannula is classified as grade 3 CRS.

‡ Low-flow nasal cannula is defined as oxygen delivered at ≤6 L/minute. Low flow also includes blow-by oxygen delivery, sometimes used in pediatrics. High-flow nasal cannula is defined as oxygen delivered at >6 L/minute.

Abbreviations: BiPAP=bi-level positive airway pressure; CPAP=continuous positive airway pressure; CRS=cytokine release syndrome; CTCAE=Common Terminology Criteria for Adverse Events.
Source: (Lee et al, 2019).

14.3. Annex 3: Immune Effector Cell-associated Neurotoxicity Syndrome Consensus Grading for Adults

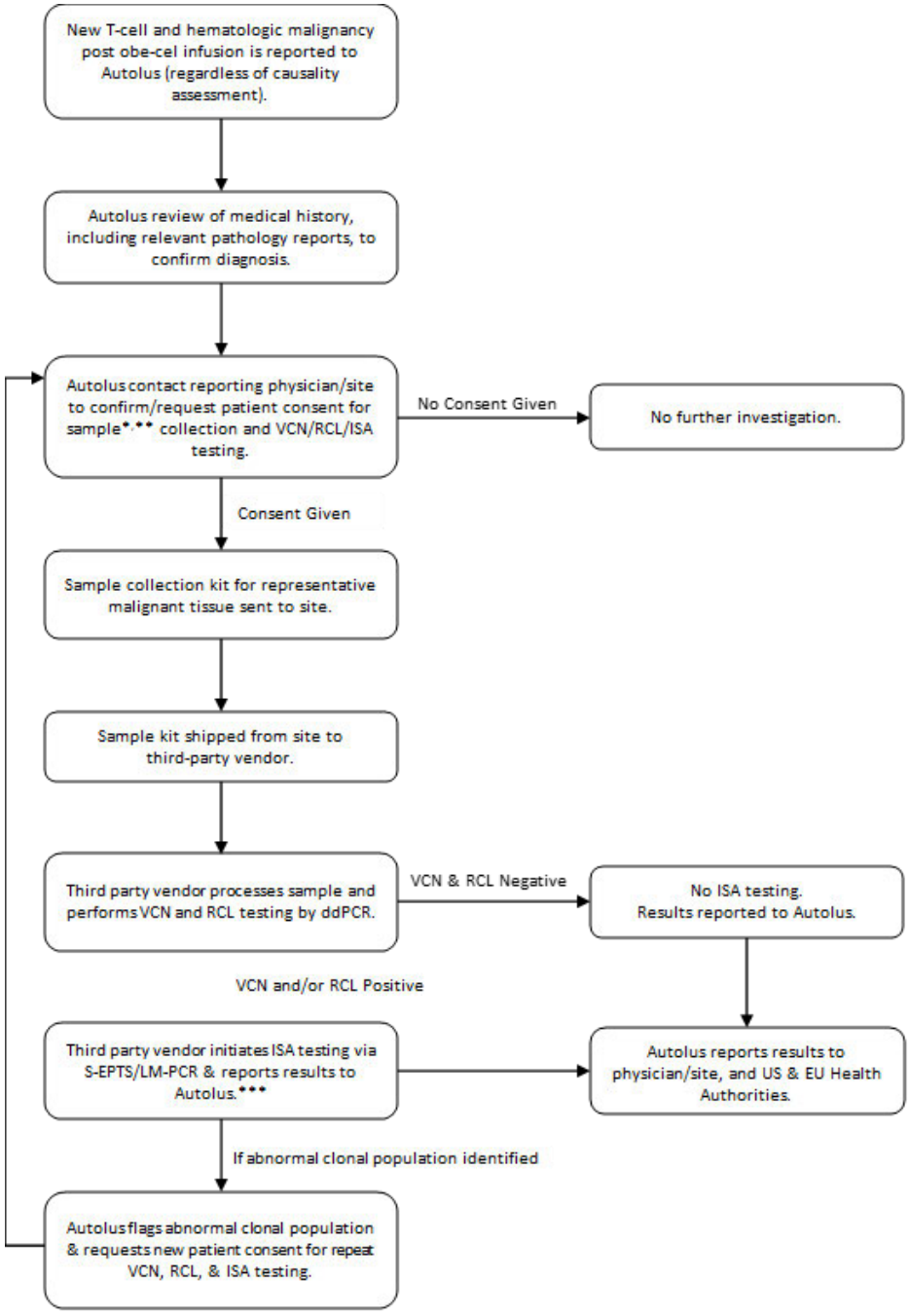
Neurotoxicity Domain	Grade 1	Grade 2	Grade 3	Grade 4
ICE score*	7-9	3-6	0-2	0 (patient is unarousable and unable to perform ICE)
Depressed level of consciousness†	Awakens spontaneously	Awakens to voice	Awakens only to tactile stimulus	Patient is unarousable or requires vigorous or repetitive tactile stimuli to arouse. Stupor or coma
Seizure	N/A	N/A	Any clinical seizure focal or generalized that resolves rapidly or nonconvulsive seizures on EEG that resolve with intervention	Life-threatening prolonged seizure (>5 min); or Repetitive clinical or electrical seizures without return to baseline in between
Motor findings‡	N/A	N/A	N/A	Deep focal motor weakness such as hemiparesis or paraparesis
Elevated ICP/ cerebral edema	N/A	N/A	Focal/local edema on neuroimaging§	Diffuse cerebral edema on neuroimaging; decerebrate or decorticate posturing; or cranial nerve VI palsy; or papilledema; or Cushing's triad

ICANS grade is determined by the most severe event (ICE score, level of consciousness, seizure, motor findings, raised ICP/cerebral edema) not attributable to any other cause; for example, a patient with an ICE score of 3 who has a generalized seizure is classified as grade 3 ICANS.
N/A indicates not applicable.
* A patient with an ICE score of 0 may be classified as grade 3 ICANS if awake with global aphasia, but a patient with an ICE score of 0 may be classified as grade 4 ICANS if unarousable.
† Depressed level of consciousness should be attributable to no other cause (eg, no sedating medication).
‡ Tremors and myoclonus associated with immune effector cell therapies may be graded according to CTCAE v5.0, but they do not influence ICANS grading.
§ Intracranial hemorrhage with or without associated edema is not considered a neurotoxicity feature and is excluded from ICANS grading. It may be graded according to CTCAE v5.0.

Abbreviations: CTCAE=Common Terminology Criteria for Adverse Events; EEG=electroencephalogram; ICANS=Immune effector cell-associated neurotoxicity syndrome; ICE=immune effector cell encephalopathy; ICP=intracranial pressure; N/A=not applicable
Source: (Lee et al, 2019).

14.4. Annex 4: Post-Marketing Secondary Malignancy Testing Algorithm, Including T Cell Malignancy and Hematologic Malignancies (Except of T Cell Origin)

Process Flow for the EU Region



Abbreviation: ddPCR=droplet digital polymerase chain reaction; DNA=deoxyribonucleic acid; ISA=insertional site analysis; EU=European Union; IEC=Institutional Ethics Committee; LM-PCR=ligation-mediated polymerase chain

reaction; RCL=replication competent lentivirus; S-EPTS=shearing extension primer tag selection; US=United States; VCN=vector copy number.
* Only tissue from pre-existing samples will be collected for analysis.
** Autolus will aim to contact prescribers to ensure they obtain consent for new second primary malignancy testing. In accordance with local regulations, the prescribing physician will secure approval, if required, from the site's IEC for testing activities and the Informed Consent Form.
*** If ISA results are inconclusive regarding causality, gene expression/transcriptome analysis as well as whole genome, whole exome or targeted DNA sequencing may be performed.
Consent will be sought for (1) VCN, RCL, and ISA testing using existing samples or a de novo collected sample from the new malignancy and (2) reporting of results to Autolus and Health Authorities.

14.5. Annex 5: Data Collection Forms for the Variables and Outcomes of Interest

Note that data collection forms from CIBMTR and EBMT are subject to change and mapping between them will change accordingly.

	CIBMTR		EBMT	
	Form	**Form Question #**	**Form**	**Question**
PATIENT-RELATED:				
Age	2804 R6 4006 R6	Q: 3 Q: 6	Patient_registration_v2.0	Date of birth
Comorbidities prior to infusion	4000 R10	Q: 92-97	Disease_status_HCT_CT_GT_IST_Day0_core_v2.2	Page: 3
Country where infusion was performed	4000 R10	Key Field (*header section*)	Patient_registration_v2.0	Key Field (*header section*)
ECOG performance score	4000 R10	Q: 80	Disease_status_HCT_CT_GT_IST_Day0_core_v2.2	Page: 2
Ethnicity	2807 R1	Q: 1-2	*Not Applicable*	*Not Applicable*
Height at the time of lymphodepleting chemotherapy	4001 R1 F4000 R11	Q: 5 Q: 93	Disease_status_HCT_CT_GT_IST_Day0_core_v2.2	Page: 2 (*at initiation of CT*)
Race	2804 R1	Q: 1-2	Patient_registration_v2.0	Page:3
Sex	2804 R6	Q: 7	Patient_registration_v2.0	Page:1
Weight at the time of lymphodepleting chemotherapy	4001 R1 4000 R11	Q: 6 Q: 94	Disease_status_HCT_CT_GT_IST_Day0_core_v2.2	Page: 2 (*at initiation of CT*)
AT DIAGNOSIS:				
11q23 / MLL rearrangement	2402 R9	Q: 109 - 114 (110 - 115/FISH) Q: 120 (116-121/Karyotyping)	Acute_Leukaemias_v2.2 (Core only)	Page: 3-4
Blast in marrow	2011 R5	Q: 7-8	Acute_Leukaemias_v2.2 (Core only)	Page: 1
BCR/ABL mutation	2402 R9	Q: 123-124	Acute_Leukaemias_v2.2 (Core only)	Page: 3
Cytogenetic risk score	2402 R9	Q: 109-165	Acute_Leukaemias_v2.2 (Core only)	Page: 1-6
Extramedullary disease	2011 R5	Q: 10	Acute_Leukaemias_v2.2 (Core only)	Page: 6
Philadelphia chromosome	2402 R9	Q: 114	Acute_Leukaemias_v2.2 (Core only)	Page: 3
WBC count	2011 R5	Q: 1-2	Acute_Leukaemias_v2.2 (Core only)	Page: 1
PRIOR TO INFUSION:				
Bone marrow blast cells percentage	2011 R5	Q: 70-71	Disease_status_HCT_CT_GT_IST_Day0_core_v2.2	Page: 7
Disease status prior to infusion	2011 R5	Q: 50	Disease_status_HCT_CT_GT_IST_Day0_core_v2.2	Page: 7
Extramedullary disease	2011 R5	Q: 82	Disease_status_HCT_CT_GT_IST_Day0_core_v2.2	Page: 8
GVHD status/grade	4100 R9	Q: 27-46	CT_FU_v2.2	Page: 2; 10-11
MRD status prior to infusion	2011 R5 2402 R9	Q: 52 Q: 169	Disease_status_HCT_CT_GT_IST_Day0_core_v2.2	Page: 8
Number of prior lines of therapy	2011 R5	Q: 27-63	Treatment non HCT_CT_GT_IST core_v1.2	Page: 1-6
Prior cellular therapy	4000 R10	Q: 18-26	CT_Day0_v2.1	Page: 6
Prior exposure to blinatumomab	2011 R5	Q: 37	Treatment non HCT_CT_GT_IST core_v1.2	Page: 2
Prior exposure to inotuzumab	2011 R5	Q: 37	Treatment non HCT_CT_GT_IST core_v1.2	Page: 2
Prior HCT	4000 R10	Q: 27	CT_Day0_v2.1	Page: 6
Response to last line of therapy prior to leukapheresis	2011 R5	Q: 27-63	Treatment non HCT_CT_GT_IST core_v1.2	Page: 4
Time from HCT to Aucatzyl infusion	4000 R10 4006 R6	Q: 27-29 Q: 6	CT_Day0_v2.1	Page: 5-6
INFUSION-RELATED:				
Bridging therapy	2011 R5 4000 R11	Q: 27-63 Q: 85-91	Treatment non HCT_CT_GT_IST core_v1.2	Page: 1-5
Cell dose infused	4006 R6	Q: 17-31	CT_Day0_v2.1	Page: 14
List of authorized treatment centers	4000 R10	Key Field (*header section*)	Patient_registration_v2.0	Key Field (*header section*)
Lot number	4006 R6	Q: 5	CT_Day0_v2.1	Page: 8
Out-of-specification product	4003 R5	Q: 2	CT_Day0_v2.1	Page: 8
Route of administration	4006 R6	Q: 10	CT_Day0_v2.1	Page: 14

	CIBMTR		EBMT	
	Form	Form Question #	Form	Question
Time from diagnosis to infusion	2402 R9 4006 R6	Q: 1 Q: 6	Acute_Leukaemias_v2.2 (Core only) CT_Day0_v2.1	Page: 1 Page: 5
Time from leukapheresis to infusion	4003 R5 4006 R6	Q: 4 Q: 6	CT_Day0_v2.1	Page: 1, 5
Time from start of lymphodepleting chemotherapy to infusion	4001 R1 4000 R11 4006 R6	Q: 10 Q: 98 Q: 6	*Not collected*	
Type of lymphodepleting chemotherapy regimen	4001 R1 4000 R11	Q: 7-8 Q: 95-96	CT_Day0_v2.1	Page: 12
Year of infusion	4006 R6	Q: 6	CT_Day0_v2.1	Page: 14
OUTCOMES:				
Aggravation of GVHD	4100 R9	Q: 27-46	CT_FU_v2.2	Page: 4-5
Autoimmune disorder	4100 R10	Q: 22-25	CT_FU_v2.2	Page: 16
B-cell aplasia	4101 R1	Q: 43-45	CT_FU_v2.2	Page: 3
Causes of death	2900 R5	Q: 4-7	CT_FU_v2.2	Page: 1
Clinically significant infections	4100 R9	Q: 178-182	CT_FU_v2.2	Page: 11
Cytokine release syndrome	4100 R9	Q: 47-49	CT_FU_v2.2	Page: 6
Duration of response	2111 R4	Q: 1-34; Q:48-80	CT_FU_v2.2	Page: 23-24
Event-free survival	2111 R4 4100 R9	Q: 48-80 Q: 2-4	CT_FU_v2.2	Page: 23-24 Page: 1, 18
HLH/ MAS	4100 R9	Q: 68-69	CT_FU_v2.2	Page: 7
Hypogammaglobulinemia	4100 R9	Q: 138-141	CT_FU_v2.2	Page: 10
ICANS	4100 R9	Q: 86-87	CT_FU_v2.2	Page: 6
Immunogenicity			CT_FU_v2.2	Page: 10
MRD	2111 R4	Q: 81-82	CT_FU_v2.2	Page: 24
Other neurologic toxicities	4100 R9	Q: 87	CT_FU_v2.2	Page: 7
Overall remission rate	2111 R4	Q: 1-34	CT_FU_v2.2	Page: 23
Overall survival	4100 R9	Q: 2-3	CT_FU_v2.2	Page: 1
Overdose	4006 R6	Q: 17	CT_Day0_v2.1	Page: 14
Pregnancy outcomes	4100 R9	Q: 190-191	CT_FU_v2.2	Page: 21
Prolonged cytopenia	4100 R9	Q: 15-23	CT_FU_v2.2	Page: 3
Secondary malignancy	4100 R9 3500 R2	Q: 26 Q: 1-24	CT_FU_v2.2	Page: 16
Tumor lysis syndrome	4100 R9	Q: 142-147	CT_FU_v2.2	Page: 9

Abbreviations: CIBMTR=Center for International Blood and Marrow Transplant Research; CT=computed tomography; EBMT=European Society for Blood and Marrow Transplantation; ECOG=Eastern Cooperative Oncology Group; FISH=fluorescence in situ hybridization; GVHD=graft versus host disease; HCT=hematopoietic cell transplantation; HLH=hemophagocytic lymphohistiocytosis; ICANS=immune effector cell-associated neurotoxicity syndrome MAS=macrophage activation syndrome; MLL=mixed-lineage leukemia; MRD=measurable residual disease; WBC=white blood cell.
Source: (CIBMTR, 2025d) and (EBMT, 2025).

14.6. Annex 6: ENCePP Checklist

ENCePP Checklist for Study Protocols (Revision 4)

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

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

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

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

Study title: Prospective, international, non-interventional study to assess short- and long-term safety and effectiveness of adult patients with relapsed or refractory B cell acute lymphoblastic leukemia receiving Aucatzyl® treatment.

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

Section 1: Milestones	**Yes**	**No**	**N/A**	**Section Number**
1.1 Does the protocol specify timelines for				
1.1.1 Start of data collection[a]	☒	☐	☐	6
1.1.2 End of data collection[b]	☒	☐	☐	6

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

Section 1: Milestones	**Yes**	**No**	**N/A**	**Section Number**
1.1.3 Progress report(s)	☒	☐	☐	6
1.1.4 Interim report(s)	☒	☐	☐	6
1.1.5 Registration in the EU PAS Register®	☒	☐	☐	6
1.1.6 Final report of study results.	☒	☐	☐	6

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)	☒	☐	☐	7
2.1.2 The objective(s) of the study?	☒	☐	☐	8
2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	9
2.1.4 Which hypothesis(-es) is (are) to be tested?	☐	☐	☒	
2.1.5 If applicable, that there is no *a priori* hypothesis?	☐	☐	☒	

Comments:

Descriptive study without formal hypothesis test.

Section 3: Study design	**Yes**	**No**	**N/A**	**Section Number**
3.1 Is the study design described? (e.g. cohort, case-control, cross-sectional, other design)	☒	☐	☐	9.1
3.2 Does the protocol specify whether the study is based on primary, secondary or combined data collection?	☒	☐	☐	9.1
3.3 Does the protocol specify measures of occurrence? (e.g., rate, risk, prevalence)	☒	☐	☐	9.3.1
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))	☐	☐	☒	
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)	☒	☐	☐	11

Comments:

Section 4: Source and study populations		**Yes**	**No**	**N/A**	**Section Number**
4.1	Is the source population described?	☒	☐	☐	9.1-9.2
4.2	Is the planned study population defined in terms of:				
	4.2.1 Study time period	☒	☐	☐	9.1.1
	4.2.2 Age and sex	☒	☐	☐	9.2
	4.2.3 Country of origin	☒	☐	☐	8-9.4
	4.2.4 Disease/indication	☒	☐	☐	9.2
	4.2.5 Duration of follow-up	☒	☐	☐	9.1.1
4.3	Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☒	☐	☐	9.2

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 categorising exposure, measurement of dose and duration of drug exposure)	☒	☐	☐	9.1.1
5.2	Does the protocol address the validity of the exposure measurement? (e.g. precision, accuracy, use of validation sub-study)	☐	☐	☒	
5.3	Is exposure categorised according to time windows?	☐	☐	☒	
5.4	Is intensity of exposure addressed? (e.g. dose, duration)	☐	☐	☒	
5.5	Is exposure categorised based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☐	☐	☒	
5.6	Is (are) (an) appropriate comparator(s) identified?	☐	☐	☒	

Comments:

In relation to exposure intensity, patients receiving overdoses of the exposure are analyzed.

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?	☒	☐	☐	9.3.1
6.2 Does the protocol describe how the outcomes are defined and measured?	☒	☐	☐	9.3.1
6.3 Does the protocol address the validity of outcome measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, use of validation sub-study)	☐	☐	☒	9.5
6.4 Does the protocol describe specific outcomes relevant for Health Technology Assessment? (e.g. HRQoL, QALYs, DALYS, health care services utilisation, burden of disease or treatment, compliance, disease management)	☐	☐	☒	

Comments:

Section 7: Bias	**Yes**	**No**	**N/A**	**Section Number**
7.1 Does the protocol address ways to measure confounding? (e.g. confounding by indication)	☒	☐	☐	9.9
7.2 Does the protocol address selection bias? (e.g. healthy user/adherer bias)	☒	☐	☐	9.9
7.3 Does the protocol address information bias? (e.g. misclassification of exposure and outcomes, time-related bias)	☒	☐	☐	9.9

Comments:

Section 8: Effect measure modification	**Yes**	**No**	**N/A**	**Section Number**
8.1 Does the protocol address effect modifiers? (e.g. collection of data on known effect modifiers, sub-group analyses, anticipated direction of effect)	☒	☐	☐	9

Comments:

Patients receiving out of specification product will be analyzed separately. Further details on analytical methodologies will be described in the SAP.

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:				

Section 9: Data sources	**Yes**	**No**	**N/A**	**Section Number**
9.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview)	☒	☐	☐	9.3
9.1.2 Outcomes? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics)	☒	☐	☐	9.3
9.1.3 Covariates and other characteristics?	☒	☐	☐	9.3
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)	☒	☐	☐	9.3.1
9.2.2 Outcomes? (e.g. date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	9.3.1
9.2.3 Covariates and other characteristics? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, lifestyle)	☒	☐	☐	9.3.1
9.3 Is a coding system described for:				
9.3.1 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System)	☐	☐	☒	
9.3.2 Outcomes? (e.g. International Classification of Diseases (ICD), Medical Dictionary for Regulatory Activities (MedDRA))	☐	☐	☒	
9.3.3 Covariates and other characteristics?	☐	☐	☒	
9.4 Is a linkage method between data sources described? (e.g. based on a unique identifier or other)	☐	☐	☒	

Comments:

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Section Number**
10.1 Are the statistical methods and the reason for their choice described?	☒	☐	☐	9.7
10.2 Is study size and/or statistical precision estimated?	☒	☐	☐	9.5
10.3 Are descriptive analyses included?	☒	☐	☐	9.7
10.4 Are stratified analyses included?	☐	☐	☒	
10.5 Does the plan describe methods for analytic control of confounding?	☐	☐	☒	
10.6 Does the plan describe methods for analytic control of outcome misclassification?	☐	☐	☒	

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Section Number**
10.7 Does the plan describe methods for handling missing data?	☒	☐	☐	9.9
10.8 Are relevant sensitivity analyses described?	☐	☐	☒	

Comments:

Statistical methods will be detailed in the statistical analysis plan (SAP).

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)	☒	☐	☐	9.6
11.2 Are methods of quality assurance described?	☒	☐	☐	9.8
11.3 Is there a system in place for independent review of study results?	☒	☐	☐	12.2

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?	☒	☐	☐	9.9
12.1.2 Information bias?	☒	☐	☐	9.9
12.1.3 Residual/unmeasured confounding? (e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods).	☐	☐	☒	
12.2 Does the protocol discuss study feasibility? (e.g. study size, anticipated exposure uptake, duration of follow-up in a cohort study, patient recruitment, precision of the estimates)	☒	☐	☐	9.2.3

Comments:

Section 13: Ethical/data protection issues	**Yes**	**No**	**N/A**	**Section Number**
13.1 Have requirements of Ethics Committee/ Institutional Review Board been described?	☒	☐	☐	10
13.2 Has any outcome of an ethical review procedure been addressed?	☐	☐	☒	

Section 13: Ethical/data protection issues	**Yes**	**No**	**N/A**	**Section Number**
13.3 Have data protection requirements been described?	☒	☐	☐	9.6

Comments:

Section 14: Amendments and deviations	**Yes**	**No**	**N/A**	**Section Number**
14.1 Does the protocol include a section to document amendments and deviations?	☒	☐	☐	5

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)?	☒	☐	☐	12
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	12

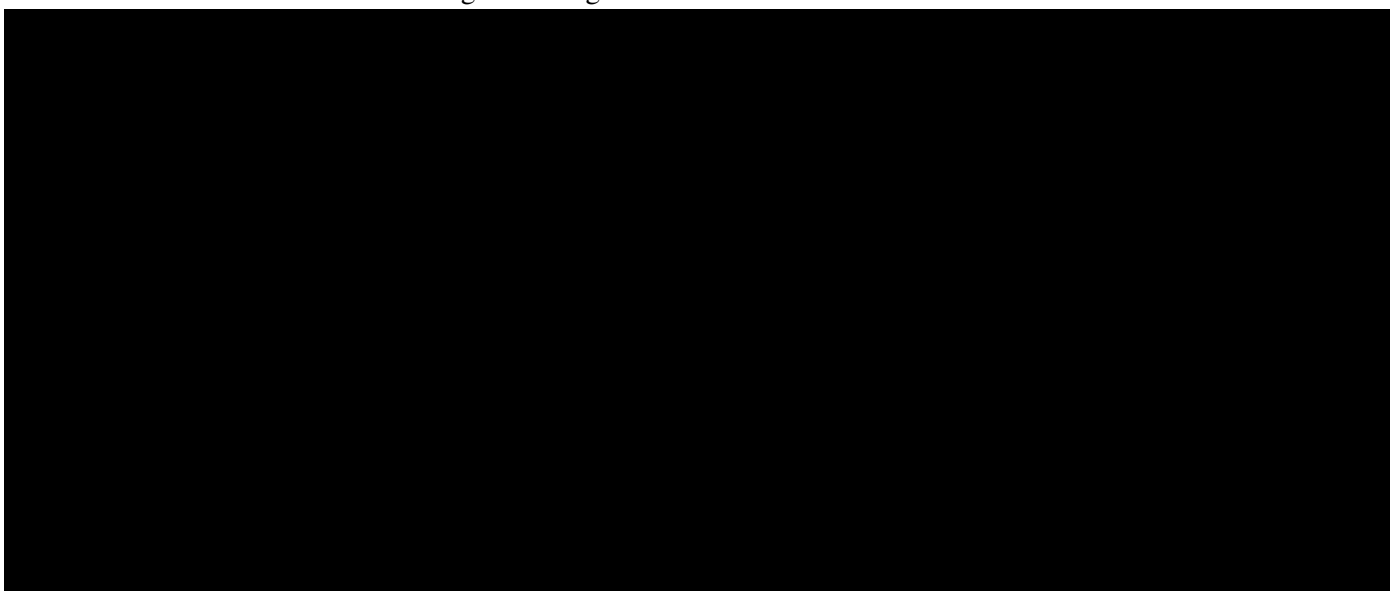
Comments:

14.7. Annex 7: Protocol Amendment Summary of Changes Table

Section # and Name	Description of Change	Brief Rationale
Title Page, Section 3 (Responsible Parties)	Updated the contact details for the study director, the EU-Qualified Person Responsible for Pharmacovigilance, and the Marketing Authorization Holder contact person.	To reflect the most up-to-date contact details.
Title Page	Added the EMA product reference and the EMA procedure number.	To reflect the most up-to-date information.
Sections 4 (Abstract), 9.3 (Variables), 9.7.1.7 (Secondary Malignancy [Analysis of the Primary Objective]), and 14.4 (Annex 4: Post-Marketing Secondary Malignancy Testing Algorithm, Including T Cell Malignancy and Hematologic Malignancies [Except of T Cell Origin])	Specified that secondary malignancies of T cell origin and hematological secondary malignancies (not of T cell origin) will be collected separately. Secondary Malignancy EU workflow updated.	To address the comments of the PRAC Request.
Title Page, Sections 4 (Abstract), 8.1.2 (Secondary Objectives), 9.3.1.2 (Secondary Endpoints Definitions), and 9.7.4. (Effectiveness Endpoints)	Added rwPFS as a secondary effectiveness objective/endpoint.	To address the comments of the PRAC Request.
Sections 4 (Abstract) and 9.1 (Study Design)	Clarified that the data collection forms will be collected per the defined registry schedule and the reporting of the AEs will be per the timelines for patients treated in the post-marketing setting.	Clarification.
Sections 6 (Milestones) and 12 (Plans For Disseminating And Communicating Study Results)	Removed that the registries will provide quarterly safety data to Autolus for 3 years and yearly thereafter. Instead, clarified that safety and effectiveness data will be provided yearly until at least the planned interim analysis, and thereafter, for the final study report.	To address the comments of the PRAC Request.
Section 6 (Milestones)	Removed the annual reporting, and clarified the planned date for submission of the final report of study results.	To reflect the comments of the PRAC that CAR T is a now better characterized modality.
Section 7 (Rationale and Background)	Revised to focus on the knowledge gaps that the study is intended to fill and the expected contribution of the study.	To address the comments of the PRAC Request.

Section # and Name	Description of Change	Brief Rationale
Section 9.1.1.1 (Baseline Period [Study Design Definitions])	Removed the specification on the number of years for the "look-back" period.	To keep consistency with the registry forms.
Sections 9.2 (Setting), 9.3 (Variables), 9.4 (Data Sources), and 14.5 (Annex 5: Data Collection Forms for the Variables and Outcomes of Interest)	Clarified that CIBMTR and EBMT forms will be used as data source.	To address the comments of the PRAC Request.
Section 9.3.1.1 (Primary Endpoints Definitions)	Added definitions for safety events to be analyzed for the primary endpoints.	To address the comments of the PRAC Request.
Section 9.3.1.2 (Secondary Endpoints Definitions)	Added the definition for treatment failure.	To address the comments of the PRAC Request.
Section 9.4.1.3 (Cellular Therapy Data)	Added EBMT.	Clarification.
Sections 4 (Abstract), 9.2.3 (Enrollment), and 9.5 (Study Size)	Clarified that 500 patients with at least 1 follow-up visit will be collected for the CIBMTR and EBMT databases.	To address the comments of the PRAC Request.
Sections 4 (Abstract) and 9.5 (Study Size)	The pre-defined enrollment quotas for the 2 registries was removed.	To allow for operational flexibility in prioritizing timely completion of the study.
Section 9.7.1 (Analysis of the Primary Objective: Safety Endpoints)	Added the descriptions for individual data analysis for each safety endpoint.	To address the comments of the PRAC Request.
Section 9.7.1 (Analysis of the Primary Objective: Safety Endpoints)	Added subgroup analyses to explore the potential risk factors.	To address the comments of the PRAC Request.
Section 9.9.3 (Selection Bias)	Added that selection bias could arise from selective patient consent or selective loss to follow-up.	To address the comments of the PRAC Request.
Throughout	Minor corrections and/or typos.	Clarification.

Signature Page for VV-CLIN-003247 v1.0



Signature Page for VV-CLIN-003247 v1.0