EU RISK MANAGEMENT PLAN
for **AUCATZYL**
(OBECABTAGENE AUTOLEUCEL)

EU Risk Management Plan for AUCATZYL (obecabtagene autoleucel)

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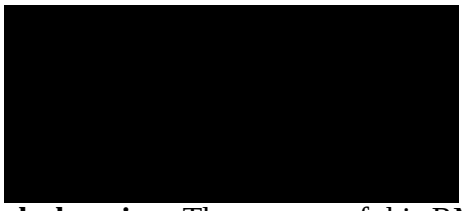

QPPV oversight declaration: The content of this RMP has been reviewed and approved by the marketing authorisation applicant´s QPPV. The electronic signature is available on file.

[1] QPPV name will not be redacted in case of an access to documents request; see HMA/EMA Guidance document on the identification of commercially confidential information and personal data within the structure of the marketing-authorisation application; available on EMA website http://www.ema.europa.eu

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List of Abbreviations

Abbreviation	Description
ADR	Adverse Drug Reaction
AE	Adverse Event
AESI	Adverse Events of Special Interest
ASTCT	American Society for Transplantation and Cellular Therapy
B-ALL	B cell precursor Acute Lymphoblastic Leukaemia
BM	Bone Marrow
CAR	Chimeric Antigen Receptor
CD	Cluster of Differentiation
CI	Confidence Interval
CNS	Central Nervous System
COSMIC	Catalogue Of Somatic Mutations In Cancer
CR	Complete Remission
CRi	Complete Remission with incomplete hematologic recovery
CRS	Cytokine Release Syndrome
CSR	Clinical Study Report
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Events
DLP	Data Lock Point
DMSO	Dimethyl Sulfoxide
DOR	Duration of Remission
DSP	Dose Schedule Planner
EFS	Event-Free Survival
EMA	European Medicines Agency
EMD	Extramedullary Disease
EU	European Union
EoS	End of Study
EPAR	European Public Assessment Report
FACT	Foundation for the Accreditation of Cellular Therapy
FDA	Food and Drug Administration
FUQ	Follow-Up Questionnaire
FPI	First Patient In
GvHD	Graft Versus Host Disease
GM	Gene Modified
HCP	Health Care Professional
HLH	Haemophagocytic Lymphohistiocytosis
ICANS	Immune effector Cell-Associated Neurotoxicity Syndrome

Abbreviation	Description
ICU	Intensive Care Unit
IL	Interleukin
ISA	Integration Site Analysis
IHC	Immunohistochemistry
JACIE	Joint Accreditation Committee ISCT-Europe & EBMT
KM	Kaplan-Meier
LD	Lymphodepletion
LT	Long-Term
MAH	Marketing Authorisation Holder
MAS	Macrophage Activation Syndrome
MRD	Minimal Residual Disease
NCI CTCAE	National Cancer Institute - Common Terminology Criteria for Adverse Events
obe-cel	Obecabtagene autoleucel
ORR	Overall Remission Rate
OOS	Out Of Specification
OS	Overall Survival
PBRER	Periodic Benefit-Risk Evaluation Reports
PCR	Polymerase Chain Reaction
PL	Package Leaflet
PSUR	Periodic Safety Update Report
PT	Preferred Term
PV	Pharmacovigilance
QPPV	Qualified Person for Pharmacovigilance
QTA	Quality Technical Agreement
r/r	Relapsed or refractory
RCL	Replication Competent Lentivirus
RfIC	Release for Infusion Cert
RMP	Risk Management Plan
RV	Retrovirus
SAE	Serious Adverse Event
SCT	Stem Cell Transplant
SOC	System Organ Class
scFv	Single-chain variable fragment
SmPC	Summary of Product Characteristics
TEAE	Treatment-Emergent Adverse Event
TFL	Tables, Figures and Listings
TLS	Tumour Lysis Syndrome

Abbreviation	Description
US	United States
VCN	Vector Copy Number
WHO	World Health Organization

Part I: Product(s) overview

Table I.1: Product(s) overview

Active substance(s) (INN or common name)	Obecabtagene autoleucel (obe-cel)
Pharmacotherapeutic group(s) (ATC Code)	L01XL12
Marketing Authorisation Applicant	Autolus GmbH
Medicinal products to which this RMP refers	1
Invented name(s) in the European Economic Area (EEA)	AUCATZYL
Marketing authorisation procedure	Centralised
Brief description of the product including	**Product description:** AUCATZYL is a cell-based gene therapy product consisting of autologous enriched T cells that are transduced with a lentiviral vector to express a novel anti-CD19 chimeric antigen receptor (CD19 (CAT) CAR). AUCATZYL also contains non-transduced autologous T cells and non-T cells. Mechanism of action: AUCATZYL is a CD19 - directed genetically modified autologous T cell immunotherapy consisting of the patient's own T cells engineered to express a chimeric antigen receptor CAR. that recognises CD19 on target cells via the murine CAT13.1E10 hybridoma (CAR) binding domain. Engagement of anti-CD19 (CAT) CAR-positive T cells with CD19 expressed on target cells, such as cancer cells and normal B cells, leads to activation of the anti-CD19 (CAT) CAR - positive T cells and downstream signalling through the CD3-zeta domain. Proliferation, and persistence by the anti-CD19 (CAT) CAR-positive T cells following activation are enhanced by the presence of the 41BB co-stimulatory domain. This binding to CD19 results in anti-tumour activity and killing of CD19 expressing target cells. Studies demonstrate obecabtagene autoleucel has a unique mode of action with a fast off-rate of 3.1×10^{-3} s^{-1} of its CD19 binding domain with a shorter half-life of interaction. The resulting shorter target interaction may lead to reduced cytokine release and immunotoxicity through a more physiological T cell activation, avoiding exhaustion of the anti-CD19 CAR-positive T cells, which in turn could lead to an improved CAR-positive T cell expansion and persistency.
Hyperlink to the Product Information	1.3.1 SPC, Labelling and Package Leaflet (Combined)
Indication(s) in the EEA	Proposed: AUCATZYL is indicated for the treatment of adult patients 26 years of age and above with relapsed or refractory (r/r) B cell precursor acute lymphoblastic leukaemia (B ALL)

Dose in EEA	Proposed: AUCATZYL is intended for autologous use. The target dose is 410×10^6 CAR-positive viable T cells (range: 308 - 512×10^6 CAR-positive viable T cells) supplied in three or more infusion bags. The treatment regimen consists of a split dose for infusion to be administered on Day 1 and Day 10 (± 2 days). The dose regimen will be determined by the tumour burden assessed by bone marrow (BM) blast percentage from a sample obtained within 7 days prior to the start of lymphodepletion.
Pharmaceutical form(s) and strengths	Colourless to pale yellow, opalescent dispersion, essentially free from visible foreign particles. Dispersion for intravenous infusion, with a dose of 410×10^6 CAR-positive viable T cells supplied in three or more infusion bags.
Is/will the product be subject to additional monitoring in EU?	Yes

Part II Module SI - Epidemiology of the indication(s) and target population(s)

Indication

AUCATZYL is indicated for the treatment of adult patients 26 years of age and above with relapsed or refractory (r/r) B cell precursor acute lymphoblastic leukaemia (B ALL).

Incidence and prevalence

Approximately 60% of B cell ALL occurs in patients aged younger than 20 years, with a peak incidence between 2 to 5 years; the incidence rises again after the age of approximately 50 years (Howlader et al, 2019). In the United States (US), there will be an estimated 5482 new cases of ALL (DRC, 2019) and an estimated 1500 related deaths in 2019 (ACS, 2019) with an overall estimated prevalence of the disease of 49415 (DRC, 2019). In Europe, there will be an estimated 5649 new cases of ALL and an estimated 1700 deaths in 2019 (CRUK, 2019; DRC, 2019) with an overall estimated prevalence of the disease of 51099 (DRC, 2019).

The prognosis of B-ALL decreases substantially with increasing age, with 5 year overall survival (OS) rates (2013-2019) of 43.8% in adults between the ages of 40-64 and 23.6% in those ≥ 65 years of age (SEER, 2023a). This is explained by older patients tending to have disease with intrinsic unfavourable biology (for example, Philadelphia chromosome-positive [Ph+] B-ALL, hypodiploidy and complex karyotype), more comorbidities and the inability to tolerate standard chemotherapy regimens (Terwilliger and Abdul-Hay, 2017).

In addition, the presence of EMD in ALL patients is a significant prognostic factor that can affect overall survival and relapse rates. EMD leukaemia spreads beyond the bone marrow often to the central nervous system and lymph nodes posing a unique challenge for therapy and is associated with a reduced response (Cappell and Kochenderfer, 2023).

Young adults (usually defined in the EU as those up to 29 years of age) have also been reported to have poor prognosis (Boissel and Baruchel 2018; Derwich et al, 2022). A study by EUROCARE5 based on cancer registries of 27 European countries showed marked differences in 5year OS according to age: 85.8% for patients 0-14 years of age, 62.2% for patients 15-19 years, and a significantly decreased 45.6% for patients 20-24 years and 47.8% for patients 25-29 years (Trama et al, 2016).

Relapsed and refractory (r/r) disease is very common in adults (including young adults) and is associated with a significant mortality rate, with median survival of less than 1 year (Gokbuget et al, 2012; Crotta et al, 2018; Maffini et al, 2019). Despite the recent approval of innovative immunotherapy treatments (see below), the prognosis and outcome for adult patients with r/r B-ALL is dismal and has remained unchanged during the last two to three decades (Malard and Mohty, 2020); according to UKALL12/ECOG2993 data, the 5-year OS rate in adults who relapse following standard multi-agent chemotherapy is only 7% (Fielding et al, 2007).

The main existing treatment options

There remains a high unmet need for therapy to deliver robust efficacy in this difficult to treat adult r/r B-ALL population while minimising the potential for serious and life-threatening side effects. A better tolerated therapy that delivers clinically meaningful and durable efficacy would serve this unmet need.

The following summarises the targeted agents and immunotherapies currently approved for r/r B ALL (see also SCE Table 1), which highlights the remaining unmet need:

- Blinatumomab is a bispecific T cell engager indicated for intravenous use for the treatment of relapsed or refractory B cell precursor acute lymphoblastic leukaemia (ALL) in adults and children.

- Inotuzumab ozogamicin is a CD22-directed antibody-drug conjugate (ADC) indicated for the treatment of adults with relapsed or refractory B cell precursor acute lymphoblastic leukaemia Tisagenlecleucel (tisa-cel) is a CD19 CAR T cell therapy (4-1BB costimulatory domain) which is administered as a single weight-based infusion (dose for ≤ 50 kg and > 50kg) for patients up to 25 years of age with B cell precursor acute lymphoblastic leukaemia (ALL) that is refractory or in second or later relapse.
- Brexucabtagene autoleucel (brexu-cel) is a CD19 CAR T cell therapy (CD28 costimulatory domain) which is administered as a single body weight-based infusion (per kg body weight up to maximum fixed dose) for patients up to 25 years of age with B cell precursor acute lymphoblastic leukaemia that is refractory or in second or later relapse.

Important co-morbidities

Outcomes of adult patients with ALL have improved over the years, however, still represent a challenge in the elderly population in part due to co-morbidities present. Comorbidities observed in patients can affect many organs and/or systems including the neurologic system, the endocrine system, skin, cardiac, and lung/respiratory systems and play a role in management and outcomes of ALL. Comorbidities can limit the intensity of chemotherapy regimens in ALL patients and can also increase the risk of complications during treatment. Furthermore, significant comorbidities can put patients' health further at risk combined with the immunocompromised state of ALL.

In one registry by the German Multicentre Study Group for Adult ALL analysing comorbidities in ALL patients, the most frequent comorbidities were infections, prior malignancies, diabetes, cardiac and moderate pulmonary disease, obesity and mild liver disease. Arrhythmias, cardiac disease, prior malignancies and diabetes were comorbidities that increased with age. Infections or obesity were not strongly correlated to age (Wermann, 2018).

Part II: Module SII - Non-clinical part of the safety specification

Toxicology

Standard toxicology studies in animal models were not performed because the human CAR binding domain of obecabtagene autoleucel does not cross react with murine or cynomolgus monkey CD19. As a result, in vivo on-target toxicities cannot be fully characterised in these animal models.

The limitations of conventional toxicological studies are acknowledged, and the focus remains on verifying specificity and potency of anti-tumour activity. Non-clinical Tissue Cross Reactivity studies suggest that no off-target toxicity of the CD19 (CAT) CAR is anticipated in human usage.

Part II: Module SIII - Clinical trial exposure

AUTO1-AL1 (FELIX) is a Phase Ib/II, open-label, single arm multi-centre study to evaluate the safety and efficacy of AUCATZYL when administered to adult patients with r/r B-ALL.

In the study, obe-cel was administered as split dose with a total target dose of 410×10^6 CD19 CAR-positive T cells. The split dose regimen was based on disease burden either 10×10^6 CAR-positive T cells on Day 1 followed by 400×10^6 CAR-positive T cells on Day 10 (± 2 days) for patients with ≥ 20% bone marrow (BM) blasts; or 100×10^6 CAR-positive T cells on Day 1 followed by 310×10^6 CAR-positive T cells on Day 10 (± 2 days) for patients with < 20% BM blasts).

The evaluation of safety was based on all patients infused with at least one dose of obe-cel in the pooled analysis of the FELIX study from all cohorts and phases of the study as of the data cut-off for the primary analysis on 07-Feb-2024. This analysis set is referred to as the Safety Set in this SCS, which is synonymous with the Infused Set for all patients (which may be utilised in some source documents) and includes a total of 127 patients. Patients across all FELIX cohorts and phases received obe-cel according to the same treatment paradigm, to the same target dose and with product manufactured using the planned commercial process.

Contribution of Cohorts

Overall, a total of 153 patients were enrolled (Enrolled Set) and 127 patients received at least one dose of AUCATZYL in the FELIX Study (Safety Set). The majority of patients in the Safety Set are from Cohort IIA (94/127; 74.0%); the contribution per cohort is summarised in Table SIII.1.

As of the cut-off date of 07-Feb-2024, half of the patients in the Safety Set remain on study (49.6%, 63/127) and the median duration of follow-up is 21.45 months (range: 8.6 – 41.4). All patients were followed up for ≥ 6 months, 98.4% of patients (125/127) were followed up for ≥ 12 months, and 34.6% (44/127) were followed up for ≥ 24 months.

In Cohort IIA, 42 of the 94 infused patients (44.7%) are in ongoing follow-up at the time of the data cut-off for this longer-term analysis (07-Feb-2024). The median duration of follow-up from first obe-cel infusion to the data cut-off date of 07 Feb 2024 was 20.25 months (range: 12.7 – 29.8) in Cohort IIA (Infused Set). All patients in Cohort IIA were followed up for ≥ 12 months.

Table SIII.1: Summary of patient contribution from FELIX study cohorts (safety set)

Parameter	Cohort IA (N=13)	Cohort IB (N=3)	Cohort IIA (N=94)	Cohort IIB (N=10)	Cohort IIC (N=7)	Total (Safety Set) (N=127)
Patients infused, n (%) [1]	13 (10.2)	3 (2.4)	94 (74.0)	10 (7.9)	7 (5.5)	**127 (100)**
Patients ongoing, n (%) [1]	4 (3.1)	2 (1.6)	42 (33)	9 (7.1)	6 (4.7)	**61 (48)**
Median duration of follow-up, months	34.79	30.19	20.25	18.15	25.86	**21.45**
Min, Max	30.4 - 41.4	29.7 - 32.0	12.7 - 29.8	8.6 - 28.7	22.6 - 27.2	**8.6 - 41.4**

Parameter	Cohort IA (N=13)	Cohort IB (N=3)	Cohort IIA (N=94)	Cohort IIB (N=10)	Cohort IIC (N=7)	Total (Safety Set) (N=127)
≥ 6 months, n (%) [1]	0	0	0	0	0	**0**
≥ 12 months, n (%) [1]	0	0	2 (20.0)	0	2 (1.8)	**2 (1.6)**
≥ 24 months, n (%) [1]	13 (100)	3 (100)	21 (22.3)	2 (20.0)	5 (71.4)	**44 (34.6)**

[1] Denominator is total number of patients in Safety Set (N=127)
Source: CSR Table 14.1.1.1.1 and Table 14.1.4.6.1

Exposure to AUCATZYL

Overall, the median dose of AUCATZYL administered in the Safety Set was the target dose of 410×10^6 CD19 CAR-positive T cells, reflecting that the large majority of patients received both administrations (94.5%, 120/127) and target dose was achieved (91.3%, 116/127) (Table SIII.2).

Table SIII.2: AUCATZYL dosing in FELIX study (safety set)

Parameter	Total(N=127)
Total infused, n (%)	127 (100)
Total calculated CAR-positive T cells received (10^6 cells)	
N	127
Mean (SD)	379.9 (89.94)
Median	410.0
Q1 - Q3	405.0 - 413.0
Min – Max	10 - 480
Patient received both obe-cel doses	120 (94.5)
Patient received only first obe-cel dose	7 (5.5)
Patients receiving the target dose [1]	116 (91.3)
Patients not receiving the target dose [2]	11 (8.7)

[1] Target dose is 410×10^6 CD19 CAR-positive T cells (± 25%)
Source: AUTO1-AL1 CSR-Table 14.1.4.4.4
[2] 4 patients received both doses, but less than the target dose (410×10^6 CD19 CAR-positive T cells)

Demographics of the population in the proposed indication and risk factors for the disease

The study enrolled a wide spectrum of patients that are considered representative of the real-world treatment setting. This included patients who typically have a poorer prognosis such as those who are refractory to many lines of prior therapy, younger adults (< 40 years), older age, Hispanic ethnicity, high disease burden, presence of EMD, complex karyotype and Ph+.

Age group, gender and ethnicity

The median age of patients in the Safety Set (n=127) was 47 years (range: 20 to 81). Twenty-five patients (19.7%) infused with AUCATZYL were ≥ 65 years old. Sex (male/female) was fairly equally distributed (52.0% and 48.0%, respectively) (Table SIII.3), most of the patients were

white (76.5%) and about a third of the study population was of Hispanic or Latino ethnicity (30.9%) (Table SIII.4).

Table SIII.3: Age group and gender

Age group	Patients	
	Male	Female
≥ 18 to ≤ 25	14	
> 25 to < 40	34	
≥ 40 to < 65	54	
≥ 65	25	
Total	66	61

Table SIII.4: Ethnic origin

Racial origin	Patients
Asian	16
Black or African American	2
White	94
Unknown	15
Ethnicity	
Hispanic or Latino	38
Not Hispanic or Latino	80
Unknown	9

Disease Characteristics

The disease characteristics prior to lymphodepletion in the Safety Set are summarised in Table SIII.5. The median time from enrolment to first AUCATZYL infusion was 37 days, so any changes in clinical status between enrolment and the start of lymphodepletion despite bridging therapy in the majority of patients is over a relatively short time period. Therefore, a worsening in a patient's condition would be indicating the aggressiveness of the underlying disease.

The median percentage of blasts in BM at lymphodepletion was 40.0% (versus 36.0% at enrolment) and the proportion of patients with > 75% blasts in BM was 31.5% (40/127), which was the same percentage as at screening. There was therefore a similar disease burden as measured by the percentage of blasts in BM between screening and lymphodepletion in the overall Safety Set. The proportion of patients presenting with EMD was also similar between screening and lymphodepletion (21.3% [27/127] versus 22.8% [29/127] at screening.

The median neutrophil count at time of lymphodepletion was 1.4×10^9/L with 25.2% of patients (32/127) having absolute neutrophil counts $< 0.5 \times 10^9$/L and for platelets the median count was 89.0×10^9/L with 37.0% of patients (47/127) having $< 50 \times 10^9$/L (Table SIII.5), likely due to a combination of bridging therapy, prior treatment and the patients underlying disease.

Table SIII.5: Summary of disease characteristics in FELIX study at lymphodepletion (safety set)

Parameter	Total (N=127)
BM blasts (%) by morphology prior to lymphodepletion [1]	
Median	40.0
Min – Max	0 - 100
BM blasts (%) by morphology prior to lymphodepletion categorized - n (%) [1]	
> 75%	40 (31.5)
> 20% to ≤ 75%	35 (27.6)
≥ 5% to ≤ 20%	16 (12.6)
< 5%	36 (28.3)
EMD status prior to lymphodepletion - n (%)	
Absent	100 (78.7)
Present	27 (21.3)
CNS	1 (0.8)
Mediastinal Lymph Node	3 (2.4)
Testis	1 (0.8)
Other	25 (19.7)
Complex karyotype	51 (40.2)
Cytogenetic risk groups for B-ALL [2] - n (%)	
Good risk	
Hyperdiploidy	5 (3.9)
TEL-AML1	2 (1.6)
Poor risk	
Hypodiploidy	4 (3.1)
IL3-IGH	1 (0.8)
t (10;14)	1 (0.8)
BCR-ABL1-like	10 (7.9)
E2A-PBX1	1 (0.8)
Philadelphia chromosome-positive	36 (28.3)
MLL rearrangement	6 (4.7)
Other	55 (35.9)
Neutrophil count (10^9/L)	
Median	1.4
Min – Max	0 - 14
< 0.5 – n (%)	32 (25.2)
Platelet count (10^9/L)	
Median	89.0
Min – Max	4 - 368
< 50 – n (%)	47 (37.0)

BM = bone marrow; CNS = central nervous system; EMD = extramedullary disease.
[1] Bone marrow blast (%) was determined by morphology as the highest value from bone marrow aspirate and trephine at screening.
[2] Cytogenetic risk groups based on karyotype collected from screening to lymphodepletion. If multiple karyotypes were recorded for the same patient, the latest record was used for the patient.
Source: AUTO1-AL1 07-Feb-2024 Analysis-Tables 14.1.2.2.4 and 14.1.2.3.3.

Part II: Module SIV - Populations not studied in clinical trials

SIV.1 Exclusion criteria in pivotal clinical studies within the development programme

Table SIV.1: Exclusion criteria in pivotal clinical studies within the development programme

Criterion	Reason for exclusion
Diagnosis of Burkitt's leukaemia/lymphoma according to World Health Organization (WHO) classification or chronic myelogenous leukaemia lymphoid in blast crisis.	CAR T cells are engineered to target specific antigens expressed on the surface of cancer cells. The unique biology of Burkitt's leukaemia/lymphoma in blast crisis might render CAR T less effective against these types of cancers or lead to unforeseen adverse reactions. Not included as missing information as the exclusion criteria was in place to allow for interpretation of the clinical trial results.
History or presence of clinically relevant CNS pathology such as epilepsy, paresis, aphasia, stroke within 3 months prior to consent, severe brain injuries, dementia, Parkinson's disease, cerebellar disease, organic brain syndrome, uncontrolled mental illness, or psychosis.	CAR T cell therapy is associated with potentially life-threatening toxicities such as cytokine release syndrome (CRS) and neurotoxicity. Patients with neurologic disorders are likely to be more vulnerable to the consequences of the identified and potential risks and require special attention. Not included as missing information as the exclusion criteria was in place to allow for interpretation of the clinical trial results.
Presence of CNS 3 disease or CNS 2 disease with neurological changes.	Patients with pre-existing CNS involvement, particularly those with advanced CNS disease or associated neurological changes, may be at an increased risk of severe or fatal neurotoxic events when treated with CAR T cells. Not included as missing information as the exclusion criteria was in place to allow for interpretation of the clinical trial results.
Presence of active or uncontrolled fungal, bacterial, viral, or other infection requiring systemic antimicrobials for management.	CAR T cell therapy involves a lymphodepleting regimen before administering the engineered T cells, which can further weaken the patient's immune system. Patients with active or uncontrolled infections are already at a compromised immune state, and the added immunosuppression from CAR T cell therapy could dangerously exacerbate the infection, leading to severe complications. Not included as missing information as Infections is included as Important Identified Risk.

Criterion	Reason for exclusion
Active or latent Hepatitis B virus or active Hepatitis C virus.	CAR T cell therapy involves a lymphodepleting regimen before administering the engineered T cells, which can further weaken the patient's immune system. Patients with active or uncontrolled infections are already at a compromised immune state, and the added immunosuppression from CAR T cell therapy could dangerously exacerbate the infection, leading to severe complications. Not included as missing information as the exclusion criteria was in place to allow for better interpretation of the clinical trial results.
Human Immunodeficiency Virus (HIV), human T cell lymphotropic virus (HTLV)-1, HTLV-2, or syphilis positive test.	The lymphodepleting regimens used before administering CAR T cell therapy can suppress the immune system, increasing the risk of severe infections and other complications. Not included as missing information as the exclusion criteria was in place to allow for better interpretation of the clinical trial results.
Patients who have received a prior stem cell transplant less than 3 months prior to AUCATZYL infusion. Active significant (overall Grade ≥ 2, Seattle criteria) acute graft versus host disease (GvHD) or moderate/severe chronic GvHD (National Institutes of Health [NIH] consensus criteria) requiring systemic steroids or other immunosuppressants within 4 weeks of consent.	Introducing CAR T cells during this vulnerable period, especially in the presence of GvHD, can lead to unpredictable and potentially severe reactions. Not included as missing information as GvHD is identified as important risk.
Prior CD19 targeted therapy other than blinatumomab. Patients who have experienced Grade 3 or higher neurotoxicity following blinatumomab.	Prior exposure to CD19 targeted agents could lead to higher risk of adverse reactions, particularly if there was a severe neurotoxic response to previous treatments, indicating a susceptibility to such adverse events. Not included as missing information as the exclusion criteria was in place to allow for better interpretation of the clinical trial results.
Clinically significant, uncontrolled heart disease (New York Heart Association Class III or IV heart failure, uncontrolled angina, severe uncontrolled ventricular arrhythmias, sick-sinus syndrome, or electrocardiographic evidence of acute ischaemia or Grade 3 conduction system abnormalities unless the patient has a pacemaker) or a recent (within 12 months) cardiac event.	Patients with pre-existing heart conditions are at a higher risk of experiencing severe cardiac complications during CRS or may not tolerate the cardiovascular stress induced by the therapy. Not included as missing information as the exclusion criteria was in place to allow for better interpretation of the clinical trial results.

Criterion	Reason for exclusion
Patients with a history (within 3 months) or evidence of pulmonary embolism. Patients requiring ongoing therapeutic anticoagulation for any reason at the time of AUCATZYL infusion.	CAR T cell therapy can lead to coagulation disorders, including increased D-dimer, increased fibrinogen degradation products, prolonged prothrombin time, decreased fibrinogen, and thrombocytopenia putting these patients at further risk of coagulopathies. Not included as missing information as the exclusion criteria was in place to allow for better interpretation of the clinical trial results.
Patients with active gastrointestinal bleeding.	CAR T cell therapy can reduce the patient's platelet count, which is essential for blood clotting, hence potentially worsening the bleeding episode and leading to severe complications. Not included as missing information as the exclusion criteria was in place to allow for better interpretation of the clinical trial results.
Presence of active or uncontrolled fungal, bacterial, viral (including COVID-19), or other infection requiring systemic antimicrobials for management.	CAR T cell therapy can cause immunosuppression, potentially exacerbating the existing infection and making it more challenging to control, leading to severe complications. Not included as missing information as the infection is the Important Identified Risk.
History of autoimmune disease (e.g., Crohn's, rheumatoid arthritis, systemic lupus) resulting in end organ injury or requiring systemic immunosuppression/systemic disease modifying agents within the last 24 months. Any autoimmune disease with CNS involvement.	CAR T cell therapy can trigger or exacerbate immune responses, potentially leading to a flare or worsening of the underlying autoimmune condition. In addition, use of corticosteroids possibly negatively impacts on the efficacy of CAR T cell therapy due to possible suppression of CAR T cell activity. Not included as missing information as the exclusion criteria was in place to allow for better interpretation of the clinical trial results.
History of other malignant neoplasms unless disease free for at least 24 months (carcinoma in situ, non-melanoma skin cancer, breast or prostate cancer on hormonal therapy allowed).	The presence of another active cancer could interfere with the assessment of the CAR T cell therapy's efficacy and safety. Not included as missing information as the exclusion criteria was in place to allow for better interpretation of the clinical trial results.

Criterion	Reason for exclusion
History of concomitant genetic syndrome such as Fanconi anaemia, Shwachman-Diamond syndrome, Kostmann syndrome or any other known BM failure syndrome.	These genetic conditions can compromise bone marrow function and make patients more susceptible to toxicities and complications associated with CAR T cell therapy. Not included as missing information as the exclusion criteria was in place to allow for better interpretation of the clinical trial results.
Presence of any indwelling line or drain (e.g., percutaneous nephrostomy tube, indwelling Foley catheter, biliary drain, or pleural/peritoneal/pericardial catheter). Ommaya reservoirs and dedicated central venous access catheters such as a Port-a-Cath or Hickman catheter are permitted.	These devices can pose an increased risk of infections. Not included as missing information as the exclusion criteria was in place to allow for better interpretation of the clinical trial results.
Research participants receiving any other investigational agents, or concurrent biological, chemotherapy, or radiation therapy after starting lymphodepletion therapy on study.	This was excluded to avoid potential interactions or confounding effects between the CAR T therapy and other investigational agents or treatments. Not included as missing information as the exclusion criteria was in place to allow for better interpretation of the clinical trial results.
Inability to tolerate leukapheresis.	Leukapheresis is the primary method for collecting the patient's T cells which will be modified to become CAR T cells. If a patient cannot tolerate leukapheresis, it would be impossible to obtain the necessary cells for the CAR T cell therapy, rendering the patient ineligible for the treatment.
Pregnant and breastfeeding women	There are insufficient data on effects of obecabtagene autoleucel in human foetal development.

SIV.2 Limitations to detect adverse reactions in clinical trial development programmes.

B-ALL is a rare disease and the AUTO1-AL1 (FELIX) study design was in line with regulatory expectations in this disease setting. However, the clinical development programme is unlikely to detect certain types of adverse reactions such as adverse reactions with a long latency.

SIV.3 Limitation in respect to populations typically under-represented in clinical trial development programmes

The AUTO1-AL1 (FELIX) study excluded patients undergoing pregnancy and breastfeeding, and contraception was mandated for the time of treatment and thereafter, nevertheless 1 pregnancy occurred (summarised in Table SIV.2), which was reported accordingly. In addition, the FELIX study enrolled only patients 18 years old and over, hence no paediatric patients were treated.

Table SIV.2: Exposure of special populations included or not in clinical trial development programme

Type of Special Population	Exposure
Pregnant and breastfeeding women	1 pregnant adult female was exposed to AUCATZYL.
Paediatric patients	No data were available during the AUTO1-AL1 (FELIX) study, as the indication is for the treatment of adult patients (≥ 18 years) with relapsed or refractory B cell precursor acute lymphoblastic leukaemia (ALL).

Part II: Module SV - Post-authorisation experience

AUCATZYL has not been authorised in any country at the time of the data lock of this RMP (07-Feb-2024). However, United States Food and Drug Administration (US FDA) approved AUCATZYL on 08-Nov-2024 and the United Kingdom Medicines and Healthcare products Regulatory Agency (UK MHRA) authorised AUCATZYL on 25 April 2025.

SV.1 Post-authorisation exposure

Not applicable.

Part II: Module SVI - Additional EU requirements for the safety specification

Potential for misuse for illegal purposes

CAR T cell therapy is an autologous treatment, to be administered in certified/accredited treatment centres by physicians and medical staff well-versed in the use of such therapies. Therefore, there is no potential for misuse for illegal purposes.

Part II: Module SVII - Identified and potential risks

At the DLP for this RMP of 07-Feb-2024 the following important identified and important potential risks and missing information were associated with use of AUCATZYL.

SVII.1 Identification of safety concerns in the initial RMP submission

SVII.1.1. Risks not considered important for inclusion in the list of safety concerns in the RMP.

Reason for not including an identified or potential risk in the list of safety concerns in the RMP:

Risks with minimal clinical impact on patients (in relation to the severity of the indication treated):

- Risks related to general disorders (pyrexia, fatigue), hypersensitivity reactions, gastrointestinal (nausea, diarrhoea, vomiting, abdominal pain, constipation), metabolism and nutrition (hypokalaemia, decreased appetite, hypomagnesaemia), vascular, respiratory (cough), skin (rash) and musculoskeletal disorders (arthralgia) can be detected, monitored and managed with routine measures and treatments used in clinical practice; and are considered to be appropriately described in the label.

Adverse reactions with clinical consequences, even serious, but occurring with a low frequency and considered to be acceptable in relation to the severity of the indication treated:

- None

Known risks that require no further characterisation and are followed up via routine pharmacovigilance (PV), namely through signal detection and adverse reaction reporting, and for which the risk minimisation messages in the product information are adhered by HCPs:

- None

Known risks that do not impact the risk-benefit profile:

- In populations not studied/underrepresented in the clinical development programme, namely, paediatric patients and pregnant and breastfeeding women, risks to these populations will be mitigated through language in the SmPC. The MAH commits to closely monitor and proactively review/monitor data regarding these populations via routine PV activities and report on these topics in future PSURs.

Other reasons for considering the risks not important:

- None

SVII.1.2. Risks considered important for inclusion in the list of safety concerns in the RMP

Important Identified Risk 1: Cytokine Release Syndrome (CRS) including Haemophagocytic Lymphohistiocytosis (HLH)/Macrophage Activation Syndrome (MAS)

CRS is a recognised and significant toxicity associated with CAR T cell therapies, identified as an important risk due to its seriousness and potential for causing severe disability, including death if left untreated. Clinical symptoms indicative of CRS may include, but are not limited to, culture-negative fever, myalgia, nausea/vomiting, tachycardia, hypoxia, hypotension, headache, confusion, tremor, and delirium. Potentially life-threatening complications of CRS can include

cardiac dysfunction, acute respiratory distress syndrome, renal and/or hepatic failure, and disseminated intravascular coagulation (DIC).

Cytokine release syndrome after CAR T cell therapy can evolve into CAR T cell related haemophagocytic lymphohistiocytosis/macrophage activation syndrome which is a manifestation of CRS and has a high mortality. CAR T related HLH is rare, with severe and fulminant cases occurring in approximately 1% of patients receiving CAR T treatment (Martin-Rojas et al, 2022).

Risk-benefit impact:

Patients might have MAS/HLH if they have a peak serum ferritin level of > 10,000 ng/mL during the CRS phase of CAR T cell therapy. Diagnostic criteria for HLH/MAS in the FELIX study were based on a peak serum ferritin measurement of > 10,000 ng/mL and at least two of the following findings (Neelapu et al, 2018):

- Grade ≥ 3 increase in serum bilirubin, aspartate aminotransferase, or alanine aminotransferase levels.
- Grade ≥ 3 oliguria or increase in serum creatinine levels.
- Grade ≥ 3 pulmonary oedema.
- Presence of haemophagocytosis in BM or organs based on histopathological assessment of cell morphology and/or CD68 IHC.

In section 6.6 of the SmPC the dose regimen based on disease burden is provided.

In section 4.2 of the SmPC, HCPs are also advised to monitor patients daily for the first 14 days post-infusion for the signs of CRS, with continued monitoring at the physician's discretion for at least 4 weeks after infusion. Patients should be instructed to remain within close proximity of the qualified treatment centre (within 2 hours of travel) for at least 4 weeks following the first infusion.

Section 4.2 of the SmPC allows for HCPs to delay the second split dose to manage toxicities.

Section 4.4 allows for delay of second dose to reduce risk of worsening CRS or discontinue treatment for Grade ≥ 3 CRS. It also provides guidelines on managing CRS. Evaluation for haemophagocytic lymphohistiocytosis/macrophage activation syndrome (HLH/MAS) is to be considered in patients with severe or unresponsive CRS.

Besides the routine risk minimisation measures, warnings and precautions outlined in the SmPC and package leaflet sections, the additional minimisation measure, risk minimisation control programme and Patient Card will be in place. In addition to the ongoing pharmacovigilance monitoring, safety events suggestive of CRS, including HLH/MAS, will be collected and analysed during the AUTO1-LT2 Study.

Important Identified Risk 2: Immune Effector Cell-associated Neurotoxicity Syndrome (ICANS)

ICANS is a recognised toxicity with CAR T cell therapies. It is an Important Identified Risk due to its seriousness and potential for associated disability, including death, if left untreated. The symptoms and the presentation of ICANS are varied and can progress from subtle signs as headaches, fatigue, and mild aphasia to more severe and potentially life-threatening presentations including seizures, raised intracranial pressure with cerebral oedema, and coma. The cause of ICANS is not well understood, although it is generally reported to be fully reversible.

Risk-benefit impact:

In section 6.6 of the SmPC the dose regimen based on disease burden is provided.

In section 4.2 of the SmPC, HCPs are advised to monitor patients daily for the first 14 days post-infusion for the signs of ICANS, with continued monitoring at the physician's discretion for at least 4 weeks after infusion. Patients should be instructed to remain within close proximity of the qualified treatment centre (within 2 hours of travel) for at least 4 weeks following the first infusion to be examined for signs and symptoms of ICANS and other toxicities.

Section 4.4 allows for delay of second dose to reduce risk of worsening ICANS or discontinue treatment for Grade ≥ 2 ICANS. Section 4.4 provides guidelines to grade and manage ICANS.

Besides the routine risk minimisation measures, warnings and precautions outlined in the SmPC and package leaflet sections, the additional minimisation measure, risk minimisation control programme and Patient Card will be in place. In addition to the ongoing pharmacovigilance monitoring, safety events suggestive of ICANS and occurring in the exposed population will be collected and analysed during the AUTO1-LT2 Study.

Important Identified Risk 3: Prolonged Cytopenia

While lymphodepleting therapy with fludarabine and cyclophosphamide is expected to result in transient cytopenia within 30 days, prolonged cytopenia (30-90 days) has also been observed after CAR T cell therapy (Locke et al, 2019; Jain et al, 2023).

Prolonged cytopenia eventually resolves in most individuals.

Risk-benefit impact:

In section 4.4 of the SmPC, HCPs are advised to monitor patients' blood count after AUCATZYL infusion.

Besides the routine risk minimisation measures, warnings and precautions in the SmPC and package leaflet sections, the additional minimisation measure, risk minimisation control programme will be in place. In addition to the ongoing pharmacovigilance monitoring, safety events occurring in the exposed population will be collected and analysed during the AUTO1-LT2 Study.

Important Identified Risk 4: Hypogammaglobulinaemia

Hypogammaglobulinaemia is caused by B cell aplasia and has been seen as a consequence of depletion of normal B cells by CD19 CAR T therapy. Hypogammaglobulinaemia has been reported in patients treated with AUCATZYL.

Hypogammaglobulinaemia predisposes patients to become more susceptible to infections. Immunoglobulin levels should be monitored after treatment with AUCATZYL and managed per using infection precautions and immunoglobulin replacement in case of recurrent infections and should be taken according to standard local guidelines.

Risk-benefit impact:

Section 4.4 of the SmPC provides warning that hypogammaglobulinaemia predisposes patients to become more susceptible to infections. Immunoglobulin levels should be monitored after treatment with AUCATZYL and managed per institutional guidelines including infection precautions, antibiotics or antiviral prophylaxis and immunoglobulin replacement.

Besides the routine risk minimisation measures, warnings and precautions in the SmPC and package leaflet sections, the additional minimisation measure, risk minimisation control

programme will be in place. In addition to the ongoing pharmacovigilance monitoring, safety events occurring in the exposed population will be collected and analysed during the AUTO1-LT2 Study.

Important Identified Risk 5: Severe Infections

Infections following CAR T cell therapy are common and have been reported in up to 70% of patients who received a CAR T cell therapy in registrational clinical studies for approved agents. Most infections occur soon after infusion and may occur for several reasons, including lymphodepleting or antecedent chemotherapy, CAR T cell mediated B cell aplasia or plasma cell depletion, prolonged cytopenia, corticosteroid treatment, or as a consequence of the underlying malignancy itself (Thompson et al, 2022).

Severe infections, including life-threatening or fatal infections, have occurred in patients after receiving AUCATZYL.

Risk-benefit impact:

Section 4.4 of the SmPC provides warning that patients should be monitored for signs and symptoms of infection before, during and after AUCATZYL infusion and treated appropriately. Prophylactic antimicrobials should be administered according to standard institutional guidelines. Treatment with AUCATZYL should be delayed in some patient groups at risk.

Febrile neutropenia has been observed in patients after AUCATZYL infusion and may be concurrent with CRS. In the event of febrile neutropenia, the infection should be evaluated and managed with broad-spectrum antibiotics, fluids and other supportive care as medically indicated.

Besides the routine risk minimisation measures, warnings and precautions in the SmPC and package leaflet sections, the additional minimisation measure, risk minimisation control programme will be in place. In addition to the ongoing pharmacovigilance monitoring, clinically significant infections occurring in the exposed population will be collected and analysed during the AUTO1-LT2 Study.

Important Identified Risk 6: Secondary Malignancies of T Cell Origin

Secondary malignancies including those of T cell origin are now a recognised class risk associated with CAR T cell therapies. This risk emerges from the long-term engraftment and persistence of genetically modified T cells, which may lead to events such as the development of secondary cancers.

Risk-benefit impact:

Section 4.4 of SmPC instructs for patients to be monitored life-long for signs of secondary malignancy. The long-term surveillance study AUTO1-LT2 will allow for further investigation upon detection of secondary malignancies. Additional process of testing is developed to collect additional information if secondary malignancy occurs, outside of the AUTO1-LT2 study.

Important Identified Risk 7: Aggravation of Graft Versus Host Disease (GvHD)

During the FELIX study, of the 127 patients who were infused with at least one dose of obe-cel (Safety Set), 56 had previous allogenic stem cell transplant (SCT). As of the latest data cut-off (07-Feb-2024), GvHD was reported in 8 patients (6.2% 8/127) post-obe-cel infusion.

Aggravation of GvHD is a consequence of obe-cel treatment in patients who received prior allogenic SCT. and is therefore considered an Important Identified Risk.

Risk-benefit impact:

Recommendation to delay of infusion if a patient has an active GvHD or within 3 months after allogeneic HSCT is included in SmPC section 4.4.

Measures described in section 4.4 in the SmPC, corresponding package leaflet sections and ongoing PV monitoring, are expected to maintain a positive risk-benefit balance. In addition, patients will be monitored for aggravation of GvHD in the AUTO1-LT2 Study.

Important Potential Risks

Important Potential Risk 1: Tumour Lysis Syndrome (TLS)

Tumour lysis syndrome comprises of a constellation of laboratory findings such as hyperuricaemia, hyperkalaemia, hyperphosphataemia, and hypocalcaemia, however with the manifestation of clinical complications such as seizures, acute renal failure, and cardiac dysrhythmias. Tumour lysis syndrome may occur during treatment with AUCATZYL due to rapid killing of malignant cells, which can be associated with a release of intracellular ions and metabolic by-products into the systemic circulation.

Risk-benefit impact:

Section 4.4 of SmPC instructs for patients to be monitored for signs and symptoms of TLS after AUCATZYL infusion and events to be managed according to standard guidelines. To minimise the risk of TLS, patients with high tumour burden should receive TLS prophylaxis as per standard guidelines prior to AUCATZYL infusion

Monitoring for early signs and symptoms of TLS and routine pharmacovigilance activities are expected to maintain a positive risk-benefit balance. In addition to the ongoing pharmacovigilance monitoring, events occurring in the exposed population will be collected and analysed during the AUTO1-LT2 study.

Important Potential Risk 2: Antigenicity and Immunogenicity

There is no evidence that cellular or humoral immunogenicity impact AUCATZYL kinetics or extend of initial expansion, persistence, efficacy, or safety.

The CD19 antigen-binding domain of AUCATZYL is derived from a murine sequence and therefore anti-CAR antibodies, or an anti-CAR T cell response could be induced. An anti-CAR antibody response is unlikely to be a concern in particular at the beginning of the treatment when the split dose is administered; firstly, patients are lymphodepleted, secondly the CAR T cells target the B cell compartment as they are targeting CD19, hence patients are expected to develop B cell aplasia and hypogammaglobulinemia (Maude et al, 2018; Locke et al, 2019).

Risk-benefit impact:

Based on the above, and the fact that a humoral immune response takes approximately 14 days to be generated, the split dosing schedule of AUCATZYL carries no additional risk of increased autoimmune activity compared to a single dosing schedule. It has been shown in previous trials with CD19 CARs that using either split dosing or re-dosing up to 3 months after the first treatment that re-dosing was not associated with the development of an immunogenicity AE (Frey et al, 2016; Neelapu et al, 2017).

In addition to the ongoing pharmacovigilance monitoring, the risk of immunogenicity, defined as hypersensitivity reactions, occurring in the exposed population will be analysed during the AUTO1-LT2 study. However, auto-antibodies testing is currently not done in clinical practice and not collected within the registries, therefore adverse events on antigenicity will not be collected in the AUTO1-LT2 study.

Important Potential Risk 3: Secondary Haematologic Malignancies (Except of T Cell Origin)

There have currently been no reported cases of haematologic malignancies, associated with obe-cel. This potential risk emerges from the long-term engraftment and persistence of genetically modified T cells, which may lead to events such as the development of secondary cancers.

Risk-benefit impact:

Section 4.4 of SmPC instructs for patients to be monitored life-long for signs of secondary malignancy. The long-term surveillance study AUTO1-LT2 will be implemented for patients who receive AUCATZYL therapy to allow for further investigation upon detection of secondary malignancies. Additional process of testing is developed to collect additional information if secondary malignancy occurs, outside of the AUTO1-LT2 study.

Important Potential Risk 4: Overdose/Medication Error

Overdose may occur if proper instructions on handling and administration of AUCATZYL are not followed.

Risk-benefit impact:

Section 4.2 of the SmPC, requires AUCATZYL be administered in a qualified treatment centre by a physician with experience in the treatment of haematological malignancies and trained for administration and management of patients treated with the medicinal product.

Section 4.2 of SmPC, requires patients should be monitored daily for approximately 14 days after the first infusion for signs and symptoms of potential CRS, ICANS and other toxicities.

Routine risk minimisation measures described in the posology and method of administration section in the SmPC, the Release for Infusion Certificate (RfIC), the Dose Schedule Planner (DSP) and colour-coded labels for split infusion bags as well as ongoing PV monitoring are expected to minimise the likelihood of overdose and maintain a positive risk-benefit balance.

Overdose events will be collected during the AUTO1-LT2 study.

Missing information 1: Use During Pregnancy and Breastfeeding

There is very limited available data with AUCATZYL use in pregnant and breastfeeding women. No animal reproductive and developmental toxicity studies have been conducted with obecabtagene autoleucel to assess whether obecabtagene autoleucel can cause foetal harm when administered to a pregnant woman. As of the cut-off date, one (1) patient has become pregnant while in the AUTO1-AL1 (FELIX) study. This patient had a high blast count in BM (99%) and was infused with the split dose obecabtagene autoleucel regimen associated with high disease burden (first dose of 10×10^6 CD19 CAR-positive T cells followed by a second dose of 400×10^6 CD19 CAR-positive T cells). She underwent a Caesarean section at week 32 and 6 days of pregnancy, and a healthy male infant was delivered. The infant initially exhibited

respiratory distress and was admitted to the neonatal intensive care unit for intubation. The infant was subsequently discharged.

Pregnancy and breastfeeding were exclusion criteria for the AUTO1-AL1 (FELIX) study protocol. A risk to the breast-fed infant cannot be excluded. Breastfeeding women must be advised by the treating physician of the potential risk to the breast-fed child. In addition, patients will be followed for pregnancy outcomes in the AUTO1-LT2 Study.

Risk-benefit impact:

It is not known if obecabtagene autoleucel has the potential to be transferred to the foetus. Based on the mechanism of action of obecabtagene autoleucel, if the transduced cells cross the placenta, they may cause foetal toxicity, including B cell lymphocytopenia. Therefore, obecabtagene autoleucel is not recommended for women who are pregnant.

It is unknown whether obecabtagene autoleucel cells are excreted in human milk or transferred to the breastfeeding child. Breastfeeding women must be advised of the potential risk to the breast-fed child.

Missing information 2: Long-term Safety

Risk-benefit impact:

Patients who receive AUCATZYL will be monitored in a separate the AUTO1-LT2 Study post-first AUCATZYL infusion.

Missing information 3: New Occurrence or Exacerbation of an Autoimmune Disorder

Risk-benefit impact:

Therapeutic intervention, especially if it involves modulation of the immune system, might inadvertently trigger or exacerbate autoimmune responses. Given that these treatments work by enhancing or altering the immune response, there is potential for off-target effects that could lead to autoimmunity. Patients who receive AUCATZYL will be monitored for new autoimmune disorders in the AUTO1-LT2 Study post first AUCATZYL infusion.

SVII.2 New safety concerns and reclassification with a submission of an updated RMP

Not applicable.

SVII.3 Details of important identified risks, important potential risks, and missing information

Table SVII.3.1: Presentation of important identified risks and important potential risks

Important Identified Risks

Important Identified Risks: Cytokine Release Syndrome (CRS) including Haemophagocytic Lymphohistiocytosis (HLH)/Macrophage Activation Syndrome (MAS)	
Potential mechanisms	The pathophysiology underlying these conditions is initiated by CAR T cell recognition of antigen, leading to the recruitment of elements of the innate immune system and a cascade of inflammatory cytokines, most notably IL-6, IL-10, and IFN-γ, as described in clinical studies (Bonifant et al, 2016). Haemophagocytic lymphohistiocytosis (HLH) / Macrophage activation syndrome (MAS) represent severe immunological disorders characterised by hyperactivation of macrophages and lymphocytes, proinflammatory cytokine production, lymphohistiocytic tissue infiltration, and immune-mediated multiorgan failure. HLH/MAS may develop in some patients where CAR mediated inflammatory responses continue to evolve, manifesting as a clinical syndrome with high grade non-remitting fever, cytopenia affecting at least two of three blood cell lineages, and hepatosplenomegaly.
Evidence source(s) and strength of evidence	CRS is a recognised toxicity associated with CAR T cell therapies, presenting with symptoms such as culture-negative fever, myalgia, nausea/vomiting, tachycardia, hypoxia, hypotension, headache, confusion, tremor, and delirium. Severe complications of CRS can include cardiac dysfunction, acute respiratory distress syndrome, renal and/or hepatic failure, and disseminated intravascular coagulation (Brudno and Kochenderfer, 2016). CRS including HLH/MAS was reported in AUTO1-AL1 (FELIX) clinical study.
Characterisation of the risk	As of the 07-Feb-2024 data cut-off for the AUTO1-AL1 (FELIX) study, 68.5% (87/127) of patients in the Safety Set experienced CRS of any grade post-AUCATZYL infusion (Lee et al, 2014). Most cases were Grade 1, with only 3 patients (2.4%) experiencing Grade 3 CRS, and none at higher grades. CRS typically occurred after the first infusion, with a median onset of 8 days and a median duration of 5 days. The majority of CRS cases were observed in patients with a higher disease burden at the time of lymphodepletion, with all Grade 3 CRS cases occurring in this subset. CRS can also progress into CAR T cell-related HLH/MAS, a rare but highly fatal complication, occurring in approximately 1% of CAR T recipients (Martin-Rojas et al, 2022). As of the data cut-off date, 1.6% (2/127) of patients experienced HLH/MAS. Due to its frequency, seriousness and potential severity if left untreated, CRS including HLH/MAS is considered an Important Identified Risk.

Important Identified Risks: Cytokine Release Syndrome (CRS) including Haemophagocytic Lymphohistiocytosis (HLH)/Macrophage Activation Syndrome (MAS)	
Risk groups and risk factors	Risk factors of CRS include tumour burden, intensity of lymphodepletion chemotherapy, CAR T cell dose, and thrombocytopenia (Siddiqi et al, 2017; Hay et al, 2017; Santomasso et al, 2018; Lee et al, 2015; Jia et al, 2019). The evaluation of the impact of disease burden at time of lymphodepletion on CRS highlighted its importance since the rate of CRS of any grade increased as the blasts in BM increased. In the AUTO1-AL1 (FELIX) study, across the 4 blast subgroups of < 5%, ≥ 5% to ≤ 20%, > 20% to ≤ 75%, > 75% the percentage of subjects with CRS of any grade was 47.2%, 62.5%, 71.4% and 87.5%, respectively. This reinforced the importance of the split dose regimen with a lower first dose administered when blasts in BM are > 20% at lymphodepletion which is also associated with enhanced CAR T cell expansion post-infusion. Subgroup analysis did not highlight any findings that would be unexpected and the key impact on safety appeared to be the disease burden in terms of blasts in BM at lymphodepletion.
Preventability	Dose regimen based on the disease burden at lymphodepletion: the rationale for the split dosing was to optimize patient safety. The spacing between the dose fractions enable adequate time for the emergence of early signals of CRS in the days following the first dose which are frequently indicative of subsequent severe toxicity and either their management prior to the second dose, or a delay of the second dose. Following the first AUCATZYL infusion patients should be closely monitored for early signs and symptoms indicative of CRS with clinical review and blood tests including: C-reactive protein, serum ferritin level, clotting, and other symptoms that meet criteria to diagnose HLH/MAS. Patients with suspected HLH/MAS should be treated with anti-IL-6 therapy and corticosteroids.
Impact on the risk-benefit balance of the product	Besides the routine risk minimisation measures, dose regimen based on the disease burden at lymphodepletion, contraindications and warnings in the SmPC and package leaflet sections, the additional minimisation measures, risk minimisation control programme and Patient Card will be in place. In addition to the ongoing pharmacovigilance monitoring, safety events suggestive of CRS and occurring in the exposed population will be collected and analysed during the AUTO1-LT2 Study.
Public Health impact	Routine and additional risk minimisation measures and pharmacovigilance activities are sufficient to minimise the impact to public health.

Important Identified Risks: Immune effector Cell-Associated Neurotoxicity Syndrome (ICANS)	
Potential mechanisms	ICANS, associated with CAR T cell therapy, represents a severe neurological complication whose exact mechanism is not completely understood. Emerging evidence suggests a complex interplay involving endothelial activation, increased blood-brain barrier permeability, and the infiltration of pro-inflammatory cytokines, potentially leading to cerebral oedema and neuroinflammation. Transient neurological complications have also been reported with CD19 bispecific T cell engagers, suggesting that the target may have some relevance (Goebeler and Bargou, 2016).
Evidence source(s) and strength of evidence	ICANS were reported in AUTO1-AL1 (FELIX) clinical trial and in patients treated with other CAR T therapies.
Characterisation of the risk	As of the 07-Feb-2024 cut-off, 22.8% of patients (29/127) in the Safety Set experienced ICANS. The most common grade of ICANS was Grade 1 (13/127 patients, 10.2%) and 9/127 (7.1%) of patients experiencing ICANS of Grade ≥ 3; one patient each experienced Grade 4 and Grade 5 ICANS (1/127, 0.8%). Of the 29 patients who experienced ICANS, the majority experienced an onset after the second infusion of AUCATZYL (18/29) and had ≥ 5% blasts in the BM at the time of lymphodepletion (26/29), with 17/29 having > 75% blasts in BM. All events (29/29) occurring within 3 months after AUCATZYL treatment. The median time to onset of ICANS after the first AUCATZYL infusion was 12.0 days (range: 1 to 31 days), and median duration was 8 days (range: 1 to 53 days). No patient experienced ICANS with seizure. ICANS is considered an Important Identified Risk due to its frequency and seriousness and the potential for severe outcomes if left untreated.
Risk groups and risk factors	Although no correlation has been observed between ICANS and CRS/MAS (Santomasso et al, 2018), ICANS appear to occur more frequently in the presence of severe CRS. Patients with a high disease burden, prior to treatment, higher peak CAR T expansion and early and higher elevations of serum cytokines may have a higher risk of neurotoxicity (Santomasso et al, 2018). Of note, patients can develop ICANS even after treatment of anti-IL-6 therapy, after the resolution of CRS. In the AUTO1-AL1 (FELIX) study, the evaluation of the impact of disease burden at time of lymphodepletion also emphasised its importance for the risk of ICANS and showed an even more important impact of the fractionated split dosing regimen. The rate of ICANS of any grade increased across the 2 subgroups within each dosing bracket (8.3% and 25.0% in the < 5% and ≥ 5% to ≤ 20% categories; 14.3% and 42.5% in the 20% to ≤ 75%, > 75% categories), whereas it can be seen that it decreased when moving across the dosing thresholds of ≤ 20% and > 20%. As described already for CRS, the relatively low rate of ICANS following AUCATZYL treatment is consistent with expectations based on the properties of AUCATZYL and the dosing regimen and makes this potential immunotoxicity consequence of therapy a much more manageable risk. A subgroup analysis did not highlight any findings that would be unexpected and the key impact on safety appeared to be the disease burden in terms of blasts in BM at lymphodepletion.

Important Identified Risks: Immune effector Cell-Associated Neurotoxicity Syndrome (ICANS)	
	Neurotoxicity may also be caused by fludarabine, but usually at higher doses than those being administered as part of lymphodepletion (Helton et al, 2013). Symptoms of fludarabine including objective weakness, agitation, confusion, seizures, visual disturbances, optic neuritis, optic neuropathy, blindness, and coma have been reported in CLL patients treated with multiple cycles of fludarabine (Fludarabine SmPC, 2019).
Preventability	Dose regimen based on the disease burden at lymphodepletion: the rationale for the split dosing was to optimise patient safety. The spacing between the dose fractions enable adequate time for the emergence of early signals of ICANS in the days following the first dose which are frequently indicative of subsequent severe toxicity and either their management prior to the second dose, or a delay of the second dose.
Impact on the risk-benefit balance of the product	Besides the routine risk minimisation measures, contraindications and warnings in the SmPC, corresponding package leaflet sections, the additional minimisation measure, risk minimisation control programme will be in place. In addition to the ongoing pharmacovigilance monitoring, safety events suggestive of ICANS and occurring in the exposed population will be collected and analysed during the AUTO1-LT2 Study.
Public Health impact	Routine and additional risk minimisation measures and pharmacovigilance activities are sufficient to minimise the impact to public health.

Important Identified Risks: Prolonged Cytopenia	
Potential mechanisms	While the cause of prolonged cytopenia in these patients is unclear, lymphodepleting therapy with fludarabine and cyclophosphamide can result in transient cytopenia within 30 days and can be prolonged as observed in several CAR T cell studies (Locke et al, 2019). Prolonged cytopenia (30-90 days) have also been observed after CAR T cell therapy, likely related to ongoing CAR T activity and disruption of haematopoiesis as the BM of patients treated with CAR T cells may show severe hypocellularity up to bone marrow failure.
Evidence source(s) and strength of evidence	Cytopenias were reported in AUTO1-AL1 (FELIX) clinical trial and in patients treated with other CAR T therapies.

Important Identified Risks: Prolonged Cytopenia	
Characterisation of the risk	As of the 07-Feb-2024 cut-off date in the AUTO1-AL1 (FELIX) study, of 99 patients who achieved CR or CRi after AUCATZYL infusion, the proportion of responders post-obe-cel infusion with Grade 3 or 4 neutropenia gradually decreased over time; 58.6% (58/99), 23.2% (23/99), and 13.1% (13/99) at Day 28, Month 2, and Month 3, respectively. Corresponding values for Grade 3 or 4 thrombocytopenia were 48.5% (48/99), 20.2% (20/99), and 11.1% (11/99), respectively. The median time to recovery (95% CI) to the lower thresholds was 0.7 months (0.5, 0.9) and 0.7 months (0.3, 1.7) for neutrophils and platelets, respectively, and to the higher thresholds was 1.9 months (1.0, 1.9) and 2.0 months (1.9, 2.1). The associated KM probability of recovery at 6 months post-infusion illustrated the high chance of recovery, being 97.6% at the 1.0×10^9/L threshold for neutrophils (100% already reached at 5 months for the 0.5×10^9/L neutrophil threshold) and 94.8% and 83.5% for the 50×10^9/L and 100×10^9/L thresholds for platelets, respectively Prolonged cytopenia is considered an Important Identified Risk due to the frequency, seriousness and severity which could lead to important clinical manifestations such as infection or bleeding.
Risk groups and risk factors	There are several factors that can be involved in CAR T cell-associated cytopenia including increased age, previous chemotherapies, underlying disease, poor bone marrow reserve, tumour burden, severity of hyperinflammation (cytokine release syndrome, neurotoxicity) and prevalence of clonal haematopoiesis of indeterminate potential (Sharma, 2022).
Preventability	Prophylactic antibiotics and antiviral treatments to be administered to those with decreased neutrophil counts, if deemed clinically suitable. In instances where patients present with fever and neutropenia, immediate measures to be taken to draw blood cultures and initiate broad-spectrum antibiotics.
Impact on the risk-benefit balance of the product	Besides the routine risk minimisation measures, warnings and precautions in the SmPC and package leaflet sections, the additional minimisation measure, risk minimisation control programme will be in place. In addition to the ongoing pharmacovigilance monitoring, safety events occurring in the exposed population will be collected and analysed during the AUTO1 Study.
Public Health impact	Routine and additional risk minimisation measures and pharmacovigilance activities are sufficient to minimise the impact to public health.

Important Identified Risks: Hypogammaglobulinaemia	
Potential mechanisms	B cell aplasia arises because CD19 is not only expressed on malignant B cells but also on normal B cells which are eliminated in the presence of effective CD19 reactive T cells. Thus, targeting of the normal CD19-positive B cell compartment is likely to impair humoral immunity, and B cell aplasia and hypogammaglobulinaemia may occur.
Evidence source(s) and strength of evidence	Hypogammaglobulinaemia is caused by B cell aplasia. It was reported in AUTO1-AL1 (FELIX) clinical trial and in patients treated with other CAR T therapies.
Characterisation of the risk	As of the 07-Feb-2024 cut-off date, in the Safety Set the Treatment-emergent adverse event (TEAE) of hypogammaglobulinaemia has been reported in a total of 12 patients (9.4%, 12/127) at any grade and regardless of causality. Two patients (1/6%, 2/127) experienced Grade ≥ 3 hypogammaglobulinaemia. Hypogammaglobulinaemia is considered an Important Identified Risk due to the risk of infections if left untreated.
Risk groups and risk factors	Individuals who have had prior treatment with rituximab and other drugs that can promote lymphopenia, are at an elevated risk when subsequently undergoing CAR T cell therapy.
Preventability	Patients undergoing CAR T therapy receive prophylactic antibiotics and antiviral medications as clinically appropriate, and all patients with fevers and neutropenia have blood cultures drawn and broad-spectrum antibiotic coverage, initiated promptly in accordance with local practices, as well as treatment with Immunoglobulin (IgG) replacement therapy, if needed.
Impact on the risk-benefit balance of the product	Besides the routine risk minimisation measures, warnings and precautions in the SmPC, corresponding package leaflet sections, the additional minimisation measure, risk minimisation control programme will be in place. In addition to the ongoing pharmacovigilance monitoring, events occurring in the exposed population in the clinical study will be collected and analysed during the AUTO1-LT2 Study.
Public Health impact	Routine and additional risk minimisation measures and pharmacovigilance activities are sufficient to minimise the impact to public health.

Important Identified Risks: Severe Infections	
Potential mechanisms	Patients receiving CAR T therapy can develop bacterial, fungal and viral infections (Hill et al, 2018). There are multiple potential contributing factors, including prior disease state and prior treatment, the lymphodepletion chemotherapy prior to CAR T therapy and any CAR T associated cytopenia, B cell aplasia, or hypogammaglobulinaemia (see section 6.2.3.7). In addition, patients who experience CRS can also be at risk of infections (Hill et al, 2018).
Evidence source(s) and strength of evidence	Infections were reported in AUTO1-AL1 (FELIX) clinical trial and in patients treated with other CAR T therapies.

Important Identified Risks: Severe Infections	
Characterisation of the risk	As of the 07-Feb-2024 cut-off date, there were 90 patients with any grade non-COVID severe infection (70.9%) and 57 patients with Grade ≥ 3 non-COVID severe infection (44.9%). The most common (≥ 5% of patients) non-COVID severe infection PTs Grade ≥ 3 were pneumonia (7.1%, 9/127) and sepsis (6.3%, 8/127). Grade 3 non-COVID severe infections were reported for 35.4% (45/127) of patients. Grade 4 and 5 non-COVID severe infections were reported for 4.7% (6/127) of patients each. There was 1 death for septic shock; 2 patients each for sepsis, neutropenic sepsis; 1 patient for abdominal infection. One event of neutropenic sepsis was possibly related to study treatment severe infections are considered an Important Identified Risk due to their frequency, seriousness and severity if left untreated.
Risk groups and risk factors	There are multiple potential contributing factors, including prior disease state and prior treatment, the lymphodepletion chemotherapy prior to CAR T therapy and any CAR T associated cytopenia, B-cell aplasia, or hypogammaglobulinaemia. In addition, patients who experience CRS can also be at risk of infections (Hill et al, 2018).
Preventability	Patients should receive prophylaxis with antimicrobials due to the use of fludarabine and the potential prolonged duration of lymphopenia and neutropenia. Prophylaxis for pneumocystis should be administered, and antivirals should be given for Herpes virus prevention from the start of conditioning chemotherapy until at least 6 months post cellular therapy infusion or longer. Consideration shall be given to initiating prophylaxis at the time of leukapheresis. Regular monitoring for specific viral infections using PCR during hospital stays is essential. All patients with fevers during periods of low neutrophil counts should undergo blood tests and be administered broad-spectrum antibiotics, adhering to institutional standards.
Impact on the risk-benefit balance of the product	Besides the routine risk minimisation measures, warnings and precautions in the SmPC, corresponding package leaflet sections, the additional minimisation measure, risk minimisation control programme will be in place. In addition to the ongoing pharmacovigilance monitoring, clinically significant infections defined as infections requiring treatment occurring in the exposed population will be collected and analysed during the AUTO1-LT2 Study.
Public Health impact	Routine and additional risk minimisation measures and pharmacovigilance activities are sufficient to minimise the impact to public health.

Important Identified Risks: Secondary Malignancy of T cell origin	
Potential mechanisms	The risk of insertional mutagenesis and development of secondary cancers in patients receiving treatment with CAR T cell therapeutics is anticipated to be low (< 0.1%). The recent FDA and EMA communications indicating that 22 cases of T cell malignancies have so far been reported from an estimated 34,400 (0.06%) patients treated with commercially available CAR T cells, represent a small risk relative to the potential benefit (Banerjee et al, 2024). Notably, it is possible that some of the reported cases of T cell malignancy may not be related to the use of RV. Secondary malignancies of T cell origin is now a recognized risk associated with CAR T cell therapies. This risk emerges from the long-term engraftment and persistence of genetically modified T cells, which may lead to oncogenic events such as insertional mutagenesis or the development of secondary cancers. The T cells' activation and proliferation, driven by the CAR construct, could also contribute to clonal expansion, increasing the likelihood of secondary malignancy. Furthermore, the use of conditioning regimens prior to CAR T cell infusion may induce immunosuppression, which could further predispose patients to secondary malignancies.
Evidence source(s) and strength of evidence	The risk of secondary malignancies of T cell origin as a class risk has been highlighted through clinical experience with CAR T cell therapies.
Characterisation of the risk	As of the 07-Feb-2024 cut-off date, in the AUTO1-AL1 (FELIX) study, two patients were categorised as having potential secondary malignancies. Each patient was reviewed in detail and these cases were not considered to be secondary malignancies associated with AUCATZYL treatment due to pre-existing conditions and confounding circumstances.
Risk groups and risk factors	Secondary malignancy is consistent with the known outcomes of immunosuppression and/or genotoxicity resulting from chemotherapy. Patient factors: Age Additive or synergistic factors: Chemotherapy and immunosuppressive treatments
Preventability	Patients should be monitored life-long for secondary malignancies. The SmPC contains information to contact MAH to receive sampling advice.
Impact on the risk-benefit balance of the product	Frequency of the risk is considered rare. The SmPC contains guidance for HCPs regarding monitoring for secondary malignancy. Additional process of testing is developed to collect additional information if secondary malignancy occurs, outside of the AUTO1-LT2 study.
Public Health impact	The long-term surveillance study AUTO1-LT2 will be implemented for patients who receive AUCATZYL therapy to allow for the detection of potential secondary malignancies. Additional process of testing is developed to collect additional information if secondary malignancy occurs, outside of the AUTO1-LT2 study.

Important Identified Risk: Aggravation of Graft Versus Host Disease	
Potential mechanisms	The therapeutic mechanism of CAR T cells involves reengineering the patient's T cells to recognise and attack cancer cells. During this process, the infused AUCATZYL CAR T cells could inadvertently recognise healthy host tissues as foreign, exacerbating GvHD.
Evidence source(s) and strength of evidence	There were cases of GvHD aggravation reported during AUTO1-AL1 (FELIX) clinical study.
Characterisation of the risk	As of the 07-Feb-2024 cut-off date, in the AUTO1-AL1 (FELIX) study Safety Set a total of 8 patients (6.3%, 8/127) have reported GvHD post-AUCATZYL infusion. These 8 patients either had a history of an allogeneic SCT (5 patients) prior to infusion or proceeded to consolidative allogeneic SCT in remission after obe-cel treatment (3 patients). The latter 3 patients are not relevant in terms of causality due to obe-cel infusion as the obe-cel autologous CAR T cells were eliminated after the allogeneic SCT. GvHD can be life-threatening or cause chronic comorbidities, it is therefore considered an important potential risk.
Risk groups and risk factors	Patients with active GvHD from prior HSCT.
Preventability	Any drug used for the treatment GvHD must be stopped > 2 weeks prior to leukapheresis and not repeated thereafter.
Impact on the risk-benefit balance of the product	Routine risk minimisation measures such as undesirable effects in the SmPC, corresponding package leaflet sections, and ongoing pharmacovigilance monitoring is expected to maintain a positive risk-benefit balance. In addition, aggravation of GvHD events will be collected in the AUTO1-LT2 study.
Public Health impact	Risk mitigation through the SmPC and pharmacovigilance activities is sufficient to minimise the impact to public health.

Important Potential Risks

Important Potential Risk: Tumour Lysis Syndrome (TLS)	
Potential mechanisms	Tumour lysis syndrome may occur on treatment with AUCATZYL due to rapid killing of malignant cells, which can be associated with a release of intracellular ions and metabolic by-products into the systemic circulation.
Evidence source(s) and strength of evidence	TLS was reported in AUTO1-AL1 (FELIX) clinical study and in patients treated with other CAR T therapies.
Characterisation of the risk	As of the 07-Feb-2024 cut-off date AUTO1-AL1 (FELIX) study, in the Safety Set there was 1 patient (0.8%, 1/127) who experienced TLS (Grade 3). This event occurred post new anticancer therapy and is considered not related to AUCATZYL. Tumour lysis syndrome is considered an important potential risk due to the seriousness of the condition.
Risk groups and risk factors	Patients with a high disease burden

Important Potential Risk: Tumour Lysis Syndrome (TLS)	
Preventability	High-risk patients, i.e. those with a high disease burden (such as > 25% BM blasts in leukaemia), should be treated prophylactically, and in accordance with local standards (e.g. be given allopurinol and i.v. fluids from the start of lymphodepletion to prevent TLS.)
Impact on the risk-benefit balance of the product	Monitoring for early signs and symptoms of TLS and routine pharmacovigilance activities are expected to maintain a positive risk-benefit balance. In addition to the ongoing pharmacovigilance monitoring, events occurring in the exposed population will be collected and analysed during the AUTO1-LT2 study.
Public Health impact	Routine and additional risk minimisation measures and pharmacovigilance activities are sufficient to minimise the impact to public health.

Important Potential Risk: Antigenicity and Immunogenicity	
Potential mechanisms	The CD19 antigen-binding domain of AUCATZYL is derived from a murine sequence and therefore anti-CAR antibodies, or an anti-CAR T cell response could be induced. Antibodies can reduce the efficacy of AUCATZYL and can cause safety issues like CRS, or autoimmune reactions that may require medical intervention and hence it is considered an important potential risk.
Evidence source(s) and strength of evidence	Two cases of immunogenicity related to AUCATZYL were observed in AUTO1-AL1 (FELIX) clinical study
Characterisation of the risk	An anti-CAR antibody response is unlikely to be a concern in particular at the beginning of the treatment when the split dose is administered; firstly, patients are lymphodepleted, secondly the CAR T cells target the B cell compartment as they are targeting CD19, hence patients are expected to develop B cell aplasia and hypogammaglobulinaemia (Maude et al, 2018; Locke et al, 2018). Based on the above, and the fact that a humoral immune response takes approximately 14 days to be generated, a split dosing schedule carries no additional risk of increased autoimmune activity compared to a single dosing schedule. It has been shown in previous trials with CD19 CARs that using either split dosing or re-dosing up to 3 months after the first treatment that re-dosing was not associated with the development of an immunogenicity AE (Frey et al, 2016; Neelapu et al, 2017). As of the 07-Feb-2024 cut-off date, 11/127 (8.7%) of patients tested positive for presence of anti-CD19 CAR antibodies pre-infusion and treatment induced anti-CD19 CAR antibodies were detected in 2/127 (1.6%) of the patients. There is no evidence that the presence of pre-existing or post-infusion anti-CD19 CAR antibodies affect the effectiveness, safety, initial expansion and persistency of AUCATZYL.
Risk groups and risk factors	Unknown
Preventability	There is no evidence that the cellular and humoral immunogenicity impacts AUCATZYL kinetics of initial expansion and persistence, efficacy, or safety.

Important Potential Risk: Antigenicity and Immunogenicity	
Impact on the risk-benefit balance of the product	Routine risk minimisation using SmPC, corresponding package leaflet sections, as well as routine pharmacovigilance monitoring are expected to maintain a positive risk-benefit balance. The risk of immunogenicity, defined as hypersensitivity reactions, occurring in the exposed population will be collected and analysed during the AUTO1-LT2 study. However, auto-antibodies testing is currently not done in clinical practice and not collected within the registries, therefore adverse events on antigenicity will not be collected in the AUTO1-LT2 study.
Public Health impact	Routine and additional risk minimisation measures and pharmacovigilance activities are sufficient to minimise the impact to public health.

Important Potential Risk: Secondary Haematologic Malignancies (except of T cell origin)	
Potential mechanisms	The occurrence of other malignant tumours is linked to immunosuppression and/or genotoxicity caused by the disease itself or its treatment. This includes the administration of conditioning therapy before AUCATZYL. Another possible mechanism includes lentiviral vectors involved in transduction of lymphocytes for CAR T cell manufacturing which comprise the risk of insertional mutagenesis (IM) of the lentiviral vector or replication-competent Lentivirus (Schubert 2021).
Evidence source(s) and strength of evidence	The risk of secondary malignancies of T cell origin as a class risk has been highlighted through clinical experience with CAR T cell therapies.
Characterisation of the risk	As of the 07-Feb-2024 cut-off date, in the AUTO1-AL1 (FELIX) study, 2 patients were categorised as having potential secondary malignancies. Each patient was reviewed in detail and these cases were not considered to be secondary malignancies associated with AUCATZYL treatment due to pre-existing conditions and confounding circumstances.
Risk groups and risk factors	Secondary malignancy is consistent with the known outcomes of immunosuppression and/or genotoxicity resulting from chemotherapy. Patient factors: Age Additive or synergistic factors: Chemotherapy and immunosuppressive treatments
Preventability	Prior to administration of CAR T treatment, patients should be carefully evaluated for underlying genetic predispositions to cancer and pre-existing malignancies to help identify those at higher risk for secondary malignancies. Implementation of long-term surveillance for patients who receive CAR T therapy for early detection and management of any potential secondary malignancies. HCPs should monitor patients' life-long for secondary malignancies. The SmPC includes recommendations for contacting the MAH to receive sampling advice.

Important Potential Risk: Secondary Haematologic Malignancies (except of T cell origin)	
	The risks of RCL formation are extremely low and to date, RCL has not been detected in any of the patients treated with lentiviral based CAR T cell therapy.
Impact on the risk-benefit balance of the product	The SmPC contains guidance for HCPs regarding monitoring for secondary malignancy. Risk minimisation using the SmPC, and routine pharmacovigilance are expected to maintain a positive risk-benefit balance. The long-term surveillance study AUTO1-LT2 will be implemented for patients who receive AUCATZYL therapy to allow for the detection of potential secondary malignancies. Additional process of testing is developed to collect additional information if secondary malignancy occurs, outside of the AUTO1-LT2 study.
Public Health impact	The SmPC informs HCPs of these risks and provides guidance. Risk mitigation through the SmPC and pharmacovigilance activities is sufficient to minimise the impact to public health.

Important Potential Risk: Overdose/Medication errors	
Potential mechanisms	Potential overdose may occur during administration of AUCATZYL
Evidence source(s) and strength of evidence	There were four observations of overdose cases during administration of the first dose of AUCATZYL during AUTO1-AL1 (FELIX) study.
Characterisation of the risk	Overall, no patient in the AUTO1-AL1 (FELIX) study received a higher total target dose of 410×10^6 CAR T-positive cells (± 25%) across all cohorts and both phases. First dose CAR T cell calculation is dependent on recorded disease burden and no patient received a meaningfully higher dose than the planned first dose of 100×10^6 CD19 CAR-positive T cells, the dosing regimen associated with low disease burden. However, during the FELIX study, there were four observations of apparent overdose in 4 patients recorded, each linked with the administration of the first dose. All 4 reports were fully investigated. In 2 of the 4 reports, on review, the number of CAR T cells administered was found to be correct, however the Dosing Form documentation relating to tumour burden had been incorrectly recorded leading to an apparent overdose assessment. In the other 2 reports, the overdose occurred at a single study site early during the FELIX study. There were 2 separate patients, each patient had a high tumour burden and therefore should have been assessed to receive a 10×10^6 CAR T cells first dose, but both received a higher dose (68 and 103×10^6 CAR T cells) respectively. Of the 4 patients, 1 patient experienced Grade 1 CRS, 1 patient experienced Grade 2 CRS and 1 patient experienced Grade 3 ICANS.
Risk groups and risk factors	Unknown
Preventability	Preventive measures such as details on Release for Infusion Certificate, colour-coded labels for split infusion bag(s) and the Dose Schedule Planner where 2 signatures are used to verify accuracy of the infused volume are described in SmPC Section 4.2.

Important Potential Risk: Overdose/Medication errors	
	Section 4.2 of the SmPC, requires AUCATZYL be administered in a qualified treatment centre by a physician with experience in the treatment of haematological malignancies.
Impact on the risk-benefit balance of the product	Routine risk minimisation measures such as those described in the posology and method of administration section in the SmPC, the Release for Infusion Certificate and the Dose Schedule Planner for colour-coded split infusion bags as well as PV monitoring are expected to minimise the likelihood of overdose and maintain a positive risk-benefit balance. Additional pharmacovigilance activities include collection of incidences of overdose cases in the AUTO1-LT2 study.
Public Health impact	Risk mitigation through the SmPC and pharmacovigilance activities is sufficient to minimise the impact to public health.

Table SVII.3.2: Presentation of the missing information

Missing Information	**Evidence source**
Use during pregnancy and breastfeeding	**Very limited data in clinical trials**
Long-term safety	**Lack of data in clinical trials**
New occurrence or exacerbation of an autoimmune disorder	**Lack of data in clinical trials**

Part II: Module SVIII - Summary of the safety concerns

Table SVIII.1: Summary of safety concerns

Important identified risks	**Cytokine release syndrome including HLH/MAS** **Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS)** **Prolonged Cytopenia** **Hypogammaglobulinaemia** **Severe Infections** **Secondary malignancies of T cell origin** **Aggravation of Graft versus Host Disease (GvHD)**
Important potential risks	Tumour Lysis Syndrome (TLS) Antigenicity and Immunogenicity Secondary Haematologic Malignancies (except of T cell origin) Overdose/Medication error
Missing information	Use during pregnancy & breastfeeding Long-term safety New occurrence or exacerbation of an autoimmune disorder

Part III: Pharmacovigilance Plan (including post-authorisation safety studies)

The Pharmacovigilance (PV) plan provides details of PV activities/studies that are intended to proactively identify and/or characterise safety concerns and will inform risk mitigation strategies for the important and potential risks.

III.1 Routine pharmacovigilance activities

Required routine pharmacovigilance will be conducted for AUCATZYL. All newly acquired safety information will continue to be actively monitored in accordance with good pharmacovigilance practices (GVP) including regular review and evaluation of data, routine systematic review of published literature and case reports and both individual case and aggregate safety reviews and analysis.

Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:

Specific adverse reaction follow-up questionnaire

A copy of each follow-up questionnaire is provided in Annex 4.

Table III.1: Specific adverse reaction follow-up questionnaires

Name of questionnaire	Description
Secondary malignancy of T cell origin and secondary haematologic malignancies (except of T cell origin)	The questionnaire is designed to obtain information regarding start and stop dates of the event, severity and seriousness, diagnostic results, pre-existing factors that may have contributed to the development of the new malignancy, relevant medical history and additional medications.

Other Forms of Routine Pharmacovigilance Activities:

None

III.2 Additional pharmacovigilance activities

AUTO-LT1 Study Summary

Study short name and title:

AUTO-LT1: 15-year long-term follow-up study of patients previously treated with obecabtagene autoleucel, according to an agreed protocol.

Rationale and study objectives:

The purpose of this study is to to further characterise the long-term safety and efficacy of Aucatzyl in adult patients with relapsed or refractory B cell precursor acute lymphoblastic leukaemia.

Study design:

All patients who have received AUCATZYL who have completed End of Study visit in the AUTO1-AL1 (FELIX) study will be eligible and asked for their consent to be enrolled onto this separate, long-term follow-up study. Patients will be monitored for all SAEs considered related

to the study treatment, AEs of special interest including any new malignancy for a period of up to 15 years. Data regarding survival and subsequent therapies will be collected.

Another aim of the long-term follow-up study is to assess for delayed consequences due to the use of a lentiviral vector during the manufacture of AUCATZYL.

Study population:

All patients who have received AUCATZYL who have completed End of Study visit in the AUTO1-AL1 (FELIX) study will be eligible and asked for their consent to be enrolled onto this separate, long-term follow-up study.

Milestones:

The milestone for the first patient to be enrolled (FPI) in the study is planned for 30-Jun-2028. Interim report will be provided 5 years after FPI by Jun-2033. Routine Periodic Benefit-Risk Evaluation Reports (PBRERs) and Development Safety Update Reports (DSUR) will be submitted regularly as required. The final FELIX interim report for is planned for 30-Jun-2039.

AUTO1-LT2 Study Summary

Study short name and title:

A prospective study, to further characterize the long-term safety and efficacy of Aucatzyl in adult patients with relapse or refractory B cell precursor acute lymphoblastic leukaemia based on data from a registry.

Rationale and study objectives:

The purpose of this study is to characterise the long-term safety profile of AUCATZYL in the post-marketing setting, including the important identified risks and potential risks associated with this product.

Study design:

The study will use secondary data available in established registries, i.e. the European Society for Blood and Marrow Transplantation (EBMT) and the Centre for International Blood and Marrow Transplant Research (CIBMTR). This study will include data from patients with r/r B-ALL who have been treated with AUCATZYL in the post-approval setting and consented to share the data with the Marketing Authorisation Holder.

Participating treatment centres will enter data into the registry database following the registry-specific procedures and requirements. The treatment centres will complete the data collection forms after a patient visit. Patients must consent to have their data reported to the registry and to submit pseudonymised data to the MAH.

If a secondary malignancy is suspected, the treatment centres must contact MAH within 72 hours of becoming aware of the diagnosis to obtain instructions on collection and transfer of tumour tissue sample for testing in a separate process of this non-interventional study.

Study population:

Adult patients diagnosed with relapsed or refractory B cell acute lymphoblastic leukaemia that have been prescribed AUCATZYL at participating centres. There are no patient-specific restrictions to enter the study. The study will last approximately 19 years, including 15 years of follow-up. It is estimated that a minimum of a 4-year recruitment period is required globally followed by a 15-year follow-up period.

Milestones:

The final protocol will be submitted within 3 months of approval. The study will be registered in the EU PASS register within 2 weeks of protocol approval. Start of data collection in US is scheduled for 30-Jun-2025 and in EU for 31-Dec-2025. End of data collection is set for 30-Jun-2043. Annual reports covering safety, effectiveness interim analyses and progress will be generated annually for the first 5 years, followed by reports once every 2 years.

The study is projected to complete by 30-Jun-2044 and the final study report is expected to be issued by 30-Jun-2045.

T cell malignancy PV activity summary

PV activity short name and title: T cell malignancy testing

Rationale and PV activity objectives:

Autolus has developed a process to enable appropriate identification of any malignancy requiring insertional mutagenesis work-up, appropriate sample collection and appropriate testing for patients who received at least 1 dose of AUCATZYL commercially and developed a new malignancy.

PV activity design:

To address the risk of secondary malignancies of T cell origin and secondary haematologic malignancies (except of T cell origin) in CAR T cell recipients, the following activities will be implemented, as outlined in Figure 1 below:

- Pathology Work-Up. A detailed review of pathology diagnosis performed at sites will be conducted for each case of secondary malignancy, including an evaluation of both archived and latest tissue samples, to confirm the malignancy is new and not pre-existing.
- Tumour Sample Collection. A standardised process for tumour sample collection, including sample request, sample collection, provision of sampling kits and analysis will be followed. Samples such as lymph node biopsies and bone marrow aspirates will be retained for further testing (subject to patient consent), especially in cases of suspected T cell lymphoma, where both lymph node and bone marrow involvement may need to be assessed.
- As part of a standard response letter, prescribers that contact Autolus to report a secondary malignancy of T-cell origin post CAR-T infusion will be provided with details of the sample and amount of material to be collected:

If recommended amount of tissue is not available, as much tissue as possible should be collected to enable assessment of causality.

- Testing Algorithm. Vector Copy Number (VCN) and Replication Competent Lentivirus (RCL) testing will be performed. If CAR genomic material and/or RCL are detected, Integration Site Analysis (ISA) will be conducted to assess integration sites near oncogenes or tumour suppressors, with comparisons made using databases such as Catalogue of Somatic Mutations in Cancer (COSMIC). This will further the understanding of the impact of the integration site. If VCN/RCL/ISA results remain inconclusive further workup may be performed (including but not limited to gene expression/transcriptome analysis as well as whole genome, whole exome or targeted DNA sequencing).
- Autolus will aim to contact sites to obtain consent for new malignancy testing when patients consent for being treated with AUCATZYL. If consent is not given at the time of infusion, consent will be sought following report of secondary malignancy. In accordance with local regulations, the prescribing physician will secure approval from the site's institutional ethics committee (IEC) for testing activities and the ICF.

PV activity population:

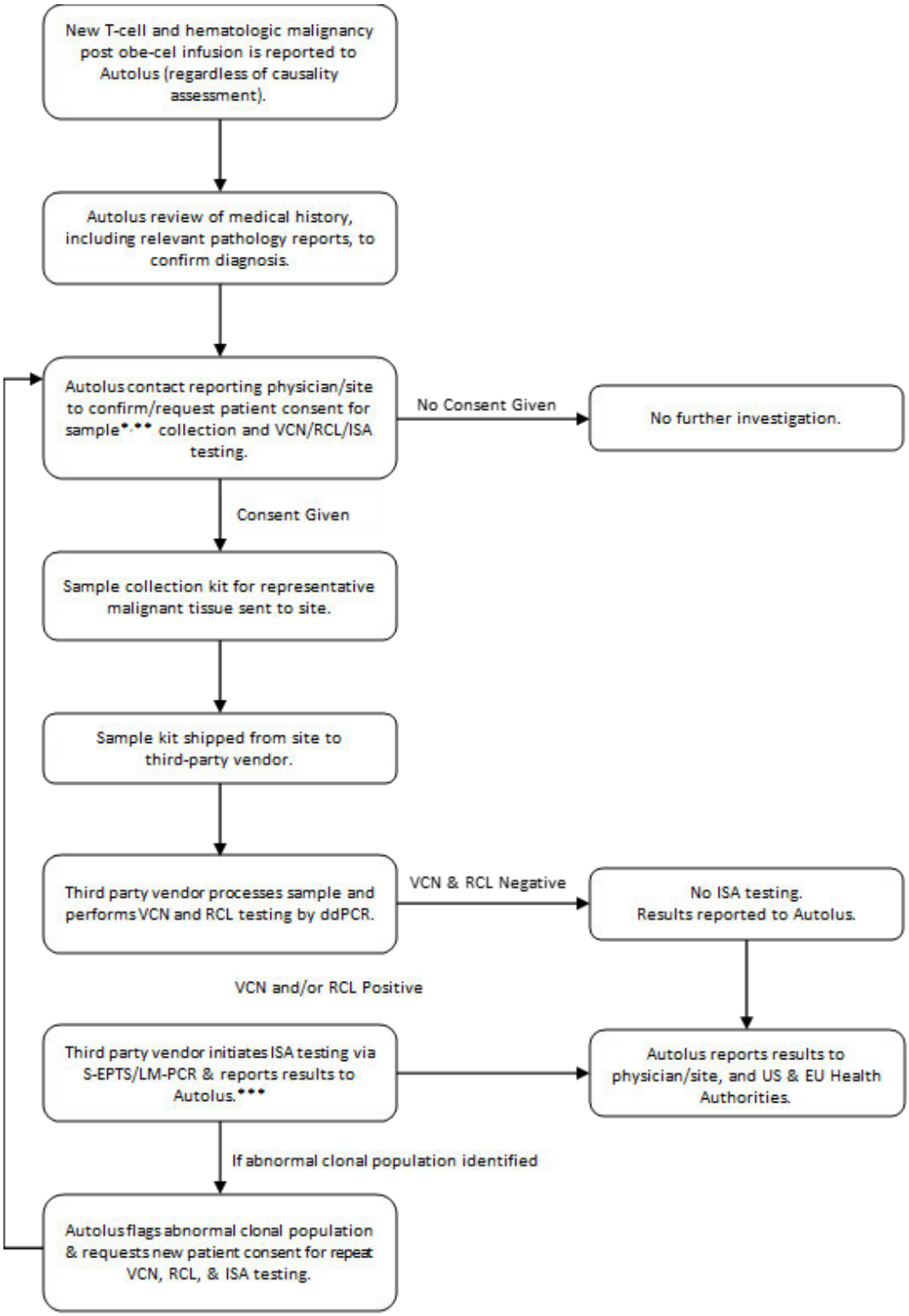
Adult patients diagnosed with relapsed or refractory B cell acute lymphoblastic leukaemia that have been prescribed AUCATZYL at participating centres and later diagnosed with secondary malignancy.

Consent is sought for (1) vector copy number, replication competent lentivirus, and insertional site analysis testing using existing samples from the new malignancy and (2) reporting of results to Autolus and Health Authorities.

Milestones:

Safety data from the study will be included in the Periodic Safety Update Reports (PSURs) and submitted in accordance with EURD list. A safety report is planned to be submitted after 5, 10 and 15 years post-approval.

Figure 1: PV activity - Testing process flow



Abbreviations: ddPCR=digital droplet polymerase chain reaction; EU=European Union; ISA=insertional site analysis; RCL=replication competent lentivirus; S-EPTS/LM-PCR=shearing extension primer tag selection ligation-mediated polymerase chain reaction; 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 Institutional Ethics Committee (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 is sought for (1) VCN, RCL, ISA testing and any other testing required using existing samples and (2) reporting of results to Autolus and Health Authorities.

III.3 Summary Table of additional Pharmacovigilance activities

Table III.2: Summary Table of Additional Pharmacovigilance Activities

Study/ Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorisation				
Prospective study to assess long-term safety and efficacy of adult patients with relapsed or refractory B cell acute lymphoblastic leukaemia receiving Aucatzyl treatment (AUTO1-LT2), based on data from a registry AUTO1-LT2 Planned	Primary objective: To further characterize the long-term safety of Aucatzyl in adult patients with relapse or refractory B cell precursor acute lymphoblastic leukaemia. Furthermore, to evaluate the rate and severity (where applicable and including CRS and ICANS) of the following adverse events: – Cytokine release syndrome (CRS), including Hemophagocytic Lymphohistiocytosis (HLH)/ Macrophage Activation Syndrome (MAS) – Immune effector cell-associated neurotoxicity syndrome (ICANS) – Prolonged cytopenia – Hypogammaglobulinemia – Clinically significant infections – Secondary malignancies – Other neurologic toxicities – Tumor lysis syndrome (TLS) – Immunogenicity, defined as hypersensitivity reactions – Aggravation of graft versus host disease (GvHD) – New occurrence of an autoimmune disorder – Overdose – Other safety concerns not yet identified in the clinical program – To evaluate pregnancy outcomes. Secondary objectives:	– CRS including HLH/MAS – ICANS – Prolonged Cytopenias – Hypogammaglobulinaemia – Clinically significant infections – Secondary malignancies – Other neurologic toxicities – Tumour Lysis Syndrome – Immunogenicity, defined as hypersensitivity reaction – Aggravation of Graft Versus Host Disease – New occurrence of an autoimmune disorder Overdose – Other safety concerns not yet identified in the clinical programme – Use during pregnancy	Final protocol submission in EU Registration in the EU PASS register Start of data collection in US Start of data collection in EU End of data collection Annual report (safety, effectiveness interim analysis progress report)	Within 3 months of marketing authorisation Within 2 weeks of protocol approval 30-Jun-2025 31-Dec-2025 30-Jun-2043 Annual report for first 5 years, followed by report once every 2 years

Study/ Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
	The secondary objectives of this study are to describe the effectiveness of AUCATZYL as well as further characterising safety in the real-world setting. Effectiveness: – To evaluate the effectiveness of AUCATZYL in terms of overall remission rate (ORR). – To determine the duration of response (DOR) post-AUCATZYL administration. – To determine the Real-world event-free survival (rwEFS) post-AUCATZYL treatment. – To determine the overall survival (OS) post-AUCATZYL treatment. – To determine rate and outcomes after subsequent allogeneic hematopoietic cell transplantation. Safety*:* – To determine the causes of death after AUCATZYL administration and mortality rate. – To characterise B cell aplasia. Exploratory objectives: – To determine MRD negativity status in patients in remission.		Study Completion Final study report	30-Jun-2044 30-Jun-2045

Study/ Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
AUTO-LT1 15-year long-term follow-up study of patients previously treated with obecabtagene autoleucel, according to an agreed protocol. Open, planned for obe-cel	Further characterise the long-term safety and efficacy of Aucatzyl in adult patients with relapsed or refractory B cell precursor acute lymphoblastic leukaemia of patients previously treated with obecabtagene autoleucel,, according to an agreed protocol. <u>Primary objectives</u>: – Long-term safety <u>Secondary objective:</u> – Survival – B cell aplasia for patients treated with an AUTO CAR T cell therapy targeting a B cell malignancy – Clinical efficacy of AUTO CAR T cell therapy in patients enrolled prior to disease progression – Chimeric antigen receptor (CAR) transgene persistence – Replication lentivirus (RCL) emergence – Insertional mutagenesis	– CRS including HLH/MAS – ICANS – Prolonged Cytopenia – Hypogammaglobulinaemia – Severe infections – Secondary haematologic malignancy (including of T cell origin) – Tumour Lysis Syndrome Antigenicity and Immunogenicity – Aggravation of Graft Versus Host Disease – Long-term safety – Use during pregnancy and breastfeeding – New occurrence or exacerbation of an autoimmune disorder	Final protocol submission in EU Enrolment of first patient (FPI) Interim report (Provided 5 years after FPI by Jun-2033) Final Study report for obe-cel	Within 3 months of marketing authorisation 30-Jun-2028 30-Jun-2033 30-Jun-2039
Category 3 - Required additional pharmacovigilance activities				
PV activity for testing of T cell and other haematologic malignancies Planned	Identification of any new T cell and other haematologic malignancy requiring insertional mutagenesis pathology work-up, appropriate sample collection and appropriate testing for patients who received at least 1 dose of AUCATZYL and developed a new malignancy.	Secondary malignancies of T cell origin	Safety data reported in PSURs Safety report – EU approval + 5 years	with PSURs Sep-2030

Part IV: Plans for post-authorisation efficacy studies

AUTO1-AL1 Study Summary

Study short name and title: AUTO1 in relapsed or refractory B-ALL.

AUTO1-AL1: An Open-Label, Multi-Centre, Phase Ib/II Study Evaluating the Safety And Efficacy Of AUTO1, A CAR T Cell Treatment Targeting CD19, In Adult Patients With Relapsed Or Refractory B Cell Acute Lymphoblastic Leukaemia.

Rationale and study objectives:

AUTO1-AL1 is an ongoing Phase Ib/II study that also includes monitoring patients for 60 months after AUCATZYL administration.

The study aims to confirm the long-term safety and efficacy of Aucatzyl in adult patients with relapse or refractory B cell precursor acute lymphoblastic leukaemia.

Study design:

Originally the study protocol foresaw patients to consent to be included in the AUTO-LT1 24 months after their last visit on the FELIX study. However, due to concerns that patients may not consent to AUTO-LT1 and be lost to follow-up, the amendment of the study protocol aims to minimise the risk of losing patients to long-term survival follow-up by offering the opportunity to continue to participate in the FELIX trial for additional 36 months.

The new End of Study (EoS) is defined as the date of the last patient's last visit, which is expected to occur 60 months after obe-cel infusion of the last patient (or earlier in the event of death or early withdrawal of the last).

Study population:

Adult patients with r/r B-ALL.

Milestones:

An interim report will be prepared after a 2-year follow-up period. This report will be due within 12 months of marketing authorisation. The final study report is scheduled for submission by 30-Jun-2029.

AUTO1-LT2 Study Summary

Study short name and title:

A prospective, non-interventional study investigating efficacy and safety based on data from the same registry used to characterize the long-term safety and efficacy of Aucatzyl, according to an agreed protocol.

Rationale and study objectives:

The purpose of this study is to characterise the short- and long-term safety profile, and effectiveness of AUCATZYL in the post-marketing setting, including the important identified risks and potential risks associated with this product.

Study design:

The study will use secondary data available in established registries, i.e. the European Society for Blood and Marrow Transplantation (EBMT) and the Centre for International Blood and Marrow Transplant Research (CIBMTR). This study will include data from patients with r/r B-ALL who

have been treated with AUCATZYL in the post-approval setting and consented to share the data with the Marketing Authorisation Holder.

Participating treatment centres will enter data into the registry database following the registry-specific procedures and requirements. The treatment centres will complete the data collection forms after a patient visit. Patients must consent to have their data reported to the registry and to submit pseudonymised data to the MAH.

If a secondary malignancy is suspected, the treatment centres must contact MAH within 72 hours of becoming aware of the diagnosis to obtain instructions on collection and transfer of tumour tissue sample for testing in a separate process of this non-interventional study.

Study population:

Adult patients diagnosed with relapsed or refractory B cell acute lymphoblastic leukaemia that have been prescribed AUCATZYL at participating centres. There are no patient-specific restrictions to enter the study. The study will last approximately 19 years, including 15 years of follow-up. It is estimated that a minimum of a 4-year recruitment period is required globally followed by a 15-year follow-up period.

Milestones:

The study interim report will be provided by 31-Jul-2030 as part of specific obligation, with *the interim results of a prospective, international, non-interventional study to assess long-term safety and effectiveness of adult patients with relapsed or refractory B-cell acute lymphoblastic leukaemia receiving Aucatzyl treatment (AUTO1-LT2), based on data from a registry, according to an agreed protocol.*

The study is projected to complete by 30-Jun-2044 and the final study report is expected to be issued by 30-Jun-2045.

Study/ Status	Summary of objectives	Efficacy uncertainties addressed	Milestones	Due dates
Efficacy studies which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances				
AUTO1-AL1 (FELIX) An Open-Label, Multi-Centre, Phase Ib/II Study Evaluating the Safety And Efficacy Of AUTO1, A CAR T Cell Treatment Targeting CD19, In Adult Patients With Relapsed Or Refractory B Cell Acute Lymphoblastic Leukaemia.	To confirm the long-term safety and efficacy of Aucatzyl in adult patients with relapse or refractory B cell precursor acute lymphoblastic leukaemia.	- CRS including HLH/MAS - ICANS - Prolonged Cytopenia - Hypogammaglobulinaemia - Severe infections - Secondary haematologic malignancy (including of T cell origin) - Tumour Lysis Syndrome - Antigenicity and Immunogenicity - Aggravation of Graft Versus Host Disease - New occurrence or exacerbation of an autoimmune disorder	Interim study report after 2-year follow-up. Final study report	Within 12 months of marketing authorisation Submission by 30-Jun-2029
AUTO1-LT2 A prospective, non-interventional study investigating efficacy and safety based on data from the same registry used to characterize the long-term safety and efficacy of Aucatzyl, according to an agreed protocol.	To confirm the efficacy and safety of Aucatzyl in adult patients with relapse or refractory B cell precursor acute lymphoblastic leukaemia, based on data from the same registry used to characterize the long-term safety and efficacy of Aucatzyl, according to an agreed protocol.	- CRS including HLH/MAS - ICANS - Prolonged Cytopenias - Hypogammaglobulinaemia - Clinically significant infections - Secondary malignancies - Other neurologic toxicities - Tumour Lysis Syndrome - Immunogenicity, defined as hypersensitivity reaction - Aggravation of Graft Versus Host Disease - New occurrence of an autoimmune disorder - Overdose - Other safety concerns not yet identified in the clinical programme - Use during pregnancy	5-year Results Report	31-Jul-2030

Part V: Risk minimisation measures (including evaluation of the effectiveness of risk minimisation activities)

Risk Minimisation Plan

V.1. Routine Risk Minimisation Measures

Table V.1: Description of routine risk minimisation measures by safety concern

Safety concern	Routine risk minimisation activities
Cytokine Release Syndrome including HLH/MAS	Routine risk communication: • SmPC sections 4.2, 4.4 and 4.8 • PL sections 2, 4 Routine risk minimisation activities recommending specific clinical measures to address the risk: In section 4.2 of the SmPC, HCPs are also advised to monitor patients daily for the first 14 days post-infusion for the signs of CRS, with continued monitoring at the physician's discretion for at least 4 weeks after infusion. Patients should be instructed to remain within close proximity of the qualified treatment centre (within 2 hours of travel) for at least 4 weeks following the first infusion. Section 4.2 of the SmPC allows for HCPs to delay the second split dose to manage toxicities. Section 4.4 allows for delay of 2nd dose to reduce risk of worsening CRS or discontinue treatment for Grade ≥ 3 CRS. It also provides guidelines to manage CRS. Other routine risk minimisation measures beyond the product information: Use restricted to physicians experienced in the treatment of haematological malignancies. Subject to restricted medical prescription.
Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS)	Routine risk communication: • SmPC sections 4.2, 4.4 and 4.8 • PL sections 2, 4 Routine risk minimisation activities recommending specific clinical measures to address the risk: In section 4.2 of the SmPC, HCPs are advised to monitor patients daily for the first 14 days post-infusion for the signs of ICANS, with continued monitoring at the physician's discretion for at least 4 weeks after infusion. Patients should be instructed to remain within close proximity of the qualified treatment centre (within 2 hours of travel) for at least 4 weeks following the first infusion to be examined for signs and symptoms of ICANS and other toxicities. Section 4.4 allows for delay of second dose to reduce risk of worsening ICANS or discontinue treatment for

	Grade ≥ 2 ICANS. Section 4.4 provides guidelines to grade and manage ICANS. Other routine risk minimisation measures beyond the product information: Use restricted to physicians experienced in the treatment of haematological malignancies. Subject to restricted medical prescription.
Prolonged Cytopenia	Routine risk communication: • SmPC sections 4.4 and 4.8 • PL sections 2, 4 Routine risk minimisation activities recommending specific clinical measures to address the risk: Recommendations for monitoring of patients' blood count after AUCATZYL infusion are included in SmPC section 4.4 Other routine risk minimisation measures beyond the product information: Use restricted to physicians experienced in the treatment of haematological malignancies Subject to restricted medical prescription
Hypogammaglobulinaemia	Routine risk communication: • SmPC section 4.4 • PL section 4 Routine risk minimisation activities recommending specific clinical measures to address the risk: Recommendations for monitoring immunoglobulin levels and management using infection precautions, antibiotic prophylaxis and immunoglobulin replacement are included in SmPC section 4.4. Other routine risk minimisation measures beyond the product information: Use restricted to physicians experienced in the treatment of haematological malignancies Subject to restricted medical prescription.
Severe Infections	Routine risk communication: • SmPC sections 4.2, 4.4 and 4.8 • PL sections 2, 4 Routine risk minimisation activities recommending specific clinical measures to address the risk: Recommendation for monitoring the signs and symptoms of infection before, during and after AUCATZYL infusion are included in SmPC section 4.4. Prophylactic antimicrobials should be administered according to standard institutional guidelines. Treatment

	with AUCATZYL should be delayed in some patient groups at risk. Other routine risk minimisation measures beyond the product information: Use restricted to physicians experienced in the treatment of haematological malignancies Subject to restricted medical prescription.
Secondary malignancies of T cell origin	Routine risk communication: • SmPC sections 4.4 and 4.8 • PL sections 4 Routine risk minimisation activities recommending specific clinical measures to address the risk: Section 4.4 of SmPC instructs for patients to be monitored life-long for signs of secondary malignancy. Other routine risk minimisation measures beyond the product information: Use restricted to physicians experienced in the treatment of haematological malignancies Subject to restricted medical prescription.
Tumour Lysis Syndrome (TLS)	Routine risk communication: • SmPC section 4.4 Routine risk minimisation activities recommending specific clinical measures to address the risk: Section 4.4 of SmPC instructs for patients to be monitored for signs and symptoms of TLS after AUCATZYL infusion and events to be managed according to standard guidelines. To minimise the risk of TLS, patients with high tumour burden should receive TLS prophylaxis as per standard guidelines prior to Aucatzyl infusion Other routine risk minimisation measures beyond the product information: Use restricted to physicians experienced in the treatment of haematological malignancies Subject to restricted medical prescription.
Antigenicity and Immunogenicity	Routine risk communication: • SmPC section 4.8. Routine risk minimisation activities recommending specific clinical measures to address the risk: None Other routine risk minimisation measures beyond the product information:

	Use restricted to physicians experienced in the treatment of haematological malignancies Subject to restricted medical prescription.
Secondary Haematologic Malignancies (except of T cell origin)	Routine risk communication: • SmPC section 4.4 Routine risk minimisation activities recommending specific clinical measures to address the risk: Recommendation for life-long monitoring for secondary malignancies is included in SmPC section 4.4 Other routine risk minimisation measures beyond the product information: Use restricted to physicians experienced in the treatment of haematological malignancies Subject to restricted medical prescription
Overdose/Medication error	Routine risk communication: • SmPC sections 4.4, 4.8 and 4.9 Routine risk minimisation activities recommending specific clinical measures to address the risk: The recommendation that any adverse reactions related to a suspected overdose are to be treated in accordance with the guidance in section 4.4, is provided in section 4.9. Details on Release for Infusion Certificate and the Dose Schedule Planner where 2 signatures are used to verify accuracy of the infused volume are described in SmPC section 4.2. Other routine risk minimisation measures beyond the product information: Use restricted to physicians experienced in the treatment of haematological malignancies Subject to restricted medical prescription
Aggravation of GvHD	Routine risk communication: • SmPC sections 4.4, 4.8. Routine risk minimisation activities recommending specific clinical measures to address the risk: Recommendation to delay of infusion if a patient has an active GvHD or within 3 months after allogeneic HSCT is included in SmPC section 4.4 Other routine risk minimisation measures beyond the product information: Use restricted to physicians experienced in the treatment of haematological malignancies

	Subject to restricted medical prescription
Use during pregnancy and breastfeeding	Routine risk communication: • SmPC section 4.6 • PL section 2 Routine risk minimisation activities recommending specific clinical measures to address the risk: Information on the need for effective contraception in patients of childbearing age is provided in section 4.6 Other routine risk minimisation measures beyond the product information: Use restricted to physicians experienced in the treatment of haematological malignancies Subject to restricted medical prescription.
Long-Term Safety	Routine risk communication: • SmPC section 4.4 • PL section 2 Routine risk minimisation activities recommending specific clinical measures to address the risk: None Other routine risk minimisation measures beyond the product information: Use restricted to physicians experienced in the treatment of haematological malignancies Subject to restricted medical prescription.
New occurrence or exacerbation of an autoimmune disorder	Routine risk communication: None Routine risk minimisation activities recommending specific clinical measures to address the risk: None Other routine risk minimisation measures beyond the product information: Use restricted to physicians experienced in the treatment of haematological malignancies Subject to restricted medical prescription.

V.2. Additional Risk Minimisation Measures

Additional risk minimisation Measure 1: Risk minimisation control programme

AUCATZYL will only be available at treatment centres that are accredited under FACT-JACIE International Standards for Hematopoietic Cellular Therapy Product Collection, Processing, and

Administration (FACT standards: https://www.factglobal.org/standards/), or, where applicable, Local Government Accreditations. Therefore, use of AUCTAZYL will be restricted to physicians experienced in the treatment of haematological malignancies.

The above-mentioned FACT-JACIE standard sets rigid global safety and quality standard and mandate adherence to guidelines and standards related to treatment administration, patient selection, laboratory procedures, and adverse events management, emphasising quality management systems, the standard includes processes for evaluating and improving patient care, maintaining proper documentation, and ensuring regulatory compliance.

The FACT-JACIE standard serves as the guideline for programmes, facilities, and individuals involved in cellular therapy. The main objective is to promote the required high quality medical and laboratory practices in hematopoietic progenitor cell transplantation and related therapies using hematopoietic-derived cellular products.

The standard's scope applies to all phases of cell collection, processing, storage, transportation, thawing and administration, and clinical application, including standard of care therapies and products and regulatory-approved clinical trials.

Objectives:

To implement and maintain a comprehensive risk minimisation control programme that aligns with FACT-JACIE standard, ensuring adherence to globally recognised safety and quality guidelines pertaining to Hematopoietic Cellular Therapy Product Collection, Processing, and Administration and ensure patient safety.

Rationale for the additional risk minimisation activity:

Only facilities conforming to FACT-JACIE standard will handle the treatment with AUCATZYL. One of the criteria of accreditation is the procedures in place to ensure availability of tocilizumab or alternative treatment prior to infusion and distribution of Patient Cards.

The standards ensure that important identified and potential risks, specifically those related to Cytokine Release Syndrome and ICANS, associated with CAR T therapies are adequately addressed and managed.

Target audience and planned distribution path:

A rigorous two-phase onboarding process was developed for treatment centres. The first phase, qualification, involves an evaluation of a centre's technical and quality credentials, as per FACT-JACIE requirements, after which they receive an approval status. This phase also focuses on training in AUCATZYL receipt, handling and reporting, alongside a tracking system for leukapheresis material and AUCATZYL through a hybrid of electronic and paper-based methods. Following qualification, the site onboarding second phase begins. Here, the facilities' systems are assessed for post-infusion patient treatment management. During onboarding, relevant personnel at centres review AUCATZYL Information Material and AE Management Guide that are part of Healthcare professionals' guide and execute a Quality Technical Agreement (QTA) that mandates ongoing notifications of any changes in their FACT-JACIE programme, accreditation status or leadership.

Plans to evaluate effectiveness of the interventions and criteria for success:

There is a rigorous assessment process for the risk minimisation control programme of AUCATZYL, ensuring it reaches only FACT-JACIE accredited centres. Access to the AUCATZYL ordering system is exclusive to qualified and activated centres.

Regular assessment conducted on risk-based approach, but not less frequent than once in 2 years, guarantee the centres maintain their FACT-JACIE accreditation, especially those categorised as high-risk. The list of ordered products will also be reconciled with a list of authorised prescribers who have been trained on the Risk minimisation control programme.

Additional Risk Minimisation Measure 2: Educational/Safety advice tools

2.1. Healthcare professionals' guides

Healthcare professionals' guide is applied through HCP educational material which consists of AUCATZYL Information Material, AE Management Guide and Read & Understood Checklist.

Objective:

The objective of AE Management Guide is to inform HCPs on how to monitor and manage symptoms associated with CRS (including HLH/MAS) and ICANS and provide guidance on reporting these serious adverse reactions associated with AUCATZYL.

The objective of AUCATZYL Information Material is to provide information on onboarding process under Risk minimisation control programme for AUCATZYL and inform on the following risks: risk of CRS (including HLH/MAS) and ICANS, overdose and medication errors, risk of secondary malignancy including of T cell origin. In addition, the material contains information about the safety and efficacy long-term follow-up studies and the importance of contributing to such studies.

Read & Understood checklist is designed to confirm that an HCP has read and understood HCP educational material.

Rationale for the additional risk minimisation activity:

The HCP educational material is provided as part of the treatment centre qualification process. The HCP educational material will highlight the risks of AUCATZYL and will help to ensure that the HCPs using AUCATZYL are made aware of the risks and will be able to monitor for them. The HCP educational materials will also remind HCPs to ensure that they have access to 2 doses of tocilizumab or suitable alternative measures in case tocilizumab is not available to treat CRS and ICANS.

Target audience and planned distribution path:

The HCP education tool which consists of AUCATZYL Information Material and AE Management Guide, target HCPs in the treatment centres that passed the first step of onboarding process as per the Risk Minimisation control tool and are qualified for the second step of onboarding process.

Plans to evaluate effectiveness of the interventions and criteria for success:

As only FACT-JACIE accredited centres will qualify into the onboarding, it is expected that the HCPs in these treatment centres are already trained on handling CRS (including HLH/MAS) and ICANS. Therefore, the Read & Understood statement will be signed by the HCPs upon review of HCP educational materials.

Assessment of the effectiveness of HCP educational materials will be done during regular assessments conducted at least every 2 years as per V.2 Risk Minimisation Measure 1.

2.2. Patient Card

Patient Card is provided to all patients receiving AUCATZYL therapy. This card contains crucial information about the patient, their treatment and emergency contact details. It is a portable, readily available source of information that can be shared with healthcare providers if required, especially in urgent situations. In addition, this card lists the symptoms associated with CRS (including HLH/MAS) and ICANS, that the patient should be aware of and with advice to head to the treatment centre should they experience any such symptoms.

Objectives:

The objective of the card is to enhance patient safety by providing critical information about their treatment, potential side effects, and contact details, which could be provided to an HCP in case of an emergency.

Rationale for the additional risk minimisation activity:

A Patient Card serves as a safety net, ensuring that both patients and healthcare providers have immediate access to vital information, promoting optimal care and rapid response in emergency situations.

Target audience and planned distribution path:

FACT-JACIE standard requires treatment centres to supply every patient with Patient Card. The card is distributed after the first AUCATZYL infusion.

Plans to evaluate effectiveness of the interventions and criteria for success:

Assessment of the effectiveness of Patient Card will be done during regular assessments conducted at least every 2 years as per V.5 Risk Minimisation Measure 1.

V.3. Summary of Risk Minimisation Measures

Table V.3: Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Cytokine Release Syndrome including HLH/MAS	Routine risk minimisation measures: SmPC sections 4.2, 4.4, 4.8 and corresponding PL sections 2, 4 Additional risk minimisation measures: 1. Risk minimisation control programme 2. Educational/Safety advice tools (Healthcare professionals' guide and Patient Card)	Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection: None Additional pharmacovigilance activities: 1. AUTO1-LT2 long-term study for post-approval patients. 2. AUTO-LT1 long-term follow-up study for clinical trial patients.
Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS)	Routine risk minimisation measures: SmPC sections 4.2, 4.4, 4.8 and corresponding PL sections 2, 4 Additional risk minimisation measures: 1. Risk minimisation control programme	Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection: None Additional pharmacovigilance activities: 1. AUTO1-LT2 long-term study for post-approval patients. 2. AUTO-LT1 long-term follow-up study for clinical trial patients.

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	2. Educational/Safety advice tools (Healthcare professionals' guide and Patient Card)	
Prolonged Cytopenia	Routine risk minimisation measures: SmPC sections 4.4, 4.8 and corresponding PL sections 2, 4. Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection: None Additional pharmacovigilance activities: 1. AUTO1-LT2 long-term study for post-approval patients. 2. AUTO-LT1 long-term follow-up study for clinical trial patients.
Hypogammaglobulinaemia	Routine risk minimisation measures: SmPC sections 4.4 and 4.8 and corresponding PL section 4 Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection: None Additional pharmacovigilance activities: 1. AUTO1-LT2 long-term study for post-approval patients. 2. AUTO-LT1 long-term follow-up study for clinical trial patients.
Severe Infections	Routine risk minimisation measures: SmPC sections 4.2, 4.4, 4.8 and corresponding PL sections 2, 4 Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection: None Additional pharmacovigilance activities: 1. AUTO1-LT2 long-term study for post-approval patients. 2. AUTO-LT1 long-term follow-up study for clinical trial patients.
Secondary malignancies of T cell origin	Routine risk minimisation measures: SmPC sections 4.4, 4.8 and corresponding PL section 4	Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection: 1.Follow-up questionnaire on Secondary malignancies of T

Safety concern	Risk minimisation measures	Pharmacovigilance activities
		cell origin and secondary haematologic malignancies (except of T cell origin) Additional pharmacovigilance activities: 1. AUTO1-LT2 long-term study for post-approval patients. 2. AUTO-LT1 long-term follow-up study for clinical trial patients. 4. T cell malignancy PV activity
Tumour Lysis Syndrome	Routine risk minimisation measures: SmPC section 4.4 Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection: None Additional pharmacovigilance activities: 1. AUTO1-LT2 long--term study for post-approval patients. 2. AUTO-LT1 long-term follow-up study for clinical trial patients.
Antigenicity and Immunogenicity	Routine risk minimisation measures: SmPC section 4.8. Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reaction reporting andsignal detection: None Additional pharmacovigilance activities: 1. AUTO1-LT2 study for post-approval patients. 2. AUTO-LT1 long-term follow-up study for clinical trial patients.
Secondary Haematologic Malignancies (except of T cell origin)	Routine risk minimisation measures: SmPC section 4.4 Additional risk minimisation measures: 1. Educational/Safety advice tools (Healthcare professionals' guide)	Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection: None Additional pharmacovigilance activities: 1. AUTO1-LT2 long-term study for post-approval patients. 2. AUTO-LT1 long-term follow-up study for clinical trial patients.

Safety concern	Risk minimisation measures	Pharmacovigilance activities
		4. T cell malignancy study
Overdose/Medication error	Routine risk minimisation measures: SmPC sections 4.4, 4.8 and 4.9 Additional risk minimisation measures: 1. Educational/Safety advice tools (Healthcare professionals' guide)	Routine pharmacovigilance activities beyond adverse reaction reporting andsignal detection: None Additional pharmacovigilance activities: 1. AUTO1-LT2 long-term study for post-approval patients.
Aggravation of GvHD	Routine risk minimisation measures: SmPC section 4.4, 4.8. Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection: None Additional pharmacovigilance activities: 1. AUTO1-LT2 long-term study for post-approval patients. 2. AUTO-LT1 Long-term follow-up study for clinical trial patients.
Use during pregnancy and breastfeeding	Routine risk minimisation measures: SmPC section 4.6 and corresponding PL section 2 Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection: None Additional pharmacovigilance activities: 1. AUTO1-LT2 long-term study for post-approval patients will only collect data on pregnancy. 2. AUTO-LT1 long-term follow-up study for clinical trial patients.
Long-term safety	Routine risk minimisation measures: SmPC section 4.4 and corresponding PL section 2	Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection: None

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	Additional risk minimisation measures: None	Additional pharmacovigilance activities: 1. AUTO1-LT2 long-term study for post-approval patients. 2. AUTO-LT1 long-term follow-up study for clinical trial patients.
New occurrence or exacerbation of an autoimmune disorder	Routine risk minimisation measures: None Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection: None Additional pharmacovigilance activities: 1. AUTO1-LT2 long-term study for post-approval patients. 2. AUTO-LT1 long-term follow-up study for clinical trial patients.

Part VI: Summary of the Risk Management Plan

This is a summary of the risk management plan (RMP) for AUCATZYL. The RMP details important risks of AUCATZYL, how these risks can be minimised, and how more information will be obtained about AUCATZYL risks and uncertainties (missing information).

AUCATZYL`s summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how AUCATZYL should be used.

This summary of the RMP for AUCATZYL should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of AUCATZYL`s RMP.

I. The medicine and what it is used for

AUCATZYL is authorised for the treatment of adult patients 26 years of age and above with relapsed or refractory (r/r) B cell precursor acute lymphoblastic leukaemia (B ALL) (see SmPC for the full indication). It contains obecabtagene autoleucel (obe-cel) as the active substance, and it is given as a two-dose infusion product for autologous and intravenous use only.

Further information about the evaluation of AUCATZYL`s benefits can be found in AUCATZYL`s EPAR, including in its plain-language summary, available on the EMA website,

http://www.ema.europa.eu.

II. Risks associated with the medicine and activities to minimise or further characterise the risks.

Important risks of AUCATZYL, together with measures to minimise such risks and the proposed studies for learning more about AUCATZYL`s risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine’s packaging;
- The authorised pack size - the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine’s legal status - the way a medicine is supplied to the patient (e.g. with or without prescription) can help to minimise its risks.

Together, these measures constitute routine risk minimisation measures.

In the case of AUCATZYL, these measures are supplemented with additional risk minimisation measures mentioned under relevant important risks, below.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including PSUR assessment, so that immediate action can be taken as necessary. These measures constitute routine pharmacovigilance activities.

If important information that may affect the safe use of AUCATZYL is not yet available, it is listed under ‘missing information’ below.

II.A List of important risks and missing information

Important risks of AUCATZYL are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of AUCATZYL. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g. on the long-term use of the medicine).

Table II.A: List of important risks and missing information

Important identified risks	Cytokine release syndrome (including HLH/MAS) Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS) Prolonged Cytopenias Hypogammaglobulinaemia Severe Infections Secondary malignancies of T cell origin Aggravation of Graft versus Host Disease (GvHD)
Important potential risks	Tumour Lysis Syndrome (TLS) Antigenicity and Immunogenicity Secondary Haematologic Malignancies (except of T cell origin) Overdose/Medication error
Missing information	Use during pregnancy & breastfeeding Long-term safety New occurrence or exacerbation of an autoimmune disorder

II.B Summary of Important Risks

Table II.B: Summary of important risks and missing information

Important identified risk:	**Cytokine Release Syndrome (CRS) including Haemophagocytic Lymphohistiocytosis (HLH)/ Macrophage Activation Syndrome (MAS)**
Evidence for linking the risk to the medicine	Cytokine release syndrome (CRS) is a recognised toxicity associated with CAR T cell therapies, presenting with symptoms such as culture-negative fever, myalgia, nausea/vomiting, tachycardia, hypoxia, hypotension, headache, confusion, tremor, and delirium. Severe complications of CRS can include cardiac dysfunction, acute respiratory distress syndrome, renal and/or hepatic failure, and disseminated intravascular coagulation (Brudno and Kochenderfer, 2016). CRS including HLH/MAS was reported in AUTO1-AL1 (FELIX) clinical study.
Risk factors and risk groups	Risk factors of CRS include tumour burden, intensity of lymphodepletion chemotherapy, CAR T cell dose, and thrombocytopenia (Siddiqi et al, 2017; Hay et al, 2017; Santomasso et al, 2018; Lee et al, 2015; Jia et al, 2019). The evaluation of the impact of disease burden at time of lymphodepletion on CRS highlighted its importance since

Important identified risk:	**Cytokine Release Syndrome (CRS) including Haemophagocytic Lymphohistiocytosis (HLH)/ Macrophage Activation Syndrome (MAS)**
	the rate of CRS of any grade increased as the blasts in BM increased. In the AUTO1-AL1 (FELIX) study, across the 4 blast subgroups of < 5%, ≥ 5% to ≤ 20%, > 20% to ≤ 75%, > 75% the percentage of subjects with CRS of any grade was 47.2%, 62.5%, 71.4% and 87.5%, respectively. This reinforced the importance of the split dose regimen with a lower first dose administered when blasts in BM are > 20% at lymphodepletion which is also associated with enhanced CAR T cell expansion post-infusion. Subgroup analysis did not highlight any findings that would be unexpected and the key impact on safety appeared to be the disease burden in terms of blasts in BM at lymphodepletion.
Risk minimisation measures	Routine risk minimisation measures: SmPC sections 4.2, 4.4, 4.8 and corresponding PL sections 2, 4. Additional risk minimisation measures: risk minimisation control programme, Educational/Safety advice tools (Healthcare professionals' guide and Patient Card).
Additional pharmacovigilance activities	Additional pharmacovigilance activities: 1. AUTO1-LT2 long-term study for post-approval patients. 2. AUTO-LT1 long-term follow-up study for clinical trial patients.

Important identified risk:	**Immune effector cell-associated neurotoxicity syndrome (ICANS)**
Evidence for linking the risk to the medicine	ICANS were reported in AUTO1-AL1 (FELIX) clinical trial and in patients treated with other CAR T therapies.
Risk groups or risk factors	Although no correlation has been observed between ICANS and CRS/MAS (Santomasso et al, 2018), ICANS appear to occur more frequently in the presence of severe CRS. Patients with a high disease burden, prior to treatment, higher peak CAR T expansion and early and higher elevations of serum cytokines may have a higher risk of neurotoxicity (Santomasso et al, 2018). Of note, patients can develop ICANS even after treatment of anti-IL-6 therapy, after the resolution of CRS. In the AUTO1-AL1 (FELIX) study, the evaluation of the impact of disease burden at time of lymphodepletion also emphasised its importance for the risk of ICANS and showed an even more important impact of the fractionated split dosing regimen. The rate of ICANS of any grade increased across the 2 subgroups within each dosing bracket (8.3% and 25.0% in the < 5% and ≥ 5% to ≤ 20% categories; 14.3% and 42.5% in the 20% to ≤ 75%, > 75%

Important identified risk:	**Immune effector cell-associated neurotoxicity syndrome (ICANS)**
	categories), whereas it can be seen that it decreased when moving across the dosing thresholds of ≤ 20% and > 20%. As described already for CRS, the relatively low rate of ICANS following AUCATZYL treatment is consistent with expectations based on the properties of AUCATZYL and the dosing regimen and makes this potential immunotoxicity consequence of therapy a much more manageable risk. A subgroup analysis did not highlight any findings that would be unexpected and the key impact on safety appeared to be the disease burden in terms of blasts in BM at lymphodepletion. Neurotoxicity may also be caused by fludarabine, but usually at higher doses than those being administered as part of lymphodepletion (Helton et al, 2013). Symptoms of fludarabine including objective weakness, agitation, confusion, seizures, visual disturbances, optic neuritis, optic neuropathy, blindness, and coma have been reported in CLL patients treated with multiple cycles of fludarabine (Fludarabine SmPC, 2019).
Risk minimisation measures	Routine risk minimisation measures: SmPC sections 4.2, 4.4, 4.8 and corresponding PL sections 2, 4. Additional risk minimisation measures: Risk minimisation control programme, Educational/Safety advise tools programme (Healthcare professionals' guide and Patient Card).
Additional pharmacovigilance activities	Additional pharmacovigilance activities: 1. AUTO1-LT2 long-term study for post-approval patients. 2. AUTO-LT1 long-term follow-up study for clinical trial patients.

Important identified risk	**Prolonged Cytopenia**
Evidence for linking the risk to the medicine	Cytopenias were reported in AUTO1-AL1 (FELIX) clinical trial and in patients treated with other CAR T therapies.
Risk factors and risk groups	There are several factors that can be involved in CAR T cell-associated cytopenia including higher age, poor bone-marrow reserve, tumour burden, severity of hyperinflammation (cytokine release syndrome, neurotoxicity) and prevalence of clonal haematopoiesis of indeterminate potential (Sharma 2022).
Risk minimisation measures	Routine risk minimisation measures: SmPC sections 4.4, 4.8 and corresponding PL sections 2, 4. Additional risk minimisation measures: None
Additional pharmacovigilance activities	Additional pharmacovigilance activities:

Important identified risk	**Prolonged Cytopenia**
	1. AUTO1-LT2 long-term study for post-approval patients. 2. AUTO-LT1 long-term follow-up study for clinical trial patients.

Important identified risk	**Hypogammaglobulinaemia**
Evidence for linking the risk to the medicine	Hypogammaglobulinaemia is caused by B cell aplasia. It was reported in AUTO1-AL1 (FELIX) clinical trial and in patients treated with other CAR T therapies.
Risk factors and risk groups	Individuals who have had prior treatment with rituximab and other drugs that can promote lymphopenia, are at an elevated risk when subsequently undergoing CAR T cell therapy.
Risk minimisation measures	Routine risk minimisation measures: SmPC sections 4.4 and 4.8 and corresponding PL sections 4. Additional risk minimisation measures: None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: 1. AUTO1-LT2 long-term study for post-approval patients. 2. AUTO-LT1 long-term follow-up study for clinical trial patients.

Important identified risk:	**Severe Infections**
Evidence for linking the risk to the medicine	Infections were reported in AUTO1-AL1 (FELIX) clinical trial and in patients treated with other CAR T therapies.
Risk factors and risk groups	There are multiple potential contributing factors, including prior disease state and prior treatment, the lymphodepletion chemotherapy prior to CAR T therapy and any CAR T associated cytopenia, B cell aplasia, or hypogammaglobulinaemia. In addition, patients who experience CRS can also be at risk of infections (Hill et al, 2018).
Risk minimisation measures	Routine risk minimisation measures: SmPC sections 4.2, 4.4, 4.8 and corresponding PL sections 2, 4. Additional risk minimisation measures: None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: 1. AUTO1-LT2 long-term study for post-approval patients. 2. AUTO-LT1 long-term follow-up study for clinical trial patients.

Important identified risk:	**Secondary malignancy of T cell origin**
Evidence for linking the risk to the medicine	The risk of secondary malignancies of T cell origin as a class risk has been highlighted through clinical experience with CAR T cell therapies.
Risk factors and risk groups	Secondary malignancy is consistent with the known outcomes of immunosuppression and/or genotoxicity resulting from chemotherapy. Patient factors: Age Additive or synergistic factors: Chemotherapy and immunosuppressive treatments
Risk minimisation measures	Routine risk minimisation measures: SmPC sections 4.4, 4.8 and corresponding PL section 4. Additional risk minimisation measure: Educational/Safety advice tools (Healthcare professionals' guide).
Additional pharmacovigilance activities	Additional pharmacovigilance activities: 1. AUTO1-LT2 long-term study for post-approval patients. 2. AUTO-LT1 long-term follow-up study for clinical trial patients. 4. T cell malignancy PV activity

Important identified risk:	**Aggravation of GvHD**
Evidence for linking the risk to the medicine	There were cases of GvHD aggravation reported during AUTO1-AL1 (FELIX) clinical study.
Risk factors and risk groups	Patients with active GvHD from prior HSCT.
Risk minimisation measures	Routine risk minimisation measures: SmPC section 4.4 Additional risk minimisation measures: None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: 1. AUTO1-LT2 long-term study for post-approval patients. 2. AUTO-LT1 long-term follow-up study for clinical trial patients.

Important potential risk:	**Tumour Lysis Syndrome (TLS)**
Evidence for linking the risk to the medicine	TLS was reported in AUTO1-AL1 (FELIX) clinical study and in patients treated with other CAR T therapies.
Risk factors and risk groups	Patients with a high disease burden
Risk minimisation measures	Routine risk minimisation measures: SmPC section 4.4 Additional risk minimisation measures: None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: 1. AUTO1-LT2 long-term study for post-approval patients. 2. AUTO-LT1 long-term follow-up study for clinical trial patients.

Important potential risk:	**Tumour Lysis Syndrome (TLS)**

Important potential risk	**Antigenicity and Immunogenicity**
Evidence for linking the risk to the medicine	Two cases of immunogenicity related to AUCATZYL were observed in AUTO1-AL1 (FELIX) clinical study
Risk factors and risk groups	Unknown
Risk minimisation measures	Routine risk minimisation measures: SmPC Section 4.8 Additional risk minimisation measures: None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: 1. AUTO1-LT2 long-term study for post-approval patients. 2. AUTO-LT1 long-term follow-up study for clinical trial patients.

Important potential risk:	**Secondary Haematologic Malignancies (except of T cell origin)**
Evidence for linking the risk to the medicine	The risk of secondary malignancies of T cell origin as a class risk has been highlighted through clinical experience with CAR T cell therapies.
Risk factors and risk groups	Secondary malignancy is consistent with the known outcomes of immunosuppression and/or genotoxicity resulting from chemotherapy. Patient factors: Age Additive or synergistic factors: Chemotherapy and immunosuppressive treatments
Risk minimisation measures	Routine risk minimisation measures: SmPC section 4.4 Additional risk minimisation measures: Educational/Safety advice tools (Healthcare professionals' guide)
Additional pharmacovigilance activities	Additional pharmacovigilance activities: 1. AUTO1-LT2 long-term study for post-approval patients. 2. AUTO-LT1 long-term follow-up study for clinical trial patients. 4. T cell malignancy study

Important potential risk:	**Overdose/Medication error**
Evidence for linking the risk to the medicine	There were four observations of overdose cases during administration of the first dose of AUCATZYL during AUTO1-AL1 (FELIX) study.
Risk factors and risk groups	Unknown

Risk minimisation measures	Routine risk minimisation measures: SmPC sections 4.4, 4.8 and 4.9. Additional risk minimisation measures: Educational/Safety advice tools (Healthcare professionals' guide).
Additional pharmacovigilance activities	Additional pharmacovigilance activities: 1. AUTO1-LT2 long-term study for post-approval patients.

Missing Information:	**Use during pregnancy and breastfeeding**
Risk minimisation measures	Routine risk minimisation measures: SmPC section 4.6 and corresponding PL section 2 Additional risk minimisation measures: None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: 1. AUTO1-LT2 long-term study for post-approval patients will collect data on pregnancy only. 2. AUTO-LT1 long-term follow-up study for clinical trial patients

Missing information:	**Long-term Safety**
Risk minimisation measures	Routine risk minimisation measures: SmPC section 4.4 and corresponding PL section 2 Additional risk minimisation measures: None
Additional pharmacovigilance activities	Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection: None Additional pharmacovigilance activities: 1. AUTO1-LT2 long-term study for post-approval patients. 2. AUTO-LT1 long-term follow-up study for clinical trial patients.

Missing Information:	**New occurrence or exacerbation of an autoimmune disorder**
Risk minimisation measures	Routine risk minimisation measures: None Additional risk minimisation measures: None
Additional pharmacovigilance activities	1. AUTO1-LT2 long-term study for post-approval patients. 2. AUTO-LT1 long-term follow-up study for clinical trial patients.

II.C Post-authorisation development plan

Table II.C.1: Studies which are conditions of the marketing authorisation

Short study name	Purpose of the study
AUTO1 in relapsed or refractory B-ALL AUTO1-AL1	AUTO1-AL1 is an ongoing Open-Label, Multi-Centre, Phase Ib/II Study Evaluating the Safety And Efficacy Of AUTO1, A CAR T Cell Treatment Targeting CD19, in Adult Patients With Relapsed Or Refractory B Cell Acute Lymphoblastic Leukaemia Thisincludes monitoring patients for 60 months after AUCATZYL administration.
AUTO-LT1	Prospective study to assess long-term safety and efficacy of adult patients with relapsed or refractory B cell acute lymphoblastic leukaemia receiving Aucatzyl treatment (AUTO1-LT2), based on data from a registry, according to an agreed protocol.
AUTO1-LT2	A prospective, non-interventional study investigating efficacy and safety based on data from the same registry used to characterize the long-term safety and efficacy of Aucatzyl.with interim results to be provided as a specific obligation.

Table II.C.2: Other studies in post-authorisation development plan

Short study name	Purpose of the PV activity
T cell malignancy PV activity	This PV activity aims to enable appropriate identification of any new T cell and haematologic malignancy requiring pathology work-up, appropriate sample collection and appropriate testing (VCN, RCL and/or insertional mutagenesis) for patients who received at least 1 dose of obe-cel, commercially, and developed a new malignancy.

Part VII: Annexes

Annex 1: EudraVigilance interface

Annex 2: Tabulated summary of planned, ongoing and completed pharmacovigilance studies

Annex 3: Protocols for proposed, ongoing, and completed pharmacovigilance study programmes

Annex 4: Specific adverse drug reaction follow-up form

Annex 5: Protocols for proposed and ongoing studies in RMP part IV

Annex 6: Details of proposed additional risk minimisation activities

Annex 7: Other supporting data (references)

Annex 8: Summary of changes to the risk management plan over time

Annex 4: Specific adverse drug reaction follow-up form

Follow-up questionnaire

FUQ Secondary Malignancies

AUCATZYL

EVENT FOLLOW-UP QUESTIONNAIRE – Secondary malignancy of T cell origin and Secondary haematologic malignancies (except of T cell origin) Version XX (XX/YY/202Z)

Background information					
Age (years): Initials:	Gender ☐ M ☐ F		Weight, kg Height, cm	Study ID (if applicable)	
Event term(s)			Event onset date: DD/MM/YYYY		
Obe-cel dose(s)	Date(s) of the dose(s) DD/MM/YYYY			Indication	
Event Information					
New Malignancy					
Location					
Staging					
Event(s) that led to the secondary malignancy diagnosis					
Start Date DD/MM/YYYY			Stop Date DD/MM/YYYY		
CTCAE Grade[a]	☐ Grade 1 Mild	☐ Grade 2 – Moderate	☐ Grade 3 – Severe	☐ Grade 4 – Life-threatening	☐ Grade 5 - Fatal
Seriousness Criteria[b]	☐ Death ☐ Life-threatening ☐ Hospitalisation/prolonged hospitalisation ☐ Significant disability ☐ Medically significant ☐ Not Applicable				
Outcome	☐ Resolved ☐ Resolving ☐ Not resolved			☐ Resolved with sequelae ☐ Death ☐ Unknown	

If the event resulted in death	Date of death: DD/MM/YYYY	Cause:	Was autopsy performed? ☐No ☐Yes (provide report if available)
If the event resulted in hospitalisation		Admission date: DD/MM/YYYY	Discharge date: DD/MM/YYYY

[a]-NCI CTCAE (Common Terminology Criteria for Adverse Events) v.5.0. [b]- NCI Instructions for the serious adverse events report form

Pre-existing factors that may have contributed to the development of a new malignancy	
In your opinion, what is the causal relationship between the new malignancy and the obe-cel therapy?	☐ Related ☐ Not Related
If NOT RELATED, what was the cause of the new malignancy?	
If RELATED, were alternate causes for the new malignancy ruled out?	☐ Yes ☐ No
If yes, please describe who and how these alternate causes were ruled out including diagnostic tests done with results:	

Additional Event Information				
Treatment for the New malignancy:				
Surgery	☐ Yes ☐ No	Surgery name	Date of Surgery DD/MM/YYYY	
Radiotherapy	☐ Yes ☐ No	Type of Radiotherapy / Dose	Start date DD/MM/YYYY	Stop Date DD/MM/YYYY
Cell Therapy	☐ Yes ☐ No	Type of cell therapy	Start date DD/MM/YYYY	
Chemotherapy	☐ Yes ☐ No	If yes, provide the details of the chemotherapies used below, with start and end dates where available		
Drugs used		Start date DD/MM/YYYY	Stop Date DD/MM/YYYY	

Additional event Information - Diagnostic Results (except Pathology) *Enter N/A if not performed*		
Diagnostic Test Date DD/MM/YYYY	Diagnostic test name	Results

Additional event Information - Diagnostic Results (Pathology and sample collection)		
Was a full pathology review conducted to confirm that the malignancy is new, not pre-existing?	☐ Yes ☐ No	Comments:
Pathology (specify date, tissue type, including any additional analysis like molecular markers)		
Was a detailed pathology work-up conducted on new and archived tissue samples?	☐ New ☐ Archived	If Yes, specify sample type and date of review: Comments:
Were both lymph node and bone marrow samples collected for cases of T cell lymphoma with suspected bone marrow involvement?	☐ Yes ☐ No	If yes, specify the collection dates for both samples: Comments:
Was tumour cellularity assessed for the sample selected for testing of insertional mutagenesis?	☐ Yes ☐ No	If yes, what was the estimated percentage of tumour cells? _____%

Prior event- relevant medical history	
History of tobacco use? ☐ Tobacco Smoker ☐ Former smoker ☐ Never used	If Smoker or former smoker, please provide the pack-year (number of cigarette pack per day * per number of years of smoking) history if applicable.
History of environmental exposure (e.g., asbestos, radiation)? ☐Yes ☐ No	If yes, please describe.
History of hereditary cancer syndromes? ☐Yes ☐No	If yes, please describe.
Family history of cancer ☐Yes ☐No	If yes, please describe.

Cancer treatment received **prior to obe-cel therapy**	
☐ Yes	
☐ No medical history or unknown	If yes, please describe below

Please include below the dates of diagnosis and stage of disease, start and stop dates and specific agents of all cytotoxic chemotherapy/targeted therapy regimens as well as therapeutic radiation exposure, prior transplant and conditioning regimens.

Diagnosis and stage:	Treatment regimen:	Start date of therapy: DD/MM/YYYY	End date of therapy: DD/MM/YYYY

Response:			
Diagnosis and stage:	Treatment regimen:	Start date of therapy: DD/MM/YYYY	End date of therapy: DD/MM/YYYY
Response:			
Diagnosis and stage:	Treatment regimen:	Start date of therapy: DD/MM/YYYY	End date of therapy: DD/MM/YYYY
Response:			
Diagnosis and stage:	Treatment regimen:	Start date of therapy: DD/MM/YYYY	End date of therapy: DD/MM/YYYY

Response:	

Cancer treatment received **after obe-cel therapy,** but prior to new cancer diagnosis			
Please include below the dates of diagnosis and stage of disease, start and stop dates and specific agents of all cytotoxic chemotherapy/targeted therapy regimens as well as therapeutic radiation exposure, transplant and conditioning regimen.			
Diagnosis and stage:	Treatment regimen:	Start date of therapy: DD/MM/YYYY	End date of therapy: DD/MM/YYYY
Response			
Diagnosis and stage:	Treatment regimen:	Start date of therapy: DD/MM/YYYY	End date of therapy: DD/MM/YYYY
Response			

Additional Medications (including concurrent medications). If the list is too long, please include a printout of the patient's medications.				
Drug Name	Indication	Dose and Frequency	Start Date DD/MM/YYYY	Stop Date DD/MM/YYYY

Please provide any additional supplemental information on a separate page.

In the event that a new malignancy occurs, contact Autolus **within 72 hours** on 00800 0825 0829 to obtain instructions on patient samples to collect for testing.

ADDITIONAL INFORMATION

Signature of person completing form: Click or tap here to enter text.	
Name of person completing the form (Print):	Date Completed: DD/MM/YYYY
Role of person completing form (e.g. Doctor, nurse, other):	
Email:	Phone:

Annex 6: Details of proposed additional risk minimisation activities

Draft key messages of the additional risk minimisation measures

Prior to the launch of AUCATZYL in each Member State the Marketing Authorisation Holder (MAH) must agree the content and format of the Risk minimisation control programme and Educational/Safety advice tools with the National Competent Authority.

Risk minimisation control programme is aimed at hospitals and their associated centres that dispense AUCATZYL to ensure:

- they undergo site qualification process
- immediate, on-site access to tocilizumab per patient prior to AUCATZYL infusion. In the exceptional case where tocilizumab is not available, the treatment centre must have access to suitable alternative measures instead of tocilizumab to treat CRS.

Educational/Safety advice tools

Healthcare professionals' guide The MAH shall ensure that in each Member State where AUCATZYL is marketed, all HCPs in the qualified treatment centres who are expected to use AUCATZYL are provided with the following educational material:

- HCP educational material
- Patient Card

HCP educational material:

- Monitor and manage CRS and neurological signs and symptoms
- Monitor and manage ICANS
- Ensure that serious adverse events suggestive of CRS or ICANS are adequately and appropriately reported
- Ensure that there is twenty-four-hour immediate access to tocilizumab, an interleukin-6 (IL-6) receptor inhibitor, prior to AUCATZYL infusion. In the exceptional case where tocilizumab is not available, the treatment centre must have access to suitable alternative measures instead of tocilizumab to treat CRS
- Provide information about the risk of secondary malignancy of T cell origin and secondary haematologic malignancies (except of T cell origin)
- Provide information about the safety and efficacy long-term follow-up studies and the importance of contributing to such studies

Patient Card:

- A warning message for healthcare professionals treating the patient at any time, including in conditions of emergency, that the patient is using AYCATZYL
- To inform and explain to patients:
  - the risks of CRS and ICANS, associated with AUCATZYL
  - the need to report the symptoms to their treating doctor immediately

- the need to remain in the proximity of the location (within 2 hours of travel) where AUCATZYL was received for at least 4 weeks following AUCATZYL infusion
- the need to carry the Patient Card at all times

– Contact details of the AUCATZYL prescriber

Annex 7: Other supporting data (including referenced material)

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