ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

Aucatzyl 410 × 10^6 cells dispersion for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

2.1 General description

Aucatzyl (obecabtagene autoleucel) is a genetically modified autologous cell-based product containing T cells transduced *ex vivo* using a lentiviral vector expressing an anti-CD19 chimeric antigen receptor (CAR), comprising a murine anti-CD19 single chain variable fragment linked to a 4-1BB co-stimulatory domain and a CD3-zeta signalling domain.

2.2 Qualitative and quantitative composition

Each patient-specific infusion bag of Aucatzyl contains obecabtagene autoleucel at a batch-dependent viable CAR T cell concentration. Aucatzyl contains autologous T cells genetically modified to express an anti-CD19 CAR-positive viable T cells. The medicinal product is packaged in 3 or more infusion bags overall containing a cell dispersion for infusion of a total recommended dose of 410 × 10^6 CAR-positive viable T cells suspended in a cryopreservative solution. The dose range is 308 to 513 × 10^6 CAR-positive viable T cells.

The total volume of the treatment is split in 3 or more bags of variable volume containing (10 + 100 + 300) × 10^6 CAR-positive viable T cells, according to the posology (see section 4.2).

The quantitative information of medicinal product, including the number of infusion bags (see section 6) to be administered, is presented in the Release for Infusion Certificate (RfIC) and located inside the lid of the cryoshipper used for transporting the medicinal product.

Excipients with known effect

This medicinal product contains 7.5% dimethyl sulfoxide (DMSO), up to 1 131 mg sodium and 39 mg potassium per total dose (see section 4.4).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Dispersion for infusion.

Colourless to pale yellow, very opalescent dispersion.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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).

4.2 Posology and method of administration

Aucatzyl must 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.

In the event of cytokine release syndrome (CRS), at least one dose of tocilizumab, and emergency equipment, must be available prior to infusion. The treatment centre must have access to additional doses of tocilizumab within 24 hours (see section 4.4). In the exceptional case where tocilizumab is not available (e.g., due to a shortage that is listed in the European Medicines Agency shortage catalogue), suitable alternative anti-interleukin (IL)-6 therapy (e.g., siltuximab) to treat CRS instead of tocilizumab must be available prior to infusion.

Posology

Aucatzyl is intended for autologous and intravenous use only (see section 4.4).

The target dose is 410×10^6 CD19 CAR-positive viable T cells (range: $308\text{-}513 \times 10^6$ CAR-positive viable T cells) supplied in 3 or more infusion bags.

The treatment regimen consists of a split dose 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 (Figure 1).

The RfIC and Dose Schedule Planner (Annex IIIA), located inside the lid of the cryoshipper, must be followed for the actual cell counts and volumes to be infused and to guide the appropriate dose regimen.

Bone marrow assessment

A BM assessment must be available from a biopsy and/or aspirate sample obtained within 7 days prior to the commencement of the lymphodepleting chemotherapy. The BM assessment will be used to determine the Aucatzyl dose regimen: High Tumour Burden Regimen if blast percentage is > 20% or Low Tumour Burden Regimen if blast percentage is ≤ 20% (see Figure 1).

If BM assessment results are inconclusive, the biopsy or aspirate must be repeated (but only once). A repeat biopsy or aspirate should only be taken prior to lymphodepleting chemotherapy.

If results remain inconclusive, the High Tumour Burden Regimen should be administered (i.e., administration of the 10×10^6 dose on day 1 per Figure 1).

Figure 1: Aucatzyl tumour burden adjusted split dose regimen

High tumour burden dose regimen
(Bone marrow blast > 20% or inconclusive)

Day 1		**Day 10 (± 2 days)**
10×10^6 dose administered via ***syringe***[*]	➡	**100×10^6 dose** administered via *bag infusion*[+] and **300×10^6 dose** administered via *bag infusion*[+]

Low tumour burden dose regimen
(Bone marrow blast ≤ 20%)

Day 1		**Day 10 (± 2 days)**
100 × 10^6 dose administered via *bag infusion*[+]		**10 × 10^6 dose** administered via ***syringe***[*] and **300 × 10^6 dose** administered via *bag infusion*[+]

[*]The exact volume to be administered via syringe is indicated in the RfIC. The 10 × 10^6 CD19 CAR-positive viable T cell bag configuration contains an overfill, and therefore it is important to withdraw only the volume specified.
[+]The 100 × 10^6 and 300 × 10^6 doses will be suspended in one or more infusion bags with no overfill.

Bridging therapy

Bridging therapy can be considered according to the prescriber's choice prior to infusion to reduce tumour burden or stabilise the disease (see section 5.1).

Pretreatment (lymphodepleting chemotherapy)

The lymphodepleting chemotherapy regimen must be administered before infusion of Aucatzyl: fludarabine (FLU) 30 mg/m^2/day intravenously and cyclophosphamide (CY) 500 mg/m^2/day intravenously on days -6 and -5, followed by fludarabine on days -4 and -3 (total dose: FLU 120 mg/m^2; CY 1 000 mg/m^2). For dose modifications of cyclophosphamide and fludarabine, see corresponding Summaries of Product Characteristics of cyclophosphamide and fludarabine.

Retreatment with lymphodepleting chemotherapy, in patients who could not receive the Aucatzyl dose on day 1 as planned, could be considered if there is an Aucatzyl dose delay of more than 10 days. Lymphodepleting chemotherapy should not be repeated after the first dose of Aucatzyl is administered.

Aucatzyl is infused 3 days (± 1 day) after completion of lymphodepleting chemotherapy (day 1), allowing a minimum 48-hour washout.

Treatment with Aucatzyl should be delayed in some patient groups at risk (see section 4.4). A delay to the second split dose may be required to manage toxicities.

Premedication

To minimise the risk of an infusion reaction, it is recommended that patients be premedicated with paracetamol (1 000 mg orally) and diphenhydramine 12.5 to 25 mg intravenously or orally (or equivalent medicinal products) approximately 30 minutes prior to Aucatzyl infusion.

Prophylactic use of systemic corticosteroids is not recommended .

Reasons to delay treatment

Delay Aucatzyl treatment if there are unresolved serious adverse reactions from preceding chemotherapies, if the patient is experiencing severe intercurrent infection, or has active graft-versus-host disease. If the patient requires supplementary oxygen, Aucatzyl should only be infused, if considered appropriate, based on the treating physician's benefit / risk assessment.

Reasons to delay the second split dose

Dose delays or discontinuation of treatment may be required after the first split dose to manage adverse reactions as described in Table 1.

Table 1: Dose delay or discontinuation - guidance intended to reduce the risk of adverse reactions

Adverse reaction	**Grade**[a]	**Actions**
		Second split dose Day 10 (± 2 days)
Cytokine release syndrome (CRS) following the first split dose	Grade 2	Consider postponing Aucatzyl infusion up to day 21 to allow for the CRS to resolve to grade 1 or less. If the CRS persist beyond day 21, do not administer the second dose.
	Grade ≥ 3	Discontinue treatment.
Immune effector cell-associated neurotoxicity syndrome (ICANS) following the first split dose (see section 4.4)	Grade 1	Consider postponing Aucatzyl infusion up to day 21 to allow for the ICANS to completely resolve. If the ICANS persist beyond day 21, do not administer the second dose.
	Grade ≥ 2	Discontinue treatment.
Pulmonary or cardiac toxicities following the first split dose [b, c]	Grade ≥ 3	Discontinue treatment.
Severe intercurrent infection at the time of Aucatzyl infusion (may affect first and second dose) (see section 4.4) [b]	Grade ≥ 3	Consider postponing Aucatzyl infusion up to day 21 until the severe intercurrent infection is considered controlled. If the severe intercurrent infection persists beyond day 21, do not administer the second dose.
Requirement for supplementary oxygen (may affect first and second dose) [b, c]	Grade ≥ 3	Consider postponing Aucatzyl treatment up to day 21 only if CRS has resolved to grade 1 or less and ICANS has completely resolved. If the adverse reaction persists beyond day 21, do not administer the second dose.
Other clinically relevant adverse reactions following the first split dose [b,]	Grade ≥ 3	Consider postponing Aucatzyl infusion up to day 21 only if CRS has resolved to grade 1 or less and ICANS has completely resolved. If the adverse reaction persists beyond day 21, do not administer the second dose.

[a] Based on the Common Terminology Criteria for Adverse Events (CTCAE) v5.0. Grade 1 is mild, grade 2 is moderate, grade 3 is severe, and grade 4 is life-threatening. Adapted from National Comprehensive Cancer Network v2.2024 Treatment Guidelines "Management of CAR T-Cell-Related Toxicities" and ASTCT/ASBMT Consensus.

[b] No dose postponement of second dose for grade 1 or grade 2 events.

[c] If O_2 saturation is less than 92% due to medical conditions.

Monitoring

Patients should be monitored daily for 14 days after the first infusion for signs and symptoms of potential CRS, immune effector cell-associated neurotoxicity syndrome (ICANS) and other toxicities (see section 4.4).

Frequency of monitoring after the first 14 days should be carried out at the physician's discretion and should be continued for at least 4 weeks after.

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.

Special populations

Elderly

No dose adjustment is required in patients over 65 years of age.

Paediatric population

The safety and efficacy of Aucatzyl in children and adolescents below 18 years of age have not yet been established. No data are available.

Method of administration

Aucatzyl is for autologous and intravenous use only.

The Administration instructions are to be strictly followed to minimise dosing errors.

- A leukodepleting filter must not be used. The product must not be irradiated.
- The Aucatzyl Dose Schedule Planner (completed with the patient's BM blast percentage and data from the RfIC) is provided with the RfIC and assists the determination of the appropriate dose regimen to be administered on day 1 and day 10 (± 2 days). The RfIC and Dose Schedule Planner are located inside the lid of the cryoshipper.
- The timing of Aucatzyl thaw, transfer and infusion time must be coordinated.
- It must be confirmed that the patient's identity matches with the patient identifiers on the infusion bag and the RfIC. Do not infuse if the information on the patient-specific label does not match.
- The total number of infusion bags to be administered must also be confirmed with the patient-specific information on the RfIC, see section 6.6.
- The volume to be administered for the 10×10^6 dose is specified on the RfIC. Use the smallest Luer-lock tip syringe necessary depending on the dosing volume specified on the RfIC.
- If more than one bag is needed, subsequent bags must be thawed only after the previous bag is fully administered.
- The entire content of the Aucatzyl infusion bag (100×10^6 and 300×10^6) must be infused at room temperature within 60 minutes post-thaw (infusion rate within 0.1 to 27 mL/minute) using a gravity or peristaltic pump.

*Dose administration for **10×10^6** CD19 CAR-positive viable T cells (syringe-based infusion)*

The 10×10^6 cell dose should be administered via syringe as this is the only way to deliver the volume specified on the RfIC. Withdrawal of the **10×10^6 cell** dose into the syringe should be carried out as follows:

- Prepare and administer Aucatzyl using aseptic technique wearing gloves, protective clothing and eye protection to avoid potential transmission of infectious diseases.
- Gently mix the contents of the bag to disperse clumps of cellular material.
- **The volume to be administered for the 10×10^6 dose is specified on the RfIC.**
- Use the smallest Luer-lock tip syringe necessary (1, 3, 5, or 10 mL) with a Luer-lock bag spike (or equivalent) to draw up the volume specified on the RfIC.
  - **Do NOT** use a leukodepleting filter.
  - **Do NOT** use the syringe to mix the cells.
- Prime the tubing with sodium chloride 9 mg/mL (0.9%) solution for injection prior to infusion.

- Once Aucatzyl has been drawn into the syringe, verify the volume and administer as an intravenous infusion (as a slow push approximately 0.5 mL/minute) through a central venous line (or large peripheral venous access line appropriate for blood products).
- Complete infusion at room temperature within 60 minutes post-thaw and flush the tubing line with 60 mL of sodium chloride 9 mg/mL (0.9%) solution for injection.
- Dispose of any unused portion of Aucatzyl according to local guidelines.

*Dose administration for **100 × 10^6** and/or **300 × 10^6** CD19 CAR-positive viable T cells*

- Refer to the RfIC for the following details:
  - The volume and total CD19 CAR-positive viable T cell number contained in each infusion bag.
  - Depending on the infusion bag configuration and disease burden of the patient, the dose may be suspended in one or more infusion bags to be administered on day 1 or day 10. Refer to the RfIC and Dose Schedule Planner for the dose to be administered on the given dosing day and the number of bags required to deliver the specified CD19 CAR-positive viable T cell dose. If more than one bag is needed, thaw subsequent bag only after the previous bag is fully administered.
- Prime the tubing with sodium chloride 9 mg/mL (0.9%) solution for injection prior to infusion.
- Administer Aucatzyl via a gravity or peristaltic pump-assisted intravenous infusion through a central venous line (or large peripheral venous access line appropriate for blood products).
  - **Do NOT** use a leukodepleting filter.
  - Aseptic techniques must be applied when performing a venepuncture (if applicable), spiking the ports, and through cell administration process.
- Gently mix the contents of the bag during Aucatzyl infusion to disperse cell clumps.
- Infuse the entire content of the Aucatzyl infusion bag at room temperature within 60 minutes post-thaw using a gravity or peristaltic pump.
  - After the entire contents of the infusion bag is infused, rinse the bag with 30 mL of sodium chloride 9 mg/mL (0.9%) solution for injection, then flush the tubing line with 60 mL of sodium chloride 9 mg/mL (0.9%) solution for injection.
  - Repeat steps 1-3 for any additional infusion bags required on the given dosing day. **Do NOT** initiate thaw of the next bag until infusion of the previous bag is complete.

For instructions on planning, preparation, administration, measures to take in case of accidental exposure and disposal of Aucatzyl, see section 6.6.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
Contraindications of the lymphodepleting chemotherapy must be considered.

4.4 Special warnings and precautions for use

Traceability

The traceability requirements of cell-based advanced therapy medicinal products must apply. To ensure traceability the name of the product, the batch number and the name of the treated patient must be kept for a period of 30 years after the expiry date of the product.

Autologous use

Aucatzyl is intended solely for autologous use and must not, under any circumstances, be administered to other patients. Aucatzyl must not be administered if the information on the product labels and RfIC do not match the patient's identity.

General

The availability of Aucatzyl must be confirmed before starting the lymphodepleting chemotherapy regimen.

Patients should be clinically re-assessed prior to administration of lymphodepleting chemotherapy and Aucatzyl to ensure that there are no reasons to delay therapy.

Warnings and precautions of lymphodepleting chemotherapy must be considered.

Reasons to delay or discontinue treatment

Aucatzyl should not be administered to patients with clinically significant active systemic infections, in the presence of significant safety concerns following lymphodepleting chemotherapy or patients who require supplementary oxygen for treatment of their medical condition (refer to section 4.2).

Cytokine release syndrome (CRS)

CRS was reported following treatment with Aucatzyl (see section 4.8). CRS is more probable in patients with a high tumour burden. CRS may appear up to 23 days post-infusion. Severe adverse reactions have been reported after Aucatzyl infusion. In general, CRS following CAR T treatment can be life-threatening.

Patients should be counselled to seek immediate medical attention should signs or symptoms of CRS occur at any time.

At the first sign of CRS, the patient should be timely evaluated for hospitalisation and for management as per guidance in Table 2 and for administration of supportive care. Use of myeloid growth factors such as granulocyte colony-stimulating factor (G-CSF) or granulocyte macrophage colony-stimulating factor (GM-CSF) should be avoided during CRS, given the potential to worsen CRS symptoms.

Patients should be monitored daily for 14 days after the first infusion for signs and symptoms of potential CRS. The most common manifestations of CRS included fever, hypotension, and hypoxia. Frequency of monitoring after the first 14 days should be carried out at the physician's discretion and should be continued for at least 4 weeks after infusion. (see section 4.2).

CRS should be managed based on the patient's clinical presentation and according to the CRS grading and management guidance provided in Table 2. At the first sign of CRS, treatment with tocilizumab or tocilizumab and corticosteroids should be instituted.

Ensure 24-hour immediate access to tocilizumab is available for each patient prior to infusion of Aucatzyl. In the exceptional case where tocilizumab is not available, suitable alternative anti-IL-6 therapy (e.g., siltuximab) to treat CRS must be available prior to infusion.

Evaluation for haemophagocytic lymphohistiocytosis (HLH)/macrophage activation syndrome (MAS) is to be considered in patients with severe or unresponsive CRS.

Resolution of any ongoing grade > 2 CRS to grade 1 or less should be ensured prior to initiating the second split infusion/dose.

Table 2: CRS grading and management guidance

CRS grade[a]	Anti-IL-6 therapy[b]	Corticosteroids[c]
Grade 1 Fever (≥ 38 °C).	For prolonged CRS (> 3 days) in patients or those with significant symptoms, comorbidities and /or are elderly, administer 1 dose tocilizumab 8 mg/kg intravenously over 1 hour (not to exceed 800 mg).	N/A
Grade 2 Fever with hypotension not requiring vasopressors, and/or, Hypoxia requiring low-flow nasal cannula or blow-by.	Tocilizumab 8 mg/kg intravenously over 1 hour (not to exceed 800 mg/dose). Repeat tocilizumab if no improvement; no more than 3 doses in 24 hours-with a maximum total of 4 doses. If there is no response to treatment with tocilizumab ± corticosteroids, siltuximab may be added.	For persistent refractory hypotension after 1-2 doses of anti-IL-6 therapy: consider dexamethasone 10 mg intravenously every 12-24 hours.
Grade 3 Fever with hypotension requiring a vasopressor with or without vasopressin, and/or Hypoxia requiring oxygen via high-flow nasal cannula, facemask, non-rebreather mask, or Venturi mask.	Tocilizumab per grade 2[c], if maximum dose not reached within 24-hour period.	Dexamethasone 10 mg intravenously every 6-12 hours. If refractory manage as grade 4.
Grade 4 Fever with hypotension requiring multiple vasopressors (excluding vasopressin), and/or Hypoxia requiring positive pressure (e.g., CPAP, BiPAP, intubation, and mechanical ventilation).	Tocilizumab per Grade 2[c], if maximum dose not reached within 24-hour period.	Dexamethasone 10 mg intravenously every 6 hours. If refractory, consider 3 doses of methylprednisolone 1 000 mg intravenously. If refractory, consider dosing every 12 hours.

BiPAP = bilevel positive airway pressure; CPAP = continuous positive airway pressure; CRS = cytokine release syndrome; CTCAE = Common Terminology Criteria for Adverse Events; IL = interleukin; N/A = not applicable; NCI = National Cancer Institute.

[a] Based on ASTCT/ASBMT = American Society for Transplantation and Cellular Therapy/American Society for Blood and Marrow Transplantation Consensus Grading and NCI CTCAE Version 5.0.

[b] See Prescribing Information for each agent.

[c] After each dose, assess need for subsequent dosing.

Immune effector cell-associated neurotoxicity syndrome (ICANS)

Severe, life-threatening or fatal neurologic adverse reactions, also known as ICANS, have been observed in patients treated with Aucatzyl (see section 4.8).

Patients should be monitored for signs and symptoms of ICANS and they should be counselled to seek immediate medical attention should signs or symptoms of neurotoxicity occur at any time. Transient neurological symptoms can be heterogeneous and include encephalopathy, aphasia, lethargy, headache, tremor, ataxia, sleep disorder, anxiety, agitation and signs of psychosis. Serious reactions include seizures and depressed level of consciousness.

Rule out other causes of neurologic signs or symptoms. Use caution when prescribing medicinal product that can cause central nervous system (CNS) depression, aside from anti-convulsant therapy which should be managed according to ICANS in Table 3. Conduct an electroencephalogram (EEG) for seizure activity for ≥ grade 2 neurotoxicity.

If concurrent CRS is suspected during the ICANS event, the following treatments should be administered:

- Corticosteroids according to the more aggressive intervention based on the CRS and ICANS grades in Table 2 and Table 3.
- Tocilizumab according to CRS grade in Table 2.
- Anti-seizure treatment according to ICANS in Table 3.

If ICANS is suspected, a neurology assessment and grading should be conducted at least twice a day to include cognitive assessment and motor weakness. A neurology consultation should be provided at the first sign of neurotoxicity, as well as MRI imaging with and without contrast (or brain CT if MRI is not feasible) for ≥ grade 2 neurotoxicity.

If ICANS is suspected, manage according to the recommendations in Table 3.
Intravenous hydration is recommended in patients as an aspiration precaution. Provide intensive care supportive therapy for severe or life-threatening neurologic toxicities.

Appropriate therapeutic treatment should be provided, and resolution of any ongoing grade > 1 ICANS should be ensured prior to initiating the second split infusion/dose (see section 4.2).

Table 3: ICANS adverse reaction grading and management guidance (all grades)

ICANS grade[a]	**Concurrent CRS**	**No concurrent CRS**
Grade 1 ICE score[b]: 7-9 with no depressed level of consciousness.	Tocilizumab 8 mg/kg intravenously over 1 hour (not to exceed 800 mg).[c]	• Supportive care.
Grade 2 ICE score[b]: 3-6 and/or mild somnolence awaking to voice.	Tocilizumab per grade 1[c], Additional treatment, please see column "No concurrent CRS". Consider transferring patient to ICU if neurotoxicity associated with grade ≥ 2 CRS.	• Supportive care. • 1 dose of dexamethasone 10 mg intravenously and reassess. Can repeat every 6-12 hours, if no improvement. • Consider anti-seizure treatment (e.g., levetiracetam) for seizure prophylaxis.
Grade 3 ICE score[b]: 0-2 and/or Depressed level of consciousness awakening only to tactile stimulus and/or	Tocilizumab per grade 1.[c] Additional treatment, please see column "No concurrent CRS".	• ICU care is recommended. • Dexamethasone 10 mg intravenously every 6 hours or methylprednisolone, 1 mg/kg intravenously every 12 hours. • Consider repeat neuroimaging (CT or MRI) every 2-3 days if patient has persistent Grade ≥ 3 neurotoxicity.

Any clinical seizure focal or generalised that resolves rapidly or nonconvulsive seizures on EEG that resolves with intervention. and/or Focal or local oedema on neuroimaging.		• Consider anti-seizure treatment (e.g., levetiracetam) for seizure prophylaxis.
Grade 4 ICE score [b]: 0 (patient is unarousable and unable to perform ICE) and/or Stupor or coma and/or Life-threatening prolonged seizure (≥ 5 minutes) or repetitive clinical or electrical seizures without return to baseline in between and/or Diffuse cerebral oedema on neuroimaging, decerebrate or decorticate posturing or papilloedema, cranial nerve VI palsy, or Cushing's triad.	Tocilizumab per grade 1.[c] Additional treatment, please see column "No concurrent CRS".	• ICU care, consider mechanical ventilation for airway protection. • High-dose steroids. • Consider repeat neuroimaging (CT or MRI) every 2-3 days if patient has persistent grade ≥ 3 neurotoxicity. • Treat convulsive status epilepticus per institutional guidelines.

ASTCT = American Society for Transplantation and Cellular Therapy; ASBMT = American Society for Blood and Marrow Transplantation; CAT = chimeric antigen receptor; CRS = cytokine release syndrome; CT=computerized tomography; ICE = immune effector cell-associated encephalopathy; EEG = electroencephalogram; ICANS = immune effector cell-associated neurotoxicity syndrome; ICP = intracranial pressure; ICU = intensive care unit; IL = interleukin; IV = intravenous; MRI = magnetic resonance imaging; NCCN = National Comprehensive Cancer Network.

[a] Adapted from ASTCT/ASBMT ICANS Consensus and NCCN Guidelines v1.2025 on Management of CAR T-Cell-Related Toxicities. ICANS grade is determined by the most severe event (ICE score, level of consciousness, seizure, motor findings, raised ICP/cerebral oedema) not attributable to any other cause.

[b] Depressed level of consciousness should be attributable to no other cause (e.g., no sedating medicinal product).

[c] Repeat tocilizumab every 8 hours as needed if not responsive to IV fluids or increasing supplemental oxygen. Limit to a maximum of 3 doses in a 24-hour period; maximum total of 4 doses. In the case of tocilizumab unavailability suitable alternative anti-IL-6 therapy (e.g., siltuximab) must be administered.

Prolonged cytopenias

In the FELIX study, grade 3 or higher prolonged cytopenias following Aucatzyl infusion occurred very commonly and included thrombocytopenia and neutropenia (see section 4.8). Patients may exhibit cytopenias for several weeks following lymphodepleting chemotherapy and Aucatzyl infusion. The majority of patients who experienced cytopenias grade 3 at month 1 following Aucatzyl treatment resolved to grade 2 or below at month 3.

Patient blood counts should be monitored after Aucatzyl infusion. Prolonged cytopenias should be managed according to institutional guidelines.

Severe infections

Aucatzyl should not be administered to patients with clinically significant active systemic infections. Patients should be monitored for signs and symptoms of infection before, during and after Aucatzyl infusion and treated appropriately. Appropriate prophylactic and therapeutic treatment for infections should be provided (see section 4.2) and complete resolution of severe intercurrent infection should be ensured prior to initiating the second dose.

Severe infections, including life-threatening or fatal infections occurred in patients after receiving Aucatzyl. Grade 3 or higher febrile neutropenia was observed in patients after Aucatzyl infusion (see section 4.8) 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.

In immunosuppressed patients, life-threatening and fatal opportunistic infections including disseminated fungal infections and viral reactivation (e.g., HHV-6) have been reported. The possibility of these infections should be considered in patients with neurologic events and appropriate diagnostic evaluations must be performed.

Viral reactivation

Viral reactivation, e.g., HBV reactivation, can occur in patients treated with medicinal products directed against B cells and could result in fulminant hepatitis, hepatic failure, and death.

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 was reported in patients treated with Aucatzyl (see section 4.8).

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.

Haemophagocytic lymphohistiocytosis and macrophage activation syndrome

HLH/MAS syndrome was reported following treatment with Aucatzyl (see section 4.8). Treatment should be administered per institutional standards.

Prior stem cell transplantation (GvHD)

It is not recommended that patients receive Aucatzyl within 3 months of undergoing an allogeneic haematopoietic stem cell transplantation (HSCT) because of the risk of Aucatzyl worsening GvHD.

Leukapheresis for Aucatzyl manufacturing should be performed at least 3 months after allogeneic HSCT.

Secondary malignancies including of T cell origin

Patients treated with Aucatzyl may develop secondary malignancies. T cell malignancies have been reported following treatment of haematological malignancies with a BCMA- or CD19-directed CAR T cell therapy. T cell malignancies, including CAR-positive malignancies, have been reported within weeks and up to several years following administration of a CD19- or BCMA-directed CAR T-cell therapy. There have been fatal outcomes.

Patients should be monitored life-long for signs of secondary malignancies. In the event that a secondary malignancy occurs, the company should be contacted to obtain instructions on the collection of patient samples for testing.

Tumour lysis syndrome (TLS)

TLS, which may be severe, has been observed in the FELIX trial. To minimise the risk of TLS, patients with high tumour burden should receive TLS prophylaxis as per standard guidelines prior to Aucatzyl infusion. Signs and symptoms of TLS after Aucatzyl infusions must be monitored, and events managed according to standard guidelines.

Hypersensitivity reactions

Serious hypersensitivity reactions, including anaphylaxis, may occur due to DMSO in Aucatzyl.

Transmission of an infectious agent

Although Aucatzyl is tested for sterility and mycoplasma, a risk of transmission of infectious agents exists. Healthcare professionals administering Aucatzyl must therefore, monitor patients for signs and symptoms of infection after treatment and treat appropriately, if needed.

Interference with virological testing

Due to limited and short spans of identical genetic information between the lentiviral vector used to create Aucatzyl and HIV, some HIV nucleic acid tests may give a false positive result.

Serological testing

Screening for HBV, HCV, HIV and other infectious agents must be performed in accordance with clinical guidelines before collection of cells for manufacturing (see section 4.2). Leukapheresis material from patients with active HIV, active HBV, or active HCV infection will not be accepted for manufacturing.

Blood, organ, tissue and cell donation

Patients treated with Aucatzyl must not donate blood, organs, tissues and cells for transplantation. This information is provided in the Patient Card which must be given to the patient after treatment.

Active CNS lymphoma

There is limited experience of use of this medicinal product in patients with active CNS lymphoma defined as brain metastases confirmed by imaging. Asymptomatic patients with a maximum of CNS-2 disease (defined as white blood cells < 5/µL in cerebral spinal fluid with presence of lymphoblasts) without clinically evident neurological changes were treated with Aucatzyl, however, data are limited in this population. Therefore, the benefit/risk of Aucatzyl has not been established in these populations.

Concomitant disease

Patients with a history of or active CNS disorder or inadequate renal, hepatic, pulmonary, or cardiac function were excluded from the studies. These patients are likely to be more vulnerable to the consequences of the adverse reactions described below and require special attention.

Prior treatment with anti-CD19 therapy

Aucatzyl is not recommended if the patient has CD19-negative disease or an unconfirmed CD19 status.

Long-term follow-up

Patients are expected to be enrolled in a long-term follow-up study or registry in order to better understand the long-term safety and effectiveness of Aucatzyl.

Sodium content

This medicinal product contains 1 131 mg sodium per target dose, equivalent to 57% of the World Health Organization (WHO) recommended maximum daily intake of 2 g sodium for an adult.

Potassium content

This medicinal product contains 39 mg potassium per target dose, equivalent to 1% of the WHO recommended minimum daily intake of 3.51 g potassium for an adult.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed.

Prophylactic use of systemic corticosteroids may interfere with the activity of Aucatzyl. Prophylactic use of systemic corticosteroids is therefore not recommended before infusion (see section 4.2).

Administration of tocilizumab or corticosteroids for the treatment of CRS and ICANS did not affect the rate or extent of expansion and persistency.

Live vaccines

The safety of immunisation with live viral vaccines during or following treatment with Aucatzyl has not been studied. As a precautionary measure, vaccination with live vaccines is not recommended for at least 6 weeks prior to the start of lymphodepletion chemotherapy, during Aucatzyl treatment, and until immune recovery following treatment.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential / Contraception in males and females

The pregnancy status of women of childbearing potential must be verified before starting Aucatzyl treatment. Aucatzyl is not recommended for women of childbearing potential who are not using contraception.

See the prescribing information for lymphodepleting therapy for information on the need for effective contraception in patients who receive the lymphodepleting chemotherapy.

There is insufficient exposure data to provide a recommendation concerning duration of contraception following treatment with Aucatzyl.

Pregnancy

There is a limited amount of data from the use of obecabtagene autoleucel in pregnant women. No animal reproductive and developmental toxicity studies have been conducted with Aucatzyl to assess whether it can cause foetal harm when administered to a pregnant woman (see section 5.3).

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

Pregnancy after Aucatzyl therapy must be discussed with the treating physician.

Assessment of immunoglobulin levels and B cells in newborn infants of mothers treated with Aucatzyl must be considered.

Breast-feeding

It is unknown whether obecabtagene autoleucel cells are excreted in human milk or transferred to the breast-feeding child. A risk to the breast-fed infant cannot be excluded. Breast-feeding women must be advised by the treating physician of the potential risk to the breast-fed child.

Fertility

There are no clinical data on the effect of Aucatzyl on fertility. Effects on male and female fertility have not been evaluated in animal studies.

4.7 Effects on ability to drive and use machines

Aucatzyl has a major influence on the ability to drive and use machines.

Due to the potential for neurological events, including altered mental status or seizures, patients should refrain from driving or operating heavy or potentially dangerous machines until at least 8 weeks after infusion or until resolution of the neurological event by the treating physician.

4.8 Undesirable effects

Summary of the safety profile

The most common non-laboratory adverse reactions of any grade included CRS (68.5%), infections - pathogen unspecified (44.9%), musculoskeletal pain (31.5%), pyrexia (29.1%), pain (27.6%), nausea (26.0%), diarrhoea (25.2%), headache (23.6%), fatigue (22.0%), and haemorrhage (21.3%).

The most common non-laboratory grade 3 or higher adverse reactions were infections - pathogen unspecified (24.4%), febrile neutropenia (23.6%), viral infections (13.4%), and bacterial infectious disorders (11.0%).

The most common serious adverse reactions of any grade included infections - pathogen unspecified (20.5%), febrile neutropenia (13.4%), ICANS (9.4%), CRS (7.9%), sepsis (7.9%) and pyrexia (7.1%).

The most common grade 3 or 4 laboratory abnormalities included neutropenia (98.4%), leucocytes decreased (97.6%), lymphocytes decreased (95.3%), thrombocytopenia (77.2%), and anaemia (65.4%).

The lymphodepleting chemotherapy prior to Aucatzyl administration also contributes to the laboratory abnormalities.

Tabulated list of adverse reactions

Table 4 summarises the adverse reactions in a total of 127 patients exposed to Aucatzyl in the Phase Ib and Phase II FELIX study. These reactions are presented by Medical Dictionary for Regulatory Activities system organ class and by frequency. Frequencies are defined as: very common (≥ 1/10), and common (≥ 1/100 to < 1/10). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 4: Adverse drug reactions identified with Aucatzyl

System organ class (SOC)	Frequency	Adverse reaction
Infections and infestations		
	Very common	Infections – pathogen unspecified Bacterial infectious disorders COVID-19 Viral infectious disorders excluding COVID-19 Fungal infectious disorders Sepsis
Blood and lymphatic system disorders		
	Very common	Neutropenia[a] Leukopenia[a] Lymphopenia[a] Thrombocytopenia[a] Anaemia[a] Febrile neutropenia Coagulopathy
Immune system disorders		
	Very common	Cytokine release syndrome
	Common	Hypogammaglobulinaemia Haemophagocytic lymphohistiocytosis Graft versus host disease
Metabolism and nutrition disorders		
	Very common	Decreased appetite
Psychiatric disorders		
	Common	Delirium[b]
Nervous system disorders		
	Very common	Headache Immune effector cell-associated neurotoxicity syndrome Encephalopathy[c] Dizziness
	Common	Tremor
Cardiac disorders		
	Very common	Tachycardia
	Common	Arrhythmia Cardiac Failure Palpitations
Vascular disorders		
	Very common	Hypotension Haemorrhage
Respiratory, thoracic and mediastinal disorders		
	Very common	Cough
Gastrointestinal disorders		
	Very common	Nausea Diarrhoea Vomiting Abdominal pain Constipation
	Common	Stomatitis
Skin and subcutaneous tissue disorders		
	Very common	Rash
Musculoskeletal and connective tissue disorders		
	Very common	Musculoskeletal pain
General disorders and administration site conditions		
	Very common	Pyrexia

System organ class (SOC)	Frequency	Adverse reaction
		Pain Fatigue Oedema
	Common	Chills
Investigations		
	Very common	Alanine aminotransferase increased[a] Weight decreased Hyperferritinaemia Aspartate aminotransferase increased[a]
Injury, poisoning and procedural complications		
	Common	Infusion related reaction

[a] Frequency based on grade 3 or higher laboratory parameter.
[b] Delirium includes agitation, delirium, disorientation, hallucination, irritability.
[c] Encephalopathy includes aphasia, cognitive disorder, confusional state, depressed level of consciousness, disturbance in attention, dysarthria, dysgraphia, encephalopathy, lethargy, memory impairment, mental status changes, posterior reversible encephalopathy syndrome, somnolence.

Description of selected adverse reactions

Cytokine release syndrome

CRS was reported in 68.5% of patients, including grade 3 CRS in 2.4% of patients. The median time to onset of CRS of any grade was 8 days following the first infusion (range: 1-23 days) with a median duration of 5 days (range: 1-21 days).

In the FELIX study, 80% of patients who experienced CRS had ≥ 5% blasts in their BM at the time of lymphodepletion, with 39% of patients presenting with > 75% blast in their BM. The most common manifestations of CRS among patients who experienced CRS included fever (68.5%), hypotension (25.2%) and hypoxia (11.8%).

The majority of patients experienced CRS after the first but prior to the second infusion of Aucatzyl. Of the 87 patients who experienced CRS, for 64.3% CRS occurred after the first, but prior to the second infusion of Aucatzyl with a median time to onset of 6 days (range: 3-9 days). Median time to onset after the second infusion was 2 days (range: 1-2 days). The primary treatment for CRS was tocilizumab (75.9%), with patients also receiving corticosteroids (22.9%) and other anti-cytokine therapies (13.8%), see section 4.4.

Haemophagocytic lymphohistiocytosis (HLH)/ macrophage activation syndrome (MAS)

HLH/MAS, including severe and life-threatening reactions may occur following treatment with Aucatzyl. HLH/MAS was reported in 1.6% of patients and included grade 3 and grade 4 events with a time of onset at day 22 and day 41, respectively. One patient experienced a concurrent ICANS event after Aucatzyl infusion (see section 4.4).

Immune effector cell-associated neurotoxicity syndrome

ICANS was reported in 29 patients (22.8%). Grade ≥ 3 ICANS occurred in 9 patients (7.1%) following treatment with Aucatzyl. One patient (1.1%) experienced grade 4 ICANS. The most common symptoms included confusional state (9.4%) and tremor (4.7%).

In the FELIX study, most patients who experienced ICANS (89.7%) and all patients who experienced grade ≥ 3 ICANS had > 5% blasts in their BM at the time of lymphodepleting treatment. Among the patients who experienced grade ≥ 3 ICANS, 5 patients presented with > 75% blasts in their BM.

The median time to onset for ICANS events was 12 days (range: 1-31 days) with a median duration of 8 days (range: 1-53 days). The median time to onset for ICANS events after the first infusion and before the second infusion was 8 days (range: 1-10 days) and 6.5 days (range: 2-22 days) after the second infusion. Onset of ICANS after the second infusion occurred in the majority of patients (62.1%).

Twenty-four patients received treatment for ICANS. All treated patients received high-dose corticosteroids and 12 patients received anti-epileptics prophylactically (see section 4.4).

Prolonged cytopenia

Among the safety set (N=127), median time from day of Aucatzyl infusion to neutrophil recovery to $\geq 0.5 \times 10^9$/L and $\geq 1 \times 10^9$/L (based on counts at screening) was 0.8 months and 1.9 months, respectively.

Grade ≥ 3 cytopenias at month 1 following infusion were observed in 68.5% of patients and included neutropenia (57.5%) and thrombocytopenia (52.0%). Grade 3 or higher cytopenias at month 3 following Aucatzyl infusion was observed in 21.3% of patients and included neutropenia (13.4%) and thrombocytopenia (13.4%) (see section 4.4).

Infections

Infections following Aucatzyl infusion (all grades) occurred in 70.9% of patients. Grade 3 or 4 non-COVID-19 infections occurred in 44.9% of patients including unspecified pathogen (24.4%), bacterial (11.0%), sepsis (10.2%), viral (5.5%), and fungal (4.7%) infections.

Fatal infections of unspecified pathogen were reported in 0.8% of patients. Fatal sepsis occurred in 3.9% of patients.

Grade 3 or higher febrile neutropenia was observed in 23.6% of patients after Aucatzyl infusion and may be concurrent with CRS (see section 4.4).

Hypogammaglobulinaemia

Hypogammaglobulinaemia was reported in 9.4% of patients, treated with Aucatzyl including 2 cases (1.6%) of grade 3 hypogammaglobulinaemia (see section 4.4).

Immunogenicity

The humoral immunogenicity of Aucatzyl was measured using an assay for the detection of anti-drug antibodies against Aucatzyl. In the FELIX study, 8.7% of patients tested positive for anti-CD19 CAR antibodies pre-infusion. Treatment induced anti-CD19 CAR antibodies were detected in 1.6% of 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.

The cellular immunogenicity of Aucatzyl was measured using an enzyme-linked immunosorbent spot assay for the detection of T cell responses, measured by production of interferon gamma (IFN-γ), to the full length anti-CD19 CAR. Only 3.1% (3/96) of patients tested positive in the cellular immunogenicity readout (IFN-γ) post-infusion. There is no evidence that the cellular immunogenicity affects the kinetics of initial expansion and persistence of Aucatzyl, or the safety or effectiveness of Aucatzyl.

Secondary malignancies

There have been cases of the following adverse reaction(s) reported after treatment with other CAR T cell products, which might also occur after treatment with Aucatzyl: secondary malignancy of T cell origin.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

During clinical studies, occurrences of overdose were observed at the administration of the first dose in 3.9% of patients. All 5 patients had high tumour burden and should have received a 10×10^6 first dose but received a higher dose between 68 and 103×10^6 CAR T cells. CRS, ICANS and HLH, including severe events, were observed in patients who experienced overdose. In the event of a suspected overdose, any adverse reactions are to be treated in accordance with guidance provided (see section 4.4).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antineoplastic agents, Antineoplastic cell and gene therapy, ATC code: L01XL12.

Mechanism of action

Obecabtagene autoleucel is an autologous immunotherapy consisting of the patient's own T cells engineered to express a CAR that recognises CD19 on-target cells via the murine CAT13.1E10 hybridoma (CAT) 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 4-1BB 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 fast off-rate of $3.1 \times 10^{-3} s^{-1}$ of its CD19 binding domain.

Pharmacodynamic effects

Serum levels of cytokines such as IL-2, IL-5, IL-6, IL-7, IL-8, IL-10, IL-15, TNF-α, IFN-γ, and granulocyte macrophage colony-stimulating factors were evaluated pre- and up to 3 months post-obecabtagene autoleucel infusion. Peak elevation of plasma cytokines was observed at day 28 of obecabtagene autoleucel infusion and levels returned to baseline by month 3.

Due to the on-target effect of obecabtagene autoleucel, a period of B cell aplasia is expected.

Clinical efficacy and safety

The efficacy and safety of obecabtagene autoleucel is based on the results of the FELIX study (EU CT number 2024-512903-38-00), an open-label, multi-centre, single arm Phase Ib/II study of obecabtagene autoleucel in adult patients with r/r B ALL.

The primary outcome of Cohort IIA was overall complete remission rate defined as proportion of patients achieving complete remission (CR) or complete remission with incomplete haematologic recovery (CRi) as assessed by an Independent Response Review Committee (IRRC) and the secondary

outcomes included duration of remission (DOR), complete remission rate (CRR) and proportion of patients achieving minimal residual disease (MRD)-negative response.

Patients in the pivotal study were adults (≥ 18 years) with r/r CD19+ B ALL, presence of ≥ 5% blasts in BM at screening and confirmed CD19 expression after blinatumomab therapy. Relapsed or refractory status was defined as follows: primary refractory disease, first relapse following a remission lasting ≤ 12 months, r/r acute lymphoblastic leukaemia (ALL) after 2 or more prior lines of systemic therapy, or r/r ALL at least greater than 3 months after allogeneic HSCT. Patients with Philadelphia chromosome positive ALL were eligible if they were intolerant to or have failed 2 lines of any tyrosine kinase inhibitor (TKI) or one line of second-generation TKI, or if TKI therapy was contraindicated. Patients with prior CD19 targeted therapy other than blinatumomab were excluded. Treatment consisted of lymphodepleting chemotherapy followed by obecabtagene autoleucel as a split dose infusion with a total target dose of 410×10^6 CD19 CAR-positive viable T cells (see section 4.2).

In the pivotal Cohort IIA, 113 patients were leukapheresed (leukapheresed set) and 94 (83.2%) patients were treated with at least one obecabtagene autoleucel infusion (infused set): 19 patients discontinued without receiving infusion for reasons related to death (12 patients), adverse reaction (neutropenic sepsis related to the underlying disease [1 patient]) and physician decision (1 patient). Five out of 113 leukapheresed patients (4.4%) did not receive obecabtagene autoleucel infusion due to manufacturing-related issues.

The median age of the 94 infused patients was 50 years; among them, 83 patients were 26 years of age and above. The sex distribution of male and female patients infused with obecabtagene autoleucel was equal with 47 males and 47 females. Seventy patients were white (74.5%); 29 patients (30.9%) were of Hispanic or Latino ethnicity (Table 5).

Eighty-eight patients (93.6%) received bridging therapy (e.g., chemotherapy, inotuzumab ozogamicin, TKIs) between leukapheresis and lymphodepleting chemotherapy to control tumour burden. All patients received obecabtagene autoleucel infusion on day 1 and were hospitalised until day 10 at minimum.

Table 5: Baseline demographic and disease-related characteristics for the FELIX study (Cohort IIA)

	Infused set (N=94)	**Leukapheresed set (N=113)**
Median age, range (years)	50 (20 – 81)	49 (20 – 81)
Age category (years), n (%)		
≥ 18 years and ≤ 25 years	11 (11.7)	13 (11.5)
> 25 years	83 (88.3)	100 (88.5)
Gender, n (M/F)	47M/47F	61M/52F
Race, n (%)		
Caucasian	70 (74.5)	87 (77.0)
Philadelphia chromosome positive status (BCR-ABL positive), n (%)	25 (26.6)	26 (23.0)
Median prior lines of treatment, n (range)	2 (1 – 6)	2 (1 – 6)
≥ 3 prior lines, n (%)	29 (30.9)	35 (31.0)
Refractory to last prior line of therapy, n (%)	51 (54.3)	60 (53.1)
Prior HSCT, n (%)	36 (38.3)	43 (38.1)
Prior blinatumomab, n (%)	33 (35.1)	42 (37.2)
Prior inotuzumab, n (%)	30 (31.9)	37 (32.7)
BM blast % at lymphodepletion, median (range)	43.5 (0 – 100)	43.5 (0 – 100)
BM blast % at lymphodepletion, n (%)		
> 75%	30 (31.9)	30 (26.5)
> 20% to 75%	27 (28.7)	27 (23.9)
5 to 20%	14 (14.9)	14 (12.4)
< 5%	23 (24.5)	23 (20.4)
Missing	0	19 (16.8)
Extramedullary disease at lymphodepletion, n (%)	19 (20.2)	21 (18.6)

ABL = Abelson murine leukaemia; BCR = breakpoint cluster region; BM = bone marrow; F = female HSCT = haematopoietic stem cell transplantation; M = male.

The primary efficacy analysis was evaluated in patients who received at least one infusion of obecabtagene autoleucel (infused set) in the pivotal Cohort IIA of the FELIX study (Table 6). Of the 94 patients in the infused set, the median dose received was 410×10^6 CD19 CAR-positive viable T cells (range: 10-480 $\times 10^6$ CD19 CAR-positive viable T cells). Eighty-five patients (90.4%) received the total target dose of 410×10^6 CD19 CAR-positive viable T cells. Six patients (6.4%) received the first dose only, primarily due to adverse reactions (3.2%), progressive disease (1.1%), manufacturing-related issues (1.1%) and death (1.1%). The median manufacturing time from leukapheresis receipt to product certification was 20 days (range: 17-43 days) and the median time from leukapheresis to obecabtagene autoleucel infusion was 35.5 days (range: 25-92 days). The median follow-up (duration from first infusion to data cut-off date of 07-Feb-2024) was 20.25 months (range: 13-30 months).

The secondary outcome MRD-negative rate among overall remission rate (ORR = CR or CRi) subjects was assessed by next-generation sequencing, polymerase chain reaction and flow cytometry.

Table 6: Efficacy analysis (Cohort IIA)

	Infused set (N=94)	**Leukapheresed set (N=113)**
Overall remission rate (ORR: CR + CRi)		
n (%)	72 (76.6)	72 (63.7)
95% CI (%)	(66.7, 84.7)	(54.1, 72.6)
Complete remission (CR) at any time		
n (%)	52 (55.3)	55 (48.7)
95% CI (%)	(44.7, 65.6)	(39.2, 58.3)
MRD-negative rate among CR or CRi (NGS/PCR/flow cytometry)[a]		

	Infused set (N=94)	Leukapheresed set (N=113)
N[b]	72	72
n (%)	64 (88.9)	64 (88.9)
95% CI (%)	(79.3, 95.1)	(79.3, 95.1)
Duration of remission (DOR)		
N[b]	72	72
Median in months[c]	14.06	14.06
95% CI (range in months)	(8.18, NE)	(8.18, NE)

BM = bone marrow; BOR = best overall response post-Aucatzyl infusion; CI = confidence interval; CR = complete remission; CRi = complete remission with incomplete recovery of counts; DOR = duration of remission; FACS = fluorescence-activated cell sorting; MRD = minimal residual disease; IRRC = Independent Response Review Committee; NE = not estimable; NGS = next-generation sequencing; ORR = overall remission rate; PCR = polymerase chain reaction; SCT = stem cell transplantation.

[a] Patients in remission by IRRC with MRD-negative BM by central ClonoSEQ NGS/PCR/FACS.

[b] Patients who achieved BOR of CR or CRi.

[c] With censoring for SCT and other new anti-cancer therapy.

Among the patients aged 26 years and above in the infused set (N=83), the ORR was 78.3% (95% CI [confidence interval]: 67.9, 86.6) with a CR rate of 57.8% (95% CI: 46.5, 68.6). The median DOR was 14.1 months (95% CI: 8.1, NE [not estimable]) in responding patients.

Among the patients who received the total recommended dose of 410×10^6 CAR-positive viable T cells, the ORR rate was 81.2% with a CR rate of 61.2%. The median DOR was 14.1 months (95% CI: 8.2, NE) in responding patients. For 9 patients (9.6%) who did not receive the target dose, including 6 patients who only received the first dose, the ORR rate was 33.3% with a CR rate of 0%. The median DOR was 5.2 months (95% CI: NE, NE) in responding patients (CRi).

For patients who received both doses (N=88; 93.6%), patients receiving a lower first dose of 10×10^6 cells (> 20% blasts in BM, high disease burden, N=56) had a numerically lower ORR (75.0%; 95% CI: 61.6, 85.6) than patients receiving a higher first dose of 100×10^6 cells (≤ 20% blasts in BM, low disease burden, N=32) (87.5%; 95% CI: 71.0, 96.5). The median DOR was 12.5 months (95% CI: 7.1, NE) in responding patients receiving a lower first dose of 10×10^6 cells and 14.2 months (95% CI: 10.7, NE) in responding patients receiving a higher first dose of 100×10^6 cells.

Among patients who experienced relapse prior to start of new anti-cancer therapies, 46.4% had CD19-negative relapse, 10.7% had CD19-mixed relapse, 42.9% had CD19-positive relapse.

Paediatric population

The European Medicines Agency has deferred the obligation to submit the results of studies with Aucatzyl in one or more subsets of the B ALL paediatric population. See section 4.2 for information on paediatric use.

Conditional approval

This medicinal product has been authorised under a so-called ‘conditional approval’ scheme. This means that further evidence on this medicinal product is awaited. The European Medicines Agency will review new information on this medicinal product at least every year and this SmPC will be updated as necessary.

5.2 Pharmacokinetic properties

Cellular kinetics

The pharmacokinetics (PK) of obecabtagene autoleucel were assessed in 94 patients with r/r CD19+

B ALL receiving a median dose of 410 × 10^6 CD19 CAR-positive viable T cells (range: 10-480 × 10^6 CD19 CAR-positive viable T cells).

A rapid expansion occurred after infusion of the first dose in the majority of the patients and continued after the second dose up to the median time of maximal expansion to peak (T_{max}) at day 14 (range: 2-55 days).

Decline of CAR T concentrations started shortly after day 28 and reached a stabilised concentration from month 6; with a maximum persistency observed at 27.7 months.

A high level of expansion was generally observed regardless of response status (CR/CRi vs. non-CR/non-CRi). A total of 84.6% (22/26) of patients who had ongoing remission had ongoing CAR T persistency at the last laboratory assessment.

Table 7: Summary of PK parameters in peripheral blood by BOR (Cohort IIA, infused set)

Parameter metric	Best overall response		Overall (N=94)
	CR/CRi (N=72)	Not CR/CRi (N=22)	
C_{max} (copies/µg DNA)			
N	72	22	94
Geometric mean (Geo-CV%)	117 381 (206.0)	107 465 (832.7)	114 982 (287.6)
Range (min - max)	2 120-478 000	129-600 000	129-600 000
T_{max} (days)			
N	72	22	94
Median	14	17	14
Range (min - max)	2-55	6-28	2-55
$AUC_{(0-28d)}$ (copies/µg DNA*days)			
N	68	14	82
Geometric mean (Geo-CV%)	1 089 908 (236.0)	1 404 899 (186.4)	1 138 188 (225.6)
Range (min - max)	17 900-6 730 000	176 000-7 230 000	17 900-7 230 000

$AUC_{(0-28d)}$ = area under the concentration-time curve from day 0 to day 28; BOR = best overall response; C_{max} = maximum concentration; CR = complete remission; CRi = complete remission with incomplete recovery of counts; DNA = deoxyribonucleic acid; Geo-CV% = geometric coefficient of variation; PK = pharmacokinetic; T_{max} = time to maximum concentration.

Patients who received a first split dose of 10 × 10^6 cells (> 20% blast) demonstrated a higher expansion of CAR T cells (C_{max} and AUC_{0-28d}) compared with patients who received a first split dose of 100 × 10^6 cells (≤ 20% blast). In turn, patients with high expansion tended to have higher rates of CRS and ICANS. Therefore, high tumour burden is the main risk factor for onset of CRS and ICANS.

In the FELIX study, the median body weight was 75.75 kg (range: 42.6-230.6 kg). The PK profile was comparable between patients with lower (< 75.75 kg) and higher (≥ 75.75 kg) body weight.

Special populations

Gender or age (below 65 years, between 65 and 74 years, and between 75 and 84 years) did not have a significant impact on the PK of Aucatzyl (C_{max}, AUC_{0-28d} or persistency).

The data in the non-white population (Table 5) are too limited to draw any conclusions on the impact of race on PK parameters.

Hepatic and renal impairment studies of Aucatzyl were not conducted.

5.3 Preclinical safety data

Aucatzyl comprises engineered human T cells; therefore, there are no representative *in vitro* assays, *ex vivo* models, or *in vivo* models that can accurately address the toxicological characteristics of the human product. Hence, traditional toxicology studies used for medicinal product development were not performed.

No carcinogenicity or genotoxicity studies have been conducted with Aucatzyl. No studies have been conducted to evaluate the effects of Aucatzyl on fertility, reproduction and development.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Disodium edetate
Phosphate buffered saline (PBS): potassium dihydrogen phosphate, sodium chloride, disodium phosphate, potassium chloride, water for injections
Human albumin solution
Dimethyl sulfoxide (DMSO)

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

6 months at ≤ –150 °C.

Once thawed: 1 hour at room temperature.

6.4 Special precautions for storage

Aucatzyl must be stored in the vapour phase of liquid nitrogen (≤ −150 °C) and must remain frozen until the patient is ready for treatment to ensure viable cells are available for patient administration. Thawed medicinal product must not be refrozen. The product must not be irradiated before or during use as this could lead to inactivation of the product.

For storage conditions and duration after thawing of the medicinal product, see section 6.3.

6.5 Nature and contents of container and special equipment for use, administration or implantation

Ethylene vinyl acetate infusion bag(s) with a sealed filling tube and 2 available spike ports, containing either 10–20 mL (50 mL bags) or 30–70 mL (250 mL bags) cell dispersion. One individual treatment regimen includes 3 or more infusion bags for the total dose of 410×10^6 CD19 CAR-positive viable T cells. Each infusion bag is individually packed within an overwrap in a metal cassette. Metal cassettes are packed into a ModPak Modular Cryogenic Packout Kit. Up to 4 cassettes can fit in a single ModPak. Two ModPak may be required to transport the maximum number of 7 cassettes.

6.6 Special precautions for disposal and other handling

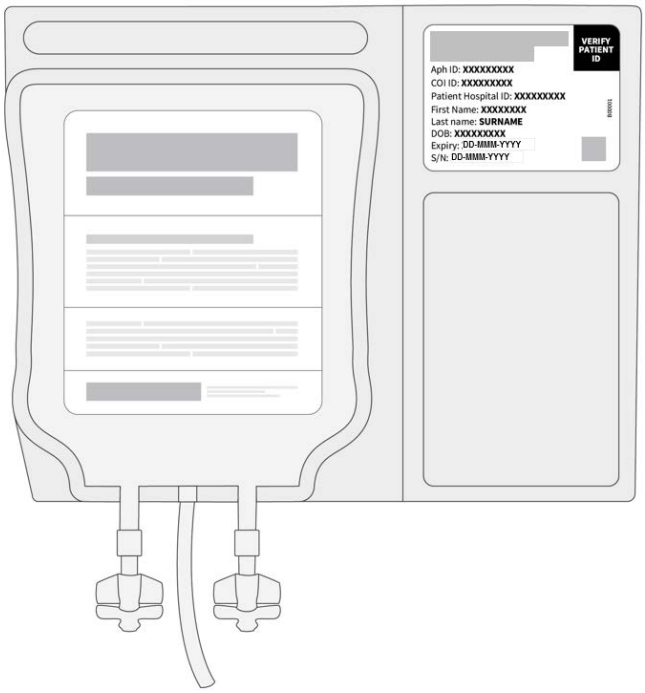
The product must not be irradiated before or during use as this could lead to inactivation of the product.

<u>Receipt and storage of Aucatzyl</u>

- Aucatzyl is supplied in the vapour phase of a liquid nitrogen cryoshipper (≤ -150 °C).

- Confirm the patient's identity. Open the cryoshipper, retrieve the RfIC and metal cassette(s). Open the metal cassette(s) to retrieve the infusion bags in their clear overwrap. The patient's identity must match the patient identifiers on the Aucatzyl RfIC located inside the cryoshipper and on the labels of the infusion bags (see Figure 2).
- Time out of the vapour phase liquid nitrogen environment should be kept to an absolute minimum to avoid premature product thaw (it is recommended not to exceed 90 seconds).
- When the patient's identity does not match the RfIC or label: Do not infuse the product. Contact Autolus at 00800 0825 0829 if there are any discrepancies between the labels and the patient identifiers.
- Keep the infusion bag(s) in the metal cassette(s), transfer Aucatzyl to the on-site controlled-access vapour phase of liquid nitrogen for storage ≤ -150 °C (until ready for transfer, thawing and infusion).

Figure 2: Patient-specific identifiers



Patient-specific identifiers:

Apheresis ID
Chain of identity ID
Hospital ID
Patient name
Patient date of birth

Precautions to be taken before handling or administering the medicinal product

Aucatzyl must be transported within the treatment centre in closed, break-proof, leak-proof containers.

This medicinal product contains genetically modified human blood cells. Healthcare professionals handling Aucatzyl must take appropriate precautions (wearing gloves, protective clothing and eye protection) to avoid potential transmission of infectious diseases.

Planning prior to Aucatzyl preparation

The patient batch-specific RfIC and Dose Schedule Planner will be provided in the cryoshipper Confirm the patient identifiers on RfIC and infusion bags match (see Figure 2).

1. Ensure the patient's BM assessment results are available (see section 4.2, Bone marrow assessment).
2. The Aucatzyl Dose Schedule Planner, provided with the RfIC, assists the determination of the appropriate dose regimen to be administered on day 1 (3 days [± 1 day] after the completion of lymphodepleting chemotherapy) and day 10 (± 2 days). Record the following information on the Dose Schedule Planner:
   a. The blast percentage from the patient's BM assessment.
   b. The Aucatzyl bag serial number(s); number of bag type required for each dose; and the

specified volume to administer via syringe (for the 10×10^6 dose) transcribed from the RfIC.

3. The completion of the Aucatzyl Dose Schedule Planner will guide the treating physician on the number of bags and the respective dose required, and the preparation of Aucatzyl for the day 1 and day 10 (± 2 days) dose, see Figure 1.

Transfer and thawing prior to infusion

- Using the completed Dose Schedule Planner for guidance, transfer ONLY the cassette(s) / infusion bag(s) required for the given dosing day from the on-site vapour phase liquid nitrogen storage to an appropriate transfer vessel (i.e., a vapour phase liquid nitrogen cryoshipper, maintaining temperature ≤ -150 °C) for transport to the bag thaw location.
- Transfer the required cassette(s) one by one, confirming the Aucatzyl bag serial numbers and patient identifiers on each infusion bag label (see Figure 2).
- Time out of the vapour phase liquid nitrogen environment should be kept to an absolute minimum to avoid premature product thaw (it is recommended not to exceed 90 seconds).
- If more than one infusion bag has been required on a given dosing day, thaw each infusion bag one at a time; Do not remove subsequent bags from the vapour phase liquid nitrogen storage (≤ -150 °C) until infusion of the previous bag is complete.
- Leave the Aucatzyl infusion bag in its overwrap, thaw at 37 °C using a water bath or thawing device until there are no visible frozen clumps left in the infusion bag. Each bag should be gently massaged until the cells have just thawed. Thawing of each infusion bag takes between 2 to 8 minutes. Remove from the water bath or thaw device immediately after thawing is complete. Carefully remove the infusion bag from the overwrap taking care to avoid damage to the bag and ports.
- Gently mix the contents of the bag to disperse clumps of cellular material and administer immediately to the patient.
- Do not refreeze or refrigerate thawed product.

Measures to take in case of accidental exposure

In case of accidental exposure, local guidelines on handling of human-derived material must be followed. Work surfaces and materials which have potentially been in contact with Aucatzyl must be decontaminated with appropriate disinfectant.

Precautions to be taken for the disposal of the medicinal product

Unused medicinal product and all material that has been in contact with Aucatzyl (solid and liquid waste) must be handled and disposed of as potentially infectious waste in accordance with local guidelines on handling of human-derived material.

7. MARKETING AUTHORISATION HOLDER

Autolus GmbH
Im Schwarzenbach 4
79576 Weil am Rhein
Germany

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/25/1951/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation:

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency https://www.ema.europa.eu

ANNEX II

A. MANUFACTURER OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

E. SPECIFIC OBLIGATION TO COMPLETE POST-AUTHORISATION MEASURES FOR THE CONDITIONAL MARKETING AUTHORISATION

A. MANUFACTURER OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer of the biological active substance

Autolus Limited
(The Nucleus)
Marshgate
Stevenage SG1 1FR
United Kingdom

Name and address of the manufacturer responsible for batch release

Marken Germany GmbH
Moenchhofallee 13
65451 Kelsterbach
Germany

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in Article 9 of Regulation (EC) No 507/2006 and, accordingly, the marketing authorisation holder (MAH) shall submit PSURs every 6 months.

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c (7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder (MAH) shall submit the first PSUR for this product within 6 months following authorisation.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile

or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

- **Additional risk minimisation measures**

Key elements:

Availability of tocilizumab and site qualification

The MAH will ensure that hospitals and their associated centres that dispense Aucatzyl are qualified in accordance with the agreed controlled distribution programme by:

- Ensuring 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.
- Ensuring healthcare professionals (HCP) involved in the treatment of a patient have completed the educational programme.

Educational/Safety advice tools

Prior to the launch of Aucatzyl in each Member State the MAH must agree the content and format of the educational materials with the National Competent Authority.

Healthcare professional's guide

The MAH shall ensure that in each Member State where Aucatzyl is marketed, all HCPs who are expected to prescribe, dispense, and administer Aucatzyl shall be provided with a guidance document to:

- monitor and manage CRS and neurological signs and symptoms
- monitor and manage ICANS
- ensure that serious adverse reactions suggestive of CRS or ICANS are adequately and appropriately reported
- ensure that there is twenty-four-hour immediate access to tocilizumab, an 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 overdose and medicinal product errors
- provide information about the risk of secondary malignancy of T cell origin
- provide information about the safety and effectiveness in long-term follow-up studies and the importance of contributing to such studies

Patient card

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
- that the patient cannot donate organs or blood
- the need to carry the Patient Card at all times

- **Obligation to conduct post-authorisation measures**

The MAH shall complete, within the stated timeframe, the below measures:

Description	Due date
In order to further characterise the long-term safety and efficacy of Aucatzyl in adult patients with relapsed or refractory B cell precursor acute lymphoblastic leukaemia, the MAH shall conduct and submit the results of a long-term follow-up study of patients previously treated with obecabtagene autoleucel, according to an agreed protocol.	30 June 2039
Non-Interventional Post-Authorisation Safety Study: In order to further characterize the long-term safety and efficacy of Aucatzyl in adult patients with relapsed or refractory B cell precursor acute lymphoblastic leukaemia, the MAH shall conduct and submit the results of a prospective study based on data from a registry.	30 June 2045

E. SPECIFIC OBLIGATION TO COMPLETE POST-AUTHORISATION MEASURES FOR THE CONDITIONAL MARKETING AUTHORISATION

This being a conditional marketing authorisation and pursuant to Article 14-a of Regulation (EC) No 726/2004, the MAH shall complete, within the stated timeframe, the following measures:

Description	Due date
In order to confirm the long-term efficacy and safety of Aucatzyl in adult patients with relapsed or refractory B cell precursor acute lymphoblastic leukaemia, the MAH shall submit final results of the FELIX clinical study, an open-label, single arm Phase Ib/II study of obecabtagene autoleucel in adult patients with relapsed or refractory B cell precursor acute lymphoblastic leukaemia.	30 June 2029
In order to confirm the efficacy and safety of Aucatzyl in adult patients with relapse or refractory B cell precursor acute lymphoblastic leukaemia, the MAH shall submit the results of 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.	31 July 2030

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

MODPAK LABEL

1. NAME OF THE MEDICINAL PRODUCT

Aucatzyl 410 × 10^6 cells dispersion for infusion
obecabtagene autoleucel (CAR+ viable T cells)

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Autologous enriched human T cells transduced *ex vivo* with a lentiviral vector to express an anti-CD19 chimeric antigen receptor (CAR).

This medicine contains cells of human origin.

Contains: 410 × 10^6 CAR+ viable T cells at a batch-dependent concentration.

3. LIST OF EXCIPIENTS

Excipients: disodium edetate, potassium dihydrogen phosphate, sodium chloride, disodium phosphate, potassium chloride, water for injections, dimethyl sulphoxide, human albumin solution. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Dispersion for infusion
Target dose may be supplied in one or two ModPaks. Each ModPak can contain up to 4 cassettes with different bag configurations.

1/1 Pack.
1/2 Pack.
2/2 Pack.

Read the Release for Infusion Certificate before use.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Read the Release for Infusion Certificate before use.
Refer to the Dose Schedule Planner for guidance on the appropriate patient-specific dose regimen.
Intravenous use.
STOP Verify patient ID.
Do NOT use leukodepleting filter.
Do NOT irradiate.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

7. OTHER SPECIAL WARNING(S), IF NECESSARY

For autologous use only.

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Ship and store in vapour phase of liquid nitrogen ≤ -150 °C. Use within 1 hour post-thaw. Do not refreeze.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

This medicine contains human cells. Unused medicine or waste material must be disposed of in compliance with the local guidelines on handling of waste of human-derived material.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Autolus GmbH
Im Schwarzenbach 4
79576 Weil am Rhein
Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/25/1951/001

13. BATCH NUMBER, DONATION AND PRODUCT CODES

Aph ID:
COI ID:

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

19. SUPPLY CHAIN INFORMATION

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CONTAINER (CASSETTE)

1. NAME OF THE MEDICINAL PRODUCT

Aucatzyl 410 × 10^6 cells dispersion for infusion
obecabtagene autoleucel (CAR+ viable T cells)

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Autologous enriched human T cells transduced *ex vivo* with a lentiviral vector to express an anti-CD19 chimeric antigen receptor (CAR).

This medicine contains cells of human origin.

Contains:
≤ 100 × 10^6 CAR+ viable T cells at a batch-dependent concentration.
100 × 10^6 CAR+ viable T cells at a batch-dependent concentration.
≤ 300 × 10^6 CAR+ viable T cells at a batch-dependent concentration.

3. LIST OF EXCIPIENTS

Excipients: disodium edetate, potassium dihydrogen phosphate, sodium chloride, disodium phosphate, potassium chloride, water for injections, dimethyl sulphoxide, human albumin solution. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Dispersion for infusion.

10 × 10^6 Bag Configuration.
10 mL per bag.

100 × 10^6 Bag Configuration.
10-20 mL per bag.
Dose may be suspended in one or more infusion bags.

100 × 10^6 Bag Configuration.
30-70 mL per bag.

300 × 10^6 Bag Configuration.
30-70 mL per bag.
Dose may be suspended in one or more infusion bags.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Extract specified volume via syringe (10 × 10^6 Bag Configuration)
Read the package leaflet before use.
Read the Release for Infusion Certificate before use.

Refer to the Dose Schedule Planner for guidance on the appropriate patient-specific dose regimen.
Intravenous use.
STOP Verify patient ID.
Do NOT use leukodepleting filter.
Do NOT irradiate.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

7. OTHER SPECIAL WARNING(S), IF NECESSARY

For autologous use only.

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Ship and store in vapour phase of liquid nitrogen ≤ -150 °C. Use within 1 hour post-thaw. Do not refreeze.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

This medicine contains human cells. Unused medicine or waste material must be disposed of in compliance with the local guidelines on handling of waste of human-derived material.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Autolus GmbH
Im Schwarzenbach 4
79576 Weil am Rhein
Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/25/1951/001

13. BATCH NUMBER, DONATION AND PRODUCT CODES

Aph ID:
COI ID:
Hospital ID:
First:
Last:
DOB:
S/N:

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

INFUSION BAG

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Aucatzyl 410 × 10^6 cells dispersion for infusion
obecabtagene autoleucel (CAR+ viable T cells)
Intravenous use

2. METHOD OF ADMINISTRATION

Extract specified volume via syringe (10 × 10^6 bag configuration).

Read the package leaflet before use.
Read the Release for Infusion Certificate before use.
Do NOT use leukodepleting filter.
Do NOT irradiate.

3. EXPIRY DATE

EXP

4. BATCH NUMBER, DONATION AND PRODUCT CODES

Aph ID:
COI ID:
Hospital ID:
First:
Last:
DOB:
S/N:

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

10 × 10^6 Bag Configuration.
10 mL per bag.
Contains: ≤ 100 × 10^6 CAR+ viable T cells.

100 × 10^6 Bag Configuration.
10-20 mL per bag.
Contains: ≤ 100 × 10^6 CAR+ viable T cells.
Dose may be suspended in one or more infusion bags.

100 × 10^6 Bag Configuration.
30-70 mL per bag.
Contains: 100 × 10^6 CAR+ viable T cells.

300 × 10^6 Bag Configuration.
30-70 mL per bag.

Contains: ≤ 300×10^6 CAR+ viable T cells.
Dose may be suspended in one or more infusion bags.

6. OTHER

STOP Verify patient ID.

For autologous use only.

PARTICULARS TO APPEAR ON THE RELEASE FOR INFUSION CERTIFICATE (RfIC) INCLUDED WITH EACH SHIPMENT FOR ONE PATIENT

1. NAME OF THE MEDICINAL PRODUCT

Aucatzyl 410 × 10^6 cells dispersion for infusion
obecabtagene autoleucel (CAR+ viable T cells)

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Autologous enriched human T cells transduced *ex vivo* with a lentiviral vector to express an anti-CD19 chimeric antigen receptor (CAR).

3. CONTENT BY WEIGHT, BY VOLUME OR BY UNIT, AND DOSE OF THE MEDICINAL PRODUCT

Target Dose	**410 × 10^6 CD19 CAR-positive viable T cells**

Bag configuration: **10 × 10^6 CD19 CAR-positive viable T cells (Blue bag)**		
DP Bag Serial Number		
Number of bags for 10 × 10^6 dose	**1**	**Bag**
Volume per bag	**10**	**mL**
Number of CD19 CAR-positive viable T cells in bag		**× 10^6**
Volume to administer via syringe to deliver **10 × 10^6 CD19 CAR-positive viable T cells**		**mL**

Bag configuration: **100 × 10^6 CD19 CAR-positive viable T cells (Orange bag)**		
DP Bag Serial Number(s)		
Number of bags required for 100 × 10^6 dose		**Bag(s)**
Volume per bag		**mL**
Number of CD19 CAR-positive viable T cells in each bag		**× 10^6**
Volume to administer via infusion	**Entire bag(s)**	

Bag configuration: **300 × 10^6 CD19 CAR-positive viable T cells (Red bag)**		
DP Bag Serial Number(s)		
Number of bags required for 300 × 10^6 dose		**Bag(s)**
Volume per bag		**mL**
Number of CD19 CAR-positive viable T cells in each bag		**× 10^6**
Volume to administer via infusion	**Entire bag(s)**	

4. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.

Intravenous use.
STOP Verify patient ID.
Do NOT use leukodepleting filter.
Do NOT irradiate.
Refer to the Dose Schedule Planner for guidance on the appropriate patient-specific dose regimen.

5. OTHER SPECIAL WARNING(S), IF NECESSARY

Save this document and have it available when preparing for administration of Aucatzyl.
For autologous use only.
For any urgent query, contact Autolus Patient Scheduling on 00800 0825 0829

6. SPECIAL STORAGE CONDITIONS

Ship and store in the vapour phase of liquid nitrogen (≤ -150 °C).
Use within 1 hour post-thaw.
Do not refrigerate or refreeze thawed medicinal product.

7. EXPIRY DATE

Product Expiry Date:

8. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

This medicine contains human blood cells. Unused medicine or waste material must be disposed of in compliance with the local guidelines on handling of waste of human-derived material.

9. BATCH NUMBER, DONATION AND PRODUCT CODES

Chain of Identity (CoI) ID: CHG2344
Single European Code:
Apheresis Identifier:
Patient Hospital ID:
Patient First Name:
Patient Middle Initial:
Patient Last Name:
Date of Birth:

10. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Autolus GmbH
Im Schwarzenbach 4
79576 Weil am Rhein
Germany

11. MARKETING AUTHORISATION NUMBER(S)

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

Aucatzyl 410 × 10^6 cells dispersion for infusion
obecabtagene autoleucel (CAR+ viable T cells)

▼This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effect(s) you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you are given this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- Your doctor will give you a Patient Card. Read it carefully and follow the instructions on it.
- Always show the Patient Card to the doctor or nurse when you see them or if you go to hospital.
- If you experience any side effects, immediately talk to your doctor or nurse. This includes any possible side effects not listed in this leaflet. See section 4.
- If you have any further questions, ask your doctor or nurse.

What is in this leaflet

1. What Aucatzyl is and what it is used for

Aucatzyl is a gene therapy product that contains the active substance obecabtagene autoleucel. The medicine is made especially for you from your own T cells. T cells are a type of white blood cells that are important for your immune system (the body's defences) to work properly.

Aucatzyl is a cancer medicine used in adults aged 26 years and above to treat B cell acute lymphoblastic leukaemia (B ALL), a type of blood cancer that affects white blood cells in your bone marrow called B lymphoblasts. It is used when your cancer has come back (relapsed) or has not improved with previous treatment (refractory).

The active substance in Aucatzyl, obecabtagene autoleucel, contains a patient's own T cells, which have been genetically modified in a laboratory so that they make a protein called chimeric antigen receptor (CAR). CAR can attach to another protein on the surface of cancer cells called CD19. When a patient is given an infusion (drip) with Aucatzyl, the modified T cells attach to and kill the cancer cells, thereby helping to clear the cancer from the body.

If you have any questions about how Aucatzyl works or why this medicine has been prescribed for you, ask your doctor.

2. What you need to know before you are given Aucatzyl

You must not be given Aucatzyl

- if you are allergic to any of the ingredients of this medicine (listed in section 6). If you think you may be allergic, ask your doctor for advice.

- if you cannot receive treatment, called lymphodepleting chemotherapy, which is used to reduce the number of white blood cells in your blood (see also section 3, How Aucatzyl is given).

Warnings and precautions

Aucatzyl is made from your own white blood cells and must only be given to you (autologous use).

Patients treated with Aucatzyl may develop new cancers. There have been reports of patients developing T cell cancers after treatment with similar medicines. Talk to your doctor if you experience any new swelling of your glands (lymph nodes) or changes in your skin such as new rashes or lumps.

Tests and checks

Before you are given Aucatzyl

Your doctor will perform checks to decide how Aucatzyl should be given to you or if you need additional medicines (see also section 3, How Aucatzyl is given). Based on the outcomes of the tests, your doctor might delay or change your planned treatments with Aucatzyl.

Your doctor will do the following tests and checks:

- Check if you have any lung, heart, liver or kidney problems.
- Look for signs of infection; any infection will be treated before you are given Aucatzyl.
- Check for signs and symptoms of graft versus host disease (GvHD) if you have had a stem cell transplantation (a procedure where a patient's bone marrow is replaced to form new bone marrow) within the past 3 months. GvHD happens when transplanted cells attack your body, causing symptoms such as rash, nausea, vomiting, diarrhoea and bloody stools.
- Check if you have or had diseases affecting the central nervous system. This includes conditions such as epilepsy, stroke, severe brain injuries or mental illnesses in the last 3 months.
- Check if your cancer is getting worse. Symptoms of your cancer getting worse might include fever, feeling weak, bleeding gums and bruising.
- Check if the cancer has spread to the brain.
- Check your blood for uric acid and for how many cancer cells there are in your blood. This will show if you are likely to develop a condition called tumour lysis syndrome. You may be given medicines to help prevent the condition.
- Check for hepatitis B, hepatitis C or HIV infection. You may have to receive treatment for any of these infections before you can be given Aucatzyl.
- Check if you have had a vaccination in the previous 6 weeks or are planning to have one in the next few months.

Tell your doctor or nurse before you are given Aucatzyl if any of the above apply to you, or you are not sure.

After you have been given Aucatzyl

Tell your doctor or nurse immediately or get emergency help right away if you have any of the following:

- Fever and chills, low blood pressure and low oxygen in the blood which may cause symptoms such as fast or uneven heartbeat and shortness of breath. These may be signs of a serious problem called cytokine release syndrome (CRS). See section 4 for other symptoms of CRS.
- Loss of consciousness or decreased level of consciousness, involuntary shaking (tremor), seizures, difficulty speaking, slurred speech and understanding speech. These may be signs of serious problems with your nervous system called immune effector cell-associated neurotoxicity syndrome (ICANS).

- Feeling warm, fever, chills or shivering, sore throat or mouth ulcers. These may be signs of an infection which can be caused by low levels of white blood cells called neutrophils.
- Feeling very tired, weak, and short of breath. These may be signs of low red blood cell levels (anaemia).
- Bleeding or bruising more easily. These may be signs of low levels of blood platelets, components that help the blood clot (thrombocytopenia).

If any of the above apply to you (or you are not sure), talk to your doctor or nurse.

To minimise the above risks, you will be monitored for side effects daily for 14 days after the first infusion. Your doctor will decide how often you will be monitored after the first 14 days and will continue monitoring for a least 4 weeks after. Your doctor may need to administer additional medicines to control the side effects, e.g., glucocorticosteroids, tocilizumab and/or antibiotics.

Your doctor will regularly check your blood counts as the number of blood cells may decrease or if already low the number of blood cells may remain low.

Stay close (within 2 hours of travel) to the treatment centre where Aucatzyl was administered for at least 4 weeks. See section 3.

You will be asked to enrol in a long-term follow-up study or registry to better understand the long-term effects of Aucatzyl.

Do not donate blood, organs, tissues or cells for transplantation.

Children and adolescents

Aucatzyl should not be used in children and adolescents below 18 years of age.

Other medicines and Aucatzyl

Tell your doctor or nurse if you are taking, have recently taken or might take any other medicines.

In particular, tell your doctor or nurse before you are given Aucatzyl if:

- You are taking any medicines that weaken your immune system such as corticosteroids, since these medicines may interfere with the effect of Aucatzyl.
- You have previously received a treatment that targets the CD19 protein.

Vaccinations

You must not be given certain vaccines called live vaccines:

- In the 6 weeks before you are given the short course of chemotherapy (called lymphodepleting chemotherapy) to prepare your body for Aucatzyl.
- During Aucatzyl treatment.
- After treatment while the immune system is recovering.

Talk to your doctor if you need to have any vaccinations.

Pregnancy and breast-feeding

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor for advice before receiving this medicine. This is because the effects of Aucatzyl in pregnant or breast-feeding women are not known, and it may harm your unborn baby or your breast-fed child.

You will be given a pregnancy test before treatment starts. Aucatzyl should only be given if the result shows you are not pregnant. You should use contraception during treatment with Aucatzyl. If you are pregnant or think you may be pregnant after treatment with Aucatzyl, talk to your doctor immediately.

Driving and using tools and machines

Do not drive, use tools or machines, or take part in activities that need you to be alert for at least 8 weeks following infusion. Aucatzyl can cause problems such as altered or decreased consciousness, confusion and fits (seizures). See section 4, Possible side effects.

Aucatzyl contains sodium, potassium, and dimethyl sulfoxide (DMSO)

This medicine contains 1 131 mg sodium (main component of cooking/table salt) in the total dose. This is equivalent to 57% of the recommended maximum daily dietary intake of sodium for an adult.

This medicine contains 39 mg potassium per dose. To be taken into consideration by patients with reduced kidney function or patients on a controlled potassium diet.

Aucatzyl also contains DMSO which can cause severe allergic reactions.

3. How Aucatzyl is given

Giving your own blood cells to make Aucatzyl

Aucatzyl is made from your own white blood cells.

- Your doctor will take some of your blood using a tube (catheter) placed in your vein.
- Some of your white blood cells will be separated from your blood and the rest of your blood is returned to your body. This is called 'leukapheresis' and can take between 3 to 6 hours.
- Your white blood cells are used to make Aucatzyl specially for you. This may take around 21 days.

Other medicines you will be given before Aucatzyl

- From day 6 to day 3 before you receive Aucatzyl, you will be given a type of treatment called lymphodepleting chemotherapy. This will allow the modified T cells in Aucatzyl to multiply in your body after Aucatzyl is given to you. A delay in Aucatzyl treatment is possible depending on how you react to the chemotherapy.
- A bone marrow assessment is required before starting the lymphodepleting chemotherapy to determine the amount of Aucatzyl to be given in the first and second infusion.
- Approximately 30 minutes before you are given Aucatzyl you will be given paracetamol and diphenhydramine (an anti-allergic). This is to help prevent infusion reactions and fever.

How Aucatzyl is given

Aucatzyl will be given to you by a doctor in a qualified treatment centre experienced with this medicine.

- Your doctor will check that the Aucatzyl was prepared from your own blood by checking the patient identification information on the Aucatzyl infusion bag matches your details.
- Aucatzyl is given by infusion (drip) into a vein.
- Aucatzyl will be given to you by 2 infusions that are separated by approximately 9 days to achieve the total target dose. The first infusion will last no more than 10 minutes. If you notice any side effects, please inform your doctor immediately. The second infusion will usually last less than one hour.

- The amount of Aucatzyl given in the first and second infusion will depend on the extent of your leukaemia. The dose of obecabtagene autoleucel given in the first and second infusions is adjusted based on your leukaemia's severity. However, the total target dose remains unchanged no matter how advanced your leukaemia is.

Ask your doctor or nurse if you have doubts about how Aucatzyl is given to you.

After the first dose of Aucatzyl is given

- Stay close to the treatment centre (within 2 hours of travel) for at least 4 weeks.
- You will be monitored daily for 14 days after the first infusion so that your doctor can check that the treatment is working and if needed help you with any side effects, such as CRS, ICANS or infections (see section 2, Warnings and precautions).
- Your doctor will assess if your second dose of Aucatzyl will proceed as planned. If you are experiencing any serious symptoms, the second dose may need to be delayed or treatment may need to be stopped. After the second dose you also have to be monitored daily for 14 days after the infusion for possible side effects as in the first infusion.

If you miss an appointment

If you miss an appointment, call your doctor or the hospital as soon as possible to reschedule your appointment.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Serious side effects

Aucatzyl may cause side effects that can be serious or life-threatening. **Tell your doctor immediately** if you get any of the following side effects after your Aucatzyl infusion:

Very common: may affect more than 1 in 10 people

- Fever and chills, low blood pressure, low oxygen in the blood which may cause symptoms such as fast or uneven heartbeat and shortness of breath. These may be signs of a serious problem called cytokine release syndrome (CRS). Other symptoms of cytokine release syndrome are nausea, vomiting, diarrhoea, fatigue, muscle pain, joint pain, swelling, headache, heart, lung and kidney failure and liver injury.
- Loss of consciousness or decreased level of consciousness, involuntary shaking (tremor), seizures, difficulty speaking, slurred speech and understanding speech. These may be signs of serious problems with your nervous system called immune effector cell-associated neurotoxicity syndrome (ICANS).
- Feeling warm, fever, chills or shivering, mouth ulcers or sore throat. These may be signs of infection.
- Feeling very tired, weak, and shortness of breath. These may be signs of low levels of red blood cells (anaemia).
- Abnormally low levels of neutrophils, a type of white blood cell (neutropenia), which may increase your risk of infection.
- Bleeding or bruising more easily. These may be signs of low levels of platelets, components that help the blood to clot (thrombocytopenia).

If you get any of the side effects above after being given Aucatzyl, **seek urgent medical help.**

Other possible side effects

Other side effects are listed below. If these side effects become severe or serious, or if you are concerned about them, tell your doctor immediately.

Very common: may affect more than 1 in 10 people

- low number of white blood cells (leukopenia)
- low levels of lymphocytes, a type of white blood cell (lymphopenia)
- neutropenia with fever (febrile neutropenia)
- feeling sick (nausea)
- constipation
- diarrhoea
- belly (abdominal) pain
- vomiting
- headache
- abnormal brain function (encephalopathy)
- dizziness
- fever (pyrexia)
- rapid heartbeat (tachycardia)
- low blood pressure (hypotension)
- bleeding (haemorrhage)
- pain
- tiredness (fatigue)
- swelling (oedema)
- cough
- decreased appetite
- joint pain (musculoskeletal pain)
- rash
- fungal infection
- weight loss
- problems with blood clotting (coagulopathy)
- high levels of serum ferritin, a protein that stores iron in the body (hyperferritinaemia)
- increase in liver enzymes seen in blood tests

Common: may affect up to 1 in 10 people

- chills
- build-up of white blood cells, damaging organs, including the bone marrow, liver, and spleen, and destroying other blood cells (haemophagocytic lymphohistiocytosis)
- low levels of immunoglobulins (antibodies) in the blood leading to a high risk of infection (hypogammaglobulinaemia)
- inflammation of the lining of the mouth (stomatitis)
- irregular heartbeat (arrhythmia)
- heart (cardiac) failure
- infusion-related reaction including symptoms like fever, chills, rash, or difficulty breathing
- uncontrolled trembling or shaking movements in one or more parts of your body (tremor)
- confusion (delirium)

Development of new types of cancer beginning in T cells (secondary malignancy of T cell origin) has been reported in patients using other CAR T medicines.

Tell your doctor if you have any of the side effects listed above. If these side effects become severe or serious, or if you are concerned about them, tell your doctor immediately.

Reporting of side effects

If you get any side effects, talk to your doctor. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects, you can help provide more information on the safety of this medicine.

5. How to store Aucatzyl

The following information is intended for doctors only.

Do not use this medicine after the expiry date which is stated on the infusion bag label after 'EXP'.

Store and transport frozen in the vapour phase of liquid nitrogen ≤ −150 °C. Do not thaw the product until it is ready to be used. Shelf life after thawing: 1 hour.

Do not refreeze.

Do not use this medicine if the infusion bag is damaged or leaking.

Local guidelines on handling of waste of human-derived material should be followed for unused medicine or waste material.

6. Contents of the pack and other information

What Aucatzyl contains

The active substance is obecabtagene autoleucel. The medicine is packaged in 3 or more infusion bags containing a target total of 410×10^6 anti-CD19 CAR-positive viable T cells to enable a split dosing regimen.

The other ingredients are disodium edetate, dimethyl sulfoxide (DMSO), human albumin solution and phosphate buffered saline (PBS), consisting of potassium dihydrogen phosphate, sodium chloride, disodium phosphate, potassium chloride, and water for injections. See section 2, Aucatzyl contains sodium, potassium and dimethyl sulfoxide (DMSO).

This medicine contains genetically modified human blood cells.

What Aucatzyl looks like and contents of the pack

Aucatzyl is a colourless to pale yellow, very opalescent dispersion for infusion. It is supplied in 3 or more infusion bags individually packed within an overwrap in a metal cassette. The metal cassettes are packed into a ModPak, which is transported in a cryoshipper.

Marketing Authorisation Holder
Autolus GmbH
Im Schwarzenbach 4
79576 Weil am Rhein
Germany

Tel: 00800 0825 0829 (toll free, this number is valid in all EU countries)

Manufacturer
Marken Germany GmbH
Moenchhofallee 13
65451 Kelsterbach
Germany

This leaflet was last revised in

This medicine has been given ‘conditional approval’.

This means that there is more evidence to come about this medicine.

The European Medicines Agency will review new information on this medicine at least every year and this leaflet will be updated as necessary.

Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu.

This leaflet is available in all EU/EEA languages on the European Medicines Agency website.

The following information is intended for healthcare professionals only (see SmPC section 6.6):

Aucatzyl is intended for autologous use.

Treatment consists of a split dose for infusion containing a dispersion of CD19 CAR-positive viable T cells in 3 or more infusion bags.

The target dose of Aucatzyl is 410×10^6 CD19 CAR-positive viable T cells supplied in 3 or more infusion bags.

The treatment regimen consists of a split dose for infusion is 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 (see section below - 'Bone marrow assessment').
- Additionally, see the Release for Infusion Certificate (RfIC) and the Dose Schedule Planner for the actual cell counts and volumes to be infused and to select the appropriate dose regimen.

Confirm availability of Aucatzyl before starting the lymphodepleting chemotherapy regimen (see SmPC section 4.4). The manufacturing time (time from leukapheresis receipt to product certification) is around 20 (range: 17-43) days.

Patients should be clinically re-assessed prior to administration of lymphodepleting chemotherapy and Aucatzyl to ensure the patient is eligible for therapy.

Receipt and storage of Aucatzyl:

- Aucatzyl is supplied directly to the cellular therapy laboratory associated with the infusion centre in the vapour phase of a liquid nitrogen cryoshipper (≤ -150 °C).
- The patient's identity must match the patient identifiers on the Aucatzyl RfIC and infusion bag label.
- **Confirm the patient's identity on the infusion bags with the patient identifiers on the cryoshipper**, see Figure 1. Contact Autolus at 00800 0825 0829 if there are any discrepancies between the labels and the patient identifiers.
- Keeping the infusion bag(s) in the metal cassette(s), transfer Aucatzyl to the on-site controlled-access vapour phase of liquid nitrogen for storage ≤ -150 °C (until ready for thaw and administration).
- **Time out of the vapour phase liquid nitrogen environment should be kept to an absolute minimum to avoid premature product thaw (it is recommended not to exceed 90 seconds).**

Administration

Strictly follow Administration instructions to minimise dosing errors.

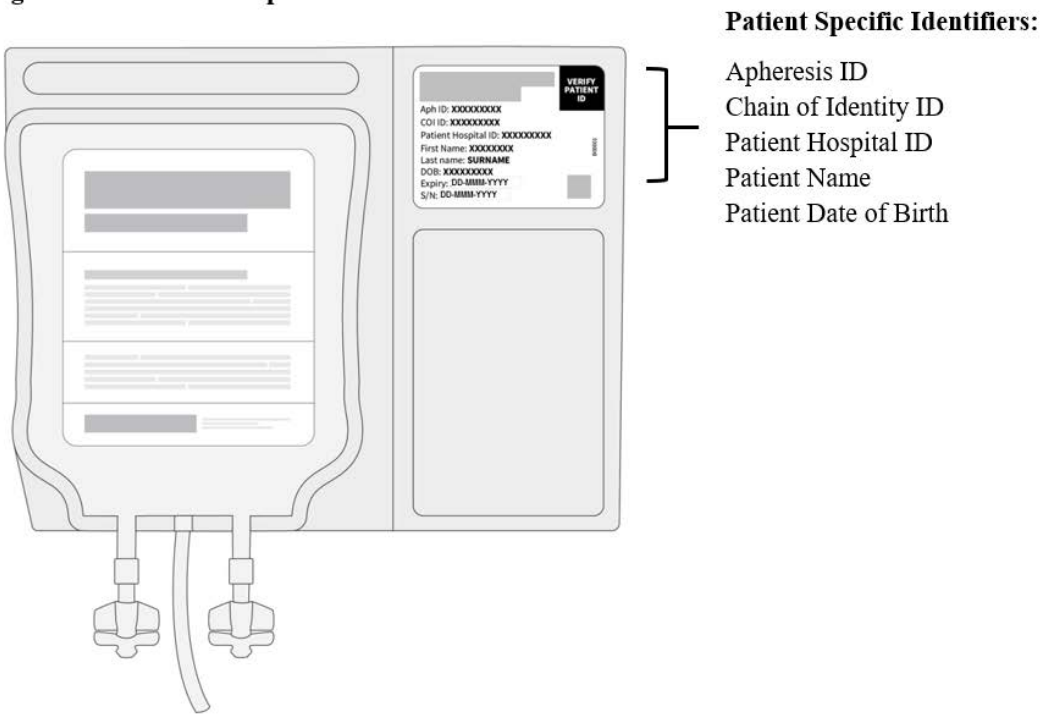
Aucatzyl is for autologous use only. The patient's identity must match the patient identifiers on the Aucatzyl infusion bag. Do not infuse Aucatzyl if the information on the patient-specific label does not match the intended patient.

Preparation of the patient for Aucatzyl infusion

Bone marrow assessment

A BM assessment must be available from a biopsy and/or aspirate sample obtained within 7 days prior to the commencement of the lymphodepleting chemotherapy. The BM assessment will be used to determine the Aucatzyl dose regimen: High tumour burden regimen if blast percentage is > 20% or Low Tumour Burden Regimen if blast percentage is ≤ 20%, see Figure 2.

Figure 1: Patient Specific Identifiers



If BM assessment results are inconclusive:

- Repeat biopsy or aspirate (but only once). NOTE a repeat biopsy or aspirate must only be taken prior to lymphodepleting chemotherapy.
- If results remain inconclusive, proceed with High tumour burden regimen (i.e., administration of the 10×10^6 dose on day 1) per the Aucatzyl tumour burden adjusted split dose regimen.

Figure 2: Tumour burden adjusted split dose regimen

High Tumour Burden Dose Regimen
(Bone marrow blast > 20% or inconclusive)

Day 1		**Day 10 (± 2 days)**
10 × 10^6 dose administered via ***syringe****	➡	**100 × 10^6 dose** administered via *bag infusion*+ and **300 × 10^6 dose** administered via *bag infusion*+

Low Tumour Burden Dose Regimen
(Bone marrow blast ≤ 20%)

Day 1		**Day 10 (± 2 days)**
100 × 10^6 dose administered via *bag infusion*+	➡	**10 × 10^6 dose** administered via ***syringe**** and **300 × 10^6 dose** administered via *bag infusion*+

* Refer to RfIC for exact volume to be administered via syringe. The 10 × 10^6 CD19 CAR-positive viable T cell bag configuration typically contains an overfill, and there it is important to withdraw Only the volume specified.
+ The 100 × 10^6 and 300 × 10^6 doses will be suspended in one or more infusion bags.

Bridging therapy

Bridging therapy can be considered according to the prescriber's choice prior to infusion to reduce tumour burden or stabilise the disease.

Pretreatment (lymphodepleting chemotherapy)

- Confirm availability of Aucatzyl prior to starting lymphodepleting chemotherapy. The manufacturing time (time from leukapheresis receipt to product certification) is around 20 days (range: 17- 43 days).
- Administer the lymphodepleting chemotherapy regimen before infusion of Aucatzyl: fludarabine (FLU) 30 mg/m^2/day intravenously and cyclophosphamide (CY) 500 mg/m^2/day intravenously. FLU and CY will be given together for 2 days and fludarabine alone on the third and fourth day (total dose: FLU 120 mg/m^2; CY 1 000 mg/m^2). For dose modifications of cyclophosphamide and fludarabine, see corresponding Summaries of Product Characteristics of cyclophosphamide and fludarabine.
- Retreatment with lymphodepleting chemotherapy in patients who could not receive the Aucatzyl dose on day 1 as planned could be considered if there is an Aucatzyl dose delay of more than 10 days. Lymphodepleting chemotherapy should not be repeated after the first dose of Aucatzyl is administered. Infuse Aucatzyl 3 days (± 1 day) after completion of lymphodepleting chemotherapy (day 1), allowing a minimum 48-hour washout.

  The Aucatzyl treatment should be delayed in some patient groups at risk. Retreatment with lymphodepleting chemotherapy in patients who could not receive the Aucatzyl dose on day 1 as planned could be considered if there is an Aucatzyl dose delay of more than 10 days. A delay to the second split dose may be required to manage toxicities.

Premedication

- To minimise the risk of an infusion reaction, premedicate with paracetamol (1 000 mg orally) and diphenhydramine 12.5 to 25 mg intravenously or orally (or equivalent medicinal products) before the infusion of Aucatzyl. Prophylactic use of systemic corticosteroids is not recommended.

Preparation of Aucatzyl

Before administration, it must be confirmed that the patient's identity matches the unique patient information on the Aucatzyl infusion bag and the RfIC presented in the Autolus Scheduling Portal, the RfIC will also be provided in the cryoshipper. The total number of Aucatzyl infusion bags to be administered must also be confirmed with the patient-specific information on the RfIC.

Precautions to be taken before handling or administering the medicinal product

Aucatzyl must be transported within the facility in closed, break-proof, leak-proof containers.

This medicinal product contains genetically modified human blood cells. Healthcare professionals handling Aucatzyl must take appropriate precautions (wearing gloves, protective clothing and eye protection) to avoid potential transmission of infectious diseases.

Preparation prior to administration

- Keep the infusion bag(s) in the metal cassette(s) and transfer Aucatzyl to the on-site controlled-access vapour phase of liquid nitrogen for storage ≤ -150 °C (until ready for thaw and administration).
- **Time out of the vapour phase liquid nitrogen environment should be kept to an absolute minimum to avoid premature product thaw (it is recommended not to exceed 90 seconds).**

Planning prior to Aucatzyl preparation

The patient batch-specific RfIC and Dose Schedule Planner will be provided in the cryoshipper and via Scheduling Portal.
Confirm the patient identifiers on RfIC and infusion bags match, Figure 1.

1. Ensure the patient's BM assessment results are available (see SmPC section 4.2, Bone marrow assessment).

   NOTE: The patient's BM blast assessment results will be used to select the appropriate dosing regimen: High tumour burden dose regimen if the blast percentage is > 20% or inconclusive or Low tumour burden dose regimen if the blast percentage is ≤ 20%, see Figure 2.

2. The Aucatzyl Dose Schedule Planner, provided with the RfIC, assists the determination of the appropriate dose regimen to be administered on day 1 (3 days (± 1 day) after the completion of lymphodepleting chemotherapy) and day 10 (± 2 days). Record the following information on the Dose Schedule Planner:
   a. The blast percentage from the patient's BM assessment.
   b. The Aucatzyl bag serial number(s); number of bag type required for each dose; and the specified volume to administer via syringe (for the 10×10^6 dose) transcribed from the RfIC.

3. The completion of the Aucatzyl Dose Schedule Planner will guide the treating physician on the number of bags and the respective dose required, and the preparation of Aucatzyl for the day 1 and day 10 (± 2 days) dose. The RfIC provides more information and is located inside the lid of the cryoshipper.

Transfer and thawing

- Using the completed Dose Schedule Planner for guidance transfer ONLY the cassette(s) / infusion bag(s) required for the given dosing day from the on-site vapour phase liquid nitrogen storage to an appropriate transfer vessel (i.e., a vapour phase liquid nitrogen cryoshipper, maintaining temperature ≤ -150 °C) for transport to the bag thaw location.

- Transfer the required cassettes one by one, confirming the Aucatzyl bag serial numbers and patient identifiers on each infusion bag label, see Figure 1.
- **Time out of the vapour phase liquid nitrogen environment should be kept to an absolute minimum to avoid premature product thaw (it is recommended not to exceed 90 seconds).**
- If more than one infusion bag has been required on a given dosing day, thaw one infusion bag at a time. Do NOT remove subsequent bags from the vapour phase liquid nitrogen storage (≤ -150 °C) until infusion of the previous bag is complete.
- Leave the Aucatzyl infusion bag in its overwrap, thaw at 37 °C using a water bath or dry thaw method until there are no visible frozen clumps left in the bag. Each bag should be gently massaged until the cells have just thawed. Thawing of each infusion bag between 2 to 8 minutes. Remove from the water bath or thaw device immediately after thawing is complete. Carefully remove the infusion bag from the overwrap taking care to avoid damage to the bag and ports.
- Gently mix the contents of the bag to disperse clumps of cellular material and administer immediately to the patient.
- Do not refreeze or refrigerate thawed product.

Infusion instructions

Aucatzyl is for autologous and intravenous use only. For premedication and availability of tocilizumab or suitable alternative anti-IL-6 therapy (e.g., siltuximab) see SmPC section 4.2.

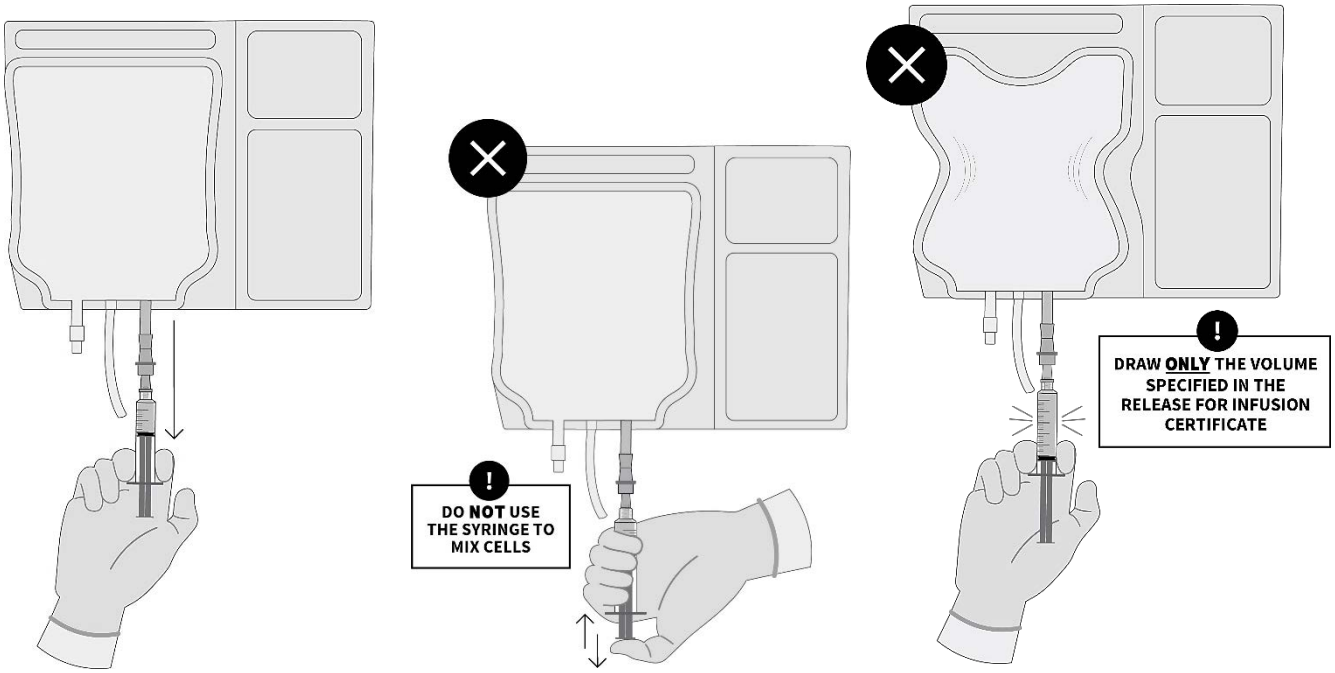
The patient's identity must match the patient identifiers on the Aucatzyl Release for Infusion Certificate (RfIC) and infusion bag.

*Dose administration for **10 × 10^6** CD19 CAR-positive viable T cells (syringe-based infusion)*

The 10 × 10^6 cell dose should be administered via syringe as this is the only way to deliver the volume specified on the RfIC. Withdrawal of the **10 × 10^6** dose into the syringe should be carried out as follows:

- Prepare and administer Aucatzyl using aseptic technique.
- Gently mix the contents of the bag to disperse clumps of cellular material.
- **The volume to be administered for the 10 × 10^6 dose is specified on the RfIC.**
- Use the smallest Luer-lock tip syringe necessary (1, 3, 5, or 10 mL) with a Luer-lock bag spike to **draw up the volume specified on the RfIC.**
    - **Do NOT** use a leukodepleting filter.
    - **Do NOT** use the syringe to mix the cells, **see Figure 3.**

Figure 3: Syringe infusion guidance for 10 × 10^6 dose



- Prime the tubing with sodium chloride 9 mg/mL (0.9%) solution for injection prior to infusion.
- Once Aucatzyl has been drawn into the syringe, verify the volume and administer as an intravenous infusion (as a slow push approximately 0.5 mL/minute) through a central venous line (or large peripheral venous access line appropriate for blood products).
- Complete infusion at room temperature within 60 minutes post-thaw and flush the tubing line with 60 mL of sodium chloride 9 mg/mL (0.9%) solution for injection.
- Dispose of any unused portion of Aucatzyl (according to local biosafety guidelines).

*Dose administration for **100 × 10^6** and/or **300 × 10^6** CD19 CAR-positive viable T cells*

- Refer to the RfIC and the Dose Schedule Planner for the following details:
  - The volume and total CD19 CAR-positive viable T cell number contained in each infusion bag.
  - The dose to be administered on the given dosing day and the number of bags required to deliver the specified CD19 CAR-positive viable T cell dose.
  - If more than one bag is needed, thaw subsequent bag after the previous bag is fully administered.
- Prime the tubing with sodium chloride 9 mg/mL (0.9%) solution for injection prior to infusion.
- Administer Aucatzyl via a gravity or peristaltic pump assisted intravenous infusion through a central venous line (or large peripheral venous access line appropriate for blood products).
  - **Do NOT** use a leukodepleting filter.
  - Aseptic techniques must be applied when performing a venepuncture, spiking the ports, and through cell administration process.
  - Gently mix the contents of the bag during Aucatzyl infusion to disperse cell clumps.
  - Infuse the entire content of the Aucatzyl infusion bag at room temperature within 60 minutes post-thaw using a gravity or peristaltic pump. After the entire contents of the infusion bag is infused, rinse the bag with 30 mL of sodium chloride 9 mg/mL (0.9%) solution for injection, then flush the tubing line with 60 mL of sodium chloride 9 mg/mL (0.9%) solution for injection.
  - Repeat steps 1-3 for any additional infusion bags required on the given dosing day. **Do Not** initiate thaw of the next bag until infusion of the previous bag is complete.

Monitoring

- Patients should be monitored daily for 14 days after the first infusion for signs and symptoms of potential CRS, ICANS and other toxicities.
- Frequency of monitoring after the first 14 days should be carried out at the physician's discretion and should be continued for at least 4 weeks after infusion.
- Instruct patients to remain within close proximity of the qualified treatment centre (within 2 hours of travel) for at least 4 weeks following the first infusion.

Measures to take in case of accidental exposure

In case of accidental exposure local guidelines on handling of human-derived material must be followed. Work surfaces and materials which have potentially been in contact with Aucatzyl must be decontaminated with appropriate disinfectant.

Precautions to be taken for the disposal of the medicinal product

Unused medicinal product and all material that has been in contact with Aucatzyl (solid and liquid waste) must be handled and disposed of as potentially infectious waste in accordance with local guidelines on handling of human-derived material.

ANNEX IV

CONCLUSIONS ON THE GRANTING OF THE CONDITIONAL MARKETING AUTHORISATION PRESENTED BY THE EUROPEAN MEDICINES AGENCY

Conclusions presented by the European Medicines Agency on:

- **Conditional marketing authorisation**

The CHMP having considered the application is of the opinion that the risk-benefit balance is favourable to recommend the granting of the conditional marketing authorisation as further explained in the European Public Assessment Report.