22 May 2025
EMA/197444/2025
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Aucatzyl

International non-proprietary name: obecabtagene autoleucel

Procedure No. EMEA/H/C/005907/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

Abbreviation	Description
4-1BB	Cluster of differentiation 137 (TNF-receptor superfamily 9)
AE	Adverse event
AML	Acute myeloid leukaemia
ALL	Acute lymphoblastic leukaemia
$AUC_{0\text{-}28d}$	Area under the curve (exposure) from Day 0 to Day 28
AUTO1	Obecabtagene autoleucel
B ALL	B-cell precursor acute lymphoblastic leukaemia
BM	Bone marrow
BOR	Best overall remission
brexu-cel	Brexucabtagene autoleucel
CAT	CD19 CAR (expressed in obe-cel); (murine) CAT13.1E10 hybridoma
CAR	Chimeric antigen receptor
CD	Cluster of differentiation
CD19 CAR	CAR directed against CD19
COVID-19	Coronavirus disease 2019
CI	Confidence interval
C_{max}	Maximum concentration
CNS	Central nervous system
CR	Complete remission
CRh	Complete remission with partial hematologic recovery
CRi	Complete remission with incomplete hematologic recovery
CRS	Cytokine release syndrome
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
ddPCR	Droplet digital polymerase chain reaction
DOCR	Duration of complete remission
DOR	Duration of remission
ECA	External control arm
ECOG	Eastern Cooperative Oncology Group
ECOG PfS	Eastern Cooperative Oncology Group performance status
EFS	Event-free survival
EMD	Extramedullary disease
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer quality of life questionnaire
EQ-5D-5L	EuroQol-5-dimensions-5-levels questionnaire
ESS	Effective sample size
FMC63	CD19 CAR (expressed in other CARs, e.g. tisagenlecleucel)

Abbreviation	Description
GM-CSF	Granulocyte macrophage colony stimulating factor
GvHD	Graft-versus-host disease
HCT	Historical clinical trial
HLH	Haemophagocytic lymphohistiocytosis
HLGT	High-level group term
HR	Hazard ratio
HRQoL	Health-related quality of life
ICANS	Immune effector cell-associated neurotoxicity syndrome
ICU	Intensive care unit
IFN	Interferon
IgG	Immunoglobulin G
IL	Interleukin
IRRC	Independent Response Review Committee
ITC	Indirect treatment comparison
ITT	Intent-to-treat
IV	Intravenous
KM	Kaplan-Meier
LD	Lymphodepletion
MAIC	Matching-adjusted indirect comparison
MAS	Macrophage activation syndrome
MDS	Myelodysplastic syndrome
MedDRA	Medical Dictionary for Regulatory Activities
mITT	Modified intent-to-treat
MRD	Minimal residual disease
NE	Not estimable
NGS	Next-generation sequencing
obe-cel	Obecabtagene autoleucel
OR	Odds ratio
ORR	Overall remission rate
OS	Overall survival
PCR	Polymerase chain reaction
PFS	Progression-free survival
Ph	Philadelphia chromosome
PK	Pharmacokinetic
PT	Preferred term
PS	Propensity score
r/r	Relapsed or refractory
RMST	Restricted mean survival time
SAE	Serious adverse event

Abbreviation	Description
SCT	Stem cell transplant
SE	Standard error
SoC	Standard of care
SOC	System organ class
TBI	Total body irradiation
TEAE	Treatment-emergent adverse event
tisa-cel	Tisagenlecleucel
TKI	Tyrosine kinase inhibitor
VAS	Visual analogue scale

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Autolus GmbH submitted on 8 February 2024 an application for marketing authorisation to the European Medicines Agency (EMA) for Aucatzyl, through the centralised procedure falling within the Article 3(1) and point 1 of Annex of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 25 March 2021.

Aucatzyl, was designated as an orphan medicinal product EU/3/22/2605 on 13 April 2022 in the following condition: Treatment of acute lymphoblastic leukaemia.

Following the CHMP positive opinion on this marketing authorisation and at the time of the review of the orphan designation by the Committee for Orphan Medicinal Products (COMP), this product was removed from the Union Register of designated orphan medicinal products on 12 June 2025. More information on the COMP's review can be found in the orphan designation withdrawal assessment report published under the 'Assessment history' tab on the Agency's website: https://www.ema.europa.eu/en/medicines/human/EPAR/aucatzyl

The applicant applied for the following indication:

Aucatzyl is indicated for the treatment of adult patients (≥18 years) with relapsed or refractory B cell precursor acute lymphoblastic leukaemia (ALL).

1.2. Legal basis, dossier content

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application. The applicant indicated that obecabtagene autoleucel was considered to be a new active substance.

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain test(s) or study(ies).

1.3. Information on paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) P/0094/2023 on the agreement of a paediatric investigation plan (PIP) and the granting of a (product-specific) waiver for paediatric population from birth to less than 6 kg of bodyweight for dispersion for infusion, intravenous use.

At the time of submission of the application, the PIP P/0094/2023 was not yet completed as some measures were deferred.

1.4. Information relating to orphan market exclusivity

1.4.1. Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did submit a critical report addressing the possible similarity with authorised

orphan medicinal products.

1.5. Applicant's request(s) for consideration

1.5.1. Conditional marketing authorisation and accelerated assessment

The applicant requested consideration of its application for a conditional marketing authorisation in accordance with Article 14-a of the above-mentioned Regulation

The applicant requested accelerated assessment in accordance to Article 14 (9) of Regulation (EC) No 726/2004.

1.5.2. New active substance status

The applicant requested the active substance obecabtagene autoleucel contained in the above medicinal product to be considered as a new active substance, as the applicant claims that it is not a constituent of a medicinal product previously authorised within the European Union.

1.6. PRIME

Aucatzyl was granted eligibility to PRIME on 25 March 2021 in the following indication: treatment of relapsed or refractory B cell acute lymphoblastic leukaemia.

Eligibility to PRIME was granted at the time in view of the following:

- Long-term survival of adult patients with relapsed B-ALL is dependent upon achieving CR induced through salvage chemotherapy (or more recently through immunotherapy) followed by allogeneic haematopoietic stem cell transplantation (HSCT).
- There is a need for improved therapies to increase remission rates, bridge patients until transplant, and ultimately improve survival in adults with relapsed/refractory ALL. Adult patients are the ones experiencing the highest unmet medical need in this condition.
- The submitted nonclinical data, showing a strong pharmacological rationale for use in ALL, further supported by results from a cell-line derived xenograft mouse model, demonstrate the anti-tumour activity of the product.
- The reported rates of complete remission are comparable to those seen in the registrational study for Kymriah, which was conducted in a younger population.
- A sustained duration of remission is especially important in a population, such as the adult one, for which allogeneic HSCT is not always an option. The safety profile appears manageable, increasing the possibility of use in the older adult population.

Upon granting of eligibility to PRIME, Carla Herberts was appointed by the CHMP as rapporteur.

A kick-off meeting was held on 13 July 2021. The objective of the meeting was to discuss the development programme and regulatory strategy for the product. The applicant was recommended to address the following key issues through relevant regulatory procedures:

- Batch release testing exemption - application for an exemption from re-testing batches upon import into the EU
- comparability of drug product
- provide information on the planned drug product specifications/acceptance criteria
- consider the use of the certification procedure for ATMPs

- explain how the risk of insertional mutagenesis and potential clonality is going to be monitored in the clinical setting
- provision of data on persistence of the product (number of memory T cells)
- discuss the split dosing regimen used in the clinical trials
- follow up of patients who only received a single dose. The applicant should discuss the criteria for not giving a 2nd dose and the expected impact (and how this will be monitored)

1.7. Scientific advice

The applicant received the following scientific advice on the development relevant for the indication subject to the present application:

Date	**Reference**	**SAWP co-ordinators**
14 November 2019	EMEA/H/SA/4252/1/2019/SME/ADT/III	Hans Ovelgönne and Rune Kjeken
27 January 2022	EMA/SA/0000069659	Karri Penttila and Ivana Haunerova

The scientific advice pertained to the following quality, non-clinical, and clinical aspects:

- The control strategy of the AUTO1 vector and cell manufacturing processes and final DP quality control; the proposed process validation strategy for both the vector and cell manufacturing processes; the strategy to omit or reduce the PPQ; plans to change the DP potency assay; stability and shelf-life proposals; the use of full patient name as part of the COI identifiers for the marketed product; the use of the current final drug product formulation for manufacturing in the commercial phase;
- the proposed non-clinical package to support a marketing authorisation application;
- the proposed study design of the AUTO1 confirmatory Phase 2 adult ALL study, in particular, the study population, the single arm design, the dose and dose schedule, the primary and efficacy endpoints, the statistical analyses, the safety monitoring and data collection;
- the long term follow-up study plan;
- the staggered approach to investigate the drug in paediatric patients in preparation of the PIP, and the proposed preliminary phase 2 paediatric study design;
- the plan to amend the AUTO1 Phase 2 study into an umbrella design to evaluate other potential CAR T cell products.

1.8. Steps taken for the assessment of the product

The CAT Rapporteur and Co-Rapporteur appointed by the CHMP were:

CAT Rapporteur: Berendina Maria van den Hoorn CAT Co-Rapporteur: Claire Beuneu

The application was received by the EMA on	8 February 2024
The procedure started on	28 March 2024
The CAT Rapporteur's first assessment report was circulated to all CAT and CHMP members on	17 June 2024
The CAT Co-Rapporteur's assessment was circulated to all CAT and CHMP members on	01 July 2024
The PRAC Rapporteur's first assessment report was circulated to all	28 June 2024

PRAC members on	
The PRAC agreed on the PRAC assessment overview and advice to CAT during the meeting on	11 July 2024
The CAT agreed on the consolidated list of questions to be sent to the applicant during the meeting on	19 July 2024
The applicant submitted the responses to the CAT consolidated list of questions on	17 January 2025
The CAT Rapporteur circulated the joint assessment report on the responses to the list of questions to all CAT and CHMP members on	25 February 2025
The PRAC agreed on the PRAC assessment overview and advice to CHMP during the meeting on	13 March 2025
The CAT agreed on a list of outstanding issues in writing and/or in an oral explanation to be sent to the applicant on	21 March 2025
The applicant submitted the responses to the CAT list of outstanding issues on	15 April 2025
The CAT Rapporteurs circulated the joint assessment report on the responses to the list of outstanding issues to all CAT and CHMP members on	13 May 2025
The CAT, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Aucatzyl on	16 May 2025
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Aucatzyl on	22 May 2025
The CAT and CHMP adopted a report on similarity of Aucatzyl with Tecartus, Blincyto, Besponsa and Kymriah on	16/22 May 2025
Furthermore, the CAT and CHMP adopted a report on new active substance (NAS) status of the active substance contained in the medicinal product	16/22 May 2025

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

The claimed therapeutic indication is:

Aucatzyl is indicated for the treatment of adult patients (≥18 years) with relapsed or refractory B cell precursor acute lymphoblastic leukaemia (B ALL).

2.1.2. Epidemiology

Approximately 60% of ALL occurs in patients aged younger than 20 years, with a peak incidence between 2 to 5 years; the incidence rises again after the age of approximately 50 years (*Pui et al, 2008*[1]). In the EU, approximately 9,250 new leukaemia cases were estimated for 2022 (*ECIS, 2023*[2]). In a recent DARWIN EU Report, the 5-year partial prevalence estimates for ALL, as of 01-Jan-2020, ranged between 0.44 (0.27 to 0.71) and 0.65 (0.59 to 0.71) per 10,000 (*ENCEPP, 2023*[3]). Similar numbers are reported in the US, with approximately 6,540 new cases and 1,390 deaths estimated in 2023 (*SEER, 2023*[4]).

Whilst the cure rates and survival outcomes for paediatric patients with ALL have improved dramatically over the past several decades (*SEER, 2023*[5]), adults have the poorest 5-year overall survival (OS) rates being 39.2% for patients between the ages of 40 and 64 and only 19.1% for patients ≥ 65 years of age. Thus, OS decreases substantially with increasing age which is likely due to older patients tending to have disease with intrinsic unfavourable biology for B ALL, more medical comorbidities and also an inability to tolerate standard chemotherapy regimens (*Terwilliger and Abdul-Hay, 2017*[6]), although there may also be a proportion of younger adults who are particularly challenging to treat as they are patients who were diagnosed at a younger age with a long history of multiple treatments and lack of durable remissions, so are less likely to respond to any additional salvage therapies (*Trama et al, 2016*[7]). Indeed, in contrast to paediatric B ALL, the prognosis for adult B ALL has remained unchanged during the last two to three decades with long-term (> 3 years) remission rates of approximately 40% (*Paul et al, 2019*[8]). Adult patients with r/r disease is therefore common and is associated with a significant mortality rate, with median survival of less than one year (*Gökbuget et al, 2012*[9]*; Kantarjian et al, 2017*[10]*; Aldoss et al, 2017*[11]).

2.1.3. Biologic features

B ALL is a serious life-threatening and debilitating malignant disease. It is characterised by the malignant transformation and proliferation of non-functional, clonal B-precursor cells in the BM leading to an abundance of lymphoblasts (frequently referred to as 'blasts') and suppression of normal haematopoiesis. Over time, this massive production of lymphoblasts leads to an insufficient production of all normal blood cells. This seriously compromises the patient's immune function, leading to infections, bleeding complications and anaemia. Moreover, the spread of lymphoblasts into any organ

[1] Pui CH, Robison LL, Look AT (2008). Acute lymphoblastic leukaemia. Lancet; 371(9617):1030-1043.
[2] ECIS (2023). Estimates of cancer incidence and mortality for 2022, for all countries. Available at: https://ecis.jrc.ec.europa.eu/explorer.php?$0-0$1-All$2-All$4-1,2$3-55$6-0,85$5-2022,2022$7-7$CEstByCountry$X0_8-3$X0_19-AE27$X0_20-No$CEstBySexByCountry$X1_8-3$X1_19-AE27$X1_-1-1$CEstByIndiByCountry$X2_8-3$X2_19-AE27$X2_20-No$CEstRelative$X3_8-3$X3_9-AE27$X3_19-AE27$CEstByCountryTable$X4_19-AE27. Last accessed on 18 December 2023.
[3] ENCePP (2023). C1-001: Prevalence of rare blood cancers in Europe - report dated 28 March 2023, Version 3.2. Available at: https://www.encepp.eu/encepp/openAttachment/studyResult/104210;jsessionid=JacoSQWLozxu43dq3t_kYo68XVAeTZYBvq9wo2dx979iTQYrYsY7!-1928679420. Last accessed on 23-Nov-2023.
[4] SEER (2023). Surveillance, Epidemiology, and End Results Program Cancer Stat Facts. Cancer Stat Facts: Leukemia — Acute Lymphocytic Leukemia (ALL) At A Glance. Available at: https://seer.cancer.gov/statfacts/html/alyl.html. Last accessed: 21-Nov-2023.
[5] SEER (2023). Surveillance, Epidemiology, and End Results Program Cancer Stat Facts. Cancer Stat Facts: Leukemia — Acute Lymphocytic Leukemia (ALL) At A Glance. Available at: https://seer.cancer.gov/statfacts/html/alyl.html. Last accessed: 21-Nov-2023.
[6] Terwilliger T, Abdul-Hay M (2017). Acute lymphoblastic leukemia: a comprehensive review and 2017 update. Blood Cancer; 7(6):e577.
[7] Trama A, Botta L, Foschi R, et al (2016). Survival of European adolescents and young adults diagnosed with cancer in 2000-07: population-based data from EUROCARE-5. Lancet Oncol; 17(7):896-906.
[8] Paul S, Rausch CR, Nasnas PE, et al (2019). Treatment of relapsed/refractory acute lymphoblastic leukemia. Clin Adv Hematol Oncol; 17(3):166-175.
[9] Gökbuget N, Stanze D, Beck J, et al (2012). Outcome of relapsed adult lymphoblastic leukemia depends on response to salvage chemotherapy, prognostic factors, and performance of stem cell transplantation. Blood;120(10):2032-2041.
[10] Kantarjian H, Stein A, Gökbuget N, et al (2017). Blinatumomab versus Chemotherapy for Advanced Acute Lymphoblastic Leukemia. N Engl J Med; 376(9):836-847.
[11] Aldoss I, Song J, Stiller T, et al (2017). Correlates of resistance and relapse during blinatumomab therapy for relapsed/refractory acute lymphoblastic leukemia. Am J Hematol; 92(9):858-865.

of the body (extramedullary disease [EMD]) makes the treatment and the prognosis even more challenging and contributes to the overall disease burden. If untreated, B ALL will progress rapidly and is generally fatal.

2.1.4. Clinical presentation, diagnosis and stage/prognosis

Typically, B ALL is classified as either immature or mature. In approximately 87% of adult B ALL cases, the malignancy occurs in the immature B precursor cells (*Moorman et al, 2010*[12]). B ALL is also classified based on the presence of the most frequent genetic aberration in ALL patients, the Philadelphia chromosome (Ph) translocation. This is present (denoted by Ph+) in approximately 20-30% of adult B ALL compared to only 5% of childhood B ALL. In addition to a high disease burden based on blast cells in the BM and extent of disease based on EMD, disease characteristics such as being Ph+ and other cytogenetic/molecular abnormalities are considered high-risk features associated with poorer outcomes (*Sawalha and Advani, 2018*[13]). There are also demographic characteristics that have been associated with poorer outcomes, including being of Hispanic ethnicity (*Bencomo-Alvarez et al, 2021*[14]), young adults (*Trama et al, 2016*[15]) and elderly (*Sawalha and Advani, 2018*[16]).

2.1.5. Management

The overall goal of treatment for patients with r/r B ALL is to induce a second (or later) morphological remission (< 5% blasts in BM), whereby blood counts have returned to acceptable levels (*Hoelzer et al, 2023*[17]). Achieving MRD negativity at a threshold of ≤ 10^{-4} is an objective as it has been shown to give patients a reduced risk of relapse and a stronger chance for longer OS (*Berry et al, 2017*[18]).

Currently, salvage therapy followed by allogeneic stem cell transplant (SCT) is the recommended treatment option, and only curative option, to achieve long term remission in r/r B ALL patients (*Hoelzer et al, 2016*[19]). However, the response rate of salvage therapy remains low, and allogeneic SCT is in itself associated with severe morbidity, significant mortality, and is only available for a subset of patients (*Fielding et al, 2007*[20]; *Giebel et al, 2019*[21]; *O'Dwyer et al, 2022*[22]).

Despite treatment advances, many patients with r/r B ALL remain incurable with the currently established therapeutic modalities, including SCT. At disease recurrence, nearly 50% of patients with B ALL present with isolated BM disease while up to 25% relapse with some combination of BM disease and EMD. Patients who proceed to SCT with unrecognised EMD may have especially poor outcomes

[12] Moorman AV, Chilton L, Wilkinson J, et al (2010). A population-based cytogenetic study of adults with acute lymphoblastic leukemia. Blood; 115(2):206-214.
[13] Sawalha Y, Advani AS (2018). Management of older adults with acute lymphoblastic leukemia: challenges & current approaches. Int J Hematol Oncol; 7(1):IJH02.
[14] Bencomo-Alvarez AE, Rubio AJ, Gonzalez MA, et al (2021). Blood cancer health disparities in the United States Hispanic population. Cold Spring Harb Mol Case Stud; 7(2):a005967.
[15] Trama A, Botta L, Foschi R, et al (2016). Survival of European adolescents and young adults diagnosed with cancer in 2000-07: population-based data from EUROCARE-5. Lancet Oncol; 17(7):896-906.
[16] Sawalha Y, Advani AS (2018). Management of older adults with acute lymphoblastic leukemia: challenges & current approaches. Int J Hematol Oncol; 7(1):IJH02.
[17] Hoelzer D, Bassan R, Boissel N, et al (2023). ESMO Clinical Practice Guideline interim update on the use of targeted therapy in acute lymphoblastic leukaemia. Ann Oncol. 2024 Jan;35(1):15-28.
[18] Berry DA, Zhou S, Higley H, et al (2017). Association of Minimal Residual Disease With Clinical Outcome in Pediatric and Adult Acute Lymphoblastic Leukemia: A Meta-analysis. JAMA Oncol; 3(7):e170580.
[19] Hoelzer D, Bassan R, Dombret H, et al (2016). Acute lymphoblastic leukaemia in adult patients: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol; 27(suppl 5):v69-v82.
[20] Fielding AK, Richards SM, Chopra R, et al (2007). Outcome of 609 adults after relapse of acute lymphoblastic leukemia (ALL); an MRC UKALL12/ECOG 2993 study. Blood; 109(3):944-950.
[21] Giebel S, Marks DI, Boissel N, et al (2019). Hematopoietic stem cell transplantation for adults with Philadelphia chromosome-negative acute lymphoblastic leukemia in first remission: a position statement of the European Working Group for Adult Acute Lymphoblastic Leukemia (EWALL) and the Acute Leukemia Working Party of the European Society for Blood and Marrow Transplantation (EBMT). Bone Marrow Transplant; 54(6):798-809.
[22] O'Dwyer KM (2022). Optimal approach to T-cell ALL. Hematology Am Soc Hematol Educ Program; 2022(1):197-205.

given the importance of achieving MRD negativity prior to SCT (*Holland et al, 2022*[23]). Overall, achieving complete remission (CR) or complete remission with incomplete hematologic recovery (CRi) with MRD-negativity after induction and consolidation therapy is highly prognostic in B ALL.

Recently targeted immunotherapies have been EU-approved and demonstrated anti-leukemic activity in adult r/r B ALL. Blinatumomab (Blincyto®), a CD3/CD19-targeted bispecific T cell engager was authorised in the EU in Nov-2015 for the treatment of adults with CD19-positive r/r B ALL. Inotuzumab ozogamicin (Besponsa®), a CD22-targeted antibody-drug conjugate, was authorised in the EU in Jun-2017. Two CD19 CAR-T products have been approved. Tisagenlecleucel (tisa-cel, Kymriah®) for r/r B-ALL in paediatric and young adult patients up to and including 25 years of age and Brexucabtagene autoleucel (brexu-cel, Tecartus®) for the treatment of adult patients 26 years of age and above.

2.2. About the product

Aucatzyl (obecabtagene autoleucel; obe-cel) is a cell-based gene therapy product comprised of autologous enriched T cells transduced ex vivo with a lentiviral vector (LV18970) to express a novel anti-CD19 chimeric antigen receptor (CAR) also referred to as CD19 (CAT) CAR. Obe-cel also contains non-transduced autologous T cells and non-T cells. The CAR in obe-cel consists of an anti-CD19 single chain variable fragment, a CD8-derived stalk and trans-membrane domain, and a compound fusion of the 4-1BB and CD3-ζ endodomains.

Obe-cel is constructed using the 4-1BB co-stimulatory domain with a novel low affinity CD19 (CAT) CAR binder, which binds to CD19 with a lower affinity and has a faster disengagement compared to the CD19 (FMC63) CAR as described by Imai et al, 2004 and reported to be used in tisagenlecleucel, axicabtagene ciloleucel and brexucabtagene autoleucel, all currently approved CD19-directed CAR therapies (*Kochenderfer et al, 2009*[24]; *Wang et al, 2020*[25]; *Cappell and Kochenderfer, 2021*[26]). Obe-cel offers a treatment option which mimics a more physiological T cell activation with the potential to reduce immuno-toxicity, improve engraftment and provide long-term persistency (*Roddie et al, 2021*[27]).

The claimed therapeutic indication was: "Aucatzyl is indicated for the treatment of adult patients (≥18 years) with relapsed or refractory B cell precursor acute lymphoblastic leukaemia (B ALL)."

The approved indication is:

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).

Aucatzyl is intended for autologous and intravenous use only.

The target dose of Aucatzyl is 410 x 10^6 CD19 CAR-positive viable T cells (range: 308-513 × 10^6 CAR-positive viable T cells) supplied in three or more infusion bags. The treatment regimen consists of a split dose to be administered on Day 1 and Day 10 (± 2 days). There are two dosage regimens, depending on the tumour burden assessed by bone marrow blast percentage from a sample obtained within 7 days prior to the start of lymphodepletion. The posology is:

[23] Holland EM, Yates B, Ling A, et al (2022). Characterization of extramedullary disease in B-ALL and response to CAR T-cell therapy. Blood Adv; 6(7):2167-2182.
[24] Kochenderfer JN, Feldman SA, Zhao Y, et al (2009). Construction and preclinical evaluation of an anti-CD19 chimeric antigen receptor. J Immunother; 32(7):689-702.
[25] Wang M, Munoz J, Goy A, et al (2020). KTE-X19 CAR T-Cell Therapy in Relapsed or Refractory Mantle-Cell Lymphoma. N Engl J Med; 382(14):1331-1342.
[26] Cappell KM, Kochenderfer JN (2021). A comparison of chimeric antigen receptors containing CD28 versus 4-1BB costimulatory domains. Nat Rev Clin Oncol; 18(11):715-727.
[27] Roddie C, Dias J, O'Reilly MA, et al (2021). Durable Responses and Low Toxicity After Fast Off-Rate CD19 Chimeric Antigen Receptor-T Therapy in Adults With Relapsed or Refractory B-Cell Acute Lymphoblastic Leukemia. J Clin Oncol; 39(30):3352-3363.

- High Tumour Burden Dosage Regimen (bone marrow blasts >20% or inconclusive):
    - Day 1: $10x10^6$ dose administered via syringe
    - Day 10: $100x10^6$ dose administered via bag infusion and $300x10^6$ dose administered via bag infusion
- Low Tumour Burden Dosage Regimen (bone marrow blasts ≤20%):
    - Day 1: $100x10^6$ dose administered via bag infusion
    - Day 10: $10x10^6$ dose administered via syringe and $300x10^6$ dose administered via bag infusion

2.3. Type of application and aspects on development

The clinical development programme

The clinical development of obe-cel for the treatment of r/r B ALL started with the ALLCAR19 (*EudraCT 2016-004027-22; NCT02935257; Roddie et al, 2021*[28]) in September 2017. ALLCAR19 study is an ongoing multi-centre, single arm, open-label Phase I clinical study investigating obe-cel in patients with high-risk, relapsed CD19-positive hematologic malignancies, including B ALL (N=20 adult B ALL patients infused), B-cell non-Hodgkin's lymphoma and chronic lymphocytic leukemia/small lymphocytic lymphoma. ALLCAR19 is considered by the applicant as supportive evidence of safety and efficacy.

A pivotal study was initiated in 2020 (Study AUTO1-AL1, referred to as FELIX; EudraCT 2019-001937-16; NCT04404660). FELIX is an open-label, multi-centre, multi-national, single arm, global Phase Ib/II study. FELIX had two phases, a Phase Ib initially providing feasibility for manufacturing and dosing in a multi-centre study as well as evaluating safety and preliminary efficacy information to enable progression to enrolment of patients into the pivotal Phase II of the study, that determined the efficacy and safety of obe-cel. Once all patients in the FELIX trial completed 60 months, long-term efficacy and safety evaluation up to 15 years after obe-cel infusion will be studied in a separate extension (AUTO-LT1). The FELIX (AUTO1-AL1) was later amended as part of protocol v11.0 (03-Oct-2024) to extend the follow-up of patients who received obe-cel from 24 months (2 years) to 60 months (5 years) from first infusion.

A PIP has been agreed with the PDCO, and Study 2 (AUTO1-PY1) started in November 2023. Study 2 is an open-label, single arm trial to evaluate safety, tolerability and activity of obecabtagene autoleucel in children with a body weight of at least 6 kg to less than 18 years of age with CD19- positive relapsed/refractory B ALL and relapsed/refractory aggressive, mature B Non Hodgkin Lymphoma.

Compliance with guidance and scientific advice

In November 2019 scientific advice was provided by the SAWP (EMA/CHMP/SAWP/586752/2019). There was a PRIME kick-off meeting in July 2021 and a pre-submission meeting in November 2023. The proposed study population was considered heterogeneous. It was emphasised that the study size should be large enough to understand sources of heterogeneity of response and appropriate subgroup analyses should be included in the SAP. It was recommended to limit the study to patients previously exposed to blinatumomab or inotuzumab ozogamicin. In response, the applicant increased the sample size to account for population heterogeneity and subgroup analysis were included. The study population was not restricted.

[28] Roddie C, Dias J, O'Reilly MA, et al (2021). Durable Responses and Low Toxicity After Fast Off-Rate CD19 Chimeric Antigen Receptor-T Therapy in Adults With Relapsed or Refractory B-Cell Acute Lymphoblastic Leukemia. J Clin Oncol; 39(30):3352-3363.

Due to the well-known shortcomings associated with the use of historical controls, the CHMP is still of the opinion that even a small, randomised trial, with a more relaxed alpha than usually required to obtain confirmatory evidence, is preferred to a single arm study. A randomised controlled trial against blinatumomab and inotuzumab ozogamicin was considered feasible in a multi-centre setting. Blinatumomab and inotuzumab ozogamicin were both authorised based on a randomised controlled study. The applicant decided to use an external control arm as comparator. It was advised to seek scientific advice for the target trial protocol for the external comparator, which was not followed. An RCT in post-marketing setting was not discussed at the time of scientific advice.

ORR was considered an acceptable endpoint for a single-arm trial. It was advised to include PFS, DOR and proportion of transplanted patients as secondary endpoints and this advice was followed.

The rationale to split the dose regimen for high disease patients was acknowledged, however the applicant was advised to provide further data supporting the target dose, split dose and timing in the MAA. To allow for assessment of duration of response and survival, the data provided in the MAA should have a follow-up of at least 6 months on the last patient treated in the FELIX trial. In the MAA, data from 87 patients followed up for ≥6 months would be included and additional data were expected to be provided with the responses to the D120 list of questions.

Accelerated assessment

The CHMP and CAT did not agree to the applicant's request for an accelerated assessment as the product was not considered to be of major public health interest. This was based on

- The applicant claims improved safety management options due to the split dosing regimen, but data was lacking to support this claim.
- The efficacy of obe-cel appeared promising, however long-term efficacy from the FELIX study cannot be concluded due to the short follow-up time, but the supportive data from the academic ALLCAR-19 study hint towards persistent responses.
- Comparison of efficacy and safety via indirect comparisons is challenging, nevertheless for efficacy it appears that CR/Cri rate is comparable to the other approved products in this setting (off the shelf and CAR T cells); the median duration of remission is longer than that reported for blinatumomab and inotuzumab ozogamicin and shorter than for Brexucabtagene autoleucel.
- Obe-cel presents a safety profile in line with that known from other CAR T cell products. Comparison was only presented for ≥ grade 3 CRS and ≥ grade 3 neurotoxicity, not the whole AE profile. Notably, comparison incidences of neurotoxicity AEs is difficult due to the different definitions used across studies, without proper discussion on the differences this is not considered informative.
- Data on ICU admittance are difficult to interpret as contextualisation is missing.

Based on the presented results and indirect non-randomised comparisons, it could therefore not be concluded that obe-cel is able to fulfil the unmet medical need by an improved safety profile.

The clinical data package could be considered to include adequate follow-up of efficacy and safety for a B/R assessment at time of MAA; whether the data package could be considered comprehensive for a full marketing approval will be assessed at MAA.

In conclusion, in light of the above, the claim "major interest from the point of view of public health and in particular from the viewpoint of therapeutic innovation" has not been sufficiently shown and/or supported by clinical data. Thus, the request for an accelerated assessment was not granted based on clinical grounds.

Conditional marketing authorisation

The applicant requested consideration of its application for a conditional marketing authorisation in accordance with Article 14-a of the above-mentioned Regulation, based on the following criteria:

- The benefit-risk balance is positive.
- It is likely that the applicant will be able to provide comprehensive data.

Additional data will be generated in accordance with the proposed completion of ongoing studies, conduct of new studies and collection of pharmacovigilance data. The proposed specific obligations to be fulfilled were as follow:

- In order to confirm the long-term efficacy and safety of Aucatzyl in adult patients with r/r B ALL, the MAH shall submit follow-up results of the FELIX clinical study.
- In order to further characterise the long-term efficacy and safety of Aucatzyl in adult patients with r/r acute lymphoblastic leukaemia (ALL) the MAH shall conduct and submit the results of a prospective, interventional study (AUTO-LT1).
- In order to confirm the long-term efficacy and safety of Aucatzyl in adult patients with r/r B ALL, the MAH should conduct and submit the results of a prospective, international, non-interventional study to assess long-term safety and effectiveness of adult patients with relapsed or refractory B-cell acute lymphoblastic leukaemia receiving Aucatzyl treatment (AUTO1-LT2).

The applicant does not foresee potential difficulties in carrying out the specific obligations after granting a conditional marketing authorisation, for instance difficulties with recruitment of subjects.

- Unmet medical needs will be addressed, as:

Despite the approval of a number of novel therapies in the last decade, the r/r B ALL patient population still faces an important unmet medical need characterised by limited treatment options, severe toxicity and low rates of patients in long-term remission without further consolidation treatment, resulting in overall dismal outcomes in a significant proportion of r/r B ALL patients.

The CD19/CD3 bispecific T cell engager blinatumomab and the CD22 antibody-drug conjugate inotuzumab ozogamicin have proven superior to standard of care chemotherapy but are taxed by relatively short duration of response and severe toxicity (CRS and neurotoxicity for blinatumomab; hepatotoxicity for inotuzumab ozogamicin).

The CD19-directed CAR T cell therapies tisagenlecleucel and brexucabtagene autoleucel are efficacious in patients with r/r B ALL, however a significant number of patients still relapse (Xu et al. 2019) due to limited CAR T persistency (especially with brexucabtagene autoleucel) (Shah and Fry 2019) and potentially limited long-term benefit (Sterner and Sterner 2021). Therefore, they are frequently being used as a bridge to transplant (Qayed et al. 2021) and consolidative allogeneic SCT remains routinely recommended for adults with B ALL with a CR after CD19-targeted CAR T cell therapy (Frey et al. 2020; Gauthier 2022). Moreover, currently approved CAR T therapies have challenging acute safety profiles, including severe, and sometimes fatal, toxicity manifestations such as CRS and ICANS that can be difficult to manage and need to be tightly monitored.

In contrast to tisagenlecleucel and brexucabtagene autoleucel, obe-cel uses a unique CAT hybridoma-derived CAR single chain variable fragment (scFv) with a lower affinity for CD19 and a faster off-rate compared to the FMC63 scFv used in those CD19-directed CAR T therapies. The resulting shorter target interaction between obe-cel with CD19 target cells mimics physiological T cell activation, markedly reduces cytokine release and immunotoxicity while promoting more robust CAR T expansion and persistency.

In the FELIX study, persistency was observed in the majority (75.0%) of responders who were still ongoing in remission as of the cut-off date, and are consistent with the data from the Investigator-led study ALLCAR19 (Roddie et al, 2021; Roddie et al, 2023), which showed that at a median follow-up of 36 months, 7 of the 8 patients (88%) with ongoing remission had CAR T cell persistency. Such persistency is not observed with other approved CAR T cell therapies in adult ALL and longer remission reduces the likelihood of the need for consolidation with SCT.

In conclusion, the applicant believes there remains a high unmet need for a therapy to deliver compelling efficacy in this difficult-to-treat adult r/r B ALL population while minimizing the risk of serious and life-threatening side effects. A better-tolerated stand-alone therapy that delivers long-term remission in a significant proportion of patients, without the need for consolidation with SCT, would serve this unmet need. Based on the results from the pivotal FELIX trial, the risk/benefit of obe-cel is improved compared to currently approved therapies for the treatment of adult patients with r/r B ALL.

- The benefits to public health of the immediate availability outweigh the risks inherent in the fact that additional data are still required as compelling efficacy and reassuring safety data are already available, in particular with a view that the majority of patients treated with CAR-T including obe-cel experience treatment related adverse events within 3 months post infusion. The product also provides improved persistency.

2.4. Quality aspects

2.4.1. Introduction

Aucatzyl (obecabtagene autoleucel; obe-cel), is a CD19-directed genetically modified autologous T cell immunotherapy consisting of the patient's own T cells expressing an anti-CD19 (CAT) CAR.

The finished product (FP) is presented as dispersion for infusion containing 410 × 10^6 cells of obecabtagene autoleucel as active substance (AS) at a concentration of 10 x 10^6 total viable cells/mL.

Other ingredients are:

Disodium edetate

Phosphate buffered saline (PBS): potassium dihydrogen phosphate, sodium chloride, disodium phosphate, potassium chloride, water for injections

Human albumin solution

Dimethyl sulfoxide (DMSO)

The product is available in 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.

2.4.2. Active Substance

The section on the active substance is separated into two parts; part 1 for the lentiviral vector (starting materials) and part 2 for the transduced cells (active substance).

Part 1: Lentiviral Vector (starting material)

2.4.2.1. General Information - LVV (Starting material)

The LVV used for transduction is LV18970, which is a third-generation self-inactivating (SIN) lentiviral vector, based on HIV-1. The LV18970 genome consists of a truncated 5' HIV LTR, where the U3 region has been deleted, the packaging signal (ψ), the Rev responsive element (RRE), the central polypurine tract (cPPT) and a 3' LTR, which contains a self-inactivating deletion in the U3 region. Expression of the transgene is driven by the human PGK1 promoter and expression is enhanced by a modified woodchuck post-transcriptional response element (ΔWPRE). The lentiviral vector particles are pseudotyped using the envelope glycoprotein G of the vesicular stomatitis virus (VSV-G). The lentiviral vector is designed to be non-replicating. The biological activity of LV18970 is measured using a combination of infectious titre, physical titre, infectivity, and measurement of vector potency (IL-2 produced by LV18970 transduced Jurkat E6.1 cells when co-cultured with Raji CCL-86).

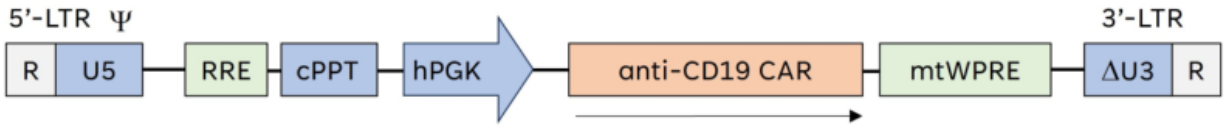

Figure 1: LV18970 vector genome

LV18970 is manufactured by co-transfection of four plasmid constructs: a transfer plasmid containing the CD19 (CAT) CAR cassette, the Gag/Pol packaging plasmid, the Envelope packaging plasmid, and the Rev packaging plasmid into HEK293T cells.

2.4.2.2. Manufacture, process controls and characterisation - LVV (Starting material)

Description of manufacturing process and process controls

Process description

LV18970 is manufactured, tested, packaged and stored by ACG Biologics (Italy). The manufacture of LV18970 is performed under GMP and consists of upstream and downstream production followed by fill and finish. A sufficiently detailed process description has been provided. Upstream manufacturing starts with thawing of a master cell bank and is followed by subsequent cell culture passage and expansion to generate a sufficient number of cells for transfection. Only a MCB is used. The applicant commits to the generation of a working cell bank (WCB) at AGC, to be completed by the agreed date . The co-transfection is performed with four plasmids, containing the therapeutic gene (Transfer plasmid) and viral structural and regulatory genes (Env helper-, Rev helper-, and Gag/Pol helper plasmid). The transfected cells are further cultured, and supernatant is harvested. The harvested supernatants are pooled and clarified. The clarified harvest is treated to digest plasmid and genomic DNA impurities, prior to the start of the downstream purification phase. The eluate is treated for additional nucleic acid digestion and is concentrated. The concentrated vector is further purified. Fill and finish starts with the pre-filtration of the eluate. A final sterile filtration (0.22 µm sterilizing-grade filter) is performed prior to dispensing, at 2 mL per vial in pre-labelled 5 mL sterile cryogenic vials. All filled cryogenic vials are visually inspected for volume and correct cap screw and positioning, and frozen at <- 65°C. Storage and shipping condition is <- 65°C. Reprocessing is not allowed as part of the LV18970 manufacturing process. The batch numbering system is clearly described.

Control of materials

Sufficient information on raw materials used in the LV18970 manufacturing process has been submitted. Compendial raw materials are tested in accordance with the corresponding monograph, while specifications (including test methods) for non-compendial raw materials are presented. The raw materials from approved suppliers are assessed using a combination of Certificate of Analysis (CoA)

review and incoming material testing. The specifications for all the non-compendial raw materials have been provided. For all raw materials CoAs have been provided. For some (culture) media the applicant has provided the qualitative composition. The applicant is notified in case the supplier introduces changes to the culture media. It is confirmed that any change of the critical material used for the manufacture of LV18970, or of the supplier of critical material is only done upon approval of the variation of the registration. For single-use equipment also CoAs were provided. The control of materials of biological origin are assessed with a view on adventitious agents under Section 3.2.A.2.

Master cell bank and End of production cells

For the MCB of HEK 293T cells a summary of the HEK293T cell banks (and LVV batches derived from these) used throughout clinical development to commercialisation and the LV18970 batches manufactured using them was provided. Testing of the MCB is in line with expectations (Ph. Eur. 5.2.3 and 5.14. and ICH Q5A). Adventitious agents are assessed under Section 3.2.A.2. Stability testing of the MCB is monitored when one or more vials are thawed for GMP production or viability testing if no GMP production occurred for a period of 5 years. Cells at the Limit of In Vitro Cell Age (LIVCA) and End of Production Cells (EPC) were characterised including demonstration of genetic stability of MCBs during passages and vector productions steps. The cells have been tested for all relevant parameters, including adventitious agents and met all acceptance criteria. The Postproduction cell testing included DNA sequencing, growth characteristics, cell morphology and QPERT (quantitative product-enhanced reverse transcriptase) for Quantification of Reverse Transcriptase of Retrovirus. The descriptions of the methods used for these analyses have been provided and are considered appropriate.

Plasmids

The four plasmids (Transfer or Transgene plasmid, Env helper, Rev helper, and Gag/Pol helper plasmids) will be manufactured at a CDMO. However, six different sets of plasmids (Sets A, B, C, D,E and F) have been used for manufacture of LV18970 throughout clinical development to commercial manufacturing. Changes involved changes to the plasmid sequences (Sets A & B, differ from Sets C, D & E). The latter share the same sequences and different manufacturing processes, and manufacturing sites as summarised in the dossier.

Sets A, B and C have been used in the clinical Phase 1b clinical studies Set D was used for the Phase II clinical study. A new plasmid manufacturer has been introduced to support commercialisation of obe-cel. Data to support the change has been generated in a stepwise approach using 2 sets of plasmids: Plasmid Set E and Plasmid Set F.

For Set E, two plasmids (Transfer and Gag/Pol) were produced using the same DH5α strain of *E. coli*, but using a modified manufacturing process. Comparability data of the plasmids and LV18970 with these two plasmids is completed and included in this submission. Comparability has been assessed for Plasmid Set A vs Plasmid Set B. While the vector from process B plasmids had generally a lower infectivity (high variability in infectivity results), similar infectivity was shown between vectors from Set A and B used in the clinical Phase 1b studies. The change between Set B and C resulted in increased infectivity of the vector but comparability was sufficiently demonstrated between the Obe-cel produced with the LVV from process B and C. That is considered sufficient for that state of development, because Sets A, B and C have been used in the clinical Phase 1b clinical studies. Comparability between plasmid Sets C and D was demonstrated in small scale studies on the LVV. No differences in infectious viral titre, 48-hour post-transfection cell viability and 48-hour transfection efficiency were observed between LV18970 manufactured with plasmid Set C and plasmid Set D. The release specifications for plasmids are slightly different at both manufacturing sites, also there are some differences in the manufacturing process. A new plasmid stability study was initiated to further confirm the stability of the plasmids manufactured at the second/new manufacturing site.

For comparability of plasmid product quality between the two manufacturing sites, a comparability study using two plasmid sets was performed. The plasmid comparability plan included three elements: Plasmid head-to-head comparison data including the full sequencing, a scale down model using the new plasmids (Transfer and Gag/Pol) in the vector upstream manufacturing process in comparison to the historical data. The results from the comparability study confirmed that the LV18970 identity, quantity and biological activity are not impacted either by the change in plasmid manufacturing site or the minor changes introduced in the manufacturing process, and demonstrates the comparability between the Transfer and Gag/Pol helper plasmid sets manufactured at the two sites.

The applicant also performed analytical comparability for the remaining two plasmids (Env helper and Rev helper) manufactured at the second/new site using the same approach. A small-scale study and reduced scale study were performed to demonstrate the functionality of Plasmid Set F in LV18970 manufacturing process. The reduced scale study showed comparable results for the LVV produced from the three plasmid sets (Sets D, E and F). The Target MOI (Multiplicity Of Infection) results were provided upon request.

Comparability of the LV18970 batches from the different manufacturing processes has sufficiently been demonstrated. Comparability of Obe-cell AS manufactured with the different Plasmid sets A, B, C, D, E are assessed in the Obe-cel AS section, where, in summary, no relevant differences were observed. The applicant provided manufacturing data of the final product using LVV manufactured with plasmid set F demonstrating comparability of the final product with the cells of the clinical and current commercial manufacturing processes.

The MCBs of all four plasmids are released, tested and monitored for stability in accordance with expectations (identity, purity, bacteriophage, viability, plasmid retention, restriction map, Identity, plasmid copy number).

The manufacturing process of the plasmids is generally described in sufficient detail. A stability testing protocol is provided. Stability studies support a shelf life of 24 months at ≤ -65℃. The proposed storage time for the Transfer and Gag/Pol plasmids is 24 months. The applicant proposed storage time for the Env Helper and Rev helper plasmids was 36 months, however this was not accepted and upon request the applicant reduced the shelf life to 24 months.

Storage at ≤ -70℃ is proposed. For this, 6 months stability data are available for the gag/pol and Rev helper and 9 months for the Env helper plasmid showing similar stability profile. Based on this it can be accepted that the initial shelf life is based on stability data obtained at the initial manufacturing site. The stability studies at Keele will be continued and any OOS results will be reported.

Raw materials used in plasmid manufacturing have been listed and none are animal derived. Plasmids are stored at ≤ -65℃.

Plasmid release criteria are acceptable and include Appearance, DNA concentration, DNA purity, Fraction supercoiled DNA, DNA sequence, Plasmid identity, endotoxin, Host cell (HC) DNA, HC RNA, HC protein, sterility, mycoplasma, pH, osmolality, residual kanamycin. There are minor differences between the two sites in acceptance criteria and methods, but these are acceptable.

Control of critical steps and intermediates

Proven acceptable ranges (PAR) have been defined for the critical process parameters (CPP). Generally, these ranges are relatively narrow, a few appear relatively broad but are supported by the development studies and these steps are well controlled and process performance qualification (PPQ) batches all were manufactured at the NOR (normal operating ranges) or target range. IPC (in-process controls) acceptance criteria have been defined for (C)PP for the different steps. For cell culture these are mainly cell number and viability. In the clarification and filtration step viral titre, endotoxin and

bioburden are set as IPC. The IPC limit for bioburden before sterile filtration is acceptable considering the small manufacturing volume). In addition, adventitious virus testing is performed on bulk harvest post-clarification/pre-treatment instead of pre-clarification. This is acceptable as the clarification step is not expected to impact the detectability of adventitious agents.

It is noted that for the sterile filtration only a post-use filter integrity test is performed. The assays used for IPCs are discussed in the control of AS (Active Substance) section, as these are also used for release of the LVV. Process intermediates hold times have been listed.

In summary, ranges of critical process parameters and the routine in-process controls along with acceptance criteria, including controls for microbial purity and endotoxin, are described for each step. The LV18970 manufacturing process is considered acceptable.

Process validation

The process validation included Process development and characterisation, PPQ and continued process verification (CPV). Robustness and consistency of the full-scale LV18970 commercial manufacturing process was shown during a PPQ campaign executed at the GMP-certified facility of AGC. The process validation studies included several additional studies to support specific aspects (hold times, filling homogeneity, freezing time, sterilising filter validation, aseptic process validation, shipping study qualification).

LV18970 manufacturing process has been validated adequately. Consistency in production has been shown on three (3) full scale batches.

The pre-defined acceptance criteria as outlined in the PPQ Protocol were met. Four deviations occurred and have sufficiently been explained, and it is agreed that these have no impact on the PPQ study. After the PPQ study, the classification of several process parameters was updated as result of further process understanding.

The process parameters during the PPQ were in line with the PARs. A difference in Target MOI assay results for the PPQ batches compared to the clinical batches has been attributed to the assay conditions, but further confirmation is sought. . Due to the Target MOI assay performance issues the strategy to base the MOI in the transduction step on the Target MOI should be further justified .

In addition to the IPC testing, additional in-process characterisation testing was performed to demonstrate process consistency and evaluate clearance of the impurities.

Manufacturing Process development

The LV18970 manufacturing process was initially developed at the initial site and later moved to AGC Biologics. The other major change is the use of six different sets of plasmids (Sets A, B, C, D and E and F) as described above (see section *Plasmids*). Comparability of the LV18970 from the different manufacturing sites and plasmid sets has been evaluated. Infectious viral titre and physical viral titre showed similar distributions for LV18970 manufactured at the two sites.

Apart from the changes to the manufacturing process also the analytical procedures have been updated/changed during process development. Furthermore, the acceptance criteria have evolved during development. All these changes have been justified.

2.4.2.3. Characterisation - LVV (Starting material)

The LV18970 has been sufficiently characterised by physicochemical and biological state-of-the-art methods revealing that the active substance has the expected structure of a Lenti Viral Vector. The analytical results are consistent with the proposed structure.

The anti-CD19 CAR open reading frame showed a 100% match to the reference sequence in all batches. Genomic DNA extracted from T cell samples transduced with LVV batches from both sites was analysed with NGS and ≥ 94% coverage of the integrated provirus sequence was found in all transduced T cell samples. Three low-frequency variants in the transduced T-cells were detected. In one of the several PPQ batches one variant, with low frequency was found. In the other PPQ batches no variants were observed. The variants occur with a low frequency and the justification for the acceptability of these variants based on the location in the genome are acceptable from a patient safety perspective.

LV18970 morphology was characterised indicating intact vector particles. Absence of aggregates was confirmed.

Functionality of LVV was shown in CD8 T cells transduced with LV18970, demonstrating dose dependent tumour cell killing. The target multiplicity of infection (MOI) that will be used for obe-cel manufacturing is determined for every batch of LV18970. The description of the target MOI assay has been provided upon request. Cryopreserved Selected T Cells are transduced at predefined MOI values utilising a small-scale manufacturing model that is representative of the obe-cel manufacturing process. Only one batch of LVV was used in the validation study, but the applicant committed to complete a supplemental validation study with additional LVV batches. The applicant also agreed to include a positive control to monitor assay performance.

Confirmation of presence of the CD19 CAR transgene in purified LV18970 is determined by PCR. Expression of CD19 CAR on the surface of T cells in obe-cel demonstrates that LV18970 encodes the CD19 CAR transgene. Non-Infectious Viral Particles are controlled firstly by the physical viral titre, based on the total amount of major structural capsid protein, p24 (ng/ml measured by ELISA; representing full, partially packaged and empty virus particles). Secondly, the infectious viral titre is determined by measuring infectivity using target cells and represents functional full virus particles expressed as TU/mL. Infectivity is the ratio between Physical Viral Titre and Infectious Viral Titre and expressed as transducing units. This ratio also reflects the number of non-infectious particles. All three analytical procedures are release and stability tests.

Replication competent lentivirus (RCL): LV18970 is replication incompetent by design of the viral vector construct. At two points in the manufacture of LV18970 (Final purified lentiviral vector and End of production cells) a test is implemented for the presence of RCL. Final purified lentiviral vector and end of production cells must meet the criteria of no RCL. RCL are also tested at release.

Evaluation of the clearance of process-related impurities during process validation showed consistent removal for each of these impurities tested.

Host cell proteins (HCPs) are process-related protein impurities derived from the producer cell line. HCP levels in LV18970 are detected by ELISA. During the PPQ campaign, the process consistently reduced total residual HCP up to multiple log reductions.

Specification - LVV (Starting Material)

The release criteria for the LVV are generally in line with expectations and include chemical and physical parameters like e.g. pH, osmolality, absence of visible particles. Furthermore, they include identity, biological activity, quantity as physical virus titre, microbial safety (sterility, endotoxin, mycoplasma), absence of replication competent lentivirus (RCL; both on purified LV18970 and in End of Production cells), absence of adventitious virus testing, purity and impurities.

For most parameters the proposed acceptance limits are in line with the batches used in the clinical studies or appropriately justified otherwise and therefore acceptable. The proposed acceptance limits

for the physical titre, infectious viral titre, infectivity based on the calculation and biological activity and endotoxin were tightened upon request.

Analytical methods

The various assays are generally adequately described and validated in accordance with ICH guidelines. Identifiers for in-house analytical methods are provided. The physical viral titre assay was validated with a product-specific validation in line with ICHQ2 requirements. However, because the results of the stability studies are indicative of large variability of this assay, the applicant has further investigated the variability and mitigation actions proposed. The acceptance criteria for each of the sources of Residual DNA are below the WHO recommendation for residual DNA and the acceptance criterion is based on commercial scale batches. Adventitious agents testing is performed on the bulk harvest post-clarification pre-treatment sample. The replication competent lentivirus (RCL) is performed on both on purified LV18970 and end of production cells (EOP). The RCL assay was validated to ensure a 95% probability of detection of RCL if present at a concentration of 1 RCL/100mL.

The residual HCP (host cell protein) assay was validated with a hybrid approach by using a commercial kit and product specific validations. The assay is used to follow HCP clearance in the process and as a release test. The HCP coverage of the assay was shown to be appropriate. Endotoxin is tested by the LAL test.

Batch analysis

Batch analysis data from all sites manufactured throughout clinical development and the batches manufactured to support commercialisation of LV18970 were provided. The results are within the specifications and confirm consistency of the manufacturing process.

2.4.2.4. Reference Standards or Materials - LVV (Starting material)

The reference standard used during the clinical studies and the current reference standard have been described. A protocol for future reference standards has been provided. Like for the LV18970 release criteria, the acceptance criteria for physical titre, infectious viral titre, calculated infectivity and biological activity were tightened. An overview of other controls and standards used in the analytical procedures is provided. In addition, for future reference standard an appropriate shelf-life is assigned. The reference standard stability study protocol has been updated to cover this shelf life.

2.4.2.5. Container Closure System - LVV (Starting material)

LV18970 is stored in 5 mL sterile cryogenic vials with cap at 2 mL of LV18970 per vial, and stored at <-65°C. Drawings with dimensions and specifications have been provided. The materials are compliant with USP class VI (USP <88>) material requirements. The container closure system (vial and cap) is gamma irradiation sterilised. Closure integrity testing has been performed including freezing/thawing. LV18970 is photosensitive and stored protected from light at -80°C. Risk of potential leachables was assessed and considered low.

2.4.2.6. Stability - LVV (Starting material)

Long-term stability studies are currently ongoing with batches of LV18970 (including an engineering batch, a GMP and the PPQ batches) stored in the primary packaging container at the long-term storage temperature of <-65°C. In addition, intermediate and accelerated stability studies are ongoing for all PPQ batches. Vector batches manufactured during plasmid comparability study will be assessed for

long term stability. The stability study protocols include the identity, biological activity, quantity and safety, appearance and general (pH, Osmolality) CQAs. The acceptance criteria for the physical titre and infectivity have been tightened in accordance with the request for the release criteria. The stress study results confirm that the parameters are stability indicating.

The provided data includes data at the long-term storage condition for an engineering batch and a GMP batch. Furthermore, data at the long-term storage condition, at the intermediate storage condition and at the accelerated storage conditions are available for all PPQ batches.

The results of the functionality test show variability. Therefore, the decision on shelf-life is primarily based on results for infectious viral titre and physical viral titre. No clear trend is observed. Based on the stability data the proposed shelf-life at -65°C is acceptable. The applicant will continue the stability study.

A post-approval stability protocol was provided and considered acceptable. The applicant commits to completing the ongoing long-term stability programs and to submit the data. The shelf-life of LV18970 will be extended based on the available stability data from the ongoing long-term stability studies.

Part 2: Obecabtagene autoleucel (active substance)

2.4.2.7. General information

The active substance is defined as the CD19 CAR-positive T cells (non-proprietary name: obecabtagene autoleucel). The autologous enriched T cells are genetically modified *ex vivo* with a lentiviral vector (LV18970) to express a novel CD19CAT-41BBζ chimeric antigen receptor (CAT CAR). A schematic depiction of the CAR protein construct within the transduced T-cell is given and a detailed description of the different domains within the CAR protein including their main function is provided. Nucleotide sequence and functionality of the domains has been provided in the part of the dossier where NAS status is claimed. The provided information is acceptable.

The CD19 (CAT) CAR single-chain variable fragment (scFv) is derived from the sequence of the variable heavy chain (VH) and variable light chain (VL) regions from a murine monoclonal antibody produced via a hybridoma (CAT13.1E10). The single-chain variable fragment scFv is linked to the stalk and transmembrane domains of human CD8α and fused to the 4-1BB co-stimulatory receptor domain and CD3ζ endodomains. In response to CD19 expressing B cells, the CAR T cells will be activated, secrete cytokines, which results in lysis of the tumour cells. The applicant claims that the CD19 (CAT) CAR scFv has a lower affinity for CD19 and a faster off-rate compared to the FMC63 scFv used in approved CD1 CAR T therapies like tisagenlecleucel and axicabtagene ciloleucel.

2.4.2.8. Manufacture, characterisation and process controls

Description of manufacturing process and process controls

The manufacture of CD19 CAR-positive T cells is performed in accordance with current Good Manufacturing Practices (cGMP) at Autolus Limited (referred to as The Nucleus), Marshgate, Stevenage, SG1 1FR, UK. Each batch of CD19 CAR-positive T cells is manufactured for an individual patient from an autologous leukapheresis starting material.

The manufacture of CD19 CAR-positive T cells consists of 7 steps, namely (1) receipt of Fresh Leukapheresis Starting Material, (2) T Cell Selection, (3) T Cell Activation, (4) Transduction of Activated T Cells with LV18970 starting material, (5) T Cell Expansion, (6) Harvest, (7) Washing and

Cell Concentration. These steps are performed within the semi-automated manufacturing system CliniMACS Prodigy. A flow diagram and narrative description of the Active Substance manufacturing process have been provided. Briefly, on Day 0, total viable T cells collected by leukapheresis are loaded into the CliniMACS Prodigy CentriCult™ Unit. T cells are selected. Then viable cells are activated and subsequently transduced at with the lentiviral vector at a predefined MOI. T cell expansion takes place until the total viable cells required to meet the target dose is achieved. The formula for the calculation of the total viable cells required to meet the target dose is included in the dossier. Cells are harvested washed and concentrated. The total processing time is dependent on when the target dose is reached.

The active substance, CD19 CAR-positive T cells, is defined as the cells at the end of Washing and Cell Concentration step at a predetermined target of "total viable cells/mL" prior to the Formulation and Final Fill step of the obe-cel Finished Product manufacturing process. The process from the leukapheresis starting material through the final finished product is continuous, with no hold step for active substance and, therefore, the patient derived batch number is maintained throughout. The batch scale is defined.

A system is in place to ensure traceability from leukapheresis material collection, to manufacture and back to the patient.

The ranges of critical process parameters and the routine in-process controls along with acceptance criteria, are described for each step. The active substance manufacturing process is considered acceptable.

Control of materials

Leukapheresis is performed using CE marked devices (Spectra Optia (Terumo BCT, Belgium) or Amicus (Fresenius Kabi, Germany)) which were also used during the Felix phase Ib and II studies. The leukapheresis is performed at leukapheresis collection sites in accordance with local procedures and standard practice for CD3+ non-mobilised mononuclear cell collections. Following initial qualification, the respective leukapheresis collection sites will be formally reassessed at a minimum frequency of every two years with additional assessments on a risk-based frequency. This is appropriate. Leukapheresis starting material collection sites in the EU/EAA meet standards of quality and safety regarding donation and procurement in accordance with relevant EU legislation, i.e., Directive 2004/23/EC or 2002/98/EC. Leukapheresis starting material is sampled at the manufacturing facility prior to the initiation of the T Cell Selection process and tested for cell count, viability, sterility, and cell phenotypic markers. Viability is included in S.2.3 as an In Process Monitoring test with a predefined acceptance limit. Sterility testing is included in S.2.3 as an In-Process Test. In case the sterility result of the starting material is positive, an impact assessment will be performed to determine if the lot is acceptable for final finished product release. Testing for infectious disease markers (IDMs) is not repeated on the Leukapheresis material as patients are screened for IDMs. Appropriate measures such as verification of patient identity and labelling of the bag with its unique identification number to ensure chain of identity (COI) are set in place. Leukapheresis can be held up to a predefined period prior to the initiation of PBMC Isolation. Respective leukapheresis shipper validation and leukapheresis hold time studies are provided.

A complete list of raw materials and reagents used in obe-cel manufacturing process along with the reference to the manufacturing step is presented. For the non-compendial materials the specifications are provided. Specifications on the non-compendial materials are appropriately set. The composition of media and other solutions used during manufacture is provided. The qualitative composition of media is included in S.2.3. Materials of biological origin are GMP growth medium supplemented with Human AB Serum, CliniMACS buffer and selection reagents, and Human Serum Albumin (HSA), used as an excipient. Specifications and CoAs are provided. The HSA that is used as excipient and as raw material is registered in the EU and its plasma starting material is linked to a certified Plasma Master File. The

human AB serum is stated to be FDA licensed. The applicant has provided a risk evaluation to justify the use of the current AB serum. The HABS is tested at the donor level for a broad panel of adventitious agents. The testing panel for donor testing complies with the requirements for Dir. 2004/33/EC. No additional testing after pooling the sera is performed, but the tests that are required at plasma pool level according to Ph. Eur. 1646 are performed at the level of the single donations. All test kits are FDA approved and most test kits are also CE-marked. One additional testing will be included in the testing panel by the agreed date to fully comply with Ph. Eur. 1646 (**REC**). Autolus commits to generate in vitro supporting data from virus-inactivated AB-serum by the agreed date. If the above data supports the change of HABS material, the implementation of it for the obe-cel commercial manufacturing will be targeted to conclude by the agreed date. An adequate traceability system is in place for each human blood- or plasma-derived product used in the manufacture of obe-cel. The information provided on the manufacturing process and control and adventitious agents safety evaluation of the reagents is adequate.

Control of critical steps and intermediates

CPPs and IPCs with acceptance criteria are provided. These include time from end of leukapheresis starting material collection to start of cell selection, temperature during transportation, total PBMC cells and total viable cells for selection, total viable cells for activation, MOI for transduction, total viable cells for determination of end of expansion and target viable cells post-wash. Several process parameters are controlled automatically within a PAR by the CliniMACS Prodigy unit. However, upon request and to ensure consistent future manufacturing, acceptance criteria (upper and lower limits) for cell concentration for cell selection, transduction and expansion, volume for activation, volume of reagent for cell selection, wash volume, number of wash cycles and centrifugation speed during washing and processing times and hold times for several processing steps were also included in the process description.

The excursion of a CPP outside of its proven acceptable range (PAR) or an IPC outside of its acceptance criterion triggers the generation of a process deviation which requires assessment of its impact on product quality, safety, and efficacy. Microbiological control of the process is described.

Process validation

The obecabtagene autoleucel active substance manufacturing process has been validated adequately. All acceptance criteria for the critical operational parameters and likewise acceptance criteria for the in-process tests are fulfilled demonstrating that the purification process consistently produces obe-cel active substance of reproducible quality that complies with the predetermined specification and in-process acceptance criteria.

The process from start of active substance manufacture to finished product is continuous, with no hold step for active substance and, therefore, details of the active substance and finished product process validation and/or evaluation are provided in the Finished Product Section.

<u>Manufacturing process development</u>

The manufacturing process development included the following elements: development of a quality target product profile (QTPP), identifying potential critical quality attributes (CQAs), defining the commercial manufacturing process, and defining a control strategy to ensure consistent obe-cel product quality and process performance. The cumulative process understanding that was gained from development studies, process characterisation and clinical manufacturing, was used to establish the control elements, process parameters, material attributes, and analytical procedures, for the commercial obe-cel manufacturing process. The identification of CQAs is considered acceptable. It has been sufficiently justified that process-related impurities can be considered non-CQAs due to sufficient dilution. Residual amounts of viral particles were detected in small-scale characterisation runs and full-

scale manufacturing using healthy donor material, but it has been shown that these residual viral particles do not cause transduction of activated cells. Therefore, it is acceptable that viral particles are not further controlled at release. For cell impurities it has been demonstrated that their occurrence is low with the current manufacturing process.

Extensive process characterisation was performed for the different steps of the manufacturing process.

Three manufacturing processes have been used to manufacture obe-cel active substance and finished product to date. Initial batches for the proof-of-concept ALLCAR19 clinical study were manufactured using an open cell manufacturing process.

Material for an additional 14 patients in the ALLCAR19 study was manufactured using an automated cell manufacturing process.

Clinical batches for the FELIX (Phase Ib and Phase II) studies were manufactured at Autolus. After the initiation of the FELIX study, improvements were made to the plasmid and LV18970 manufacturing processes. Plasmids from a first plasmid manufacturer and LV18970 from a first vector manufacturer were used in the FELIX Phase Ib study. Plasmid from a second plasmid manufacturer and LV18970 from AGC were used in the FELIX Phase II study. Further process improvements were the use of fresh Leukapheresis material only, the introduction of a new integrated analytical procedure for in-process control testing for cell counting, cell viability and immunophenotyping. It has been shown that the effect of the integrated flow cytometry method on the estimation of number of cells to calculate the target dose is minimal.

A comparability assessment was performed to demonstrate comparability between FP (finished product) manufactured using different processes. First comparability study was concluded non comparable in the transduction efficiency and VCN. Different batches of LV18970 were used for each of the paired comparability batches and might present variability in transduction patterns thus requiring different MOIs to reach the desired transduction and VCN level. Follow up comparability study was performed with the same lentiviral batch and using MOI based on the count on a predefined day. This comparability study concluded as comparable. As a result, it was decided to estimate the optimal target MOI for each batch of LVV. Also, a comparability study was performed to demonstrate comparability between FP manufactured with LV18970 produced at the first vector manufacturer and AGC.

Also the other process improvements were supported by process characterisation and comparability data showing that the product before and after the change remains comparable. The updated process is the proposed commercial manufacturing process for obe-cel. Commercial manufacture will be performed at The Nucleus at Autolus. The introduction of The Nucleus as the commercial manufacturing facility for obe-cel is supported by an extensive comparability study. Several methods were updated, and equivalency of the updated methods was shown after which transfer to the Nucleus was performed. Transfer data to the Nucleus have been provided for the flow cytometry method and potency method showing equivalent results between the two testing sites for stability samples and positive control.

Characterisation

An extensive characterisation of obe-cel has been performed on FELIX Phase Ib and Phase II clinical lots. Obe-cel is a single chain Fv antibody (scFv)that recognises human CD19 and is fused to intracellular signalling domains from CD137 (4-1BB) and CD3ζ. The CD3ζ domain induces T cell activation, while CD137 (4-1BB) co-stimulatory domain, enhances the cytolytic function of T cells. The CD137 (4-1BB) domain also impacts in vivo persistence and facilitating survival of memory cells. Cell phenotype data for CD19 CAR-positive T cells and the corresponding pre-selection material (leukapheresis starting material), using flow cytometry, are presented. A clear desired cell enrichment

is seen in all lots as well as a depletion in undesired cell populations. Also, immunophenotyping of starting material and obe-cel was performed showing similar percentages of different memory cell populations.

Reduction of process-related impurities throughout the process has been shown.

In summary, the Obe-cel active substance has been sufficiently characterised by physicochemical and biological state-of-the-art methods revealing that the active substance has the expected structure of CAR-T cell. The analytical results are consistent with the proposed structure.

2.4.2.9. Specification and stability

The process from the leukapheresis starting material through the final finished product is continuous, with no hold step for active substance. Therefore, the specifications, analytical procedures, reference standards, batch analysis, container closure and stability are described in Module 3.2.P.

2.4.3. Finished Medicinal Product

2.4.3.1. Description of the product and pharmaceutical development

Obecabtagene autoleucel finished product is formulated as a cell dispersion for intravenous (IV) infusion (referred to as obe-cel). The finished product is formulated and cryopreserved in a cryopreservation medium suitable for infusion containing CliniMACS PBS/EDTA buffer, Dulbecco's Phosphate Buffer Saline (DPBS), human serum albumin (HSA) and 7.5% (v/v) Dimethyl Sulfoxide (DMSO). The material complies with Ph. Eur. and EC requirements. All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur. standards. There are no novel excipients used in the finished product formulation.

The target concentration of obe-cel is 10 x 10^6 total viable cells/mL filled into bags containing 10-20 mL (50 mL bags) and bags containing 30-70 mL (250 mL bags). The target dose for obe-cel is 410 x 10^6 CD19 CAR-positive viable T cells and is filled into three different bag configurations at 10 x 10^6, 100 x 10^6, and 300 x 10^6 CD19 CAR-positive viable T cells to enable the split dosing regimen. The fill volume and the concentration of CD19 CAR-positive T cells is variable. Depending on the volume needed for filling Finished Product is filled in three or more infusion bags. Each infusion bag of obe-cel is individually packed in a metal cassette. Obe-cel is stored in the vapor phase of liquid nitrogen at $\leq$ -150°C and supplied in a liquid nitrogen dry vapor shipper.

Table 1. Obe-cel suspension for infusion: description of finished product

Infusion Bag Configuration	Maximum Number of CD19 CAR-positive Viable T cells per Bag	Fill Volume Per Bag
10×10^6 CD19 CAR-positive viable T cells	125×10^6 CD19 CAR-positive viable T cells	10 mL (50 mL bag) Contains overfill
100×10^6 CD19 CAR-positive viable T cells	125×10^6 CD19 CAR-positive viable T cells	10 – 20 mL (50 mL bags) or 30 – 70 mL (250 mL bags) No overfill
300×10^6 CD19 CAR-positive viable T cells	375×10^6 CD19 CAR-positive viable T cells	30 – 70 mL No overfill

A detailed composition per mL is provided in **Table 2**.

Table 2. Obe-cel dispersion for infusion: composition (detailed)

Ingredient	Quantity/Amount per mL	Function
Total viable cells	10×10^6	Active ingredient
CD19 CAR-positive viable T cells	Variable based on Transduction Efficiency	
Human Serum Albumin (HSA)		Stabilizer
Dimethyl Sulfoxide (DMSO)	7.5% (v/v)	Cryoprotectant
Etheylenediaminetetraacetic Acid (EDTA), Disodium Edetate		Stabilizer
Phosphate Buffered Saline (PBS)	Potassium Chloride	Buffering and Tonicity agent
	Potassium Dihydrogen Phosphate	
	Sodium Chloride	
	Disodium Phosphate	
Water for injection (WFI)		Solvent

Pharmaceutical development

During clinical studies minor changes were made to the formulation. Excipients are compendial and are commonly used for cryopreserved cell products.

A FMEA analysis was performed for steps in the FP manufacturing, resulting in several studies to support formulation and final fill, cryopreservation and storage. Impact of the DMSO hold time, Fill Volume and Viable cell concentration on obe-cell QA is performed. The freezing profile is qualified.

The container closure system is deemed suitable. The freezing bags supplier has assigned a shelf life from the date of sterilisation under the recommended storage conditions. Every design variant of the freezing bags was subjected to severe and repeated freeze-thaw cycles by immersion in liquid nitrogen (-196 °C) and warm water (+40 °C). Chemical tests were performed by an ISO 17025 certified testing facility. Results conform to the limits specified in EN ISO 3826-1 as the chemical requirements for containers for blood components. CCI was tested by subjecting CCS to distribution stresses followed by pressure test. Extractable and leachable study was performed. All leachable compounds identified were discussed in respect to risk that was assessed to be negligible or low.

Microbiological safety is controlled through release testing of mycoplasma Endotoxin and Sterility, Control of materials for sterility, stability testing for sterility, CCIT, APS, environmental monitoring in the manufacturing suites, and in-use testing.

Compatibility study to demonstrate administrations set is adequate. Dose accuracy studies during administration are performed.

2.4.3.2. Manufacture of the product and process controls

The manufacturing process has been validated. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner. The in-process controls are adequate.

Manufacture

Finished product manufacturing is performed at Autolus (the Nucleus), Marshgate, Stevenage, SG1 1FR, UK. The manufacture of obe-cel consists of 2 steps: Formulation and Final Fill and Cryopreservation and Storage. After the final step of cell manufacture- Washing and Cell concentration, the cell suspension is diluted and slowly mixed with cryopreservation buffer consisting of DPBS containing HSA and DMSO to reach a final target concentration of 10 $\times 10^6$ (±25%) total viable cells/mL, HSA and 7.5% DMSO. *All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur standards. There are no novel excipients used in the finished product formulation.*

Traceability system for obe-cel manufacture and delivery is ensured by the Chain of Identity/Chain of Custody, established at collection site and maintained throughout the process.

Batch release for the EU is performed by a third party. Satisfactory demonstration of GMP has been provided for these sites.

Process controls

CPPs are time from the addition of DMSO to the start of the cryopreservation, freezing rate and storage temperature. Fill volume and dose is based on a calculation. The calculation is included in the dossier.

Process validation/verification

FP process validation strategy consists of: process design, process qualification and continued process verification. Process qualification elements are qualification of the Nucleus facility, PPQ of FP manufacturing, production capacity, CoI/CoC, Aseptic Process Simulation, Extractable/Leachable study, FP transport validation.

The proposed commercial manufacturing process at The Nucleus was validated using PPQ runs from Leukapheresis material. Results met all the pre-established acceptance criteria for CPPs, IPCs and release testing. Data for hold times and production time for each step have been provided. Validated hold times are included in S.2.2 or S.2.4. A filling accuracy study was conducted. The presence of cellular debris is expected to be part of cell-based products and will not lead to batch rejection as this is not considered a safety concern. Sufficient controls are in place to minimise the risk of foreign particles.

A capacity challenge was performed at the Nucleus to demonstrate the successful execution of the obe-cel manufacturing process (inclusive of the continuous Active Substance and Finished Product processes) when operating at a full production capacity.

Aseptic process simulation was performed at the Nucleus to validate the aseptic process. Representative processing times were covered as part of the APS study and extended processing times were part of the PPQ study. Finished product shipping qualification has been performed.

2.4.3.3. Product specification

Specifications

Specifications are provided and include Appearance, Clarity, Visible Particles, CD19 CAR expression as an identity test, number of CD19 CAR + T cells, cell viability upon thaw, VCN, CD19 CAR expression as a purity indicator. CAR T Cell functional testing by Impedance based technology is included as an estimate of FP Potency. Further, Sterility, Endotoxin, Mycoplasma and RCL is measured.

The number of CD19+ CAR-positive T cells after Washing and Concentration" is included as a CPP in section S.2.2 and S.2.4. For Quantity the release specification "Number of CD19 CAR+ T cells meets the dose (410×10^6 $\pm$25%)" with as acceptance criterion "Yes" is included. No actual release testing is performed for Quantity. The release result for total number of CD19+ CAR-positive T cells is obtained by derivative calculation.

Bag fill volumes are calculated to obtain the target number of CD19 CAR+ T cells for each infusion bag configuration (10, 100 or 300 $\times10^6$ CD19 CAR-positive T cells). A control on viability is in place at release on the cryovial.

It has been shown in characterisation studies that cellular impurities are low. A specification has been included for an undesired cell type. For process related impurities it has been shown that these are sufficiently reduced throughout the manufacturing process, and it is acceptable that these are not controlled at release.

Shelf-life acceptance limits have been included for appearance and clarity. The acceptance criteria for Visible particles is described. This is acceptable as aggregates of cellular debris may be present in the FP.

The acceptance criteria for transduction efficiency is low in comparison to clinical experience. However, it has been sufficiently shown that there is no correlation between transduction efficiency and the clinical outcome.

Release testing of each batch is performed at the Nucleus in Stevenage, UK. An exemption of batch retesting in EU was requested. To substantiate the request, data is provided on the total batch size- that varies on the amount of leukapheresis starting material, that may be highly variable and low in the diseased population. As limited amount of material available for an autologous products and testing is performed in a GMP-certified facility, the exemption of batch release testing can be granted based on point 11.16 of Part IV-GMP requirements for Advanced Therapy Medicinal Products of EudraLex Volume 4.

The excipients are listed. All non-compendial excipients are composed of compendial components. The specifications for each non-compendial excipient and for Human Serum Albumin is provided as well as the analytical testing methods for the incoming tests. Where compendial testing was performed, the suitability of the analytical procedure was verified against pharmacopoeia; where non-compendial testing was performed, the analytical procedure was described and qualified, specifications are justified. Also, the suppliers of the excipients are listed. CoAs are provided for each excipient. The HSA that is used as excipient is approved for human use and its plasma starting material is linked to a certified Plasma Master File.

A risk evaluation concerning the presence of nitrosamine impurities in the finished product has been performed \ considering all suspected and actual root causes in line with the "Questions and answers for marketing authorisation holders/applicants on the CHMP Opinion for the Article 5(3) of Regulation (EC) No 726/2004 referral on nitrosamine impurities in human medicinal products" (EMA/409815/2020) and the "Assessment report- Procedure under Article 5(3) of Regulation EC (No) 726/2004- Nitrosamine impurities in human medicinal products" (EMA/369136/2020). Based on the

information provided it is accepted that no risk was identified on the possible presence of nitrosamine impurities in the active substance or the related finished product. Therefore, no additional control measures are deemed necessary.

Analytical methods

Analytical procedures for testing of general properties (colour, clarity, visible particles), identity, quantity, purity, potency and safety attributes were described in sufficient detail. Equipment, operating parameters, analytical procedure and reagents/sample preparation procedures were defined, list of reagents used in the procedure was provided. Positive and negative controls are used in the analysis. Appropriate system suitability criteria were defined. Calculations and interpretation of results were discussed accordingly. Identifiers for in-house analytical methods are included in the dossier.

Summary of validation results as well as validation reports are provided. Compendial methods were verified in line with Ph. Eur. (Ph. Eur. 2.2.2. and Ph. Eur. 2.2.1 - Appearance, Ph. Eur. 2.9.20 - visible particles). A method has been validated for sterility testing according to Ph. Eur. 2.6.27 and following the ICH Q2 principles. Method for endotoxin detection was validated according to Ph. Eur. 2.6.32. All in-house analytical procedures were validated for relevant method performance characteristics in line with ICH Q2. Method validation summary with pre-defined acceptance criteria was provided. Analytical procedures were validated the proposed quality control testing site for purpose of release and stability testing and corresponding validation reports were submitted.

Analytical development history was provided to introduce and justify changes to the analytical procedures performed during development. Changes in the analytical methods were described in sufficient detail. Changes included transfer between testing sites, changes to the analytical procedures used to assess quality attributes and their acceptance criteria. All test methods were finally transferred to the commercial QC testing site or replaced by a new method validated at this site. Briefly, compendial Ph. Eur. analytical methods for visual inspection (colour, clarity and visible particles) were introduced at the Nucleus QC lab, for identity, purity (cell phenotype) and potency (transduction efficiency) new integrated flow-cytometry analytical procedure was subsequently introduced with transfer to the Nucleus QC site, the LAL endotoxin procedure was replaced by a new procedure, for mycoplasma, VCN and RCL testing qPCR methods were replaced a new procedure and cytotoxicity analytical procedure (potency) was replaced by real time impedance-based technology method at Nucleus QC site. The sterility procedure was optimised during development and transferred to the proposed commercial QC site. Provided data generally support the equivalence between original and transferred, improved or replaced methods. No concerns were identified.

Batch analysis

Batch analysis data of all Finished Products manufactured during clinical trials and for Commercial process validation are provided.

Reference materials

There is no reference standard used in identification, purity test, or potency assay of obe-cel, instead a positive control (PC) is used in the control of obe-cel. Obe-cel PC is manufactured per an internal manufacturing protocol using healthy donor leukapheresis starting material. Each manufacturing run produces one specific lot of obe-cel PC.

Container closure

The container closure systems are non- compendial freezing bags which consists of an EVA (ethylene vinyl acetate) freezing bag and a corresponding overwrap bag which are CE marked in EU. Two sizes are used, depending on the fill volume. After cryopreservation, the overwrapped bag is inserted into the secondary container closure, cassette, for storage. One Freezing bag is inserted per cassette. For

the transportation to the administration site, the cassettes are inserted into ModPak. Detailed description is provided. The choice of packaging materials is addressed as part of the development. Suitability of the freezing bags has been shown by stability, integrity and extractables/leachables studies. The sites responsible for sterilisation are included in section P.7. The sterilisation method has been validated in accordance with ISO 11137-1 and ISO 11137-2 and Ph. Eur. 5.1.1.1.

2.4.3.4. Stability of the product

The proposed shelf life of 6 months at < - 150°C is considered acceptable. Real time stability data are submitted for one stability lot using healthy leukapheresis material and for patient lots, both manufactured with the same process. No trends for any of the parameters studied is observed during storage at < - 150°C. Also, one month, one month and three month stability data are submitted for respectively PPQ batches, pre-PPQ batches and technology transfer pre-PPQ batches manufactured according to the commercial manufacturing process. Considering that comparability has been shown between the process used for initial stability data and the commercial manufacturing process, it can be accepted that the claimed shelf life is based on these stability data. The stability protocol and the matrix design to cover the different bag configurations is considered acceptable. The in- use stability data are provided in the development section and support the time of 60 minutes from the time of thaw to the time of administration and maximum administration time 60 minutes.

Based on available stability data, the shelf-life while stored in vapour phase of liquid nitrogen (≤ −150 °C) as stated in the SmPC is acceptable.

2.4.3.5. Adventitious agents

The applicant has evaluated the adventitious agents' safety of all the relevant materials of human or animal origin used as raw or starting materials or used in their manufacture. The evaluation included the materials of the LV19870 process and Obe-cel process. All materials of biological origin were identified, materials of animal/human origin were subjected to risk assessment with regard to TSE, viral, bacteria/fungi and mycoplasma risk and risk mitigation rationale was discussed. Certificates of analysis/origin were provided for all relevant materials and compliance with EMA/410/01 was declared. Cell banks were appropriately characterised in line with ICH and pharmacopoeial requirements.

Leukapheresis starting material was included in risk assessment. Within 30 days prior to leukapheresis, patients are screened for infectious disease markers in accordance with EU Directive 2004/23/EC. As concluded by risk assessment, this material presents medium risk for viral contamination however, as autologous material risk is considered acceptable. Leukapheresis starting material is sampled and tested as addressed in S.2.3.

For the LV18970 manufacturing the evaluation of the materials does not raise specific concerns. Reagents of animal origin used in the manufacture of Obe-cel are the reagents which were manufactured using a murine hybridoma cell line, human AB serum and Human serum albumin. CoAs and TSE/BSE statements are provided. For the Human AB serum reference is made to the question raised at section S.2.3 with regards to the viral safety.

FBS from all suppliers used as raw material is gamma irradiated and tested for absence of microbial contamination and specific viruses. Certificate of suitability by EDQM was provided for FBS. Human serum albumin used in Obe-cel production is a licensed finished product. Human serum albumin is a derivative of human plasma authorised product. No safety concerns were identified with regard to the use of FBS and human serum albumin as raw material.

Monoclonal antibodies in CliniMACS reagents are used as raw materials in Obe-cel production. Proteins of recombinant origin produced in *E. coli* are compliant with EMA/410/01 and Ph. Eur. 5.2.12. and sterility testing is performed on input material.

Monoclonal antibodies expressed in murine cell line do not pose risk with regard to TSE. Virus safety testing, virus removal and inactivation is performed according to relevant ICH guidelines as part of manufacturing process of those raw materials.

Sterility (Ph. Eur. 2.6.1) and endotoxins (Ph. Eur. 2.6.14) are tested as part of raw material specifications.

Human AB Serum is human derived, animal derived components free material which meets FDA requirements as declared by the applicant. As described above it is recommended to implement an additional testing at single donation level for the human AB-serum and to implement the virus-inactivated AB serum for the obe-cel commercial manufacturing post-approval. In general, specifications for critical raw materials are provided and further discussed in assessment in section S.2.3.

2.4.3.6. GMO

The transgene of Aucatzyl does not contain sequences capable of complementing the non-replicating lentiviral vector, the molecular characterisation of Aucatzyl does not implicate environmental risks and the possibility of RCL formation with a 3rd generation SIN vector system is considered negligible.

The medicinal product may still contain residual infectious vector particles at the time of administration, but the applicant has provided additional justification supporting the conclusion that negligible amounts of infectious residual vector particles are present in the final medical product Overall, the risks for human health and the environment associated with the presence of these particles will be negligible.

2.4.4. Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

The CHMP endorses the CAT discussion on chemical, pharmaceutical and biological aspects as described above.

2.4.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way. Data has been presented to give reassurance on viral/TSE safety.

The CHMP endorses the CAT discussion on chemical, pharmaceutical and biological aspects as described above.

2.4.6. Recommendations for future quality development

In the context of the obligation of the MAHs to take due account of technical and scientific progress, the CAT recommends the following points for investigation:

1. The applicant is recommended to generate a working cell bank (WCB) at AGC (to be completed by the agreed date).
2. The applicant is recommended to implement an additional testing at single donation level for the human AB-serum (to be completed by the agreed date).
3. The applicant is recommended to evaluate an alternative to the current human AB-serum stock; The applicant is recommended to generate in vitro supporting data from virus-inactivated AB-serum (to be completed by the agreed date). If the above data supports the change of HABS material, it is recommended to implement the virus-inactivated AB serum for the obe-cel commercial manufacturing (by the agreed date).
4. The difference in %TE between LVV PPQ batches and clinical batches in the Target MOI test and the strategy to base the MOI in the transduction step on the Target MOI have not been sufficiently explained considering the results of the Target MOI of the different batches in. The applicant should address the following issues.
    a. Provide specific details regarding the cause of the difference of the PPQ batches in the Target MOI tests results compared to the clinical batches. If this is due to the donor cells used the applicant is requested to provide further evidence to support this by testing the PPQ and clinical batches side by side in the same donor cells. Furthermore, if indeed the different donor cells are an explanation for the lower TE than it should be explained why the selection criterion for minimal transduction efficiency has not been adapted.
    b. The strategy to base the MOI in the transduction step on the Target MOI should be further justified taking into account the differences in the Target MOI results between clinical batches and PPQ batches while a similar MOI is chosen in the transduction step. Also the criteria by which a MOI in the MOI-range is chosen should be clarified and justified. The proposed strategy should ensure that a similar profile is achieved as in the clinical batches.
5. The applicant is recommended to do a supplementary validation to assess selected performance parameters of the current analytical procedure (as described in the dossier) as a post-authorisation measure. Upon completion of the supplementary validation, a predefined number of vector batches will be covered by a validation package. To be completed by the agreed date.
6. The applicant is recommended include a LV18970 reference standard batch to serve as positive control in each MOI analytical procedure at a predefined MOI to monitor the assay performance and to update the analytical procedure description. To be completed by the agreed date.

2.5. Non-clinical aspects

2.5.1. Introduction

Obe-cel is a gene therapy product comprised of genetically modified, autologous human T lymphocytes that have been transduced with a lentiviral vector (LV) to express a chimeric antigen receptor (CAR)

gene that recognises CD19 on target cells via the murine CAT13.1E10 hybridoma (CAT) binding domain. The nonclinical data were mostly based on in vitro and ex vivo data in addition to data from the literature as summarised and discussed in this section.

2.5.2. Pharmacology

2.5.2.1. Primary pharmacodynamic studies

IN VITRO

Biophysical Characterisation of the CD19 (CAT) Binding Domain

The applicant used the CD19 CAT scFv instead of the CD19 FMC63 scFv that was used by the MAHs of registered anti CD19 CAR T-cell products. *In vitro* the kinetics of binding between the anti-CD19 (CAT) CAR antibodies and the target (CD19), the CD19 target epitope, the stability and CAR cell surface expression were determined as follow:

- Determination of scFv Affinity by Surface Plasmon Resonance: The CAT scFv-Fc has a similar on-rate (k_a) as FMC63 scFv-Fc (2.153×10^5 $M^{-1}s^{-1}$ vs 2.076×10^5 $M^{-1}s^{-1}$, respectively), but a faster off-rate (k_d; 3.096×10^{-3} s^{-1} vs 6.810×10^{-5} s^{-1} respectively). The resulting binding affinity (KD) to CD19 of CAT scFv was 14.4 nM and is approximately 40-fold weaker than the KD of FMC63 scFv (0.328 nM).

The applicant used the CD19 CAT scFv instead of the CD19 FMC63 scFv that was used by the MAHs of registered anti CD19 CAR T-cell products. *In vitro* the kinetics of binding between the anti-CD19 (CAT) CAR antibodies and the target (CD19), the CD19 target epitope, the stability and CAR cell surface expression were determined as follow:

- Determination of scFv Affinity by Surface Plasmon Resonance
- Epitope Determination by Alanine Scanning
- Binding Domain Thermal Stability
- Cell surface stability
-

CD19 (CAT) CAR In Vitro Function

The *in vitro* evaluation of the function of the CD19 CAT CAR T-cell includes characterisation of the cytotoxic activity, cytokine production and proliferative capacity of CD19 (CAT) CAR T cells, compared to these functionalities of CD19 (FMC63) CAR T cells.

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- Chromium-51 Release Cytotoxicity Assay
- Flow based killing assays
- Cytokine Measurements
- Proliferation

In vivo

The efficacy of CD19 (CAT) CAR T cells has been evaluated in the *in vivo* NALM-6 tumour xenograft mouse model and has been compared to the efficacy of CD19 (FMC63) CAR T cells in the same model. Female NSG mice (6-10 weeks of age), lacking mature T cells, B cells, and natural killer cells, were sub-lethally irradiated at 2.8 Gy on Day -8 relative to CAR T injection and 1 day prior to receiving i.v. injections of 1.0×10^6 NALM-6 (tumour) cells expressing firefly luciferase (FLuc) at Day -7. Tumour engraftment was assessed on Day -1 and recipient animals with similar tumour burdens were distributed evenly across the groups prior to CAR T cell injection (2.5×10^6 CD19 (FMC63) CAR or CD19 (CAT) CAR transduced T cells) or injection of Not Transduced (NT, 2.5×10^6) T cells, as negative control on Day 0. Tumour burden was followed by bioluminescence imaging (BLI) that measures Photon emission from NALM-6 cells expressed in photon per second per cm^2 per steradian ($p/s/cm^2/sr$). After sacrifice (Day 16), splenic and bone marrow (BM) single cells suspensions were analysed for residual tumour and persisting CAR T cells by flow cytometry. Intracellular cytokines were assessed following fixation and permeabilisation of cells.

CD19 (FMC63) CAR T cells appeared capable of slowing down tumour growth, but no regression has been shown. In contrast, equivalent numbers of CD19 (CAT) CAR T cells resulted in tumour regression. At Day 12, mice treated with CD19 (CAT) CAR T cells had 1.1×10^8 to 9.3×10^7 tumour cells left, and mice treated with CD19 (FMC63) CAR T cells had 3.2×10^9 to 7.7×10^8 tumour cells (mean $p/s/cm^2/sr$; $n = 18$; $p < 0.001$).

Conversely, a significantly greater absolute number of CD19 (CAT) CAR T cells were seen in BM compared to CD19 (FMC63) CAR T cells (mean CAR T cells/ml: $5.1x10^4$ CD19 (CAT) CAR T cells; $2.0x10^4$ CD19 (FMC63) CAR T cells, n=9, $p<0.05$). The same was observed in blood (mean: CD19 CAT CAR T cells 18743, CD19 (FMC63) CAR T cells 2843, n=9, $p<0.001$).

The expression of exhaustion markers LAG3, PD-1 and TIM3 on CAR+ T cells was similar in mice receiving CAT19 CAR or CD19 (FMC63) CAR T cells. However, CAR T cells from the BM and blood showed significantly higher levels of CD127 (IL7-Rα) and intracytoplasmic expression of the anti-apoptotic molecule Bcl-2 in CD19 (CAT) CAR treated mice as compared to mice treated with CD19 (FMC63) CAR T cells. CD127 is a marker for naive and memory T cells, whilst Bcl-2 protein plays a role in regulating apoptosis.

Intracellular staining of Th1 like cytokines revealed greater expression of TNF-α in CD19 (CAT) CAR T cells as compared to CD19 (FMC63) CAR T cells, reflecting previous *in vitro* findings.

2.5.2.2. Secondary pharmacodynamic studies

In line with ICHS6 it is acceptable that secondary pharmacology studies were not conducted.

2.5.2.3. Safety pharmacology programme

Obe-cel is a human specific product that will not survive in an animal unless the animal species is immunocompromised animals. Given the fact that safety aspects with this type of therapy are immune related, a toxicity study in immune compromised animal is of limited relevance. Lack of safety pharmacology testing is acceptable.

2.5.2.4. Pharmacodynamic drug interactions

It is accepted that pharmacodynamic interaction studies are not conducted as it is unlikely that it will negatively interfere with other type of therapies unless these therapies are modulating the immune system.

2.5.3. Pharmacokinetics

Traditional non-clinical pharmacokinetic studies (absorption, distribution, metabolism, excretion and in vitro drug-drug interaction) have not been conducted because obe-cel is an autologous gene therapy product and there is no pharmacologically relevant species. This is agreed.

The only 'distribution' data available for Aucatzyl can be derived from the *in vivo* PD study in which human CAR T cell persistence was evaluated in NALM-6-bearing NSG mice. CAR T cells were present in peripheral blood as well as bone marrow two weeks post-injection. CAR T cell persistence is monitored and assessed clinically. No additional data or discussion on PK will be needed non-clinically.

2.5.4. Toxicology

2.5.4.1. Single dose toxicity

The applicant has not performed general toxicity studies with their product.

2.5.4.2. Repeat dose toxicity

Not applicable.

2.5.4.3. Genotoxicity

Standard *in vitro* and *in vivo* genotoxicity studies are not applicable to ATMPs.

2.5.4.4. Carcinogenicity

Carcinogenicity studies are not needed for indications falling under ICH S9 scope (advanced cancer). In addition, there is no cross-reactivity of the CD19-CAR T cells from Aucatzyl with the murine antigen. Moreover, evaluation of oncogenesis in e.g. mice would be difficult, considering the high resistance of murine T cells against transformation by LV-related genetic insertions.

2.5.4.5. Reproductive and developmental toxicity

DART studies are not needed for indications falling under ICH S9 scope (advanced cancer) and no pharmacologically relevant animal species is available. Moreover, germline transmission studies are not recommended for genetically modified human cells, according to the *Guideline on non-clinical testing for inadvertent germline transmission of gene transfer vectors* (EMEA/273974/2005).

2.5.4.6. Toxicokinetic data

Not applicable.

2.5.4.7. Local tolerance

No local tolerance study has been conducted, as the autologous product is used intravenously.

2.5.4.8. Other toxicity studies

The applicant has conducted a tissue cross-reactivity (TCR) study. The GLP tissue cross-reactivity study was conducted to determine potential binding of 1 or 3 µg/mL CAT19 to 42 normal human tissues and blood smears. Per tissue, three different donors were used. For the negative control anti-H5N1, only the highest concentration was used. The approach of the applicant with the selected concentrations and tissues seems to be acceptable.

Following on-target membranous staining confirmation with CAT19 in human tonsil tissues and evaluation of integrity and morphology of the tissues (endothelia), the analysis of the actual tissue panel revealed positive (membranous) staining of cells primarily in lymphoid (follicular) tissues throughout the body with both concentrations. Lymphoid cell infiltrates in other tissues were also stained.

2.5.5. Ecotoxicity/environmental risk assessment

The conclusion of the applicant that the transgene of Aucatzyl does not encode sequences that can complement the replication incompetent lentiviral vector is supported.

Based on the information provided on the transfer and packaging plasmids and the viral vector used for the production of Aucatzyl there is no reason to expect Aucatzyl to pose risks for human health and the environment.

In a production system for 3rd generation SIN lentiviral vectors, at least three recombination events are required to generate RCL and requires the SIN deletion to be repaired. Therefore, RCL formation during the production of 3rd generation SIN lentiviral vectors is not possible. The chance that RCL is formed during manufacturing is considered negligible.

Data on the reduction of residual vector particles is provided with a p24 ELISA. Residual particles (p24) were detected in supernatant from Day 6 development runs at manufacturing scale. The applicant also provided data on the number of infectious particles that is present in Day 6 supernatant from different donors. It has been shown that these residual viral particles do not cause transduction of activated T cells. In conclusion, negligible amounts of infectious residual vector particles are present in the final medical product.

2.5.6. Discussion on the non-clinical aspects

Pharmacology

In vitro

In vitro, the kinetics of binding between the anti-CD19 (CAT) CAR antibodies and the target, the CD19 target epitope, the stability and CAR cell surface expression were determined. The applicant continued with the *in vitro* evaluation of the function of the CD19 CAT CAR T-cell by characterizing the cytotoxic activity, cytokine production and proliferative capacity of CD19 (CAT) CAR T cells *in vitro* and compared to these functionalities of CD19 (FMC63) CAR T cells.

Apart from the difference in sequence it is shown that the CD19-CAT scFv domain has a 40-fold lower binding affinity to its target as compared to CD19 FMC63 scFv, which is determined by a faster off-

rate. CD19 (CAT) CAR T cells have a higher cytotoxic capacity (especially at lower E:T ratios), higher levels of secreted TNF-α and higher proliferation rates as compared to CD19 (FMC63) CAR T cells.

In vivo

The applicant set out to evaluate the efficacy of CD19 (CAT) CAR T cells in the NALM-6 *in vivo* tumour xenograft mouse model and compared this to the efficacy of CD19 (FMC63) CAR T cells in the same model. Tumour burden was followed for approximately 2 weeks and after sacrifice (Day16), splenic and BM single cells suspensions were analysed for residual tumour, persisting CAR T cells and cytokines. The data suggest that CD19 CAT CAR T cells are more efficient in tumour cell killing and seem to survive longer as compared to CD19 FMC63 CAT CAR T cells. This data also suggest that CD19 CAT CAR T cells seem to display decreased apoptosis and increased IL7 signalling through CD127 which contributes to increased proliferation and long-term survival. The increased TNF-α expression/secretion shown in vitro is also observed in vivo.

Together, all these non-clinical results indicate that, under conditions designed to give CAR T cells a numeric disadvantage relative to the number of tumour cells, lower affinity CD19 CAT CAR T cells mediate enhanced anti-tumour responses and expansion as compared to higher affinity CD19 (FMC63) CAR T cells. Whether this translates into a clinical effect is not known.

Toxicology

The absence of general toxicity studies is accepted, considering that there are no pharmacologically responsive animal species (as also mentioned in the scientific advice, EMA/CHMP/SAWP/586752/2019). Aucatzyl, a patient-specific product, is not appropriate for administration to immunocompetent animals, as the T cells will not engraft. Furthermore, use of this product in immune compromised animals will not provide reliable general toxicity or off-target toxicity data on the potential toxicity of the CAR T cells, as (interaction with) the murine immune system is lacking, and CAR T-cell related toxicity is known to be associated with patient-specific parameters (such as tumour load).

Known risks of CAR T cell therapies (e.g., CRS or neurotoxicity) can be clinically monitored and managed. As no unexpected safety issues have arisen in the clinical studies that would require additional non-clinical evaluation, the absence of acute non-clinical toxicity data can be endorsed.

Risk of insertional mutagenesis:

Despite the lack of standard in vitro and in vivo genotoxicity studies, according to the written recommendations provided in the minutes of the pre-submission meeting (7 November 2023), the risk of insertional mutagenesis related to the vector has been discussed, without request for additional non-clinical studies. A literature-based overview of the retroviral risk of insertional mutagenesis has been provided indicating the mechanisms by which retroviral integration may induce cellular expansion/transformation/oncogenesis. However, it is also explained that the risk of transformation and oncogenesis with the current third generation SIN LVs and moderately active non-viral promoters is low (but not zero), especially in terminally differentiated cell types such as T cells. For Aucatzyl specifically, 3 patients have developed a secondary malignancy. These secondary malignancies were likely not directly related to the CAR T cell treatment (and LV insertion sites), but the cellular treatment and/or earlier immunosuppressive regimens may have contributed to development of the new tumour, e.g. by providing space for proliferation of an already existing minor (pre-)leukemic clone. Nevertheless, no (genetic) information is available with respect to VCN and/or LV integration in these secondary malignancies. As such, the absence of any relation between these malignancies and Aucatzyl is not substantiated. This is further assessed in the Clinical section.

CAR T cell-related secondary malignancies is a warning in section 4.4 of the SmPC and long-term follow-up of efficacy and safety of patients treated with Aucatzyl will be captured. This is endorsed. Further assessment of the proposed tumour surveillance strategies can be found in the Clinical section.

Follicular dendritic cells (DCs) reside in lymphoid organs and can also express CD19. Considering that these cells play a role in B cell activation, positive staining in some tissues of the TCR study may have incorrectly be assigned to B cells. As such, Aucatzyl may not only result in B cell aplasia but may also eliminate follicular DCs. A discussion was provided on the potential of dendritic cell staining in lymphoid tissues (in B cell rich regions) in the IHC sections, the chance of CAR T cell-mediated depletion of these DCs in patients and the clinical consequence related to such on-target off-tumour toxicity. This discussion included an overview of the characteristics of follicular DCs and their role in B cell maturation within germinal centres. As these DCs can express CD19, they could be depleted by Aucatzyl, which would subsequently result in loss of/reduced B cell maturation. Reference was made to a study from Tur et al. (2024), in which this phenomenon of follicular DC depletion was observed following CAR T cell therapy in the context of autoimmune disease. Whether this resulted in any (off-disease) toxicity was not evaluated. Nevertheless, when B cell aplasia will occur following CAR T cell treatment, loss of follicular DCs will likely not have an exacerbating effect. Even when this would be the case, longer B cell aplasia would be considered more beneficial from an efficacy point of view. No additional toxicity from depletion of follicular DCs by CAR T cell therapy has been reported. Adverse effects due to B cell aplasia (e.g. immunoglobulin deficiency) can be managed clinically.

The risk for bystander cell transduction with the product has been discussed, based on the vector particle removal from the cells during manufacturing and presence of *in vivo* LV inactivating factors. A discussion on literature review has been provided. Reference is made to the potential increased risk of RCL generation or secondary primary malignancies when bystander cell transduction would occur. It should, however, be mentioned that infectious viral particles do not need to be replication competent to result in bystander transduction. The risk of bystander transduction is largely related to the potential for LV insertion in and CAR expression by cells other than T cells, which could lead to unpredictable effects in and by these cells (which are different from e.g. T cell lymphomas/malignancies due to LV insertion in the meant-to-transduce cell type). Yet, the absence of RCL generation is considered a relevant safety control step in the manufacturing process.

To prevent (or limit as much as possible) the risk for bystander cell transduction, -infectious- vector particles in the drug product and especially those sticking on the outside of T cell membranes are to be removed during the manufacturing process and/or inactivated *in vivo*. Description of the control steps in the manufacturing process to reduce residual infectious viral particles (e.g. several washing steps, multi-day culture at 37°C) has been submitted and provided more insight in *in vivo* inactivating factors present in human serum. The residual particle level in the final drug product is considered too low to transduce activated T cells and too low to result in bystander cell transduction in patients. Whether other cell types could be more sensitive to transduction (i.e. require a lower particle level) has not been mentioned. Nevertheless, it is agreed that the risk of bystander cell transduction by Aucatzyl is very limited, especially when considering that *in vivo* residual infectious particles will likely be inactivated in serum.

Conclusions on ERA:

Considering the nature of the product the impact on environment of Aucatzyl is considered negligible

The CHMP endorses the CAT discussion on the non-clinical aspects as described above.

2.5.7. Conclusion on the non-clinical aspects

Overall, the primary pharmacology studies provide evidence that the CD19 CAT CAR T cells are capable of binding the target (CD19) and upon encountering this target on (tumour) cells, proliferate and execute cytotoxic function. This has been shown in vitro (MoA) and *in vivo* (PoC). Data indicate that CD19 CAT CAR has a lower affinity for CD19 as compared to CD19 FMC63 CAR which is determined by its lower K_{off} rate. Data might indicate that under conditions designed to give CAR T cells a numeric disadvantage, lower affinity CD19 CAT CAR T cells mediate enhanced anti-tumour responses and expansion as compared to higher affinity CD19 (FMC63) CAR T cells.

Considering the type of product, the absence of general PK and dedicated biodistribution data is endorsed. Evaluation of long-term persistence is part of the clinical assessment.

Only limited non-clinical toxicity data have been obtained with Aucatzyl. Considering the type of product and the absence of pharmacologically relevant animal species in which T cells can engraft and reliable on- and off-target toxicity data can be obtained, the lack of general toxicity studies can be endorsed. The absence of genotoxicity, carcinogenicity and reproduction toxicity data can be accepted, as this is in line with ICH S9. The literature-based risk evaluation of insertional mutagenesis instead of actual insertion site analysis is sufficient from a non-clinical perspective. Tissue cross-reactivity data and potential for bystander transduction have been sufficiently discussed.

Overall, the risks for human health and the environment of Aucatzyl are considered negligible.

In conclusion, the product is considered approvable on the non-clinical aspects of the dossier.

The CHMP endorses the CAT conclusions on the non-clinical aspects as described above.

2.6. Clinical aspects

2.6.1. Introduction

GCP aspects

The clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the Community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

Tabular overview of clinical studies

Study Identifier	Study Design	Number of Patients Enrolled / Infused	Patients Diagnosis	Efficacy Data	Study Status; Type of Report
FELIX EudraCT: 2019-001937-16	Global, multi-centre, single arm, open label Phase Ib/II; follow-up duration: 60 months Once all	Cohort A from Phase II (Cohort IIA): 113 leukapheresed / 94 infused	Adult r/r B ALL with morphological disease (≥ 5% blasts in BM at screening) (Cohort A)	**Primary analysis:** ORR, CR, MRD-neg remission, DOR, EFS, OS DCO: 09-	Follow-up ongoing; CSR

Study Identifier	Study Design	Number of Patients Enrolled / Infused	Patients Diagnosis	Efficacy Data	Study Status; Type of Report
NCT04404660	patients completed 60 months, long-term safety evaluation up to 15 years after obe-cel infusion in a separate extension (AUTO-LT1).			Jun-2023 DCO longer follow-up: 07-Feb-2024	
		Pooled Cohort A from both phases (Ib/II): 133 enrolled / 107 infused	Adult r/r B ALL with morphological disease (≥ 5% blasts in BM at screening) (Cohort A)	ORR, CR, MRD-neg remission, DOR, EFS, OS DCO: 07-Feb-2024	Follow-up ongoing; CSR
		Pooled All Cohorts from both phases (Ib/II): 153 enrolled / 127 infused	Adult r/r B ALL with: morphological disease i.e. ≥ 5% blasts in BM at screening (Cohort A) morphological remission and MRD-positive status at screening (Cohort B) isolated EMD at screening (Cohort C)		
ALLCAR19 NCT02935257	National (UK), multi-centre, single arm, open label Phase I	25 enrolled/ 20 infused	Adult r/r CD19-positive B ALL	ORR, CR, MRD-negative CR, EFS, OS	Follow-up ongoing; publication (*Roddie et al, 2021*[29], *Roddie et al, 2023*[30])

[29] Roddie C, Dias J, O'Reilly MA, et al (2021). Durable Responses and Low Toxicity After Fast Off-Rate CD19 Chimeric Antigen Receptor-T Therapy in Adults With Relapsed or Refractory B-Cell Acute Lymphoblastic Leukemia. J Clin Oncol; 39(30):3352-3363.
[30] Roddie C, Dias J, O'Reilly M, et al (2023). Long-Term Follow-up of AUTO1, a Fast-Off Rate CD19 CAR, in Relapsed/Refractory B-Cell Acute Lymphoblastic Leukemia and Factors Associated with Durable Response. Poster presented at: American Society for Transplantation and Cellular Therapy Meeting, Feb 15-19, 2023, Orlando, Florida, USA.

Study Identifier	Study Design	Number of Patients Enrolled / Infused	Patients Diagnosis	Efficacy Data	Study Status; Type of Report
AUTO1-EC1 (ECA)	Prospective, non-interventional study comparing FELIX Cohort IIA to an ECA	Matched patients from FELIX Cohort IIA and eligible patients receiving SoC [a] from the database: 107 enrolled / 84 infused	Adult r/r B ALL	ORR, OS, EFS DCO: 09-Jun-2023	Completed; report
3964a (MAIC)	MAIC of FELIX Cohort IIA versus ZUMA-3 Phase II patients	Matching-adjusted patients from FELIX Cohort IIA (N=94 infused and N=112 enrolled) and patients receiving brexu-cel in the Phase II of ZUMA-3 (N=55 infused and N=71 enrolled)	Adult r/r B ALL	ORR, CR, EFS DCO: 09-Jun-2023	Completed; report

B ALL=B-cell precursor acute lymphoblastic leukemia; BM=bone marrow; brexu-cel=brexucabtagene autoleucel; CR=complete remission; CSR=clinical study report; DCO=data cut-off; DOR=duration of remission; ECA=external control arm; EFS=event-free survival; EMD=extramedullary disease; MAIC=matching-adjusted indirect comparison;; MRD=minimal residual disease; ORR=overall remission rate; OS=overall survival; r/r=relapsed or refractory; SoC=standard of care; TKI=tyrosine kinase inhibitor.
[a] Blinatumomab, inotuzumab ozogamicin, or standard chemotherapy (fludarabine, cytarabine and filgrastim ± anthracycline-based regimen; high-dose cytarabine-based regimen; high-dose methotrexate-based regimen; clofarabine or clofarabine-based combination regimen); TKIs were allowed to be used in combination with above chemotherapies for Ph+ patients.

2.6.2. Clinical pharmacology

2.6.2.1. Pharmacokinetics

No dedicated clinical pharmacology/pharmacokinetic studies were conducted. Traditional PK analyses are not relevant for this CAR T cell product. The assessment of clinical pharmacology was based on the pivotal FELIX study. The ALLCAR19 study provided supportive PK data. The main analysis for PK and PD was based on the patients that received at least one obe-cel infusion in the pivotal FELIX trial Cohort IIA. For the analysis of PK/PD and clinical safety events, the safety set of all infused patients was used.

In the FELIX study, the protocol-specified secondary objectives and endpoints relevant to PK are to evaluate the expansion and persistency of obe-cel in phase IB and phase II. Additional analyses were prespecified in the Pharmacokinetics, Pharmacodynamics and Safety Biomarkers SAP with the aim of evaluating the relationship between pharmacokinetics and efficacy, safety and dose. The impact of intrinsic and extrinsic factors on pharmacokinetics was evaluated including, but not limited to, the

tumour burden and its impact on expansion, safety, and efficacy endpoints. However, no POPPK model was used.

The study design is described in more detail in the clinical efficacy section.

Peripheral blood was sampled from all treated patients and the AUTO1 transgene concentrations (copies/µg DNA) were analysed by ddPCR during pre-conditioning treatment, during the treatment phase, during the efficacy and safety follow-up visit, during the end of study visit and at relapse.

Two different validated methods were used to provide quantitative measurements of Aucatzyl in patient samples. The ddPCR analysis is used for the quantitative analysis of the obe-cel transgene in genomic DNA and flow cytometry is used as a supportive method for the assessment of intracellular CD19 CAR-positive T cell antigens. The two methods are commonly employed to track the genetically modified T cells even if official regulatory guidance is lacking for these technologies. No standardised method/assay for CD19-CAR measurement is established yet. Both qPCR and ddPCR quantify low amounts of gene copies in complex samples with high reproducibility and sensitivity while ddPCR seems to be a reliable "relatively new" tool for gene quantification in clinical routine and research setting.

It is not clear whether the applicant investigated the incurred sample reproducibility in the ddPCR method used for Aucatzyl. In a white paper from Wissel et al.2022, ISR is not recommended due to insufficient data to understand utility and feasibility. According to Hays et al. 2022, the current consensus in the industry is to not assess ISR in qPCR and ddPCR assay in-study validations due to limited availability of the data to understand suitable criteria on how to conduct this assessment.

Otherwise, flow cytometric methods pose particular validation challenges due to the complexity of cellular measures, the lack of reference materials, and the fact that data are not derived from a calibration curve. Given that regulatory guidance for this technology is lacking, a fit-for-purpose validation was performed (sensitivity, accuracy, linearity and precision).

The applicant has used standard non-compartmental analyses (NCA) to describe cellular kinetics which is described by the time course of transgene copies per microgram of genomic DNA as measured by ddPCR. To describe PK in peripheral blood, the terms expansion and persistency were used. Expansion refers to the initial period of engraftment of the CAR T following infusion and was described with the conventional PK terms Cmax (maximum level of transgene), time to reach maximum plasma concentration following drug administration (Tmax) and AUC0-28d (transgene area under the plasma-concentration curve over the initial 28 days post infusion). Persistency refers to the continued presence of transgene in peripheral blood after Day 28.

The following PK parameters were reported: Tmax (day), Cmax (copies/µg), AUC0-28 (day*copies/µg), AUC0-84 (day*copies/µg), T1/2 (day), Tlast (day), Clast (copies/µg) and AUClast (day*copies/µg).

B cell aplasia is an expected on-target effect of obe-cel and the duration of B cell aplasia was measured as an assessment of functional CAR T cell persistency.

Antigen specific immune activation of T cells within peripheral blood mononuclear cells (PBMCs) results in the production of IFN-γ. Detection of antigen-specific immune activation in patients' PBMCs against obe-cel derived peptides at lymphodepletion and post infusion was assessed.

To assess humoral immunogenicity, a validated electro chemiluminescent direct binding immunoassay was used to assess anti-drug antibody (ADA) to obe-cel.

Dose proportionality and time dependencies

The dose regimen was informed by the disease burden (≤20% or >20% blasts) of the patient at lymphodepletion. The following regimens were administered:

- 56 patients received 10 x 10^6 cells followed by 400 x 10^6 cells (High burden disease patients)
- 32 patients received 100 x 10^6 cells followed by 310 x 10^6 cells (low burden disease patients)

A small number of patients only received a single dose (n=7), but this number was too small to draw conclusions on PK parameters per dose regimen.

Amongst patients who received 2 doses, those with 10 x 10^6 CD19 CAR-positive T cells at first dose (>20% disease burden) demonstrated a higher expansion and a later peak than patients with 100 x 10^6 CD19 CAR-positive T cells at first dose (≤20%).

Table 3. PK parameters by dose regimen (cohort IIA, infused set – patients who received 2 Obe-Cel doses)

Parameter	**Statistic**	**100 x 10^6 / 310 x 10^6** **Low disease burden regimen (≤ 20%)** **(N=32)[2]**	**10 x 10^6 / 400 x 10^6** **High disease burden regimen (>20%)** **(N=56)[1]**	**Total** **(N=88)**
Cmax (copies/µg DNA)	n	32	56	88
	Geometric Mean (Geo-CV%)	76,097 (184.3)	150,562 (305.4)	117,477 (269.6)
	Range (min – max)	9,290 – 589,000	129 – 600,000	129 – 600,000
Tmax (days)	n	32	56	88
	Median	11	17	14
	Range (min – max)	2 - 28	6 - 55	2 - 55
AUC0-28d (copies/µg DNA*day)	n	29	50	79
	Geometric Mean (Geo-CV%)	675,763 (233.5)	1,569,813 (190.5)	1,152,057 (224.6)
	Range (min – max)	70,400 – 7,230,000	17,900 – 6,730,000	17,900 – 7,230,000

1 Two doses and first dose was 10 x 10^6 CD19 CAR-positive T cells

2 Two doses and first dose was 100 x 10^6 CD19 CAR-positive T cells

Persistency was observed in both patients with low (green) and high (blue) first dose (Figure 2). A total of 84.6% (22/26) of the patients who had ongoing remission as of the data cut-off date (07-Feb-2024) had ongoing CAR T persistency.

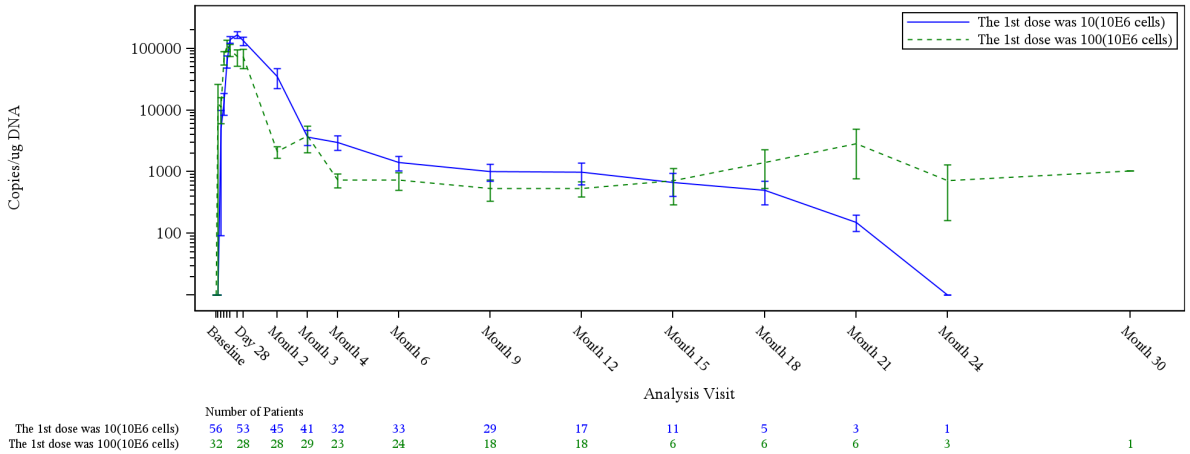


Figure 2. CAR T cell persistency (mean [SE]) in peripheral blood according to number of cells in first dose (cohort IIA, infused set) DCO 07-Feb-2024

In the supportive ALLCAR19 study, an expansion was observed with a Cmax of 127,152 copies/µg DNA and a mean AUC0-28d of 1,251,802 copies/µg DNA*days.

The expansion for the Infused Set of Cohort IIA (N=94) is shown in figure 2 and 3. An initial expansion followed by a bi-exponential decline is common for the different CAR T cells products currently available. In the Infused Set of Cohort IIA (N=94) for Aucatzyl, the PK of Aucatzyl is characterised by rapid and high level of expansion of the cells following infusion. The CAR transgene levels started to decline at approximately Day 28 and stabilised at Month 6 up to Month 15 (figure 2).

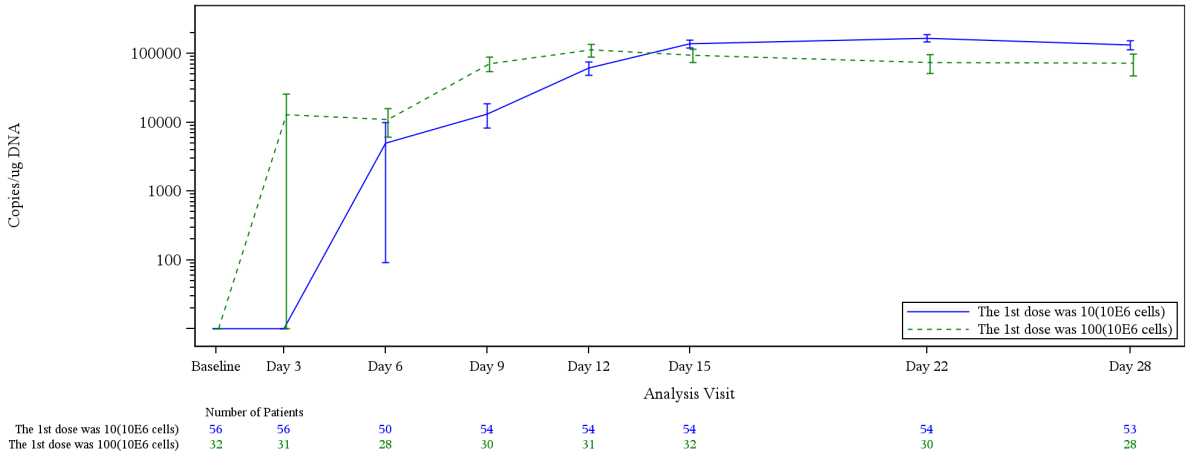


Figure 3. CAR T cell pharmacokinetic profile up to one month: mean (SE) and individual concentration vs time profiles of obe-cel transgene levels in peripheral blood (cohort IIa, infused set)

Special populations

Table 4. Age range of elderly population, phase II cohort A

	Age 65-74 (Older subjects number /total number)	**Age 75-84 (Older subjects number /total number)**	**Age 85+ (Older subjects number /total number)**
FELIX	17 / 94	4 / 94	0 / 94

The age range of the elderly population is provided in **Table 4**. No population PK analysis has been proposed to investigate the effect of the various demographic and disease characteristics on Aucatzyl PK parameters. The impact of intrinsic (sex, age, weight, extramedullary disease [EMD] presence, disease burden, Philadelphia chromosome/BCR-ABL status, race) and extrinsic factors (number of lines of prior therapies, and by response to previous lines of therapy (including time to relapse), previous allogeneic SCT therapy and the use of previous targeted therapy (blinatumomab and/or inotuzumab ozogamicin) on PK were evaluated by means of the comparison of subgroups.

When comparing groups of patients based on age or gender, numerical differences of less than 2-fold were observed in the geometric means of C_{max} and $AUC_{0\text{-}28d}$.

Patients were categorised in two subgroups based on their weight relative to the median (<75.75kg and ≥75.75kg). PK parameters were comparable between both weight subgroups. The fixed non-weight-adjusted target dose was both effective and safe in patients with a low (<median) and high (≥median) body weight.

Race was the only demographic parameter where up to 3-fold increase in geometric mean Cmax was observed in patients of Asian or Unknown race (Cmax 270,091 copies/µg DNA and 181,725 copies/µg DNA respectively) compared to Black or African American or White race (Cmax around 95,000 copies/µg DNA). This difference was also reflected in geometric mean AUC0-28d: Asian 2,581,885 copies/µg DNA*day, compared to Black or African American 861,123 copies/µg DNA*day or White 950,778 copies/µg DNA*day, Unknown 1,906,780 copies/µg of DNA*day). CAR T persistency was observed in all race sub-groups. The number of patients in the non-White categories are limited (Asian n=10, Black n=2, unknown n=12) and it is difficult to conclude on whether there are systematic differences in CAR T cell kinetics across races. Race has not been included in a population PK model as a covariate to study the impact on Aucatzyl PK. Therefore, the data in the non-white population are too limited to draw any conclusions on the impact of race on PK parameters.

No formal studies have been performed in renal or hepatic impaired patients. Aucatzyl is a cell based therapeutic and does not undergo renal elimination or hepatic metabolism/elimination.

No formal studies have been performed in paediatric patients below 18 years of age.

Pharmacokinetic interaction studies

No in vitro or in vivo interaction studies have been conducted which is acceptable considering the type of medicinal product.

Influence of tocilizumab on pharmacokinetics

Tocilizumab was administered following the onset of CRS (mean onset of CRS 7.8 days). Peak expansion occurred on Day 13 for patients not treated with tocilizumab and on Day 15 for patients treated with tocilizumab. Obe-cel continued to expand after tocilizumab administration. C_{max} and $AUC_{0\text{-}}$

$_{28d}$ were higher in patients receiving tocilizumab for CRS management (C_{max} 221,123 copies/µg DNA; AUC_{0-28d} 2,599,792 copies/µg DNA·day) compared with patients not receiving tocilizumab (C_{max} 43,863 copies/µg DNA; AUC_{0-28d} 396,135 copies/µg DNA·day). CAR T cell persistency was observed in both patients where tocilizumab was administered and in patients without tocilizumab administration.

Influence of corticosteroids on pharmacokinetics

Corticosteroids were administered following the onset of CRS and ICANS (mean time to onset of CRS and ICANS on days 7.8 and 13.0 days, respectively). Peak CAR T cell expansion occurred on Day 14 for patients not treated with corticosteroids and on Day 21 for patients treated with corticosteroids. Obe-cel continued to expand after corticosteroid administration. C_{max} and AUC_{0-28d} were higher in patients who received corticosteroids for CRS and/or ICANS management (C_{max} 282,740 copies/µg DNA; AUC_{0-28d} 2,396,542 copies/µg DNA·day) compared with patients who did not receive corticosteroids (C_{max} 69,056 copies/µg DNA; AUC_{0-28d} 789,711 copies/µg DNA·day). CAR T cell persistency was observed in both in patients where corticosteroids were administered and in patients without corticosteroid administration.

Neither tocilizumab nor corticosteroids appear to have a direct impact on CAR T cell expansion or persistency. The difference in expansion is more likely due to high tumour burden, which leads to a higher probability of CRS and ICANS than the use of tocilizumab or corticosteroids.

2.6.2.2. Pharmacodynamics

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 as described by Ghorashian et al 2019[31].

Primary and Secondary pharmacology

B cell aplasia

B cell aplasia was measured as an assessment of functional CAR T cell persistency. A patient was considered to display B cell aplasia (CD45+ CD3- CD19+ cells) if the absolute numbers of B cells was <20 cells/µl. Time to recovery was defined as the days between the first obe-cel infusion and the first time at which ≥20 cell/µl of B cells was measured in peripheral blood using a validated flow cytometry assay. B cell aplasia was evaluated for the Infused Set (Cohort IIA, N=94). B cell recovery is described in **Table 5**.

[31] Ghorashian S, Kramer AM, Onuoha S, Wright G, Bartram J, Richardson R, Albon SJ, Casanovas-Company J, Castro F, Popova B, Villanueva K, Yeung J, Vetharoy W, Guvenel A, Wawrzyniecka PA, Mekkaoui L, Cheung GW, Pinner D, Chu J, Lucchini G, Silva J, Ciocarlie O, Lazareva A, Inglott S, Gilmour KC, Ahsan G, Ferrari M, Manzoor S, Champion K, Brooks T, Lopes A, Hackshaw A, Farzaneh F, Chiesa R, Rao K, Bonney D, Samarasinghe S, Goulden N, Vora A, Veys P, Hough R, Wynn R, Pule MA, Amrolia PJ. Enhanced CAR T cell expansion and prolonged persistence in pediatric patients with ALL treated with a low-affinity CD19 CAR. Nat Med. 2019 Sep;25(9):1408-1414.

Table 5. Time of B cell recovery - Kaplan-Meier analysis (DCO 07-Feb-2024)

	CR/CRi (N=72) n (%)	Not CR/CRi (N=22) n (%)	Total (N=94) n (%)
No. of events - n (%)	16 (22.2)	1 (4.5)	17 (18.1)
B cell recovery	16 (22.2)	1 (4.5)	17 (18.1)
No. of censored observations - n (%)	56 (77.8)	21 (95.5)	77 (81.9)
Death	18 (25.0)	11 (50.0)	29 (30.9)
Ongoing B cell aplasia	28 (38.9)	0	28 (29.8)
SCT	10 (13.9)	4 (18.2)	14 (14.9)
No evaluable results post infusion	0	5 (22.7)	5 (5.3)
Withdrew consent	0	1 (4.5)	1 (1.1)
Minimum, Maximum follow-up (months)	0.9+ , 24.0+	0.0+ , 3.7+	0.0+ , 24.0+
Median follow-up (months) [1]	9.0 (6.08, 11.99)	1.1 (0.89, 2.27)	6.0 (3.75, 8.97)
Quartile Estimates (95% CI) (month) [2]			
75th	6.14 (4.17, NE)	NE	6.14 (4.17, NE)
50th	NE	NE	NE
25th	NE	NE	NE

Time to recovery was defined as the days between the first AUTO1 infusion and the first time at which >= 20 cells/uL in CD19+ cells in lymphocytes in blood is achieved. NE = Not Estimable.
Patients who had death, proceeded to stem cell transplant, withdrew consent, were lost to follow-up, or had ongoing B cell aplasia were censored on the day of last evaluable laboratory assessment.
[1] Median follow-up is calculated using reverse Kaplan-Meier method.
[2] Percentiles with 95% CIs are calculated from PROC LIFETEST output using method of Brookmeyer and Crowley (1982).
[3] % Event-free probability estimates are obtained from the Kaplan-Meier (KM) survival estimates, with 95% CIs estimated using Greenwood formula.
/lsafshared/SASWorkspaces/.transient/t_km.job-d1587dda-c08e-426d-9330-074958d1a368/Development/AUTO1/AUTO1-AL/AUTO1-AL1/Ad_Hoc/ASCO_2024/Programs/TFL/Generated/t_km_bcap_bor_inf_iia.sas (y.wang 10DEC2024 02:22 SAS Linux 9.4)

- Serum biomarkers

IgG levels were lower than the normal clinical range at 37.3 µmol/L at baseline (last available measurement prior to obe-cel infusion) and remained low until Month 12. Beyond Month 12, the number of patients with results to date is too small to draw any conclusion. The percentage of patients with value below the lower limit of normal was 44.3% at baseline, 54.5% at Day 28, 56.8% at Month 3, 45.5% at Month 6 and 29.5% at Month 12.

Cytokine levels post obe-cel infusion were generally consistent with levels seen in healthy individuals (*Biancotto et al, 2013*[32]), reached a peak concentration within the first month post infusion and reverted to baseline at the next time point (Day 90).

Mean peak concentrations of serum biomarkers were increased with the presence of CRS and with increasing grade of ICANS, compared to patients without CRS or ICANS.

- Immunological events

As obe-cel is an autologous product, significant cellular or humoral immunogenicity is not expected. Positive cellular immunogenicity findings occurred in 3 patients (2.4%). No significant cellular immunogenicity signal was seen in 3/75 patients with evaluable samples. All 3 patients demonstrated CR and any safety events were unlikely to be related to the cellular immunogenicity signal.

Positive humoral immunogenicity findings occurred at any time (pre- or post-infusion) in 13/127 patients (10.2%); 11/127 (8.7%) patients tested positive for humoral immunogenicity at baseline, and 2/127 (1.6%) patients were positive for humoral immunogenicity post-infusion. These 2 patients who were negative for anti-drug antibodies (ADAs) at baseline. Both patients with treatment induced ADA achieved a best overall response of CR or CRi. Both patients developed post-infusion CRS, but the onset of CRS occurred within days of obe-cel administration; neither CRS nor any other safety events observed in these 2 patients appear to be related to the ADA positivity signal.

[32] Biancotto A, Wank A, Perl S, et al (2013). Baseline levels and temporal stability of 27 multiplexed serum cytokine concentrations in healthy subjects. PLoS One; 8(12):e76091.

Updated data (cut-off October 2024) were provided. All additional samples which could be analysed (n = 11/15 for cellular immunogenicity and n = 38/38 for humoral immunogenicity) tested negative, including the samples taken at or around relapse.

Dose versus efficacy

The primary endpoint of the FELIX study was overall remission rate (ORR) at any time post-infusion, defined as the proportion of patients achieving a BOR post-infusion of either CR or CRi, as assessed by the Independent Response Review Committee (IRRC).

A summary of PK parameters by BOR is provided in **Table 6**. Small differences were seen in the geometric mean or median (IQR) of C_{max} or $AUC_{0\text{-}28d}$. A numerically later median T_{max} was observed for patients not in complete remission (17 days vs 14 days). No apparent trend was observed in response rate with increasing C_{max} or $AUC_{0\text{-}28d}$.

Table 6. 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)	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
$AUC_{(0\text{-}28d)}$ (copies/µg DNA*days)	n	68	14	82
	Geometric mean (Geo-CV%)	1,089,908 (236)	1,404,899 (186.4)	1,138,188 (225.6)
	Range (Min - Max)	17,900-6,730,000	176,000-7,230,000	17,9007,230,000

Dose-efficacy analysis based on dosing regimen showed that patients receiving a lower first dose of 10 × 10^6 cells (>20% blasts in BM, high disease burden) have a numerically lower ORR (75.0% CR/CRi) than patients receiving a higher first dose of 100 × 10^6 cells (≤20% blasts in BM, low disease burden) (87.5% CR/CRi), with overlapping 95% CI (**Table 7**).

Table 7. Relationship between dosing parameters and clinical efficacy (cohort IIa, infused set, patients who received 2 Obe-cel doses)

Metric	10 × 10^6, then 400 × 10^6 cells High disease burden regimen (> 20% blasts) (N=56)	100 × 10^6, then 310 × 10^6 cells Low disease burden regimen (≤ 20% blasts) (N=32)	Total (N=88)
ORR (CR+CRi) - n (%)	42 (75.0)	28 (87.5)	70 (79.5)
95 % CI (%)	61.6, 85.6	71.0, 96.5	69.6, 87.4

CI=confidence interval; CR=complete remission; CRi=complete remission with incomplete recovery of counts; ORR=overall response rate.

Measurements of the presence of CAR T cells were not performed from the time of discontinuation from the study. The maximum follow-up period for non-CR/CRi patients was approximately 3.7 months. Therefore, analysis of duration of persistency was only performed in CR/CRi patients. In the

CR/CRi group (N=72), 84.6% had ongoing CAR T persistency at the last laboratory assessment. CAR T persistency was observed up to a maximum of 30 months.

In the supportive ALLCAR19 study, 8/20 (40%) of patients have ongoing CR at median follow-up of 36 months. Long term remission was associated with CAR T persistency in 7/8 patients at last follow-up.

Dose versus safety

The relationship between dosing parameters and the incidence of CRS or ICANS was investigated in the Safety Set, and results are shown below in **Table 8**. The incidence of all Grade ≥ 3 CRS and ICANS, as well as Grade ≥3 CRS and ICANS is low. The incidence of CRS and ICANS was higher in the patients who received 10 × 10^6 cells in their first dose (with higher disease burden) compared to those who received 100 × 10^6 cells in the first dose (lower disease burden).

Table 8. Relationship between dosing parameters and clinical safety (cohort Ib and II, safety set, patients who received 2 Obe-cel doses)

	10 × 10^6, then 400 × 10^6 cells **High disease burden regimen (> 20% blasts)** **(N=72)**	**100 × 10^6, then 310 × 10^6 cells** **Low disease burden regimen (≤ 20% blasts)** **(N=48)**	**Total** **(N=120)**
CRS			
Any Grade n (%)	60 (83.3)	24 (50.0)	84 (70.0)
≥Grade 3 n (%)	2 (2.8)	0	2 (1.7)
ICANS			
Any Grade n (%)	22 (30.6)	5 (10.4)	27 (22.5)
≥Grade 3 n (%)	7 (9.7)	0	7 (5.8)

CRS=cytokine release syndrome; ICANS=immune effector cell-associated neurotoxicity syndrome.

Patients with Grade 2 CRS and/or Grade 1 ICANS following the first split dose may receive the second dose on Day 10 (±2 days) only if CRS has resolved to Grade 1 or less and ICANS has completely resolved. If necessary, the infusion of the second split dose may be postponed beyond Day 10 (±2 days) up to Day 21 to allow for the resolution of Grade 2 CRS and/or Grade 1 ICANS. Onset of CRS and/or ICANS was the reason for a delayed second dose in 7 out of the 9 patients receiving a delayed dose. The other 2 patients were due to Grade 4 hyperferritinaemia and Grade 3 elevated alanine aminotransferase (ALT).

The expansion parameters were generally elevated in patients with a delayed second dose with a range of 212,000 to 467,000 copies/µg DNA for Cmax and 2,160,000 to 7,230,000 copies/µg DNA*day for AUC0-28d. A wide range was also observed for Tmax (10-22 days).

2.6.3. Discussion on clinical pharmacology

No dedicated clinical pharmacology/pharmacokinetic studies were conducted which is acceptable considering the type of medicinal product.

Cellular kinetics were studied using droplet digital PCR technology and measured as obe-cel transgene levels in peripheral blood. The sampling frequency and reported PK parameters are considered adequate. B cell aplasia was used as a PD biomarker of functional CAR T cell persistency. Both cellular (IFN-γ) and humoral (antidrug antibodies) immunogenicity were tested. The data analysis and evaluation are adequately described.

Pharmacokinetics

In patients receiving both two doses, obe-cel demonstrated a rapid expansion with a T_{max} after a median of 14 days. The T_{max} was faster in the low disease burden (11 days) compared to the high disease burden (17 days) regimen. The median time to peak levels are comparable to other CAR T products. A high expansion (C_{max}, $AUC_{0\text{-}28d}$) was observed in both low and high disease burden regimens. Patients with a higher disease burden received a lower first dose but demonstrated higher expansion. This suggests that the tumour burden is the driver of expansion. The reported C_{max} and $AUC_{0\text{-}28d}$ are higher than reported in the literature for other CAR T products (*Song et al, 2021*[33], *Rotte 2022*[34]). Although the target dose is administered as a split dose on day 1 and day 10, only a single peak was seen, and no bi-modal profile was observed. This is probably due to the limited sampling time points between the two doses.

Two different dosing regimens (10/400 x 10^6 cells for high disease burden and 100/310 x 10^6 cells for low disease burden) were used. From a safety perspective, the low first dose in patients with a high disease burden is understood. However, the value of using a different regimen in patients with a low disease burden is unclear.

The applicant claims improved CAR T expansion and long-term persistency of obe-cel because of the different CAT CAR construct. Although multiple factors influence CAR T cell kinetics and comparing data across trials is methodologically difficult, the reported CAR T persistency is higher than reported in the literature for other CAR T products.

Persistency was observed in both low and high disease burden regimens. Persistency was maintained for 15 months both in high and low tumour burden patients. After 15 months, there was a drop in persistency, however only a small number of patients were available to contribute to the analysis beyond 15 months. The subgroup analyses (age, gender, race, weight) for C_{max}, geometric mean $AUC_{0\text{-}28d}$, and persistency revealed no notable differences between groups, or subgroups were too small to allow reliable conclusions.

The influence of tocilizumab and corticosteroids on PK was studied. C_{max} and $AUC_{0\text{-}28d}$ were higher in patients that received tocilizumab, and the peak expansion was two days later compared to patients that did not receive tocilizumab. Persistency was observed in both patients treated with and without tocilizumab. Similar results were reported for patients treated with corticosteroids following CRS or ICANS, with a higher C_{max} and $AUC_{0\text{-}28d}$ and later peak expansion in patients treated with corticosteroids. There is major confounding, since tocilizumab and corticosteroids are used for the treatment of CRS and ICANS, which develops predominantly in patients with a high tumour burden.

Pharmacodynamics

The mechanism of action of CAR T cells is generally understood. The applicant showed that the different binder domain of obe-cel leads to a lower affinity with a similar on-rate, but a faster off-rate compared to tisa-cel and brexu-cel. As per the submitted dossier and applicant view, the novel low affinity CD19 (CAT) CAR binder has a faster disengagement compared to the CD19 (FMC63) CAR

[33] Song et al (2021), Pharmacology of Chimeric Antigen Receptor–Modified T Cells, Annual Review of Pharmacology and Toxicology Vol. 61:805-829
[34] Rotte A, Frigault MJ et al (2022). Dose-response correlation for CAR-T cells: a systematic review of clinical studies. J Immunother Cancer. 10(12):e005678

reported to be used in tisagenlecleucel, axicabtagene ciloleucel and brexucabtagene autoleucel, all currently approved CD19-directed CAR therapies (*Kochenderfer et al, 2009*[35]; *Wang et al, 2020*[36]; *Cappell and Kochenderfer, 2021*[37]). Obe-cel it is claimed by the applicant to offers a treatment option which mimics a more physiological T cell activation with the potential to reduce immuno-toxicity, improve engraftment and provide long-term persistency (*Roddie et al, 2021*[38]). However, based on the assessment of the evidence provided a comparison across trials is difficult as several factors influence CAR T cell kinetics and there are differences in sampling frequency and reported PK measurements across trials. Although the rationale is understood, a head-to-head comparison has not been provided to conclude that obe-cel results in faster expansion and improved long-term persistency compared to tisa-cel and brexu-cel.

B cell aplasia was measured as an assessment of functional CAR T cell persistency. The probability of B cell aplasia was 70.4% (95% CI 55.5 – 81.1) after 12 months and probabilities of B cell aplasia did not differ substantially by obe-cel dosing regimen (high/low disease burden). The median time to B-cell recovery could not be estimated.

As expected, pro-inflammatory biomarker concentrations were increased in patients with CRS and increasing grade of ICANS compared to patients without CRS or ICANS.

Cellular and humoral immunogenicity was studied. The number of patients with positive immunogenicity tests at 3 months after obe-cel infusion was low and a positive cellular immunogenicity signal or anti-CD19 CAR ADA at baseline or post-infusion had no impact on the effectiveness, safety, or initial expansion and persistency of obe-cel in adult patients with B ALL.

The dose-efficacy analysis showed a clinical response regardless of the low (≤ 20% blasts) or high tumour burden (> 20% blasts) dosage regimen, however a lower response rate was observed in the high tumour burden patients, which is in line with the expectation that patients with a higher disease burden are typically a more difficult-to-treat patient group. The observed differences in efficacy between the different dosage regimens are difficult to attribute to the dosage regimens, since they are most likely caused by the difference in tumour burden. The long-term persistency was high, with ongoing persistency at the last laboratory assessment in 84.6% of responders. Long term CAR T cell persistence is associated with lower relapse rates and longer PFS (*Wittibschlager, 2023*[39]). However, the length and degree of persistence necessary for a durable response are unclear (*Cappell, 2023*[40]). For some products B-cell levels are used as surrogate marker for persistency, however a comparison to other CAR T products is difficult due to differences in sampling frequency.

The dose-safety analysis showed that both CRS and ICANS (any grade) were associated with higher CAR expansion, driven primarily by disease burden at lymphodepletion. Higher expansion is known to be the driver for the onset of CRS and ICANS, therefore the higher incidence of CRS and ICANS (any grade) in the high disease burden regimen is in line with expectations. More discussion on the CRS, ICANS in relation to the split dose is provided in the safety discussion.

[35] Kochenderfer JN, Feldman SA, Zhao Y, et al (2009). Construction and preclinical evaluation of an anti-CD19 chimeric antigen receptor. J Immunother; 32(7):689-702.
[36] Wang M, Munoz J, Goy A, et al (2020). KTE-X19 CAR T-Cell Therapy in Relapsed or Refractory Mantle-Cell Lymphoma. N Engl J Med; 382(14):1331-1342.
[37] Cappell KM, Kochenderfer JN (2021). A comparison of chimeric antigen receptors containing CD28 versus 4-1BB costimulatory domains. Nat Rev Clin Oncol; 18(11):715-727.
[38] Roddie C, Dias J, O'Reilly MA, et al (2021). Durable Responses and Low Toxicity After Fast Off-Rate CD19 Chimeric Antigen Receptor-T Therapy in Adults With Relapsed or Refractory B-Cell Acute Lymphoblastic Leukemia. J Clin Oncol; 39(30):3352-3363.
[39] Wittibschlager V, Bacher U et al (2023). CAR T-Cell Persistence Correlates with Improved Outcome in Patients with B-Cell Lymphoma. Int J Mol Sci;24(6):5688.
[40] Cappell, K.M., Kochenderfer, J.N (2023). Long-term outcomes following CAR T cell therapy: what we know so far. Nat Rev Clin Oncol 20, 359–371

2.6.4. Conclusions on clinical pharmacology

Obe-cel cellular kinetics and exposure responses have been generally well characterised. Therefore, the current application for obe-cel in r/r B ALL is acceptable from a clinical pharmacology point of view. No major issues have been identified.

The CHMP endorses the CAT assessment regarding the conclusions on the clinical pharmacology as described above.

2.6.5. Clinical efficacy

2.6.5.1. Dose response study(ies)

The selection of the proposed dosing regimen for obe-cel is primarily based on the initial proof-of-concept study, ALLCAR19, which was taken forward into the pivotal FELIX study. No dedicated dose selection studies were performed.

The ALLCAR19 was a single country, multi-centre, open label, non-randomised phase I trial to evaluate the safety, efficacy and duration of remission of obe-cel. The primary endpoints were toxicity and feasibility of adequate leukapheresis collection and generation of obe-cel. Twenty patients were infused. For patients with a low tumour burden (BM blasts ≤20%) a first dose of 1 x 10^8 total CD19 CAR T-cells (or 1-2 x 10^6/kg based on a patient weight of 50-100kg), was used which was in line with the UCL paediatric study of the same vector in patients with relapsed/refractory high grade B-cell malignancies where a single dose of 1 x 10^6/kg CD19 CAR T-cells was used (*CARPALL; EUDRACT 2015-001-10*). For patients with a high tumour burden (BM blasts >20%), a lower first dose of 1 x 10^7 CD19 CAR T-cells (or 1-2 x 10^5/kg based on a patient weight of 50-100kg) was used which was in line with the dose reductions employed by the Seattle group (*NCT01865617; Turtle et al, 2016*[41]) to avoid toxicity in patients with a higher disease burden.

Literature in support of the split-dosing regimen was provided. Firstly, single dose approach has been reported to expose patients with high disease burden to increased risks of toxicities (more severe CRS), while patients with low disease burden may not receive enough cells to ensure appropriate target engagement and exposure; therefore it had been proposed to either administer a lower dose of CAR T cells to patients with higher disease burden, or split the total dose (*Davila et al, 2014*[42]; *Lee et al, 2015*[43]; *Turtle et al, 2016*[44]). Secondly, dosing without consideration of disease burden or fractionation without an appropriate interval for management of side effects has already been demonstrated to be non-optimal (*Frey et al, 2020*[45]).

2.6.5.2. Main study(ies)

FELIX (AUTO1-AL1) Study

Methods

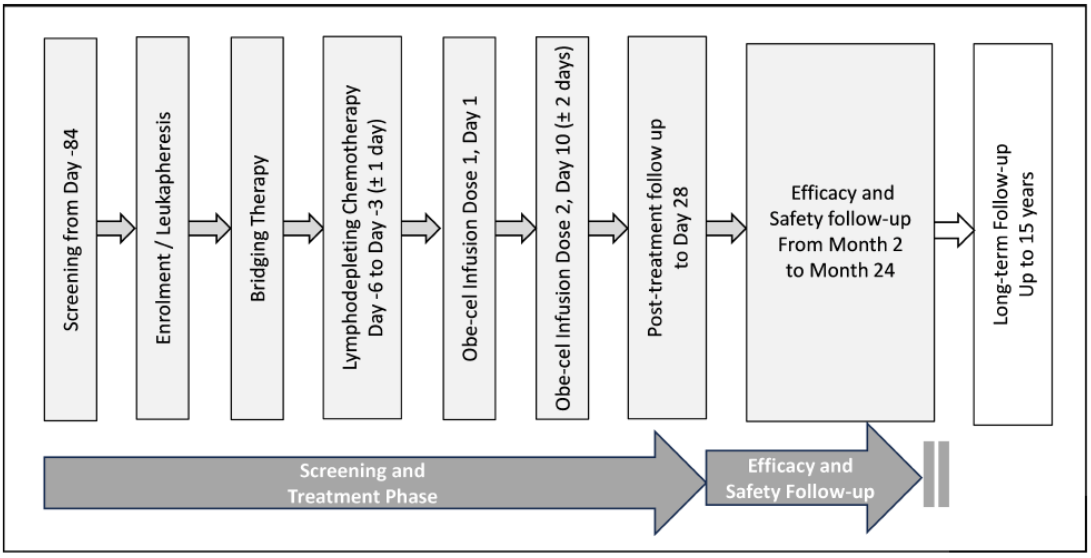
[41] Turtle, C.J., et al., CD19 CAR-T cells of defined CD4+:CD8+ composition in adult B cell ALL patients. J Clin Invest, 2016. 126(6): p. 2123-38.
[42] Davila, M.L., et al., *Efficacy and toxicity management of 19-28z CAR T cell therapy in B cell acute lymphoblastic leukemia.* Sci Transl Med, 2014. **6**(224): p. 224ra25.
[43] Lee, D.W., et al., *T cells expressing CD19 chimeric antigen receptors for acute lymphoblastic leukaemia in children and young adults: a phase 1 dose-escalation trial.* Lancet, 2015. **385**(9967): p. 517-28.
[44] Turtle, C.J., et al., CD19 CAR-T cells of defined CD4+:CD8+ composition in adult B cell ALL patients. J Clin Invest, 2016. 126(6): p. 2123-38.
[45] Frey NV, Shaw PA, Hexner EO, et al (2019). Optimizing Chimeric Antigen Receptor T-Cell Therapy for Adults with Acute Lymphoblastic Leukemia. J Clin Oncol; 38:415–22.

The FELIX study is an open-label, multi-centre, multi-national, single-arm Phase Ib/II study in adult patients with r/r B ALL evaluating the safety and efficacy of AUTO1, a CAR T cell treatment targeting CD19, in adult patients with relapsed or refractory B-cell acute lymphoblastic leukemia. The FELIX study consists of two phases: Phase Ib for feasibility of manufacturing and dosing as well as safety and preliminary efficacy to enable progression into the pivotal Phase II of the study. There were three cohorts with different disease presentation:

- Cohort A: Morphological disease at screening (≥ 5% blasts in the BM at screening), enrolled in Phase Ib and Phase II.
- Cohort B: Morphological remission but MRD-positive at screening (blasts ≥ 10-4 and < 5% for Phase IIb; blasts ≥ 10-3 and < 5% for Phase II), enrolled in Phase Ib and Phase II.
- Cohort C (exploratory): Isolated extra medullary disease (EMD) only at screening, only enrolled in Phase II.

The recruitment for Phase Ib and Phase II Cohort A is complete, and follow-up is ongoing. For Phase II Cohort B recruitment was permanently discontinued for feasibility reasons and for Cohort C enrolment was completed. Phase II Cohort A (Cohort IIA) is the primary focus to determine the efficacy of obe-cel.

Eligible patients who had their leukapheresate accepted for manufacturing were considered enrolled into the study and could receive bridging therapy whilst awaiting manufacture of obe-cel. Patients with successful production of obe-cel received a Lymphodepletion (LD) chemotherapy regimen with fludarabine and cyclophosphamide prior to obe-cel infusion, with fludarabine on Days -6, -5, -4, and -3 (total dose 120 mg/m^2) and cyclophosphamide on Days -6 and -5 (total dose 1,000 mg/m^2).



Note: Enrolment is defined as all eligibility criteria being fulfilled and leukapheresate accepted by the manufacturing facility. Dose 2 of obe-cel could be administered up to Day 21, if required, due to clinical status.

Figure 4. FELIX study design

- **Study Participants**

A total of 34 centres have enrolled patients in the US, Spain, and the United Kingdom (UK) and follow-up of patients in the study is currently continuing.

The main criteria for inclusion were:

- Male or female adult patients (aged 18 years and older);
- Relapsed or refractory CD19-positive B ALL defined as one of the following:
    - Primary refractory disease (not achieving CR after two cycles of induction chemotherapy).
    - First relapse if first remission ≤ 12 months (Phase Ib Cohort IA and Phase II Cohort IIA).
    - Relapsed or refractory disease after two or more lines of systemic therapy.
    - Relapsed or refractory disease after allogeneic transplant provided the obe-cel infusion occurs at least 3 months after the stem cell transplant.
- Cohort A: Presence of ≥ 5% blasts in BM at screening
- Cohort B: MRD-positive defined as ≥ 10^{-3} and < 5% blasts in the BM at screening.
- Cohort C: Adults aged ≥18 years with B ALL with isolated extramedullary disease (EMD) (including isolated CNS disease), with or without MRD.

Other key inclusion criteria were ECOG performance status 0 or 1, and adequate renal, hepatic, pulmonary, and cardiac function. Patients with Philadelphia chromosome positive ALL were eligible if they were intolerant to or have failed two lines of any TKI or one line of second-generation TKI, or if TKI therapy was contraindicated. In patients treated with blinatumomab, CD19 expression had to be confirmed after blinatumomab therapy was stopped.

The main criteria for exclusion were:

- Diagnosis of Burkitt's leukemia/lymphoma or chronic myelogenous leukemia lymphoid in blast crisis;
- History or presence of clinically relevant CNS pathology within 3 months prior to enrolment;
- Presence of CNS 3 disease or CNS 2 disease with neurological changes;
- Prior stem cell transplantation less than 3 months prior to obe-cel infusion;
- Prior CD19-targeted therapy other than blinatumomab (unless ≥ Grade 3 neurotoxicity was experienced). Use of inotuzumab ozogamicin as bridging therapy was permitted.

- **Treatments**

Patients received a total target dose of Aucatzyl 410 x 10^6 cells dispersion for infusion after lymphodepletion with fludarabine and cyclophosphamide. The dose was administered as a split dose infusion based on the disease burden, as assessed by the percentage of blasts in the BM at lymphodepletion (**Table 9**). Post-infusion patients were to be followed up through to Month 24 in the FELIX study.

Table 9. Fractionation of obe-cel dose based on bone marrow blast counts at lymphodepletion

BM Blasts %	**Dosing Schedule**	
	Dose 1 on Day 1	**Dose 2 on Day 10 (± 2 days)**
≤ 20% blasts	100 × 10^6 CD19 CAR-positive T cells	310 × 10^6 CD19 CAR-positive T cells
> 20% blasts	10 × 10^6 CD19 CAR-positive T cells	400 × 10^6 CD19 CAR-positive T cells

- **Objectives**

The primary objective for Phase Ib was to evaluate the safety of AUTO1. There was no formal hypothesis testing planned for the Phase Ib part.

The primary objective for Phase II was to evaluate the clinical efficacy of AUTO1 (Cohort A only). The primary efficacy endpoint of ORR was evaluated by testing whether the ORR was less than or equal to 40% against the alternative hypothesis that ORR was greater than 40% at one-sided 2.5% level of significance. The null hypothesis was rejected if the lower bound of the 2-sided 95% exact confidence interval (CI) for ORR was greater than 30%.

Secondary objectives for Phase II, Cohort A included complete remission at any time by IRRC, proportion achieving MRD-negative remission in BM at 10^{-4} level, duration of remission (DOR), duration of complete remission (DOCR), event-free survival (EFS), overall survival (OS), best overall response (BOR) assessed by the Investigator, proportion undergoing SCT prior to leukaemia relapse, proportion in CR/CRi without SCT or other subsequent therapies at 6, 12 and 24 and incidence of CD19-negative relapse.

- **Outcomes/endpoints**

Primary endpoint:

- ORR defined as proportion of patients achieving CR or CRi as assessed by an IRRC (see **Table 10** for criteria to fulfil each)

Key secondary endpoint

- CR at any time post obe-cel infusion as assessed by an IRRC
- DOR defined as the time from the first documented CR/CRi post obe-cel infusion to the earliest of morphological relapse or death due to any reason

Table 10. Summary of morphological disease response criteria applied in FELIX study

Response Allocated	Criteria to be Fulfilled
Complete Remission (CR)	All of the following should be met within the same disease assessment: BM: • Trilineage haematopoiesis, and • < 5% blasts in BM Peripheral blood: • No circulating lymphoblasts in peripheral blood, and • ANC > 1000/µL, and • Platelet count > 100,000/µL, and • No platelet transfusions in the last 7 days and • No administration of short-acting G-CSF and long-acting G-CSF in the last 3 and 14 days, respectively EMD [1]: • No EMD: e.g. no lymphadenopathy, splenomegaly, skin/gum infiltration, testicular mass, or CNS involvement, and • If additional assessments (e.g. cerebrospinal fluid assessment by lumbar puncture, CNS imaging, biopsy, etc.) are performed, results must show remission status
Complete remission with incomplete hematologic recovery (CRi)	Meets all criteria for CR except platelet count or ANC: • Recovery of platelets to ≤ 100,000/µL, and/or • Recovery of ANC to < 1000/µL
Relapsed	Only in patients who previously achieved a CR or CRi and who have: • Reappearance of blasts in the blood, or • Reappearance of lymphoblasts in BM (≥ 5%), or • (Re-)appearance of any EMD [1] after CR.
No response	Failure to meet the criteria for CR/CRi categories
Unknown	Assigned when the response assessment is not performed, or it is incomplete, indeterminate, within the respective time frame related to a given timepoint. Note: any evidence of relapse should determine relapsed disease with the relapsed component alone.

ANC=absolute neutrophil count; BM=bone marrow; CNS=central nervous system; CR=complete remission; CRi=complete remission with incomplete hematologic recovery; EMD=extramedullary disease; G-CSF=granulocyte colony-stimulating factor.

[1] definitions related to EMD were also provided.

Table 11. Estimand for the primary objective, remission rate

Population	Adults aged ≥18 years with CD19 positive B ALL who have r/r disease and presence of ≥5% blasts in the bone marrow (BM) regardless of extramedullary disease (EMD) status at screening, who would receive at least one administration of obe-cel treatment.
Treatment condition	There is no comparator arm. A planned treatment regimen including optional bridging therapy, pre-conditioning therapy and obe-cel infusions. TKI and intrathecal therapies are allowed in patients who achieved remission.
Endpoint (variable)	BoR: defined as the best disease response assigned according to the following order: CR, CRi, No response, Unknown
Population-level summary	ORR is defined as the proportion of proportion of patients who achieve CR or CRi post obe-cel infusion without initiation of any non-protocol anticancer therapies as assessed by the IRRC.
Intercurrent events and strategy to handle them	
Patients not receiving obe-cel infusion	Interest is in the principal stratum of patients who would receive at least one obe-cel dose.
Patients not receiving the target dose of 410×10^6 obe-cel CAR-positive T cells (whether due to clinical or CMC reasons)	Treatment policy. Patients will be evaluated regardless of whether the target dose is received.
Patients went into morphological remission after bridging therapy	Treatment policy. The main estimand relates to the full target population hence this event will be ignored for the ORR evaluation.
Patients achieved remission and blood count recovery with the help of platelet transfusion or GCSF administration	Composite strategy. This is reflected in the variable attribute as CRi.
Use of new anti-cancer therapy	While on treatment. Patients are only evaluated for BOR up until they receive new anti-cancer therapy including HSCT.

Three supplementary analyses to target supplementary estimands were also specified. These focused on the definition of the population:

- Target dose estimand: Patients who would receive obe-cel at 410×10^6 CAR-positive T cells in 2 split infusions in the proposed treatment regimen. All patients estimand:

- All patients who initiated the obe-cel treatment regimen (i.e., leukapheresed and enrolled).
- Sub-population estimand: who had r/r disease at pre-conditioning with ≥5% blasts in the BM, regardless of EMD status, who would receive at least one obe-cel dose in the proposed treatment regimen.

Table 12. Estimand for the secondary objective, duration of remission

Population	Adults aged ≥18 years with CD19 positive B ALL who have r/r disease and presence of ≥5% blasts in the bone marrow (BM) regardless of extramedullary disease (EMD) status at screening, who would receive at least one administration of obe-cel treatment and achieved a BOR of CR or CRi.
Treatment condition	There is no comparator arm. A planned treatment regimen including optional bridging therapy, pre-conditioning therapy and obe-cel infusions. TKI and intrathecal therapies are allowed in patients who achieved remission.
Endpoint (variable)	Duration of remission (DOR): defined as time from the date of achieving CR/CRi post obe-cel infusion to the date of relapse or death due to any reason.
Population-level summary	The median DOR and estimated event-free probability at different timepoints (e.g., 6, 12, 18 months etc.) along with 95% CIs will be presented if appropriate.
Intercurrent events and strategy to handle them	
Patients not receiving the target dose of 410×10^6 obe-cel CAR-positive T cells (whether due to clinical or CMC reasons)	Treatment policy
Patients received TKI in remission post obe-cel infusion	Treatment policy: Interest lies in the treatment effect of obe-cel treatment regimen with or without post TKI, therefore post TKI will be ignored in the evaluation of DOR
Patients received intrathecal therapies in remission post obe-cel infusion	Treatment policy: Interest lies in the treatment effect of obe-cel treatment regimen with or without intrathecal therapies, therefore post intrathecal therapies will be ignored in the evaluation of DOR.
Patients received SCT in remission post obe-cel infusion	Hypothetical: Interest lies in the treatment effect of obe-cel concerning the hypothetical outcome without consolidation of SCT, therefore patients receiving post SCT will be censored at the time of SCT.
Patients received other non-protocol anticancer therapy or SCT in remission post obe-cel infusion	Hypothetical: Interest lies in the treatment effect concerning the hypothetical outcome without initiation of additional non-protocol anti-cancer therapy or SCT, therefore analysis will be censored at the last adequate disease assessment on or prior to start of new non-protocol therapy.

The primary treatment effect of interest for DOR is defined as: The effect of obe-cel treatment regimen

with or without post TKI in remission among Ph-positive patients, or intrathecal therapies for CNS prophylaxis, in delaying the composite events of morphological relapse or death due to any reason, in adults aged ≥18 years with CD19 positive B ALL who have r/r disease at screening with ≥5% blasts in the BM regardless of EMD status, who would achieve remission after receiving at least one administration of obe-cel treatment.

Two supplemental estimands were defined, which differed by how the use of new anticancer therapy or SCT was handled:

Supplementary estimand 1: The effect of obe-cel treatment regimen without any subsequent systemic anticancer therapies including SCT. (i.e. hypothetical for all anticancer therapies)

Supplementary estimand 2: The effect of obe-cel treatment regimen with or without any subsequent anti-cancer therapies including SCT (treatment policy for all anticancer therapies)

- **Sample size**

The primary efficacy analysis for Cohort IIA in the Phase II part was performed by testing whether the ORR was ≤ 40% against the alternative hypothesis that ORR was > 40% at overall one-sided 2.5% level of significance. According to the hypothesis testing strategy, 90 patients in the Infused Set will provide > 94% power to demonstrate statistical significance at one-sided 2.5% level of significance, if the underlying ORR is 60%.

- **Randomisation and Blinding (masking)**

Not applicable as the FELIX study was an open-label, single-arm study.

- **Statistical methods**

The primary efficacy analysis was performed on the Infused Set and the Enrolled Set in Cohort A of Phase II of the study (Cohort IIA) (**Table 13**).

Table 13. Analysis sets for efficacy analysis in the FELIX study

Analysis Set	Description
Screened Set	All patients who had signed informed consent and were screened.
Enrolled Set	All patients who meet all eligibility criteria, and whose leukapheresate was accepted for manufacturing.
Infused Set	All patients who received at least one obe-cel infusion.
Target Dose Analysis Set	All patients in the Infused Set who had received obe-cel within ± 25% of the total target total dose of 410×10^6 total CAR-positive T cells.

The primary analysis for the FELIX study was triggered when 90 patients reached at least 6 months post-infusion or discontinued prior to the 6-month time point. The data cut-off for the primary analysis was 09-Jun-2023. All endpoints were summarised descriptively with 95% CIs provided as appropriate. In addition, updated data with a data cut-off of 07-Feb-2024 were provided.

For time-to-event efficacy parameters such as DOR, EFS and OS, Kaplan-Meier (KM) analyses were utilised. Point estimates of proportion of patients free of events at different time points (such as 6 months, 12 months, etc.) were to be reported, together with 95% confidence interval.

For DOR and EFS, patients who did not yet have the specified event prior to data cut-off, were censored using the date of the last adequate assessment. Patients who proceeded to SCT or received new non-protocol anticancer therapies for B ALL were censored for the primary analysis.

Results

- **Participant flow**

The Felix study is ongoing; key study milestone dates for this report are listed in **Table 14**.

Table 14. Key study milestones

First patient enrolled	Data cutoff	Database lock date	Data cutoff (update)
03-Jun-2020	09-June-2023	03-Aug-2023	07-Feb-2024

The disposition of patients is provided in figure 5. A total of 217 adult patients with r/r B ALL were screened and 153 patients were enrolled in the FELIX study. In total 113 patients underwent leukapheresis, and 112 patients were enrolled in the pivotal Cohort IIA of which 94 patients (83.2%) received at least 1 infusion of obe-cel. One patient in the pivotal Cohort IIA had leukapheresis product collected but was not enrolled in the FELIX study as the obe-cel manufacturing was terminated on Day 2 because the patient died of progressive disease. Based on all leukapheresed set, nineteen patients (16.8%) were not infused. Reasons for not receiving an obe-cel infusion included death (12 patients, 10.6% of the enrolled population), manufacturing related issues (5 patients, 4.4%), AE and physician decision (1 patient each, 0.9%). Forty-one patients (36.6%) discontinued the study after infusion. Reasons included death (39 patients, 34.8%; most of them [28 patients] due to progressive disease), withdrawal by patient (1 patient, 0.9%) and "other" (1 patient, 0.9%). Fifty-three patients (47.3%) are in ongoing follow-up at the time of the data cut-off.

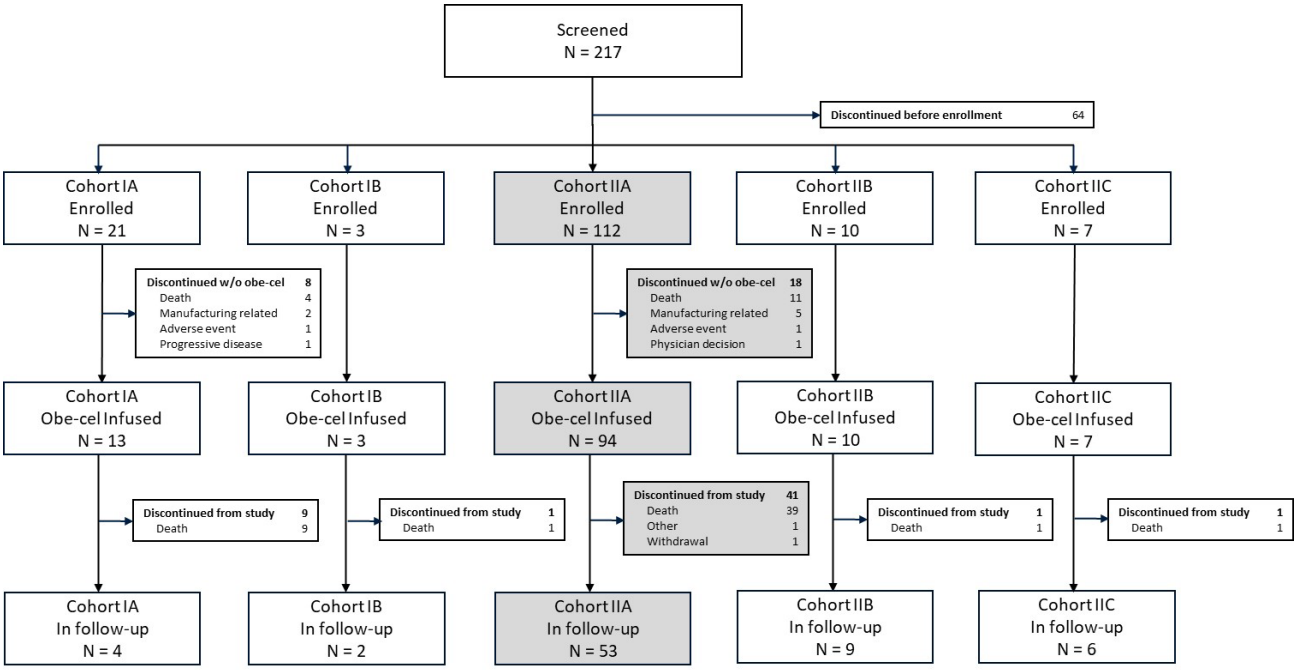


Figure 5. Participant flow based on enrolled set

B ALL=B-cell precursor acute lymphoblastic leukemia; BM=bone marrow; CR=complete remission; CRi=complete remission with incomplete haematologic recovery; EMD=extramedullary disease; MRD=minimal residual disease; r/r=relapsed or refractory.
Enrolled = all inclusion/exclusion criteria were met AND the patient's leukapheresate was accepted for manufacturing.
Infused = all patients who have received at least one infusion of obe-cel.
Cohort A: Adults with r/r B ALL who have ≥ 5% blasts in the BM at screening.
Cohort B: Adults with r/r B ALL with MRD at screening (≥ 10^{-4} and < 5% blasts in the BM for Phase Ib; ≥ 10-3 and < 5% blasts in the BM for Phase II) and ≥ second CR or CRi (for Phase II).
Cohort C: Adults with r/r B ALL with isolated EMD at screening with or without MRD.

- **Recruitment**

The first patient in the FELIX study was enrolled on 03-Jun-2020. Recruitment for Cohort IIA is completed and follow-up is ongoing.

- **Conduct of the study**

The original protocol was amended as described in **Table 15**. Changes to earlier amendments than protocol version 3.0 were made prior to the enrolment of any patients in FELIX. The most important change to the clinical study protocol was the allowance of inotuzumab ozogamicin as bridging therapy (version 6.0).

Table 15. Version history of clinical study protocol

Version	Date	Rationale
1.0	4-Nov-2019	EU Clinical Trial Application.
1.1	02-Jan-2020	Amendment following regulatory authority feedback (MHRA, UK).
2.0	19-Dec-2019	Not submitted and not implemented.
3.0	02-Jan-2020	US IND Submission.
4.0	24-Apr-2020	Amendment following regulatory authority feedback (FDA, US).
5.0	10-Dec-2020	Amendment to include an additional cohort of patients in morphological remission with MRD-positive disease and increase the overall number of patients in Phase Ib.
6.0	28-Apr-2021	Amendment to include central laboratory testing for B-cell aplasia and modify the management of bridging therapy and washout period.
7.0	23-Feb-2022	Amendment to include additional efficacy interim analysis and expand Cohort IIB (patients with MRD-positive disease).
8.0	1-Jun-2022	Amendment to alter Phase IIb NGS screening cut-off and changing into central testing per FDA request; correct the oversight for not updating the eligibility in the synopsis in ver 6 to 7 change.
9.0	13-Oct-2023	Updates to study endpoints and statistics section as requested by Health Authority (FDA). Clarification to Table 28: Reporting Period for All AEs

In Cohort IIA 82% of patients had a protocol deviation, most commonly related to study assessments and procedure compliance (71%), visit assessments (42%) and visit compliance (25%).

Twenty patients had at least 1 important protocol violation (IPD). Most of the IPDs were related to study assessments and procedure compliance (8 patients) and eligibility criteria (4 patients).

No GCP inspections were conducted.

- **Baseline data**

Baseline and disease characteristics of patients enrolled are shown in **Table 16** and **Table 17**.

Table 16. Summary of demographics in FELIX

Parameter	Phase II - Cohort A		Phase Ib and II - All Cohorts	
	Infused (N=94)	Enrolled (N=112)	Infused (N=127)	Enrolled (N=153)
Age (years)				
Median	50.0	49.0	47.0	45.0
Min - Max	20 - 81	20 - 81	20 - 81	20 - 81
Age (years) categorised - n (%)				
<65	73 (77.7)	88 (78.6)	102 (80.3)	124 (81.0)
≥18 to ≤25	11 (11.7)	13 (11.6)	14 (11.0)	16 (10.5)
>25 to <40	20 (21.3)	26 (23.2)	34 (26.8)	45 (29.4)
≥40 to <65	42 (44.7)	49 (43.8)	54 (42.5)	63 (41.2)
≥65	21 (22.3)	24 (21.4)	25 (19.7)	29 (19.0)
Sex - n (%)				
Male	47 (50.0)	60 (53.6)	66 (52.0)	82 (53.6)
Female	47 (50.0)	52 (46.4)	61 (48.0)	71 (46.4)
Race - n (%)				
Asian	10 (10.6)	11 (9.8)	16 (12.6)	17 (11.1)
Black or African American	2 (2.1)	2 (1.8)	2 (1.6)	3 (2.0)
White	70 (74.5)	86 (76.8)	94 (74.0)	117 (76.5)
Unknown	12 (12.8)	13 (11.6)	15 (11.8)	16 (10.5)
Ethnicity - n (%)				
Hispanic or Latino	29 (30.9)	33 (29.5)	38 (29.9)	44 (28.8)
Not Hispanic or Latino	58 (61.7)	72 (64.3)	80 (63.0)	100 (65.4)
Unknown	7 (7.4)	7 (6.3)	9 (7.1)	9 (5.9)

Enrolled = all inclusion/exclusion criteria have been fulfilled and leukapheresate has been accepted for manufacturing.
Infused = all patients who have received at least one infusion of obe-cel

In the pivotal Cohort IIA for efficacy (n=94), a high proportion of patients were refractory to the last prior line of therapy (51 patients, 54.3%). Patients had received a median of 2 prior lines of anticancer therapy (range: 1 - 6). Sixty-five patients (69.1%) had ≥ 2 lines and 12.8% had ≥ 4 lines of prior therapies, 35.1% patients had received prior blinatumomab, 31.9% prior inotuzumab ozogamicin, 16.0% prior blinatumomab and inotuzumab ozogamicin and 38.3% of patients had prior SCT.

Thirty-one patients (33.0%) had > 75% blasts in the BM at screening. Nineteen patients (20.2%) had EMD at lymphodepletion. Nineteen patients (20.2%) had EMD at screening. Twenty-five patients (26.6%) had Ph+-disease.

Baseline and disease characteristics for the All Enrolled Set (n=153), the Cohort IIA Enrolled Set (n=112) and the subgroup of patients in Cohort IIA with ≥ 5% blasts at lymphodepletion (n=71) were overall in line with demographics of the analysis set (Cohort IIA) (**Table 17**).

Table 17. Disease characteristics at screening

Parameter	Phase II - Cohort A		Phase Ib and II - All Cohorts	
	Infused (N=94)	Enrolled (N=112)	Infused (N=127)	Enrolled (N=153)
Prior Therapies				
Refractory to all prior lines of anti-cancer therapy - n (%)	12 (12.8)	13 (11.6)	13 (10.2)	15 (9.8)
Refractory to first line therapy - n (%)	24 (25.5)	28 (25.0)	32 (25.2)	37 (24.2)
Refractory to last prior line of therapy: - n (%)	51 (54.3)	59 (52.7)	67 (52.8)	80 (52.3)
Relapsed to first line therapy within 12 months - n (%)	41 (43.6)	52 (46.4)	60 (47.2)	75 (49.0)
Number of prior lines of therapy				
Median	2.0	2.0	2.0	2.0
Min – Max	1 - 6	1 - 6	1 - 6	1 - 6
Number of prior lines of therapy categorised - n (%)				
1	29 (30.9)	34 (30.4)	30 (23.6)	36 (23.5)
2	36 (38.3)	43 (38.4)	53 (41.7)	62 (40.5)
3	17 (18.1)	21 (18.8)	25 (19.7)	32 (20.9)
≥4	12 (12.8)	14 (12.5)	19 (15.0)	23 (15.0)
Previous alloSCT - n (%)	36 (38.3)	43 (38.4)	56 (44.1)	69 (45.1)
Previous blinatumomab - n (%)	33 (35.1)	41 (36.6)	53 (41.7)	64 (41.8)
Previous inotuzumab ozogamicin - n (%)	30 (31.9)	37 (33.0)	40 (31.5)	49 (32.0)
Previous blinatumomab and inotuzumab ozogamicin - n (%)	15 (16.0)	20 (17.9)	21 (16.5)	27 (17.6)
Previous blinatumomab or inotuzumab ozogamicin - n (%)	48 (51.1)	58 (51.8)	72 (56.7)	86 (56.2)
Cytogenetics				
Complex karyotype	37 (39.4)	45 (40.2)	51 (40.2)	63 (41.2)
Philadelphia-chromosome positive B ALL - n (%)	25 (26.6)	26 (23.2)	36 (28.3)	39 (25.5)
Disease Characteristics at Screening				
EMD Present - n (%)	19 (20.2)	21 (18.8)	29 (22.8)	32 (20.9)
BM blasts by morphology categorised - n (%) [1]				
>75%	33 (35.1)	41 (36.6)	40 (31.5)	54 (35.3)
>20% to ≤ 75%	32 (34.0)	40 (35.7)	37 (29.1)	47 (30.7)
≥5% to ≤ 20%	29 (30.9)	31 (27.7)	30 (23.6)	32 (20.9)
<5%	0	0	20 (15.7)	20 (13.1)
Disease Characteristics at Lymphodepletion				
EMD Present – n (%)	19 (20.2)	21 (18.8)	27 (21.3)	30 (19.6)
BM blasts by morphology categorised - n (%) [1]				
>75%	31 (33.0)	31 (27.7)	40 (31.5)	40 (26.1)
>20% to ≤ 75%	26 (27.7)	26 (23.2)	35 (27.6)	35 (22.9)
≥5% to ≤20%	14 (14.9)	14 (12.5)	16 (12.6)	16 (10.5)
<5%	23 (24.5)	23 (20.5)	36 (28.3)	36 (23.5)

alloSCT=allogeneic stem cell transplant; B ALL=B-cell precursor acute lymphoblastic leukemia; BM=bone marrow; EMD=extramedullary disease.
[1] BM blast (%) was determined by morphology as the highest value from BM aspirate and trephine.

The baseline demographic and disease characteristics for the leukapheresed set (cohort IIA) are

reported here below:

Table 18. 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.

- **Numbers analysed**

The primary analysis was conducted on the subset of patients in Phase II Cohort A who received at least 1 infusion of obe-cel (n=94, Cohort IIA). The safety set comprises of all patients who have been enrolled and received at least 1 obe-cel infusion.

Table 19. Analysis sets

	Phase Ib			Phase II				PhIb/PhII
	Cohort A n (%)	Cohort B n (%)	Total n (%)	Cohort A n (%)	Cohort B n (%)	Cohort C n (%)	Total n (%)	Total n (%)
Screened Set								217
Enrolled Set [1]	21	3	24	112	10	7	129	153
Infused Set [2]	13 (61.9)	3 (100)	16 (66.7)	94 (83.9)	10 (100)	7 (100)	111 (86.0)	127 (83.0)
TDAS [3]	11 (52.4)	3 (100)	14 (58.3)	85 (75.9)	10 (100)	7 (100)	102 (79.1)	116 (75.8)
Safety Set [4]	13 (61.9)	3 (100)	16 (66.7)	94 (83.9)	10 (100)	7 (100)	111 (86.0)	127 (83.0)

FAS=Full analysis set; ITT=Intent-to-treat; PhIb=Phase Ib; PhII=Phase II; TDAS=Target Dose Analysis Set
Percentages are based on total number of patients in the Enrolled Set.
[1] Enrolled Set (=ITT) comprises of all patients who have been enrolled in the study. A patient was considered enrolled when all inclusion/exclusion criteria were met and the patient's leukaphereses was accepted for manufacturing.
[2] Infused Set (= modified ITT or FAS) comprises of all patients who have been enrolled and received at least 1 obe-cel infusion.
[3] Target Dose Analysis Set (TDAS) comprises of all patients who have received the target dose of 410 x 10^6 (+/- 25%) CD19 CAR-positive T cells.
[4] Safety Set comprises of all patients who have been enrolled and received at least 1 obe-cel infusion.
Data cut-off: 09-June-2023

The data included in the SmPC refers to the leukapheresed set including 113 patients for Phase II cohort A.

- **Outcomes and estimation**

In the pivotal Cohort IIA for efficacy, 88 of 94 patients received bridging therapy after leukapheresis until 1 week prior to lymphodepletion, most of them chemotherapy alone or in combination with TKI (total of 65 patients, 69.1%). Inotuzumab ozogamicin alone or in combination with chemotherapy was administered to 17 patients (18.1%).

In Cohort IIA, 6 patients received only the first dose of obe-cel.

Primary efficacy results

The primary endpoint in Cohort IIA (patients with r/r B ALL and presence of ≥ 5% blasts in the BM at screening) was ORR. At the time of the data cut-off (09-Jun-2023), the ORR was 76.6% (95% CI: 66.7, 84.7) in patients who received at least 1 infusion of obe-cel (**Table 20**).

In 112 patients in the Cohort IIA, Enrolled Set, the ORR was 64.3% (95% CI: 54.7, 73.1). In 113 patients in the Cohort IIA, Leukapheresed Set, the ORR was 63.7% (95% CI: 54.1, 72.6).

In 85 patients who received the target dose of 410 x 10^6 CD19 CAR-positive T cells in Cohort IIA, the ORR was 81.2% (95% CI: 71.2, 88.8). Of the patients who did not receive the target dose, three patients achieved CRi, and six patients had no response or response unknown.

Table 20. Overview of key efficacy results in FELIX (Cohort IIA, primary analysis, DCO 09-Jun-2023)

Efficacy parameter	Infused (N=94)	Enrolled (N=112)
Overall remission rate (CR/CRi)		
n (%)	72 (76.6)	72 (64.3)
95% CI (%) [1]	66.7, 84.7	54.7, 73.1
p-value [2]	<0.0001	-
Complete remission (CR) any time post infusion		
n (%)	52 (55.3)	55 (49.1)

Efficacy parameter	Infused (N=94)	Enrolled (N=112)
95% CI (%) [1]	44.7, 65.6	39.5, 58.7
p-value [3]	<0.0001	-
MRD negativity (10^{-4})		
Responders with evaluable MRD samples post obe-cel infusion	69	69
MRD-negative CR/CRi (%) [4]	65 (94.2%)	65 (94.2%)
Duration of remission (DOR) [5]		
Median (95% CI) (months)	11.6 (8.1, NE)	12.5 (8.1, NE)
6 months probability estimate (%) [6]	73.5	76.5
95% CI (%) [1]	59.2, 83.4	63.1, 85.5
Event-free survival (EFS) [5]		
Patients with event, n (%)	46 (48.9)	63 (56.3)
Median (95% CI) (months)	9.0 (6.0, 14.3)	7.7 (4.3, 10.6)
6 months probability estimate (%) [6]	63.2	57.4
95% CI (%)	52.1, 72.3	47.5, 66.0
Overall survival (OS) [7]		
Patients with event (death), n (%)	41 (43.6)	55 (49.1)
Median (95% CI) (months)	14.1 (10.1, 17.1)	11.7 (9.9, 16.8)
6 months probability estimate (%) [6]	78.6	72.9
95% CI (%)	68.8, 85.6	63.6, 80.2

CI=confidence interval; CR=complete remission; CRi=complete remission with incomplete hematologic recovery;; DOR=duration of remission; EFS=event-free survival; FACS=fluorescence-activated cell sorting; IRRC=Independent Response Review Committee; KM=Kaplan-Meier; MRD=minimal residual disease; NE=not estimable; NGS=next-generation sequencing; ORR= overall remission rate; OS=overall survival; PCR=polymerase chain reaction; SCT=stem cell transplant.
[1] The 95% exact Clopper-Pearson CIs are displayed.
[2] Exact p-value testing H_{10}: ORR ≤ 40% vs H_{11}: ORR > 40% in all infused patients.
[3] Exact p-value testing H_{20}: CR at any time ≤ 20% vs H_{21}: CR at any time > 20% in all infused patients.
[4] Patients in remission by IRRC with MRD-negative BM by central ClonoSEQ NGS/PCR/FACS.
[5] With censoring for SCT and other new anti-cancer therapy.
[6] Probability estimates obtained from the KM survival estimates, with 95% CIs estimated using Greenwood formula.
[7] Without censoring for SCT and other new anti-cancer therapy.

Table 21. Overall response with disease assessment by IRRC – enrolled set, leukapheresed set, phase II, cohort A, DCO 07-Feb-2024

	Enrolled Set (N=112) n (%)	Leukapheresed Set (N=113) n (%)
Best overall response (BOR)		
CR	55 (49.1)	55 (48.7)
CRi	17 (15.2)	17 (15.0)
No response	21 (18.8)	21 (18.6)
Unknown	19 (17.0)	20 (17.7)
Overall remission rate (ORR: CR + CRi)		
n (%) [1]	72 (64.3)	72 (63.7)
95% CI (%) [2]	(54.7, 73.1)	(54.1, 72.6)
Complete remission rate		
n (%) [3]	55 (49.1)	55 (48.7)
95% CI (%) [2]	(39.5, 58.7)	(39.2, 58.3)

Abbreviations: BOR=best overall response post-leukapheresis; CI=confidence interval; CR=complete remission; CRi=complete remission with incomplete recovery of counts; IRRC=Independent Response Review Committee.
[1] Including patients who achieved best overall response of CR or CRi after leukapheresis.
[2] The 95% exact Clopper-Pearson CIs are displayed.
[3] Including patients who achieved best overall response of CR after leukapheresis.

Data cut-off for FELIX: 07-Feb-2024.

The ORR by disease status at lymphodepletion in Cohort IIA is shown in **Table 22**. The ORR in patients who received obe-cel and had ≥ 5% blasts in the BM at lymphodepletion was 74.6% (95% CI: 62.9, 84.2) and in patients who had < 5% blasts in BM without EMD was 88.9% (95% CI: 65.3, 98.6). The subgroup of patients who had < 5% blasts in BM with EMD at lymphodepletion had an ORR of 60.0% (95% CI: 14.7, 94.7).

Table 22. Overall remission rate by IRCC by disease status at lymphodepletion (cohort IIA, infused set)

	≥ 5% Blast in BM (N=71)	< 5% Blast in BM without EMD (N=18)	< 5% Blast in BM with EMD (N=5)	Total (N=94)
BOR - n (%)				
CR	41 (57.7)	9 (50.0)	2 (40.0)	52 (55.3)
CRi	12 (16.9)	7 (38.9)	1 (20.0)	20 (21.3)
No response	14 (19.7)	1 (5.6)	2 (40.0)	17 (18.1)
Unknown	4 (5.6)	1 (5.6)	0	5 (5.3)
ORR (CR + CRi) - n (%)				
n (%) [1]	53 (74.6)	16 (88.9)	3 (60.0)	72 (76.6)
95% CI (%) [2]	(62.9, 84.2)	(65.3, 98.6)	(14.7, 94.7)	(66.7, 84.7)

Abbreviations: BOR = Best overall response post obe-cel infusion; CI=Confidence interval; CR = Complete remission; CRi = Complete remission with incomplete recovery of counts; IRRC = Independent Response Review Committee; ORR=Overall remission rate.
Infused set comprises of all patients who have received at least 1 infusion of obe-cel.
Best overall response was defined as the best response in the order of CR > CRi > No Response > Unknown for all disease assessments post obe-cel infusion and prior to any new non-protocol anticancer therapies (including SCT).
[1] Including patients who achieved best overall response of CR or CRi after obe-cel infusion.
[2] The 95% exact Clopper-Pearson CIs are displayed.
Data cut-off: 09-June-2023

Secondary objective - ORR assessed by Investigator

The ORR assessed by Investigator in Cohort IIA was 78.7% [69.1, 86.5] and the ORR in the subgroup of patients with ≥ 5% blasts in the BM at lymphodepletion was 76.1%; [64.5, 85.4]. The concordance between responses assessed by the Investigator and responses assessed by IRRC was 93.6% of response assessments concordant for ORR and 94.7% for CR among all patients infused in Cohort IIA.

Secondary objective - Time to Onset of Remission (CR or CRi)

Fifty-two of 94 patients (55.3%) infused with obe-cel in Cohort IIA achieved CR at any time after infusion. The median time to onset of CR was 2.07 months (range: 0.9 - 7.2). Forty-three patients (82.7%) achieved CR within 3 months of infusion.

The median time to onset of CR or CRi was 0.95 months (range: 0.8 - 7.2) in 72 patients who achieved CR or CRi in Cohort IIA. Most of the patients (69 patients, 95.8%) had an onset of CRi or CR within 3 months post obe-cel infusion.

At the updated DCO (07-Feb-2024) the time to onset of remission remained the same as during the primary efficacy analysis.

Secondary objective - Complete Remission Rate

The proportion of patients infused with obe-cel in Cohort IIA who achieved a BOR of CR by IRRC at any time during the study without initiation of any non-protocol anticancer therapy was 55.3% (95% CI: 44.7, 65.6).

The proportion of patients infused with obe-cel in Cohort IIA who achieved a CR within 3 months was 45.7% (95% CI: 35.4, 56.3).

The proportion of patients infused with obe-cel in the Enrolled Set who achieved a BOR of CR by IRRC at any time during the study without initiation of any non-protocol anticancer therapy (n=112) was 49.1% (95% CI: 39.5, 58.7).

The proportion of patients infused with obe-cel in the Leukapheresed Set who achieved a BOR of CR by IRRC at any time during the study without initiation of any non-protocol anticancer therapy (n=113) was 48.7% (95% CI: 39.2, 58.3).

At the updated DCO (07-Feb-2024) the complete remission rate remained the same as during the primary efficacy analysis.

Secondary objective - MRD-negative Remission Rate

The MRD-negative remission rate was defined as the proportion of patients achieving CR or CRi with MRD-negative BM by central assessment at 10^{-4} (0.01%) level. The MRD in BM was assessed by central ClonoSEQ NGS, flow cytometry, and/or qPCR, whenever sufficient sample was available to allow the central assessment.

Of all 94 patients infused with obe-cel in Cohort IIA, 65 patients (69.1%) achieved MRD-negative CR/CRi by central ClonoSEQ NGS/flow cytometry/qPCR. Among 72 patients in Cohort IIA with CR/CRi by IRRC, the proportion with MRD-negative CR or CRi by central ClonoSEQ NGS/flow cytometry/qPCR was 90.3% (95% CI: 81.0, 96.0). Four patients (5.6%) had MRD-positive CR/CRi. Three patients (4.2%) did not have an evaluable sample post obe-cel infusion, and hence had CR/CRi with MRD status unknown.

At the updated DCO (07-Feb-2024), among 72 patients in Cohort IIA with CR/CRi by IRRC, the proportion with MRD-negative CR or CRi by central ClonoSEQ NGS/flow cytometry/qPCR was 88.9% (64 of 72 patients with CR/CRi by IRCC).

Secondary objective - Duration of Remission

All patients in remission at any time post-infusion (CR or CRi by IRRC) were included in the DOR analysis. DOR was defined as the time from first remission onset to morphological relapse or death due to any reason, whichever was earlier. Patients who did not observe an event of morphological relapse or death or were lost to follow-up were censored at the last adequate disease assessment. In addition, if a patient received SCT, or other non-protocol anti-cancer therapy, then the DOR was also censored. Overall, 48 patients (66.7%) were censored for this analysis.

With a median DOR follow-up of 7.7 months, the estimated probability for being in remission at Month 6 after onset of remission was 73.5% (95% CI: 59.2, 83.4). Median DOR was 11.56 months (95% CI: 8.11, NE).

At the updated DCO (07-Feb-2024), the median DOR follow-up was 13.8 months. The estimated probability for being in remission at Month 6 after onset of remission was 75.0% (95% CI: 62.3, 83.9). Median DOR was 14.06 months (95% CI: 8.18, NE).

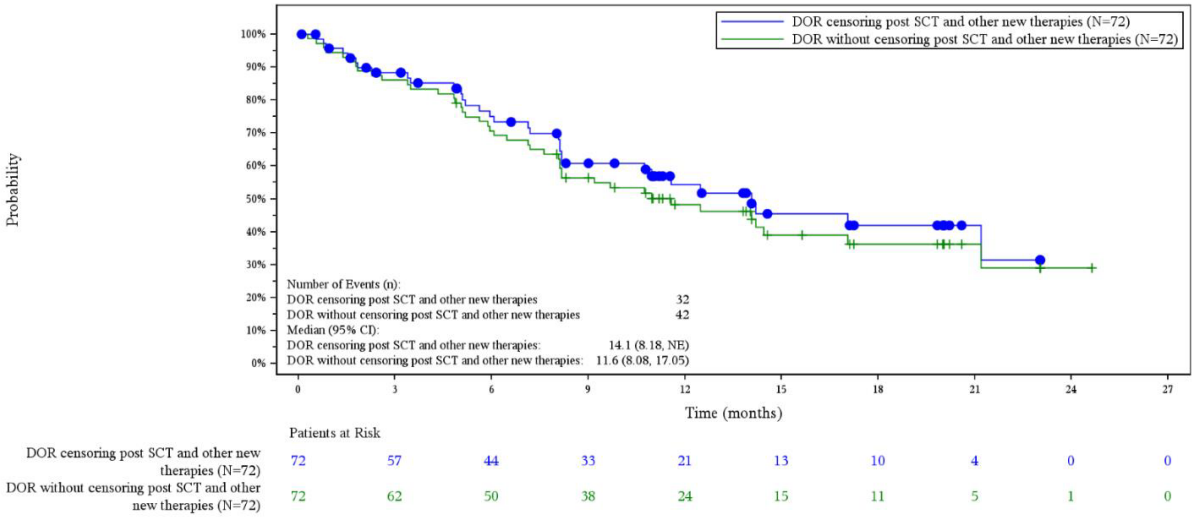
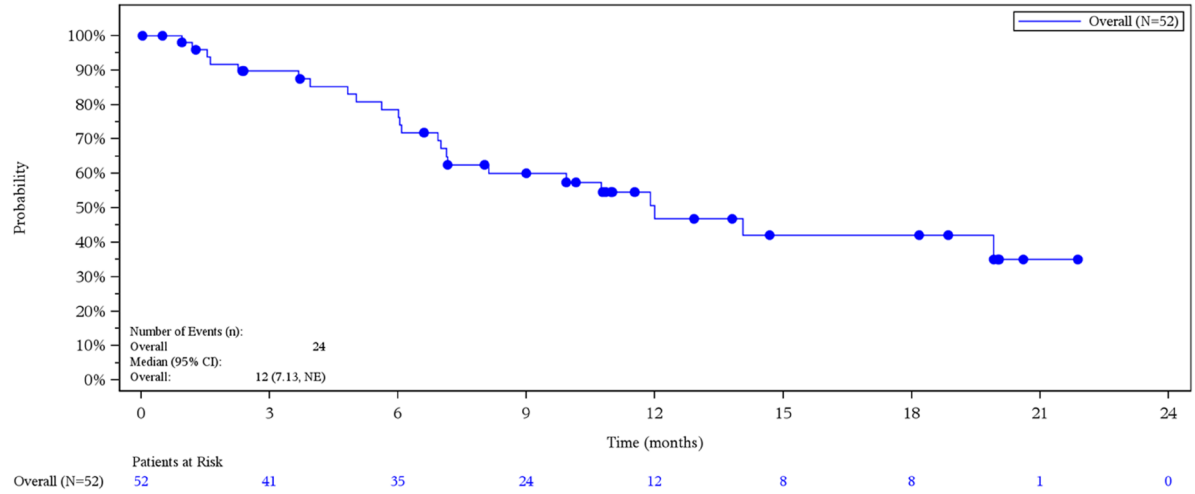


Figure 6. KM-curve duration of remission (cohort IIA, infused set) DCO 07-Feb-2024

Secondary objective - Duration of Complete Remission

For patients infused with obe-cel who achieved a BOR of CR by IRRC, the probability of remaining in CR at Month 6 after achieving of CR was 77.6% (95% CI: 60.5, 87.9). With a median follow-up of 6.0 months, the median DOCR was 14.06 months (95% CI: 6.93, NE).

At the updated DCO (07-Feb-2024), the median follow-up for complete response was 11.5 months and the DOCR was 11.99 months (95% CI: 7.13, NE).



Abbreviations: BOR = best overall response; CI = confidence interval; CR = complete remission; IRRC = Independent Response Review Committee; SCT = stem cell transplantation.
Medians with 95% CIs are calculated from PROC LIFETEST output method (Brookmeyer and Crowley 1982).
Time is relative to onset of remission; 1 month = 30.4375 days.
The analysis includes all patients in the Infused Set – Phase II – Cohort A who achieved BOR of CR post-obe-cel infusion.
Data cut-off: 07-Feb-2024

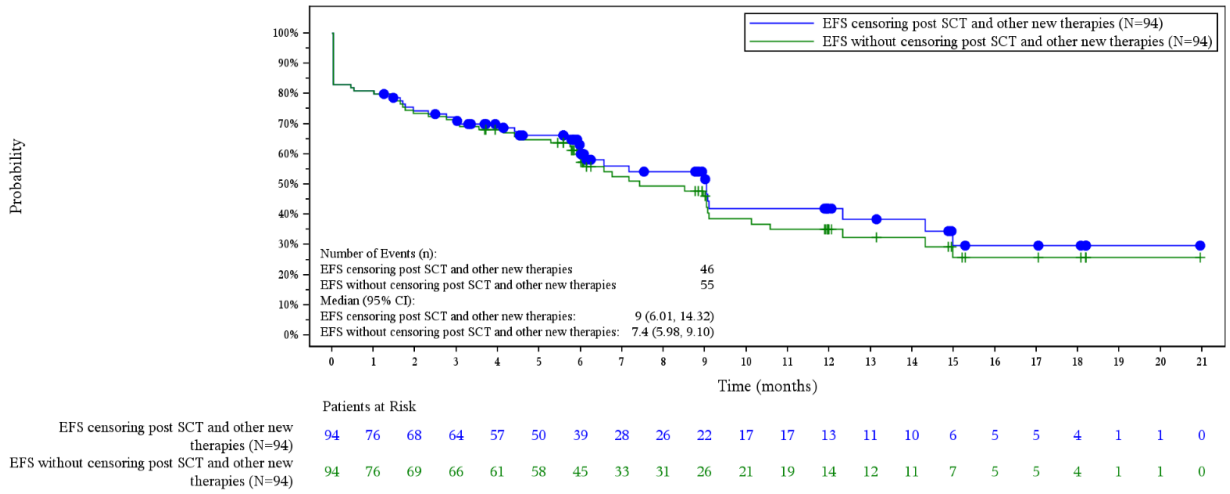
Figure 7. Kaplan-Meier plot of duration of complete remission by IRRC censoring new non-protocol anticancer therapies including sct (cohort IIA, infused set), DCO 07-Feb-2024

Secondary objective - Event-free Survival

Event-free survival was defined as the time from the first obe-cel infusion to the earliest of the following events: treatment failure, morphological relapse, or death due to any cause.

As of the data cut-off (09-Jun-2023), 46 of 94 patients (48.9%) infused with obe-cel in Cohort IIA had an EFS event (21 patients [22.3%] had morphological relapse, 16 patients [17.0%] had treatment failure, and 9 patients [9.6%] died due to reason other than their underlying disease). Thirty-six patients (38.3%) were ongoing without an event and were censored for this analysis. Eleven patients (11.7%) had SCT and were also censored for the analysis.

The estimated event-free probability was 63.2% (95% CI: 52.1, 72.3) at Month 6. With a median follow-up of 8.8 months, the median EFS was 9.03 months (95% CI: 6.01, 14.32).



CI=confidence interval; EFS=event-free survival; IRRC=Independent Response Review Committee; SCT=stem cell transplant.
Time is relative to first obe-cel infusion; 1 month=30.4375 days.
Medians with 95% CIs are calculated from PROC LIFETEST output using method of Brookmeyer and Crowley, 1982.

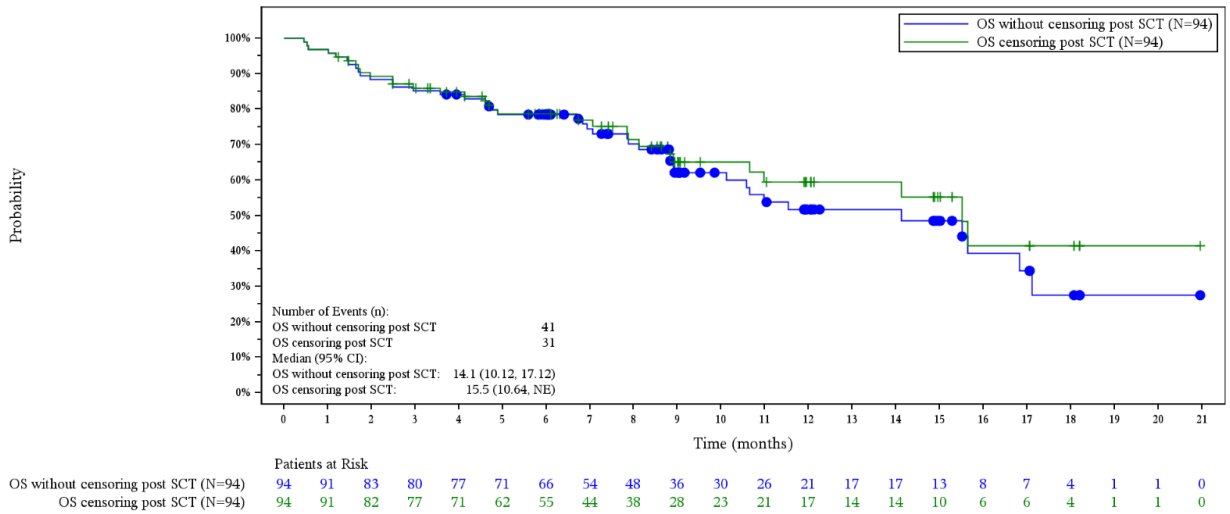
Figure 8. KM-curve of event-free survival (cohort IIA, infused set), DCO 07-Feb-2024

At the updated DCO (07-Feb-2024) the estimated event-free probability was 59.2% (95% CI: 46.5, 69.8) at Month 6. With a median follow-up of 14.8 months, the median EFS was 9.03 months (95% CI: 6.14, 14.98).

Secondary objective - Overall Survival

Overall survival was calculated from the date of first obe-cel infusion to the date of death. Patients still alive were censored at the date of last contact.

At the data cut-off (09-Jun-2023), 41 patients (43.6%) died after infusion with obe-cel. The estimated probability for being alive in this analysis set was 78.6% (95% CI: 68.8, 85.6) at Month 6. At a median follow-up for survival of 11.0 months, the median OS was 14.13 months (95% CI: 10.12, 17.12) in patients infused with obe-cel in Cohort IIA.



CI=confidence interval; OS=overall survival; SCT=stem cell transplant.
Time is relative to first obe-cel infusion; 1 month=30.4375 days.
Median with 95% CIs are calculated from PROC LIFETEST output using method of Brookmeyer and Crowley, 1982.

Figure 9. KM-curve of overall survival (cohort IIA, infused set), DCO 07-Feb-2024

At the updated DCO (07-Feb-2024), 52 patients (55.3%) died after infusion with obe-cel. The estimated probability for being alive in this analysis set was 78.7% (95% CI: 69.0, 85.7) at Month 6, 57.4% (95% CI: 46.8, 66.7). At a median follow-up for survival of 17.3 months, the median OS was 14.16 months (95% CI: 10.97, 23.75) in patients infused with obe-cel in Cohort IIA.

Secondary objective - Stem Cell Transplantation or other subsequent therapies post Obe-cel Infusion
In Cohort IIA 11 patients (11.7%) proceeded to allogeneic SCT post obe-cel infusion while still in remission. Of the 11 patients, 9 patients (81.8%) had high disease burden (≥ 20% blasts in the BM), and 2 patients (18.2%) had low disease burden (< 20% blasts in the BM) at lymphodepletion. All 11 patients were in MRD-negative CR/CRi prior to receiving SCT and received SCT 38 to 229 days post obe-cel infusion. Eight of 11 patients (72.7%) had either died or relapsed following their SCT, and for the remaining 3 patients (27.3%), the clinical status' were in ongoing remission without additional anti-cancer therapy as of the cut-off date

An additional 5 patients in Cohort IIA received SCT post obe-cel infusion, after no response or relapse.

As of the data cut-off (09-Jun-2023), 36 of 72 responders (50.0%) in Cohort IIA were in ongoing remission at the last follow-up and did not have SCT or other subsequent therapies.

At the updated DCO (07-Feb-2024), 12 patients (12.8%) proceeded to SCT while still in remission and 6 patients received SCT after no response or relapse. All 12 patients were in MRD-negative CR/CRi prior to receiving SCT and received SCT 38 to 421 days post obe-cel infusion. Nine of 12 patients (75.0%) had either died or relapsed following their SCT, and for the remaining 3 patients (25.0%), the clinical status was in ongoing remission without additional anticancer therapy as of the cut-off date.

As of the data cut-off (07-Feb-2024), 26 of 72 responders (36.1%) in Cohort IIA were in ongoing remission at the last follow-up and did not have SCT or other subsequent therapies.

Secondary objective - Incidence of CD19-negative Relapses
There were 27 infused patients in Cohort IIA who had relapsed; a slight majority were CD19-negative (14 patients, 51.9%). Seven patients (25.9%) were CD19-positive, 2 patients (7.4%) had a mixed CD19 status and the CD19 status of 4 patients (14.8%) was unknown.

At the updated DCO (07-Feb-2024), 28 infused patients in Cohort IIA had relapsed; a slight majority were CD19-negative (13 patients; 46.4%). Twelve patients (42.9%) were CD19-positive, and 3 patients (10.7%) had a mixed CD19 status.

Secondary objective - Patient Reported Outcomes

In 70 patients infused with obe-cel in Cohort IIA with a CR or CRi and evaluable scores, the mean (standard deviation [SD]) observed VAS Score was 64.74 (SD 21.988) at baseline (last available measurement before obe-cel infusion). The longitudinal trajectory of patients' VAS scores (using a global rating of the respondents self-perceived health status) showed a reduction in health state from baseline to Day 28 (mean change of – 1.83 from baseline). Starting at Month 3, and in all subsequent months, median scores exceeded baseline scores and remained at that level throughout the 12 months (mean VAS Scores of 66.53, 77.87 and 80.06 on Day 28, at Month 6, and at Month 12, respectively).

Results obtained by various symptoms, functioning, and GHS scores from the EORTC QLQ-C30 questionnaire were generally in line with EQ-5D-5L VAS scores.

Secondary objective - Efficacy for Patients in other cohorts

For Phase Ib the median follow-up was 25.31 months and 11 of 16 patients (68.8%) infused with obe-cel achieved a CR or CRi, 3 patients (18.8%) had no response, and the responses of 2 patients (12.5%) were unknown.

At the updated DCO (07-Feb-2024), with a median follow-up of 33.30 months (range: 29.7 - 41.4), the results remained the same for Phase Ib.

For Cohort IIB the median follow-up was 10.17 months and 9 of 10 patients (90.0%; 95% CI: 55.5, 99.7) achieved CR or CRi after obe-cel infusion. Seven patients (70.0%) were in CR and 2 patients (20.0%) were in CRi. The response of 1 patient (10.0%) was unknown at the time of the data cut-off.

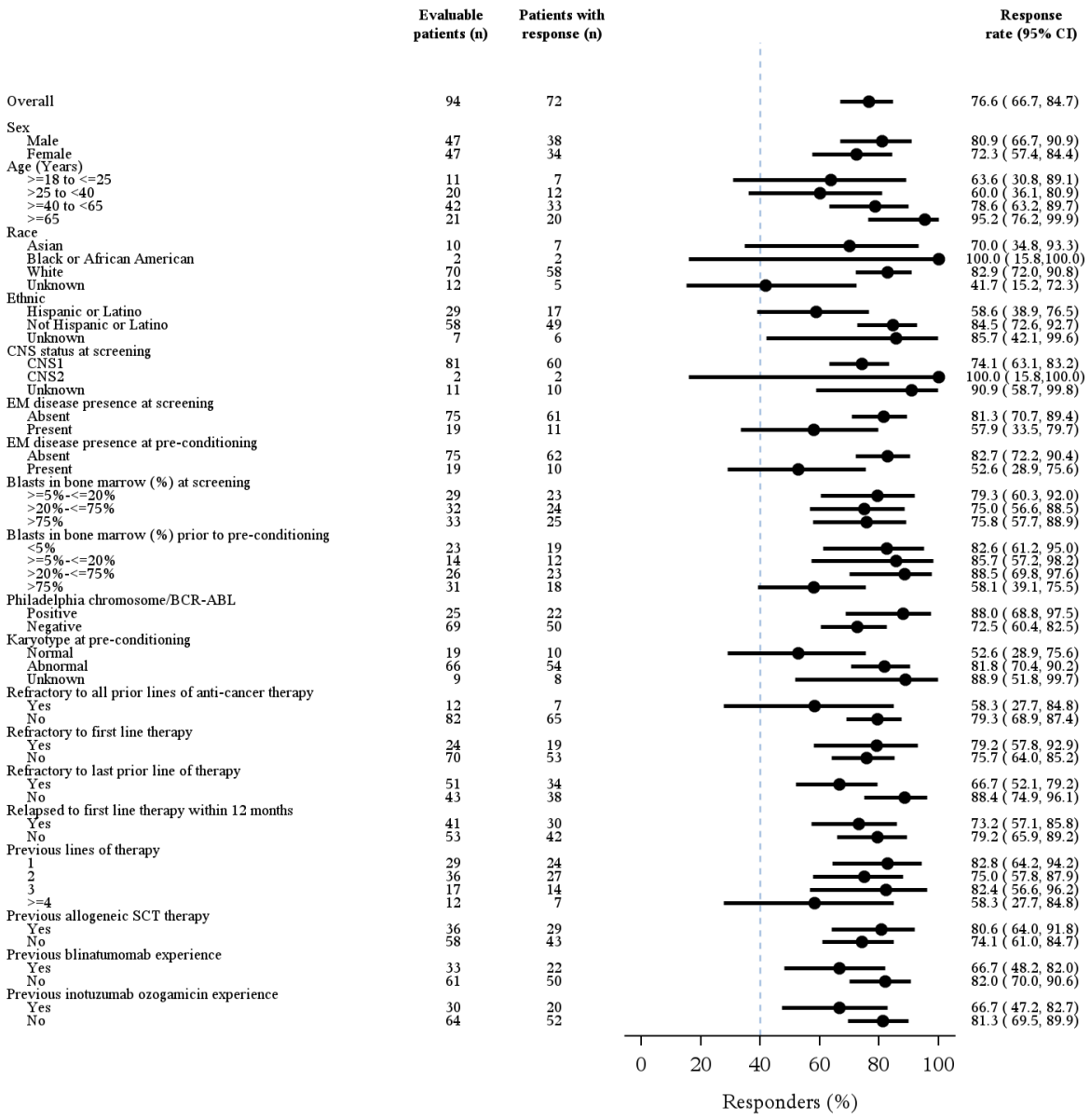
At the updated DCO (07-Feb-2024), at a median follow-up of 18.15 months, all 10 patients (100.0%; 95% CI: 69.2, 100.0) achieved CR (n=9) or CRi (n=1) after obe-cel infusion in Cohort IIB.

Fort Cohort IIC the median follow-up was 17.87 months and 6 of 7 patients (85.7%; 95% CI: 42.1, 99.6) achieved CR or CRi after obe-cel infusion. Four patients (57.1%) were in CR and 2 patients (28.6%) were in CRi. One patient (14.3%) did not respond to obe-cel treatment.

At the updated DCO (07-Feb-2024), with a median follow-up of 25.86 months (range: 22.6 – 27.2), the results remained the same for Cohort IIC.

- **Ancillary analyses**

Efficacy analyses of the primary endpoint (ORR assessed by IRRC) were performed in a broad range of patient subgroups, including those typically associated with a poor prognosis or poorer outcome with other treatments for B ALL (Hispanic ethnicity, older age, Ph+, high disease burden based on blasts in BM, and presence of EMD). All pre-specified subgroups achieved an estimated ORR of >40%. Subgroups with a lower bound of the CI for ORR of < 40% were generally small (n ≤ 20% of the Infused Set) and CIs wide.



CI=confidence interval; CNS=central nervous system; EM=extramedullary; ORR= overall remission rate; SCT = stem cell transplant.
The dotted reference line represents the pre-specified null hypothesis of ORR (40%)

Figure 10. Forest plot for subgroup analysis of overall remission rate (cohort IIa, infused set)

Consistent results were observed across regions (North America versus Europe) and in the subgroup of patients bridged with inotuzumab ozogamicin.

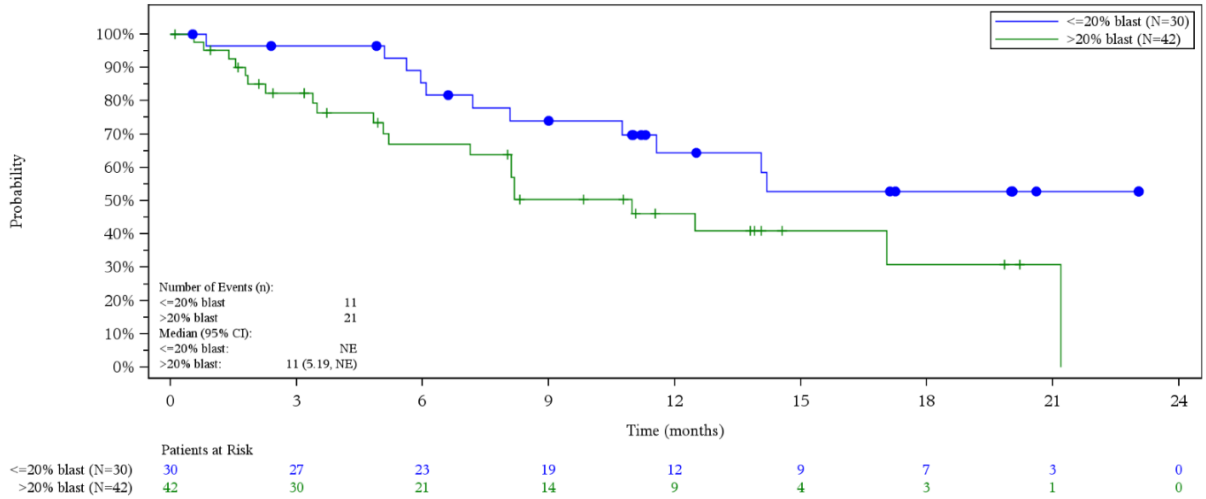
Subgroup analysis by dosing regimen and disease burden

Table 23. Overall response with disease assessment by IRRC by low vs high disease burden (% bone marrow blasts) at lymphodepletion cohort IIa (infused set), DCO 07-Feb-2024

	Low Disease Burden at LD (≤ 20% BM Blasts) (N=37)	High Disease Burden at LD (> 20% BM Blasts) (N=57)	Total Infused (N=94)
Best overall response (BOR) - n (%)			
CR	20 (54.1)	32 (56.1)	52 (55.3)
CRi	10 (27.0)	10 (17.5)	20 (21.3)
No response	4 (10.8)	13 (22.8)	17 (18.1)
Unknown	3 (8.1)	2 (3.5)	5 (5.3)
Overall remission rate (ORR: CR + CRi)			
n (%) [1]	30 (81.1)	42 (73.7)	72 (76.6)
95% CI (%) [2]	(64.8, 92.0)	(60.3, 84.5)	(66.7, 84.7)

Abbreviations: BM=bone marrow; BOR=best overall response; CI=confidence interval; CR=complete remission; CRi=complete remission with incomplete blood count recovery; IRRC=Independent Response Review Committee; LD=lymphodepletion; ORR=overall response rate; SCT=stem cell transplantation.
Infused Set is comprised of all Cohort IIA patients who have received at least one infusion of obe-cel.
Patient responses were based on the Overall Disease Status recorded on the "Overall Disease Response" page by IRRC.
BOR was defined as the best response in the order of CR > CRi > No Response > Unknown for all disease assessments post obe-cel infusion and prior to any new non-protocol anti-cancer therapies (including SCT).
[1] Including patients who achieved best overall response of CR or CRi after obe-cel infusion.
[2] The 95% exact Clopper-Pearson CIs are displayed.

In patients with high tumour burden, the median DOR was 10.97 months (95% CI: 5.19, NE) with a KM estimate of the probability of ongoing event-free remission at 12 months after onset of 46.2% (95% CI: 28.2, 62.4) and 30.8% (95% CI: 11.4, 52.8) at 21 months, and a median follow-up of 11.5 (95% CI: 8.31, 14.06) months.



Abbreviations: CI=confidence interval; IRRC=Independent Response Review Committee; NE=not estimable.
Time is relative to onset of remission: 1 month=30.4375 days.

Figure 11. Kaplan-Meier plot of duration of remission censoring new non protocol anti-cancer therapies including stem cell transplant – disease assessment by IRRC – by disease burden (% bone marrow blasts) at lymphodepletion – cohort IIa (infused set), DCO 07-Feb-2024

Summary of main efficacy results

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 24. Summary of efficacy for FELIX trial

Title: An open-label, multi-center, phase Ib/II study evaluating the safety and efficacy of AUTO1, a CAR T cell treatment targeting CD19, in adult patients with relapsed or refractory B cell acute lymphoblastic leukemia			
Study identifier	FELIX, AUTO1-AL1, EudraCT: 2019-001937-16, NCT04404660		
Design	Global, multi-centre, single arm, open label Phase Ib/II		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		24 months Not applicable Up to 15 years (patients are eligible for monitoring under a separate long-term follow-up study protocol)
Hypothesis	Superiority		
Treatments groups	Obe-cel		Total target dose of Aucatzyl 410 x 10^6 cells administered as a split dose infusion based on the disease burden, as assessed by the percentage of blasts in the BM at lymphodepletion. 112 patients enrolled; 94 patients infused
Endpoints and definitions	Primary endpoint	Overall Response Rate (ORR)	Defined as proportion of patients achieving CR or CRi as assessed by an Independent Response Review Committee (IRRC).
	Key secondary endpoint	Complete Remission Rate (CRR)	The proportion of patients who achieve a best overall response of CR without initiation of any non-protocol anticancer therapies.
	Secondary endpoint	CRR within 3 months post AUTO1 infusion	The proportion of patients who achieved a best overall response of CR within 3 months post obe-cel infusion.
	Secondary endpoint	MRD-negative remission	Proportion of patients achieving MRDnegative remission by central ClonoSEQ NGS testing (<10-4 leukaemic cells), PCR and/or flow cytometry.
	Secondary endpoint	Duration of remission (DOR)	Time from the first achievement of CR or CRi to relapse or death due to any reason
	Secondary endpoint	Duration of complete remission (DOCR)	Time from first documented CR after obe-cel infusion to the earliest of morphological relapsed disease, or death due to any reason.
	Secondary endpoint	Event free survival (EFS)	Time from first obe-cel infusion to the earliest of the following: treatment failure,

			morphological relapse disease and death due to any cause.
	Secondary endpoint	Progression free survival (PFS)	Time from first infusion to date of progressive disease (including any investigator's claim of a clinical progression) or date of death from any cause.
	Secondary endpoint	Overall survival (OS)	Time from the date of first obe-cel infusion to the date of death due to any reason.
	Secondary endpoint	ORR [CR+CRi] as assessed by the Investigator.	Defined as proportion of patients achieving CR or CRi as assessed by the Investigator.
	Secondary endpoint	Subsequent stem cell transplantation prior to leukaemia relapse.	Proportion of patients undergoing stem cell transplantation prior to leukaemia relapse
Database lock	Primary completion date (data base lock date): 03-Aug-2023 Data cut-off for primary analysis: 09-Jun-2023		
Results and Analysis			
Analysis description	**Primary Analysis**		
Analysis population and time point description	Modified Intention to treat, Cohort IIA, Infused Set: subset of patients in Phase II who had morphological disease at the time of lymphodepletion (≥ 5% blasts in the BM) and received at least 1 infusion of obe-cel (n=94)		
Descriptive statistics and estimate variability	Analysis set	Interim Analysis Primary Analysis (Infused Set)	Primary Analysis (leukapheresed Set)
	Number of subject	50 94	113
	ORR (CR + CRi) - n (%)	35 (70.0) 72 (76.6)	72 (63.74)
	95% CI (%)	55.4, 82.1 66.7, 84.7	54.1, 72.6
	CR - n (%)	21 (42.0) 52 (55.3)	55 (48.7)
	CRi - n (%)	14 (28.0) 20 (21.3)	17 (15.0)
Effect estimate per comparison	Primary endpoint Interim analysis	Comparison groups	ORR vs 40% historic ORR
		P-value	1-sided 0.0026 significance level
	Primary endpoint Primary Analysis	Comparison groups	ORR vs 40% historic ORR
		P-value	1-sided 2.5% level of significance
Notes	The main population of interest was the Infused Set, which consisted of all patients who received at least one obe-cel infusion. The Enrolled Set consisted of patients who had their leukapheresate accepted for manufacturing.		
Analysis description	Secondary analysis		

Secondary endpoints		**Primary Analysis (Infused Set) n=94**	**Primary Analysis (leukapheresed Set) n=113**
	Median DOR in responders (95% CI) DCO 09-Jun-2023	11.6 (8.1, NE)	12.5 (8.1, NE)*
	Median DOR in responders (95% CI) DCO 07-Feb-2024	14.06 (8.18, NE)	14.06 (8.18, NE)
	MRD-negative remission in responders (n=72)	64 (88.9%)	64 (88.9%)
	Median EFS* (95% CI) (months)	9.0 (6.0, 14.3)	7.7 (4.3, 10.6)
	Median OS* (95% CI) (months)	14.1 (10.1, 17.1)	11.7 (9.9, 16.8)
Notes	NE = Not estimated *data reported for PFS and OS refers to the primary analysis of the enrolled set (n=112)		

2.6.5.3. Clinical studies in special populations

No individual efficacy studies or analyses in specific populations were conducted. Twenty-one percent of patients in the infused set were aged ≥65 years and the maximum age was 81 years.

Table 25. Clinical studies in special populations

	Controlled Trials	**Non-controlled Trials**
Renal impairment* patients (Subjects number /total number)	N/A	0/127 (FELIX) Data not available (ALLCAR19)
Hepatic impairment** patients (Subjects number /total number)	N/A	0/127 (FELIX) Data not available (ALLCAR19)
Pediatric patients <18 years (Subjects number /total number)	N/A	0/127 (FELIX) 0/20 (ALLCAR19)
Age 65-74 (Subjects number /total number)	N/A	21/127 (FELIX) 0/20 (ALLCAR19)
Age 75-84 (Subjects number /total number)	N/A	4/127 (FELIX) 0/20 (ALLCAR19)
Age 85+ (Subjects number /total number)	N/A	0/127 (FELIX) 0/20 (ALLCAR19)
Other (Subjects number /total number)	N/A	N/A

* Renal impairment is defined as having chronic kidney disease Stage 3b, 4 or 5 (KDIGO definition).
** Hepatic impairment is defined as having Child-Pugh score B or C.

2.6.5.4. In vitro biomarker test for patient selection for efficacy

Not applicable

2.6.5.5. Analysis performed across trials (pooled analyses and meta-analysis)

Not applicable

2.6.5.6. Supportive study(ies)

Three supportive studies were provided.

- *ALLCAR19:* academic-led, proof-of-concept, open-label, multi-centre, single arm, Phase I clinical study investigating obe-cel in patients with high-risk, relapsed CD19-positive hematologic malignancies
- *External Control Arm Study (AUTO1-EC1):* prospectively designed, non-interventional study utilizing data from the FELIX study Cohort IIA and patient-level data from historical clinical trials (HCT) in r/r adult B ALL
- *Matching-Adjusted Indirect Comparison Study (Study 3694a):* prospectively designed, non-interventional study using MAIC methods for the comparison of obe-cel with CAR T cell comparator brexu-cel

ALLCAR19

Patients with r/r B-ALL following ≥2 prior lines were eligible for inclusion. The median age of the 20 patients infused with obe-cel in ALLCAR19 was 41.5 years (versus 50.0 years in the FELIX Cohort IIA), the median percentage of blasts in the BM was 43% at registration (versus 41.1% in the FELIX Cohort IIA), 15% of patients had EMD (versus 20.2% in the FELIX Cohort IIA) and 30% were Ph+ (versus 26.6% in the FELIX Cohort IIA). In addition, patients in ALLCAR19 were highly refractory, having received a median of 3 lines of prior therapy (versus 2 lines in FELIX Cohort IIA).

At a median follow-up of 36 months (range 24 to 47 months), 8 of 20 patients infused with obe-cel (40.0%) were reported as ongoing with CR more than 2 years post obe-cel treatment. Seven of the 20 infused patients (35.0%) are reported to be in ongoing remission post obe-cel treatment without any subsequent therapies, including SCT; this represents 41.2% (7/17) of the patients who achieved remission after obe-cel infusion. All 7 patients had persistency of CAR T cells at time of last evaluation (*Roddie et al, 2023*[46]).

External Control Arm Study (AUTO1-EC1, Non-CAR T Cell Therapy)

Study AUTO1-EC1 is a prospectively designed, non-interventional study utilizing data from the FELIX study Cohort IIA and patient-level data from historical clinical trials (HCT) in r/r adult B ALL contained within the database, which is a collection of thousands of previous clinical trials with subject-level data recorded through the electronic data capture system. The primary objective of AUTO1-EC1 was to assess the difference in ORR (CR + CRi) between patients enrolled/infused with obe-cel of the FELIX study Cohort IIA and patients in the ECA arm who received one of the following SoC as approved: blinatumomab (as monotherapy), inotuzumab ozogamicin (as monotherapy), or standard chemotherapy. Tyrosine kinase inhibitors were allowed to be used in combination with above therapies for Ph+ patients. CAR T therapies were not included due to lack of data availability. Secondary objectives included the assessment of differences of OS in infused patients in FELIX Cohort IIA versus the ECA arm, and differences in ORR and OS in enrolled patients in FELIX Cohort IIA versus the ECA arm. Other objectives included EFS and safety comparisons.

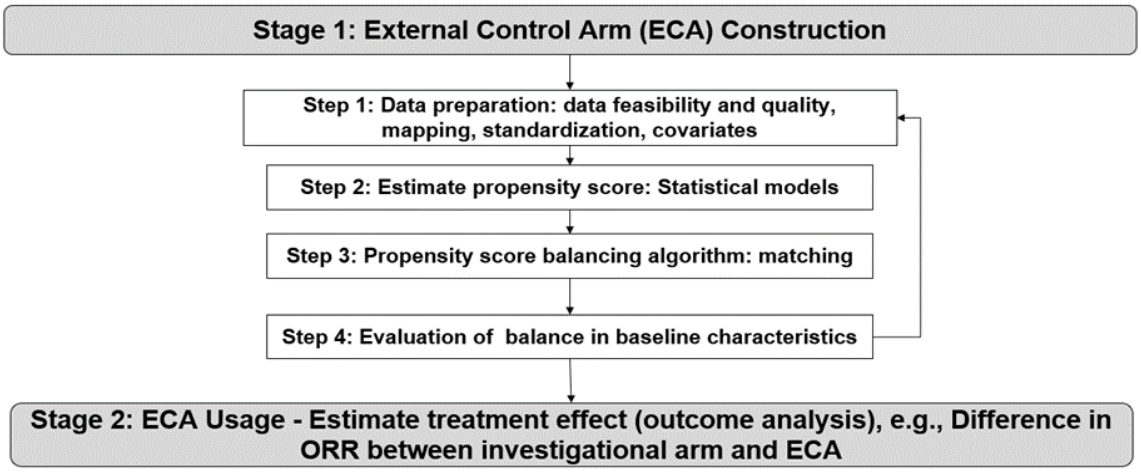
Two separate ECAs (ECA 1 and ECA 2) were created to conduct two types of comparative analyses:

- Treated Comparison (ECA 1), which used matched patients from the HCTs and treated patients in the FELIX Cohort IIA Infused Set.
- All Patient Comparison (ECA 2), which used matched patients from the HCTs and the FELIX Cohort IIA Enrolled Set.

A total of 415 HCT patients were eligible for ECA creation. Since the treatments were not randomly assigned between the historical patients and investigational patients from the investigational trial, a

[46] Roddie C, Dias J, O'Reilly M, et al (2023). Long-Term Follow-up of AUTO1, a Fast-Off Rate CD19 CAR, in Relapsed/Refractory B-Cell Acute Lymphoblastic Leukemia and Factors Associated with Durable Response. Poster presented at: American Society for Transplantation and Cellular Therapy Meeting, Feb 15-19, 2023, Orlando, Florida, USA.

propensity score method to balance the baseline characteristics of the ECAs with that of the infused (for ECA 1) or the enrolled (for ECA 2) patients from the FELIX study was applied.



ECA=external control arm; ORR=overall remission rate.

Figure 12. External control arm construction

The Treated Comparison arm and the All Patient Comparison arm included 84 and 107 matched FELIX and HCT patients, respectively. The ECA comprised primarily of patients who received blinatumomab (**Table 26**).

Table 26. Treatment summary by group

	Treated Comparison		All Patients Comparison	
	FELIX (N=84) n (%)	ECA 1 (N=84) n (%)	FELIX (N=107) n (%)	ECA 2 (N=107) n (%)
Obe-cel	84 (100.0)	0	89 (83.2)	0
Blinatumomab	0	71 (84.5)	0	86 (80.4)
Inotuzumab ozogamicin	0	1 (1.2)	0	2 (1.9)
Standard chemotherapy	0	12 (14.3)	0	19 (17.8)
Bridging therapies only	0	0	10 (9.3)	0
Not received study treatment	0	0	8 (7.5)	0

ECA=external control arm.

For ECA 1 (Infused Set) the primary efficacy endpoint of ORR was statistically significant with a 25% higher ORR in matched patients receiving obe-cel (79.8% vs 54.8%, p-value of 0.0009) (**Table 27**).

Table 27. ORR by treatment group

Treated Comparison						
FELIX (N=84)		ECA 1 (N=84)		Treatment Difference		
n	ORR (%) (95% CI)	n	ORR (%) (95% CI)	Difference in % (95% CI)	Odds Ratio (95% CI)	p-value [1]
67	79.8 (69.6, 87.7)	46	54.8 (43.5, 65.7)	25.0 (9.4, 38.6)	3.3 (1.6, 6.5)	0.0009
All Patient Comparison						
FELIX (N=107)		ECA 2 (N=107)		Treatment Difference		
n	ORR (%) (95% CI)	n	ORR (%) (95% CI)	Difference in % (95% CI)	Odds Ratio (95% CI)	p-value [1]
72	67.3 (57.5, 76.0)	55	51.4 (41.5, 61.2)	15.9 (2.3, 28.8)	1.9 (1.1, 3.4)	0.0257

CI=confidence interval; ECA=external control arm; ORR=overall remission rate.
[1] p-value is estimated for the rate difference from Fisher's exact test.

The secondary endpoint of OS showed the median survival time for matched patients, and was longer in patients receiving obe-cel (14.13 [10.12 – 16.82] months) compared to ECA 1 (10.48 [7.39 – 12.52] months), but the difference between the two groups did not reach statistical significance. The EFS was statistically significant longer in patients receiving obe-cel (9.03 [6.14 – 14.98] months) compared to ECA 1 (2.79 [0.95 – 5.13] months).

For ECA2 (All Patient Comparison) the ORR was statistically significantly higher in enrolled patients in FELIX compared to the ECA 2 patients (67.3% vs 51.4%) with an odds ratio of 1.9 (95% CI [1.1, 3.4]) and Fisher's exact p-value = 0.0257 (**Table 27**).

The secondary endpoint of OS, whereby all patients still alive were censored at last contact date, showed that the median was longer for the FELIX patients (11.7 vs 7.8 months), but did not reach statistical significance (HR 0.73, 95% CI [0.51, 1.05], p-value 0.0893). The median follow-up time was shorter in FELIX compared to ECA 2 (11.53 vs 17.77 months). The median EFS was statistically significantly longer for the FELIX patients compared to ECA 2 (8.18 vs 2.46 months, log-rank test p-value < 0.0001). The hazard ratio for the treatment difference was 0.47 with 95% CI of 0.32 to 0.67.

Matching-Adjusted Indirect Comparison Study (CAR T Cell Therapy)

Study 3964a is a prospectively designed, non-interventional study using MAIC methods for the comparison of obe-cel with the CAR T cell comparator, brexu-cel, based on data from the pivotal ZUMA-3 study (*Shah et al, 2021*[47]). The overall objective of the MAIC analyses was to estimate the relative efficacy and safety of obe-cel compared with brexu-cel for adult patients with B ALL. Individual obe-cel-treated patients were assigned statistical weights that adjust for their over- or underrepresentation relative to the average prognostic factors and treatment effect modifiers observed in ZUMA-3. These weights were then incorporated into the analyses. Two populations were considered for the comparison, the mITT population (patients infused) and the ITT population (patients enrolled).

The baseline characteristics of FELIX Cohort IIA and ZUMA-3 are described in **Table 28**. Patients in FELIX Cohort IIA were on average older than those in ZUMA-3, with FELIX Cohort IIA having a higher median by 10 years compared with ZUMA-3, and FELIX Cohort IIA enrolled a greater proportion of patients of Hispanic or Latino ethnicity (30.9% in FELIX Cohort IIA and 20.0% in ZUMA-3). The population in FELIX Cohort IIA received fewer prior lines of therapy compared with ZUMA-3, with 30.9% of patients having received ≥ 3 prior lines of therapy, and 47.3% of patients in ZUMA-3 having received ≥ 3 prior lines of therapy.

Table 28. Summary of patient baseline characteristics in FELIX cohort IIA and ZUMA-3

Study ID	**FELIX Cohort IIA**	**ZUMA-3**
Year	2023	2021
Treatment	Obe-cel	Brexu-cel
Sample size	94	55
Age (years)		
Mean (SD)	48.3 (17.1)	42.4 (16.1)
Median (IQR)	50 (33, 62)	40 (28, 52)
≥ 65 years	21 (22.3)	8 (14.5)
Sex (male), n (%)	47 (50.0)	33 (60.0)
Race (white), n (%)	70 (74.5)	37 (67.27)
Ethnicity (Hispanic/Latino), n (%)	29 (30.9)	11 (20.0)
BM blasts prior to pre-conditioning, n (%)		
≤ 5%	23 (24.5)	5 (9.1)

[47] Shah BD, Bishop MR, Oluwole OO, et al (2021). KTE-X19 anti-CD19 CAR T-cell therapy in adult relapsed/refractory acute lymphoblastic leukemia: ZUMA-3 phase 1 results. Blood; 138(1):11-22.

> 5%–25%	15 (16.0)	10 (18.2)
> 25%–50%	13 (13.8)	11 (20.0)
> 50–75%	12 (12.8)	10 (18.2)
> 75%	31 (33.0)	19 (34.5)
Prior allo-SCT, n (%)	36 (38.3)	23 (41.8)
Extramedullary disease prior to pre-conditioning, n (%)	19 (20.2)	6 (10.9)
Ph chromosome prior to pre-conditioning, n (%)	25 (26.6)	15 (27.3)
ECOG PS score at baseline, n (%)		
0	35 (37.2)	16 (29.1)
1	58 (61.7)	39 (70.9)
Unknown	1 (1.1)	0 (0)
Number of prior therapies, n (%)		
1	29 (30.9)	10 (18.2)
2	36 (38.3)	19 (34.5)
3	17 (18.1)	14 (25.5)
4	10 (10.6)	≥ 4
5	1 (1.1)	12 (21.8)
6	1 (1.1)	
Bridging chemotherapy, n (%)	87 (92.6)	51 (92.7)
Duration of first remission < 12 months, n (%)	41 (43.6)	16 (29.1)
Primary refractory, n (%)	24 (25.5)	18 (32.7)
Key: allo-SCT, allogeneic stem-cell transplant; BM, bone marrow; BMI, body mass index; ECOG PS, Eastern Cooperative Oncology Group Performance		

When considering patients who received CAR T cell therapy (i.e., the mITT population), the odds of experiencing ORR and CR were similar for obe-cel and brexu-cel patients and results were not statistically significant (**Table 29**). The ITT analysis showed numerically favourable odds of ORR and CR for obe-cel, but the results were not statistically significant.

Table 29. Odds ratios for ORR and CR - obe-cel versus brexu-cel

Method	OR (95% CI) Obe-cel vs Brexu-cel	
	mITT Population	ITT Population
Odds Ratio for Overall Remission Rate		
Obe-cel ESS	38.0	53.2
OR (95% CI) from weighted logistic regression model (robust SE)	1.008 (0.355 to 2.865)	1.246 (0.596 to 2.605)
Odds Ratio for Complete Remission		
Obe-cel ESS	38.0	53.2
OR (95% CI) from weighted logistic regression model (robust SE)	1.041 (0.443 to 2.449)	1.313 (0.630 to 2.736)

CI=confidence interval; CR=complete remission; ESS=effective sample size; ITT=intent-to-treat; mITT=modified intent-to-treat; OR=odds ratio; ORR=overall remission rate; SE=standard error.
OR of > 1 is favorable for obe-cel and indicates greater odds of ORR or CR. Results are considered statistically significant if the 95% CI does not include 1.
Based on Scenario 2, matched on characteristics identified as prognostic for any endpoint.
Source: 3964a Report-Table 18 and Table 20.

For EFS, results of the analysis based on the reweighted obe-cel population (censoring new non-protocol anticancer therapies or SCT) found no statistically significant difference between obe-cel and

brexu-cel (HR 0.810 [0.465 to 1.411], favouring obe-cel) with the current data cutoff and median duration of follow-up, which was shorter for FELIX compared to ZUMA-3 (12.3 months vs 16.4 months, respectively).

Healthcare professional/provider engagement

Obe-cel was selected for early dialogue with healthcare providers. The healthcare providers described the current standard of care for r/r B ALL with blinatumomab or inotuzumab, but as these are not curative by themselves, patients should receive alloHSCT or therapy with CAR T. Of special need are older patients with ALL, since the rate of CR with blinatumomab or inotuzumab in this population is considered limited and therefore the rate of subsequent alloHSCT is low. CAR T with brexu-cel could cover part of these limitations. A CAR T construct with similar efficacy to brexu-cel but less toxicity could increase the fraction of older and elderly patients as candidate to CAR T. CAR T will not cover all needs for therapy of r/r ALL patients, and therefore current investigations are focused on the incorporation of immunotherapy into first line therapy in order to increase the efficacy and reduce the toxicity of the current first line therapies.

2.6.6. Discussion on clinical efficacy

Design and conduct of clinical studies

The efficacy was mainly based on Cohort A (patients with morphological disease i.e. ≥ 5% blasts in BM at screening) from Phase II (Cohort IIA) of the FELIX study. Supportive data were provided from an academia-led study (ALLCAR19; with an earlier manufacturing process) and 2 indirect comparison studies AUTO-1 EC1 (external control arm using data from historical clinical trials) and 3964a (MAIC for the comparison of obe-cel with CAR T cell comparator brexu-cel).

The pivotal FELIX study is a single arm trial. During scientific advice (EMEA/H/SA/4252/1/2019/SME/ADT/III), it was discussed that a randomised control trial against blinatumomab and inotuzumab ozogamicin might be feasible in a multi-centre setting. According to the applicant this was not appropriate because there is no standard of care across the r/r B ALL population and some patients already received blinatumomab or inotuzumab ozogamicin in a previous line. Although blinatumomab and inotuzumab ozogamicin are only approved for the treatment of r/r ALL in the EU, several studies have investigated the incorporation of these agents into front-line treatment regimens (Hoelzer et al, 2023[48]) with promising results. A comparison with CAR T cells poses possible supply and logistical challenges. In addition, tisa-cel was considered not a suitable comparator because it is only approved for patients up to 25 years of age and brexu-cel was not yet approved in the EU at the time the FELIX trial started. Although a randomised trial would have been preferred, the considerations of the applicant are acknowledged, and the single arm trial design is considered acceptable in the context of a CMA.

Obe-cel is administered in a split dose based on disease burden (bone marrow blast counts) with an interval of 9 days [± 2 days] between doses. The data provided in support of the proposed posology were limited and based on literature and the proof-of-concept ALLCAR19 study for which no CSR was available. Nevertheless, the final proposed posology is considered acceptable.

Bridging therapy was allowed whilst awaiting manufacture of obe-cel based on investigator's choice and local practice, this is acceptable.

Inclusion and exclusion criteria were considered acceptable, although very heterogeneous. Prior

[48] Hoelzer D, Bassan R, Boissel N, et al (2023). ESMO Clinical Practice Guideline interim update on the use of targeted therapy in acute lymphoblastic leukaemia. Ann Oncol. 2024 Jan;35(1):15-28.

treatment with blinatumomab (anti-CD19) was allowed, but CD19 expression was to be confirmed and a warning in SmPC 4.4 has been included for patients with CD19-negative disease after treatment with previous anti-CD19 treatments.

The primary efficacy endpoint was ORR as assessed by IRCC. ORR is acceptable as primary endpoint for a single-arm trial and provided together with the evaluation of durability of responses with adequate follow-up and was previously agreed during scientific advice (EMA/CHMP/SAWP/586752/2019). The secondary endpoints include duration of remission and are considered appropriate.

Efficacy data and additional analyses

In total 217 patients were screened; 112 patients were enrolled in Cohort IIA and 94 patients received at least 1 infusion of obe-cel in Cohort IIA. A patient was considered enrolled when the patients' leukapheresate was accepted for manufacturing. In one patient leukapheresis product was collected which proceeded to manufacturing, however obe-cel manufacturing was terminated on Day 2 because the patient died of progressive disease. This patient was not considered enrolled by the applicant, although it appears that the definition of enrolment as defined by the applicant was fulfilled since the patients' leukapheresate was accepted for manufacturing (e.g. proceeded to manufacturing). Although the impact of one additional patient in the ITT population on the benefit risk assessment is limited, the ITT analysis and SmPC (section 5.1) have been updated to use the leukapheresed patients set in order to provide the data in the EPAR and SmPC. The results for the total leukapheresed set (n=113), which included all patients who had leukapheresis, were in line with the enrolled set (n=112). The number of patients not infused due to manufacturing related issues was comparable to other CAR T products. In total, 11 patients died before receiving obe-cel.

The baseline data reflect a heterogenous r/r ALL population, in line with the sought indication. The median age in the mITT population of Cohort IIA was 50 years (range 20 – 81), half of patients were refractory to the last prior line of therapy and patients had received a median of 2 prior lines of anticancer therapy (range: 1 - 6). Half of the patients did not receive blinatumomab or inotuzumab ozogamicin, meaning that these patients also had alternative treatment options.

Within the ongoing FELIX study, a large number of protocol changes and amendments were implemented, mostly minor and they did not change any key features of the study design. An important modification was the allowance of inotuzumab ozogamicin as bridging therapy after the majority of patients (n=76) were already included in Cohort IIA. Emerging data suggest that prior inotuzumab ozogamicin may confer inferior CAR T outcomes as inotuzumab-induced B-cell depletion can potentially compromise CAR-T expansion and persistence (*Hoelzer et al, 2023*[49]). Despite this, subgroup analyses showed similar efficacy and CAR T persistence in the subgroup of patients that were bridged with inotuzumab ozogamicin. The expansion was lower after bridging with inotuzumab ozogamicin, which is likely due to the substantial reduction in tumour burden by inotuzumab ozogamicin.

The median time from leukapheresis (vein) to release of the product (certification) was 20 days (range 17 – 49). The time between enrolment and infusion is discussed in more detail in the safety discussion.

The results from the primary analysis show a convincing clinical response. The ORR was 76.6% in the mITT, in line with what is expected with CAR T in this setting. An additional analysis was performed in the ITT set (a supplementary estimand definition) in which an ORR of 64.3% (for leukapheresed set ORR of 63.7%) was reported and in patients receiving the target dose ORR was 81.2%. The difference in ORR between the mITT and ITT set demonstrate that the mITT set results in a higher estimate of

[49] Hoelzer D, Bassan R, Boissel N, et al (2023). ESMO Clinical Practice Guideline interim update on the use of targeted therapy in acute lymphoblastic leukaemia. Ann Oncol. 2024 Jan;35(1):15-28.

ORR compared to trials where an ITT population is used. Therefore, the mITT is not suitable for comparison to external (non-CAR T) cohorts.

Obe-cel is the first CAR T product with a split dose regimen. As a result, it takes longer before the total target dose is reached because the second dose is administered after 10 days. The time to response and time to peak, as reported in *Clinical Pharmacology section of this report* are however in line with results for single dose CAR T products, providing reassurance that patients are not undertreated by a split dose regimen compared to a single dose regimen.

The concordance between responses assessed by the Investigator and responses assessed by IRRC was high (94% for ORR). The median time to response was short (0.95 months) and most patients who reached CR did so within 3 months post obe-cel infusion. Most patients (69%) with CR/CRi achieved MRD-negative bone marrow, which demonstrates the depth and quality of ORR. The median duration of remission for ORR was 11.56 months at the primary efficacy analysis. A data update with a median duration of follow-up of 20.25 months showed a median DOR of 14.06 months (95% CI: 8.18, NE). This is considered a clinically relevant and durable response. The median EFS was 9.03 months with a median follow-up of 8.8 months. The median OS was 14.13 months with a median follow-up of 11 months. Results on time-to event outcomes are considered unreliable in a single arm trial design. The interpretability of PRO measures is hampered by the open-label single-arm study design. Furthermore, PRO measures were only assessed in patients with a CR or CRi.

To determine the obe-cel dose regimen (high/low tumour burden), a BM assessment was performed before LD chemotherapy. This is different from other pivotal studies with CAR T products, whereby BM morphology was only assessed at screening (*EPAR Tecartus II-08,* *EPAR Kymriah*). While all patients had ≥5% blasts at screening, 18 patients (18/94, 19%) had <5% blasts without EMD before LD chemotherapy. This shows a decrease in disease burden between screening and LD, possibly caused by bridging therapy. Patients with <5% blasts without EMD before LD chemotherapy had a higher ORR of 88.9% (16/18), however also in patients with ≥5% blast after bridging a response was observed with an ORR of 74% (56/76).

The ORR of patients included in Phase Ib (69%), Cohort IIB (90%) and Cohort IIC (86%) provided further support of the observed efficacy in Cohort IIA.

Subgroup analyses showed that the ORR was comparable between patients with low or high disease burden based on the percentage of blasts at screening. The ORR was 81.1% in low disease burden patients and 73.7% in high disease burden patients. In low disease burden patients, CR was 54.1% (20/37), and in patients with high disease burden CR was 56.1% (32/57). In patients with low tumour burden, the median DOR was NE while in patients with high tumour burden, the median DOR was 10.97 months (95% CI: 5.19, NE).

Consistent results were observed for patients who were treated with 1, 2 or 3 prior lines of therapy, while the small subgroup of patients with ≥4 prior lines showed a lower ORR of 58.3%. Patients with prior blinatumomab and inotuzumab ozogamicin had a slightly lower but still clinically relevant ORR of 66.7%. It is reassuring that all subgroups exceeded the pre-specified ORR margin of 40%. Based on the subgroup analyses in a limited number of patients, there were no patients with lack of efficacy, who should be reflected in a restricted label.

Contextualisation

Supportive data from the ALLCAR19 study was provided. The data was limited because no CSR was provided as ALLCAR19 is an academic study. Furthermore, a different manufacturing process was used. Altogether, the added value of the supportive ALLCAR19 for efficacy is limited.

In the AUTO1-EC1 study, a propensity score method was used to balance baseline characteristics of

Cohort IIA (FELIX) with the external control arm (standard of care, non-CAR T cell therapy). Most patients in the external control arm received blinatumomab, and only a limited number of patients received inotuzumab ozogamicin. In the FELIX trial, these treatments were commonly used in earlier lines. The primary outcome was ORR. A significant better ORR was reported for the ITT set of obe-cel (67%) compared to historical clinical trial data (51%). There was no significant difference in OS although the follow-up in the FELIX study was short. Study AUTO1-EC1 has limitations because several known prognostic factors were not included in the propensity score due to lack of data feasibility. Also, the evolving treatment landscape with novel therapies used in earlier lines hampers comparison.

The MAIC compared obe-cel (FELIX) to brexu-cel (ZUMA-3) for patients over 25 years (in line with the indication for brexu-cel). Patients were matched based on prognostic factors and treatment-effect modifiers. No clinically relevant difference between treatment arms was observed in regard to ORR, CR and EFS. OS was not studied. The MAIC study suggests that the outcomes of ORR, CR and EFS could be comparable between obe-cel and brexu-cel. While no formal conclusions regarding similar efficacy can be concluded, these results can be considered as supportive. There are however substantial limitations, namely the lack of head-to-head trial evidence meaning the MAIC is unanchored, the small sample sizes in both trials (further reduced because of the matched comparisons), different definitions related to EFS and methodological issues.

Additional efficacy data needed in the context of a conditional MA

Taking into consideration the single arm trial design of the pivotal study, the limited number of patients enrolled in the pivotal study, and the short time follow up available of the treated patients in the clinical trial, the committees considered that long-term efficacy data is lacking. In the context of a conditional MA approval, the applicant shall conduct and submit the results of long-term studies to provide the relevant long-term efficacy data.

The CHMP endorses the CAT discussion on clinical efficacy as described above.

2.6.7. Conclusions on the clinical efficacy

Clinically meaningful ORR rates for r/r B ALL are presented. Taking in due consideration the single-arm study design, exploratory nature of the pivotal trial, and limited sample size, the activity of obe-cel is considered demonstrated.

The CAT considered the following measures necessary to address the missing efficacy data in the context of a conditional MA:

- 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. (due date: 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 characterise the long-term safety and efficacy of Aucatzyl, according to an agreed protocol. (Due date: 31 July 2030)

The CAT considers the following additional measures necessary to address issues related to efficacy:

- 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. (due date 30 June 2039)

- Non-Interventional Post-Authorisation Safety Study: 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 prospective study based on data from a registry. (due date 30 June 2045)

The CHMP endorses the CAT conclusion on clinical efficacy as described above.

2.6.8. Clinical safety

2.6.8.1. Patient exposure

The safety profile for the use of obe-cel for the treatment of r/r B ALL in adults is based primarily on the safety data from the pivotal study AUTO1-AL1 (FELIX study). The safety focuses on all patients infused with at least one dose of obe-cel from all cohorts and phases of the study as of the data cut-off (DCO) for the primary analysis on 09-Jun-2023 and additional 8 month data update with DCO 07-Feb-2024. The Safety Set consists of data from a total of 127 adult patients with r/r B ALL. The median duration of follow-up from first obe-cel infusion to the DCO (09-Jun-2023) for the primary analysis was 13.47 months (range: 0.6 - 33.4) and increased to a median duration of follow-up of 21.45 months (range: 8.6-41.4 months) with DCO 07-Feb-2024.

The median time from leukapheresis (vein) to release of the product (certification) was 20 days (range: 17 - 49 days) across the 31 clinical sites. The majority (92.9%, 118/127) received bridging therapy, with chemotherapy being the most common bridging therapy used. All 127 patients (100%) received LD therapy prior to obe-cel infusion, with a median dose of IV fludarabine of 120 mg/m^2 (range 68 to 240 mg/m^2) and median dose of IV cyclophosphamide of 1,000 mg/m^2 (range 700 to 2,000 mg/m^2).

Obe-cel is administered according to a split-dose. Overall, the median dose of obe-cel administered in the Safety Set was the target dose of 410 × 10^6 CD19 CAR-positive T cells, achieved in 116/127 patients (91.3%). A majority of patients received both administrations (94.5%, 120/127), but seven patients did not receive the second infusion due to AE (n=3), PD (n=2), death (n=1) or manufacturing issue (n=1). A total of 9 patients received their second dose after the protocol pre-specified Day 10 ± 2 days due to the occurrence of AE (range: Day 13 - Day 21). No patient had the second split dose infusion beyond the protocol allowed Day 21.

2.6.8.2. Adverse events

Prior to obe-cel administration

In the period after enrolment but prior to first obe-cel infusion, which includes the administration of bridging and LD therapies, the majority of enrolled patients (Enrolled Set, N=153) experienced at least one AE (84.3%, 129/153) and the majority of patients had at least one AE ≥ Grade 3 (66.0%, 101/153). The most common ≥ Grade 3 AEs (≥ 10% of patients) prior to obe-cel infusion were febrile neutropenia (19.6%, 30/153), anaemia (13.1%, 20/153), and neutrophil count decreased (11.1%,

17/153). At least one serious adverse event (SAE) was experienced by 45.8% of patients (70/153) prior to obe-cel infusion, the most common (≥ 5% of patients) being febrile neutropenia (13.7%, 21/153) and pyrexia (5.2%, 8/153). In addition, a total of 14.4% (22/153) of patients died *prior* to obe-cel infusion: 11 died due to progressive disease, 10 died due to AEs (coronavirus disease 2019 [COVID-19], septic shock, haemoptysis, neutropenic sepsis, pneumonia, pneumonia fungal, subdural hematoma) and 1 due to unknown cause.

After Obe-cel administration

All adult patients with r/r B ALL treated with obe-cel in the Safety Set experienced at least one AE any time post obe-cel infusion (i.e. at least one treatment emergent adverse event [TEAE]), the majority of which were ≥ Grade 3 (104 patients, 81.9%)). To date (07-Feb-2024), 50.4% of patients (64/127) have discontinued from the study due to death, mostly due to progressive disease (45 patients, 35.4%) and TEAEs (17 patients, 13.4%).

The most common TEAE was CRS, which was reported in 68.5% (87/127) of patients, although only 2.4% (3/127) experienced CRS of ≥ Grade 3. The TEAE of ICANS was reported in 22.8% (29/127) of patients, although only 7.1% (9/127) reported ICANS of ≥ Grade 3, despite the high tumour burden in many of the patients.

The most common individual preferred terms (PTs) (≥ 10% of patients) of ≥ Grade 3 were febrile neutropenia (23.6%), anaemia and neutropenia (20.5% each), neutrophil count decreased (19.7%), thrombocytopenia and platelet count decreased (12.6% each), and hyperferritinaemia (10.2%). The most common TEAEs (≥ 10% of patients) after obe-cel infusion, regardless of causality, are presented in **Table 30**.

Table 30. Treatment-emergent adverse events in ≥ 10% of patients (system organ class or preferred term) at any time after obe-cel infusion (phase Ib and phase II, safety set), DCO 07-Feb-2024

System Organ Class Preferred Term	Infused (N=127)	
	All grades n (%)	Grade ≥ 3 n (%)
Number of patients with any TEAE	**127 (100)**	**104 (81.9)**
Blood and lymphatic system disorders	76 (59.8)	65 (51.2)
Febrile neutropenia	31 (24.4)	30 (23.6)
Anaemia	30 (23.6)	26 (20.5)
Neutropenia	29 (22.8)	26 (20.5)
Thrombocytopenia	18 (14.2)	16 (12.6)
Cardiac disorders	20 (15.7)	2 (1.6)
Eye disorders	14 (11.0)	1 (0.8)
Gastrointestinal disorders	79 (62.2)	17 (13.4)
Nausea	33 (26.0)	3 (2.4)
Diarrhoea	32 (25.2)	2 (1.6)
Vomiting	21 (16.5)	1 (0.8)
Abdominal pain	16 (12.6)	2 (1.6)
Constipation	16 (12.6)	0
General disorders and administration site conditions	66 (52.0)	9 (7.1)
Pyrexia	37 (29.1)	2 (1.6)
Fatigue	24 (18.9)	2 (1.6)
Hepatobiliary disorders	14 (11.0)	8 (6.3)
Immune system disorders	91 (71.7)	12 (9.4)
Cytokine release syndrome	87 (68.5)	3 (2.4)

System Organ Class Preferred Term	Infused (N=127)	
	All grades n (%)	Grade ≥ 3 n (%)
Infections and infestations	99 (78.0)	66 (52.0)
COVID-19	23 (18.1)	8 (6.3)
Injury, poisoning and procedural complications	23 (18.1)	3 (2.4)
Investigations	64 (50.4)	48 (37.8)
Neutrophil count decreased	25 (19.7)	25 (19.7)
Platelet count decreased	18 (14.2)	16 (12.6)
Alanine aminotransferase increased	15 (11.8)	6 (4.7)
Weight decreased	13 (10.2)	2 (1.6)
Metabolism and nutrition disorders	62 (48.8)	29 (22.8)
Hypokalaemia	27 (21.3)	8 (6.3)
Hyperferritinaemia	17 (13.4)	13 (10.2)
Decreased appetite	15 (11.8)	4 (3.1)
Hypomagnesaemia	14 (11.0)	0
Musculoskeletal and connective tissue disorders	50 (39.4)	7 (5.5)
Arthralgia	13 (10.2)	0
Nervous system disorders	73 (57.5)	13 (10.2)
Headache	30 (23.6)	0
Immune effector cell-associated neurotoxicity syndrome	29 (22.8)	9 (7.1)
Psychiatric disorders	35 (27.6)	6 (4.7)
Confusional state	16 (12.6)	3 (2.4)
Renal and urinary disorders	21 (16.5)	5 (3.9)
Respiratory, thoracic and mediastinal disorders	44 (34.6)	14 (11.0)
Cough	15 (11.8)	0
Skin and subcutaneous tissue disorders	30 (23.6)	1 (0.8)
Vascular disorders	40 (31.5)	10 (7.9)
Hypotension	28 (22.0)	6 (4.7)

Almost all patients (119 patients, 93.7%) reported at least one TEAE suspected to be related to obecel by the Investigator (**Table 31**). For TEAEs reported as treatment-related by the Investigator, the most commonly reported were CRS and ICANS, irrespective of grade (68.5% [87/127] and 22.8% [29/127], respectively). The most common treatment-related TEAEs (≥ 10%) with severity ≥ Grade 3 did not include these events, rather were febrile neutropenia (20 patients, 15.7%), neutropenia (19 patients, 15.0%), neutrophil count decreased (17 patients, 13.4%), anaemia (14 patients, 11.0%), and hyperferritinaemia (13 patients, 10.2%).

Table 31. Treatment emergent adverse events in more than 10% of patients (all grades) any time post obe-cel infusion, with suspected relationship to obe-cel by the investigator, by preferred term, maximum grade and disease status at lymphodepletion (Phase Ib and Phase II, Safety Set), DCO 07-Feb-2024

Preferred Term	≥ 5% Blast in BM (N=91)		< 5% Blast in BM Without EMD (N=29)		< 5% Blast in BM With EMD (N=7)		Total (N=127)	
	All grades n (%)	Grade ≥ 3 n (%)	All grades n (%)	Grade ≥ 3 n (%)	All grades n (%)	Grade ≥ 3 n (%)	All grades n (%)	Grade ≥ 3 n (%)
Number of patients with any TEAE with suspected relationship to obe-cel	85 (93.4)	51 (56.0)	27 (93.1)	23 (79.3)	7 (100)	3 (42.9)	119 (93.7)	77 (60.6)
Cytokine release syndrome	70 (76.9)	3 (3.3)	14 (48.3)	0	3 (42.9)	0	87 (68.5)	3 (2.4)
Immune effector cell-associated neurotoxicity syndrome	26 (28.6)	9 (9.9)	2 (6.9)	0	1 (14.3)	0	29 (22.8)	9 (7.1)
Pyrexia	21 (23.1)	0	6 (20.7)	1 (3.4)	0	0	27 (21.3)	1 (0.8)
Febrile neutropenia	11 (12.1)	11 (12.1)	8 (27.6)	8 (27.6)	1 (14.3)	1 (14.3)	20 (15.7)	20 (15.7)
Neutropenia	13 (14.3)	13 (14.3)	7 (24.1)	6 (20.7)	0	0	20 (15.7)	19 (15.0)
Anaemia	11 (12.1)	9 (9.9)	7 (24.1)	5 (17.2)	0	0	18 (14.2)	14 (11.0)
Headache	14 (15.4)	0	2 (6.9)	0	1 (14.3)	0	17 (13.4)	0
Hyperferritinaemia	15 (16.5)	12 (13.2)	1 (3.4)	0	1 (14.3)	1 (14.3)	17 (13.4)	13 (10.2)
Nausea	9 (9.9)	1 (1.1)	8 (27.6)	1 (3.4)	0	0	17 (13.4)	2 (1.6)
Neutrophil count decreased	7 (7.7)	7 (7.7)	9 (31.0)	9 (31.0)	1 (14.3)	1 (14.3)	17 (13.4)	17 (13.4)
Fatigue	11 (12.1)	1 (1.1)	4 (13.8)	0	1 (14.3)	0	16 (12.6)	1 (0.8)
Hypotension	13 (14.3)	1 (1.1)	2 (6.9)	0	1 (14.3)	1 (14.3)	16 (12.6)	2 (1.6)
Confusional state	13 (14.3)	3 (3.3)	0	0	1 (14.3)	0	14 (11.0)	3 (2.4)
Thrombocytopenia	12 (13.2)	10 (11.0)	2 (6.9)	2 (6.9)	0	0	14 (11.0)	12 (9.4)

Abbreviations: AE = adverse event; BM = bone marrow; CTCAE = Common Terminology Criteria for Adverse Events; EMD = extramedullary disease; MedDRA = Medical Dictionary for Regulatory Activities; NCI = National Cancer Institute; TEAE = treatment-emergent adverse event.
AEs were coded using MedDRA 26.0. TEAE was defined as any AE with onset during the post-infusion period.
AE severity was graded according to NCI's CTCAE V5.0. Grade 1 = Mild; Grade 2 = Moderate; Grade 3 = Severe; Grade 4 = Life-threatening consequences; Grade 5 = Fatal.
Preferred terms were presented in descending order of counts in the column of "All grades" under "Total". Multiple AEs were counted only once per patient for each preferred term.
Data cut-off: 07-Feb-2024

2.6.8.3. Serious adverse event/deaths/other significant events

2.6.8.3.1. Deaths and other serious TEAEs

A total of 64 of 127 patients in the Safety Set (50.4%) died at any time post-obe-cel treatment as of the data cut-off of 07-Feb-2024 and 65.4% (83/127) of patients experienced at least one SAE of any grade as of the data cut-off of 07-Feb-2024. Within 30 days post obe-cel infusion, 5 patients (3.9%) died (3 due to progressive disease and 2 due to AE [sepsis and cerebrovascular accident]). None of these early deaths were suspected to be related to obe-cel.

The primary reason for deaths at any time post obe-cel infusion was progressive disease (45 of 127 patients, 35.4%). The second most common reason for death was TEAE (17 patients, 13.4%). The reason for death for 2 patients was "other". Of the 17 patients who died due to AEs, 2 patients (1.6%) experienced a total of 3 fatal TEAEs that were suspected to be related to obe-cel treatment (acute respiratory distress syndrome, ICANS and neutropenic sepsis). The other 15 deaths (11.8%) were not suspected to be related to obe-cel treatment.

The most common serious TEAEs (≥ 10% of patients), regardless of relationship to study treatment, was febrile neutropenia which occurred at any grade in 13.4% of patients and at ≥ Grade 3 in 12.6% of patients. Serious TEAEs assessed suspected to be related to study treatment by the Investigator occurred in 39.4% of patients. The most common SAEs (≥ 5% of patients) assessed as related to study treatment by the Investigator were ICANS (9.4%), CRS (7.9%), febrile neutropenia (6.3%), and hyperferritinaemia (5.5%).

2.6.8.3.2. Adverse events of special interest

A summary of the analyses pertaining to TEAEs that could potentially be significant for the treatment of B ALL following CAR T cell therapy is described below and in **Table 32** below.

Table 32. Overview of other significant adverse events after obe-cel infusion (phase Ib and phase II, safety set*)*

Significant Event	Infused (N=127)				
	All grades n (%)	Grade 3 n (%)	Grade 4 n (%)	Grade 5 n (%)	≥ Grade 3 n (%)
Cytokine release syndrome	87 (68.5)	3 (2.4)	0	0	3 (2.4)
Immune effector cell-associated neurotoxicity syndrome	29 (22.8)	7 (5.5)	1 (0.8)	1 (0.8)	9 (7.1)
Prolonged cytopenia [1]	Not applicable [1]				
Haemophagocytic lymphohistiocytosis / macrophage activation syndrome	2 (1.6)	1 (0.8)	1 (0.8)	0	2 (1.6)
B cell aplasia and Hypogammaglobulinaemia	12 (9.4)	2 (1.6)	0	0	2 (1.6)
Severe infections	99 (78.0)	54 (42.5)	6 (4.7)	6 (4.7)	66 (52.0)
Tumour lysis syndrome	1 (0.8)	1 (0.8)	0	0	1 (0.8)
Graft-versus-host disease	(6.3)	4 (3.1)	0	1 (0.8)	5 (3.9)
Secondary malignancies [2]	3 (2.4)	1 (0.8)	0	1 (0.8)	2 (1.6)
Hypersensitivity reactions [3]	0	0	0	0	0
Antigenicity and immunogenicity [4]	Not applicable [4]				

COVID-19=coronavirus disease 2019; ELISpot=enzyme-linked immunosorbent spot.

[1] Based on laboratory data.

[2] Source table (AUTO1-AL1 CSR-Table 14.3.4.2.1) includes 2 patients with malignancies, however neither were considered as secondary malignancies.

[3] Note that output in source table (AUTO1-AL1 CSR-Table 14.3.4.2.1) does not include this event since none were reported.

[4] Based on ELISpot assay.

- Cytokine release syndrome:

A total of 87 patients (68.5%, 87/127) experienced CRS of any grade post obe-cel infusion (criteria for CRS per Lee et al, 2014[50]). Only 3 patients (2.4%, 3/127) experienced Grade 3 CRS; none experienced Grade 4 or 5. Of the 87 patients who experienced CRS, the majority (56/87) experienced this after the first but prior to the second infusion of obe-cel. The overall median duration of CRS was 5.0 days (range 1 to 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

[50] Lee, DW, Gardner R, Porter DL, et al. (2014). Current concepts in the diagnosis and management of cytokine release syndrome. Blood; 124(2):188-95.

their BM. The most common manifestations of CRS among patients who experienced CRS included fever (68.5%), hypotension (25.2%) and hypoxia (11.8%). Of the 87 patients who experienced CRS, for 64.3% CRS occurred after the first, but prior to the second infusion of Aucatzyl. The median time to onset of CRS after the first obe-cel infusion was 6.0 days (range: 1 - 10 days). The median time to onset of CRS after the second obe-cel infusion was 2.0 days (range: 1 - 14 days). The primary treatment for CRS was tocilizumab 75.9% (66/87), with 23% of patients also receiving corticosteroids (20/87) and 13.8% other anti-cytokine therapies (12/87).

A total of 7.9% (10/127) of patients experienced CRS as a SAE, although no deaths were due to CRS.

- Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS)

A total of 22.8% of patients (29/127) experienced ICANS of any grade. There were 7.1% (9/127) of patients who experienced ICANS of ≥ Grade 3 (7 patients with Grade 3 ICANS, 1 patient with Grade 4 ICANS, and 1 patient with Grade 5 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. Of those patients who experienced ICANS, the onset occurred for the majority (18/29) after the second infusion of obe-cel. The median time to onset of ICANS after the first obe-cel infusion was 12.0 days (range 1 to 31 days). The median duration of ICANS was 8.0 days (range 1 to 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%).

The majority of patients who experienced ICANS (24/29) received treatment for the event, with all receiving high-dose corticosteroids and half (12/24) receiving anti epileptics prophylactically; no patients experienced a seizure associated with ICANS.

A total of 9.4% of patients (12/127) experienced ICANS as a SAE, with 1 patient dying due to acute respiratory distress syndrome with ongoing ICANS.

- Prolonged Cytopenia

Prior to enrolment in the study, the last available laboratory result shows 34.6% of patients (44/127) had ≥ Grade 3 neutropenia, 33.9% of patients (43/127) had ≥ Grade 3 thrombocytopenia, and 13.4% of patients (17/127) had low haemoglobin (anaemia) of ≥ Grade 3. As expected after LD therapy, the last available laboratory result prior to obe-cel infusion showed that these percentages increased to 74.8% (95/127), 40.9% and (52/127) 40.2% (51/127) for ≥ Grade 3 neutropenia, thrombocytopenia and anaemia, respectively.

After obe-cel infusion, the median time to recovery (95% confidence interval [CI]) of neutrophils to ≥ 0.5×10^9/L in responders was 0.7 months (0.5, 0.9) and the Kaplan-Meier (KM) probability estimate of recovery was 100% by 5 months post obe-cel infusion. The median time to recovery (95% CI) of platelets to ≥ 50×10^9/L was 0.7 months (0.3, 1.7), and by 6 months post obe-cel infusion the KM probability estimate of recovery (95% CI) was 94.8% (88.5, 98.3).

The recovery profile of neutrophils and platelets in responders is reflected in the progressively lower percentage of patients with Grade 3 or 4 neutropenia or thrombocytopenia post obe-cel infusion:

- For neutropenia Grade 3 or 4: 59.2% (58/98), 23.5% (23/98), and 13.3% (13/98) at Day 28, Month 2, and Month 3, respectively.
- For thrombocytopenia Grade 3 or 4: 49.0% (48/98), 20.4% (20/98), and 11.2% (11/98) at Day 28, Month 2, and Month 3, respectively.

Beyond Month 3 post obe-cel infusion, no patient who achieved remission had neutropenia less than 1 × 10^9/L lasting for more than 6 months. Seven patients had thrombocytopenia lasting longer than 6 months without recovering to levels above 100 × 10^9/L. No bleeding events were reported in these 7 patients.

Median time to recovery for neutrophils for the entire Safety Set (including non-responders) to ≥ 0.5 × 10^9/L was consistent with the subgroup of responders only (0.8 months and 0.7 months, respectively). Median time to recovery for platelets to ≥ 50 × 10^9/L was longer compared to the subgroup of responders only (1.5 months and 0.7 months, respectively), however median time to recovery for platelets to ≥ 100 × 10^9/L was consistent (2.1 months and 2.0 months, respectively).

Among the safety set (N=127), median time from day of Aucatzyl infusion to neutrophil recovery to ≥ 0.5 × 109/L and ≥ 1 × 109/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%).

- Severe 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. As would be expected, the majority of infections occurred within 3 months of obe-cel infusion.

- Secondary malignancies

There is the potential for gene vector-related risks with obe-cel (risks of insertional mutagenesis and replication competent lentivirus [RCL]). Secondary malignancy could be caused by viral vectors involved in the transduction of lymphocytes for CAR T cell manufacturing resulting in the risk of insertional mutagenesis and genotoxicity. There have been three cases (3/127, 2.4%) in the FELIX study categorised as having potential secondary malignancies; these included 2 patients identified as of the 09-Jun-2023 data cutoff and one additional patient for whom a new potential secondary malignancy case was received on 11-Jan-2024 as a suspected unexpected serious adverse reaction

- one patient was a female initially diagnosed with B ALL post breast cancer therapy. On day 39 the patient experienced a grade 4 SAE of SPM (AML), the sponsor considered the case of AML not related due to a preexisting DNMT3A R882 mutations.
- One patient had received 3 previous lines of prior B cell treatments and experienced basal cell carcinoma post obe-cel infusion (more than a year and half after). The Investigator assessed the event of treatment related malignancy as not related to obe-cel. Previous immunosuppressants post-hematopoietic SCT and ongoing chronic GvHD provided a plausible alternative aetiology.
- One patient experienced an SAE of treatment related MDS. The patient's relevant medical history included an allogeneic SCT after cyclophosphamide and TBI-based myeloablative conditioning. At screening, the cytogenetic analysis revealed a complex karyotype. About

slightly less than a year and half after the 1st dose of obe-cel, the patient experienced MDS. The Investigator assessed the event of MDS as possibly related to obe-cel product and LD treatment. The Sponsor considered the event as unlikely related to obe-cel (due to previously cyclophosphamide and TBI-based myeloablative conditioning).

- Other significant safety topics

Other TEAEs that were evaluated as potential significant safety events following obe-cel treatment include HLH/macrophage activation syndrome (MAS), hypogammaglobulinemia, tumour lysis syndrome (TLS), graft-versus-host disease (GvHD), secondary malignancies, and hypersensitivity reactions.

There were low rates of haemophagocytic lymphohistiocytosis (HLH) / macrophage activation Syndrome(MAS) ≥ Grade 3 (2 patients, 1.6%). One patient (0.8%, 1/127) experienced Grade 3 HLH with onset at Day 22 post-infusion and although the patient recovered from HLH, the patient subsequently died due to progressive disease. The other patient experienced Grade 4 HLH with onset on Day 41 post-infusion and died due to sepsis with ongoing HLH that had not resolved.

As of the 07-Feb-2024 cut-off date, the TEAE of hypogammaglobulinemia has been reported in 9.4% of patients (12/127) at any grade and regardless of causality. Two patients (1.6%) experienced Grade 3 hypogammaglobulinemia.

There was 1 patient (0.8%, 1/127) who experienced TLS (Grade 3) which occurred post new anti-cancer therapy and is considered not related to obe-cel. A total of 7 patients (5.5%, 7/127) have reported GvHD post obe-cel infusion of which 6 had received prior SCT before entering the study.

Eight patients (6.3%, 8/127) have reported GvHD post obe-cel infusion, of which 6 received prior SCT. The 2 remaining patients received SCT post obe-cel treatment and subsequently experienced GvHD. Five patients (3.9%) were reported with Grade ≥ 3 GvHD.

Replication competent lentivirus (RCL) could be caused by a recombination event during vector production and may be pathogenic in humans. No cases of RCL have been identified in the FELIX study.

There are limited available data with obe-cel use in pregnant and breast-feeding women in the clinical setting and no reproductive and developmental toxicity animal studies have been conducted with obe-cel. It is not known if obe-cel has the potential to be transferred to the foetus. Based on the mechanism of action of obe-cel, if the transduced cells cross the placenta, they may cause fetal toxicity, including B cell lymphocytopenia. Therefore, obe-cel is not recommended for women who are pregnant and any patient who becomes pregnant after obe-cel infusion should discuss this with their treating physician. As of the cut-off date (07-Feb-2024) 1 patient has become pregnant while in the FELIX study, she underwent a Caesarean section, and a healthy male infant was delivered (weight 1.64 kg, Apgar score of 7 at 1 minute and 8 at 5 minutes). The infant initially exhibited respiratory distress and was admitted to the neonatal ICU for intubation. The infant was subsequently discharged.

2.6.8.3.3. Hospitalisation

During the FELIX study, all patients were hospitalised for obe-cel infusions for at least 10 days according to the study protocol requirements. The majority of patients (53.5%; 68/127) had a single hospitalisation following obe-cel infusion and so no re-admission. The median total duration of hospital stay (general hospitalisation and ICU stay) per patient following obe-cel infusion among all infused patients was 35 days (range: 8 to 169 days) including the 10-day mandated hospitalisation by protocol.

The majority of patients (85.0%, 108/127) did not require transfer to ICU following obe-cel infusion. A total of 19/127 (15.0%) patients had at least one admission to the ICU post obe-cel infusion with a median duration of ICU stay per patient of 5.0 days (range: 1 - 37 days). Across all admissions for these 19 patients, there were 7 patients where the primary reason was due to ICANS or CRS whereas 12 patients were admitted to ICU for TEAEs for other reasons. There were also 3 patients admitted for technical/social/practical reasons to allow an increase in the level of monitoring, and 1 patient (0.8%) with disease progression.

2.6.8.4. Laboratory findings

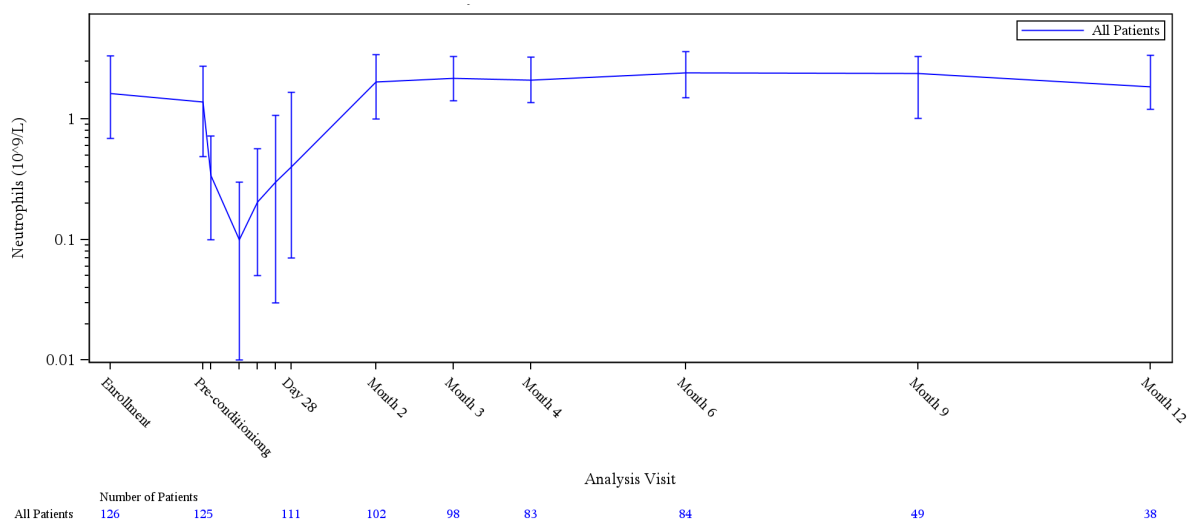
A summary of all common Grade 3 or 4 laboratory abnormalities per Common Terminology Criteria for Adverse Events (CTCAE) criteria (occurring in ≥ 10% of patients) is presented in **Table 33** below, with grading using the worst laboratory values post obe-cel infusion.

Table 33. Grade 3 or 4 laboratory abnormalities occurring in ⩾ 10% of patients after obe-cel infusion (safety set)

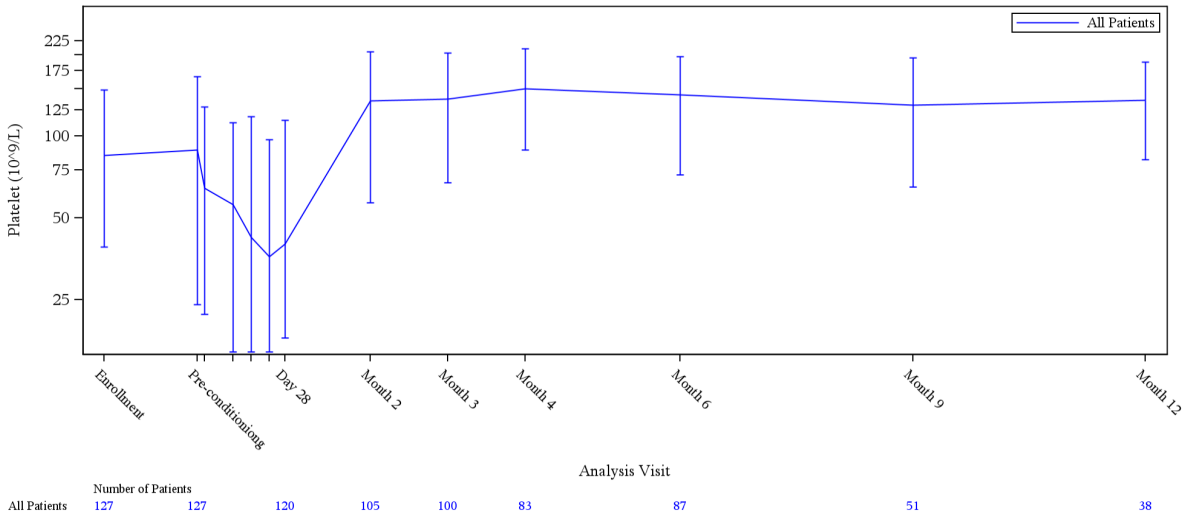
Laboratory Parameter	Infused (N=127) n (%)
Haemoglobin (g/L) (Decreased)	83 (65.4)
Lymphocytes (10^9/L) (Decreased)	121 (95.3)
Neutrophils (10^9/L) (Decreased)	125 (98.4)
Platelets (10^9/L) (Decreased)	98 (77.2)
Leukocytes (10^9/L) (Decreased)	124 (97.6)
Alanine Aminotransferase (U/L) (Increased)	13 (10.2)
Aspartate Aminotransferase (U/L) (Increased)	13 (10.2)

Percentage in the table were based on N. Grading was based on the worst case of all post-baseline visits within the time range, including non-scheduled visits of a patient.
Data cut-off: 07-Feb-2024

(A) Neutrophils



(B) Platelets



(C) Haemoglobin

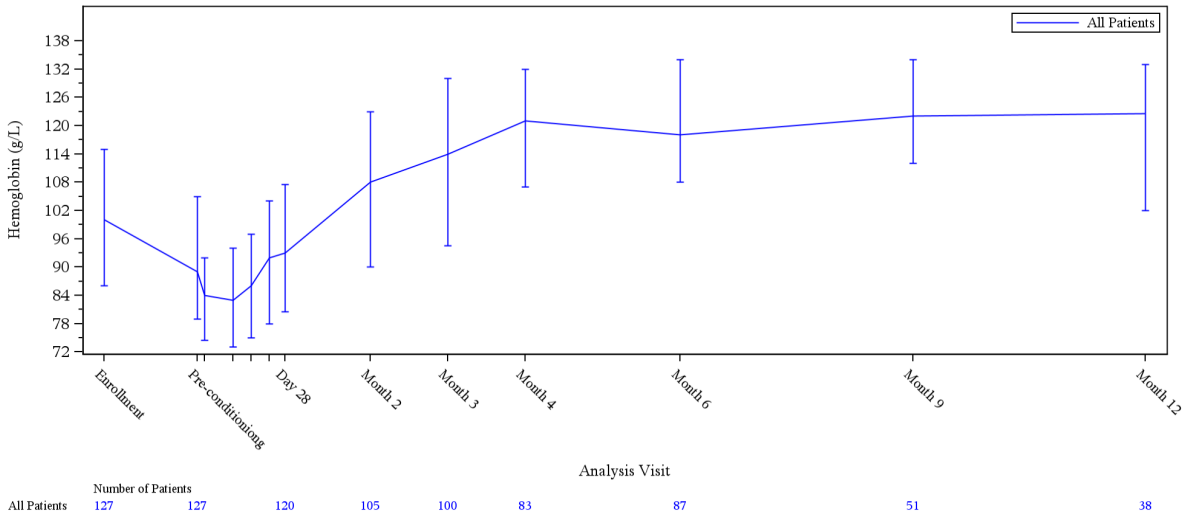


Figure 13. Median (Q1, Q3) Laboratory values over time to month 12 for (A) Neutrophil count; (B) Platelet count; (C) Haemoglobin concentration (Phase Ib and Phase II, Safety Set)

The most commonly reported, clinically significant, Grade 3 or 4 biochemistry laboratory events (≥ 5% of patients) post obe-cel treatment were related to liver function tests. These were alanine aminotransferase increased (10.2%, 13/127), aspartate aminotransferase increased (10.2%, 13/127) and bilirubin increased (6.3%, 8/127). Such findings are consistent with the treated B ALL population which included patients with high tumour burden and liver EMD.

2.6.8.5. Safety in special populations

Age

A generally similar safety profile was observed across 3 age groups (≥ 18 to < 40, ≥ 40 to < 65, and ≥ 65 years of age) (see **Table 34** below). Of note, the 25 patients in the ≥ 65 years group were mostly in the 65-< 75 years range, with only 4 people older than 75 years. The rates of CRS (any grade and ≥ Grade 3) were similar between patients ≥ 65 years of age and the younger population. Any grade and ≥ Grade 3 ICANS were more frequently reported in patients ≥ 65 years of age than in

the younger population, which can be expected considering the general health and the comorbidities in the older patient population.

Table 34. Treatment-emergent adverse events any time post obe-cel infusion by age group (phase Ib and phase II, safety set)

Parameter	≥ 18 to < 40 years (N=48) n (%)	≥ 40 to < 65 years (N=54) n (%)	≥ 65 years* (N=25) n (%)	Total (N=127) n (%)
Any TEAE	48 (100)	54 (100)	25 (100)	127 (100)
≥ Grade 3 TEAE	34 (70.8)	51 (94.4)	19 (76.0)	104 (81.9)
Any obe-cel-related TEAE	44 (91.7)	53 (98.1)	22 (88.0)	119 (93.7)
≥ Grade 3 obe-cel-related TEAE	25 (52.1)	37 (68.5)	15 (60.0)	77 (60.6)
Any serious TEAE	28 (58.3)	36 (66.7)	19 (76.0)	83 (65.4)
Obe-cel-related serious TEAE	17 (35.4)	20 (37.0)	13 (52.0)	50 (39.4)
Any grade CRS	30 (62.5)	39 (72.2)	18 (72.0)	87 (68.5)
≥ Grade 3 CRS	2 (4.2)	0	1 (4.0)	3 (2.4)
Any grade ICANS	8 (16.7)	9 (16.7)	12 (48.0)	29 (22.8)
≥ Grade 3 ICANS	4 (8.3)	1 (1.9)	4 (16.0)	9 (7.1)

CRS=cytokine release syndrome; ICANS=immune effector cell-associated neurotoxicity syndrome; TEAE=treatment-emergent adverse event. *only 4 patients were older than 75 year.

In view of the restricted indication data on young adult patients 18-25 year of age versus the total population have been provided.

Table 35. Treatment-emergent adverse events any time post obe-cel infusion in those 18-25 years of age (phase Ib and phase II, safety set)

Parameter	≥ 18 to < 25 years (N=14) n (%)	Total (N=127) n (%)
Any TEAE	14 (100)	127 (100)
≥ Grade 3 TEAE	10 (71.4)	104 (81.9)
Any obe-cel-related TEAE	12 (85.7)	119 (93.7)
≥ Grade 3 obe-cel-related TEAE	8 (57.1)	77 (60.6)
Any serious TEAE	8 (57.1)	83 (65.4)
Obe-cel-related serious TEAE	5 (35.7)	50 (39.4)
Any grade CRS	8 (57.1)	87 (68.5)
≥ Grade 3 CRS	0	3 (2.4)
Any grade ICANS	1 (7.1)	29 (22.8)
≥ Grade 3 ICANS	1 (7.1)	9 (7.1)

CRS=cytokine release syndrome; ICANS=immune effector cell-associated neurotoxicity syndrome; TEAE=treatment-emergent adverse event.

Disease burden:

The evaluation of the impact of disease burden at time of LD on CRS and ICANS highlighted that a higher percentage of blasts tended to result in a higher risk of CRS/ICANS. Across the 4 subgroups of < 5%, ≥ 5% to ≤ 20%, > 20% to ≤ 75%, and > 75% blasts in BM, the percentage of patients with CRS of any grade was 47.2%, 62.5%, 71.4% and 87.5%, respectively. The percentage of patients with ≥ Grade 3 CRS was not increased with blast counts but only limited cases were evaluable. The

percentage of patients experiencing ICANS (any grade) was 8.3%, 25.0%, 14.3% and 42.5% in the < 5%, ≥ 5% to ≤ 20%, > 20% to ≤ 75% and > 75% blast in BM subgroups, respectively.

2.6.8.6. Immunological events

The cellular immunogenicity data from patients infused with obe-cel (samples available from 96 patients) showed 3 patients (3.1%, 3/96) with a positive immunogenicity test at approximately 3 months after obe-cel infusion, and no safety events likely to be related to the cellular immunogenicity signal were identified. Regarding humoral immunogenicity data, 11/127 (8.7%) patients tested positive for humoral immunogenicity at baseline, and 2/127 (1.6%) patients were positive at Month 3 post-infusion while being negative at baseline. These 2 patients developed post-infusion CRS on day 10 with resolution within 4 days of these events appeared not related to the ADA positivity signal.

2.6.8.7. Safety related to drug-drug interactions and other interactions

No formal drug interaction studies have been conducted. Nevertheless section 4.5. states the following;

1. 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).

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

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.

2.6.8.8. Discontinuation due to adverse events

In contrast to other CAR T cells, the second dose of obe-cel can be withheld. There were 7 patients who did not receive their second dose in the Safety set. Seven patients did not receive the second infusion due to AE (n=3), PD (n=2), death (n=1) or manufacturing issue (n=1). Reasons for not receiving the second dose included AEs in 3 patients (Grade 3 CRS in 1 patient and Grade 3 ICANS in 2 patients).

2.6.8.9. Supportive safety data

- **ALLCAR19**

ALLCAR19 (NCT02935257) is an academia-led Phase 1 proof-of-concept single-arm, open-label study. Patients with lower (≤ 20% BM blasts) and higher (> 20% BM blasts) disease burden prior to LD were infused using the split dosing as already described for the FELIX study. A total of 20 adult patients with high risk, r/r B ALL were treated with obe-cel that used earlier manufacturing processes. The effect of this manufacturing change on the safety parameters has not been discussed.

The presented results are based on publications by Roddie et al. (*Roddie et al, 2021*[51], *Roddie et al, 2023*[52]), with a median follow-up of 36 months (range 24 to 47 months). The applicant concludes that no new safety signals are reported. Of note, no CSR is available thus assessment of the results is not feasible.

- **Indirect comparison studies**

Obe-cel Versus Standard of Care (Non-CAR T cell Therapy)

The applicant performed a Prospectively Designed Non-interventional Study to Compare Obe-cel, a CAR T Cell Treatment Targeting CD19, with an External Control Arm (ECA) in Adult Patients with Relapsed or Refractory B Cell Acute Lymphoblastic Leukaemia (R/R B All). This was a prospectively designed, non-interventional study utilizing data from the FELIX study Cohort IIA and patient-level data from historical clinical trials (HCT) in r/r B-ALL contained within the database. The safety analyses were performed using the after matching safety analysis set (FELIX N = 84 and ECA 1 N = 84). For the FELIX investigational arm patients, the reporting period of TEAE and SAE is from the infusion of obe-cel up to the primary analysis data cutoff or the date of any non-protocol specified anticancer therapy (including HSCT), whichever earlier. Importantly this comparison excludes the bridging and lymphodepletion necessary before CAR T cell infusion. For HCT patients, the reporting window of TEAE and SAE starts on or after the first dose of SOC treatment to end of study, or the date of any non-protocol specified anticancer therapy (including HSCT), whichever was the earliest. In the external control arm (ECA 1 arm), the SoC treatments received by the matched patients included blinatumomab (71/84, 84.5%), inotuzumab ozogamicin (1/84, 1.2%) and standard chemotherapy (12/84, 14.3%) thus not representative of the prior treatment of the FELIX cohort (more than half of the patients enrolled in FELIX had been previously treated with blinatumomab or inotuzumab ozogamicin).

Post obe-cel, the proportion of patients with TEAEs (any grade) as well as any Grade 3 or higher TEAE were similar between FELIX patients and ECA 1. The percentage of patients with at least 1 SAE was higher in FELIX compared to ECA 1, both for any grade (63.1% versus 44.0%) and ≥ Grade 3 (51.2% vs 40.5%). There were fewer early deaths (within 30 days and within 3 months of treatment start date) and overall death events in FELIX compared to ECA 1 (42.9% versus 60.7%), longer follow-up of safety was not investigated. The most common TEAE within 3 months after treatment start, were expected based on the different mode of action of CAR-T cell therapy. As expected, based on the different mode of action of CAR T cell therapy, the rate of any grade CRS was higher following obe-cel treatment in the FELIX study compared to the ECA 1 (76.2% versus 26.2%), but the proportion of patients with ≥ Grade 3 CRS was the same as that in ECA 1 (3.6% versus 3.6%). With respect to neurological AEs, specifically immune-mediated neurotoxicity, it is not known whether the criteria were similar between FELIX and ECA 1.

Obe-cel Versus Brexucabtagene Autoleucel

Study 3964a was a prospectively designed, non-interventional study using MAIC methods for the comparison of obe-cel (FELIX) with its identified comparator, the CAR T cell therapy brexu-cel (ZUMA-3; based on Shah et al. (2021[53] and 2022[54])). The comparison only included patients over 25 years, in line with the approved indication for brexu-cel. With respect to neurological AEs, specifically immune-

[51] Roddie C, Dias J, O'Reilly MA, et al (2021). Durable Responses and Low Toxicity After Fast Off-Rate CD19 Chimeric Antigen Receptor-T Therapy in Adults With Relapsed or Refractory B-Cell Acute Lymphoblastic Leukemia. J Clin Oncol; 39(30):3352-3363.
[52] Roddie C, Dias J, O'Reilly M, et al (2023). Long-Term Follow-up of AUTO1, a Fast-Off Rate CD19 CAR, in Relapsed/Refractory B-Cell Acute Lymphoblastic Leukemia and Factors Associated with Durable Response. Poster presented at: American Society for Transplantation and Cellular Therapy Meeting, Feb 15-19, 2023, Orlando, Florida, USA.
[53] Shah BD, Bishop MR, Oluwole OO, et al (2021). KTE-X19 anti-CD19 CAR T-cell therapy in adult relapsed/refractory acute lymphoblastic leukemia: ZUMA-3 phase 1 results. Blood; 138(1):11-22
[54] Shah BD, Cassaday RD, Park JH, et al (2023). Impact of prior therapies and subsequent transplantation on outcomes in adult patients with relapsed or refractory B-cell acute lymphoblastic leukemia treated with brexucabtagene autoleucel in ZUMA-3. J Immunother Cancer; 11(8):e007118.

mediated neurotoxicity, the criteria were similar between ZUMA-3 and FELIX despite the ICANS consensus grading used in FELIX Cohort IIA (Lee et al, 2019[55]) being developed after the ZUMA-3 study. However, in addition, comparison of AEs in the nervous system or psychiatric disorders SOCs was also used as a supportive analysis. Cytopenia's, hypogammaglobulinemia and infections could not be compared due to the lack of detailed laboratory results from ZUMA-3 or lack of harmonisation of reporting across the studies. Odds ratios (ORs) were calculated using a weighted logistic regression model to compare the occurrence of AEs between obe-cel and brexu-cel for CRS, immune-mediated neurotoxicity, and nervous system/psychiatric disorders. An OR of < 1 suggests a reduced chance of the event occurring following obe-cel treatment relative to brexu-cel, with statistical significance achieved if the 95% CI of the OR does not cross 1 for the relevant base case analysis (weighted logistic regression model with robust standard error [SE]).

The results suggest decreased odds for obe-cel versus brexu-cel for ≥ Grade 3 CRS, any grade and ≥ Grade 3 immune-mediated neurotoxicity AEs as well as ≥ Grade 3 for obe-cel versus brexu-cel (**Table 36**).

Table 36. Odds ratios for safety endpoints – Obe-cel (FELIX Cohort IIA) versus Brexucabtagene Autoleucel (ZUMA-3)

Method	OR (95% CI) Any Grade mITT (Infused) ESS=38.0	OR (95% CI) ≥3 Grade mITT (Infused) ESS=38.0
Odds Ratio for Cytokine Release Syndrome		
OR (95% CI) from weighted logistic regression model (robust SE)	0.618 (0.207 to 1.845)	0.126 (0.029 to 0.542)
Odds Ratio for Immune-Mediated Neurotoxicity Adverse Events		
OR (95% CI) from weighted logistic regression model (robust SE)	0.245 (0.101 to 0.594)	0.231 (0.078 to 0.683)
Odds Ratio for Adverse Events in Nervous System or Psychiatric Disorder SOCs		
OR (95% CI) from weighted logistic regression model (robust SE)	0.517 (0.178 to 1.496)	0.374 (0.143 to 0.980)

CI=confidence interval; ESS=effective sample size; mITT=modified intent-to-treat; OR=odds ratio; SE=standard error.
OR < 1 is favourable for obe-cel and indicates lower odds of event. Results are considered statistically significant if the 95% CI does not include 1.
Data are based on Scenario 2, matched on characteristics identified as prognostic for any endpoint.

2.6.8.10. Post marketing experience

Not applicable, obe-cel is not commercialised in any region.

2.6.9. Discussion on clinical safety

The safety database for this application is derived from the single arm FELIX study (phase 1b and phase II) using the commercial manufacturing process and consisted of 127 patients with R/R B ALL. This is supported by an academia-led study (ALLCAR19; with an earlier manufacturing process) and 2 indirect comparison studies AUTO-1 EC1 (Prospective, non-interventional study comparing FELIX Cohort IIA to standard of care) and 3964a (Matching-adjusted patients from FELIX Cohort IIA and patients receiving brexu-cel). The safety focuses on all patients infused with at least one dose of obe-cel from all cohorts and phases of the study as of the data cut-off 07-Feb-2024. The median duration of follow-up for the safety set from first obe-cel infusion to the DCO was 21.45 months (range: 8.6-

[55] Lee DW, Santomasso BD, Locke FL, et al (2019). ASTCT Consensus Grading for Cytokine Release Syndrome and Neurologic Toxicity Associated with Immune Effector Cells. Biol Blood Marrow Transplant; 25(4):625-638

41.4 months). In total, the number of evaluable subjects is limited (n=127) in order to assess AE that occur less frequent, and the comparative safety assessment is hampered by the single arm trial design.

The median time from leukapheresis (vein) to release of the product (certification) was 20 days (range: 17 - 49 days) across the 31 clinical sites. The majority (92.9%) of patients received bridging therapy, with chemotherapy being the most used. All 127 patients (100%) received LD therapy prior to obe-cel infusion with fludarabine and cyclophosphamide. In contrast to commercially available CAR T cells, obe-cel is administered according to a split-dose regimen in order to manage the safety concerns associated with CAR T cells (CRS, ICANS). Overall, the median dose of obe-cel administered was the target dose of 410×10^6 CD19 CAR-positive T cells, administered in 91.3% of subjects. Seven patients (5.5%) did not receive their second infusion of obe-cel due to AE (n=3), PD (n=2), death (n=1) or manufacturing issue (n=1). A delay in the administration of the second dose, after the protocol pre-specified Day 10 ± 2 days (range: Day 13 - Day 21) occurred in 9 patients (7,0%) due to the occurrence of AE. This illustrates the added value for management of AEs due to the split dosing.

Treatment with obe-cel is associated with a high number of AE/ADR which are in part due to the conditioning regimen, cytotoxic pretreatment and underlying disease (e.g. anaemia, neutropenia, febrile neutropenia, nausea). The applicant does not report the AEs due to conditioning regimen separately but per treatment phase (e.g. pre obe-cel and post obe-cel).

The adverse events related to obe-cel are in line with that observed with other CAR T cells such as CRS, ICANS and AEs from the SOC blood and lymphatic system disorders. Most TEAEs occurred within 3 months after obe-cel infusion.

AEs of special interest were in line with those reported for other CD19 CAR T cell products. Cytokine release syndrome (CRS) was observed in approximately 69% of the subjects but mainly consisted of grade 1, 2 (2.4% grade 3) with a time to onset of 8 days thus mainly occurring after the first dose of obe-cel and prior to the second dose (65% of the subjects). Although the split dosing regimen could have led to a decreased incidence and severity of CSR it cannot be excluded that practitioners gained experience in management of CRS and as such CRS is likely more adequately managed compared to prior CD19 CAR T cell pivotal studies.

ICANS was reported in 23% of the subjects with 7.1% of patients (9/127) ICANS of ≥ Grade 3. The time to onset of ICANS was longer than for CRS with 12.0 days (range 1 to 31 days) thus in contrast to CRS, the majority was reported after the second dose of obe-cel (62%) and 19% received a treatment for ICANS (anti-epileptics or corticosteroids).

The FELIX study enrolled a heavily pre-treated population, including a large proportion of patients having received previous allogeneic SCT (44.1%). This could have result in reduced BM reserve in transplanted patients impacting the ability to reach normal blood counts. Moreover, cytopenias and infections are an expected AE from the underlying disease, cytotoxic pre-treatment and the conditioning chemotherapy. A large proportion of the subjects (app. 35%) had a grade 3 or higher cytopenia at enrolment which is illustrative of the underlying disease. Recovery post obe-cel treatment was generally fast for neutrophils ($\geq 0.5 \times 10^9$/L) and platelets ($\geq 50 \times 10^9$/L) (median time to recovery in responders was 0.7 months). There was no apparent increase in the risk for bleeding associated with obe-cel in infused patients.

In the FELIX study, 52% of patients developed severe infections ≥ Grade 3 (sepsis, pneumonia); the majority of infections were related to unspecified pathogens (34.9%), viral (33.1%) and 26% bacterial infections and occurred within the first 3 months after obe-cel infusion. The contribution of COVID infections was limited. Although the rate of severe infections is considered high, fatal infections

occurred in only 5 cases due to sepsis (2 patients), neutropenic sepsis (2 patients) and abdominal infection (1 patient) of which 1 case was considered possibly related.

High risk of infection is known from pretreatment, underlying disease, and the CAR T cell treatment in general. It appears that infections were not related to neutrophil recovery but rather to low IgG status. B cell aplasia (defined as absolute numbers of B-cells < 20 cells/µL) was observed in most patients and hypogammaglobulinemia was reported in 12 subjects (9.4%; all grade). Two patients (1.6%%, 2/127) experienced Grade 3 hypogammaglobulinemia. Beyond day 90, 46 patients (36.2%) experienced any grade infection, including 35 patients (27.6%) who experienced ≥ Grade 3 infection, most infections were of viral origin.

Sepsis (including neutropenic sepsis) was one of the most frequently reported SAEs (5.5%) and fatal AE (3.1%) with obe-cel. Because of overlapping clinical presentations, HLH should be included in the differential diagnosis for patients who develop a sepsis-like syndrome. Considering the seriousness of the condition of sepsis and taking into account the potential causal relationship between obe-cel and sepsis, sepsis has been included as a separate ADR (separated from "infections – pathogen unspecified") in the ADR table in SmPC section 4.8.

Recently, several cases of T cell leukaemia have been reported post marketing for registered CAR T cels (FDA, 2023; EMA, 2024) which has led to additional warning and precautions for all CAR T cells. SPM was observed in 3 patients, not considered related. Nevertheless, the same level of pharmacovigilance as for the other CAR-T cell has been implemented in the SmPC and in the RMP for Aucatzyl and a monitoring of such adverse event is actively requested to collect necessary information on any possible further case. A study to collect information on T cell and other haematological malignancies has been included among the additional pharmacovigilance activities of the RMP and instruction on activities to adopt for observed secondary malignancies in CAR-T treated patients have been implemented.

A generally similar safety profile was observed across 3 age groups (≥ 18 to < 40, ≥ 40 to < 65, and ≥ 65 years of age. The rates of CRS (any grade and ≥ Grade 3) were similar between age groups, any grade and ≥ Grade 3 ICANS were more frequently reported in elderly patients (≥ 65 years) than in the younger population, which can be expected considering the general health and the comorbidities in the older patient population.

Furthermore, in the context of the requested conditional marketing authorisation it has to be considered that Tisa-cel (Kymriah) is a fully authorised product with a similar mechanism of action. A Major therapeutic advantage (MTA) over tisa-cel (Kymriah) for the population of young adults (18-25 y/o) was not demonstrated in this overlapping population. In this frame, the applicant has also performed a subgroup analysis for patients 18-25 years of age versus the total population. In general, similar frequencies for any TEAE, CRS and ICANS and grade 3 or higher TEAE were observed. While the rationale for reduced immunotoxicity with obe-cel is understood and the split dosing regimen is a promising tool, there are too many uncertainties preventing any firm conclusions. An MTA of obe-cel over tisa-cel based on improved safety is not considered demonstrated. Therefore, the indication was amended to exclude the patient population of 18-25 years old, thus specifying "treatment of adult patients 26 years of age and above".

For disease burden, as assessed by blasts in BM at LD, a higher percentage tended to result in a higher risk of CRS and ICANS, being highest in the subgroup with > 75% blasts but this difference was not seen with the 20% cut-off, thus this supports the adapted dosing regimen (lower first dose) for patients with 20% blast counts. Alternative dosing regimens to further minimise the risk for CRS and ICANS were not explored and as such cannot be recommended. The expected risk of developing ≥ Grade 3 CRS and ≥ Grade 3 ICANS after the split dose of obe-cel was low. Additionally, the split

dosing regimen provides an advantage in case of immediate toxicity (CRS) due to the possibility to withhold or discontinue the second dose.

In the FELIX study, the number of patients with positive immunogenicity tests at 3 months after obe-cel infusion was low (3.1% for cellular immunogenicity and 1.6% had treatment induced ADA) and the reported cases all achieved a best overall response of CR or CRi.

The applicant provides 2 supportive studies (AUTO1-EC1 and MAIC analysis 3964a) in order to contextualise the safety results from the single arm trials performed with obe-cel. This comparison is considered of limited value as several methodological issues inherent to indirect comparisons (e.g. changing treatment landscape within the historical cohort) but also of importance is that the comparison for CAR T cell did not take into account the pretreatment (bridging and lymphodepletion) which is an integrative part of this immunological treatment.

From the safety database all the relevant adverse reactions reported in clinical trials have been included in the Summary of Product Characteristics.

Additional safety data needed in the context of a conditional MA

Long term safety follow-up in the FELIX study is limited, preventing the detection of AEs emerging later in time such as secondary malignancies, gene vector risks and hypogammaglobulinemia. Post authorisation the applicant should submit the results of the extension of follow-up for 15 years post initial obe-cel infusion from the FELIX study (AUTO-LT1) and long-term safety and effectiveness data of obe-cel in adult patients with r/r B ALL, from a prospective, non-interventional post-authorisation safety study (AUTO1-LT2).

The CHMP endorses the CAT discussion on clinical safety as described above.

2.6.10. Conclusions on the clinical safety

In general, the safety profile of obe-cel consists of adverse drug reactions known from the underlying disease and other CD19 CAR T -cell products with CRS, ICANS, leukopenia, and infections as main contributors. Overall Aucatzyl is approvable based on the safety profile described.

The CAT considers the following measures necessary to address the missing safety data in the context of a conditional MA:

- 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. (Due date 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 characterise the long-term safety and efficacy of Aucatzyl, according to an agreed protocol. (due date 31 July 2030)

The CAT considers the following measures necessary to address issues related to safety:

- 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. (due date 30 June 2039)

- Non-Interventional Post-Authorisation Safety Study: 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 prospective study based on data from a registry. (due date 30 June 2045)

The CHMP endorses the CAT conclusion on clinical safety as described above.

2.7. Risk Management Plan

2.7.1. Safety concerns

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

2.7.2. Pharmacovigilance plan

Study/ Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorisation				
Prospective study to assess long-term safety and efficacy of adult patients with relapsed or refractory B cell acute lymphoblastic	Primary objective: To further characterize the long-term safety of Aucatzyl in adult patients with relapse or refractory B cell precursor acute lymphoblastic leukaemia. Furthermore, to evaluate the rate and severity (where applicable and including CRS and ICANS) of the following adverse events:	– CRS including HLH/MAS – ICANS – Prolonged Cytopenias – Hypogammaglobulinaemia – Clinically significant infections – Secondary malignancies	Final protocol submission in EU Registration in the EU PASS register	Within 3 months of marketing authorisation Within 2 weeks of protocol approval

Study/ Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
leukaemia receiving Aucatzyl treatment (AUTO1-LT2), based on data from a registry AUTO1-LT2 Planned	– Cytokine release syndrome (CRS), including Hemophagocytic Lymphohistiocytosis (HLH)/ Macrophage Activation Syndrome (MAS) – Immune effector cell-associated neurotoxicity syndrome (ICANS) – Prolonged cytopenia – Hypogammaglobulinemia – Clinically significant infections – Secondary malignancies – Other neurologic toxicities – Tumor lysis syndrome (TLS) – Immunogenicity, defined as hypersensitivity reactions – Aggravation of graft versus host disease (GvHD) – New occurrence of an autoimmune disorder – Overdose – Other safety concerns not yet identified in the clinical program – To evaluate pregnancy outcomes. Secondary objectives: The secondary objectives of this study are to describe the effectiveness of AUCATZYL as well as further characterising safety in the real-world setting. Effectiveness: – To evaluate the effectiveness of AUCATZYL in terms of overall remission rate (ORR). – To determine the duration of response (DOR) post-AUCATZYL administration. – To determine the Real-world event-free survival (rwEFS) post-AUCATZYL treatment. – To determine the overall survival (OS) post-AUCATZYL treatment. – To determine rate and outcomes after subsequent allogeneic hematopoietic cell transplantation.	– Other neurologic toxicities – Tumour Lysis Syndrome – Immunogenicity, defined as hypersensitivity reaction – Aggravation of Graft Versus Host Disease – New occurrence of an autoimmune disorder Overdose – Other safety concerns not yet identified in the clinical programme – Use during pregnancy	Start of data collection in US Start of data collection in EU End of data collection Annual report (safety, effectiveness interim analysis progress report) Study Completion Final study report	30-Jun-2025 31-Dec-2025 30-Jun-2043 Annual report for first 5 years, followed by report once every 2 years 30-Jun-2044 30-Jun-2045

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

2.7.3. Risk minimisation measures

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Cytokine Release Syndrome including HLH/MAS	Routine risk minimisation measures: SmPC sections 4.2, 4.4, 4.8 and corresponding PL sections 2, 4	Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection: None

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

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

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Long-term safety	Routine risk minimisation measures: SmPC section 4.4 and corresponding PL section 2 Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection: None Additional pharmacovigilance activities: 1. AUTO1-LT2 long-term study for post-approval patients. 2. AUTO-LT1 long-term follow-up study for clinical trial patients.
New occurrence or exacerbation of an autoimmune disorder	Routine risk minimisation measures: None Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection: None Additional pharmacovigilance activities: 1. AUTO1-LT2 long-term study for post-approval patients. 2. AUTO-LT1 long-term follow-up study for clinical trial patients.

2.7.4. Conclusion

The CAT considers that the risk management plan version 1.0 is acceptable.

The CHMP endorses the CAT conclusion on the RMP as described above.

2.8. Pharmacovigilance

2.8.1. Pharmacovigilance system

The CHMP and CAT considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

2.8.2. Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the Annex II, Section C of the CHMP Opinion. The applicant did request alignment of the PSUR cycle with the international birth date (IBD). The IBD is 08 November 2024. The new EURD list entry will therefore use the IBD to determine the forthcoming data lock points.

2.9. Product information

2.9.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

2.9.2. Labelling exemptions

A request to omit certain particulars from the labelling as per Art.63(3) of Directive 2001/83/EC has

been submitted by the applicant and has been found acceptable by the QRD Group for the following reasons:

The QRD Group agreed to use minimum particulars on the immediate packaging labelling (infusion bags) in accordance to Article 63(3) of Directive 2001/83/EC. With regard to the inclusion of a dose schedule planner in the package, the QRD Group agreed on the principle of the acceptance of a dose schedule planner, however it was highlighted during the discussion that it should be provided in the national language.

The particulars to be omitted as per the QRD Group decision described above will however be included in the Annexes published with the EPAR on EMA website, and translated in all languages but will appear grey-shaded to show that they will not be included in the printed materials.

A request for translation exemption of the labelling as per Art.63(1) of Directive 2001/83/EC has been submitted by the applicant and has been found acceptable by the QRD Group for the following reasons:

The QRD Group agreed to the use of English language only for the labelling components of Aucatzyl (inner and outer labels) in accordance to Article 63(1) of Directive 2001/83/EC.

The labelling components subject to translation exemption as per the QRD Group decision above will however be translated in all EU official languages in the Annexes published with the EPAR on EMA website, but the printed materials will only be provided in the English language as agreed by the QRD Group.

2.9.3. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Aucatzyl (Obecabtagene autoleucel) is included in the additional monitoring list as

- it contains a new active substance which, on 1 January 2011, was not contained in any medicinal product authorised in the EU
- It has a PASS imposed
- It is approved under a conditional marketing authorisation [REG Art 14-a]

Therefore, the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

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).

3.1.2. Available therapies and unmet medical need

Patients with B ALL who have relapsed or are refractory to the initial treatment receive second-line therapy (immunotherapy or TKI-immunotherapy with or without chemotherapy) with the goal to achieve a second CR/CRi, followed by allo-SCT or CAR-T. However, only a small number of patients in this setting are eligible for SCT; moreover, SCT is in itself associated with severe morbidity and significant mortality, even for the fraction of patients who are eligible and good candidates for allogeneic SCT.

Available therapeutic treatment options in this clinical setting include: blinatumomab (Blincyto) which is a CD3/CD19-targeted bispecific T cell engager associated with CRS and neurotoxicity; inotuzumab ozogamicin (Besponsa) which is an antibody-drug conjugate associated with hepatotoxicity; authorised CAR T cells are tisagenlecleucel (tisa-cel, Kymriah) for the treatment of B-cell ALL that is refractory, in relapse post-transplant or in second or later in pediatric and young adult patients up to and including 25 years of age and brexucabtagene autoleucel (brexu-cel, Tecartus) for the treatment of adult patients 26 years of age and above with relapsed or refractory B-cell precursor ALL. Toxicity of CAR T therapy includes immunotoxicity (CRS and ICANS) which varies according to the CAR T trial and product, and it is also dependent on pretreatment disease burden. Longer-term follow-up data suggest that 40%-60% of patients will relapse within the first year after CAR-T therapy *(Hoelzer et al, 2023*[56]*)*. Therefore, there remains an unmet medical need for a therapy with a durable efficacy while minimizing side effects in patients with r/r B ALL.

3.1.3. Main clinical studies

The clinical package of obe-cel was primarily supported by data from the multi-centre, single arm, open label Phase Ib/II FELIX trial. Phase Ib was designed to assess the feasibility of manufacturing and dosing obe-cel in a multi-centre setting and provide data to enable initiation of the pivotal phase II of the study. The pivotal Phase II included three B ALL disease cohorts (A/B/C). Efficacy is mainly based on the Phase II portion of Cohort A who enrolled patients with morphological disease at screening (≥ 5% blasts in the BM at screening, Cohort IIA, n=94) while the safety set consists of all infused patients from the FELIX study (n=127). Obe-cel was administered in a split dose based on disease burden (bone marrow blast counts).

3.2. Favourable effects

In Cohort IIA of the FELIX study, 113 patients underwent leukapheresis (leukapheresed set), and 94 patients received obe-cel treatment. The baseline data reflect a heterogenous r/r ALL population, in line with the sought indication. The primary endpoint was ORR (defined as proportion of patients who received obe-cel treatment achieving CR or CRi) and at the time of the data cut-off (07-Feb-2024) the ORR was 76.6% (95% CI: 66.7, 84.7) in patients who received at least 1 infusion of obe-cel and 63.7% (95% CI: 54.1, 72.6) for the leukapheresed set. The CR rate was 55.3% (95% CI: 44.7, 65.6) in patients who received at least 1 infusion of obe-cel and 48.7% (95% CI: 39.2, 58.3) for the leukapheresed set.

At the DCO of 07-Feb-2024, with a median follow-up of 20.25 months, the median DOR was 14.06 months (95% CI: 8.18, NE). Obe-cel is the first CAR T product that is administered according to a split dose. The time to response and time to peak were in line with results for CAR T products using a single dose.

[56] Hoelzer D, Bassan R, Boissel N, et al (2023). ESMO Clinical Practice Guideline interim update on the use of targeted therapy in acute lymphoblastic leukaemia. Ann Oncol. 2024 Jan;35(1):15-28.

3.3. Uncertainties and limitations about favourable effects

Efficacy is based on a single uncontrolled pivotal trial with a small sample size resulting in uncertainty about the efficacy and the duration of effects. Nevertheless, the compelling ORR results considered together with the data on duration of response capture an anti-cancer activity which is considered to provide proof of clinical relevance of the treatment. To further characterize long-term data on the effectiveness of treatment, data are expected from the imposed clinical studies as per the specific obligations imposed in the frame of the approved conditional marketing authorisation and long-term safety and efficacy study imposed as conditions to the MA in general.

Time-to event outcomes (e.g. EFS, OS) are considered unreliable in a single arm trial design and have not been considered in the definition of the final B/R at this stage.

The data provided in support of the split dose regimen remain limited and there is a trend in differential treatment outcomes in terms of duration of remission (DOR) in patients depending on the chosen fractionation of obe-cel for low and high disease burden and the time interval between the two doses. Therefore, uncertainty remains as regards the longer-term efficacy outcomes overall and by dosing regimen in two subpopulations (with lower and higher tumour burden).

The included population is small and heterogeneous; therefore it is possible that there are subgroups for which the estimated effect is not applicable. Furthermore, relevant differences in terms of treatment effect across clinically meaningful subgroups cannot be excluded.

3.4. Unfavourable effects

As of the cut-off date of 07-Feb-2024, 81.9% (104/127) of patients experienced TEAEs of ≥ Grade 3 and 60.6% (77/127) experienced at least one serious TEAE (any grade). Any serious TEAEs suspected to be related to obe-cel occurred in 39.4% of patients (50/127), with 31.5% (40/127) grade 3 or higher.

The most common TEAE was CRS (68.5%; 87/127), of which 2.4% (3/127) experienced CRS of ≥ Grade 3. Time to onset of CRS was 8 days (range: 1 to 23 days), thus mainly occurring after the first dose of obe-cel and prior to the second dose (64% of the subjects). ICANS was reported in 22.8% (29/127) of patients, with 7.1% (9/127) ICANS of ≥ Grade 3. The time to onset of ICANS was longer than for CRS with 12 days (range 1 to 31 days). Thus, in contrast to CRS, the majority was reported after the second dose of obe-cel (62%). In total 19% received a treatment for ICANS (anti-epileptics or corticosteroids).

The most common individual AEs (≥ 10% of patients) of ≥ Grade 3 were febrile neutropenia (23.6%), anaemia and neutropenia (20.5% each), neutrophil count decreased (19.7%), platelet count decreased and thrombocytopenia (12.6% each), and hyperferritinaemia (10.2%).

Obe-cel is administered as a split dose. Seven patients (5.5%) did not receive their second infusion of obe-cel due to AE (n=3), PD (n=2), death (n=1) or manufacturing issue (n=1). A delay in the administration of the second dose, after the protocol pre-specified Day 10 ± 2 days (range: Day 13 - Day 21) occurred in 9 patients (7.0%) due to the occurrence of AE.

Seventeen patients died due to TEAEs, of which 2 patients (1.6%) experienced a total of 3 fatal TEAEs that were suspected to be related to obe-cel treatment (acute respiratory distress syndrome, ICANS and neutropenic sepsis). The other 15 deaths (13.4%) were not suspected to be related to obe-cel treatment.

Grade ≥ 3 cytopenia's at Month 1 following infusion were observed in 69% of patients and included neutropenia (59%) and thrombocytopenia (49%). The median time to recovery post obe-cel treatment

to the lower thresholds for neutrophils (≥ 0.5 × 10^9/L) and platelets (≥ 50 × 10^9/L) (95% CI) was 0.7 months (0.5, 0.9) and 0.7 months (0.3, 1.8) for neutrophils and platelets. Severe infections ≥ Grade 3 were reported in 52% of patients (sepsis, pneumonia), the majority of infections were related to unspecified pathogens (34.9%), viral (33.1%) and bacterial infections (26%) and occurred within the first 3 months after obe-cel infusion. Beyond day 90, 46 patients (36.2%) experienced any grade infection, including 35 patients (27.6%) who experienced ≥ Grade 3 infection, most infections were of viral origin. Fatal infections occurred in 5 cases due to sepsis (2 patients), neutropenic sepsis (2 patients) and abdominal infection (1 patient) of which 1 possibly related.

B-cell aplasia (defined as absolute numbers of B-cells < 20 cells/µL) was observed in most patients. Hypogammaglobulinemia was reported in 12 subjects (9.4%). Two patients (1.6%, 2/127) experienced Grade 3 hypogammaglobulinemia.

A generally similar safety profile was observed across age subgroups. Any grade and ≥ Grade 3 ICANS were more frequently reported in elderly patients (≥ 65 years) than in the younger population.

3.5. Uncertainties and limitations about unfavourable effects

The CAR in obe-cel is constructed using the 4-1BB co-stimulatory domain with a novel low affinity CD19 (CAT) CAR binding domain compared to commercially available CD19 (FMC63) CAR T cells. In addition, obe-cel is administered according to a split-dose in order to manage the safety concerns associated with CAR T cells (CRS, ICANS). This dose fractionation allows a delay (FELIX study; 9 patients) or withholding (FELIX study; 3 patients) of the administration of the second dose in case of immune mediated toxicity as well as a low first dose fractionation for patients with high disease burden as assessed by the percentage of blasts in the BM at lymphodepletion (20% cut-off). The BM assessment at lymphodepletion showed a decrease in disease burden between screening and LD, possibly caused by bridging therapy. High response rates were observed both in patients with low (<5%) and high (≥5%) blasts. A potential risk associated with the dose fractionation could be underdosing, however reassuringly the main efficacy outcome (ORR) as well as pharmacokinetics (time to peak, Cmax and AUC0-28d and persistency) appear in line with single dose CAR T regimens. As the data provided in support of the split dose regimen are limited and a trend in differential treatment outcomes (DOR) was observed in patients depending on the chosen fractionation of obe-cel for low and high disease burden, uncertainties remain at long term from efficacy perspective.

All together the results from the FELIX study show that the risk of developing ≥ Grade 3 CRS (2.4%) and ≥ Grade 3 ICANS (7.1%) after obe-cel was low. Cross study comparisons are methodologically challenging, however the rationale for reduced immunotoxicity with obe-cel is understood and might be considered an advantage of the split dose regimen, when appropriately confirmed by data from the specific post-authorisation obligations, in particular from the registry-based non-interventional study.

The number of evaluable subjects is limited (n=127) in order to assess AEs that occur less frequent and the comparative safety assessment is hampered by the single arm trial design.

The median duration of follow-up for the safety set from first obe-cel infusion to the DCO (07-Feb-2024) was 21.45 months (range: 8.6-41.4 months). The detection of rare AEs and AEs emerging later in time such as secondary malignancies and long-term immunogenicity will only be captured by imposed follow-up post authorisations studies. Studies have been imposed as conditions and specific obligations (under the conditional marketing authorisation) to further characterise the safety profile of Aucatzyl in the long-term.

3.6. Effects Table

Table 37. Effects table for Aucatzyl (obe-cel) for the treatment of adult patients 26 years of age and above with relapsed or refractory B cell precursor acute lymphoblastic leukaemia (data cut-off: 07-Feb-2024)

Effect	Short Description	Unit	Treatment	Uncertainties/ Strength of evidence	References
Favourable Effects					
Objective Response Rate	CR or CRi as assessed by IRCC	Rate	94 Infused Patients Cohort IIA (mITT) 76.6% (66.7, 84.7) 113 patients leukapheresed Cohort IIA (ITT) 63.7% (54.1, 72.6)	Single-arm trial Limited sample size	FELIX Cohort IIA
Duration of Remission	Median duration	Months	72 Responders 14.06 (95% CI: 8.18, NE)	Median follow-up 20.25 months.	FELIX Cohort IIA (mITT/ITT)
Unfavourable Effects					
Severe infections	Proportion (%) of patients who had **Grade ≥ 3** infections post obe-cel infusion		Safety (N=127): 45%	45 deceased due to progressive disease, **17 deceased due to TEAEs**. 2 patients (1.6%) experienced a total of 3 fatal TEAEs that were suspected to be related to obe-cel. Limited number of subjects, long term follow up needed for detection of rare and late AEs.	FELIX All Cohorts/All Phases

CRS	Proportion (%) of patients who had **≥ Grade 3** CRS post obe-cel infusion		Safety (N=127): 2.4% (3/127)	CRS (all grade) was observed in 69% of patients. Limited number of subjects.	FELIX All Cohorts/All Phases
ICANS	Proportion (%) of patients who had **≥ Grade 3** ICANS post obe-cel infusion		Safety (N=127): 7.1% (9/127)	ICANS (all grade) was observed in 23% of patients. Limited number of subjects	FELIX All Cohorts/All Phases

Abbreviations: CR=Complete Response, CRS=cytokine release syndrome, EFS=Event-Free Survival, ICANS=immune effector cell-associated neurotoxicity syndrome, IRC=Independent Response Review Committee, OS=Overall Survival

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

The primary endpoint (ORR) of the pivotal FELIX trial was met and a clinically relevant overall response rate of 76.6% was observed in patients who received at least 1 infusion of obe-cel (mITT). In the context of a single-arm trial in this later-line setting, ORR (per IRCC) can be accepted as primary endpoint also considering durability of response which is captured as median duration of remission which was of 14.06 months. The data are considered sufficient to demonstrate efficacy and safety of obe-cel in the context of a CMA. Results from time-to event outcomes are considered uninterpretable in the context of a single arm trial.

In general, the safety profile of obe-cel consists of adverse drug reactions known from the underlying disease and other CD19 CAR T cell products with CRS, ICANS, leukopenia, and infections as main contributors.

The CAR in obe-cel is constructed using the 4-1BB co-stimulatory domain with a novel low affinity CD19 (CAT) CAR binding domain compared to commercially available CD19 (FMC63) CAR T cells. In addition, obe-cel is administered according to a split-dose in order to manage the safety concerns associated with CAR T cells (CRS, ICANS). This dose fractionation allows a delay (FELIX study; 9 patients) or withholding (FELIX study; 3 patients) of the administration of the second dose in case of immune mediated toxicity as well as a low first dose fractionation for patients with high disease burden as assessed by the percentage of blasts in the BM at lymphodepletion (20% cut-off). The BM assessment at lymphodepletion showed a decrease in disease burden between screening and LD, possibly caused by bridging therapy. High response rates were observed both in patients with low (<5%) and high (≥5%) blasts.

A potential risk associated with the dose fractionation could be underdosing, however reassuringly the main efficacy outcome (ORR) as well as pharmacokinetics (time to peak, Cmax and AUC0-28d and persistency) appear in line with single dose CAR T regimens. As the data provided in support of the split dose regimen are limited and a trend in differential treatment outcomes (DOR) was observed in patients depending on the chosen fractionation of obe-cel for low and high disease burden, uncertainties remain at long term from efficacy perspective. All together the results from the FELIX study show that the risk of developing ≥ Grade 3 CRS (2.4%) and ≥ Grade 3 ICANS (7.1%) after obe-cel was low. Cross study comparisons are methodologically challenging, however the rationale for

reduced immunotoxicity with obe-cel is understood and might be considered an advantage of the split dose regimen, when appropriately confirmed by data from the specific post-authorisation obligations, in particular from the registry-based non-interventional study.

The agreed labelled indication of obe-cel is for the treatment of adult patients 26 years of age and above with r/r B ALL and a CMA was requested by the applicant. The indication is in line with the heterogenous r/r ALL study population from the FELIX trial. Patients aged 18-25 years old were however excluded from the labelling as a major therapeutic advantage as part of the CMA requirements over tisa-cel (Kymriah) for the population of young adults (18-25 y/o) was not demonstrated in this overlapping population. The prerequisites for a CMA are discussed in more detail in section 3.7.3. *Additional considerations on the benefit-risk balance*.

Long term follow-up is needed for the detection of rare AEs and AEs emerging later in time such as secondary malignancies and long-term immunogenicity data will be generated with 5 year follow-up in the FELIX study and a total of 15 year follow-up in the AUTO1-LT1 study (long term follow up study of rolled over patients from the FELIX study). Post marketing safety and effectiveness of obe-cel will be collected also in an imposed noninterventional registry-based study (see annex II of the opinion for imposed studies).

3.7.2. Balance of benefits and risks

Overall the efficacy of obe-cel is considered demonstrated and clinically relevant. Furthermore, considering the life-threatening disease, the safety profile of obe-cel seems acceptable for the target population and in line with other products in the same class, and the identified uncertainties and limitations are of limited relevance. No new safety signals were identified in the data provided in the submitted dossier. In conclusion a positive B/R is agreed in the proposed population in the context of a CMA.

3.7.3. Additional considerations on the benefit-risk balance

As discussed above, uncertainties remain as related to the single uncontrolled pivotal trial, small sample size in heterogenous population, lack of interpretable time-to-event outcomes, use of tumour-burden adjusted fractionated dosing regimen and the limited safety follow-up. While the reported response rates indicate high magnitude of the therapeutic effect, the duration of remission cannot be precisely estimated, considering the limited efficacy follow-up, the trend for potentially different duration of remission according to the fractionated dosing regimen, and the absence of data in a broader patient population. In terms of safety, findings to date are in line with what is expected based on the mechanism of action of the product but the number of patients exposed to obe-cel and duration of follow-up is limited. In addition, the prolonged persistence associated with the 4-1BB costimulatory domain raises concerns regarding the potential for secondary malignancies and other long-term toxicities, such as prolonged cytopenia's.

In conclusion, the data provided are regarded as sufficient for benefit-risk conclusion to qualify for a CMA, but the clinical data cannot be considered comprehensive. Post-authorisation studies are imposed to reduce uncertainties and contribute to data comprehensiveness. These studies will provide longer term data as well as further efficacy and safety information on other subgroups, which may not be fully represented in the pivotal study submitted for this application. The provision of this data post-authorisation will complement the data in order to have a comprehensive understanding of efficacy and safety and to confirm the positive benefit-risk balance of Aucatzyl in relapsed or refractory B ALL.

Conditional marketing authorisation

As comprehensive data on the product are not available as discussed above, a conditional marketing authorisation was requested by the applicant in the initial submission.

The product falls within the scope of Article 14-a of Regulation (EC) No 726/2004 concerning conditional marketing authorisations, as it aims at the treatment of a seriously debilitating and life-threatening disease. In addition, the product is designated as an orphan medicinal product.

Furthermore, the CAT considers that the product fulfils the requirements for a conditional marketing authorisation:

- The benefit-balance of obe-cel is considered positive, as discussed above.
- it is likely that the applicant will be able to provide comprehensive data as the following specific obligations are proposed:
    - 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.
    - 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 characterise the long-term safety and efficacy of Aucatzyl, according to an agreed protocol.

  These post authorisation studies will provide longer term data as well as further efficacy and safety information on other potential patient subgroups, interpretability of the use of tumour-burden adjusted fractionated dosing regimen, use of the split dose, and the effect of prolonged persistence to address the remaining uncertainties.
- Unmet medical needs will be addressed, as:

  The prognosis of adult patients with B-cell precursor ALL in the relapse or refractory clinical setting gets worse at each relapse and a clear unmet medical need in this disease is acknowledged. Several medicinal products have been authorised in adult patients with B-cell precursor ALL, including blinatumomab, inotuzumab ozogamicin and ponatinib.

  Nevertheless the CHMP noted that based on indirect side by side comparison between obe-cel and blinatumomab, inotuzumab ozogamicin and ponatinib respectively, taking into consideration the objective response rate, complete response rate and duration of responses the results of the FELIX study for Aucatzyl appear to indicate improved efficacy of Aucatzyl, therefore offering a major therapeutic advantage over these three existing therapies.

  Tecartus is another CAR-T cell product approved for the treatment of B-cell precursor ALL in patients aged 26 years of age and above under a conditional Marketing authorisation. In this context and in line with relevant guidelines, the applicant provided a justification in the form of an unanchored matching-adjusted indirect comparison comparing efficacy and safety endpoints, supporting the conclusion that the efficacy and safety of obe-cel can be regarded as addressing the unmet medical need in the targeted patient population to a similar extent than brexucabtagene autoleucel (Tecartus), acknowledging the methodological difficulties using less-comprehensive data and resulting uncertainties.

In addition, Kymriah (tisagenlecleucel) is approved for the treatment of paediatric and young adult patients up to and including 25 years of age with B-cell acute lymphoblastic leukaemia (ALL) that is refractory, in relapse post-transplant or in second or later relapse. Aucatzyl therefore addresses an unmet medical need in the adult patient population aged 26 years and above.

Overall Aucatzyl, in view of the demonstrated efficacy and safety, provides a suitable treatment option in the described clinical setting and interpreting the indirect treatment comparisons with caution, it can be agreed that the availability of Aucatzyl represents a major therapeutic advantage over existing treatments for adult patients 26 years of age and above.

- The benefits to public health of the immediate availability outweigh the risks inherent in the fact that additional data are still required. In general, the benefit risk of Aucatzyl has been demonstrated at this point in time through the submitted data and therefore it represents an additional therapeutic option in the specific clinical setting included in the indication.

The CHMP endorses the CAT conclusion on conditional marketing authorisation as described above.

3.8. Conclusions

The overall benefit/risk balance of Aucatzyl is positive, subject to the conditions stated in section 'Recommendations'.

The CHMP endorse the CAT conclusion on Benefit Risk balance as described above

4. Recommendations

Similarity with authorised orphan medicinal products

The CAT by consensus is of the opinion that Aucatzyl is not similar to Blincyto, Besponsa, Kymriah and Tecartus within the meaning of Article 3 of Commission Regulation (EC) No. 847/2000.

The CHMP endorses the CAT conclusion on similarity as described above.

Outcome

Based on the CAT review of data on quality, safety and efficacy, the CAT considers by consensus that the benefit- risk balance of Aucatzyl is favourable in the following indication(s):

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).

The CAT therefore recommends the granting of the conditional marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

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

Based on the draft CHMP opinion adopted by the CAT and the review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit- risk balance of Aucatzyl in 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) is favourable and therefore recommends the granting of the

conditional marketing authorisation subject to the following conditions:

Other conditions and requirements of the marketing authorisation

- **Periodic Safety Update Reports**

The requirements for submission of periodic safety update reports 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 shall submit the first periodic safety update report for this product within 6 months following authorisation.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk Management Plan (RMP)**

The marketing authorisation holder (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.

<u>Healthcare professional's guide</u>

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 medication 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

The CHMP endorses the CAT conclusion on the additional risk minimisation measures.

- **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

The CHMP endorses the CAT conclusion on the obligation to conduct post-authorisation measures as described above.

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

The CHMP endorses the CAT conclusion on the specific obligation to complete post-authorisation measures for the conditional marketing authorisation as described above.

New active substance status

Based on the review of available data on the active substance, the CAT considers that obecabtagene autoleucel is to be qualified as a new active substance in itself as it is not a constituent of a medicinal product previously authorised within the European Union.

The CHMP endorses the CAT conclusion on the new active substance status claim.