Medicines & Healthcare products
Regulatory Agency

Public Assessment Report

National Procedure

Aucatzyl 410 × 10^6 cells dispersion for infusion

obecabtagene autoleucel

PLGB 46113/0001

Autolus Limited

LAY SUMMARY

Aucatzyl 410 × 10^6 cells dispersion for infusion
obecabtagene autoleucel

This is a summary of the Public Assessment Report (PAR) for Aucatzyl 410 × 10^6 cells dispersion for infusion. It explains how this product was assessed and its authorisation recommended, as well as its conditions of use. It is not intended to provide practical advice on how to use this product.

This product will be referred to as Aucatzyl in this lay summary for ease of reading.

For practical information about using Aucatzyl, patients should read the Patient Information Leaflet (PIL) or contact their doctor or pharmacist.

What is Aucatzyl and what is it used for?
This application is a full-dossier application. This means that the results of pharmaceutical, non-clinical and clinical tests have been submitted to show that this medicine is suitable for treating the specified indications.

Aucatzyl is used to treat adult patients with B cell acute lymphoblastic leukaemia, a type of blood cancer that affects white blood cells in the bone marrow called B lymphoblasts. It is given when previous treatment for a patient's cancer has not worked, or the cancer has come back.

How does Aucatzyl work?
Aucatzyl is made by taking T cells from the blood and putting a new gene into them. This enables T cells to target the cancer cells in the body.

When Aucatzyl is infused into the blood, the modified T cells will kill the cancer cells.

Aucatzyl will be given to the patient by 2 infusions that are separated by about 9 days to achieve the total target dose. The amount of Aucatzyl given in the first infusion and second infusion will depend on the extent of the patient's leukaemia. The total target dose of Aucatzyl is not affected by the extent of the patient's leukaemia.

If the patient has any questions about how Aucatzyl works or why this medicine has been prescribed for them, they should ask their doctor.

How is Aucatzyl used?
The pharmaceutical form of this medicine is a dispersion for infusion and the route of administration is intravenous (drip through a tube into a vein).

Giving the patient's own blood cells to make Aucatzyl
Aucatzyl is made from the patient's own white blood cells.

- The patient's doctor will take some of their blood using a tube (catheter) placed in their vein.
- Some of their white blood cells will be separated from their blood and the rest of their blood is returned to their body. This is called 'leukapheresis' and can take between 3 to 6 hours.
- The patient's white blood cells are sent away to manufacture Aucatzyl specifically for them.

Other medicines the patient will be given before Aucatzyl

- A few days before the patient receives Aucatzyl, they will be given a type of treatment called lymphodepleting chemotherapy. This will allow the modified T cells in Aucatzyl to multiply in their body after Aucatzyl is given to them.
- Approximately 30 minutes before the patient is given Aucatzyl they will be given paracetamol. This is to help prevent infusion reactions and fever.

How Aucatzyl is given

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

- The patient's doctor will check that the Aucatzyl was prepared from the patient's own blood by checking the patient identification information on the Aucatzyl infusion bag matches their details.
- Aucatzyl will be given to the patient in 2 infusions that are separated by approximately 9 days to achieve the complete total target dose.
- Aucatzyl is given by infusion (drip) through a tube into a vein.

After the first dose of Aucatzyl is given

- The patient should stay close to the treatment centre for at least 4 weeks.
- The patient will be monitored daily for 14 days after the first infusion so that their doctor can check that the treatment is working and if needed help them with any side effects.
- The patient's doctor will assess if their second dose of Aucatzyl will proceed as planned. If the patient is experiencing any serious symptoms the second dose may need to be delayed or discontinued.

For further information on how Aucatzyl is used, refer to the PIL and Summary of Product Characteristics (SmPC) available on the Medicines and Healthcare products Regulatory Agency (MHRA) website.

This medicine can only be obtained with a prescription.

The patient should ask the administering healthcare practitioner if they have any questions concerning the medicine.

What benefits of Aucatzyl have been shown in studies?

The applicant has submitted data from the FELIX study, an on-going open-label, uncontrolled, non-randomised clinical study that has recruited adult subjects with relapsed or refractory CD19-positive B-cell acute lymphoblastic leukaemia.

153 subjects have been enrolled into the FELIX study and 127 subjects have been administered Aucatzyl. The FELIX study has 5 cohorts; the main analysis population of the applicant is cohort IIA.

Cohort IIA is composed of 94 subjects: median age 50yrs (min 20yrs, max 81yrs); 67% subjects were >40yrs; 50% male.

Subjects had received between 1 and 6 prior therapies with a median of 2.

Subjects underwent leukapheresis to obtain material that was sent to a distant site to manufacture the CAR-T cells. Bridging therapy was permitted.

A bone marrow assessment was available from a biopsy and / or aspirate sample obtained within 7 days prior to the commencement of the lymphodepleting chemotherapy. Bone marrow assessment was used to determine the Aucatzyl dosage regimen based on tumour burden.

Subjects underwent lymphodepletion (at day -6 to day -3 after exposure to Aucatzyl) with a regimen of fludarabine and cyclophosphamide.

Aucatzyl was administered as a split dose according to tumour load.

Low tumour burden regimen (bone marrow lymphoblasts make up ≤20% of total number of nucleated cells of bone marrow assayed up to 7 days prior to lymphodepletion):

- Day 1: 100 x 10^6 cells administered via bag infusion
- Day 10 (±2days): 10 x 10^6 cells administered via syringe and 300 x 10^6 cells administered via bag infusion

High tumour burden regimen (bone marrow lymphoblasts make up >20% of total number of nucleated cells of bone marrow assayed up to 7 days prior to lymphodepletion):

- Day 1: 10 x 10^6 cells administered via syringe
- Day 10 (±2days): 100 x 10^6 cells administered via bag infusion and 300 x 10^6 dose administered via bag infusion

The time taken from enrolment to first infusion was 25- 92 days. The second dose may be delayed if the recipient experiences significant toxicities. The total target dose of Aucatzyl for all patients is 410 × 10^6 CD19 CAR-positive T cells.

52 of the 94 patients administered Aucatzyl showed complete remission (by the definition of the applicant) of the disease with an 81% probability of overall survival at 12 months (in a disease where the expectation of survival would otherwise be about 10-15% at 12 months).

Those subjects who showed either an incomplete response or "no response" have a less favourable outcome.

Unfavourable effects are known to the medical community and are amenable to management.

The overall survival of about 81% at 12 months for those who showed complete remission is considered remarkable and is considered to outweigh the risk of exposure to product.

What are the possible side effects of Aucatzyl?

For the full list of all side effects reported with this medicine, see Section 4 of the PIL or the SmPC available on the MHRA website.

If a patient gets any side effects, they should talk to their doctor, pharmacist or nurse. This includes any possible side effects not listed in the product information or the PIL that comes with the medicine. Patients can also report suspected side effects themselves, or a report can be made on their behalf by someone else who cares for them, directly via the Yellow Card scheme at https://yellowcard.mhra.gov.ukor search for 'MHRA Yellow Card' online. By reporting side effects, patients can help provide more information on the safety of this medicine.

Why was Aucatzyl approved?
It was concluded that Aucatzyl has been shown to be effective in the treatment of adult patients (≥18 years) with relapsed or refractory B cell precursor acute lymphoblastic leukaemia. Furthermore, the side effects observed with use of this product are considered to be typical for this type of treatment. Therefore, the MHRA decided that the benefits are greater than the risks and recommended that this medicine can be approved for use.

Aucatzyl has been authorised with a Conditional Marketing Authorisation (CMA). CMAs are intended for medicinal products that address an unmet medical need, such as a lack of alternative therapy for a serious and life-threatening disease. CMAs may be granted where comprehensive clinical data is not yet complete, but it is judged that such data will become available soon.

Aucatzyl has been authorised as a GB Orphan medicine. Orphan medicines are intended for use against rare conditions that are life-threatening or chronically debilitating. To qualify as an orphan medicine, certain criteria, for example concerning the rarity of the disease and the lack of currently available treatments, must be fulfilled.

What measures are being taken to ensure the safe and effective use of Aucatzyl?
As for all newly-authorised medicines, a Risk Management Plan (RMP) has been developed for Aucatzyl. The RMP details the important risks of Aucatzyl, how these risks can be minimised, any uncertainties about Aucatzyl (missing information), and how more information will be obtained about the important risks and uncertainties.

The following safety concerns have been recognised for Aucatzyl:

Important identified risks	• Cytokine release syndrome (CRS) • Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS) • Prolonged Cytopenia • Hypogammaglobulinaemia • Severe Infections • Secondary Malignancy of T cell origin • Haemophagocytic Lymphohistiocytosis (HLH)/Macrophage Activation Syndrome (MAS)
Important potential risks	• Tumour Lysis Syndrome (TLS) • Antigenicity and Immunogenicity • Secondary malignancy except secondary malignancy of T cell origin • Graft versus Host Disease (GvHD) • Generation of replication-competent lentivirus • Overdose/Medication error
Missing information	• Pregnancy & Lactation • Long-term safety • New occurrence or exacerbation of an autoimmunee disorder • Patients with chronic controlled HIV, HBV or HCV

Additional risk minimisation measures include:
1) Risk minimisation control programme,
2) Educational programme (Healthcare Professional educational programme and patient card).

The information included in the SmPC and the PIL is compiled based on the available quality, non-clinical and clinical data, and includes appropriate precautions to be followed by healthcare professionals and patients. Side effects of Aucatzyl are continuously monitored and reviewed including all reports of suspected side-effects from patients, their carers, and healthcare professionals.

An RMP and a summary of the pharmacovigilance system have been provided with this application and are satisfactory.

Other information about Aucatzyl
A marketing authorisation application for Aucatzyl was received on 25 July 2024 and a marketing authorisation was granted in the United Kingdom (UK) on 25 April 2025.

The full PAR for Aucatzyl follows this summary.

This summary was last updated in June 2025.

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I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the Medicines and Healthcare products Regulatory Agency (MHRA) considered that the application for Aucatzyl 410 × 10^6 cells dispersion for infusion (PLGB 46113/0001) could be approved.

The product is approved for the following indication:

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

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

This application was approved under Regulation 50 of The Human Medicines Regulation 2012, as amended (previously Article 8(3) of Directive 2001/83/EC, as amended), a full-dossier application. All non-clinical data submitted were from studies conducted in accordance with Good Laboratory Practice (GLP). All clinical data submitted were from studies conducted in accordance with Good Clinical Practice (GCP).

Aucatzyl has been authorised as a Conditional Marketing Authorisation (CMA). CMAs are granted in the interest of public health and are intended for medicinal products that fulfil an unmet medical need and the benefit of immediate availability outweighs the risk posed from less comprehensive data than normally required. Unmet medical needs include, for example, treatment or diagnosis of serious and life-threatening diseases where no satisfactory treatment methods are available. CMAs may be granted where comprehensive clinical data is not yet complete, but it is judged that such data will become available soon. Adequate evidence of safety and efficacy to enable the MHRA to conclude that the benefits are greater than the risks is required, and has been provided, for Aucatzyl. The CMA for Aucatzyl, including the provision of any new information, will be reviewed every year and this report will be updated as necessary.

This application was evaluated for fulfilment of orphan designation criteria and was examined by the Commission on Human Medicines (CHM) on 21 & 22 November 2024. It was concluded that fulfilment of the criteria for approval as an orphan medicinal product was satisfactorily demonstrated. Please see Annex 1 for a summary of the orphan approval.

In line with the legal requirements for children's medicines, the application included a licensing authority decision on the agreement of a paediatric investigation plan (PIP) MHRA-100866-PIP01-23.

At the time of the submission of the application the PIP was not yet completed as some measures were deferred.

The application included a licensing authority decision on the agreement of a waiver in the paediatric population from birth to less than 6 kg of bodyweight.

The MHRA has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place for this product at all sites responsible for the manufacture, assembly and batch release of this product.

A Risk Management Plan (RMP) and a summary of the pharmacovigilance system have been provided with this application and are satisfactory.

Advice was sought from the Commission of Human Medicines (CHM) on 21 & 22 November 2024 on grounds relating to quality, safety and efficacy. Following provision of additional data the CHM were reassured on the quality of the product.

A marketing authorisation application for Aucatzyl was received on 25 July 2024, and marketing authorisation was granted in the United Kingdom (UK) on 25 April 2025.

II QUALITY ASPECTS

II.1 Introduction

Obe-cel is a gene therapy cellular product consisting of autologous enriched T cells that are genetically modified ex vivo with a lentiviral vector (LV18970) to express a novel CD19CAT-41BBζ chimeric antigen receptor (CAT CAR). The drug substance (obe-cel) is defined as the CD19 CAR-positive T cells (Non-proprietary Name: obecabtagene autoleucel) and the obe-cel dispersion for intravenous infusion is the final formulated drug product. The finished drug product is cryopreserved and packaged in three or more infusion bags containing a target total of 410 × 10^6 CD19 CAR-positive viable T cells to enable a split dosing regimen. Each infusion bag contains 10-20 mL or 30-70 mL of cells dispersion for infusion in a cryopreservative solution. The fill volume and the amount of CD19 CAR-positive T cells is variable.

The other ingredients are: disodium edetate; dimethyl sulfoxide; human albumin solution; phosphate buffered saline: potassium chloride, potassium dihydrogen phosphate, sodium chloride, disodium phosphate, water for injections.

The finished product is supplied in three or more infusion bags individually packed within an overwrap in a metal cassette. Obe-cel is stored in the vapor phase of liquid nitrogen at ≤ -150 °C and supplied in a liquid nitrogen dry vapour shipper. The Patient Information Leaflet (PIL) will be provided in a wallet of each Cryoshipper. The information for the Health Care Professional (HCP) is supplemented by a Release for Infusion Certificate and Dose Schedule Planner to ensure correct dosing to the correct patient. Specific instructions for the volume (mL) of the 10 × 10^6 CD19 CAR-positive T cells to be administered from this bag configuration will be provided on the release for infusion certificate.

II.2 ACTIVE SUBSTANCE

rINN: obecabtagene autoleucel

Nomenclature

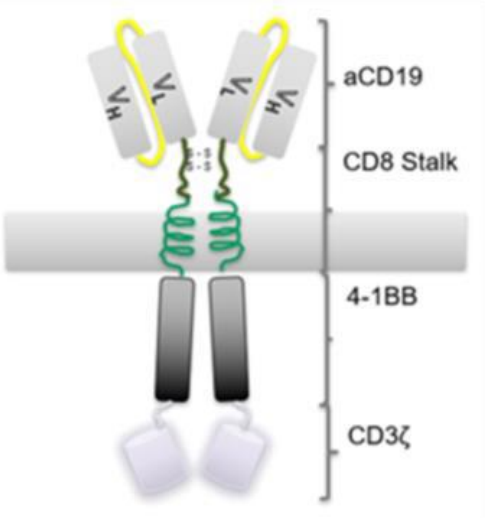
Applicant or Laboratory Code
AUTO1
Obe-cel

Structure

The obe-cel drug substance consists of autologous T cells that are genetically modified ex-vivo with a lentiviral vector (LV18970) to express a CD19 chimeric antigen receptor (CAR). Obe-cel also contains non-transduced autologous T cells and non-T cells. A schematic representation of the structure of the obe-cel CD19 (CAT) CAR, as predicted to be displayed on the surface of the transduced T-cell membrane, is shown in Figure 1. 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). CAT scFv has a lower affinity for CD19 and a faster off-rate compared to the FMC63 scFv used in other approved CD19 CAR T therapies like tisagenlecleucel and axicabtagene ciloleucel. An scFv was constructed by linking the VH and VL chains together with a serine-glycine (GGGGS) triple linker. This scFv was then linked in frame to the stalk and

transmembrane domains of human CD8α, and subsequently fused to the 4-1BB co-stimulatory receptor and CD3ζ endodomains.

Figure 1: Schematic Representation of the Structure of CD19 (CAT) CAR.



Biological Properties
Once administered to patients, CD19 CAR-positive T cells circulate throughout the body and encounter normal and malignant B cells, mainly located in the bone marrow (BM). CAR T cells specifically recognize CD19. Engagement of CD19 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. The CAR is designed to have a fast off rate to minimise the negative side effects. Activated T cells will then in turn cause tumour destruction via several physiological effector mechanisms. These mechanisms include the release of Granzyme B and cytokines IL-2, IFN-γ and TNF-α, which can activate other components of the immune system and further promote the cytolytic mechanism. Activated CAR T cells proliferate after antigen encounter by several log and, unlike traditional medicine, the exposure achieved is significantly higher than the dose administered and can be variable from patient to patient.

Lentiviral Vector LV18970 is designed for ex vivo genetic modification of patient T cells during the manufacture of obe-cel. It is a third-generation self-inactivating (SIN) lentiviral vector, based on HIV-1 and intended for *ex vivo* use. It was designed to lack viral coding sequences that could result in replication competent lentivirus or immunogenic peptides and lentiviral enhancer-promoter sequences known to be involved in insertional mutagenesis by retroviruses and derived vectors.

II.3 DRUG PRODUCT

Pharmaceutical development
A satisfactory account of the pharmaceutical development has been provided.

All excipients comply with either their respective European/national monographs, or a suitable in-house specification. Satisfactory Certificates of Analysis have been provided for all excipients.

With the exception of human albumin solution, no excipients of animal or human origin are used in the final products. A valid certificate of suitability for TSE risk was provided for the bovine serum.

Manufacture of the product
The manufacture of obe-cel drug substance begins with the collection of the patient's white blood cells using a standard leukapheresis procedure. Fresh leukapheresis starting material is obtained from the patient at a qualified collection site and transported to the manufacturing site. T cells are stimulated to proliferate, transduced with the lentiviral vector LV18970 to introduce the CAR gene into the cell genome and ex vivo expanded, until target CAR T cell dose is achieved. The engineered T cells are then washed, formulated and cryopreserved to produce obe-cel drug product., which is shipped back to the clinical centre to be administered to the patient. obe-cel drug product is stored in the vapor phase of liquid nitrogen at ≤ -150 °C. The manufacturing process is performed in a closed environment, which is operated continuously, with no hold steps during processing. Raw materials and components used in the manufacturing process are considered suitable.

A description and flow-chart of the manufacturing method has been provided. Satisfactory batch formulation data have been provided for the manufacture of the product, along with an appropriate account of the manufacturing process. The manufacturing process has been validated and has shown satisfactory results. Obe-cel has been adequately characterised.

Finished Product Specifications
The finished product specifications at release and shelf-life are satisfactory. The test methods have been described and adequately validated. Batch data have been provided that comply with the release specifications.

Stability
Finished product stability studies have been conducted in accordance with current guidelines, using batches of the finished product stored in the packaging proposed for marketing. Based on the results, a shelf-life of 6 months at ≤ -150 °C (frozen) is accepted, with the following storage conditions: must be stored in the vapour phase of liquid nitrogen (≤ -150 °C) and must remain frozen until the patient is ready for treatment to ensure viable cells are available for patient administration. Thawed medicinal product should not be refrozen.

Shelf-life once thawed: 1 hour at room temperature.

II.4 Discussion on chemical, pharmaceutical and biological aspects

The grant of a marketing authorisation is recommended.

III NON-CLINICAL ASPECTS

III.1 Introduction

The following non-clinical studies were submitted with this application:

Pharmacology

Overview			Test Article: CD19 (CAT) CAR T Cells			
Type of Study	**Test System**	**Method of Administration**	**Testing Facility**	**Study Number**	**Location Vol.**	**Page**
Primary Pharmacodynamics						
Biophysical Characterization of CD19 (CAT) Binding Domain	N/A	In Vitro	Autolus		N/A	N/A
Design of CAT19 Chimeric Antigen Receptor	N/A	In Vitro	UCL		N/A	N/A
CD19 (CAT) CAR In Vitro Function	Cell Lines or Transfected Cell Lines	In Vitro	UCL		N/A	N/A
CD19 (CAT) CAR In Vivo Function in the NALM-6 NSG xenograft model	Female NSG Immunodeficient Mice	In Vivo	UCL		N/A	N/A
Secondary Pharmacodynamics						
No secondary pharmacodynamic studies have been performed						
Safety Pharmacology						
No safety pharmacology studies have been performed						
Pharmacodynamic Drug Interactions						
No pharmacodynamic drug interaction studies have been performed						

Abbreviations: CAR=chimeric antigen receptor; CAT=(murine) CAT13.1E10 hybridoma; CD=cluster of differentiation; N/A=not applicable; NOD=non-obese diabetic severe combined immunodeficiency gamma; UCL=University College London.

Primary Pharmacodynamics

				Test Article: CD19 (CAT) CAR T Cells	
Type of Study	**Species/Strain**	**Method of Admin.**	**Doses (µg/kg)**	**Gender and No. per Group**	**Noteworthy Findings**
Biophysical Characterization of CD19 (CAT) Binding Domain	N/A	In Vitro	N/A	N/A	Binding affinities of 14.4 nM and 0.328 nM were measured between CD19 and CAT and FMC63 binding domains, respectively. CAT demonstrated an approximately 40-fold weaker affinity than FMC63, primarily driven by a more rapid dissociation rate. Thermal stability and cell surface expression of both clones were comparable.
Design of CAT19 Chimeric Antigen Receptor	N/A	In Vitro	N/A	N/A	CAT19 CAR was designed by replacing the scFv of FMC63 with a scFv derived from CAT13.1E10 hybridoma which was previously established by the fusion of PX63AG8.653 cells with spleen cells from a mouse immunized with EBV-transformed B cells from a patient with MHC class-II deficiency. The VH and VL chains of this scFv were linked via serine-glycine (GGGGS) x 3 linker in frame to the stalk and transmembrane domains of human CD8α that was subsequently fused to 4-BB co-stimulatory receptor and CD3ζ endodomains.

				Test Article: CD19 (CAT) CAR T Cells	
Type of Study	**Species/Strain**	**Method of Admin.**	**Doses (µg/kg)**	**Gender and No. per Group**	**Noteworthy Findings**
CD19 (CAT) CAR In Vitro Function	Cell Lines or Transfected Cell Lines as Target Cells; CD19 (CAT) CAR T cells from 5 donors	In Vitro	N/A	N/A	CD19 (CAT) CAR T cells demonstrated cytotoxicity towards SupT1 cells engineered to express CD19, but not towards unmodified SupT1 cells. In comparison to CD19 (FMC63) CAR T cells, CD19 (CAT) CAR T cells showed statistically significantly greater cytotoxicity, particularly at lower E:T ratios. In co-culture with CD19 expressing target cells, CD19 (CAT) CAR stimulated comparable (IFN-γ, IL-2) or higher (TNF-α) production of proinflammatory cytokines compared to CD19 (FMC63) CAR T cells. CD19 (CAT) CAR T cells showed significantly greater proliferation than CD19 (FMC63) CAR T cells in response to CD19+ (Raji and NALM-6) cells.

				Test Article: CD19 (CAT) CAR T Cells		
Type of Study	**Species/Strain**	**Method of Admin.**	**Doses (µg/kg)**	**Gender and No. per Group**	**Noteworthy Findings**	
CD19 (CAT) CAR In Vivo Function in the NALM6 NSG mouse xenograft model	NSG Immunodeficient Mice	i.v.	2.5 × 10^6 CD19 (CAT) CAR T Cells 2.5 × 10^6 CD19 (FMC63) CAR T Cells	Female 18/group	Tumor regression was observed in mice receiving CD19 (CAT) CAR T cells. CD19 (FMC63) CAR T cell treatment slowed but did not prevent tumor growth. Absolute numbers of NALM-6 cells in bone marrow were statistically significantly lower in mice treated with CD19 (CAT) CAR T cells compared to CD19 (FMC63) CAR T cells. Mean absolute cell numbers of CD19 (CAT) CAR T cells in both bone marrow and blood were significantly higher than corresponding numbers of CD19 (FMC63) CAR T cells.	

Abbreviations: CAR=chimeric antigen receptor; CAT=(murine) CAT13.1E10 hybridoma; CD=cluster of differentiation; E:T=effector to target; MHC=major histocompatibility complex; N/A=not applicable; NOD=non-obese diabetic severe combined immunodeficiency gamma; VH-variable heavy; VL=variable light.

Compliance with Good Laboratory Practice (GLP) is accepted.

III.2 Pharmacology

Brief summary

Obe-cel, is a CD19 CAR T cell therapy. This is a well-established mode of action with several CAR T cell products approved that target CD19 and treat patients with cancer. Obe-cel is the only product based around the CAT19 binder and is designed to have a fast target binding off-rate with the intent that this minimises excessive activation of programmed T cells. This may result in better tolerability and a reduction in T cell exhaustion which could enhance persistence and improve the ability of the programmed T cells to engage in serial killing of target cancer cells.

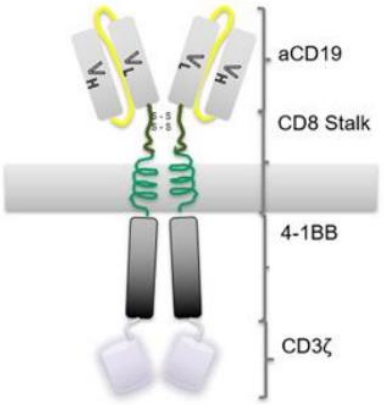
The CAR in obe-cel does not recognise CD19 from animal species and therefore studies in normal animals are not relevant. The applicant presented studies on the novel kinetics of this CAR in comparison with that of an established CAR T cell product. Anti-tumour activity was shown in a xenograft experiment in immunodeficient mice.

Physical chemistry

A Chimeric antigen receptor (CAR) is a recombinant receptor that combines a single chain variable fragment (scFv) against a tumour-associated antigen and an intracellular activation domain of the T cell receptor, recognising membrane-bound antigen. Obe-cel contains autologous enriched T cells transduced ex vivo with a lentiviral vector (LV18970) to express a novel anti-CD19 CAR. It may also contain non-transduced autologous T cells and other cell types.

The CAR in obe-cel was derived from a murine CAT13.1E|10 hybridoma. It consists of an anti-CD19 scFv, a CD8-derived stalk and trans-membrane domain and a compound fusion of the 4-1BB and CD3ζ endodomains (see Figure 1).

Figure 1: Schematic of Obe-cel, An Anti-CD19 (CAT) CAR



The vector, LV18970, is a self-inactivating (SIN) lentiviral vector, based on HIV-1. It lacks viral coding sequences that could result in replication competent lentivirus or immunogenic peptides and lentiviral enhancer-promoter sequences known to be involved in insertional mutagenesis by retroviruses and derived vectors. It encodes the CAR.

Primary pharmacodynamics

Report Mpx02272 was a short report on the design of the CAR in obe-cel, a 2nd generation 41BB-ζ CAR with a CD19 recognition domain derived from CAT13.1E10. It is based on a published CAR (Chimeric receptors with 4-1BB signaling capacity provoke potent cytotoxicity against acute lymphoblastic leukaemia) which has an FMC63 scFv connected via the CD8α stalk as a spacer domain to a compound endodomain comprised of a fusion between the 4-1BB and CD3ζ endodomains. In obe-cel, the FMC63 scFv is replaced with a scFv derived from CAT13.1E10 hybridoma (hence the name CAT). CAT-13.1E10 was established in 1988 by fusion of PX63AG8.653 cells with spleen cells of a mouse immunised with EBV-transformed B cells from a patient with MHC class-II deficiency. Variable heavy and variable light (VH and VL) chains of CAT13.1E10 were linked via a serine-glycine (GGGGS) x 3 linker and the scFv then linked to the stalk and transmembrane domains of human CD8α and subsequently fused to the 4-1BB co-stimulatory receptor and CD3ζ. The annotated amino acid sequence of the CAR is in Figure 1 below.

Figure 1: Annotated amino acid sequence of CAT19 CAR

```
<------signal-------><--------------------VH-------------------------
MGTSLLCWMALCLLGADHADAQVQLQQSGPELVKPGASVKISCKASGYAFSSSWMNWVKQRPGKGLEW

-----------------------------------VH---------------------------------
IGRIYPGDEDTNYSGKFKDKATLTADKSSTTAYMQLSSLTSEDSAVYFCARSLLYGDYLDYWGQGTTL

---><---linker----><----------------------VL-------------------------
TVSSGGGGSGGGGSGGGGSQIVLTQSPAIMSASPGEKVTMTCSASSSVSYMHWYQQKSGTSPKRWIYD

-------------------------VL------------------------------><B><------
TSKLASGVPDRFSGSGSGTSYFLTINNMEAEDAATYYCQQWNINPLTFGAGTKLELKRSDPTTTPAPR

--------------------------CD8STK-TM-A----------------------><-----
PPTPAPTIASQPLSLRPEACRPAAGGAVHTRGLDFACDIYIWAPLAGTCGVLLLSLVITLYCKRGRKK

---------------41BB_endo-----------><---------CD3Zeta_endo----------
LLYIFKQPFMRPVQTTQEEDGCSCRFPEEEEGGCELRVKFSRSADAPAYQQGQNQLYNELNLGRREEY

----------------------------CD3Zeta_endo---------------------------
DVLDKRRGRDPEMGGKPRRKNPQEGLYNELQKDKMAEAYSEIGMKGERRRGKGHDGLYQGLSTATKDT

----------->
YDALHMQALPPR
```

Signal = signal peptide; VH = variable heavy chain from CAT; linker = serine glycine linker; VH = variable region heavy chain CAT; B = chain break / BamHI site; CD8STK-TM-A = CD8alpha stalk, transmembrane domain and anchor; 41BB_endo = endodomain of 41BB; CD3Zeta_endo = CD3 endodomain.

In study 10289, binding characteristics of the scFv part of the CAR in obe-cel to its target, human CD19, were explored. The applicant compared its performance in these assays with that of FMC63, a different anti-CD19 CAR currently in clinical use. The applicant noted that published data suggest that FMC63 and its own anti-CD19 scFv compete for the same binding site on CD19.

Performance of the applicant's CAR was determined in immunological assays as well as assays which measure motility and target engagement.

To test these reagents by flow cytometry, HEK293T cells were transfected to express human CD19. Transfected and non-transfected HEK293T cells were incubated with FMC63 or CAT scFv-Fc construct at a concentration of 10 µg/ml and labelled cells were dual stained with anti-V5 to show CD19 expression and antibody to the Fc tag to show binding of the scFv constructs. Dual staining allows correlation of FMC- and CAT-scFc binding with CD19 expression.

For the CAR backbones, T cells were transduced with lentiviral vectors encoding bicistronic cassettes expressing the marker gene mCherry upstream of an in-frame 2A ribosomal skipping sequence, followed by the CAR containing either CAT scFV or FMC63 scFv fused to a V5 epitope on the amino terminus. The DNA sequence for anti-CD19 scFvs were obtained from publications. Transduction efficiency was confirmed by flow cytometry analyses using antibodies described in Table 2.

Anti-CD19 scFV-Fc and FMC63, expressed in scFv format fused to a murine IgG2a Fc constant domain, were captured on a sensor chip and recombinant CD19 at known concentrations was injected over the respective flow cells with 150 s contact time and 600 s dissociation at 30 µl/minute of flow rate with a constant temperature of 37 °C.

Table 2: Antobody Panel for Flow Cytometry

Antigen	Antibody	Concentration
CD3	aCD3-BV365	1:80
V5	aV5-FITC	1:100
Live	LIVE/DEAD fixable dye	1:100

Table 2: Antobody Panel for Flow Cytometry (Continued)

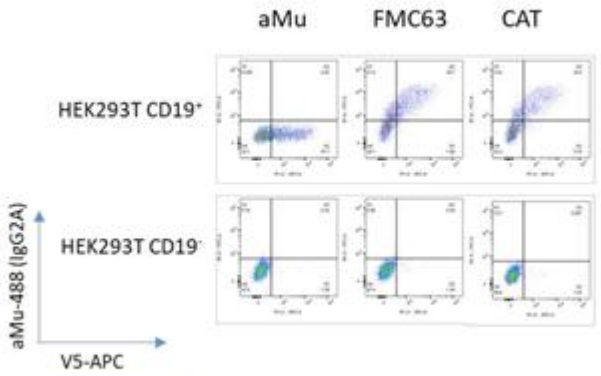
Antigen	Antibody	Concentration
Anti-CD19 CAR	CD19-RbFc	1:1
	Anti-Rabbit Fc AF488	1:100
mCherry	-	-

The sequence for the extracellular domain of human CD19 was obtained and experiments done to determine the key CD19 residues required for a CAT CAR and FMC63 binding.

To compare CAR expression of anti-CD19 scFv-Fc and FMC63, peripheral blood mononuclear cells transduced with anti CD19 CARs were stained with anti-CD3, to gate on the T-cell population and CAR expression was detected by staining for V5 epitope (for CAR independent staining) or soluble CD19-Rb Fc tagged (for CAR dependent staining). Cells displaying mCherry signature were considered transduced. Quantification of CAR positive cells was performed via MFI of V5 staining or MFI of CD19-Rb Fc on mCherry positive cells.

Results: As a negative control, non-transfected HEK293T cells were used. Both anti-CD19 scFv-Fc (here called CAT) and FMC63 scFv-Fc specifically recognised CD19 expressing cells (Figure 4).

Figure 4: Characterization of Anti CD19 Binding Domains by Flow Cytometry on HEK293T Cell Lines



aMu-488 (IgG2a): IgG2a specific anti-mouse antibody conjugated to AlexaFluor 488aV5-APC: anti V5 tag specific antibody conjugated to Allophycocyanin. aMu = secondary antibody alone.

Binding kinetics of the two antibodies were determined by surface plasmon resonance binding with results as shown in Figure 5. The CD19 concentration range was 1.95-500 nM for anti-CD19 scFv-Fc and was 7.8-250 nM for FMC63. The KD for anti-CD19 scFv-Fc was 1.44x10(-8) for anti-CD19 scFv-Fc and was 3.28x10(-10) for FMC63, when fitted with a Langmuir 1:1 binding model. CAT scFv-Fc construct had a similar on-rate as FMC63 scFv-Fc (2.153x10(5) 1/Ms versus s 2.076x10(5) 1/Ms), but a faster off-rate (3.096x10(-3) 1/s versus 6.810x10(-5)1/s).

Based on the measured dissociation rate, the half-life (t½) (t½ = ln/kd) of the interaction between anti-CD19 scFv-Fc and CD19 is predicted to be 3.7 minutes as compared to 2.8 hours for that between FMC63 and CD19 (Table 3).

Figure 5: Surface Plasmon Resonance Sensograms of Binding Kinetics Between CAT and FMC63 to CD19

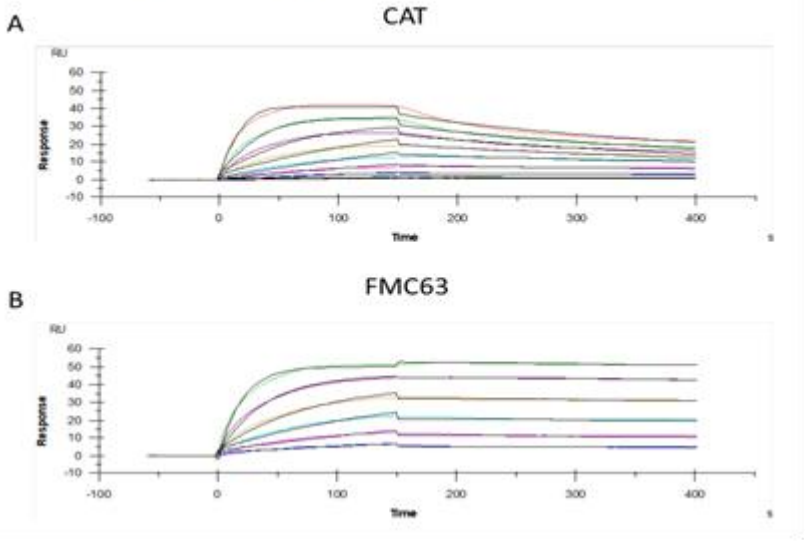


Table 3: Kinetic Measurements

Clone	*ka* (1/Ms)	*kd* (1/s)	KD (M)	$t_{½}$
CAT scFv	2.153E+5	3.096E-3	1.44E-8	3.7 minutes
FMC63 scFv	2.076E+5	6.810E-5	3.28E-10	2.8 hours

Results of epitope mapping showed that some of the same residues in CD19 were targeted by the two antibodies. Based on this information (not presented in detail here), FMC63 and its anti-CD19 scFv-Fc (here called CAT) were judged to bind to the same epitope on CD19.

To compare cell surface expression of the antibodies bound to CD19 without taking into account the binding affinity of the scFvs, expression was detected by staining for the tag added to the construct, V5. No difference was seen in the estimated number of CD19 binding sites per cell in CD19 positive cells. Both CAR T constructs were able to target soluble CD19.

CD19 binding affinities were 14.4 and 0.328 nM for anti-CD19 scFv-Fc and FMC63, respectively. The applicant concluded that its anti-CD19 scFv-Fc retained binding capacity for CD19 as measured by surface plasmon resonance and flow cytometry on transfected cell lines. Differences in affinities were mostly due to differences in kinetic dissociation rates. Finally, CAR constructs carrying a V5 tag on the CAR ectodomain, highlighted similar cell surface binding between anti-CD19 scFv-Fc and FMC63.

The basis of development of obe-cel is that it can offer different kinetics of engagement with CD19 from current CAR T cell products and that this difference will provide a benefit to patients of greater tolerability and better persistence leading to better efficacy overall. To support these claims, the applicant reported (Report Mpx2383a) in vitro experiments in which the performance of cells with its scFv construct was compared with that of cells with the established CD19 CAR T cells, with the FMC63 scFV.

Both CAR products were as designed (Chimeric receptors with 4-1BB signaling capacity provoke potent cytotoxicity against acute lymphoblastic leukaemia) except the FMC63 scFv was replaced with the scFv used in obe-cel.

The methods selected by the applicant sought to show attributes important for clinical activity.

1- Efficiency at killing antigen positive target cells

This was measured by 51-chromium release against a T cell leukaemia cell line (SupT1) engineered to express CD19: cell lysis was quantified. Flow cytometric cytotoxicity assays were done with effector and target cells co-cultured at varying ratios for 24 hours. Cells were stained for expression of CD2 and a live/dead marker as an assessment of viability, to estimate remaining viable target cells: this sought to determine activity of CAR T cells against target cells expressing CD19 at lower, physiological levels.

2- CAR T cell proliferation in response to target antigen

Proliferation was assessed by co-culturing effector and irradiated target cells at a 1:1 ratio in triplicates in 96 well plates. After 48 hours, the cells were pulsed with 1 µCi/well titrated thymidine and processed and specific proliferation was calculated.

3- Cytokine release.

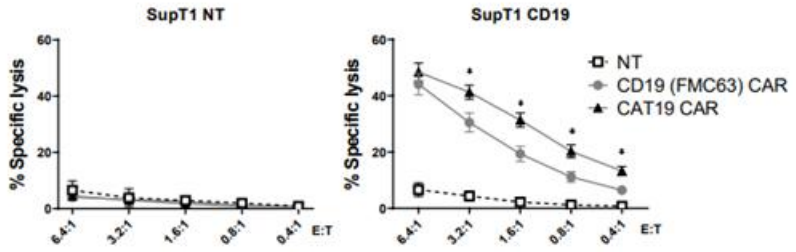
Cytokine concentrations in supernatants were quantified after 48 hours of 1:1 co-culture of effector and target cells in triplicate wells using a commercially available human Th1/Th2/Th17 cytokine kit.

Results: Cytotoxic activity of CAR T cells against the T cell leukaemia cell line (SupT1) engineered to express CD19 is shown in Figure 1 below. This figure shows that cytotoxicity of obe-cel (here called CAT19 CAR T cells) was greater than that of CD19 (FMC63) CAR T cells, particularly at low E:T ratios.

As shown in Figure 2, in flow-based killing assays using NALM-6 cells and SupT1 cells engineered to express low levels of CD19, cytotoxicity was seen, with obe-cel showing greater activity at low E:T ratios, although this did not reach statistical significance.

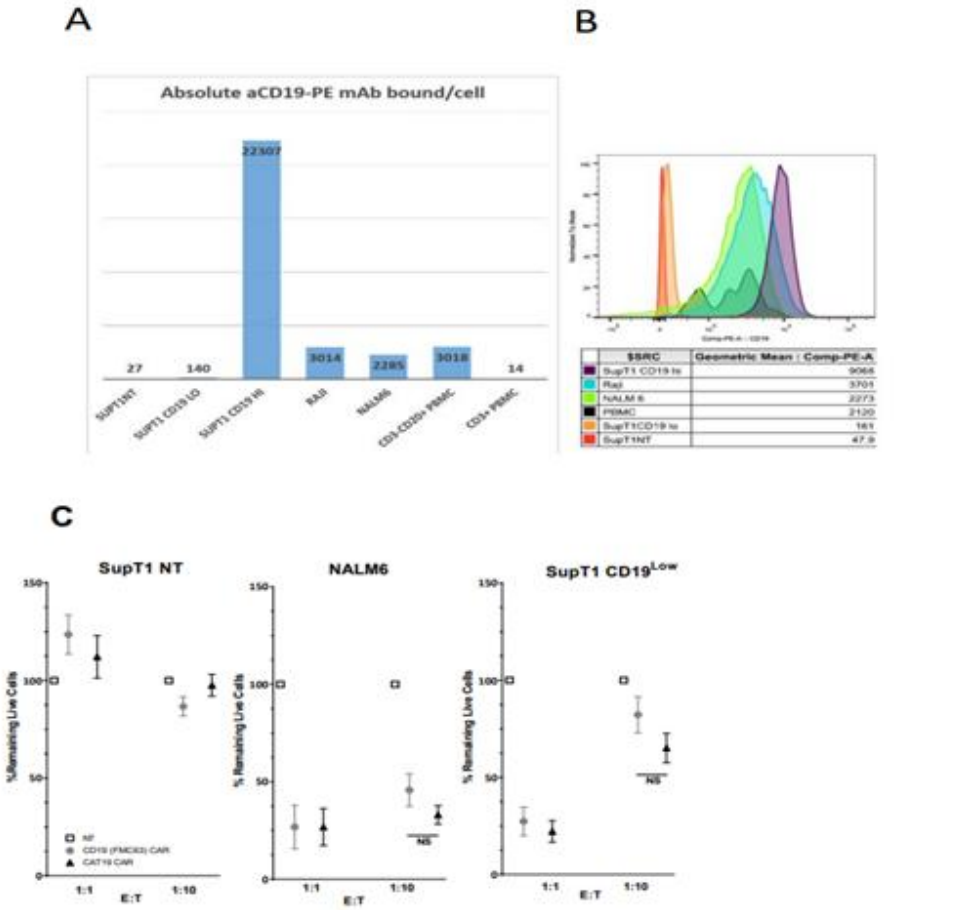
As in Figure 3, there was a proliferative response of each of the T cell products on stimulation with CD19+ target cells (Raji and NALM6). Obe-cel showed greater antigen-specific proliferation than did cells transduced with the FMC63 CAR.

Figure 1: CD19 CAR T Cells Demonstrate Antigen-Specific Killing of CD19+ Tumour Cells



The cytotoxic activity of CAR T cells was measured by standard 4 hour 51-Chromium release assay against a T cell leukemia cell line (SupT1) engineered to express CD19. Key: NT=non-transduced T cells; E=effector cells; T=target cells. Data, mean ± SE, n = 5; *, P<0.05, 2-way ANOVA.

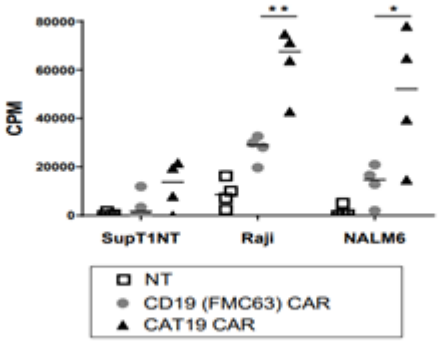
Figure 2: Flow-Cytometric Quantification of CD19 Expression Levels on Target Cells and in Response to CD19 CAR T Cells



CD19 expression levels measured using flow cytometric analysis and following exposure to CD19 CAR T cells in cells lines with different CD19 expression densities, using a PE QuantiBRITE Kit. Abbreviations: E=effector cells; HI=high density CD19; LO=low density CD19; NT=non-transduced; PBMC=peripheral blood mononuclear cells; SSRC= Side SCatter; T=target cells.
(A) Bars and numbers represent absolute CD19 phycoerythrin (PE) monoclonal antibody (mAb) bound per cell

(B)Distribution of CD19 expression (B, X axis = CD19)
(C) CD19 CAR+ T cells were incubated at 1:1 and 1:10 E:T ratios with non-irradiated target cells (SupT1NT, SupT1CD19LO and NALM6) for 24 hours. The remaining live cell fraction was calculated relative to the live cell fraction in the well co-cultured with non-transduced T cells. Comparisons were analysed using Wilcoxon matched-pairs signed rank test (non-parametric paired t-test)

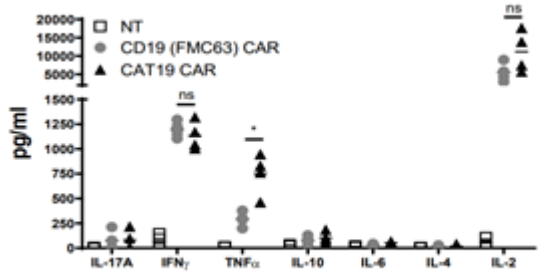
Figure 3: Proliferation of T Cells Transduced with CAT19 CAR and CD19 (FMC63) CAR



Proliferation was measured by the incorporation of ^{3}H-thymidine following a 72 hour 1:1 co-culture with irradiated CD19-positive (Raji & NALM-6) and CD19-negative (SupT1) cell lines.
Data, mean SEM, n=4; *, P<0.05, ** p<0.01, statistical comparisons were made with a two-tailed paired Student t-test;

Cytokine production by obe-cel and by CD19 (FMC63) CAR T cells in response to stimulation with CD19+ targets was similar except that cells from obe-cel secreted significantly more TNFα than did cells from the comparator (Figure 4).

Figure 4: Cytokine Production by CAT19 CAR and CD19 (FMC63) CAR T Cells



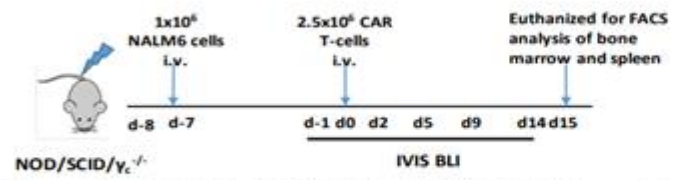
Production of cytokines in response to 1:1 co-culture with irradiated Raji cells measured by Cytokine Bead Array of culture supernatants taken at 48 hours. Data, mean SEM, n=4; **, P<0.01; NS, non= significant, statistical comparisons were made with a two-tailed paired Student t-test

The applicant concluded that CAT19 CAR transduced T cells show enhanced CD19-specifc cytotoxicity and proliferation compared to CD19 (FMC63) CAR T cells.

Proof of principle was established in a study described in report MPX2383b in which the product was tested for antitumour activity in nude mice bearing a human tumour NALM 6 xenograft. NALM6 is a human B-cell line established from a patient with acute lymphoblastic leukaemia (ALL) and cells express CD19. The cells were modified to express firefly Luciferase which emits visible light after exposure to D-Luciferin to quantify tumours by bioluminescence imaging (BLI).

Female NOD scid gamma mice (NOD.Cg-PrkdcSCIDIl2rgtmlWjl/SzJl) were used. These mice lack mature T cells, B cells and natural killer (NK) cells and have defective innate immunity. Briefly, mice aged 6-10 weeks old, were irradiated and then 1 day later were given an intravenous dose of ~1 million NALM 6 tumour cells, with fluorescent marker. Mice were then randomly assigned to 1 of 3 treatment groups: mice in Group 1 were given a control human T cell product that had not been transduced and thus expressed no CD19-targetting component; mice in Group 2 were given obe-cel; mice in Group 3 were given a CAR T cell product in which the scFv, as used in obe-cel, was replaced with FMC63 scFv and called CD19 (FM63) CAR; this scFv was used in earlier published studies and the applicant considered this to be a gold standard CAR. Mice were dosed 7 days after they were injected with the tumour cells at a dose of 2.5 million cells and were monitored to day 12 or 16 after injection of tumour cells when they were killed and FACS analysis of bone marrow and spleen undertaken to determine presence of disease and of CAR T cells. The study design is in Figure 1 below: it was based on initial testing by the applicant which showed an anti-cancer effect of CAR T cell products.

Figure 1: Experimental Schema



Mice were injected with 1x106 GFP+ Fluc+ NALM-6 cells 24 hours after sublethal irradiation and 7 days prior to CAR T cell injection or non-transduced T cells as negative control. Post termination of the experiment the animals' spleen and bone marrow were analyzed by flow cytometry

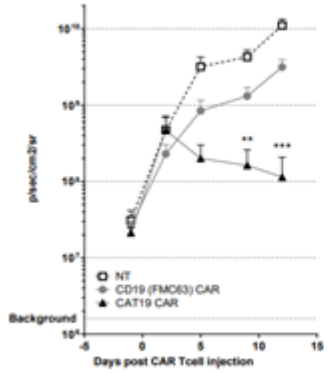
Results: Results are shown in Figures 2 (in which mice were followed to day 12) and 3 (in which mice were followed in a separate experiment to day 16). Control mice given untransduced T cells showed rapid, disseminated tumour infiltration as measured by the amount of bioluminescence (Figure 2, where NT = not treated i.e. given no CAR T cell). Treatment with obe-cel (called CAT 19 CAR) led to tumour regression whereas the same dose of CD19 (FMC63) resulted in lesser tumour burden but did not lead to regression.

In quantifying tumour burden, substantial differences were seen:
Gp 2 mice (CAT19 CAR T cells): 1.1x10(8) – 9.3x10(7) mean photons/sec/sq cm,
Gp 3 mice (CD19 (FMC63) CAR T cells) 3.2x10(9) – 7.7x10(8) mean photons/sec/sq cm

Two weeks after infusions of CAR T cells, blood and bone marrow were analysed for residual tumour and persisting CAR T cells. A higher number of NALM-6 tumour cells were seen in the bone marrow of mice treated with CD19 (FMC63) CAR T cells compared to CAT19 CAR T cell treated mice (mean NALM-6 cells/ml: 3x102 in CAT19 CAR T cell, 2.8x105 in CD19 (FMC63) CAR T cell cohort). Conversely, a greater absolute number of CAT19 CAR T cells were seen in bone marrow compared to CD19 (FMC63) CAR T cells (mean CAR T cells/ml: 5.1x104 CAT19 CAR; 2.0x104 CD19 (FMC63) CAR T cells (Figure 4) and blood (mean: CAT19 CAR T cells 18743, CD19 (FMC63) CAR T cells 2843 (also Figure 4).

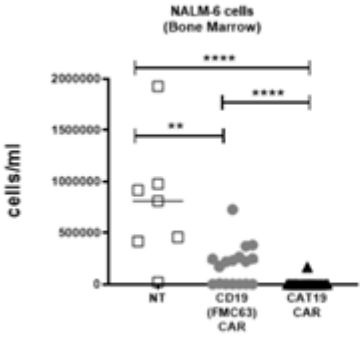
The expression of exhaustion markers LAG3, PD-1 and TIM3 on CAR+ T cells was similar in mice receiving CAT19 CAR or CD19 (FMC63) CAR T cells (Figure 5). Intracellular staining of Th1 like cytokines revealed greater expression of TNF-α in CAT19 CAR T cells. CAR T cells from the bone marrow and blood showed higher levels of CD127 (IL7-Rα) and intracytoplasmic expression of the anti-apoptotic molecule Bcl-2 (Figure 6) in CAT19 CAR treated mice.

Figure 2: Tumor Growth Experiments in Mice Bearing Fluc$^+$ NALM-6 Tumors



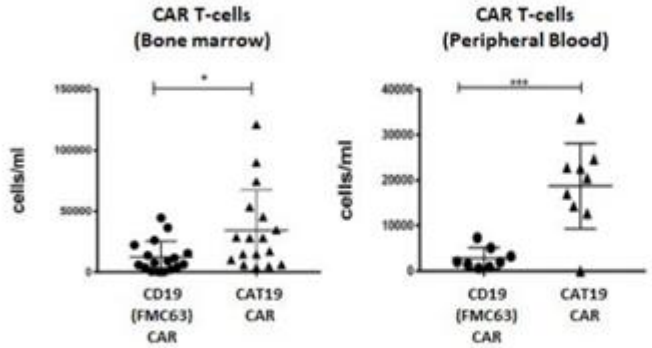
Photon emissions from FLuc$^+$ tumor cells were quantified and measured as maximum photon/sec/cm^2 /steradian (p/s/cm^2/sr). Lines represent cumulative results of light emission values ± SEM. Bioluminescence was determined in 2 separate experiments, n=18, Student t-test, **p<0.01, *** p<0.001

Figure 3: Residual NALM-6 Tumor Cells in the Bone Marrow of Mice Two Weeks Post CAR T Cell Infusion



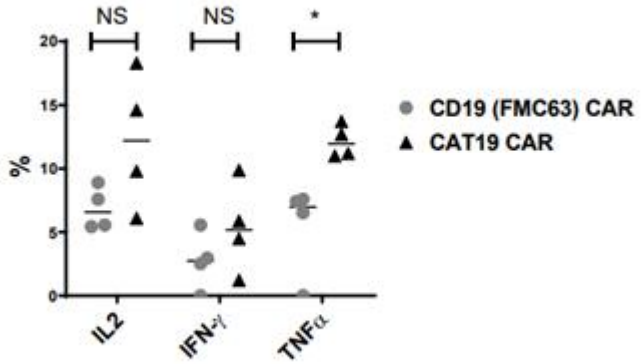
After termination of the experiment at 16 days following infusion of CAR T cells, absolute numbers of NALM-6 cells were assessed in bone marrow by flow cytometry, n=18, statistical analysis was done using a two-sided student t test; **, p<0.01, ****, p<0.0001

Figure 4: Persistence of CAR T Cells in Bone Marrow and Peripheral Blood of Mice Two Weeks Post Infusion



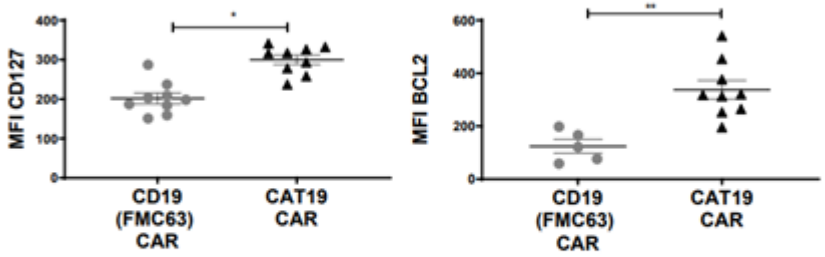
Left - Bone marrow CAR T cells: Mean number SEM CAT19 CAR T cells $3.4x10^4 \pm 8.1x10^3$, CD19 (FMC63) CAR T cells $1.3x10^4 \pm 3.1x10^3$ n=18, P<0.05. Right - there were greater numbers of CAT19 CAR T cells compared to CD19 (FMC63) CAR T cells in peripheral blood (CAT19 CAR T cells $1.9x10^4 \pm 3.1x10^3$, CD19 (FMC63) CAR T cells $2.8x10^3 \pm 8.2x10^2$, n=9, P<0.001. Statistical comparisons were made using a two-sided student t-test;

Figure 5: Cytokine Production in the Bone Marrow of Mice Infused with CAR T Cells



Percentage of cytokine-producing CAR T cells in bone marrow was determined by flow cytometry after gating on CAR+ T cells. Mean percent producing ± SD, n=4; two-sided student t test; *p< 0.05 are shown

Figure 6: CD127 and Bcl-2 Expression in the Bone Marrow of Mice Infused with CAR T Cells



Mean fluorescence of CD127 (left figure), and Bcl2 (right figure) positive cells in bone marrow as determined by flow cytometry after gating on CAR+ T cells. Data, mean SD, n=5 in CD19 (FMC63) CAR T cells and n=9 in CAT19 CAR T cells; *, $p< 0.05$, **, $p< 0.01$, two-sided student t test

These results indicate that, as the applicant noted, under conditions designed to give CAR T cells a numeric disadvantage, lower affinity CAR T cells mediate enhanced anti-tumour responses and expansion compared to high affinity CAR T cells. The applicant concluded that its obe-cel product (here called CAT19 CAR T cells) showed better efficacy and engraftment versus CD19 (FMC63) CAR T cells in mice given a leukaemic cell xenograft.

Secondary pharmacodynamics
No secondary pharmacodynamic studies were done.

Safety pharmacology
No safety pharmacology studies were done.

Pharmacodynamic drug interactions
No pharmacodynamic drug-drug interaction studies were done.

Overall conclusions on pharmacology
Obe-cel is a gene therapy product of autologous T cells transduced with a lentivirus to express a novel anti-CD19 chimeric antigen receptor (CAR). It is intended for use in adult patients with relapsed or refractory B-cell acute lymphoblastic leukaemia. CD19 is present on tumour cells and there are several approved CAR T cell products that target CD19 and are used in patients with cancer (e.g. Kymriah, Yescarta and Tecartus): the principle that treatment of patients with CD19+ve tumours with a CAR T cell product that targets CD19 is well-established. The use of T cells is expected to have a possible benefit of sustained anti-tumour activity if cells can engraft.

Obe-cel contains the 4-1BB costimulatory domain and the applicant designed the product with the intent that it has lower affinity binding with longer cell persistence. It is the applicant's contention that reduced affinity could confer improved CAR T cell survival after antigen (CD19) encounter, resulting in greater number of viable effector cells being available for effector function over time.

Cell binding in CAR T cells is dependent on their scFv region: in certain approved CAR T cell products, this is FMC63 is termed FMC634: in obe-cel, it is termed CAT or a term used in this report of CAT scFv-Fc.

CD19 binding affinities for the scFV in obe-cel and for FMC63 were determined by surface plasmon resonance and were 14.4 and 0.328 nM respectively, a difference of ~44-fold. This difference in binding affinity was due to an increase in the dissociation rate between CAT and CD19 compared with FMC63 and CD19, with similar association rates.

This means that obe-cel (or at least, its scFv part) binds to CD19 epitopes with a faster off-rate (3.1 × 10-3 s-1) giving a short half-life for engagement with CD19, estimated at 3.7 minutes in in vitro testing in comparison with FMC63, the scFv present in the approved CAR T cells (tisagenlecleucel, brexucabtagene autoleucel and axicabtagene ciloleucel): that has an estimated half-life for engaging with CD19 of 2.8 hours.

The applicant indicates this shorter duration of binding of obe-cel resembles more how endogenous T cells naturally engage with CD19. It is the applicant's expectation that this results in benefit to the patient of a more physiological T cell stimulatory effect from the engineered T cells, with a product that is better tolerated and less prone to risks from excessive T cell stimulation of cytokine release syndrome, a notable and potentially fatal risk of use of CAR T cells.

The concept of this product includes that this difference in binding profile translates to longer persistence of the engineered cells arising from less propensity of cell exhaustion. To prove these aspects clinically is beyond the scope of preclinical investigations but the promise was shown in the experiments in mice. To this extent, a novel CAR T cell product can be licensed on the basis of the data summarised here without a need to prove the differences claimed by the applicant. Expressed differently, the existing approved CAR T cell products, at the time of their initial approval, did not need to compare potential activity against products that were approved before them and so this standard need not be applied for a licensing decision for this product. Nevertheless, the uptake and use of this product will depend on its differentiation from existing products and the information presented can support the claim that the product has different binding characteristics and a suggested better efficacy profile. These results do not indicate that the product will be better tolerated by patients than existing products, however, as experiments in mice are not able to inform on that aspect.

Specificity for CD19 of obe-cel was shown in target cell lysis assays using cells engineered to express CD19 and greater cytotoxicity was seen with obe-cel than with product bearing the FMC63 scFv.

Production of cytokines (INF-gamma, TNF-alpha and IL-2) was generally similar between the two products, obe-cel and one containing the FMC63 scFv. Proliferative responses of CD19 (CAT) CAR T cells and CD19 (FMC63) CAR T cells were analysed on stimulation with CD19 positive target cells with the result indicating greater antigen-specific proliferation with FMC63 product than with obe-cel. Overall, the proposition that obe-cel may have reduced proinflammatory side-effects can be sustained by these data.

In an in vivo study in mice grafted with a human tumour cell expressing CD19, firstly, anti-tumour activity of obe-cel was shown in absolute terms, compared to mice given untransduced cells. The study also showed better anti-tumour activity of obe-cel as compared to a different CD19 CAR T cell product, CD19 (FMC63) CAR T cells. There were also reduced absolute numbers of tumour cells in bone marrow in mice given obe-cel compared to mice given the CD19 (FMC63) FMC63 CAR T cell product. The absolute count of CAR T cells in bone marrow and blood showed a higher amount of cells in mice given obe-cel as compared to mice given CD19

(FMC63) CAR T cells. The % cytokine-producing CAR T cells was also higher from mice given obe-cel than from mice given CD19 (FMC63) CAR T cells. Finally, both CAR T cell products had similar effects on expression of markers of T cell activation and exhaustion, but with obe-cel, there was a greater proportion of CAR T cells from obe-cel that expressed CD127 and Bcl-2 at the tumour site.

For the applicant, this set of findings provides evidence for its claim that use of obe-cel in human patients will result in a product with a better profile, in terms of cells showing decreased apoptosis, a longer duration of survival and thus better efficacy. It is difficult to see that the in vitro profile shown here should lead to demonstrably superior safety, but there is an extent to which the applicant acknowledge this e.g. in its statement: 'Although, it is difficult to directly correlate in vitro cytotoxicity of a CAR T cell therapeutic with clinical performance, given that the overall antileukaemia effect may be influenced by many other factors (e.g. CAR T cell expansion), however, enhanced in vitro cytotoxicity may indicate improved therapeutic potency, given a key requirement of the therapeutic is the killing of leukaemic cells.'

In terms of regulatory decision-making, it is not essential for the applicant to prove in its preclinical profile that its product will have a better safety profile: the preclinical data can be used to support this as a hypothesis, but its confirmation is dependent on clinical studies in patients. It suffices for this application that the applicant has shown that its scFv targets CD19 and leads to anti-tumour activity in experiments in mice xenografted with CD19+ tumour.

Secondary pharmacodynamics studies, safety pharmacology studies and studies into pharmacodynamic interactions were not done due to a lack of suitable methods. This is accepted.

In conclusion, the applicant's data set suffices to support expectation of benefit. There are no suitable means to prove the claims put forward for better tolerability and longer persistence other than testing in patients.

Pharmacokinetics

Pharmacokinetic studies
The applicant noted that conventional toxicology studies do not provide clinically relevant information for a CAR T cell therapy and the same applies to its pharmacokinetics and distribution. If given to normal animals, the human cells would be expected to be cleared in a manner not indicative of anything likely to happen to patients; the applicant view was expressed that as there is extensive prior clinical experience with other CAR T cell products, it is not relevant to consider this sort of testing in animals further.

Absorption
No absorption studies were done.

Distribution
No distribution studies were done.

Metabolism
No metabolism studies were done.

Excretion
No excretion studies were done.

Pharmacokinetic drug interactions
No pharmacokinetic drug-drug interaction studies were done.

Other pharmacokinetic studies
No other pharmacokinetic studies were done.

Overall conclusions on pharmacokinetics
The applicant argued that studies in animals into the kinetics of obe-cel are not relevant as the product engages only with human CD19 and is an autologous human cell therapy product. If the product were given to a human subject by mistake, it would be expected to be cleared in the same way as if given to an animal assuming each had a functional immune system. The absence of kinetic studies with this product is agreed.

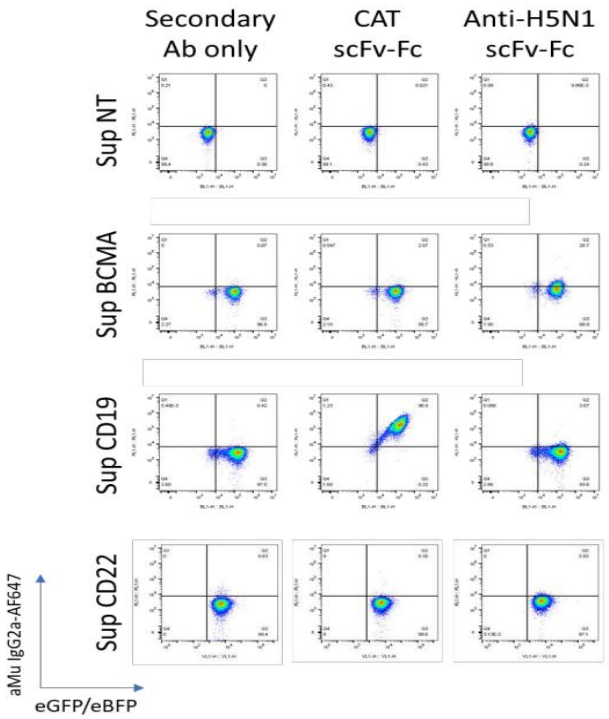
Toxicology
The CAR in obe-cel does not recognise CD19 from animal species and no preclinical safety studies in normal animals were done. The applicant view is that conventional toxicology studies would not provide clinically relevant information and this is agreed. Safety assessment was based on tissue cross reactivity studies and on literature-based evidence, including of a risk of insertional mutagenesis.

Tissue cross reactivity studies
Study 10288 described the production and profile of material to be used in subsequent tissue cross reactivity studies. In brief, the applicant fused the scFv region to a murine IgG2a construct and produced this in CHO cells: the resulting construct is called anti-CD19 CAT scFv-Fc. Separately, the applicant also made an IgG2a murine antibody with an scFv region targeting a totally different antigen, and anti-H5N1 flu antigen. The final purified protein for CAT scFv-Fc and anti-H5N1 scFv-Fc was >95% pure.

Flow cytometry was used to detect binding of anti-CD19 scFv-Fc to human CD19 expressed on SupT1 cells. As a negative control, non-transduced SupT1 and SupT1 cells transduced to express CD22 or BCMA were also tested. Binding of CAT scFv-Fc was compared to a non-relevant scFv-Fc antibody under similar experimental conditions.

Results: As shown in Figure 7, of anti-CD19 scFv-Fc (here called CAT scFv-Fc) specifically recognised CD19 expressing cells: the control anti-H5N1 scFv construct showed no binding to any of the cell lines.

Figure 7: Characterization of Reagents by Flow Cytometry in SupT1 Cell Lines



Cells were stained with 2 µg/ml of scFv-Fc antibody and detected with anti-mu IgG2a AF647 (Y-axis). Expression of GFP marker (for SupT1 CD19 and SupT1 BCMA) or eBFP (for SupT1 CD22) on X-axis. Control stain condition omitted primary scFv-Fc antibody.

The applicant concluded that the anti-CD19 CAT scFv-Fc construct retained specificity for CD19 and had no reactivity for CD22 or BCMA.

Study 10308 was a method validation study not intended to be in compliance with Good Laboratory Practice. Its objective was to define the best assay conditions for the staining of human CD19-expressing tissues with test item anti-CD19 CAT scFv-Fc and then to proceed to validate the method in terms of specificity, sensitivity, range, linearity, precision and reproducibility.

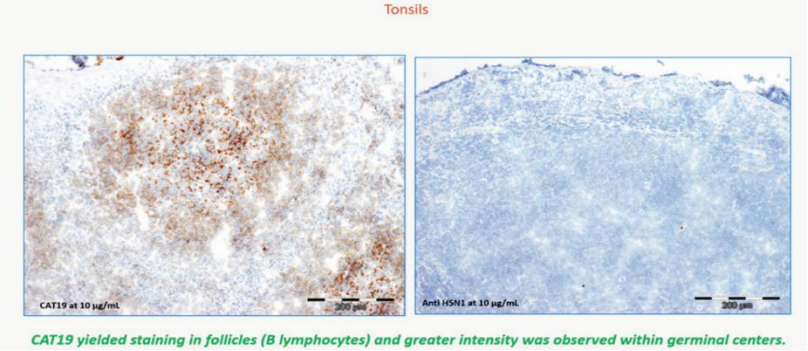
The method used sections of snap-frozen CD19 positive/negative control cells and sections from CD19-expressing tissues (human tonsil). All tissues were incubated with concentrations ranging from (0.03 - 30 microg/ml) for both test items, anti-CD19 CAT scFv-Fc and the negative control item, the anti-H5N1 antibody noted above.

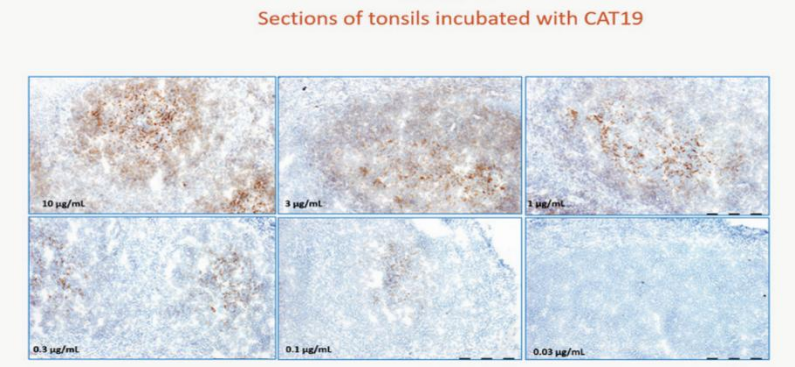
Specificity was tested by confirming (1) minimal to marked membranous, variably cytoplasmic, positive staining of tonsillar lymphoid cells consistent with B lymphocytes with anti-CD19 CAT scFv-Fc at concentrations 0.1 - 10 microg/ml and (2) no staining on CD19 negative control cells with anti-CD19 CAT scFv-Fc and none with the anti-H5N1 antibody in tissues and control cells, at the same range. Sensitivity was tested by membranous/cytoplasmic staining with the test item at the lowest concentration (0.1 microg/ml) in the human tonsil. For linearity, an increase of staining area and/or intensity approximately proportional to the increase of the test item concentration was tested at 0.1 - 3 microg/ml in human tonsil. The peak of specific staining intensity was reached at 3 µg/ml.

Sections of liver, kidney, spleen, cerebral cortex and colon were immunostained at 0.3, 1 and 3 microg/ml with anti-CD19 CAT scFv-Fc and with the negative control item, the anti-H5N1

antibody (3 microg/ml only). There was specific minimal-to-slight membranous, variably cytoplasmic, staining with anti-CD19 CAT scFv-Fc in splenic follicles, in cells suggestive of B lymphocytes at 1 and 3 microg/ml; no specific staining was observed at 0.3 microg/ml: no specific staining was observed with the negative control item Anti-H5N1 in any of the five selected tissues. Background staining was at an acceptable degree.

Both repeatability (intra-assay variation, precision) and reproducibility (inter-assay variation) were qualitatively evaluated with anti-CD19 CAT scFv-Fc and Anti-H5N1 at 0.3, 1 and 3 microg/ml in three independent assays run on three different days: they were deemed satisfactory. Images below show binding to human tonsil tissue of anti-CD19 CAT scFv-Fc (top picture, left) and of the negative control antibody targeting H5N1 from influenza virus (top picture right). The lower set of images shows binding to human tonsil tissue of anti-CD19 CAT scFv-Fc at concentrations 0.03 – 10 microg/ml. Based on these studies, concentrations of 1 and 3 microg/ml were selected for use in the full study: the lower concentration was judged optimal and the higher concentration was judged the highest not associated with non-specific binding.





Using the methods concluded as suitable from the work described above, the applicant conducted a human tissue cross reactivity study in compliance with Good Laboratory Practice. The report calls the test item CAT19 but for consistency in this assessment report, anti-CD19 CAT scFv-Fc, is used. As a negative control, the same anti-H5N1 scFv as was described above was used.

Frozen sections of human tonsil were used as a positive control, to show the capacity to identify binding to tissues. Briefly the method consisted of the main following steps.

- frozen sections were air-dried for at least 45 minutes at room temperature and fixed in zinc formalin for 2 minutes
- after rinsing the sections in distilled water, endogenous peroxidase activity was blocked
- sections were washed and slides uploaded for automated immunohistochemical staining

- test items, in antibody diluents, were incubated for one hour at room temperature, then blocking solution was applied for 4 minutes
- the detection system was applied as per the manufacturer's recommendations, for 16 minutes
- sections were stained with haematoxylin and bluing reagent and washed and dehydrated and then mounted.

As noted from preliminary studies, two concentrations of anti-CD19 CAT scFv-F were used - 1 and 3 microg/ml and one concentration of the negative control anti-H5N1 antibody was used 3 microg/ml. In addition, tissue was stained for tissue integrity evaluation: this involved staining endothelia with von-Willebrand antibody. Run conformity was assessed by including positive and negative control items on human tonsil tissue.

Slides were visualised and evaluated using a light microscope. Specific positive staining was graded according to the area and intensity on a 6 point scale as 0: negative, 1: minimal, 2: slight, 3: moderate, 4: marked, and 5: strong. Specific positive staining was also defined as a % of the number of positive cells stained as: very rare (<5% of cells of a particular cell type), rare (5-25% of cells of a particular cell type), occasional (25-50% of cells of a particular cell type) and frequent (50% of cells of a particular cell type).

The age of human donors ranged from 7 – 82 years old, with one exception of eye tissue sourced from a 96 year old female. The great majority were Caucasian.

42 tissues were selected for use in this study with tissue from at least 3 different donors used for each tissue: adrenal, blood cells/smears, bone marrow, breast/mammary gland, cecum, cerebellum, cerebral cortex, colon, duodenum, endothelium, eye, oesophagus, Fallopian tube (oviduct), gall bladder, heart (ventricle), ileum, jejunum, kidney, cortex, liver, lung, lymph node, muscle, striated, skeletal, peripheral nerve, ovary, pancreas, parotid, parathyroid pituitary, placenta, prostate, rectum, skin, spinal cord, spleen, stomach, testis, thymus, thyroid, tonsil, ureter, urinary bladder, uterus, cervix and uterus (endometrium).

Tissue integrity was shown to be acceptable - staining in endothelia was consistently observed with anti-Von-Willebrand antibody.

Results: Anti-CD19 scFv-Fc stained cells in lymphoid organs, particularly in lymphoid follicles. It produced minimal-marked and occasional-frequent membranous staining of resident lymphoid cells in follicles of the lymph node, tonsil, spleen (white pulp), thymus, in the Gut-Associated-Lymphoid-Tissue (GALT) throughout the gastrointestinal tract (stomach, duodenum, jejunum, ileum, cecum colon and rectum) and lymphoid nodules in the oesophagus and ureter. There were also instances of cytoplasmic staining too. There was also minimal (in intensity) and very rare-to-occasional membranous (with variable cytoplasmic) staining in lymphoid cell infiltrates in some other tissues, including breast and parotid salivary gland. Cell morphology and tissue distribution were consistent with the expected profile of CD19 expression on B lymphocytes. Staining was generally observed at both concentrations (1 and 3 microg/ml) but was more evident at the higher concentration.

The applicant concluded that in human tissues, of anti-CD19 scFv-Fc stained cell membranes (with variable cytoplasmic) in lymphoid follicular compartments of lymphoid organs and within lymphoid aggregates/infiltrates in some other tissues. Binding was consistent with lymphocytes and was therefore expected.

Single dose toxicity
No single dose toxicity studies were done.

Repeat-dose toxicity
No repeat dose toxicity studies were done.

Toxicokinetics
There are no toxicokinetic data.

Interspecies comparison
As no studies were done in animals, interspecies comparisons are not relevant.

Genotoxicity
No genotoxicity studies were done.

Carcinogenicity
No experimental studies into risks of carcinogenicity were done.

The applicant provided a discussion of the risk of carcinogenicity and of insertional mutagenesis as part of its non-clinical overview, as summarised here.
- patient characteristics
- risk recognised with approved CAR T cell products
- mechanisms of insertional mutagenesis
- features of obe-cel that relate to a reduced risk of insertional mutagenesis
- summary and conclusion.

The patient population to be treated have a very poor prognosis and will be those who have relapsed following prior treatment or who are refractory to treatment. Standard of care chemotherapy followed by autologous haematopoietic stem cell transplant has an increased risk of secondary malignancies, at ~8-29%. It is noted that this prior treatment is likely to include vincristine, which is a mutagen associated with secondary malignancies.

A retrospective review of data from 340 patients with r/r haematological or solid malignancies across 27 investigator-initiated clinical studies that were treated with immune effector (CAR T) cells, genetically modified with gamma retroviral vectors, demonstrated that in a cumulative 1027 years of long-term follow-up, 13 (3.8%) patients developed secondary cancer with a total of 16 events (4 haematologic malignancies and 12 solid tumours); 11 of these 16 tumours for which biopsies were available, were found to be transgene negative by polymerase chain reaction and replication competent retrovirus testing of peripheral mononuclear cells was negative in all 13 patients with secondary malignancies.

The applicant noted that there is a recognised risk of a secondary cancer arising following treatment with approved CAR T cells (Table 1) in patients with B cell malignancies or with multiple myeloma: both the US FDA and the EU EMA have highlighted this in public documents. The risk of insertional mutagenesis and development of secondary cancers is considered low: FDA and EMA communications indicating that, to 31 December 2023, 22 cases of T cell malignancies have so far been reported from an estimated 34,400 patients treated with commercially available BCMA- or CD19-directed autologous CAR T cell products a rate of <0.1%. Although 12 of these reports were from patients who had received 4 of the 6 marketed products (7 for Kymriah, 3 for Yescarta and 1 for Breyanzi and Carvykti), the regulators

indicated that the risk of T-cell malignancies was applicable to all 6 currently approved CAR T products. It is possible that some of these cases may not be due to insertional mutagenesis and they may instead be incidental as secondary cancers in patients who had prior chemotherapy, or they may represent a lineage switch of the underlying B cell malignancy. The possibility of viral vectors used to deliver CAR T cells inserting themselves into the host genome remains a major concern for inducing secondary cancers. Therefore, secondary cancer is a class warning on the labels of FDA-approved CAR T products: nevertheless, regulators consider that benefits of treatment continue to outweigh potential risks the applicant notes.

Table 1: FDA Approved BCMA- and CD19-Directed CAR T-Cell Therapeutics

CAR T Therapy	Manufacturer	Indication(s)
Tisagenlecleucel (Kymriah[1])	Novartis	r/r B-ALL (≤25 years of age) adult r/r LBCL; DLBCL; FL
Lisocabtagene maraleucel (Breyanzi[2])	Juno (Bristol-Myers Squibb)	Adult r/r LBCB; DLBCL; BCL; FL
Axicabtagene ciloleucel (Yescarta[3]),	Kite (Gilead)	Adult r/r LBCL, DLBCL
Brexucabtagene autoleucel (Tecartus[4])	Kite (Gilead)	Adult r/r MCL, r/r B-ALL
Idecabtagene vicleucel (Abecma[5])	Bristol-Myers Squibb	Adult r/r MM
Ciltacabtagene autoleucel (Carvykti[6]).	Janssen Biotech, Inc	Adult r/r MM

Abbreviations: B-ALL = B-cell acute lymphoblastic leukemia; DLBCL = diffused large B cell lymphoma; LBCL = large B cell lymphoma; FL = follicular lymphoma; MCL = mantle cell lymphoma; MM = multiple myeloma; r/r = relapsed or refractory

The applicant summarised clinical evidence of risk from products that were not marketed. The applicant summarised early clinical evidence to the effect that haematopoietic stem cell (HSC) gene therapy using gamma retroviral-modified HSCs to treat severe congenital immunodeficiency and other congenital disorders sometimes gave rise to unexpected instances of leukaemia. In 20 children with X-linked severe combined immunodeficiency (X-SCID) treated with autologous CD34+ HSC progenitors transduced ex vivo with a gamma retrovirus, RV, 6 developed T cell acute lymphoblastic leukaemia (T-ALL) as long as 6 years post-gene therapy which was considered due to LTR transactivation of proto-oncogenes mainly by LMO2 and CDKN2A. Development of leukaemia has also been reported from the treatment of X-linked chronic granulomatous disease (X-CGD), Wiskott-Aldrich syndrome and recently adenosine deaminase (ADA)-SCID by LTR transactivation of the proto-oncogenes (LMO2 and MECOM) driven by the gamma retroviral promoter in the LTR of the integrated provirus. The use of SIN LV has been proposed to reduce the risk of insertional mutagenesis due to the lack of promoter/enhancer activity in the LTRs of the integrated vector sequence. The provirus sequence of these vectors in host cells lacks any viral promoter or enhancer sequence in their LTRs rendering it SIN.

Insertional mutagenesis has been reported in studies of HSC gene-therapy using SIN LVs. 3 patients treated with elivaldogene autotemcel for X-linked cerebral adrenoleukodystrophy (CALD) were diagnosed with myelodysplastic syndrome (MDS) between 14- and 92-months post-infusion, due perhaps to LTR transactivation of the MECOM gene likely caused by the strong internal viral promoter used in the transgene.

However, insertional oncogenesis in clinical trials involving gamma retrovirally-transduced mature T cells has not been reported. T cells are considered terminally differentiated so that the integration of the vector into the locus of an oncogene or tumour suppressor gene is considered

unlikely to cause oncogenesis. Two cases of malignant transformation of CAR T cells have been described from a single clinical study. However, this study used high-voltage electroporation of naked plasmid transposon DNA and transposase for modification. A high insertion copy number was observed in one of the patients, but not the second. A clear molecular cause of malignancy due to transposon insertion was not determined. Transformation was related to the use of a transposase and does not easily inform on risks regarding retroviral vectors.

A patient treated with ciltacabtagene autoleucel for multiple myeloma who developed CAR-positive T cell lymphoma (TCL) 5-months post-infusion was reported. Clonality of TCL was confirmed with vector integration analysis with insertion in the 3' untranslated region of the PBX2 gene. Whole genome sequencing of germline samples revealed the presence of a heterozygous JAK3 variant that has previously been associated with antigen induced TCL. Although the contribution of the vector insertion into the PBX2 gene to TCL formation remains uncertain, this malignancy further appears to have arisen from a pre-existing clone present in the apheresis prior to CAR T manufacture.

Integrating vectors have been associated with adverse events related to vector integration which could cause malignancy. However, not all vector insertions that affect cell growth lead to malignant transformation. There are reports of transient clonal expansion of HSCs treated with SIN LV expressing beta (β)-globin for β-thalassemia and for X-linked SCID. Growth advantage in both cases was caused by the production of an aberrant splice variant of the high mobility group protein 2 (HMAG2) gene but did not result in malignant transformations.

In terms of the means by which insertional mutagenesis leads to a malignant transformation, the applicant summarised that this appears to result from a multistep process, in which the initial hit in most cases, an integration activating an oncogene, is followed by rearrangements, chromosomal translocations and other somatic mutations. T cells have an intrinsic resistance to transformation when modified with either gamma retroviral or self-inactivating lentivirus, as supported by long follow up studies of patients treated with CAR T-cell therapies with extremely low rates of occurrence of insertional oncogenesis.

The retroviral life cycle relies on integration of the viral genome into the host cell genome. This integrated genome is known as the provirus. Viral replication is driven by highly active enhancer and promoter sequences in the long terminal repeats (LTRs) of the provirus. Insertion of these promoters in the genome of host cells is a potent mechanism that can lead to the dysregulation of gene expression causing neo-oncogenesis. Studies in laboratory animals demonstrated that the integration of retroviruses can cause malignancy by integrating near proto-oncogenes. Integration sites that were identified repeatedly in multiple independent studies (termed common integration sites) were compiled in retroviral tagged cancer gene database. Vector integration can cause cellular malignancy by mutating host cell genes in several ways. The result is either the enhanced transcription or translation of oncogenes, chimeric and truncated transcripts or the inactivation of tumour suppressors.

The applicant highlighted features of obe-cel that it considers suggest a low risk of insertional mutagenesis.

• Obe-cel uses a self-inactivating lentiviral vector, which has a lower risk of cellular transformation through activation of LTRs, since the LTRs do not contain any viral promoter/enhancer sequences. This reduces likelihood of LTR activation of an oncogene leading to cellular transformation.

• Obe-cel uses an internal phosphoglycerate kinase-1 (PGK) promoter. This is a non-viral promoter with moderate activity in primary T cells. Avoiding a powerful or viral promoter may reduce the risks of cellular transformation.

• The median vector copy number (VCN) for all obe-cel patient lots in the FELIX phase II study is 2.4. VCN values above 4 are thought to be associated with an increased risk of cancer.

The applicant also note that long-lived cells can accumulate somatic mutations which may lead to cellular transformation. Analysis of long-term persistent CAR T cells with a product in two patients expressing the same CD19 CAR as obe-cel displayed a polyclonal integration pattern with no evidence of clonal expansion. In 5 years of follow-up, there have been no reports of secondary T cell malignancies.

In addition, in clinical experience with obe-cel to date, >200 patients have been dosed with follow up now >5 years after treatment with no reports of secondary T cell malignancies. 3 patients (2.4%) had potential secondary malignancies but in each case this was finally concluded to be linked to pre-existing conditions and confounding circumstances. As insertional oncogenesis is a rare event and may take years to develop, longer follow-up of patients receiving treatment with CAR T cells is required. It is the applicant's intent that all secondary malignancies arising in patients treated with obe-cel will be tested for obe-cel lentiviral insertion

In conclusion, the applicant proposed that with obe-cel, the use of SIN LV, low VCN and an internal non-viral promoter may reduce the risk of leukaemogenesis and the benefit-risk balance of obe-cel is favourable.

Reproductive and developmental toxicity
No reproductive toxicity or juvenile toxicity studies were done.

Local tolerance
No local tolerance studies were done.

Other toxicity studies
No other toxicity studies were done.

III.5 Ecotoxicity/Environmental Risk Assessment

The applicant provided an environmental risk assessment (ERA) of the use of this product. The product contains genetically modified cells created from use of a lentivirus to transduce the cells: that virus is a replication incompetent, self-inactivating (SIN) vector derived from human immunodeficiency virus type 1 (HIV-1).

Several clinical trials were done with obe-cel in the UK and approval for GMO manufacturer for use in these trials was obtained under the Genetically Modified Organisms (Contained Use) Regulations 2014.

Obe-cel is likely to be administered to a small number of patients: the applicant estimate that in the UK there are 5,813 patients with acute lymphoblastic leukaemia (5,649 in Britain).

The applicant indicates that it considers the transduced cells to be the genetically modified organism. The recipient patient is not to be classified as a genetically modified organism. The cells are not pathogenic and do not survive, persist or replicate outside the autologous host

organism unless special laboratory conditions and growth media are applied. Obe-cel is created from the cells of one patient and transfer of cells to another person would only arise by accident. In this case, it is likely that that recipient's immune system will eliminate the transferred T cells; only if that recipient is immunosuppressed would there be an expectation of notable exposure to the unintended recipient. The applicant consider that it follows that potential hazards of the commercial use of obe-cel for therapeutic purposes are therefore only related to human health. Potential hazards to animal health or the environment are not applicable.

Potential toxicity is considered for persons who could be unintentionally but directly exposed to obe-cel, e.g. those who administer the product or who may be in direct contact with the patient and potential effects for the environment at large that may be exposed to the product. Treated patients are most unlikely to consider blood donation but if they did, the SPC advises they should not and, in any case, they would be considered as unsuitable donors so no risk from exposure is identified by this means.

The four plasmids used for obe-cel manufacture are produced in the UK with measures in place to assure lack of contamination by other plasmids that could gave raised to a different GMO than obe-cel. Sequences of the plasmids are confirmed by next generation sequencing (NGS). All 4 plasmids have a 100% match with reference sequence.

The virus used to transfect cells is called LV18970 and is third-generation self-inactivating lentiviral vector based on Human Immunodeficiency Virus type 1 (HIV-1) and pseudo-typed with Vesicular Stomatitis Virus glycoprotein (VSV-G). It is not considered to be pathogenic as all pathogenic and replicative properties of the HIV virus have been removed.

LV18970 was designed to lack viral coding sequences that could result in replication competent lentivirus or immunogenic peptides. It is devoid of lentiviral enhancer-promoter sequences. Besides the transgene, the vector genome contains all the minimal components required for efficient packaging, reverse transcription and integration of the viral vector genome into the transduced T cells.

Expression of the CAR transgene is driven by the human PGK1 promoter and expression is enhanced by a modified woodchuck post-transcriptional response element (ΔWPRE or mtWPRE).

An assay for replication competent lentivirus is applied at release testing on both the purified vector and on the end of production cells from manufacturing of LV18970.

No shedding of the lentiviral vector from the treated patient into the environment is expected: the risk of formation of replication competent virus particles is negligible and the amount of residual infectious LV18970 particles in obe-cel drug product is negligible.

To manufacture obe-cel, patient samples are tested prior to leukapheresis for multiple pathogenic viruses: Human Immunodeficiency Virus 1 & 2 (Anti-HIV-1,2), Hepatitis B (HBsAg and anti-HBc), Hepatitis C (anti-HCV-Ab), Syphilis (anti Treponema pallidum) and Human T cell lymphotropic virus (Anti HTLV-1 and -2). Samples are required to be negative for further processing. The patient's white blood cells are collected by leukapheresis and material purified to isolate T cells, which are then stimulated to proliferate, transduced with the lentiviral vector, LV18970 to introduce the CAR gene, and expanded until the target CAR T cell dose is achieved. The cells are then washed, formulated and cryopreserved at -150°C.

After its manufacture, obe-cel is supplied for use in the patient who supplied the white blood cells with systems in place to ensure that only that patient receives the product. Supply is only to qualified treatment centres, with use overseen by a physician with experience in the treatment of haematological malignancies and trained in its administration and in managing patients given the product. Specific training on obe-cel handling is provided. Those handling the product will be trained healthcare professionals with use of appropriate precautions (gloves, protective clothing and eye protection). Once thawed, the product does not require reconstitution or dilution and is to be used on days 1 and 10 (± 2 days). After dosing, unused obe-cel or waste material is to be disposed in line with applicable biosafety guidelines. Treated patients are to be enrolled in a 15-year long-term follow-up scheme to gather data in the longer term.

Obe-cel is not intended to be released directly introduced into the environment.

A hazard is identified of mobilisation or recombination of integrated lentiviral vector constructs upon infection of the transplanted cells with HIV or retroviruses in the patients with an active infection.

A risk is identified that a recombination event may occur during vector production that results in a replication competent lentivirus (RCL) in the product which may be pathogenic in humans. Both the lentiviral vector and obe-cel are tested for the presence of RCL based on detection of VSV G DNA, which is indicative of the presence of RCL. With a limit of detection of 5 VSV-G copies per reaction, no detectable RCL has been observed in obe-cel batches manufactured thus far.

The cells in which the lentiviral vector is produced was confirmed negative for several adventitious viruses, including HIV-1, HIV-2, HTLV-1, HTLV-2 and retroviruses before use in the LVV manufacturing process and so should not give rise to RCL.

The applicant view is that the risk of transmission of RCL, either through direct accidental exposure or through shedding, is negligible.
In registering obe-cel, the MHRA is the Competent Authority for medicinal products but is not the Competent Authority for release into the environment of a genetically modified organism. In accordance with Human Medicines Regulations (2012), the national Competent Authority should be consulted.

The use of obe-cel is not expected to result in a significant risk to the environment. It was considered that cells in obe-cel are not an organism (isolated human cells cannot be considered to be an organism) and therefore they are also not a genetically modified organism. However, the product contains the lentiviral vector, which is genetically modified and an organism. It was considered there to be no greater risk to the environment than with other CAR T cell product that are used in a similar manner as proposed for obe-cel.

Overall conclusions on toxicology
Obe-cel is an autologous product with each batch manufactured for a specific patient: it is not to be used in any patient other than that for whom it was made.

CD19 is a well-established target for CAR T-cells used in patients with B cell cancers. In a tissue cross reactivity study, no unexpected binding was seen. As the cell product itself cannot be used in tissue cross reactivity studies, the tested material was the scFv part of the CAR used in obe-cel and this is an acceptable approach: this is the part of obe-cel that targets the cells to CD19. There

was binding of this scFv construct in obe-cel to lymphocytes, as expected, and this was noted in B cells in lymphoid organs and in other organs with lymphocyte cell infiltration.

General toxicity studies have not been done: the scFv in this product targets human CD19 and studies in normal animals are not able to indicate general toxicological effects of potential relevance to humans. There are risks of cytokine release syndrome (CRS) or of immune cell associated neuronal toxicity syndrome (ICANS) but these are already recognised based on prior clinical experience with other products and no further animal studies are needed or are appropriate to assess these risks.

Due to the risk of acute toxicity arising from use of this product, the SPC indicates that the product should only be used where there is immediate access to tocilizumab and emergency equipment to manage CRS should that arise. CRS did occur in the majority of treated patients (69%) with median onset time of 8 days and a duration of 5 days. The split dosing schedule with a lower dose on day 1 then a higher dose of day 10 offers capacity to withhold the second dose should the first dose not be tolerated.

Reproductive and developmental toxicity studies have not been done: these are not feasible in animals for CAR T cell products and are also not required for products intended for use in patients with advanced cancer. For this product, patients will also be given chemotherapy (fludarabine and cyclophosphamide) which are genotoxic and pose a risk of foetal harm if used in pregnancy and can be present in milk and pose a hazard to breastfed neonates.

Genotoxicity and carcinogenicity studies have not been done and are not required for a medicinal product intended for use in patients with advanced cancer, according to regulatory guidance (ICHS9 Non-clinical evaluation for anticancer pharmaceuticals).

There is some risk of genomic insertion and thereafter of insertional mutagenesis and a T cell cancer arising after use of obe-cel. It is likely that with any integrating virus, this risk cannot be eliminated completely and the risk therefore needs to be set in the context of the clinical benefit demonstrated for the product. Vector integration could cause cellular malignancy by mutating host cell genes which could result in either enhanced transcription or translation of oncogenes or inactivation of tumour suppressors. As summarised in the report above, obe-cel has design features that seek to reduce risk of insertional mutagenesis.

For each individual patient treated, the risk of a cancer arising from the treated cells is theoretical. Noting the prognosis of the population without treatment, the chance of cancer arising would only be relevant in those who benefited from treatment i.e. withholding treatment to prevent the risk of a tumour arising from insertional mutagenesis is not an appropriate approach, as evidenced by the fact that approved CAR T cell products remain licensed and used as they are considered to retain a positive risk:benefit balance, in regard to this risk of insertional mutagenesis. Recent FDA and EMA communications indicate that 22 cases of T cell malignancies were reported from an estimated 34,40, a rate of 0.06%, which is likely to be an overestimate and some of these cases of T cell malignancy may not be related to the use of retroviral vectors. The same judgement can be applied to obe-cel. Patients already have one cancer and the prior treatment/conditioning regimen might be associated with an increased risk of cancer arising in patients given obe-cel. Should a cancer arise following an insertional mutagenic effect, it would likely be rare (it has not been seen to date in treated patients) but it may also take years to develop, in which case, the absence of cases, thus far, is less reassuring. The applicant proposes to monitor patients in the long term after treatment with the intent to identify cancer

arising in T cells treated with obe-cel. Further cancers that do arise in treated patients will be analysed for obe-cel lentivirus insertion. The applicant has given a detailed and thorough consideration of this risk.

Another identified risk is that a recombination event may occur giving rise to replication-competent lentivirus (RCL), despite that the vector used in obe-cel is replication-deficient and its production uses a split-genome design to avoid formation of RCL.

The vector used in obe-cel contains the woodchuck post-transcriptional response element to, presumably, increase gene product expression. It is not clear if this may also promote expression of the woodchuck hepatitis virus X protein which may be linked to liver cancer. The applicant has discussed this further below.

The woodchuck post-transcriptional regulatory element (WPRE) present in the obe-cel vector is derived from woodchuck hepatitis virus (WHV). When transcribed to RNA, this region of WHV plays an important role in facilitating nuclear export of viral mRNA, with all four of the major mRNAs required for viral replication containing this sequence. The WPRE has a tripartite structure, with each individual element able to promote the nuclear export of RNA, but when combined they function co-operatively. Nuclear mRNA export mediated by the WPRE occurs via CRM1-dependent and -independent mechanisms. Reporter studies have demonstrated that when placed in the sense direction in the 3' untranslated region (UTR) of heterologous transcripts, the WPRE can increase transgene expression. Its use has been widely adopted in retroviral and lentiviral vectors to increase nuclear export of viral and transgene mRNA, to increase viral titres and transgene expression, respectively.

Inclusion of the WPRE in the obe-cel vector is advantageous because it facilitates the following processes: 1) the termination of transcription, which improves the safety profile of the vector by reducing the likelihood of transcriptional readthrough occurring; and 2) nuclear export of mRNA when included as a cis-acting element, thereby improving transgene expression and viral titre.

Regarding the risks associated with the use of the WPRE, it contains additional elements within its sequence, including the 5' end of the WHV X protein, which encodes an N-terminal fragment of the protein, the X protein promoter sequence and an enhancer sequence.

The X protein plays a role in the replication of viral DNA, by transactivating viral and cellular promoters, and the generation of infectious virions. As woodchucks infected with WHV frequently develop hepatocellular carcinoma (HCC), and the X protein is required for viral replication and infection, it was originally thought that the X protein contributed to oncogenesis. However, this appears not to be the case, with insertional mutagenesis being the main driver of oncogenesis. Insertion site analysis of HCC tumours from woodchucks infected with WHV showed that the genome inserted close to or into genes of the myc family, including N-myc1 and N myc2. Rearrangement of the c-myc gene, leading to increased expression, has also been reported. Insertion of the WHV genome into the 3' end of the myc genes was found to increase myc expression and contribute to oncogenic transformation. Further evidence supporting insertional mutagenesis, as opposed to X protein expression, as a factor triggering oncogenesis comes from in utero genotoxicity studies demonstrating that primate lentivirus (human HIV) does not promote HCC when either a wildtype or a mutant WPRE that cannot express X protein is used, whereas infection with non-primate lentivirus does cause HCC to develop. Integration site analysis of HCC tumours from mice infected with non primate lentivirus showed that provirus

integration frequently occurred in known oncogenes or tumour suppressor genes. Therefore, oncogenesis is linked to insertional mutagenesis and not X protein expression.

It should be noted that the WPRE used in vector for this product contains the 5' end of the gene, encoding an N-terminal fragment, and the C-terminal domain of the X protein is important for its function, with the deletion of the last 16 amino acids rendering WHV mutants unable to produce infectious virus. Similarly, complete ablation of X protein expression, by mutation of the start codon from ATG to TTG, also prevents viral infection. Mutation of the ATG start codon of the X protein gene is a simple mechanism to block its translation and expression.

An alternative approach to blocking translation is to mutate the promoter region of the X protein gene to prevent expression. Transcription of the X protein is driven by a short promoter located immediately upstream of the ATG start codon. Deletion mapping of the X protein promoter showed that the 21 nucleotides before the ATG start codon were essential for its function, with mutational analysis identifying key nucleotides for promoter activity.

The WPRE present in the vector corresponds to nucleotides 1093 to 1681 of the WHV genome. To reduce the risk of using the WPRE in the obe-cel vector the following steps were taken: 1) mutation of the promoter sequence upstream of the X protein gene to ablate its activity; and 2) mutation of ATG start codon of the X protein gene to TTG to block translation.

In conclusion, for the development of this product, there were no data provided from testing in animals as such data are not of relevance to indicate potential clinical toxicity of obe-cel. The absence of in vivo studies for general toxicity, genotoxicity, carcinogenicity and reproductive toxicity is acceptable.

III.6 Discussion on the non-clinical aspects

The grant of a marketing authorisations was recommended.

A condition was applied to the approval that the MAH work with the MHRA to resolve, to the satisfaction of the Department for the Environment, Food and Rural Affairs (Defra), any concerns it may have with this product, about deliberate release of a GMO into the environment.

IV CLINICAL ASPECTS

IV.1 Introduction

Clinical Development Plan for Obe-cel

Study Identifier	Study Design	Number of Patients Enrolled/ Infused	Patients Diagnosis	Efficacy Data	Safety Data	Study Status; Type of Report
FELIX	Global, multi-center, single arm, open label Phase Ib/II; follow-up duration: 24 months Once all patients completed 24 months, long-term efficacy and safety evaluation up to 15 years after obe-cel infusion in a separate extension (AUTO-LT1).	Cohort A from Phase II: 112 enrolled / 94 infused	Adult r/r B ALL with morphological disease (≥ 5% blasts in BM at screening) (Cohort A)	**Primary:** ORR, CR, MRD-neg remission, DOR, EFS, OS	NR	Follow-up ongoing; CSR
		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	NR	
		Pooled All Cohorts from both phases (Ib/II): 153 enrolled / 127 infused	Adult r/r B ALL with: • morphological disease (≥ 5% blasts in BM at screening) (Cohort A) • morphological remission and MRD-positive status at screening (Cohort B) • isolated EMD at screening (Cohort C)	ORR, CR, MRD-neg remission, DOR, EFS, OS	**Primary:** AEs, laboratory results, vital signs	

Study Identifier	Study Design	Number of Patients Enrolled/ Infused	Patients Diagnosis	Efficacy Data	Safety Data	Study Status; Type of Report
ALLCAR19	National (UK), multi-center, single arm, open label Phase I	26 enrolled/ 20 infused	Adult r/r CD19-positive B ALL	ORR, CR, MRD-negative CR, EFS, OS	AEs, CRS, ICANS	Follow-up ongoing; publication (Roddie et al, 2021; Roddie et al, 2023)
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 MEDS database: 107 enrolled / 84 infused	Adult r/r B ALL	ORR, OS, EFS	AEs, deaths	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	CRS, ICANS/ immune-mediated neuro-toxicity AEs, nervous system or psychiatric disorder AEs	Completed; report

B ALL=B-cell precursor acute lymphoblastic leukaemia; BM=bone marrow; brexu-cel=brexucabtagene autoleucel; CRS=cytokine release syndrome; CR=complete remission; CSR=clinical study report; DOR=duration of remission; ECA=external control arm; EFS=event-free survival; EMD=extramedullary disease; ICANS=immune effector cell-associated neurotoxicity syndrome; MAIC=matching-adjusted indirect comparison; MEDS=Medidata Enterprise Data Store; MRD=minimal residual disease; NR=not reported; ORR=overall remission rate; OS=overall survival; Ph+=Philadelphia chromosome translocation present; 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.

Bioanalytical methods

The cellular kinetics and immunogenicity of obe-cel were characterized in Study AUTO-AL1, referred to as the FELIX Study. In addition, replication competent lentivirus (RCL) testing was performed. All these analytical methods were developed by the sponsor or by vendors on behalf

of the sponsor. Bioanalytical methods used to characterise the kinetics, immunogenicity and RCL by the Applicant are summarised in Table 1.

Table 1: Summary of Analytical Methods Developed by and/or for Autolus and Associated Validation Status

Purpose of Method	Scientific Basis of Method	Validated / Qualification	Critical Validation Characteristics	Comments
Assessment of CAR- T cell expansion and persistence in peripheral blood	ddPCR	Yes / GCLP	**Specificity**: No interference detected assay is a specific duplex assay to L-Psi CAR-T DNA and reference gene RPP30 without significant cross-reactivity **Sensitivity**: LOD = 11 copies per reaction; LOQ = 21 copies per reaction **Accuracy**: not tested **Reproducibility**: 1.6-16.4% CV **Precision**: 1.6-27.6% CV	Autolus designed primers and probe for L-Psi vector Autolus provided positive controls
Assessment of CAR-T expansion and persistence in the BM	ddPCR	Yes / GCP	**Specificity**: Not tested. **Sensitivity**: LOD = 11 copies per reaction; LOQ = 21 copies per reaction. **Accuracy**: Not stated. **Precision**: Not tested.	Autolus designed primers and probe for Lenti Psi vector
Assessment of RCL in DNA/PBMC	qPCR	Yes / GCP	**Specificity**: Primers are specific to VSV-G sequence **Sensitivity**: LLOD = 4.14 copies per reaction; LOQ = 18.4 copies per reaction **Accuracy**: For CQ values <28, average replicate to be within 2.5 CQs from each other. **Precision**: $R^2 \geq 0.97$	Biogazelle (now Cellcarta) took over the RCL qPCR assay from October 2022 onwards Autolus provided VSV-G gene sequence
Assessment of RCL in whole blood	qPCR	Yes/CGMP	**Specificity**: specific to VSV-G sequence **Sensitivity**: LOD = 5 copies per reaction; LOQ = 25 copies per reaction **Accuracy**: met acceptance criteria for QC samples (%RE-25% to 50%) **Precision**: Intra-plate 0.1-5.5% CV; Inter-plate 0.3%-7.0% CV; Inter-operator 2.0-4.7% CV	Avance Bioscience performed RCL qPCR from January 2021 to September 2022 Autolus provided VSV-G gene sequence
Assessment of cellular immunogenicity in PBMCs	ELISpot	Yes/ GCP	**Specificity**: not tested. **Sensitivity**: LOD = 5 spots/well at $3x10^5$ cells/well or 2 spots/well at $1x10^5$ cells/well; LOQ = 20 spots/well (all cell concentrations); ULOQ= 450 spots/well (all cell concentrations). **Accuracy**: not tested **Precision** Intra-assay precision ≤ 30% CV	Autolus provided the CAR sequence for peptide control. Screening of peptide pools against the CAR is non-regulated (there is no positive peptide control against the CAR).
Assessment of humoral immunogenicity in serum	ECL direct binding immunoassay	Yes/ GCP/GCLP	**Specificity**: To AUTO1 CAR protein antibody **Sensitivity**: Screening/titer cut point determined as 1.05* in study cut point (normalized signal) with a 5.0% false positive rate. Screening assay to ≤ 100 ng/mL of surrogate positive control antibody. **Accuracy**: Robustness for each control CV ≤ 20% **Precision**: Inter-assay: negative control CV ≤ 20%; positive control (high low and mid) CV < 20%.	Autolus provided the soluble CAR

Purpose of Method	Scientific Basis of Method	Validated / Qualification		Critical Validation Characteristics	Comments
				Intra-assay: negative control CV ≤ 20%; positive control (high low and mid) CV < 20%.	
Assessment of CAR-T detection in whole blood by intracellular staining	Flow cytometry	Yes/ GScP		**Specificity**: Specific to CAT19 CAR-T cells **Sensitivity**: LOD= Intracellular 0.85 CAT19 CAR-T cells/µL; LLOQ= Intracellular 3.11 CAT19 CAR-T cells/µL **Precision**: Inter-operator < 20% CV	An anti-idiotypic antibody specific for the CAT19 binding region was developed at Autolus

Abbreviations: BM=bone marrow; CAR=chimeric antigen receptor; CQ=quantification cycle; CV=coefficient of variation; ddPCR=droplet digital polymerase chain reaction; ECL=electrochemiluminescence; ELISpot=enzyme-linked immunosorbent spot; GScP=good scientific practice; GCP=good clinical practice; GCP=good clinical laboratory practice; LOD=limit of detection; LLOD=lower limit of detection; LLOQ=lower limit of quantification; LOQ =limit of quantification; L-psi=Lentiviral psi; PBMC=peripheral blood mononuclear cell; qPCR=quantitative polymerase chain reaction; RCL=replication competent lentivirus; RPP30=ribonuclease P/MRP subunit p30; VSV-G=vesicular stomatitis virus G protein.
[a] In study modify cut point based on the signal of pre-dose study samples (please see Bioanalytical Report).

Pharmacokinetics/ Pharmacodynamics analytical methods

B Cell Aplasia

B cell aplasia in patients' peripheral whole blood was assessed using flow cytometry. B cells were defined as CD45+CD3-CD19+ cells. True count beads used in the assay determined absolute cell numbers and a patient was considered to be in B cell aplasia if B cells were <20 cells/µl.

Across publications, no standard cut-off has been used for B cell aplasia. For example, very different cut-offs were used in the ELIANA study, where the cutoff was ≥1% CD19+ cells in viable white blood cells. In the ALLCAR19 study, the cutoff was of >110 CD19+ B cells/µL. In a later publication, a simple cutoff of ≥20/µL was used and this cut-off was used to determine B cell aplasia in the FELIX study.

Minimal Residual Disease

Minimal residual disease (MRD) refers to the measurable number of cancer cells that remain in the patient during and following treatment. Several methods were used during the conduct of the FELIX study to ascertain accurate and sensitive detection of low levels of MRD,

MRD by Next-generation Sequencing (NGS)

An in vitro diagnostic assay which utilizes NGS to identify frequency and distribution of clonal sequences in DNA extracted from bone marrow from patients with B cell acute lymphoblastic leukaemia (B ALL) was used. The assay measures MRD to monitor changes in the disease burden during and after treatment. The assay has a sensitivity of 10-6 (1 B ALL cell in a background of 1,000,000 nucleated cells) and requires a calibration archival sample to enable identification of leukemic clones of interest.

MRD by Flow Cytometry Method MRD by flow cytometry was assessed in bone marrow aspirate by a validated assay. The MRD flow panel measures leukemic-associated immunophenotype with a 10-4 (1 B ALL cell in a background of 10,000 nucleated cells) MRD detection level.

MRD by Immunoglobulin/T Cell Receptor Real-Time Quantitative Polymerase Chain Reaction Method

Real-time quantitative polymerase chain reaction (RQ-PCR) MRD analysis was performed by a validated assay at blood glucose level on DNA extracted from bone marrow using real-time quantitative (RQ-PCR) analysis of immunoglobulin (Ig) and T cell receptor (TCR) gene rearrangements. The RQ-PCR assay has a 10-4 MRD detection level. The assay requires a

calibration sample (at least 3-5% blasts) at screen to enable identification of Ig/TCR rearrangements.

Cytokines
An electrochemiluminescence platform was used alongside a validated panel of 10 multiplex pro-inflammatory off-the-shelf kits measuring biomarker analytes including IFN-γ, GM-CSF, IL-2, IL-5, IL-6, IL-7, IL-8, IL-10, IL-15, and TNF-α that are associated with the inflammatory response and regulation of the immune system. Serum samples of obe-cel patients were used to quantify cytokines.

Immunogenicity
Cellular Immunogenicity 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 at day 28, month 3 and relapse was assessed using an off-the-shelf validated IFN-γ enzyme-linked immunosorbent spot (ELISpot) assay.

This assay was qualified, rather than being fully validated, as full validation could not be performed since positive control samples could not be identified ahead of initiating validation.

Humoral Immunogenicity To assess humoral immunogenicity, a validated electrochemiluminescent direct binding immunoassay was used to assess anti-drug antibody (ADA) to obe-cel. The presence or absence of anti obe-cel CAR protein ADA in serum was assessed at baseline (Day -6) and post obe-cel infusion at Day 28, at Month 3 and at relapse. Additionally, the ADA titre was determined in samples that screened positive for ADA. The titre reported corresponds to the lowest dilution for which a signal above the cut-off value was measured.

Replication Competent Lentiviral Analyses of Vector To demonstrate absence of RCL in patients transduced cells, RCL detection by quantitative polymerase chain reaction (qPCR) was performed on peripheral whole blood of patients.

Pharmacokinetic data analysis

PK Data Analysis Method
The pharmacokinetic parameters evaluated for obe-cel included C_max (maximum concentration of CAR T cells in peripheral blood), T_max (time to reach maximum concentration), $AUC_{0–28}d$ (area under the concentration-time curve from day 0 to day 28, representing overall exposure), and persistence (duration of detectable CAR T cells in peripheral blood and bone marrow). These parameters were derived from measurements of CAR T-cell levels in peripheral blood using digital drop polymerase chain reaction (ddPCR) assays and flow cytometry.

Non-compartmental analysis (NCA) was used to calculate the PK parameters. NCA is suitable for therapies where the compartmental distribution is complex or not well-defined, as is the case with cell-based therapies. The specific software used for NCA was not explicitly mentioned in the provided data. Standard NCA assumptions were applied, such as linear kinetics over the time interval assessed.

Statistical Methodology
Descriptive statistics—including mean, median, standard deviation, and range—were calculated for PK parameters across the patient population. Exploratory analyses were performed using simple linear regression to evaluate relationships between PK parameters (log_{10}-transformed C_max and $AUC_{0–28}$d) and critical quality attributes (CQAs) such as vector copy number (VCN) and transduction efficiency. Ninety-five per cent confidence intervals (CIs) were calculated for the estimated effects in the regression analyses. Reported p-values were descriptive and not intended for formal statistical inference. No specific acceptance ranges were defined for the PK parameters or statistical analyses, given the exploratory nature of the studies.

Models and Software Used
Simple linear regression models were employed to assess relationships between PK parameters and CQAs. The purpose was to identify potential factors influencing CAR T-cell expansion and exposure, which could impact efficacy and safety. These models were part of exploratory analyses aimed at understanding variability and informing dosing strategies. The specific statistical software used was not detailed in the provided information; however, statistical analyses of this nature are commonly conducted using software such as SAS, R, SPSS, or GraphPad Prism.

Appropriateness of Methods Used
Non-compartmental analysis is appropriate for cell therapies like obe-cel, where traditional compartmental modelling is challenging due to the complex kinetics of living cells. However, NCA does not account for inter-individual variability or allow for predictive simulations in the same way that population PK modelling does. Simple linear regression is suitable for initial exploratory analyses to identify potential relationships between variables. Nonetheless, these analyses may not capture non-linear relationships or interactions between multiple covariates. Given the exploratory objectives and the nature of the therapy, the methods used were appropriate for the preliminary assessment of PK parameters and potential influencing factors.

Divergence Between NCA and Modelled Approaches
Advanced pharmacokinetic modelling, such as compartmental models or population PK models, was not utilised in the analyses. Such models could offer a more detailed characterisation of PK behaviour and account for variability between patients. The applicant focused on NCA and simple regression analyses due to the inherent complexities of modelling CAR T-cell kinetics and the limited applicability of traditional PK models to cell-based therapies. The high variability and individualised nature of CAR T-cell expansion may reduce the feasibility and utility of more complex modelling approaches in this context.

IV. 2 Pharmacokinetics
The clinical development of obe-cel is based on the pivotal AUTO1-AL1 Phase Ib/II study (referred to hereafter as the FELIX study), which evaluated the safety and efficacy, as well as pharmacokinetics (PK) and pharmacodynamics (PD) of obe-cel following a split-dose infusion of a total target dose of 410 × 106 CAR-positive viable T cells in adult patients with relapsed or refractory (r/r) B cell acute lymphoblastic leukaemia (B ALL).

The study was conducted in adherence to applicable medical, scientific and regulatory guidelines.

The Summary of Clinical Pharmacology Studies submitted by the applicant presents clinical pharmacology data from 94 patients infused in the pivotal Cohort IIA (Phase II) of the FELIX study, specified as the Infused Set. The correlations between PK-PD and safety data include all

127 patients from all cohorts of Phase Ib and Phase II, specified as the Safety Set.

The PK of obe-cel post-infusion were assessed by measuring CAR transgene level in peripheral blood with limited sampling in bone marrow (BM) by digital droplet polymerase chain reaction (ddPCR). The ddPCR assay was validated by the bioanalytical laboratory adhering to Good Laboratory Practice principles. Flow cytometry assessment of CAR presence was also performed as supportive information. Important PK terms like expansion and persistency are central to understanding the PK of obe-cel in peripheral blood. Expansion refers to the initial period of the engraftment phase of the CAR T following infusion, while persistency denotes the continued presence of the transgene in the blood.

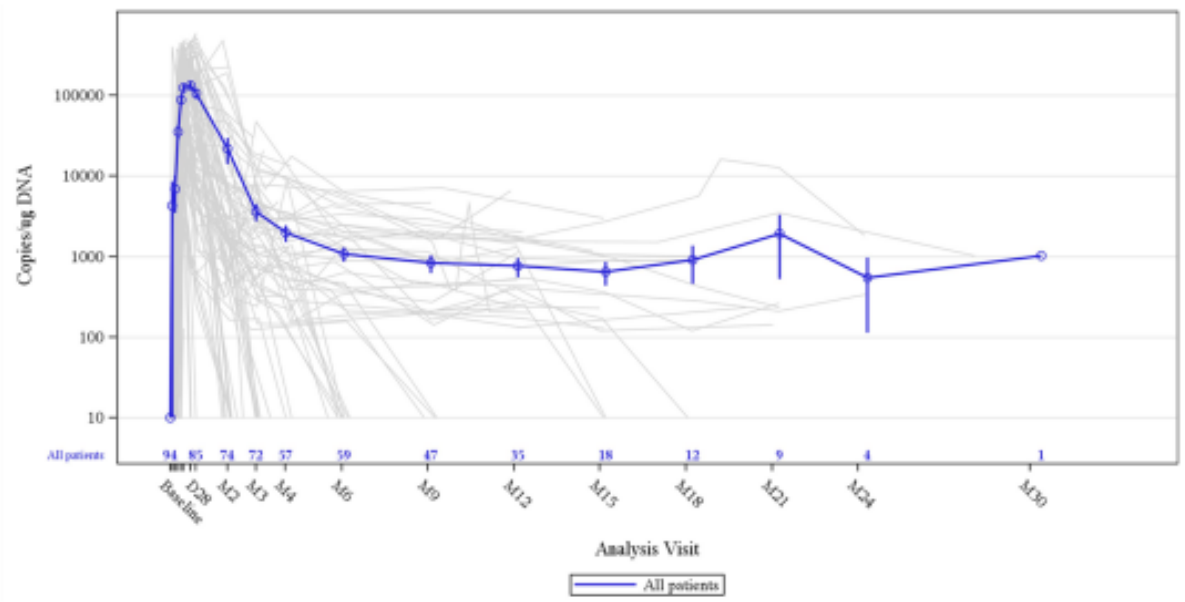
The PK-PD report, provides a comprehensive evaluation of the expansion and persistency as well as duration of B cell aplasia as an assessment of functional CAR T cell persistency. Additionally, serum biomarker concentrations were examined in relation to PK. The influence of various intrinsic and extrinsic factors on PK parameters were also critically evaluated.

A Phase I, proof-of-concept, academic-led study which recruited 20 patients dosed with obe-cel, provides supportive PK data in the context of long-term patient follow-up.

FELIX Study Clinical Pharmacology Results
The PK, impact of intrinsic and extrinsic factors, dose-exposure, dose-response, exposure-response, presence of RCL and other results covering the overall clinical pharmacology characteristics of obe-cel in adult patients with r/r B ALL are summarized in the sections below.

Pharmacokinetics
In the Infused Set of Cohort IIA (N=94), the PK of obe-cel is characterized by rapid and high level of expansion of the cells following infusion. Figure 2 shows the PK profile (mean [standard error of the mean estimate (SE)]) and expansion between Day 1 and Day 28 for each patient individually. The overall geometric mean of Cmax was 114,982 copies/µg deoxyribonucleic acid (DNA) (range 129-600,000 copies/µg DNA), with a median time to maximum (or peak) concentration (Tmax) of 14 days (range 2-55 days) and a geometric mean AUC0-28d of 1,138,188 copies/µg DNA·day (range 179,000-7,230,000 copies/µg DNA·day).

Figure 2: CAR T Cell Pharmacokinetic Profile: Mean (SE) and Individual Concentration vs Time Profiles of Obe-Cel Transgene Levels in Peripheral Blood (Cohort IIA, Infused Set)



CAR=chimeric antigen receptor; D=day; M=month; SE=standard error of the mean estimate.
The blue line indicates mean (± SE) concentration of transgene level in peripheral blood over time; gray lines indicate individual patient concentrations over time. Obe-cel transgene levels measured by droplet digital polymerase chain reaction.
Data cut-off: 07-Feb-2024.

CAR=chimeric antigen receptor; D=day; M=month; SE=standard error of the mean estimate.
The blue line indicates mean (± SE) concentration of transgene level in peripheral blood; grey lines indicate individual concentrations. Obe-cel transgene levels measured by droplet digital polymerase chain reaction.

Despite receiving the target dose via the 2 doses through the split-dose regime on Day 1 and Day 10 (±2 days), a single peak is seen rather than a bi-modal profile.

Expansion was high regardless of whether patients achieved CR/CRi or not. Indeed, no biologically significant differences were seen in the geometric mean (Table 3) or median and interquartile ranges (IQR) of Cmax (Figure 3). Furthermore, a numerically later median Tmax was observed for patients not in CR (17 days [range 6-18 days] vs 14 days [range 2-55 days]); however, this is unlikely to be biologically significant given the overlapping range.

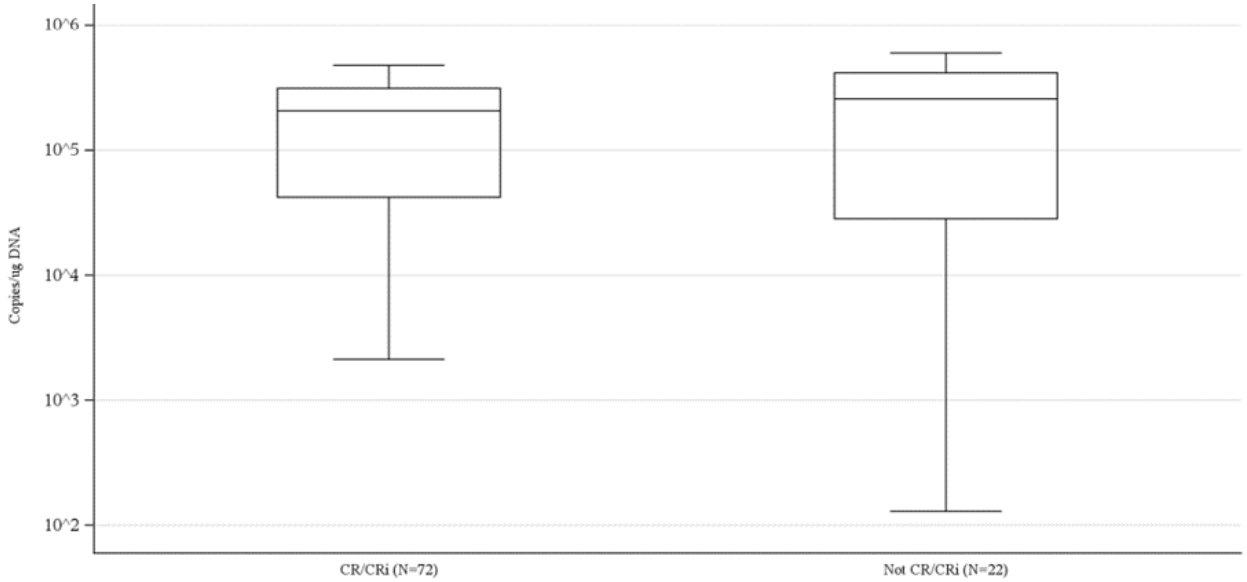
In CR/CRi patients, approximately 68.4% (95% CI, 54.6%-78.7%) demonstrated persistency at 6 months, with a maximum duration of 21 months. Furthermore, 75% (27/36) of the patients who had ongoing remission as of the data cut-off date had ongoing CAR T persistency at the last laboratory assessment.

Table 3: Summary of Pharmacokinetic Parameters in Peripheral Blood by Best Overall Response (Cohort IIA, Infused Set)

Parameter	Statistics	Best Overall Response		Overall (N=94)
		CR/CRi (N=72)	Not CR/CRi (N=22)	
C_{max} (copies/µg DNA)	n	72	22	94
	Geometric mean (Geo-CV%)	117,381 (206.0)	107,465 (832.7)	114,982 (287.6)
	Range (min-max)	2120-478,000	129-600,000	129-600,000
T_{max} (days)	n	72	22	94
	Median	14	17	14
	Range (min-max)	2-55	6-28	2-55
AUC_{0-28d} (copies/µg DNA·day)	n	68	14	82
	Geometric mean (Geo-CV%)	1,089,908 (236.0)	1,404,899 (186.4)	1,138,188 (225.6)
	Range (min-max)	17,900-6,730,000	176,000-7,230,000	179,000-7,230,000

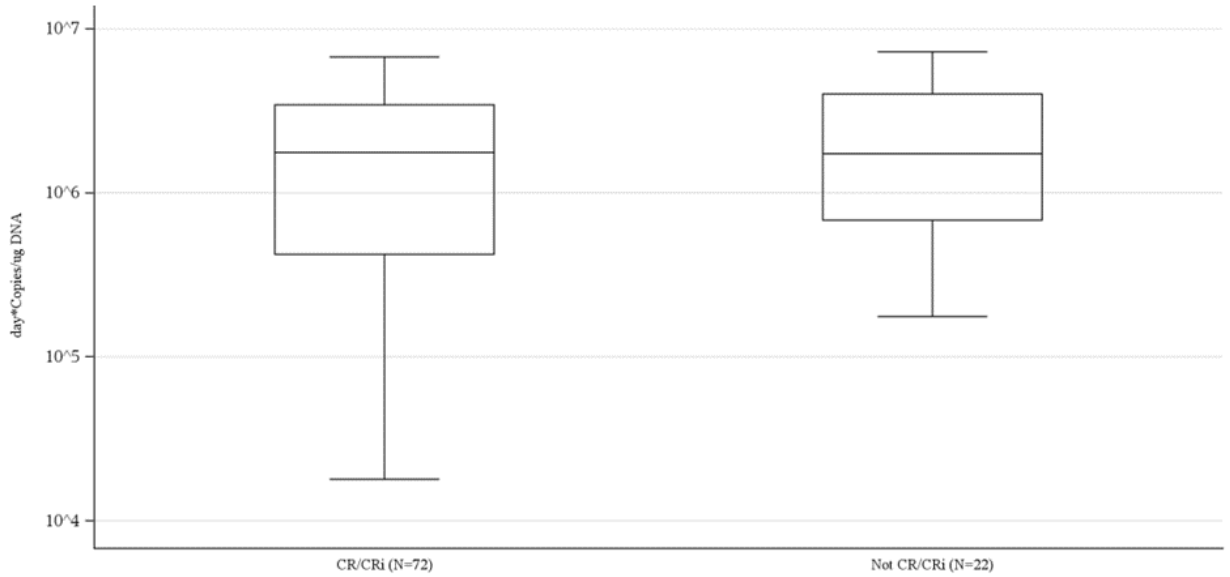
AUC_{0-28d}=area under the curve from time zero to day 28; C_{max}=maximum (or peak) concentration; CR=complete remission; CRi=complete remission with incomplete recovery of counts; Geo-CV%=geometric coefficient of variation; T_{max}=time to maximum (or peak) concentration.

Figure 3: Boxplot of Cmax (Copies/µg DNA) in Peripheral Blood by Best Overall Response (Cohort IIA, Infused Set)



Cmax=maximum (or peak) concentration; CR=complete remission; CRi=complete remission with incomplete recovery of counts.

Figure 4: Boxplot of AUC0-28d (Copies/µg DNA·Day) in Peripheral Blood by Best Overall Response (Cohort IIA, Infused Set)



AUC0-28d=area under the curve from time zero to day 28; CR=complete remission; CRi=complete remission with incomplete recovery of counts.

Overall, the PK observed in the FELIX study is consistent with the data from the Investigator-led study ALLCAR19, where a robust expansion was observed with a Cmax of 127,152 copies/µg DNA and a mean AUC0-28d of 1,251,802 copies/µg DNA·day. At the last available assessment, with a median follow-up of 36 months (IQR 24-47), 8/20 (40%) of patients have ongoing CR. Seven of these 8 patients (88%) with ongoing remission showed CAR T persistency.

The cellular kinetics observed during the ALLCAR19 study are thus very similar to those observed in FELIX, notably with regards to long-term persistency. As described above, 75% (27/36) of the patients in the FELIX study who had ongoing remission as of the data cut-off date had ongoing CAR T persistency at the last laboratory assessment.

Given the previous experience with ALLCAR19, based on the similarities in expansion and persistency, this is considered as an indication that patients in the FELIX study patients will also have long-term remission with longer follow-up.

Summary of the Investigator-led ALLCAR19 Study

The ALLCAR19 study was a Phase I, proof-of-concept, academic-led clinical trial that evaluated the safety, PK, and efficacy of obe-cel in patients with relapsed or refractory B-cell acute lymphoblastic leukaemia (r/r B ALL). A total of 20 patients were recruited and dosed with obe-cel, providing supportive PK data and insights into long-term patient outcomes.

Pharmacokinetics and Pharmacodynamics

The study demonstrated a robust expansion of CAR T cells following obe-cel infusion. The observed C_max was 127,152 copies/µg DNA, and the mean area under the concentration-time curve from day 0 to day 28 ($AUC_{0–28}$d) was 1,251,802 copies/µg DNA·day. These PK parameters indicate significant proliferation and persistence of CAR T cells in patients, similar to the findings from the pivotal FELIX study.

Efficacy and Long-term Outcomes
At the last available assessment, with a median follow-up of 36 months (interquartile range [IQR] 24–47 months), 8 out of 20 patients (40%) achieved ongoing complete remission (CR). Notably, 7 of these 8 patients (88%) with sustained remission exhibited continued CAR T-cell persistence. This suggests a strong correlation between long-term CAR T-cell presence and durable clinical responses.

Comparison with the FELIX Study
The cellular kinetics observed in the ALLCAR19 study closely mirror those seen in the FELIX study. Both studies reported robust CAR T-cell expansion and significant long-term persistence. In the FELIX study, 75% of patients who had ongoing remission at the data cut-off date also showed continued CAR T-cell persistence at their last laboratory assessment. The similarities between the two studies strengthen the evidence that obe-cel can lead to long-term remission in patients with r/r B ALL.

In the FELIX study, patients exhibited a geometric mean peak concentration (C_max) of 114,982 copies/µg DNA, with a median time to reach T max of 14 days. Despite the split-dose regimen administered on Day 1 and Day 10, a single peak in CAR T-cell expansion was observed, indicating swift and sustained proliferation post-infusion. Importantly, high levels of CAR T-cell expansion were seen regardless of whether patients achieved complete remission (CR) or not, suggesting that peak expansion may not directly correlate with clinical response.

However, the persistence of CAR T cells appears to be associated with durable remission. Approximately 68.4% of patients achieving CR or CR with incomplete haematological recovery (CRi) demonstrated CAR T-cell persistence at six months, with some patients showing persistence up to 21 months. Furthermore, 75% of patients with ongoing remission at the data cut-off had detectable CAR T cells at their last assessment.

The ALLCAR19 study corroborated these findings, showing similar CAR T-cell expansion and long-term persistence. With a median follow-up of 36 months, 40% of patients achieved ongoing CR, and 88% of these patients exhibited continued CAR T-cell persistence. The consistency between the two studies reinforces the reliability of obe-cel's pharmacokinetic profile and its potential to provide long-term remission.

Overall, the applicant has provided the requested stratified PK data, successfully distinguishing CR from CRi and non-responders. Their findings support the conclusion that peak CAR T-cell expansion alone does not predict remission status. However, further modelling and additional analyses are strongly recommended to better characterise exposure-response relationships and inter-patient variability.

In conclusion, the pharmacokinetic data indicate that obe-cel leads to rapid, robust, and sustained CAR T-cell expansion and persistence in adult patients with r/r B ALL. These findings support the use of obe-cel, highlighting its potential to offer sustained remission through long-term CAR T-cell persistence.

Cellular pharmacokinetics and pharmacokinetic/pharmacodynamic analyses
The PK of obe-cel were captured from peripheral blood with limited sampling in BM and were analysed by digital droplet polymerase chain reaction (ddPCR) to measure the integration of the CAR transgene of obe-cel into genomic DNA in T lymphocytes.

Pharmacokinetics of obe-cel were also measured by flow cytometry as a supportive exploratory assessment of intracellular CD19 CAR-positive T cell antigens.

The ddPCR PK data were generated by the bioanalytical laboratory working to GLP principles using a validated ddPCR assay to assess transgene level (lentiviral Psi vector copy number/ug DNA).

Due to the limited samples collected to assess presence of CAR T cells in BM, the data from BM are listed and summarised descriptively by visit only.

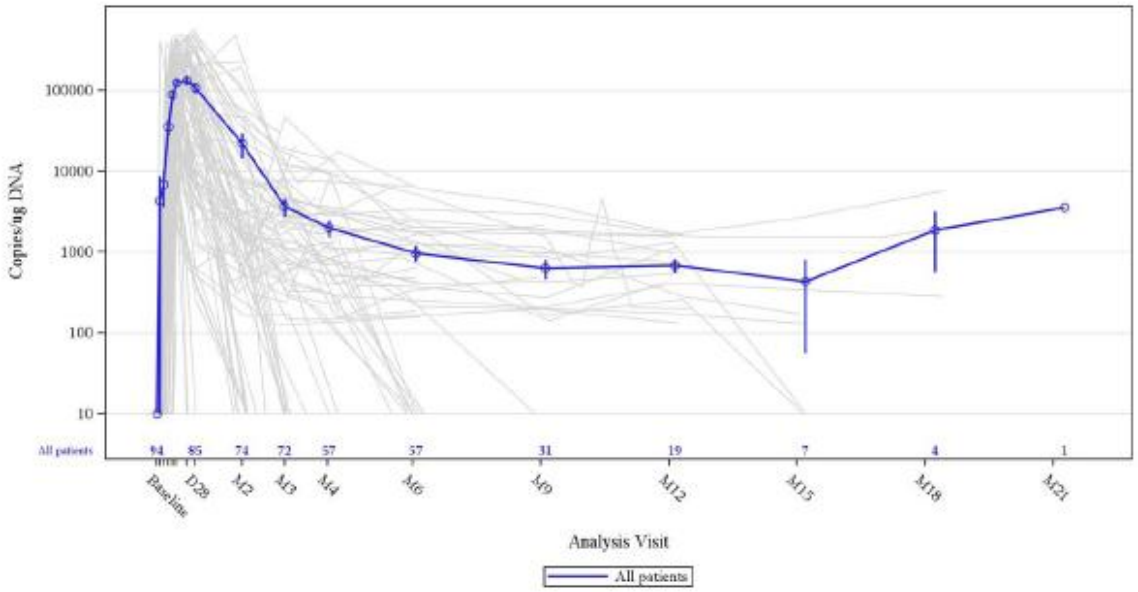
The data from peripheral blood will be used as the main source of PK analyses and peripheral blood results will be discussed and used throughout this PK/PD companion report, unless stated otherwise.

Overall, the PK analysis is based on the Infused Set of Cohort IIA (N=94) and is also described in the FELIX CSR. PK parameters are summarized in descriptive statistics overall and by BOR and concentrations of transgene level in peripheral blood are presented by visit (Figure 2).

Pharmacokinetics in Peripheral Blood

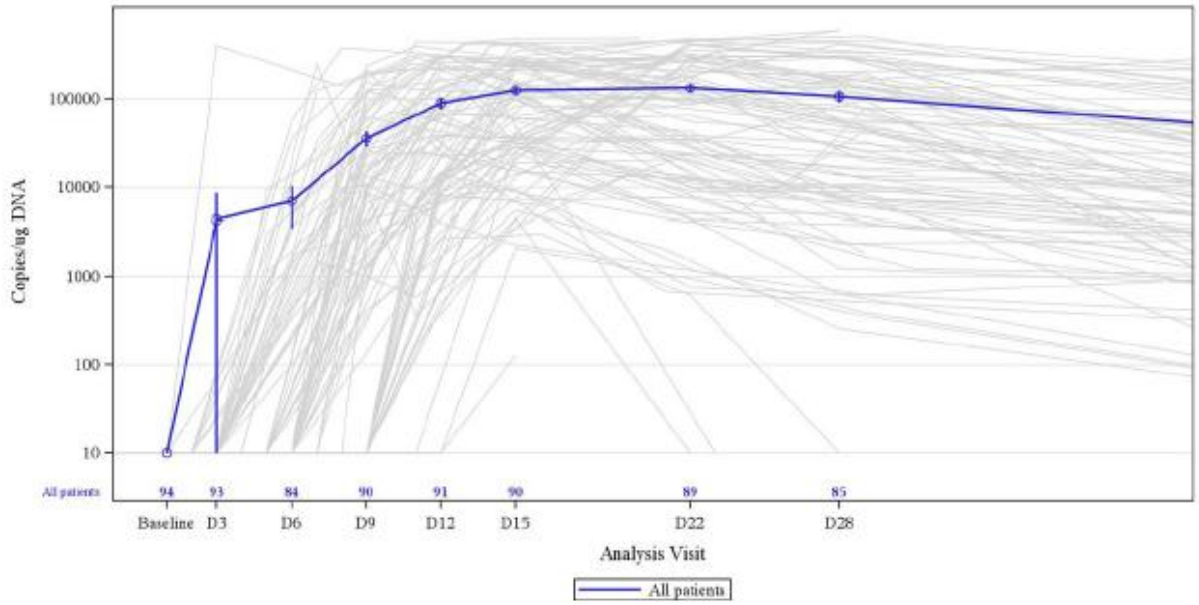
Overall, in the Infused Set of Cohort IIA (N=94), the PK of obe-cel are characterized by a rapid and high level of expansion of the cells following infusion (Figure 2). The expansion between Day 1 and Day 28 for each individual patient is shown along with the overall mean (SE) in Figure 3. The overall geometric mean of Cmax was 114,982 copies/µg DNA (range 129-600,000 copies/µg DNA) with a median Tmax of 14 days (range 2-55 days) and a geometric mean of the AUC0-28d of 1,138,188 copies/µg DNA * day (range 17,900-7,230,000 copies/µg DNA * day).

Figure 2: CAR T Cell Pharmacokinetic Profile: Mean (SE) and Individual Concentration vs Time Profiles of Obe-Cel Transgene Levels in Peripheral Blood (Cohort IIA, Infused Set)



Despite receiving the target dose via 2 doses through the split-dose regimen on Day 1 and Day 10 (±2 days), in general, a single peak is seen rather than a bi-modal profile (Figure 3).

Figure 3: CAR T Cell Expansion: Mean [SE]) and Individual Concentration vs Time Profiles of Obe-Cel Transgene Levels in Peripheral Blood Between Days 1 and 28 (Cohort IIA, Infused Set)



The primary endpoint of the FELIX study is 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). The 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 the start of new anticancer therapy for ALL (including hematopoietic stem cell transplantation).

Expansion was high regardless of whether patients achieved CR/CRi or not. Indeed, no biologically significant differences were seen in the geometric mean or median (IQR) of Cmax or AUC0-28d (Table 5, Figure 4 and Figure 5). Furthermore, a numerically later median Tmax was observed for patients not in complete remission (17 days vs 14 days), however, this is unlikely to be biologically significant given the overlapping range.

Table 5: 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

Figure 4: Boxplot of Cmax (Copies/µg DNA) in Peripheral Blood by BOR (Cohort IIA, Infused Set)

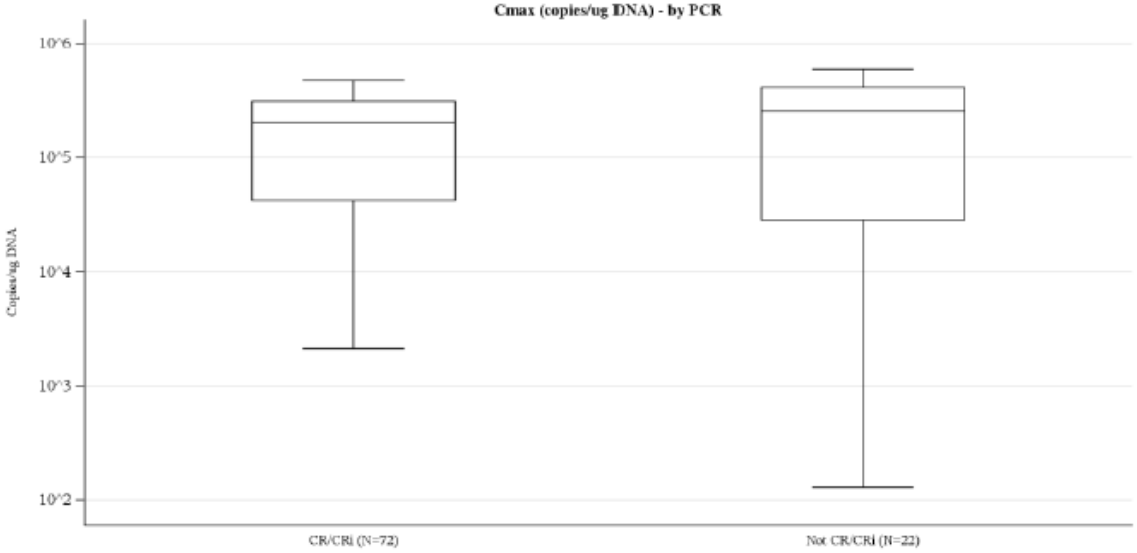
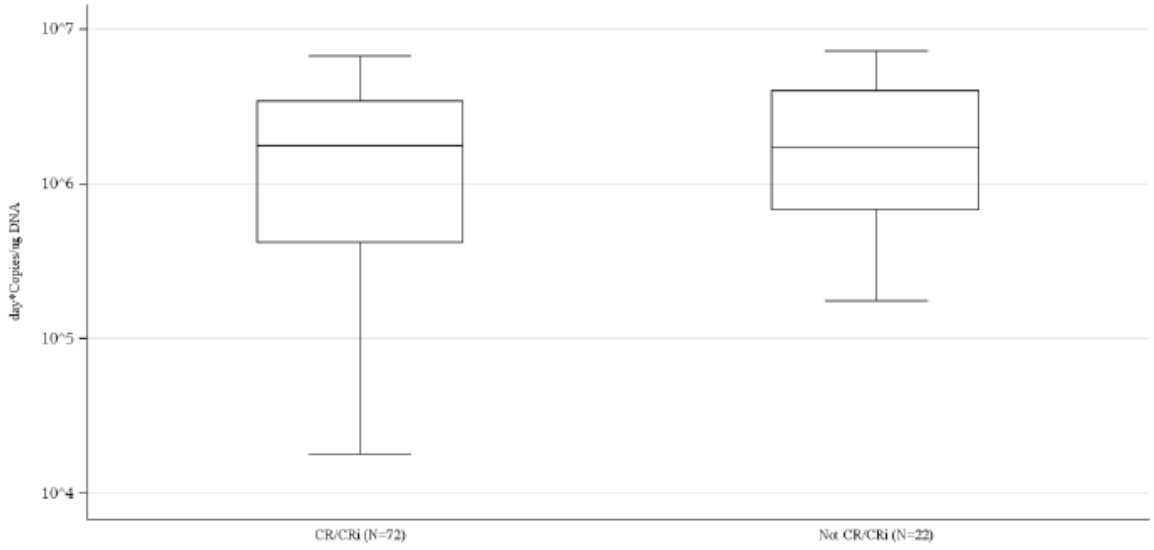
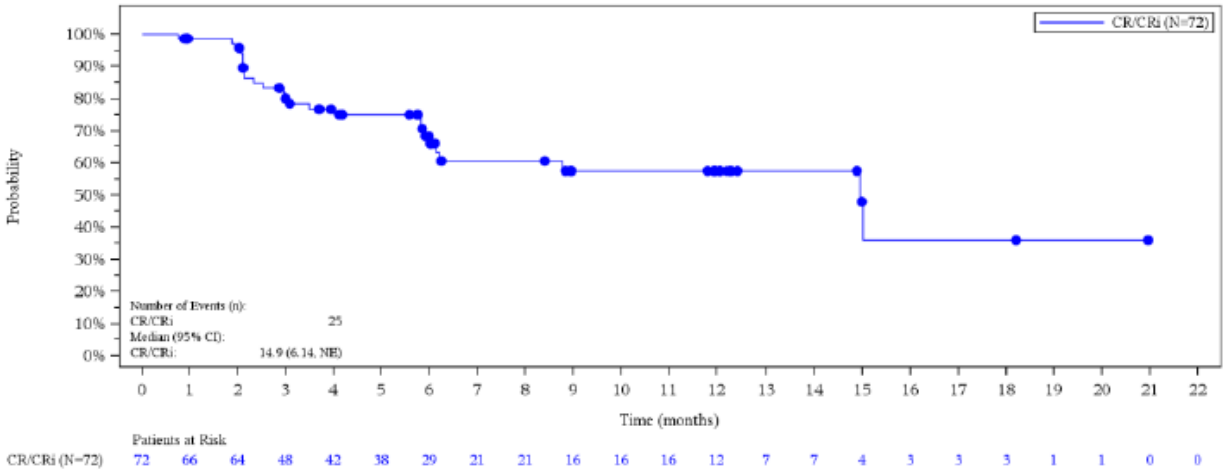


Figure 5: Boxplot of AUC0-28d (Copies/µg DNA * Day) in Peripheral Blood by BOR (Cohort IIA, Infused Set)



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, any analysis of duration of persistency can only be performed meaningfully in CR/CRi patients. A Kaplan-Meier (KM) analysis of the time to loss of CAR T cell persistency in patients with CR/CRi is shown below (Figure 6). In the CR/CRi group (N=72), the probability of continued persistency at 6 months was 68.4% (54.6%-78.7% 95% CI) with a maximum duration of 21 months. Of note the tail of the KM curve needs to be interpreted with caution given the number of patients available at the current data cutoff. Furthermore, 75% (27/36) of the patients who had ongoing remission as of the data cut-off date had ongoing CAR T persistency at the last laboratory assessment as of the data cut-off date. Taken together the data suggest that most, but not all patients in CR/CRi, have continued persistency. Current median follow up is not long enough to draw definitive conclusions on long term persistency, however the data suggests continued persistency is observed up to 21 months.

Figure 6: Time to Loss of CAR T Cell Persistency in Peripheral Blood in Patients in CR/CRi (Cohort IIA, Infused Set)



Overall, the cellular pharmacokinetics observed in the FELIX study are consistent with the data from the Investigator led study ALLCAR19 where a robust 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. In ALLCAR19, 8/20 (40%) of patients have ongoing CR at median follow up of 36 months. Long term remission is associated with CAR T in 7/8 patients at last follow up. In the data presented in this report, 75% of the patients who had ongoing remission as of the data cut-off date had ongoing CAR T persistency at the last laboratory assessment as of the data cut-off date. Given the previous experience with ALLCAR19, based on the similarities in expansion and persistency, there is a possibility that long term in the FELIX study may lead to long term remission.

In conclusion, the levels of obe-cel transgene over time in peripheral blood for the Cohort IIA patients display a rapid and robust expansion with a median peak at Day 14 followed by decrease over time. A similar high expansion is observed regardless of BOR status (CR/CRi vs not CR/CRi).

In CR/CRi patients, 68.4% of patients demonstrate persistency at 6 months and with a maximum observed persistency of 21 months. Current follow-up is not long enough to draw definitive conclusions on long term but 75% patients in CR/CRi have continued persistency at their last assessment as off the data cut-off, suggesting that long term persistency could be expected if the FELIX data continues to follow results observed in the ALLCAR19 study.

Exposure-Safety Analysis

Exposure-safety analyses were performed using logistic regression analysis to evaluate the relationship between obe-cel PK parameters (Cmax and AUC0-28d as covariates) and CRS and ICANS in the Safety Set. Cmax and AUC0-28d were the exposure metrics selected because CRS and ICANS typically resolves by Day 16 and Day 22 post-infusion respectively. Logistic regression analyses were performed between the rate of any grade CRS event or the rate of any grade ICANS event vs log10(Cmax) or log10(AUC0-28d), leading to four models in total (Figure 15). The analyses were only performed for any grade CRS and ICANS as the number of events for ≥Grade 3 CRS (N=3) or ICANS (N=9) are too small for the analysis to be meaningful. With a 2-fold increase of Cmax, the odds of observing a CRS event or an ICANS event of any grade are multiplied by 1.84 (95% CI: 1.43, 2.37) and 2.86 (95% CI: 1.65, 4.96), respectively. Similarly, with a 2-fold increase of AUC0-28d, the odds of observing a CRS event or an ICANS event of any grade are multiplied by 2.33 (95% CI: 1.67, 3.24) and 2.02 (95% CI: 1.35, 3.00), respectively. These results indicate that a higher expansion is associated with higher chance of observing CRS or ICANS of any grade (Table 16).

In Figure 15, the dots represent individual data points (CRS/ICANS events with y value of 1 and no CRS/ICANS events with y value of 0), the fitted line represents the estimated probability of observing an event based on a linear logistic regression model, and the shaded area corresponds to the pointwise 95% CI for a given value on the x-axis.

Figure 15: Logistic Regression of CRS and ICANS with PK Parameters Cmax and AUC0-28d in Peripheral Blood (Cohort Ib and II All Cohorts, Infused Set)

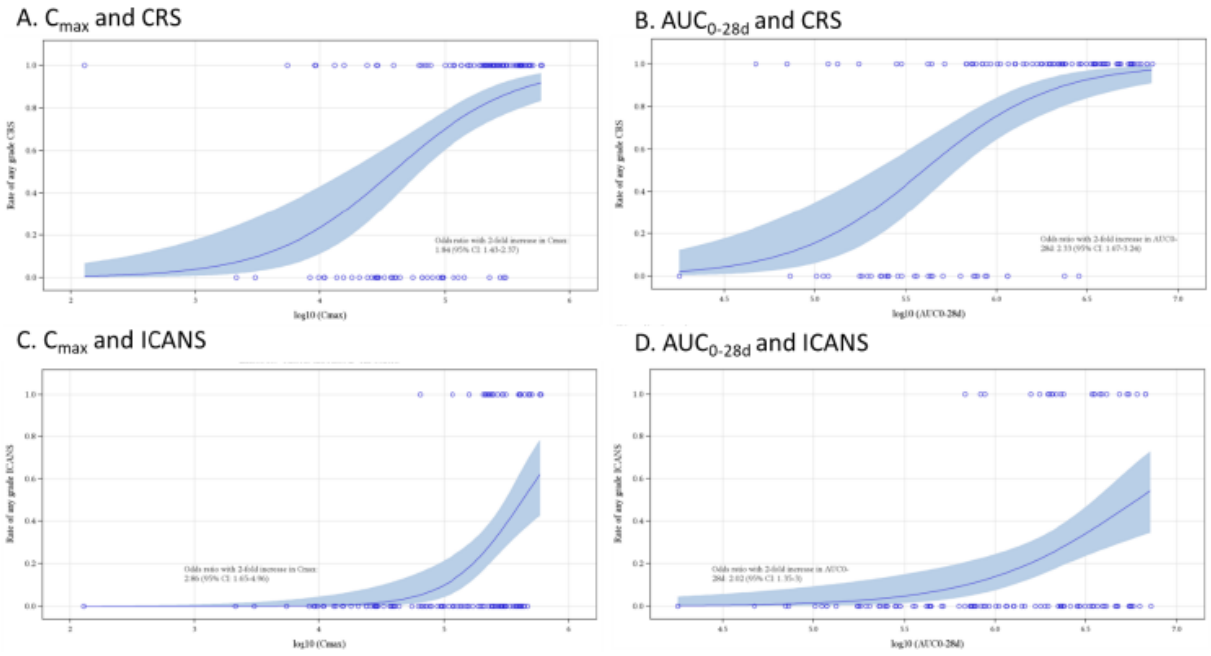


Table 16: Relationship Between PK (Peripheral Blood) and Safety Endpoints CRS and ICANS (OR for a 2-Fold Change in the PK Parameter [95%CI]), (Cohort Ib and II All Cohorts, Infused Set)

Endpoint	OR (95% CI) with 2-Fold Increase in C_{max}	OR (95% CI) with 2-Fold Increase in AUC_{0-28d}
CRS any grade	1.84 (1.43, 2.37)	2.33 (1.67, 3.24)
ICANS any grade	2.86 (1.65, 4.96)	2.02 (1.35, 3.00)

In conclusion, increasing Cmax and AUC0-28d correlates with an increased odds ratio (OR) of developing CRS or ICANS. As discussed previously, higher disease burden is associated with higher expansion and is in turn associated with higher chances of developing CRS/ICANS. This observation is consistent with the safety finding that CRS and ICANS are in general more common among patients with higher disease burden.

Pharmacokinetics By Flow Cytometry

As a supportive assessment, cellular pharmacokinetics of intracellular CD3 positive CAR T positive cells were assessed by flow cytometry in peripheral. Because of infrequently scheduled flow sample collection timing in the first 28 days, only peak expansion was reported. Overall, a high median peak of 71.05 (IQR 17.8-208.1) cells/µL was observed.

The median peak of expansion by flow cytometry (in cells/µL) is generally consistent across percentage BM at lymphodepletion according to tumour burden: ≥5% blast (median 71.4 [IQR 15.3-181.1] cells/µL), <5% blasts in BM without EMD (median 79.45 [IQR 32.8-255.8] cells/µL) or <5% blasts in BM with EMD (median 68.8 [IQR 67.0-242.6] cells/µL).

Pharmacokinetics in Bone Marrow

The data on CAR T cell expansion and persistency in BM aspirate is summarized descriptively by visit in Table 17. CAR T can be identified in BM aspirate in 96.4% of patients with available samples at Day 28 and 65.7% of patients with available samples at Month 6. Persistency can be observed up to 18 months.

Although the number of patients with available data reduced over time, CAR T presence in BM was consistent with results in peripheral blood (68.4% of patients at 6 months and was observed up to 21 months).

Table 17: PK Parameters (copies/µg DNA) in Bone Marrow Over Time (Cohort IIA, Infused Set)

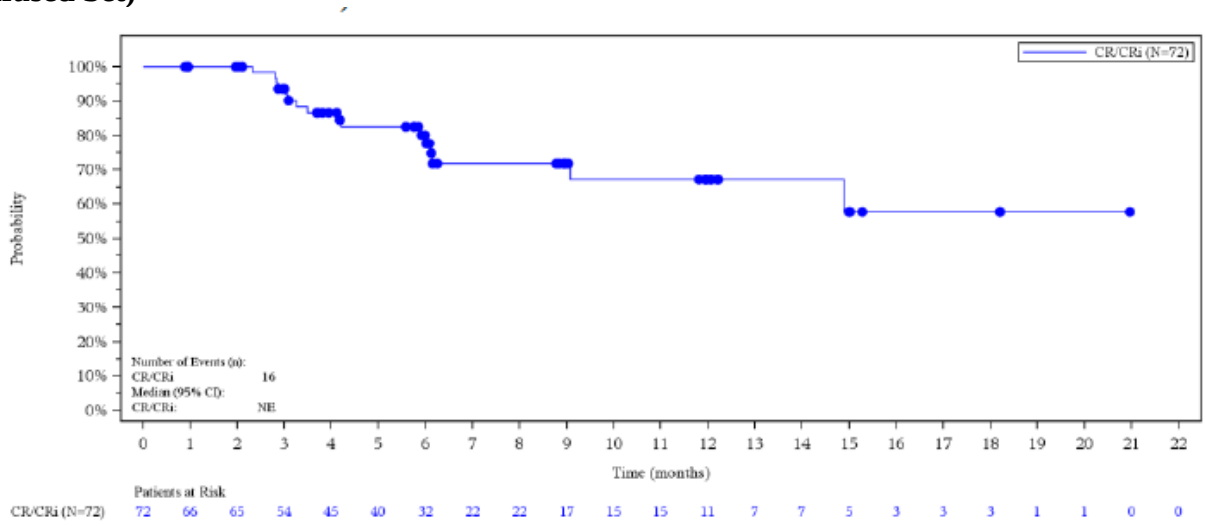
Statistic	Visit				
	Day 28	Month 3	Month 6	Month 12	Month 18
n*	55	49	35	12	3
m**	53	37	23	11	1
Geometric mean (Geo-CV%)	14,302.9 (981.6)	2,234.8 (174.0)	1,491.4 (184.7)	740.7 (152.7)	1,337.3 (NA)

*n is the number of patients with available data; **m is the number of patients with non-zero values

B CELL APLASIA

A patient is considered to display B cell aplasia (CD45+ CD3- CD19+ cells) if the absolute numbers of B cells is <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 cell aplasia was evaluated for the Infused Set (Cohort IIA, N=94). Recovery from B cell aplasia was assessed by KM analysis. Patients were censored either at time of first obe-cel infusion for patients with no evaluable B cell result post infusion or censored on the day of last evaluable laboratory assessment following death, patients who proceeded to stem cell transplant, withdrawal of consent, lost to follow up or for patients with ongoing B cell aplasia (Figure 16).

Figure 16: Kaplan-Meier Curve for Recovery from B Cell Aplasia by BOR (Cohort IIA, Infused Set)



B cell aplasia is an expected on-target effect of obe-cel. B cell aplasia resolved slowly overtime with estimated 93.1% of responders with B cell aplasia at 3 months and 80.0% at 6 months.

The observed trend of B cell aplasia (Figure 16) and loss of persistency (Figure 6) are generally comparable. At a given time, the estimated percentage of patients with resolution of B cell aplasia is lower than the percentage of patients who lost persistency, suggesting that loss of persistency does precede resolution of B cell aplasia.

The maximum follow-up period for patients who had not achieved CR/CRi was 3.7 months with 21/22 patients being discontinued by Month 3. From the time of discontinuation, measurement of B cell aplasia was no longer performed, hence any assessment of B cell aplasia and therefore, comparison between patients in CR/CRi and patients not in CR/CRi would not be valid. Thus, a KM plot was generated only for patients in CR/CRi (see Figure 16).

In conclusion, as expected by the mode of action of obe-cel, B cell aplasia was observed in most patients. B cell aplasia appeared to resolve slowly over time (93.1% of patients at 3 months and 80.0% at 6 months) and may be resolving following loss of persistency.

Summary

Cellular kinetics of obe-cel were captured primarily from peripheral blood with limited sampling in bone marrow, using digital droplet polymerase chain reaction (ddPCR) to measure the integration of the CAR transgene into genomic DNA in T lymphocytes. The established lower

limit of quantification (LLOQ) for the assay was 21 copies per reaction, equating to 73.3 copies per µg of DNA. Peripheral blood was used as the main source for pharmacokinetic analyses, and the kinetics of obe-cel were summarised using descriptive statistics across the patient sets involved in the study, including the Infused Set of Cohort IIA (N=94).

The expansion and persistency of CAR T cells were characterised by rapid and high expansion following infusion, with the peak observed around day 14 and a gradual decline in cell count afterward. "The overall geometric mean of Cmax was 114,982 copies/µg DNA," with a median Tmax of 14 days. These kinetics did not show a significant correlation between clinical responses such as complete remission and the observed cellular expansion. For example, in some patients achieving complete remission, a sustained CAR T cell persistency was documented, with 75% of patients still showing CAR T cell persistence at their last laboratory assessment, and the maximum persistency recorded up to 21 months.

Furthermore, limited bone marrow sampling was conducted, and the findings from peripheral blood were consistent with bone marrow assessments. The analysis indicated that obe-cel presence in the bone marrow diminished over time, with "96.4% of patients showing CAR T cells at Day 28" and "65.7% at Month 6." The maximum follow-up period for persistency reached 18 months. The study also noted that CAR T cell presence in bone marrow aligned with peripheral blood observations, suggesting similar dynamics in both compartments.

The applicant presented further stratified PK data, successfully distinguishing CR from CRi and non-responders. Their findings support the conclusion that peak CAR T-cell expansion alone does not predict remission status. However, further modelling and additional analyses are strongly recommended to better characterise exposure-response relationships and inter-patient variability.

Overall conclusion

The PK of obe-cel were assessed through the pivotal AUTO1-AL1 Phase Ib/II study, also known as the FELIX study, which focused on patients with relapsed or refractory (r/r) B-cell acute lymphoblastic leukaemia (B-ALL). The study evaluated the PK, PD, and overall safety and efficacy of obe-cel following split-dose administration. The data from 94 patients in the Infused Set provided valuable insights into the PK profile of obe-cel, while additional correlations with safety data were explored in 127 patients across all study cohorts.

The PK of obe-cel was primarily measured through digital droplet polymerase chain reaction (ddPCR) to quantify CAR T transgene levels in peripheral blood. This approach enabled the analysis of key PK terms such as "expansion" and "persistency," referring to the initial engraftment phase and the ongoing presence of transgene in blood, respectively. A validated ddPCR assay was used to ensure accuracy and compliance with Good Laboratory Practice (GLP) standards.

The PK data demonstrated a robust and rapid expansion of CAR T cells following infusion, with a geometric mean Cmax of 114,982 copies/µg DNA and a geometric mean AUC0-28d of 1,138,188 copies/µg DNA·day. Expansion occurred regardless of whether patients achieved complete remission (CR) or incomplete remission (CRi), with no significant differences between these groups in terms of Cmax and AUC0-28d. Moreover, CAR T persistency was observed in 68.4% of CR/CRi patients at 6 months, with a maximum persistency duration of 21 months.

Data from the investigator-led ALLCAR19 study, which evaluated 20 patients with obe-cel, were consistent with the FELIX study results, further supporting long-term CAR T cell persistency and remission. The exposure-safety analysis also confirmed that higher expansion (Cmax and AUC0-28d) was associated with an increased likelihood of developing cytokine release syndrome (CRS) or immune effector cell-associated neurotoxicity syndrome (ICANS). A two-fold increase in Cmax or AUC0-28d led to a higher probability of experiencing these adverse events.

The limited sampling from bone marrow (BM) and additional PK evaluations using flow cytometry confirmed that obe-cel expansion and persistency patterns were consistent between peripheral blood and BM. The study also examined B-cell aplasia, an expected on-target effect, and found that it resolved slowly over time, with 93.1% of responders still showing B-cell aplasia at 3 months and 80% at 6 months.

In conclusion, the PK data from the FELIX study provided comprehensive insights into the expansion, persistency, and safety of obe-cel in r/r B-ALL patients. The evidence supports the proposed dosing regimen and posology, demonstrating that obe-cel offers a long-term therapeutic effect with manageable safety risks, particularly regarding CRS and ICANS. The data from the study support the proposed labelling and the rationale for further follow-up to confirm long-term remission.

Dose – Exposure, Dose – Efficacy and Dose – Safety Analysis
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. It is further supported by other published literature relating to CAR T cell-based gene therapy dosing regimens.

Patients who received a first split dose of 10 × 106 cells demonstrated a higher expansion of CAR T cells with a later peak compared to patients who received a first split dose of 100 × 106 cells, suggesting that tumour burden is the main driver of the expansion. Most patients in Cohort IIA infused with obe-cel received the total target dose of 410 × 106 cells. The number of patients who did not receive the target dose as per protocol (n=11) is too small, and the reasons for not receiving the target dose are too heterogenous to draw any conclusion on dose-efficacy or dose-safety relationship.

All patients, regardless of the number of cells infused at the first dose, demonstrate compelling remission rates. While patients with ≤20% and those with >20% tumour burden at lymphodepletion demonstrate compelling efficacy, despite a higher CAR T cell expansion the ORR (CR or CRi) is numerically lower in patients receiving a first dose of 10 × 106 cells (>20% [high] disease burden) compared to those receiving a first split dose of 100 × 106 cells (≤20% [low] disease burden), with ORR of 75.0% and 87.5%, respectively. The numerically lower ORR is more likely a consequence of the higher tumour burden. This is in line with the expectation that patients with a high disease burden are a more difficult-to-treat patient population. On the contrary, increasing the dose further in this population would increase the likelihood of CRS and ICANS. Therefore, it is likely that the split dose, with a low first dose of 10 × 106 cells (given to patients with high disease burden), helped to manage the impact of disease burden on expansion, thus reducing the rates of CRS and ICANS.

Timing of Second Dose –Pharmacokinetic Analysis
The planned time intervals between fractions of the obe-cel dose were the same for all patients: 10±2 days. Delayed infusion of the second dose (up to Day 21 as per protocol) was generally due to CRS or ICANS, and an elevated CAR T cell expansion observed in those patients (N=9) may

be more related to disease burden, which increases the likelihood of experiencing CRS or ICANS. Persistency was also observed in patients with delayed infusion of the second dose. While the number of patients was small, delayed administration of the second dose did not seem to impact efficacy.

Taken together, all these data suggest that disease burden, rather than the number of CAR T cells infused at the first dose of obe-cel, is a major driver for a high expansion, which in turn may lead to the onset of CRS and ICANS. High disease burden also impacts response to obe-cel and suggests that patients with high disease burden are more difficult to treat.

The dose–exposure, dose–efficacy, and dose–safety analyses support the current dosing regimen of obe-cel, particularly the use of a split-dose approach in patients with high disease burden. The timing of the second dose is strategically planned to optimise therapeutic benefits while minimising risks. The rationale behind this dosing strategy is sound, aiming to reduce the incidence and severity of CRS and ICANS by controlling the rate of CAR T-cell expansion and the associated immune activation.

Pharmacokinetics in the target population

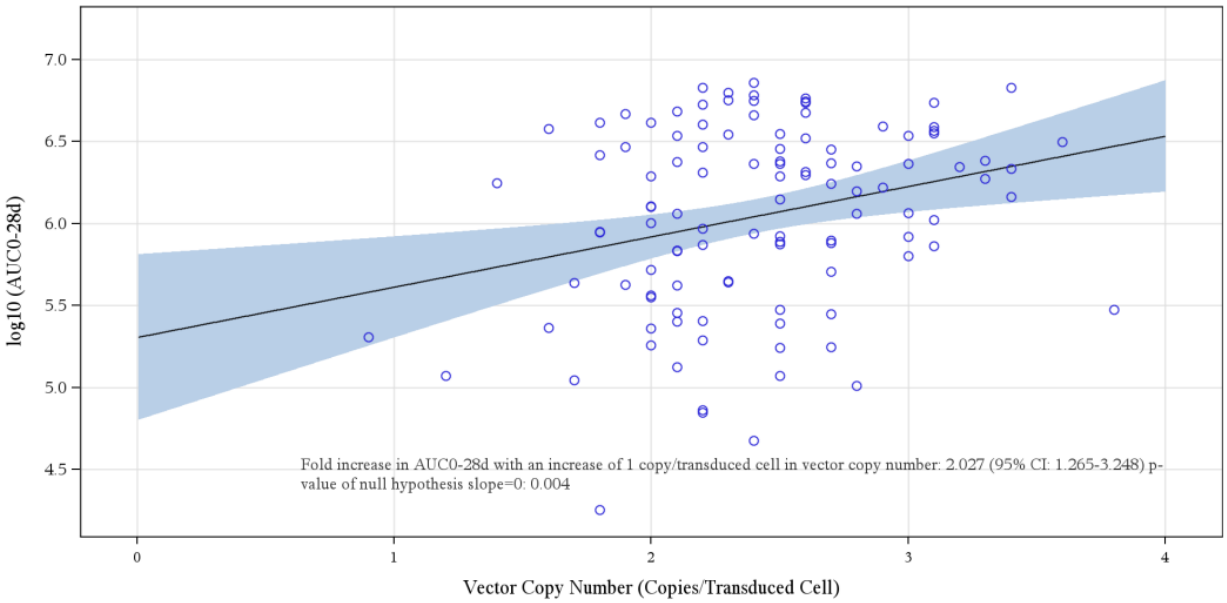
Intra- and inter-individual variability

Exploratory analyses were performed, using a simple linear regression analysis, to evaluate the relationship between obe-cel PK parameters (log10(Cmax) and log10(AUC0-28d) as covariates) and CQAs (potency [cytotoxicity], transduction efficiency [%], vector copy number (copies/transduced cell) and viability [%]). Note that all p-values are descriptive only and not meant for statistical inference.

No obvious trends were observed between expansion (Cmax and AUC0-28d) and potency or percent viability (Figures 14.6.6.5.3.1; 14.6.6.5.3.2; 14.6.6.5.3.3; 14.6.6.5.3.4; 14.6.6.5.4.1; 14.6.6.5.4.2; 14.6.6.5.4.3 and 14.6.6.5.4.4). Some trend was observed between vector copy number (VCN) vs AUC0-28d, but not Cmax, with an increase of VCN by 1 copy/transduced cell leading to a 2.0-fold (95% CI 1.3-3.2) increase in AUC0-28d (Figure 18); however variability is large and data should be interpreted with caution.

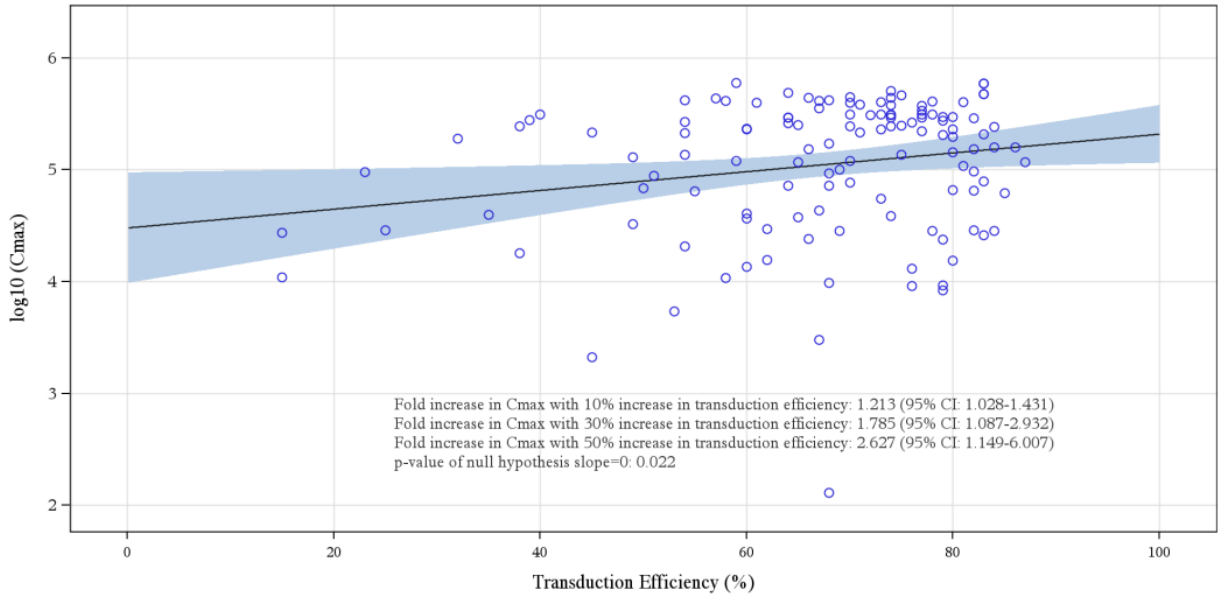
In Figure 18, the dots represent individual data points, the black line represents the fitted linear trend, and the shaded area corresponds to the pointwise 95% CI for a given value on the x-axis.

Figure 18: Linear Regression of Log10 (AUC0-28d) on Vector Copy Number (Cohorts Ib and II, Safety Set)



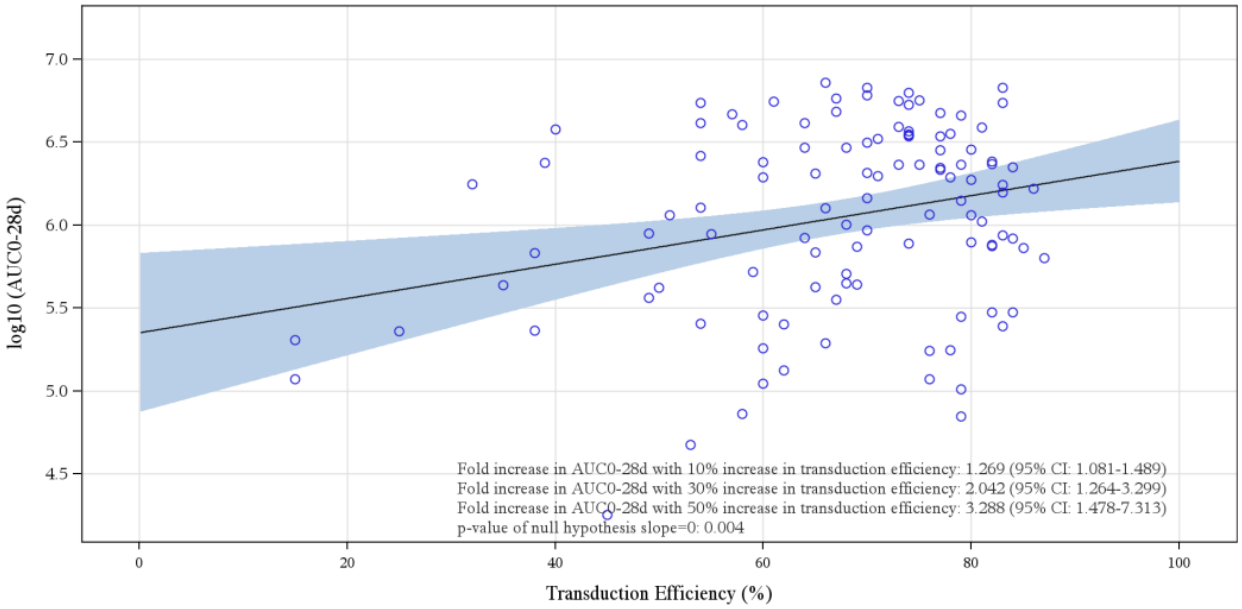
Some trend was seen between transduction efficiency vs Cmax and AUC0-28d. For Cmax, an increase of transduction efficiency by 10% leading to a 1.2-fold (95% CI 1.0-1.4) increase in Cmax and up to a 50% increase in transduction efficiency leading to a 2.6-fold (95% CI 1.1-6.0) increase in Cmax (Figure 19); however variability is large and may not be clinically relevant.

Figure 19: Linear Regression of Log10 (Cmax) on Transduction Efficiency (Cohorts Ib and II, Safety Set)



For AUC0-28d, an increase of transduction efficiency by 10% leads to a 1.3-fold (95% CI 1.1-1.5) increase in AUC0-28d and up to a 50% increase in transduction efficiency leading to a 3.3-fold (95% CI 1.5-7.3) increase in AUC0-28d (Figure 20); however variability is large and data should be interpreted with caution.

Figure 20: Linear Regression of Log10 (AUC0-28d) on Transduction Efficiency Percentage (Cohort Ib and II, Safety Set)



In conclusion, while some trends are observed between vector copy number and transduction efficiency with expansion, variability is high and data need to be interrupted with caution.

The applicant discusses exploratory analyses investigating the relationships between obe-cel PK parameters (Cmax and $AUC_{0–28}$d) and critical quality attributes (CQAs) of the product, including vector copy number (VCN), transduction efficiency, potency (cytotoxicity), and viability. The aim is to understand whether these CQAs contribute to variability in PK and, by extension, influence dosing decisions.

Special populations

Impaired renal function
Not applicable as obe-cel is a cell based therapeutic and does not undergo hepatic or renal elimination or metabolism.

Impaired hepatic function
Not applicable as obe-cel is a cell based therapeutic and does not undergo hepatic or renal elimination or metabolism.

Gender
In the context of obe-cel treatment, gender-specific data was not explicitly provided in the available clinical trial results or reports. The data discussed focused primarily on efficacy, safety, and the pharmacokinetics of obe-cel as a cellular gene therapy in adult patients with relapsed or refractory B-cell acute lymphoblastic leukaemia (r/r B ALL). There were no reported differences or specific findings associated with gender in terms of response rates, adverse events, or other clinical outcomes. The available studies, such as the pivotal FELIX trial, did not emphasize any gender-related analysis or variability in treatment response, which could suggest that gender was not a significant variable in the evaluated cohorts.

The exposure parameters (Cmax AUC0 -28d) appeared to be similar in male vs female ALL populations, it can be agreed that gender has no meaningful impact on obe-cel expansion. However, the gender effect on persistence is unknown.

Ethnic factors

Race was the only demographic parameter where up to a 3-fold increase in geometric mean Cmax was observed in patients of Asian or Unknown race compared to Black or African American or White race. Caution is required when interpreting these data as the numbers of patients in the non-White race groups are small (Asian n=10, Black or African American n=2, Unknown n=12 compared to White n=70).

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 is 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), (Table 14.6.1.6.17.1.iia). CAR T persistency is observed in all race sub-groups (Figure 14.6.1.6.17.4.iia). Caution is required when interpreting these data as the number of patients in non-White race groups are small (Asian n=10, Black or African American n=2, Unknown n=12) compared to White, n=70.

Overall, persistency can be observed in all sub-groups.
In conclusion, patients of Asian or unknown race may have a higher expansion compared to Black/African American or White race; however, small numbers in subgroups preclude firm conclusions. Otherwise, clinico-demographic factors as well as previous therapy or response to previous therapy had a negligible impact on PK parameters.

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Table 14.6.1.6.17.1.iia Summary of Pharmacokinetics Parameters for Obe-cel Transgene Levels by ddPCR in Peripheral Blood By Race
Infused Set - Phase II - Cohort A

Parameter	Statistics	ASIAN (N=10)	BLACK OR AFRICAN AMERICAN (N=2)	WHITE (N=70)	UNKNOWN (N=12)	Total (N=94)
Cmax (copies/ug DNA)	n	10	2	70	12	94
	Mean (SD)	325760 (171830.5)	100450 (40375.8)	191825 (156680.1)	251200 (163215.5)	211709 (162489.9)
	CV	52.8	40.2	81.7	65	76.8
	Geometric Mean	270091	96307	94573	181725	114982
	Geo-CV%	83.1	43.2	350.1	134.4	287.6
	Median	353000	100450	206500	243000	215500
	Min - Max	65600 - 600000	71900 - 129000	129 - 589000	15400 - 510000	129 - 600000
Tmax (days)	n	10	2	70	12	94
	Mean (SD)	N/A	N/A	N/A	N/A	N/A
	CV	N/A	N/A	N/A	N/A	N/A
	Geometric Mean	N/A	N/A	N/A	N/A	N/A
	Geo-CV%	N/A	N/A	N/A	N/A	N/A
	Median	11	12	14	20	14
	Min - Max	2 - 27	10 - 14	7 - 55	6 - 28	2 - 55

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Table 14.6.1.6.17.1.iia Summary of Pharmacokinetics Parameters for Obe-cel Transgene Levels by ddPCR in Peripheral Blood
By Race
Infused Set - Phase II - Cohort A

Parameter	Statistics	ASIAN (N=10)	BLACK OR AFRICAN AMERICAN (N=2)	WHITE (N=70)	UNKNOWN (N=12)	Total (N=94)
AUC 0-28d (day*copies/ug DNA)	n	8	2	62	10	82
	Mean (SD)	3733375 (2811757.4)	861500 (36062.5)	1909689 (1767580.6)	2359900 (1563392.5)	2116948 (1909153.7)
	CV	75.3	4.2	92.6	66.3	90.2
	Geometric Mean	2581885	861123	950778	1906780	1138188
	Geo-CV%	131.7	4.2	259.1	80.7	225.6
	Median	3875000	861500	1660000	2195000	1760000
	Min - Max	740000 - 7230000	836000 - 887000	17900 - 6260000	681000 - 5330000	17900 - 7230000
AUC 0-84d (day*copies/ug DNA)	n	5	2	59	8	74
	Mean (SD)	4694000 (3590477.7)	974500 (36062.5)	3343039 (3690217.8)	4123875 (2783771.9)	3454720 (3549918.5)
	CV	76.5	3.7	110.4	67.5	102.8
	Geometric Mean	3315037	974166	1443692	3300721	1652248
	Geo-CV%	135.9	3.7	313.4	91.3	270.1
	Median	5510000	974500	1900000	3540000	2340000
	Min - Max	1070000 - 9440000	949000 - 1000000	24000 - 14400000	681000 - 10000000	24000 - 14400000

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Table 14.6.1.6.17.1.iia Summary of Pharmacokinetics Parameters for Obe-cel Transgene Levels by ddPCR in Peripheral Blood
By Race
Infused Set - Phase II - Cohort A

Parameter	Statistics	ASIAN (N=10)	BLACK OR AFRICAN AMERICAN (N=2)	WHITE (N=70)	UNKNOWN (N=12)	Total (N=94)
Tlast (days)	n	10	2	70	12	94
	Mean (SD)	N/A	N/A	N/A	N/A	N/A
	CV	N/A	N/A	N/A	N/A	N/A
	Geometric Mean	N/A	N/A	N/A	N/A	N/A
	Geo-CV%	N/A	N/A	N/A	N/A	N/A
	Median	46	152	121	41	93
	Min - Max	26 - 455	122 - 182	11 - 637	14 - 181	11 - 637
Clast (copies/ug DNA)	n	10	2	70	12	94
	Mean (SD)	105905 (186341.1)	4679 (5941.8)	39037 (104720)	63198 (138271.8)	48504 (119370.2)
	CV	176	127	268.3	218.8	246.1
	Geometric Mean	18967	2058	2237	10506	3415
	Geo-CV%	2287.7	841.9	1274.9	926.9	1625.8
	Median	37200	4679	1245	6080	1980
	Min - Max	130 - 600000	477 - 8880	129 - 589000	322 - 490000	129 - 600000

Weight

The provided information does not include analyses of PK parameters based on body weight or body mass index (BMI). There are no subgroup analyses comparing PK profiles between obese, normal-weight, and underweight patients.

Obe-cel is administered as a fixed total dose of CAR-positive T cells (410 × 10^6 cells), with dosing adjustments based on disease burden rather than patient weight. Patients with higher disease burden receive a lower initial dose to mitigate the risk of adverse events, but this adjustment is independent of body weight.

Given that obe-cel is a cell-based therapy administered in cell numbers rather than weight-based dosing (e.g., mg/kg), the influence of body weight on pharmacokinetics may be minimal. The expansion and persistence of CAR T cells are more likely influenced by factors such as disease burden, immune status, and prior therapies.

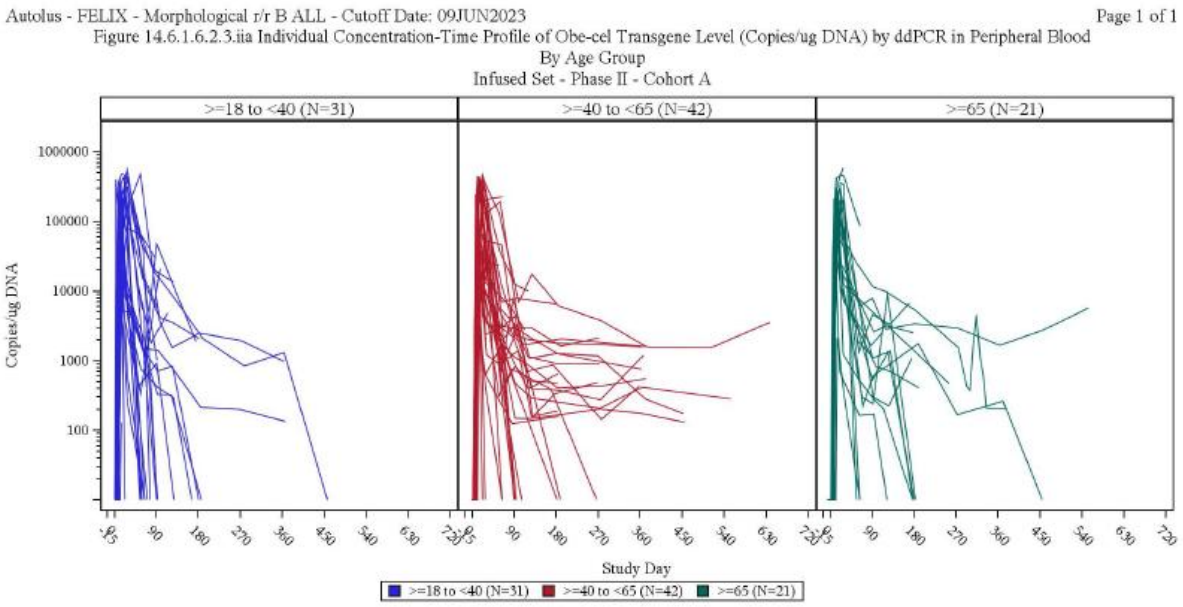
The applicant has appropriately stratified patients into two weight-based subgroups using the median weight of 78.9 kg and analysed PK parameters, including Cmax, $AUC_{0–28}d$, and Tmax, separately for these groups. This provides a clear quantitative comparison of obe-cel exposure in lower-weight versus higher-weight patients.

As expected with a fixed total dose regimen, higher-weight patients received a lower dose per kilogram. However, PK exposure remained comparable between the subgroups, with no clinically significant differences in key parameters. Robust CAR T-cell expansion was observed in both weight groups, indicating that body weight does not have a meaningful impact on obe-cel kinetics or therapeutic exposure.

The study appropriately used geometric means and geometric coefficients of variation (Geo-CV%) to assess variability. While high variability was observed (Geo-CV% ~ 211–253%), this is expected for CAR T-cell therapies, where expansion is influenced more by disease burden than by dose per kilogram. The absence of a clear exposure-response relationship with body weight supports the applicant's conclusion that obe-cel pharmacokinetics are independent of weight. The applicant's fixed-dose approach is consistent with previous approvals for similar CAR T-cell therapies, such as Yescarta (axicabtagene ciloleucel), which also do not use weight-based dosing.

Overall, the applicant has adequately addressed concerns regarding the impact of body weight on obe-cel pharmacokinetics through a well-conducted analysis. The data support the appropriateness of the fixed total dose regimen, and no further studies are required unless post-marketing data reveal unexpected variability in response or safety related to body weight.

Elderly
Age had no apparent effect on the cellular kinetics of obe-cel.



Paediatric population
Not applicable for the paediatric and young adult ALL patients.

IV.3 Pharmacodynamics

Obecabtagene autoleucel (obe-cel, also known as AUTO1) is a cell-based gene therapy composed of autologous T cells engineered to express a novel anti-CD19 chimeric antigen receptor (CAR). This therapy is designed to mimic physiological T cell activation, featuring a fast off-rate that promotes improved CAR T cell expansion and long-term persistence while reducing potential toxicity.

Mechanism of action

Obecabtagene autoleucel (obe-cel), also known as AUTO1, is an autologous T-cell therapy designed to treat adult patients with relapsed or refractory B-cell acute lymphoblastic leukaemia (r/r B ALL). Its mechanism of action involves modifying a patient's own T cells to target and eliminate cancerous B cells expressing the CD19 antigen. The CAR incorporates an scFv that specifically binds to the CD19 antigen present on B cells, including malignant ones. This region connects the antigen-binding domain to the intracellular signalling domains, maintaining structural stability. The intracellular portion consists of a costimulatory domain from 4-1BB (CD137) and an activation domain from CD3ζ. This fusion enhances T-cell activation, proliferation, and survival. Obe-cel is engineered to have a fast off-rate when binding to the CD19 antigen. This means the CAR T cells disengage quickly after interacting with the target, reducing prolonged cell-to-cell contact.

Primary pharmacology

Primary Pharmacology of Obe-cel

Obe-cel is an autologous T-cell therapy designed to treat adult patients with relapsed or refractory B-cell acute lymphoblastic leukaemia (r/r B ALL). The therapy involves collecting a patient's own T cells and genetically modifying them ex vivo to express a chimeric antigen receptor (CAR) that specifically targets the CD19 antigen on B cells.

The CAR construct in obe-cel includes:

- **Antigen Recognition Domain**: A single-chain variable fragment (scFv) that binds to CD19.
- **Transmembrane and Hinge Regions**: Derived from CD8, ensuring structural integrity.
- **Intracellular Signalling Domains**: Incorporating 4-1BB (CD137) as a co-stimulatory domain and CD3ζ as the activation domain.

A key feature of obe-cel is its **fast off-rate binding** to CD19. This design mimics physiological T-cell interactions, allowing for rapid disengagement after antigen recognition. The fast off-rate reduces prolonged T-cell activation, minimising the risk of T-cell exhaustion and decreasing the likelihood of severe immune-mediated toxicities such as cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS).

Upon infusion back into the patient, obe-cel CAR T cells recognise and bind to CD19-expressing malignant B cells. This triggers T-cell activation, proliferation, and cytotoxic activity, leading to the elimination of cancerous cells. The inclusion of the 4-1BB co-stimulatory domain enhances T-cell persistence and memory formation, contributing to sustained antitumour immunity.

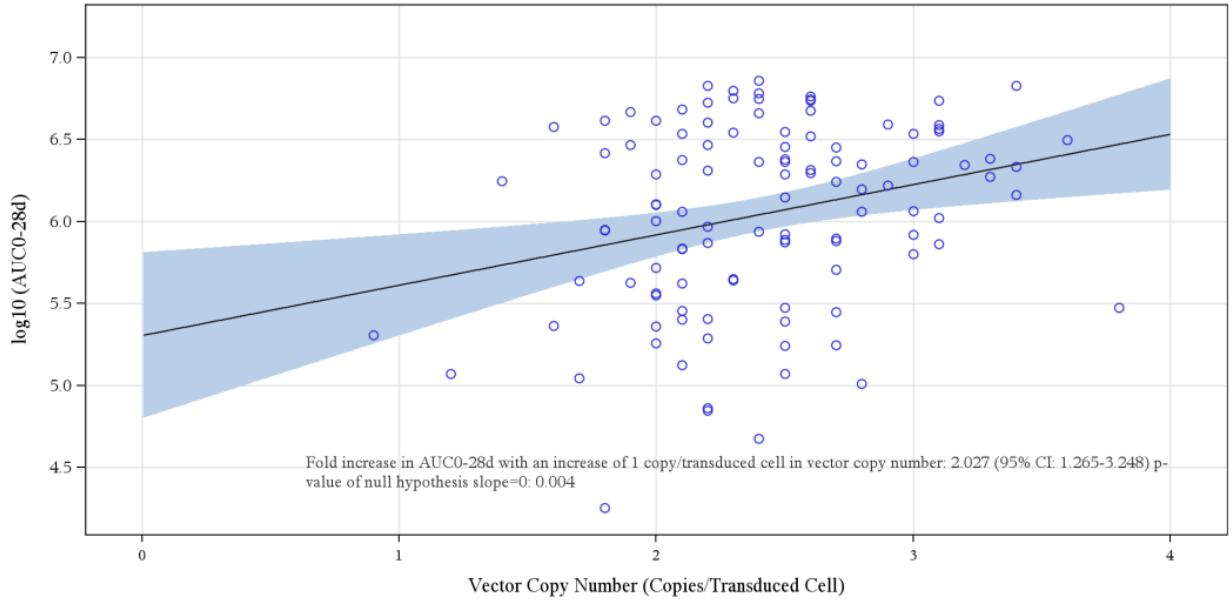
Modelling and Simulation Approaches Linking Dose, Exposure, and Pharmacodynamics

In the clinical development of obe-cel, exploratory analyses were conducted to assess the relationships between dose, exposure (pharmacokinetics), and pharmacodynamics (PD). Simple linear regression analyses evaluated the association between pharmacokinetic parameters—such as peak concentration (Cmax) and area under the curve from day 0 to day 28 ($AUC_{0–28}d$)—and critical quality attributes (CQAs) like vector copy number (VCN) and transduction efficiency.

Key observations include:

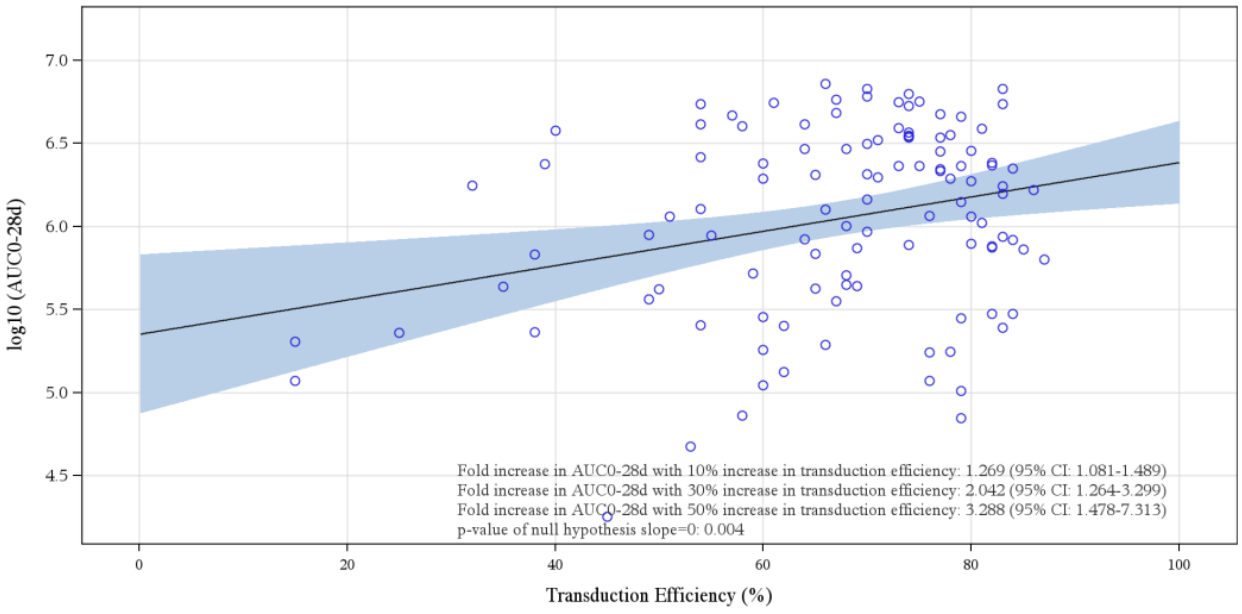
- **Vector Copy Number (VCN)**: A trend suggested that higher VCN might be associated with increased $AUC_{0–28}d$, indicating greater overall exposure. However, significant variability was noted, and the clinical relevance remains uncertain.

Figure 18: Linear Regression of Log10 (AUC0-28d) on Vector Copy Number (Cohorts Ib and II, Safety Set)



- **Transduction Efficiency**: Some correlation was observed between transduction efficiency and both Cmax and $AUC_{0–28}d$. Higher transduction efficiency could lead to increased CAR T-cell expansion and exposure.

Figure 20: Linear Regression of Log10 (AUC0-28d) on Transduction Efficiency Percentage (Cohort Ib and II, Safety Set)



- **Potency and Viability**: No clear relationship was established between these CQAs and pharmacokinetic parameters.

These analyses were descriptive and exploratory, with high variability limiting definitive conclusions. There was no extensive use of advanced modelling and simulation approaches, such as population pharmacokinetic/pharmacodynamic (PK/PD) modelling, to robustly characterise the relationships and quantify covariate effects.

Covariate Effects and Population Differences
Covariate analyses explored the impact of intrinsic factors such as age, sex, race, and disease burden on pharmacokinetics and pharmacodynamics:

- **Age**: The influence of age on obe-cel pharmacokinetics was assessed by comparing patients aged ≥65 years with younger patients. The findings indicated negligible differences in CAR T-cell expansion and persistence between these groups.

- **Efficacy in Older Adults**: Despite the lack of significant pharmacokinetic differences, it remains important to consider potential pharmacodynamic changes in older adults due to age-related alterations in immune function. However, the available data did not demonstrate a reduction in efficacy in older patients.

- **Disease Burden**: Higher disease burden was associated with greater CAR T-cell expansion and a later peak concentration. This suggests that tumour burden is a significant driver of pharmacokinetics and pharmacodynamics.

Potential Reduction of Efficacy in Different Populations
Based on the analyses conducted, there is no clear evidence to suggest that efficacy is reduced in specific populations, such as older adults, due to pharmacodynamic changes. The therapy demonstrated robust expansion and persistence of CAR T cells across different age groups, and remission rates were high irrespective of age.

However, the possibility of reduced efficacy in certain populations cannot be entirely ruled out without more comprehensive studies. Factors such as immune senescence in older adults could potentially affect T-cell function and the therapeutic response. Further research involving larger patient cohorts and focused analyses on different subpopulations would be necessary to draw definitive conclusions.

Consistency of Assumptions on Primary Pharmacology Across Development
There is consistency in the assumptions regarding the primary pharmacology of obe-cel throughout non-clinical and clinical development:

- **Non-Clinical Studies**: Preclinical investigations demonstrated that obe-cel CAR T cells effectively target and eliminate CD19-positive cells, with the fast off-rate design reducing prolonged activation and potential exhaustion. Animal models supported the therapy's antitumour activity and favourable safety profile.
- **Clinical Studies**: Clinical trials confirmed the mechanism of action observed in non-clinical studies. Patients exhibited rapid and robust CAR T-cell expansion, sustained persistence, and high remission rates. The safety profile aligned with expectations based on the therapy's design, with manageable incidences of CRS and ICANS.
- **Pharmacodynamic Outcomes**: Both non-clinical and clinical data showed that obe-cel

induces B-cell aplasia as an on-target effect, consistent with CD19-directed therapies. The pharmacodynamic responses observed clinically mirrored those predicted by preclinical models.

Overall, the continuity of pharmacological assumptions across non-clinical and clinical phases supports the validity of the therapy's design and its intended mechanism of action. This consistency enhances confidence in the therapeutic approach and informs clinical practice.

Obe-cel's primary pharmacology is well-characterised, with a mechanism of action centred on targeted elimination of CD19-positive B cells through genetically modified autologous T cells. While exploratory analyses provided initial insights into the relationships between dose, exposure, and pharmacodynamics, the high variability and limited scope of modelling approaches suggest that further, more rigorous studies are needed. These should employ advanced modelling techniques to better understand covariate effects and optimise dosing strategies.

There is no significant evidence indicating reduced efficacy in older adults or other specific populations based on the available data. Nonetheless, ongoing research should continue to evaluate efficacy and safety across diverse patient groups to ensure equitable therapeutic outcomes.

The consistent assumptions regarding primary pharmacology across non-clinical and clinical development reinforce the therapy's scientific foundation and support its continued investigation and application in treating r/r B ALL.

Secondary pharmacology
Obe-cel is an autologous CD19-directed CAR T-cell therapy developed for the treatment of adult patients with relapsed or refractory B-cell acute lymphoblastic leukaemia (r/r B ALL). While the primary pharmacology focuses on the specific targeting and elimination of CD19-positive B cells, secondary pharmacology examines the effects of the therapy on non-target cells and systems, providing insights into potential off-target effects and the overall safety profile.

In Vitro Secondary Pharmacology Studies
Off-Target Cytotoxicity Assessment

- **Objective**: To evaluate whether obe-cel exhibits cytotoxic activity against cells not expressing CD19, indicating potential off-target effects.
- **Methods**: In vitro cytotoxicity assays were conducted using obe-cel CAR T cells co-cultured with various CD19-negative cell lines, including normal human cells and tumour cell lines representing different tissue types.
- **Results**: Obe-cel did not exhibit significant cytotoxicity against CD19-negative cell lines, demonstrating high specificity for CD19-expressing cells. Cytotoxic activity was confined to CD19-positive target cells.
- **Conclusion**: The in vitro data suggest that obe-cel has a favourable specificity profile, with minimal off-target cytotoxic effects on non-B cells.

Cytokine Release Profile

- **Objective**: To assess the cytokine secretion profile of obe-cel upon activation, which can indicate the potential for systemic inflammatory responses.
- **Methods**: Cytokine levels were measured in the supernatants of in vitro cultures where obe-cel CAR T cells were co-cultured with CD19-positive target cells. Key cytokines analysed included IL-2, IFN-γ, TNF-α, and IL-6.

- **Results**: Upon engagement with CD19-positive cells, obe-cel CAR T cells produced cytokines characteristic of T-cell activation, primarily IL-2 and IFN-γ. Levels of pro-inflammatory cytokines such as IL-6 were moderate.
- **Conclusion**: The cytokine release profile is consistent with expected T-cell activation and does not indicate excessive cytokine production that might lead to severe cytokine release syndrome in patients.

Impact on Non-Haematopoietic Cells

- **Objective**: To determine if obe-cel CAR T cells recognise and react against non-haematopoietic tissues, which could lead to unintended tissue damage.
- **Methods**: Obe-cel CAR T cells were tested against primary human cells from various tissues (e.g., endothelial cells, epithelial cells, cardiomyocytes) to assess binding and activation.
- **Results**: There was no significant binding or activation of obe-cel CAR T cells in the presence of non-haematopoietic cells, indicating a low risk of off-tumour toxicity in non-B-cell tissues.
- **Conclusion**: The data support the specificity of obe-cel for CD19-expressing B cells, with minimal impact on other cell types.

General Features of Tolerability in Healthy Volunteers

Due to the nature of CAR T-cell therapies and the associated risks of immune activation, studies involving obe-cel have not been conducted in healthy volunteers. Administering a genetically modified T-cell product intended to target CD19-positive cells would pose unnecessary risks to healthy individuals, including potential depletion of normal B cells and severe immune-mediated adverse events.

Secondary Pharmacology in Clinical Studies

While direct data from healthy volunteers are not available, clinical studies in patients with r/r B ALL provide valuable information regarding tolerability and secondary pharmacology:

- **Cardiovascular Parameters**: No significant changes in 24-hour blood pressure monitoring were observed that could be attributed to off-target effects of obe-cel. Electrocardiograms (ECGs) did not reveal arrhythmias or conduction abnormalities linked to the therapy.
- **Biochemistry and Organ Function**: Routine biochemistry panels, including liver and renal function tests, showed no unexpected abnormalities. Any observed changes were consistent with the patients' underlying conditions or concurrent treatments.
- **Viral Levels**: Monitoring for replication-competent lentivirus (RCL) was performed due to the use of a lentiviral vector in obe-cel manufacturing. No RCL was detected in any patient samples, indicating a favourable safety profile regarding viral reactivation or insertional mutagenesis.
- **Neurological Assessments**: Electroencephalograms (EEGs) were not routinely performed; however, neurological evaluations focused on identifying signs of immune effector cell-associated neurotoxicity syndrome (ICANS). Incidences of ICANS were manageable and consistent with the known risks of CAR T-cell therapies.

Results and Strength of Evidence

- **Validity and Relevance**: The in vitro secondary pharmacology studies demonstrate that obe-cel has high specificity for CD19-positive B cells with minimal off-target effects on other cell types. Although data from healthy volunteers are not available, the clinical studies in patients provide relevant insights into the therapy's tolerability and safety.

- **Strength of Evidence**: The evidence is robust within the context of CAR T-cell therapy development. The in vitro studies are appropriate for assessing specificity and potential off-target effects. Clinical data further support the safety profile, with careful monitoring for known risks.
- **Support for Proposed Labelling**:
    - **Indication**: The data support the use of obe-cel in adult patients with r/r B ALL, as the therapy specifically targets CD19-expressing malignant B cells with minimal impact on other cell types.
    - **Posology**: The absence of significant off-target effects and the predictable pharmacodynamic response support the proposed dosing regimen. Adjustments based on secondary pharmacology are not indicated.
    - **SmPC Sections**: The Summary of Product Characteristics (SmPC) should reflect the specificity of obe-cel, its mechanism of action, and the safety profile observed in clinical studies. The lack of data from healthy volunteers is typical for this class of therapies and does not detract from the validity of the findings.

The secondary pharmacology in vitro data for obe-cel indicate a high degree of specificity for CD19-expressing B cells and a low potential for off-target effects on non-B-cell tissues. While studies in healthy volunteers were not conducted for ethical and safety reasons, clinical data from patients with r/r B ALL corroborate the favourable safety profile suggested by the in vitro findings.

The results and strength of evidence support the proposed labelling, including the indication, posology, and safety information in the SmPC. The therapy's targeted action and manageable safety profile align with its intended use, and the available data adequately support its clinical application.

Although off-target effects are minimal, continued vigilance in monitoring patients for unexpected adverse events remains important.

Ongoing studies and post-marketing surveillance will continue to build on the understanding of obe-cel's safety profile and support its use in the target population.

Pharmacodynamic interactions with other medicinal products or substances

Influence of Tocilizumab on Pharmacokinetics
Tocilizumab is approved for the treatment of CRS and was administered to patients in FELIX based on the CRS treatment algorithm specified in the study protocol (Appendix 16.1.1-Table 19). In the FELIX study, patients with higher disease burden were more likely to have a higher CAR T cell expansion than patients with lower disease burden. CRS was also more likely to occur in patients with high disease burden. The impact of tocilizumab on the PK of obe-cel was investigated.

Tocilizumab was administered following onset of CRS (median onset of CRS 8.0 days). Peak expansion occurred on Day 13 for patients not treated with tocilizumab and Day 15 for patients treated with tocilizumab. Obe-cel continued to expand after tocilizumab administration. Cmax and AUC0-28d were higher in patients that received tocilizumab for CRS management (Cmax 221,123 copies/µg DNA; AUC0-28d 2,599,792 copies/µg DNA*day) compared with patients that did not receive tocilizumab (Cmax 43,863 copies/µg DNA; AUC0-28d 396,135 copies/µg DNA*day), see Table 8.

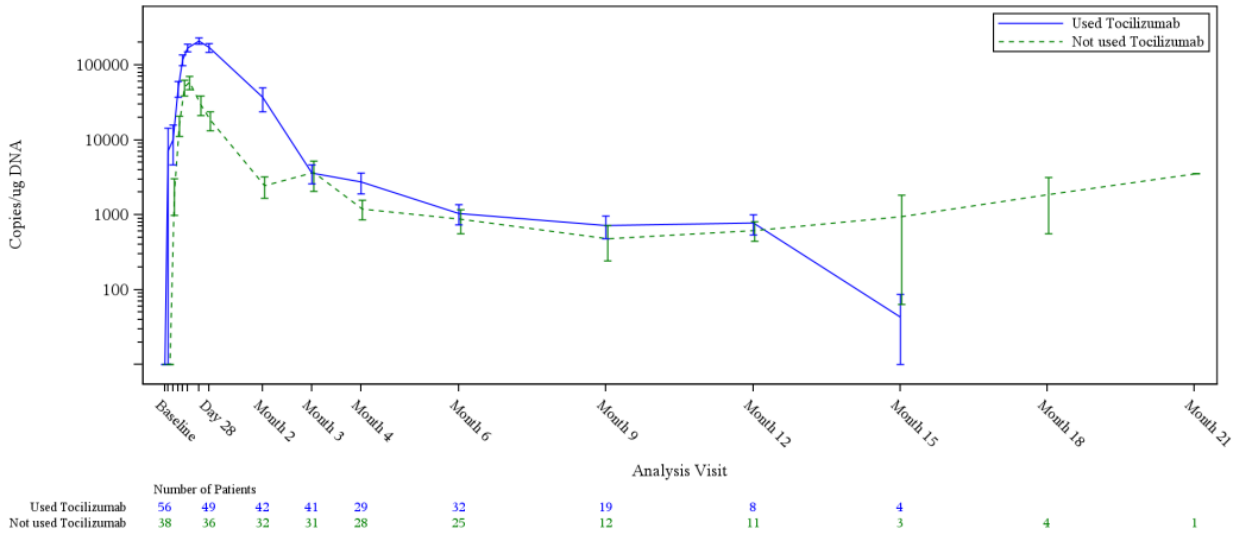
CAR T cell Persistency was observed in both, patients where tocilizumab was administered and in patients without tocilizumab administration (Figure 10).

Since tocilizumab is administered to treat CRS, which is associated with a higher CAR T cell expansion, any interpretations need to take major confounding impact of CRS into account. The difference in expansion is more likely to be due to higher tumour burden in these patients resulting in CRS than to be caused by tocilizumab. This is consistent with previous cellular CAR T cells therapies that have shown tocilizumab administration does not impact the rate or extent of expansion.

Table 8: Summary of PK in Peripheral Blood, Based on Use of Tocilizumab Post Obe-Cel Infusion (Cohort IIA, Infused Set)

Parameter	Statistic	Used Tocilizumab (N=56)	Not used Tocilizumab (N=38)
C_{max} (copies/µg DNA)	n	56	38
	Geometric Mean (Geo-CV%)	221,123 (213.2)	43,863 (180.7)
	Range (Min – max)	129 - 600,000	2,120 - 312,000
T_{max} (days)	n	56	38
	Median	15	13
	Range (Min – max)	2-55	8-28
AUC_{0-28d} (copies/µg DNA*day)	n	46	36
	Geometric Mean (Geo-CV%)	2,599,792 (105.2)	396,135 (150.2)
	Range (Min – max)	47,300 – 7,230,000	17,900 - 2,930,000

Figure 10: CAR T persistency: Mean (SE) of Obe-Cel Transgene Level in Peripheral Blood Over Time Based on Use of Tocilizumab Within 28 Days Post Obe-Cel Infusion (Cohort IIA, Infused Set)



In conclusion, consistent with other CAR T cell therapies, tocilizumab administration is unlikely to impact the rate or extent of expansion and persistency. The difference is expansion is more likely to be due to higher tumour burden resulting in CRS than to be caused by tocilizumab administration.

Influence of Corticosteroids Use on Pharmacokinetics

Corticosteroids are used for the treatment of CRS and ICANS and were administered to patients in FELIX based on the treatment guidance specified in the protocol. CRS and/or ICANS were more likely to occur in patients with high disease burden. The impact of corticosteroids on the PK of obe-cel was investigated.

Corticosteroids were administered following onset of CRS and ICANS (median onset of CRS and ICANS 8.0 and 12 days respectively). Peak CAR T cell expansion occurred on Day 14 for patients not treated with corticosteroids and Day 21 for patients treated with corticosteroids. Obe-cel continued to expand after corticosteroids administration. Cmax and AUC0-28d were higher in patients that received steroids for CRS and/or ICANS management (Cmax 282,740 copies/µg DNA; AUC0-28d 2,396,542 copies/µg DNA*day) compared with patients that did not receive corticosteroids (Cmax 69,056 copies/µg DNA; AUC0-28d 789,711 copies/µg DNA*day, and median Tmax was later (21 days for patients who received corticosteroids compared to 14 days for patients who did not (Table 9).

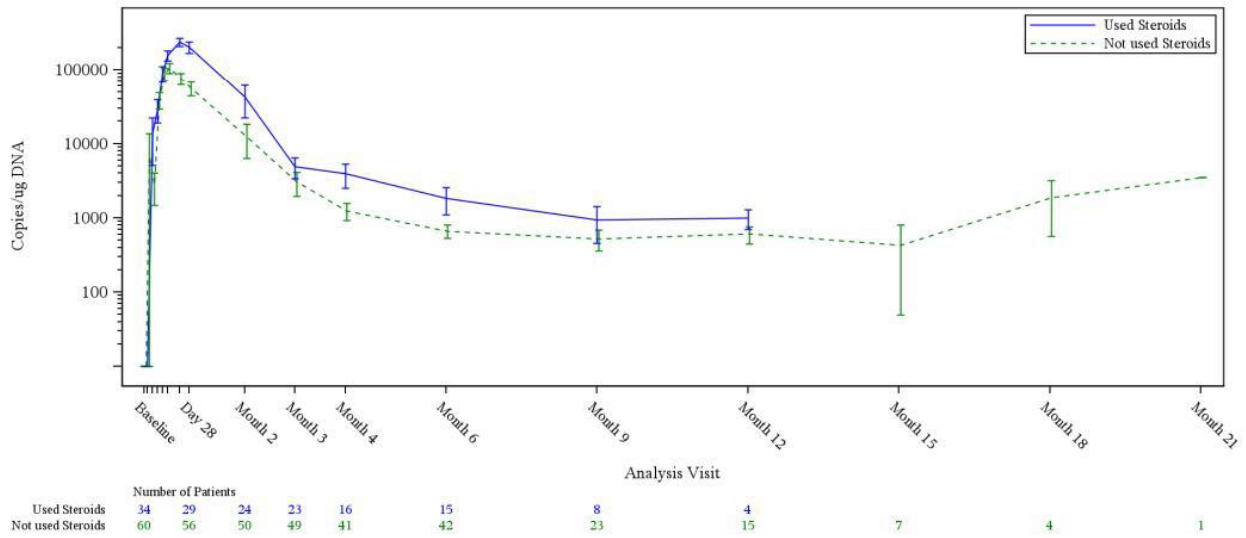
CAR T cell persistency was observed both in patients where corticosteroids were administered and in patients without corticosteroid administration (Figure 11).

Since corticosteroids are administered to treat CRS and ICANS which develop predominantly in patients with high tumour burden (associated with a higher CAR T cell expansion), any interpretations needs to take the major confounding impact of CRS and ICANS into account. The difference in expansion is more likely to be due to CRS and ICANS than due to the administration of corticosteroids. This is consistent with previous cellular CAR T cell therapies that have shown corticosteroids administration does not impact the rate or extent of expansion.

Table 9: Summary of PK Based on Use of Corticosteroids Post Obe-Cel Infusion (Cohort IIA, Infused Set)

Parameter	Statistic	Used Steroids (N=34)	Not used Steroids (N=60)
C_{max} (copies/µg DNA)	n	34	60
	Geometric Mean (Geo-CV%)	282,740 (58.8)	69,056 (355.7)
	Range (Min – max)	64,500-600,000	129-440,000
T_{max} (days)	n	34	60
	Median	21	14
	Range (Min – max)	6-55	2-28
AUC_{0-28d} (copies/µg DNA*day)	n	27	55
	Geometric Mean (Geo-CV%)	2,396,542 (84.5)	789,711 (258.3)
	Range (Min – max)	421,000-6,730,000	17,900-7,230,000

Figure 11: CAR T Cell Expansion and Persistency: Mean (SE) Obe-Cel Transgene Level in Peripheral Blood Over Time by Use of Corticosteroids Within 28 Days Post Obe-Cel Infusion (Cohort IIA, Infused Set)



In conclusion, administration of corticosteroids is unlikely to impact the rate or extent of CAR T cell expansion and persistency. The increased extent of expansion observed is likely linked to tumour burden and due to CRS and or ICANS for which corticosteroids were administered.

Potential pharmacodynamic interactions with tocilizumab and corticosteroids have been thoroughly investigated and characterised. The findings demonstrate that these medications do not negatively impact obe-cel's pharmacokinetics, pharmacodynamics, efficacy, or safety. Interactions with other immunosuppressive agents, immunomodulatory drugs, and vaccinations have been previously addressed. While data on herbal remedies are limited, general precautions are recommended due to their potential immunomodulatory effects.

Genetic differences in PD response

Currently, there is no evidence to suggest that genetic differences significantly affect the PD response to obe-cel in adult patients. The therapy involves using a patient's own T cells, genetically modified to target CD19, which is uniformly expressed on B cells in B ALL patients. Human leukocyte antigen (HLA) polymorphisms and other genetic factors influencing immune response could theoretically impact T-cell function and efficacy. However, the data provided do not include specific analyses of HLA types or genetic polymorphisms affecting PD response to obe-cel.

Similarly, while genetic mutations or alternative splicing in the CD19 gene could alter antigen expression and potentially affect obe-cel efficacy, the clinical data do not report significant issues with CD19-negative relapse. The high remission rates observed suggest that CD19 expression was sufficient for effective targeting across the patient population.

Regarding genetic factors that might affect T-cell function, such as polymorphisms in cytokine receptors or signalling molecules, there is no specific data indicating that these have impacted the expansion and persistence of CAR T cells in patients treated with obe-cel.

The absence of specific analyses on genetic differences limits the ability to draw definitive conclusions about their impact on PD response. However, the therapy's effectiveness across a

genetically diverse adult population suggests that significant genetic differences in PD response may not be common. Therefore, no changes to the proposed labelling are necessary concerning genetic differences, and routine genetic testing before initiating obe-cel therapy is not required. Regarding the paediatric population, the lack of clinical data means that potential differences due to maturation and immune system development cannot be assessed. Until dedicated paediatric studies are conducted, the use of obe-cel in children cannot be recommended. The proposed labelling appropriately limits the indication to adult patients with r/r B ALL and should state that the safety and efficacy of obe-cel in paediatric patients have not been established.

Based on the data provided, there is no evidence to suggest that genetic differences significantly affect the pharmacodynamic response to obe-cel in adult patients. The therapy appears effective across a genetically diverse population without the need for genetic stratification. The proposed labelling is supported by the available data, and no adjustments are necessary regarding genetic differences in PD response.

Pharmacokinetics-Pharmacodynamics (PK/PD) and Exposure-response relationship.
Relationship between plasma concentration and efficacy/safety PK/PD Studies in Patients
In the clinical development programme, the PK/PD profile of obe-cel was characterised primarily through the FELIX study (AUTO1-AL1), a Phase Ib/II trial involving adult patients with r/r B ALL. The pharmacokinetic analyses focused on assessing the expansion, peak concentration (Cmax), area under the curve from day 0 to day 28 ($AUC_{0–28}d$), and persistence of CAR T cells in peripheral blood and bone marrow.

Exposure-Response and PK/PD Approaches
Exploratory analyses were performed to evaluate the relationships between obe-cel dose, pharmacokinetic parameters (Cmax and $AUC_{0–28}d$), and clinical outcomes, including efficacy and safety endpoints.

Dose-PK Relationship: The relationship between the administered dose and PK parameters was explored by comparing PK profiles between patients who received the target dose and those who did not. The standard dosing regimen involved administering a total target dose of 410 × 10^6 CAR-positive T cells (±25%) in a two-step fractionated dosing regimen, adjusted based on disease burden at lymphodepletion.

Exposure-Efficacy Relationship: Logistic regression analyses were conducted to evaluate the relationship between PK parameters (log-transformed Cmax and $AUC_{0–28}d$) and clinical efficacy endpoints, such as overall remission rate (ORR) and minimal residual disease (MRD) negativity.

Exposure-Safety Relationship: Similar analyses assessed the association between PK parameters and the incidence of adverse events, particularly cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS).

Covariate Effects on PK/PD and Drug-Exposure-Response
Disease Burden: Higher disease burden at lymphodepletion was associated with greater CAR T-cell expansion, higher Cmax and $AUC_{0–28}d$, and a later peak concentration (Tmax). Patients with higher disease burden demonstrated higher incidence and severity of CRS and ICANS.

Age, Sex, and Race: Exploratory analyses indicated negligible differences in PK parameters based on age, sex, or race. No significant covariate effects were identified for these demographic factors.

Prior Therapies: Previous treatments, including chemotherapy and other CD19-directed therapies, did not significantly impact CAR T-cell expansion or persistence.

Results and Strength of Evidence
Exposure-Efficacy Relationship: The analyses did not demonstrate a clear correlation between increased CAR T-cell expansion (Cmax and $AUC_{0–28}d$) and improved efficacy outcomes. Patients achieving complete remission (CR) or complete remission with incomplete haematological recovery (CRi) had similar PK parameters to non-responders, suggesting that beyond a certain threshold, additional CAR T-cell expansion does not enhance efficacy.

Exposure-Safety Relationship: A positive correlation was observed between increased CAR T-cell expansion and the likelihood of experiencing CRS and ICANS. Patients with higher Cmax and $AUC_{0–28}d$ had increased odds of developing these adverse events.

Strength of Evidence: The exploratory nature of the analyses and the high variability observed limit the strength of the conclusions. The lack of advanced modelling and simulation approaches, such as population PK/PD modelling, reduces the robustness of the findings.

Support for Proposed Labelling
The PK/PD data support the proposed labelling for obe-cel, particularly regarding the dosing regimen adjusted based on disease burden and the need for monitoring and management of CRS and ICANS. The lack of a clear exposure-efficacy relationship suggests that the current dosing strategy is appropriate. The observed exposure-safety relationship underscores the importance of vigilant monitoring for adverse events in patients with higher disease burden and greater CAR T-cell expansion.

Impact of Variability on Benefit/Risk Profile and Risk Minimisation Measures
The variability in PK parameters, particularly related to disease burden, may influence the benefit/risk profile of obe-cel in certain clinical scenarios.

Unexplained Variability: While disease burden explains some variability in CAR T-cell expansion, significant variability remains unexplained. This variability could affect the predictability of efficacy and safety outcomes.

Benefit/Risk Profile: Patients with higher disease burden may experience greater CAR T-cell expansion, leading to increased risk of CRS and ICANS without a proportional increase in efficacy. This could alter the benefit/risk balance in these patients.

Risk Minimisation Measures: Specific measures should be included in the Risk Management Plan (RMP) to address this variability:

- **Restrictions/Precautions**: Careful assessment of disease burden prior to dosing is essential. Adjusting the initial dose based on disease burden helps mitigate the risk of severe adverse events.
- **Dose Adjustments in Special Populations**: Although no specific adjustments are required based on age, sex, or race, patients with high disease burden should receive a lower initial dose, as per the dosing regimen.
- **Post-Authorisation Safety Study**: A post-authorisation safety study could further evaluate the impact of PK variability on safety outcomes, particularly in patients with high disease burden.

The PK/PD data from clinical studies provide valuable insights into the pharmacological profile of obe-cel. While the analyses were exploratory and limited by variability and the absence of advanced modelling techniques, they support the proposed labelling and dosing regimen adjusted based on disease burden. The exposure-response relationships highlight the need for careful patient monitoring, especially regarding safety.

Evaluation and qualification of E-R and PK/PD models
The primary objectives of the PK/PD modelling for obe-cel were to characterise CAR T-cell expansion and persistence, evaluate the exposure-response relationship, and assess how intrinsic and extrinsic factors such as age, gender, race, disease burden, hepatic and renal function, and prior medications influence PK/PD parameters and clinical responses. Due to the nature of CAR T-cell therapies, traditional PK modelling approaches are less applicable. Instead, the PK of obe-cel was characterised by measuring the expansion and persistence of CAR T cells in peripheral blood and bone marrow using quantitative polymerase chain reaction (qPCR) and flow cytometry methods.

Exploratory analyses were conducted to evaluate the relationships between exposure (C_max and $AUC_{0–28}$d) and clinical outcomes, including efficacy endpoints such as overall remission rate (ORR), best overall response (BOR), and minimal residual disease (MRD) negativity, and safety endpoints like the incidence and severity of cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS). Simple linear and logistic regression models were employed to explore these exposure-response relationships. Covariate analyses considered factors such as disease burden (stratifying patients based on disease burden at lymphodepletion), demographic factors (age, gender, and race), prior medications (including chemotherapy and CD19-directed treatments), and hepatic and renal function.

Due to ethical considerations and the nature of obe-cel as a personalised cellular therapy with potential risks of severe immune reactions, PK/PD studies were not conducted in healthy volunteers. Therefore, the PK/PD analyses were based on data from clinical studies involving patients with r/r B ALL. CAR T-cell levels were measured at multiple time points post-infusion, with key PK parameters including C_max (peak CAR T-cell levels in peripheral blood), T_max (time to reach peak levels), and $AUC_{0–28}$d (area under the curve from day 0 to day 28, representing overall exposure). PD assessments included monitoring B-cell aplasia as a marker of obe-cel activity and measuring cytokine levels such as IL-6, IL-10, and IFN-γ to assess immune activation and correlate with CRS and ICANS.

Regarding potential biomarkers and disease progression, B-cell aplasia was observed as an expected on-target effect indicating successful depletion of CD19-positive B cells. Elevated cytokines and inflammatory markers were associated with CRS and ICANS. Achieving MRD negativity was a key efficacy endpoint, indicating deep remission, and CAR T-cell persistence was linked to sustained remission and prolonged disease control.

Given the exploratory nature of the analyses, formal population PK/PD modelling with advanced simulation methods was not performed. Therefore, traditional model evaluation techniques such as prediction-corrected visual predictive checks (pcVPCs) and estimation of parameter precision were not applicable. Statistical analyses included descriptive statistics to summarise PK parameters across patient subgroups and regression analyses to evaluate relationships between exposure and response variables. Significant inter-patient variability in CAR T-cell expansion and exposure was noted, and limitations included the preliminary nature of the analyses and the absence of population PK/PD models, which limited the ability to quantify variability and make

predictive simulations.

The results indicated that there was no clear correlation between higher CAR T-cell exposure and improved efficacy outcomes. Patients achieving remission had similar exposure levels to those who did not, suggesting that beyond a certain threshold, additional CAR T-cell expansion does not enhance efficacy. A positive correlation was identified between higher CAR T-cell exposure and increased incidence of CRS and ICANS. Patients with higher disease burden experienced greater CAR T-cell expansion and were at higher risk for these adverse events. Disease burden was a significant factor influencing CAR T-cell expansion, while no substantial effects of age, gender, race, hepatic or renal function, or prior medications on PK/PD parameters were identified.

The findings are relevant to the clinical use of obe-cel, emphasising the importance of disease burden in dosing decisions and monitoring for adverse events. However, the analyses were limited by high variability and the lack of sophisticated modelling techniques. The small sample sizes in certain subgroups reduced the statistical power to detect covariate effects.

The data support the indication of obe-cel for adult patients with r/r B ALL, demonstrating efficacy across the studied population. The dosing regimen, involving a total target dose of 410 × 10^6 CAR-positive T cells with adjustments based on disease burden, is supported by the exposure-safety relationship. Patients with high disease burden receive a lower initial dose to mitigate the risk of severe adverse events due to higher CAR T-cell expansion.

Immunological events
Humoral immunogenicity sample analysis is ongoing and will be presented as a stand-alone report submitted during the first 30 days after BLA submission as agreed during the pre-BLA meeting.

Cellular immunogenicity was performed using an off the shelf validated ELISpot assay that was appropriately qualified. Full validation could not be performed as positive control samples could not be identified ahead of initiating validation. Each sample is tested against 3 peptide pools.

Samples for assessment of cellular immunogenicity were available for 161/313 samples corresponding to 75/127 patients from the Safety Set patients (59.1%). Data was missing for 152 samples because:
• 99 samples had too few cells for analysis
• 37 samples had unacceptable positive control response
• 6 samples had a high background
• 6 samples were contaminated post Day 1 incubation
• 4 samples had plating issue

Results are presented in Listing 16.2.8.9. Positive immunogenicity findings occurred in only 3 patients (2.4%) and are summarised in Table 20 at the Month 3 visit. All 3 patients demonstrated CR and any safety events were unlikely to be related to the immunogenicity signal.

All events of CRS and ICANS in these 3 patients occurred and resolved/recovered within approximately 1 month post first obe-cel infusion. The positive immunogenicity results occurred at approximately Month 3; no further immunogenicity testing was performed thereafter.

Table 20: Summary of Patients with Positive Immunogenicity Result At 3 Months

Disease Burden At Lymphodepletion	BOR	Safety Event (CTCAE Grade)
9%	CR	CRS (GR1)
96.5%	CR	CRS (GR2), ICANS (GR3)
37%	CR	CRS (GR1)

In conclusion, no significant cellular immunogenicity signal was seen in 3/75 patients with evaluable sample and results from humoral immunogenicity data will be provided in the first 30 days after BLA submission. As obe-cel is an autologous product, significant cellular or humoral immunogenicity are not expected.

Dose justification

Rationale for Dose and Dose Regimen

The protocol-specified target dose for the pivotal FELIX study is 410 × 106 CD19-positive CAR T cells. Dosing was split across 2 administrations on Day 1 and on Day 10 (± 2 days), with the number of CAR T cells per dose being dependent on the individual patient's initial disease burden at the time of lymphodepletion (referred to as pre-conditioning in the protocol and statistical outputs) (Table).

Table: Fractionation of Obe-cel Based on Bone Marrow Blast Counts at Pre-Conditioning

BM Blast %	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

Dose-Pharmacokinetics Analysis

Pharmacokinetic Analysis per Dose Regimen

Among patients who received 2 doses, those who received 10 × 106 CD19 CAR-positive T cells at first dose (>20% blasts in BM, high disease burden) demonstrated a higher expansion and a later peak than patients who received 100 × 106 CD19 CAR-positive T cells at first dose (≤20% blasts in BN, low disease burden) (Table 4), suggesting that tumour burden, rather than the dose, drives the extent and timing of the peak of CARs. Persistency was observed in both patients with low and high first doses.

Table 4: Pharmacokinetic Parameters By Dose Regimen (Cohort IIA, Infused Set – Patients Who Received 2 Obe-cel Doses)

Parameter	Statistics	100 × 10^6 / 310 × 10^6 Low disease burden regimen (≤ 20% blasts) (N=32) [1]	10 × 10^6 / 100 × 10^6 High disease burden regimen (> 20% blasts) (N=56) [2]	Total (N=88)
C_{max} (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
T_{max} (days)	n	32	56	88
	Median	11	17	14
	Range (min-max)	2-28	6-55	2 -55
AUC_{0-28} (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

AUC_{0-28d}=area under the curve from time zero to day 28; C_{max}=maximum (or peak) concentration; Geo-CV%=geometric coefficient of variation; T_{max}=time to maximum (or peak) concentration.
Source: AUTO1-AL1 CSR-Table 14.6.1.2.3.1.iia.
[1] Two doses and the first dose was 100 × 10^6 CD19 CAR-positive T cells.
[2] Two doses and the first dose was 10 × 10^6 CD19 CAR-positive T cells.

The number of patients who received a single dose (n = 7) is too small to draw conclusions on PK parameters per dose regimen.

Timing of Second Dose – Pharmacokinetic Analysis
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.

Only 9 patients received a delayed second dose (Cohort IIA, Infused Set). The onset of CRS and/or ICANS was the reason for a delayed second dose in 7 out of the 9 patients receiving a delayed second dose. Despite the small number of patients receiving a delayed second dose, persistency is observed and is comparable to patients receiving the second dose without delay. Despite small numbers, no indication of decreased efficacy is observed in patients receiving a delayed second dose.

Dose-Response Analysis
The relationship between obe-cel dose and response (efficacy and safety) was explored using efficacy and safety analysis sets, respectively. Efficacy endpoints were evaluated to assess the impact of dose on response for ORR, BOR, MRD. Furthermore, the impact of dose on the occurrence of CRS, including any Grade and Grade 3/4 CRS, was evaluated. Similarly, the occurrence of ICANS was also explored.

Dose-Efficacy Analysis

All patients, regardless of disease burden or number of cells infused at the first dose, demonstrate a compelling efficacy. Patients receiving a lower first dose of 10 × 106 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 × 106 cells (≤20% blasts in BM, low disease burden) (87.5% CR/CRi), with overlapping 95% CI and despite demonstrating a higher expansion and similar duration of persistency (Table 5). This numerical difference in ORR is likely to be due to the disease burden, as patients with a higher disease burden are more difficult to treat.

Table 5: 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.

Dose-Safety Analysis

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 6.

Table 6: 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.

The incidence of all Grade ≥ 3 CRS and ICANS, as well as Grade ≥3 is low. The incidence of CRS and ICANS was higher in the patients who received 10 × 106 cells in their first dose (with higher disease burden) compared to those who received 100 × 106 cells in the first dose (lower disease burden), suggesting that these safety signals are associated with disease burden rather than with the number of cells infused at first obe-cel dose.

The FELIX data confirm that the selected tumour burden-adjusted dosing regimen, in addition to the unique mode of action of obe-cel, helps to manage the impact of disease burden on the frequency and severity of CRS and ICANS.

The applicant's justification for the proposed posology of obe-cel is robust and well-supported by clinical data from the FELIX study. The adjustments based on disease burden are logical and effective in optimising the balance between efficacy and safety:

Efficacy is Maintained: Comparable remission rates are achieved across dosing groups, indicating that the adjusted dosing does not compromise therapeutic outcomes.

Safety is Enhanced: Reducing the initial dose in patients with high disease burden helps to mitigate the risk of severe CRS and ICANS.

Personalised Treatment: The dosing strategy reflects a personalised approach, taking into account individual patient factors to optimise treatment.

Overall, the dosing regimen for obe-cel is justified by comprehensive pharmacokinetic, efficacy, and safety data. The tailored approach based on disease burden enhances patient outcomes and aligns with best practices in personalised medicine. The recommendations are appropriate, and no additional adjustments are necessary for coadministration with other medicines used in managing treatment-related adverse events.

Overall assessment of clinical pharmacology

Discussion
Obecabtagene autoleucel (obe-cel) is an autologous CD19-directed chimeric antigen receptor (CAR) T-cell therapy intended for adult patients with relapsed or refractory B-cell acute lymphoblastic leukaemia (r/r B ALL). The clinical pharmacology data submitted provide a comprehensive overview of obe-cel's PK and PD, highlighting several strengths and some areas of uncertainty.

Strengths:
Pharmacokinetics: The PK profile of obe-cel has been characterised through the FELIX and ALLCAR19 studies. Both studies demonstrate rapid and robust CAR T-cell expansion post-infusion, with a median time to peak concentration (T_max) around 14 days. Sustained persistence of CAR T cells is observed, correlating with durable clinical responses.

Pharmacodynamics: The PD effects are well-understood. B-cell aplasia serves as a direct pharmacodynamic marker of obe-cel's activity, confirming effective targeting and depletion of CD19-positive B cells. Cytokine monitoring provides essential information for managing cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS).

Dose Justification: The proposed dosing regimen, adjusted based on disease burden, is supported by clinical data. Patients with higher disease burden receive a lower initial dose to mitigate the risk of severe adverse events without compromising efficacy.

Interactions with Other Medicines: Potential pharmacodynamic interactions with tocilizumab and corticosteroids have been thoroughly investigated. The findings demonstrate that these medications do not adversely impact obe-cel’s pharmacokinetics, efficacy, or safety.

Weaknesses:

Advanced PK/PD Modelling: The lack of advanced population PK/PD modelling limits the understanding of inter-patient variability and predictive factors influencing PK and PD responses. This absence hinders the ability to perform predictive simulations and fully characterise the pharmacological profile.

Immunogenicity Data: While cellular immunogenicity assessments suggest a low incidence of antibody formation without significant clinical impact, the humoral immunogenicity analysis is incomplete. Pending data on anti-CAR antibodies leave a gap in fully understanding the immunogenicity profile.

Genetic Differences and Special Populations: There is a lack of specific analyses on genetic differences affecting PD response. Additionally, no clinical data are available for paediatric patients or those with hepatic and renal impairment, limiting the applicability of the findings to these populations.

IV.4 Clinical efficacy

In support of the application, the following was submitted:

Main clinical study

An open-label, multi-centre, phase Ib/II study evaluating the safety and efficacy of obe-cel, a CAR-T cell treatment targeting CD19 in adult patients with relapsed or refractory B cell acute lymphoblastic leukaemia.

The FELIX study was conducted in the UK, Spain and the USA. The numbers of sites and subjects enrolled are summarised in the following table:

Table 2. Total number of sites and subjects enrolled per country from 03-Jun-2020 to 17-Mar-2023.

Country	Total number of sites enrolling patients	Total number of subjects enrolled
Spain	3	17
United Kingdom	8	56
United States	20	80

This study was conducted in accordance with the ethical principles of Good Clinical Practice, according to the International Council for Harmonisation.

Duration of follow-up within the FELIX study is 24 months.
After a subject has completed 24 months: long-term efficacy and safety will be evaluated for up to 15 years after exposure to obe-cel in a separate extension study: study AUTO-LT1.

Study objectives and efficacy endpoints

The primary objectives and endpoints are provided in Table 1:

Table 1: Primary Objectives and Endpoints

Objectives	Endpoints
Phase Ib	
To evaluate the safety of obe-cel.	Frequency and severity of AEs and SAEs occurring after obe-cel infusion.
Phase II	
To evaluate the clinical efficacy of obe-cel.	Cohort IIA: ORR defined as the proportion of patients achieving CR or CRi as assessed by an IRRC. Cohort IIB: Proportion of patients achieving MRD-negative remission by central ClonoSEQ NGS testing (<10^{-4} leukemic cells).

AE=Adverse event; CR=Complete remission; CRi=Complete remission with incomplete hematologic recovery; IRRC=Independent Response Review Committee; MRD=Minimal residual disease; NGS=Next Generation Sequencing; ORR=Overall remission rate; SAE=Serious adverse event.

It is considered that overall survival of adult subjects with relapsed / refractory B-cell acute lymphoblastic leukaemia is dire; most will likely die within 1 year with current treatments. For this reason, emphasis is given to the outcome of overall survival with other outcomes being regarded as 'of interest' and / or regarded in a 'general sense' only.

All subjects in the 'phase I and phase II' sections were exposed to product by the same protocol; the outcome of overall survival in subjects is seeked as a whole.

Secondary objectives and endpoints are provided in Table 2:

Table 2: Secondary Objectives and Endpoints

Objectives	Endpoints
Phase Ib	
To evaluate the feasibility of manufacturing and administering obe-cel.	Proportion of enrolled patients for whom an obe-cel product can be manufactured and administered as per protocol.
To evaluate the clinical efficacy of obe-cel	ORR, defined as proportion of patients achieving CR or CRi. Proportion of patients achieving MRD-negative remission in BM by PCR and/or flow cytometry.
To evaluate the expansion and persistency of obe-cel	Detection of CD19 CAR T cells measured by PCR in the peripheral blood and BM following obe-cel infusion.

Table 2: Secondary Objectives and Endpoints

Objectives	Endpoints
Objectives	**Endpoints**
To evaluate the clinical efficacy of obe-cel.	• CRR at any time post obe-cel infusion as assessed by an IRRC. • CRR within 3 months post obe-cel infusion as assessed by an IRRC. • Proportion of patients achieving MRD-negative CR/CRi by central ClonoSEQ NGS testing ($<10^{-4}$ leukemic cells), PCR and/or flow cytometry • DOR, defined as duration from the date of achieving CR/CRi post obe-cel infusion to the date of relapse or death due to any cause. • DOCR, defined as duration from the date of achieving CR post obe-cel infusion to the date of relapse or death due to any cause. • EFS, defined as duration from first obe-cel infusion to the earliest of treatment failure, relapse or death from any cause • PFS [1], defined as the time from first infusion to date of progressive disease, including Investigator's claim of clinical progression, date of death from any cause. • OS, calculated from the date of first obe-cel infusion to the date of death. • ORR [CR+CRi] as assessed by the Investigator. • Proportion of patients undergoing SCT prior to leukemia relapse. • Proportion of patients in CR/CRi without SCT or other subsequent therapies at 6, 12 and 24 months following obe-cel infusion. • Incidence of CD19-negative relapse.
To assess the safety and tolerability of obe-cel.	Frequency and severity of AEs and SAEs. Incidence and duration of severe hypogammaglobulinemia.
To evaluate the feasibility of manufacturing and administering obe-cel.	Proportion of enrolled patients for whom an obe-cel product can be manufactured and administered.
To evaluate the expansion and persistencey of obe-cel.	Detection of CAR T cells measured by PCR in the peripheral blood and BM following obe-cel infusion.
To evaluate the duration of B cell aplasia.	Depletion of circulating B cells assessed by flow cytometry in the peripheral blood.
To evaluate PRO and QoL.	Changes over time in symptom, functioning and quality of life scores of the EuroQoL (EQ-5D-5L and VAS) and the EORTC QLQ-C30 instruments
To evaluate health care resource utilization for the management of obe-cel related toxicity.	Frequency and duration of hospitalization and/or critical care support to manage obe-cel related toxicity.

Abbreviations: AE=Adverse event; BM=Bone marrow; CAR=Chimeric antigen receptor; CR=Complete remission; CRi=Complete remission with incomplete recovery of counts; CRR=Complete remission rate; DOCR=Duration of complete remission; DOR=Duration of remission; EFS=Event-free survival; EQ-5D-5L= EuroQoL 5 dimension 5 level; EORTC=European Organisation for Research and Treatment of Cancer; IRRC=Independent Response Review Committee; MRD=Minimal residual disease; NGS=Next Generation Sequencing; ORR=Overall remission rate; OS=Overall survival; PFS=Progression-free survival; PRO=Patient reported outcome; QLQ=Quality of life questionnaire; QoL=Quality of life; qPCR=Quantitative polymerase chain reaction; RFS=Relapse-free survival; SAE=Serious adverse event; SCT=Stem cell transplantation; VAS=Visual analog scale.
[1] PFS was not analyzed in this report, because the definition of PFS was identical to EFS in this study (treatment failure was not counted as an event for EFS).

Given the high mortality for adult subjects associated with B-cell acute lymphoblastic leukaemia, it is considered that overall survival and quality of life measures will be the most informative towards claimed efficacy. Other outcomes will be regarded in a supportive sense.

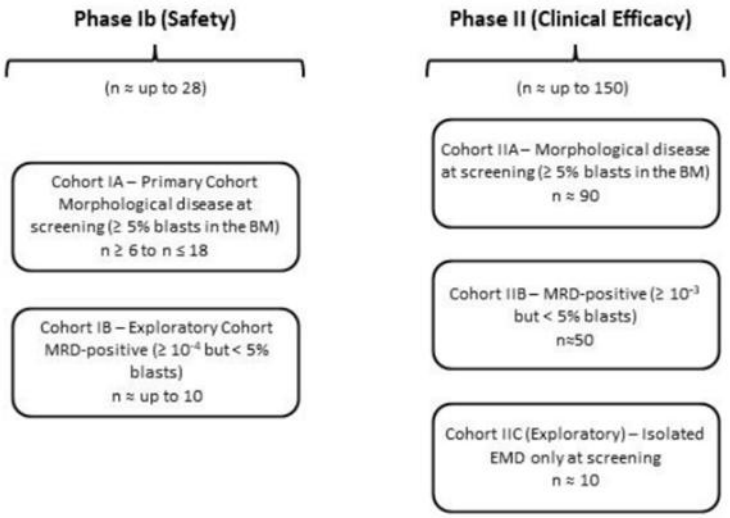
The applicant also describes pharmacokinetic and pharmacodynamic exploratory objectives; refer to the Pharmacokinetic section of this PAR for comment on these aspects and also on expansion /

persistence of CAR-T cells.

Aspects of study design
The FELIX study is an on-going open-label, single-arm, multi-centre study.
The applicant also describes the study as phase Ib/II i.e. the applicant regards the FELIX study as an exploratory study.

The study has a sentinel phase I component (to explore safety and feasibility) and a main phase II component (there are 3 cohorts in phase II), as summarised in the following diagram:

Figure 1: FELIX Study Design



Lymphodepletion: Fludarabine / cyclophosphamide (Days -6, -5, -4, -3)
Obe-cel treatment: All patients were to receive the target dose of 410 x 10^6 CD19 CAR-positive T cells administered as a split dose based on disease burden
BM = Bone marrow; EMD = Extra medullary disease; MRD = Minimal residual disease

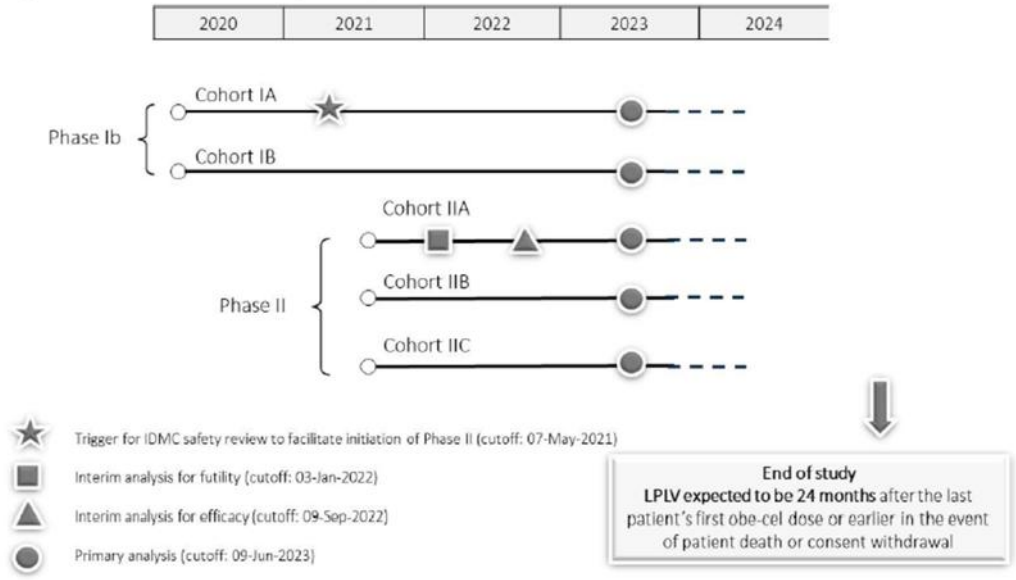
The Phase II part of the study was to evaluate the efficacy of obe-cel by determining overall remission rate in response to obe-cel.

Cohort IIA was to include at least 40 patients who were blinatumomab and / or inotuzumab ozogamicin experienced and at least 40 patients who were naïve to both these drugs.

An Independent Response Review Committee determined the remission rate for the analysis of the primary endpoint. An Independent Data Monitoring Committee reviewed safety data.

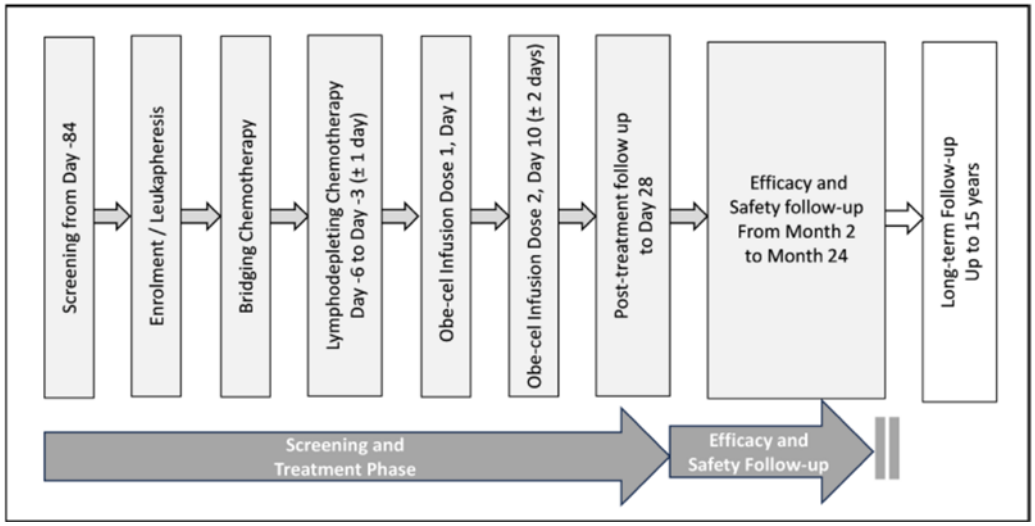
Overall time-course of the study is shown:

Figure 2: FELIX Study Design on a Time Course



Subjects went through 5 sequential stages: screening, leukapheresis, lymphodepletion (also referred to as pre-conditioning), treatment and follow-up (Figure 3).

Figure 3: Study Treatment and Follow-up Stages



Aspects of statistics

Randomisation was not carried out; this trial was conducted as a deterministic trial.

Blinding: was not done; this is an open-label study.

Allocation: was based on pathology findings, as described below, and not by a concealed method; this trial was conducted as a deterministic trial.

Applicant position on the analysis:
The following hypotheses will be tested for the primary and the key secondary endpoint

hierarchically for all patients treated with obe-cel from Cohort IIA in Phase II part of the study.

- H01: ORR ≤40% vs. H11: ORR >40% (Primary endpoint)
- H02: CR ≤20% vs. H12: CR >20% (Key secondary endpoint)

In addition, analysis will be performed according to the disease burden prior to the start of the preconditioning therapies as follows:

- ≥5% blast in BM
- <5% blast in BM without EMD
- <5% blast in BM with EMD

Justification of the applicant:
The primary efficacy analysis for Cohort IIA in the Phase II part will be performed by testing whether the ORR is ≤40% against the alternative hypothesis that ORR is > 40% at overall one-sided 2.5% level of significance.

At the start of the FELIX clinical study, another CD19 targeting therapy approved for adult ALL is blinatumomab. In the Phase III TOWER study of blinatumomab versus standard of care chemotherapy the ORR (CR/CRh) within 3 months of starting treatment was 42% [95% CI 37 to 49] and that of standard of care chemotherapy was 20% [95% CI 14 to 28].

In the FELIX study, enrolled patients will have either already relapsed after blinatumomab treatment with chemotherapy being an option for subsequent treatment or be blinatumomab naïve, where treatment with blinatumomab maybe an option. As the expected ORR with these treatments would be in the range of 20% to 42%, the null hypothesis that the true remission rate with obe-cel is 40% is considered reasonable.

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%.

Use of external controls and cut-points, as described by the applicant, is noted.

The applicant has conducted a single arm trial with five compartments / cohorts. The applicant has provided suitable justification for not conducting a randomised, controlled trial.

Cohorts of the study
Phase Ib
Primary Cohort IA: Adults aged ≥18 years with B-cell acute lymphoblastic leukaemia who had relapsed / refractory disease and ≥5% blasts in the bone marrow at screening.

Exploratory Cohort IB: Adults aged ≥18 years with B-cell acute lymphoblastic leukaemia in morphological remission with minimal / measurable residual disease (≥10^{-4} and <5% blasts in the bone marrow at screening).

Phase II
Cohort IIA: Adults aged ≥18 years with B-cell acute lymphoblastic leukaemia who had relapsed / refractory disease and presence of ≥5% blasts in the bone marrow at screening.

Cohort IIB: Adults aged ≥18 years with B-cell acute lymphoblastic leukaemia in ≥2nd complete response or “complete response with incomplete haematologic recovery” with minimal /

measurable residual disease (≥10^{-3} by central ClonoSEQ Next Generation Sequencing testing and <5% blasts) in the bone marrow at screening.

Cohort IIC (exploratory cohort): Adults aged ≥18 years with B-cell acute lymphoblastic leukaemia with isolated extramedullary disease (including isolated central nervous system disease), with or without minimal / measurable residual disease.

This single-arm study has a deterministic design to allocate subjects to cohorts.

Cohort IA: ≥5% blasts in the bone marrow
Cohort IB: minimal residual disease
Cohort IIA: ≥5% blasts in the bone marrow
Cohort IIB: minimal residual disease
Cohort IIC: with isolated extramedullary disease with or without minimal residual disease.
To note that the definition of minimal residual disease changed from cohort IB (≥10^{-4} and <5% blasts) to cohort IIB (≥10^{-3} and <5% blasts in bone marrow).

The schedule of assessments is shown on the following pages:

SCHEDULE OF ASSESSMENTS 1:

Table 1: Assessments from Screening to End of Treatment Phase

Applies to all patients unless otherwise stated. Please refer to the relevant abbreviations and footnotes.

Visits / Assessments	Screening From D-84	Leuka-pheresis	Pre-conditioning	Treatment Phase*									
			D-6, -5, -4, -3 ±1d	D1	D3 ±1d	D6 ±1d	D8 ±1d	D9 ±1d	D10 ±2d	D12 ±1d	D15 ±2d	D22 ±2d	D28 ±2d
PATIENT INFORMATION													
Informed consent	X												
Enrolment confirmation [1]		X											
Demographic data [2]	X												
Eligibility criteria [3]	X		X D-6	X									
Medical/ALL history [4]	X												
Prior/Concomitant Medication [5]	◄						X						►
Quality of Life: EORTC QLQ-C30 (Phase II only)			X D-6										X
Quality of life: EQ-5D-5L (Phase II only)			X D-6										X
Survival status [6]	◄						X						►
EXAMINATIONS, INVESTIGATIONS AND SAFETY EVALUATIONS													
Performance status [7]	X		X D-6										X
Weight	X		X D-6										X
Physical examination [8]	X		X D-6	X			X				X	X	X
Neurocognitive assessment [9]			X D-6	X	X as clinically indicated e.g. ICANS								

Visits / Assessments	Screening From D-84	Leuka-pheresis	Pre-conditioning	Treatment Phase*									
			D-6, -5, -4, -3 ±1d	D1	D3 ±1d	D6 ±1d	D8 ±1d	D9 ±1d	D10 ±2d	D12 ±1d	D15 ±2d	D22 ±2d	D28 ±2d
Vital signs and O_2 saturation [10]	X		X D-6	X					X				X
ECHO or MUGA [11]	X	X as clinically indicated											
Haematology [12]		X	X D-6	X			X				X	X	X
Biochemistry [13]	X		X D-6	X			X				X	X	X
C-Reactive Protein and ferritin			X D-6	X	X	X		X		X	X	X	X
Coagulation [14]		X	X D-6	X	X as clinically indicated e.g. severe CRS								
Infectious disease screen [15]	X	X											
Pregnancy test [16]	X		X D-6	X									X
Adverse events [17]	X												
TREATMENTS													
Cyclophosphamide [18]			X D-6, D-5										
Fludarabine [18]			X										
Antimicrobial prophylaxis [19]		◄ X ►											
AUTO1 infusion [20]				X					X				
DISEASE ASSESSMENTS													
Overall Disease Response			X D-6										X
Bone Marrow													
Morphology [21]	X		X D-6 to D-13										X
MRD & Immunophenotyping [21]	X		X D-6 to D-13										X
Cytogenetics [22]	X												

Visits / Assessments	Screening From D-84	Leuka-pheresis	Pre-conditioning	Treatment Phase*									
			D-6, -5, -4, -3 ±1d	D1	D3 ±1d	D6 ±1d	D8 ±1d	D9 ±1d	D10 ±2d	D12 ±1d	D15 ±2d	D22 ±2d	D28 ±2d
Peripheral Blood													
Morphology and blood count	X	X	X D-6 to D-13										X
Extramedullary Disease													
CSF examination [23]	X												X [23]
Imaging [24]	X [24]		X D-6 to D-13 [24]										X [24]
BIOMARKERS													
Bone Marrow													
AUTO1 persistence [25]													X
Peripheral Blood													
IgG levels			X D-6										X
Cytokine Profile [25]			X D-6	X	X	X		X		X	X	X	X
AUTO1 persistence [25]			X D-6	X	X	X		X		X	X	X	X
Immunogenicity [25]			X D-6										X
Immunophenotyping of AUTO1 [25]						X				X			X
Genomic profiling													X
RCL [26]			X D-6										X
Insertional Mutagenesis			X D-6										X
B-cell aplasia [25]			X D-6	X									X
Cerebrospinal Fluid													
AUTO1 detection and other markers													X [23]

AE = adverse event; AESI = adverse event of special interest; ALL = acute lymphoblastic leukaemia; ALT = alanine aminotransferase; AST = aspartate aminotransferase; CAR = chimeric antigen receptor; CD = cluster of differentiation; CNS = central nervous system; CR = complete remission; CRi = complete remission with incomplete count recovery; CRS = cytokine release syndrome; CSF = cerebrospinal fluid; CT = computed tomography; D/d = day; ECOG = Eastern Cooperative Oncology Group; ECHO = echocardiogram; eCRF = electronic case report form; EORTC = European Organization for Research and Treatment of Cancer; EM = extramedullary; EQ-5D-5L = EuroQol; FDG = fluorodeoxyglucose; Hep = hepatitis; HIV = human immunodeficiency virus; HTLV = human T-cell lymphotropic virus; ICANS = Immune effector Cell-Associated Neurotoxicity Syndrome; ICE = Immune effector Cell-Associated Encephalopathy; IFN-γ = interferon gamma; Ig(G) = immunoglobulin (G); IL = interleukin; LDH = lactate dehydrogenase; LVEF = left ventricular ejection fraction; MRD = minimal residual disease; MUGA = multigated acquisition scan; O_2 = oxygen; PCR = polymerase chain reaction; PET = positron emission tomography; QLQ-C30 = Quality of life Questionnaire; RCL = replication competent lentivirus; SAE = serious adverse event; TNF-α = tumour necrosis factor alpha.
*: The end of the treatment phase is defined as 1 Month (Day 28 ±2 days) post first AUTO1 infusion.
**: The End of Study visit is to be performed upon completion of all study visits or in case of early withdrawal.
$X^{D3, D7 \text{ etc}}$: Test/Assessments to be performed on a particular day of the schedule rather than systematically at every visit. Please refer to the number to determine the day of assessment.
#: In the event a patient is unable to attend clinic for protocol specified visits for any reason (e.g. Covid-19 outbreak), some visits may be conducted by a home health care provider selected by the Sponsor. Wherever feasible, the home health care provider may perform safety assessments in lieu of clinic visits at the protocol specified visits as per local and institutional guidelines (please refer to Schedule of Assessments 2 and 3).

[1] Enrolment:	Enrolment confirmed once all incl./excl. criteria have been fulfilled and leukapheresate has been accepted by the manufacturing facility.
[2] Demographics:	Race/ethnicity, height, age, and gender will be collected.
[3] Eligibility criteria:	Selected eligibility criteria will be re-assessed prior to pre-conditioning on Day -6 and prior to AUTO1 infusion. Please refer to Sections 6.3 and 6.4. Central ClonoSEQ NGS testing is required for screening in Cohort IIB.
[4] Medical/ALL history:	Clinically significant diseases, surgeries, cancer history (including prior cancer therapies and procedures) and prior medications. Record disease status at last assessment and complications since last assessments.
[5] Prior/Concomitant Medication:	Prior to Day -6 and after Day 60 only concomitant medications relevant to study related procedures or prophylaxis or AUTO1 treatment will be recorded. Any medication the patient is receiving on Day -6 must be recorded. After the 24-month observation period in the efficacy and safety follow-up or in the safety and survival follow-up, only intravenous Ig and therapeutic steroids will be recorded.
[6] Survival status:	All enrolled patients will be followed up for survival. If a visit is skipped where survival status is required or if the time point does not align with a scheduled visit, the information can be obtained over the phone.
[7] Performance status:	Performance status will be assessed by using ECOG.
[8] Physical examination:	Complete physical examination including neurological examination to be performed at screening and Day -6 then focused examination as appropriate at following visits.
[9] Neurocognitive assessment:	Two baseline measurements (ICE scale, Section 10.6) to be taken (Day-6 and prior to AUTO1 infusion) and then in the event of any neurological symptom.
[10] Vital signs and O_2 saturation:	Temperature, systolic and diastolic blood pressure, pulse rate, respiratory rate and oxygen saturation will be performed. On dosing days, perform vital signs immediately prior to AUTO1 infusion and then hourly (±15 minutes) for 4 hours post infusion, and thereafter monitored as per hospital policy but no less than daily during hospital stay. Clinically significant abnormalities will be recorded as AEs. Once discharged, the patient or the patient's caregiver should continue to monitor the patient's temperature daily for the first 28 days after the first AUTO1 infusion.
[11] ECHO or MUGA:	ECHO or MUGA will be performed only in patients with history of coronary artery disease or cardiovascular disease or those with history of low LVEF and to be repeated if clinically indicated. The same method should be used for a patient throughout the study as much as possible.
[12] Haematology:	Haemoglobin, platelet count, and white blood cell count with differential (neutrophils, monocytes and lymphocytes). This is performed daily during admission as standard care and results from the indicated time points will be recorded in the electronic case report form (eCRF).
[13] Biochemistry:	AST/ALT, alkaline phosphatase, LDH, total bilirubin, urea/blood urea nitrogen, creatinine, uric acid. Glomerular filtration rate should be calculated at screening as per the institutional preferred method. The results from the indicated time points will be recorded in the eCRF. These tests are generally performed daily during admission as part of standard care. All tests must be performed prior to AUTO1 infusion on dosing days.
[14] Coagulation:	Prothrombin time, international normalised ratio, activated partial thromboplastin time, fibrinogen after baseline assessment may be repeated if patient experiences severe CRS.
[15] Infectious disease screen:	Must be performed within 30 days prior to leukapheresis and must be confirmed negative then repeated on the day of leukapheresis (or within 7 days after the leukapheresis). HIV-1 and HIV-2, Hep B virus, Hep C virus, HTLV-1, HTLV-2, Syphilis and other pathogens (per local requirements).
[16] Pregnancy test:	Serum β-human chorionic gonadotropin or urine pregnancy testing for women of childbearing potential.
[17] Adverse events:	Adverse events will be collected on an ongoing basis throughout the study. Please refer to eCRF completion guidelines. After month 6, all SAEs, AESI and ONLY non-serious AEs that are deemed related to AUTO1 treatment or study related procedure will be collected. Please refer to Section 12 of the protocol for reporting requirements.
[18] Pre-conditioning regimen:	The pre-conditioning regimen will include Cyclophosphamide 500 mg/m² and Fludarabine 30 mg/m² at the indicated time points.
[19] Antimicrobial prophylaxis:	Patients should receive Pneumocystis prophylaxis with trimethoprim-sulfamethoxazole or suitable alternative agents, and either acyclovir or valacyclovir for herpes virus prophylaxis from the start of conditioning chemotherapy until at least 3 to 6 months post AUTO1 infusion or longer as per institutional guidelines. Additional anti-microbial (e.g. ciprofloxacin) and anti-fungal prophylaxis should be given as per institutional practice. Consider starting antimicrobial prophylaxis from the time of leukapheresis. Patients should be monitored for cytomegalovirus, adenovirus and Epstein-Barr at least 6 months post AUTO1 infusion or longer as per institution guidelines for allogenic stem cell transplant.
[20] AUTO1 infusion:	AUTO1 will be administered as a split dose for a target dose of 410 x 10^6 CD19 CAR-positive T cells. The first AUTO1 infusion will take place on Day 1 followed by the second infusion on Day 10 (±2 days). Of note, in the event of adverse event preventing the administration of the 2nd split dose, the infusion can be delayed beyond Day 10 (±2 days) up to Day 21 to allow the adverse event to resolve. Please refer to Section 6.4 of the protocol for information. The fractionation of the dose is driven by the patient's disease burden. Patients with low disease burden, defined as ≤20% blasts in the bone marrow performed within 7 days of the start of the pre-conditioning (assessed by morphology), will receive a first dose of 100 x 10^6 CD 19 CAR-positive T cells and a second dose of 310 x 10^6 CD19 CAR-positive T cells; while patients with high disease burden, defined as >20% blasts in the bone marrow performed within 7 days of the start of the pre-conditioning (assessed by morphology), will receive a first dose of 10 x 10^6 CD 19 CAR-positive T cells and a second dose of 400 x 10^6 CD19 CAR-positive T cells.
[21] Bone Marrow	**Analysis performed centrally:** For all patients, at each disease assessment visit requiring a BM aspirate/biopsy as specified in the Schedule of Assessments, the first BM aspirate sample draw should be sent for central ClonoSEQ MRD testing by next generation sequencing (NGS). **Please note**: the NGS MRD assay requires a baseline calibration using a bone marrow sample containing leukaemic blasts. For Phase IIA, this is either from the patient at screening, Day-6 or a historical sample. For Phase IIB, due to the low disease burden at screening, we require both a screening sample for MRD NGS testing as well as a historical sample for calibration. Please see Section 9.2.1. Furthermore, additional BM aspirate samples (unscheduled visits) for disease status assessment should be collected and sent for assessment centrally of immunophenotyping and MRD (NGS, Flow Cytometry and PCR) if: - A patient is not in CR/CRi at M1 then the assessment is required at the 1st time of clinical evidence of CR observed by peripheral blood and EM disease assessment (physical examination and CNS symptoms). - At any time, if morphological or molecular relapse is suspected post AUTO1 infusion. - A patient in CR/CRi (independently of the MRD status) starts a new treatment for ALL, a BM sample should be collected prior to beginning the new therapy. - A safety event occurs. **Analysis performed locally:** The disease burden defined as the % of blasts in the BM will be assessed by morphology on both trephine and aspirate whenever possible. Trephine will be performed as per Investigator clinical judgment. The bone marrow aspirate smear slide may be sent to the Sponsor or third-party laboratory for central storage should additional reading be required. The first screening assessment for morphology can be collected locally or at the referring institution and reports should be available, including leukaemic blasts CD19 expression levels. A copy of the BM aspirate/ trephine analysis report will be provided to the Sponsor as part of the eligibility package.

	Prior to the initiation of the pre-conditioning, the sample must be taken and analysed **within 7 days of the start of the pre-conditioning start.** All efforts should be made to have the bone marrow sample taken as close to the start of the pre-conditioning, as possible. The leukaemic blast count and/or MRD status used to determine the dosing schedule will be based on analysis performed locally and Investigator's assessment. In the event that the bone marrow sample is not evaluable at baseline prior to dosing, the procedure must be repeated to determine disease burden on which dosing regimen is based. If the repeated sample is still not evaluable, a discussion with the medical monitor is warranted to select the appropriate dose. Please refer to the laboratory manual for further details.
[22] Bone Marrow cytogenetics:	To be performed locally at screening and at relapse.
[23] CSF examination:	White blood cells, presence or absence of lymphoblasts. The screening assessment can be performed at the referring institution and reports should be available. • All patients will be assessed for CNS disease by CSF examination at screening and if clinically indicated. • For patients with CNS disease between screening and AUTO1 treatment, CSF examination to be repeated at Day 28 to confirm disease response. Additional samples to be collected at disease relapse and where possible during or after a neurological event. • For patients without CNS disease between screening and AUTO1 treatment a CSF examination at Day28 and subsequent visits is not required to confirm response, but can be collected at relapse or after a neurological event.
[24] Imaging:	Imaging for EM disease is to be conducted for all patients at screening with known or suspected EM disease. After screening, to be repeated only for patients with EM disease at screening or based on clinical indication. In the event of suspected EM disease, CT of the neck/chest/abdomen/pelvis with intravenous contrast, FDG-PET/CT, imaging, magnetic resonance angiography, ultrasonography or appropriate physical measurements should be performed to assess response and should be repeated if clinically indicated after CR has been confirmed. The same imaging modality/physical measurements should be used thereafter. For patients included in Cohort IIC with EM disease only, imaging will be performed at screening.
[25] Biomarkers:	Additional samples will be collected at relapse and may be collected in case of safety events or as clinically indicated. In the event CAR T persistence is lost at any point, an additional sample may be taken ad hoc for confirmation visit if required. Please refer to the laboratory manual. The serum cytokine profile analysis will include IL-2, IL-5, IL-6, IL-7, IL-8, IL-10, IL-15, TNF-α, IFN-γ, and granulocyte-macrophage colony-stimulating factors [GM-CSF]. B cell aplasia will be assessed at a Central Laboratory (flow based assay) using the peripheral blood samples at the time points indicated.
[26] RCL Testing	If all results are negative during the first year post first AUTO1 infusion, the subsequent sample will be collected and stored in case further follow-up analysis may be required. After 24 months, sample for RCL testing will be collected annually until the end of the study.
[27] Insertional Mutagenesis	Samples will be collected and stored for subsequent analysis as required.

Note: If an assessment was performed as part of the patient's routine clinical evaluation and not specifically for this study, it does not need to be repeated after signed informed consent has been obtained provided that the assessments fulfil the study requirements and are performed within the specified timeframe prior to the AUTO1 infusion.

Overall survival, performance status (assessed by ECOG score) and quality of life assessments are considered to be the most informative data over the first 28 days to create a baseline against which to compare progress (though it is acknowledged that quality of life may suffer in the initial aftermath of exposure to product).

SCHEDULE OF ASSESSMENTS 2:

Table 2: Efficacy and Safety Follow-up

Applies to all patients unless otherwise stated. Please refer to the relevant abbreviations and footnotes in Table 1and to Section 8.10.1 for further details.

Visits / Assessments	EFFICACY AND SAFETY FOLLOW-UP											END OF STUDY
	M2* ±7d	M3 ±7d	M4* ±7d	M6 ±7d	M9 ±7d	M12 ±7d	M15* ±7d	M18 ±7d	M21* ±7d	M24 ±7d	q6M until EoS** ±4wk	EoS**
PATIENT INFORMATION												
Concomitant Medication [5]	X											
Quality of Life: EORTC QLQ-C30 (Phase II only)		X		X	X	X		X		X	X	X
Quality of life: EQ-5D-5L (Phase II only)		X		X	X	X		X		X	X	X
Survival Status [6]	X											
EXAMINATIONS, INVESTIGATIONS AND SAFETY EVALUATIONS												
Performance status [7]		X		X		X		X		X		
Weight		X		X		X		X		X		
Physical examination [8]	X	X	X	X	X	X	X	X	X	X	X	X
Neurocognitive assessment [9]	X as clinically indicated e.g. ICANS											
Vital signs and O_2 saturation [10]	X	X	X	X	X	X	X	X	X	X		X
Haematology [12]	X	X	X	X	X	X	X	X	X	X		X
Biochemistry [13]	X	X	X	X	X	X	X	X	X	X		X

Visits / Assessments	EFFICACY AND SAFETY FOLLOW-UP											END OF STUDY
	M2* ±7d	M3 ±7d	M4* ±7d	M6 ±7d	M9 ±7d	M12 ±7d	M15* ±7d	M18 ±7d	M21* ±7d	M24 ±7d	q6M until EoS** ±4wk	EoS**
Coagulation [14]	X as clinically indicated e.g. severe CRS											
Pregnancy test [16]		X		X		X				X		X
Adverse events [17]	X											
DISEASE ASSESSMENTS												
Overall Disease Response	X	X	X	X	X	X	X	X	X	X	X	X
Bone Marrow												
Morphology [21]		X		X	X	X		X		X		
MRD & Immunophenotyping [21]		X		X		X		X		X		
Cytogenetics	X at relapse											
Peripheral Blood												
Morphology and blood count	X	X	X	X	X	X	X	X	X	X		
Extramedullary Disease												
CSF examination [23]	X as clinically indicated											
Imaging [24]	X as clinically indicated [24]											
BIOMARKERS												
Bone Marrow												
AUTO1 persistence [25]		X		X		X		X		X		

Visits / Assessments	EFFICACY AND SAFETY FOLLOW-UP											END OF STUDY
	M2* ±7d	M3 ±7d	M4* ±7d	M6 ±7d	M9 ±7d	M12 ±7d	M15* ±7d	M18 ±7d	M21* ±7d	M24 ±7d	q6M until EoS** ±4wk	EoS**
Peripheral Blood												
IgG levels		X		X		X		X		X		
Cytokine Profile [25]		X										
AUTO1 persistence [25]	X	X	X	X	X	X	X	X	X	X	X	X
Immunogenicity [25]		X	X at relapse									
Immunophenotyping of AUTO1 [25]		X		X	X	X		X		X		
Genomic profiling		X		X		X				X		
RCL [26]		X		X		X				X	X	X
Insertional Mutagenesis [27]		X		X		X				X	X	X
B-cell aplasia	X	X	X	X	X	X	X	X	X	X	X	X
Cerebrospinal Fluid												
AUTO1 detection and other markers		X as clinically indicated										

CRS = cytokine release syndrome; CSF = cerebrospinal fluid; d = days; EORTC = European Organization for Research and Treatment of Cancer; EoS = end of study; EQ-5D-5L = EuroQol; ICANS = Immune effector Cell-Associated Neurotoxicity Syndrome; IgG = Immunoglobulin G; M = month; MRD = minimal residual disease; O_2 = oxygen; QLQ-C30 = Quality of life Questionnaire; q6M = every 6 months; RCL = replication competent lentivirus; wk = weeks.

Overall survival, performance status (assessed by ECOG score) and quality of life assessments are considered to be the most informative data in the efficacy & safety follow-up.

SCHEDULE OF ASSESSMENTS 3:

Table 3: Safety and Survival Follow-Up

Applies to all patients unless otherwise stated. Please refer to the relevant abbreviations and footnotes in Table 1 and to Section 8.10.2 for further details.

Visits / Assessments	SAFETY AND SURVIVAL FOLLOW-UP							END OF STUDY
	M2 ±7d	M3 * ±7d	M6 * ±7d	M9 ±7d	M12 * ±7d	M24 * ±7d	q6M until EoS** * ±4wk	EoS**/Early Withdrawal
PATIENT INFORMATION								
Disease status	X							
Subsequent therapy and response	X							
Survival Status	X							
Concomitant Medication [5]	X							
EXAMINATIONS, INVESTIGATIONS AND SAFETY EVALUATIONS								
Pregnancy test [16]		X	X			X		
Adverse events [17]	X							
BIOMARKERS								
PERIPHERAL BLOOD								
AUTO1 persistence [25]	X as clinically indicated							
RCL [26]		X	X		X	X	X yearly	X
Insertional Mutagenesis [27]		X	X		X	X	X	X

d = days; EoS = end of study; M = month; q6M = every 6 months; RCL = replication competent lentivirus; wk = weeks.

Table 4: Survival Follow-up for Enrolled Patients who did Not Receive AUTO1

Applies to all enrolled patients. Please refer to abbreviations and footnotes in Table 1 and to Section 8.10.3 for further details.

Visits / Assessments	SURVIVAL FOLLOW-UP POST LEUKAPHERESIS
	At Month 3 (±4wk) post leukapheresis then every 3 to 6 months thereafter up to EoS**
PATIENT INFORMATION	
Disease status	X
Subsequent therapy and response	X
Survival status	X

Overall survival data are considered to be the most informative data in the safety follow-up. A measure of quality of life would also be considered as most informative.

The applicant employed 3 oversight committees:

- An Independent Data Monitoring Committee consisting of two independent physicians and one statistician to review serious safety events.
- An Independent Response Review Committee comprising two to three members to review data related to disease response assessments during the treatment and follow-up of the study. Patient management will be based upon local Investigator assessments.
- A Study Steering Committee comprising 5 members to provide expert advice on the overall study conduct of the study. All members are Principal Investigators involved in the study.

MRD-Negative Remission Rate is defined as the proportion of patients achieving CR or CRi with MRD-negative bone marrow by central assessment at less than one tumour cell for every 10,000 cells i.e. 10^{-4}

The applicant clarified that denominator for cell measurement was nucleated cells.
In the course of the application procedure, it became apparent that the applicant had employed 3 different methods to assess minimal residual disease; it was found that the arrangement of the applicant hampered interpretation of results for minimal residual disease; and so data on minimal residual disease are viewed in a general sense only.

To note that the applicant used the following definitions for “CR” and “CRi”:

Complete remission:

- Bone marrow: trilineage haematopoiesis and <5% blasts in bone marrow
- Peripheral blood: no circulating lymphoblasts; neutrophil count >1000/µL; platelet count >100,000/µL and no platelet transfusions in last 7 days and no administration of granulocyte colony stimulating factor in last 3 days for short-acting GCSF products and 14 days for long-acting GCSF products.
- No extramedullary disease

Complete remission with incomplete recovery of counts:

- Meet all criteria for complete remission except: recovery of platelets to <=100,000 ul and / or recovery of neutrophil count to <1000 ul

Duration of Remission is measured by the time from the first achievement of CR or CRi to relapse or death due to any reason.

Duration of Complete Remission will be analysed in a similar way as Duration of Remission except that first achieved of CR will be considered as starting point for the evaluation instead of any remission (CR or CRi).

Event free survival is the time from date of first obe-cel infusion to the earliest of treatment failure, relapse or death from any cause.

Progression free survival is defined as the time from first infusion to date of progressive disease, including investigator's claim of clinical progression, date of death from any cause.

Overall survival will be calculated from the date of first obe-cel infusion to the date of death. Patients with primary refractory disease, defined as patients who fail to obtain a complete remission with induction therapy (≥2 cycles).

Patients with relapse are those who have experienced early relapse after first remission, relapse after stem cell transplant or have multiple relapses.

The applicant employed recognised standards for the definitions of (i) refractory disease, (ii) relapsed disease and (iii) 'early relapse'.

Overall response rate (ORR) is defined as proportion of patients achieving CR or CRi.

Protocol Deviations

An important protocol deviation is a deviation that could have a significant effect on the patient's safety, rights, or welfare and/or on the integrity of the study data.

23 patients enrolled in FELIX had at least 1 important protocol deviation (Table 5). Most of the important protocol deviations were related to study assessments and procedure compliance (8 patients) and eligibility criteria (6 patients) or dosing compliance (5 patients). None of the protocol deviations met the criteria for a serious breach or led to exclusion from the per protocol analysis.

Table 5: Important Protocol Deviations in FELIX (Phase Ib/Phase II, Enrolled Set)

	Phase Ib			Phase II				Total
	Cohort A (N=21) n (%)	Cohort B (N=3) n (%)	Total (N=24) n (%)	Cohort A (N=112) n (%)	Cohort B (N=10) n (%)	Cohort C (N=7) n (%)	Total (N=129) n (%)	(N=153) n (%)
Patients with at least one IPD	2 (9.5)	0	2 (8.3)	18 (16.1)	1 (10.0)	2 (28.6)	21 (16.3)	23 (15.0)
Study Assessments & Procedure Compliance	1 (4.8)	0	1 (4.2)	6 (5.4)	0	1 (14.3)	7 (5.4)	8 (5.2)
Eligibility Criteria	0	0	0	6 (5.4)	0	0	6 (4.7)	6 (3.9)
Dosing & Administration	0	0	0	2 (1.8)	1 (10.0)	1 (14.3)	4 (3.1)	4 (2.6)
Visit Compliance	1 (4.8)	0	1 (4.2)	2 (1.8)	0	0	2 (1.6)	3 (2.0)
Prohibitive Medication or Treatment	0	0	0	2 (1.8)	0	0	2 (1.6)	2 (1.3)
AE/SAE/AESI Assessment	0	0	0	0	1 (10.0)	0	1 (0.8)	1 (0.7)
Dosing Compliance	0	0	0	1 (0.9)	0	0	1 (0.8)	1 (0.7)
Pregnancy	0	0	0	1 (0.9)	0	0	1 (0.8)	1 (0.7)

Abbreviations: AE = adverse event; AESI = adverse event of special interest; IPD = important protocol deviation; SAE = serious adverse event.
Enrolled Set comprises 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 leukapheresate was accepted for manufacturing.
Percentages are based on total number of patients in the Enrolled Set.
Data cut-off: 07-Feb-2024

18 subjects in cohort IIA discontinued the study without receiving an obe-cel infusion – 11 subjects died before infusion, 5 did not receive the drug due to manufacturing issues, 1 subject had an adverse event and 1 subject discontinued due to physician's decision.
94 subjects in cohort IIA were infused with obe-cel; of these, 52 discontinued the study (50 died and 1 withdrew) and 42 are in ongoing follow-up.

Population

Key inclusion criteria

1. Age 18 years or older
2. Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1
3. Relapsed or refractory CD19-positive B-cell acute lymphoblastic leukaemia defined as one of the following:
   - Primary refractory disease (not achieving complete remission 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 obe-cel infusion occurs at least 3 months after stem cell transplant.
4. Patients with Philadelphia chromosome positive acute lymphoblastic leukaemia (Ph+ ALL) are eligible if they are intolerant to or have failed two lines of any tyrosine kinase inhibitor or one line of second generation tyrosine kinase inhibitor or if tyrosine kinase inhibitor therapy is contraindicated.
5. In patients treated with blinatumomab, CD19 expression should be confirmed after blinatumomab therapy has been stopped.
6. Adequate renal (creatinine clearance >50mL/min), hepatic (Aspartate aminotransferase ≤2.5 x upper limit of normal (ULN), pulmonary (oxygen saturation >92% on air) and cardiac function, as described.

Additional criteria

For phase I:
Primary Cohort IA: presence of ≥5% blasts in bone marrow at screening.
Exploratory Cohort IB: MRD -positive defined as ≥10^{-4} and <5% blasts in the bone marrow at screening.

For phase II:
Cohort IIA: Presence of ≥5% blasts in BM at screening.
Cohort IIB: Patients with B-ALL in ≥2nd CR or CRi with MRD-positive disease defined as ≥10^{-3} by central ClonoSEQ NGS testing and <5% blasts in the BM at screening.
Cohort IIC (Exploratory): Isolated extramedullary disease (including CNS disease) with or without MRD.

Entry into each cohort was deterministic, based on clinical history and pathology findings.

Exclusion criteria

1. Burkitt's leukaemia / lymphoma
2. History or presence of clinically relevant pathology of the central nervous system.
3. Presence of CNS 3 disease or CNS 2 disease with neurological changes. Patients developing CNS 3 disease or symptomatic CNS 2 disease at any time after consent will also be excluded until they no longer meet these criteria.
   CNS-1 = No lymphoblasts in CSF regardless of WBC count; CNS-2 = WBC < 5/μL in CSF with presence of lymphoblasts; CNS-3 = WBC ≥ 5/μL in CSF with presence of lymphoblasts.
4. active or uncontrolled infection (including latent hepatitis B or C and HIV)
5. Patients who have received a stem cell transplant less than 3 months prior to obe-cel infusion. Active significant (overall Grade ≥II, Seattle criteria) acute graft versus host disease (GVHD) or moderate/severe chronic GVHD (National Institutes of Health consensus criteria) requiring systemic steroids or other immunosuppressants within 4 weeks of consent
6. Prior CD19 targeted therapy other than blinatumomab. Patients who have experienced Grade 3 or higher neurotoxicity following blinatumomab

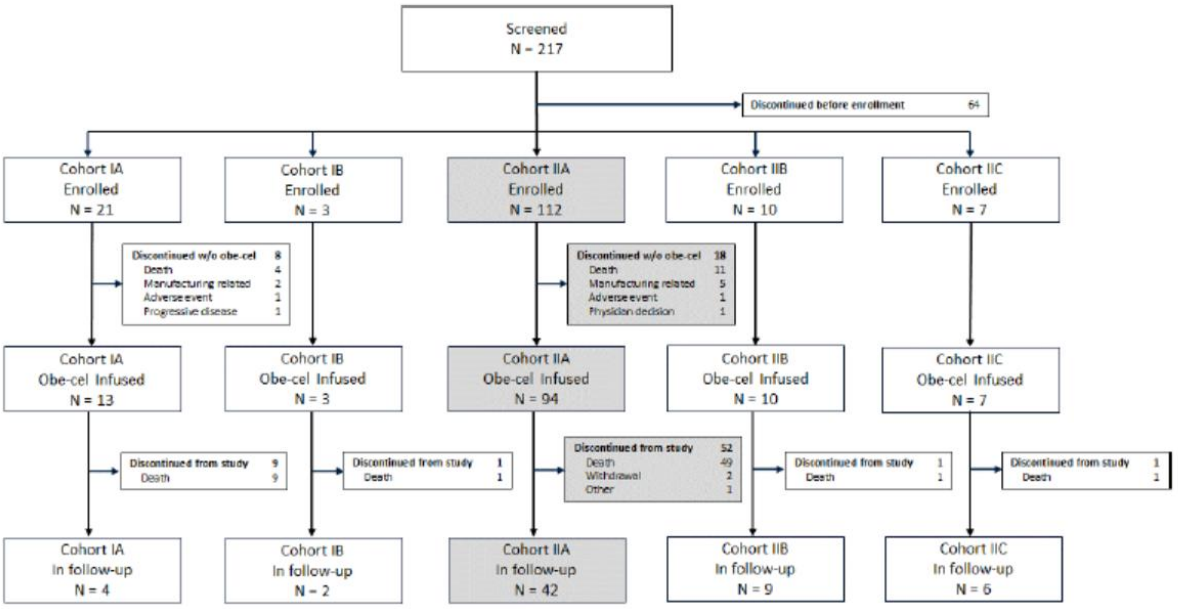
7. The following medications are excluded:

- Therapeutic doses of corticosteroids (greater than 10mg daily of prednisone or its equivalent) within 7 days of leukapheresis or 72 hours prior to obe-cel administration
- Immunosuppressive medication must be stopped ≥2 weeks prior to leukapheresis and obe-cel infusion
- Donor lymphocyte infusions must be completed >2 weeks prior to leukapheresis and not repeated thereafter
- Any drug used for graft-versus-host disease must be stopped >2 weeks prior to leukapheresis and not reinitiated thereafter
- Chemotherapy must be stopped 1 week prior to leukapheresis or starting pre-conditioning chemotherapy. Tyrosine kinase inhibitors for Ph+ ALL must be stopped >72 hours prior to pre-conditioning chemotherapy
- Treatment with any T cell lytic or toxic antibody within 6 months prior to leukapheresis or treatment with clofarabine or cladribine within 3 months prior to leukapheresis
- Live vaccine ≤4 weeks prior to leukapheresis
- Intrathecal therapy within 2 weeks prior to starting pre-conditioning chemotherapy
- Use of blinatumomab after leukapheresis

- Inotuzumab may be used as a bridging therapy. 7 days washout is required prior to the start of preconditioning chemotherapy following 1 cycle of inotuzumab. 2 weeks washout is required if 2 cycles of inotuzumab are administered.

Disposition of subjects at the data cut-off of 07-Feb-2024 is summarised in the following figure:

Figure 4: Disposition of Patients (Phase Ib/Phase II, Screened Set)



Abbreviations: B ALL = B cell precursor acute lymphoblastic leukemia; BM = bone marrow; EMD = extramedullary disease; MRD = minimal residual disease; NGS = next-generation sequencing; 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 in morphological remission with MRD at screening (Cohort IB: ≥ 10^{-4} and < 5% blasts in the BM; Cohort IIB: ≥ 10^{-3} by central ClonoSEQ NGS testing and < 5% blasts in the BM).
Cohort C: Adults with r/r B ALL with isolated EMD at screening.
Data cut-off: 07-Feb-2024.

No further patients have been enrolled in the FELIX study or treated with obe-cel since the 09-Jun-2023 data cut-off used for primary analysis.

In Cohort IIA, 42 of the 94 infused patients (44.7%) are in ongoing follow-up at the time of the data cut-off for the analysis t 07-Feb-2024. This is 11 patients less than at the time of the primary analysis of July 2023; all 11 patients discontinued the study due to death (9 deaths due to progressive disease, 2 deaths due to adverse events).

11 deaths are reviewed:

For the 2 subjects who died after adverse events: 1 subject died after a prolonged pulmonary failure and general decline; 1 subject died with graft-versus-host disease.

For the 9 subjects who died with progressive disease: 2 died without achieving CR or CRi; 2 died after achieving CRi; 5 died after achieving CR.

See Clinical Safety section of this PAR for additional comment.

A summary of demographic data for subjects in the FELIX study is presented in Table 1:

Table 7: Summary of Demographics in FELIX (Phase Ib/Phase II, Enrolled Set)

	Phase II - Cohort A		Phase Ib and II - All Cohorts	
	Infused (N=94)	Enrolled (N=112)	Infused (N=127)	Enrolled (N=153)
Age (years)				
n	94	112	127	153
Mean (SD)	48.3 (17.12)	47.9 (17.04)	47.1 (16.89)	46.7 (16.87)
Median	50.0	49.0	47.0	45.0
Q1 - Q3	33.0 - 62.0	33.5 - 62.5	33.0 - 60.0	32.0 - 60.0
Min - Max	20 - 81	20 - 81	20 - 81	20 - 81
Age (years) categorized - n (%)				
≥ 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)
Country - n (%)				
United States	47 (50.0)	54 (48.2)	66 (52.0)	80 (52.3)
United Kingdom	36 (38.3)	42 (37.5)	49 (38.6)	56 (36.6)
Spain	11 (11.7)	16 (14.3)	12 (9.4)	17 (11.1)

Abbreviations: BM = bone marrow; Q = quartile; SD = standard deviation.
Enrollment = All inclusion/exclusion criteria have been fulfilled and leukapheresate has been accepted for manufacturing.
Infused set comprises of all patients who have received at least 1 infusion of obe-cel.
Data cut-off: 07-Feb-2024

Demographic data are broadly similar for the various phases and cohorts of the study.

For the phase IIA cohort who were enrolled: median age 49yrs (min 20yrs, max 81yrs); 65% subjects were >40yrs; 54% male; 77% White.

For the phase IIA cohort who were administered product: median age 50yrs (min 20yrs, max 81yrs); 67% subjects were >40yrs; 50% male; 74% White.

For phase IB and all phase II cohorts: 127 subjects were infused; median age 47yrs (min 20yrs, max 81yrs); 52% male; 74% White.

Other Baseline Characteristics are summarised in the following tables:

Table 8: Disease Characteristics at Screening (Phase Ib/Phase II, Enrolled Set)

	Phase II - Cohort A		Phase Ib and II - All Cohorts	
	Infused (N=94)	Enrolled (N=112)	Infused (N=127)	Enrolled (N=153)
Prior ALL Treatment History				
Number of prior lines of therapy				
Mean (SD)	2.2 (1.08)	2.2 (1.08)	2.3 (1.10)	2.3 (1.10)
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 categorized - n (%)				
1	29 (30.9)	34 (30.4)	30 (23.6)	36 (23.5)
2	36 (38.3)	43 (38.4)	52 (40.9)	61 (39.9)
3	17 (18.1)	21 (18.8)	26 (20.5)	33 (21.6)
≥ 4	12 (12.8)	14 (12.5)	19 (15.0)	23 (15.0)
Refractory to all prior lines of anticancer 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)	66 (52.0)	79 (51.6)
Relapsed to first-line therapy within 12 months - n (%)	41 (43.6)	52 (46.4)	60 (47.2)	75 (49.0)
Previous allogeneic SCT - 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)
Disease Status at Screening				
BM blasts (%) by morphology prior to enrollment [1]				
Median	58.9	61.0	40.0	52.0
Min - Max	6 - 100	6 - 100	0 - 100	0 - 100
BM blasts by morphology prior to enrollment categorized - n (%) [1]				
> 75%	34 (36.2)	42 (37.5)	41 (32.3)	55 (35.9)
> 20%-≤ 75%	32 (34.0)	40 (35.7)	37 (29.1)	47 (30.7)
≥ 5%-≤ 20%	28 (29.8)	30 (26.8)	30 (23.6)	32 (20.9)
< 5%	0	0	19 (15.0)	19 (12.4)

	Phase II - Cohort A		Phase Ib and II - All Cohorts	
	Infused (N=94)	Enrolled (N=112)	Infused (N=127)	Enrolled (N=153)
EMD status prior to enrollment - n (%)				
Absent	75 (79.8)	91 (81.3)	98 (77.2)	121 (79.1)
Present	19 (20.2)	21 (18.8)	29 (22.8)	32 (20.9)
CNS	2 (2.1)	2 (1.8)	3 (2.4)	3 (2.0)
Mediastinal lymph node	2 (2.1)	2 (1.8)	2 (1.6)	2 (1.3)
Testis	1 (1.1)	1 (0.9)	1 (0.8)	1 (0.7)
Other	15 (16.0)	17 (15.2)	25 (19.7)	28 (18.3)
Other Patient Characteristics at Screening				
ECOG score [2] - n (%)				
0	35 (37.2)	39 (34.8)	50 (39.4)	58 (37.9)
1	58 (61.7)	72 (64.3)	76 (59.8)	94 (61.4)
≥ 2	0	0	0	0
Missing	1	1	1	1
CD19 status at screening (by flow cytometry) - n (%)				
Positive	94 (100)	111 (99.1)	127 (100)	152 (99.3)
Negative	0	0	0	0
Mixed population (positive + negative)	0	1 (0.9)	0	1 (0.7)
CNS disease history - n (%) [3]				
CNS1	81 (86.2)	97 (86.6)	112 (88.2)	136 (88.9)
CNS2	2 (2.1)	2 (1.8)	3 (2.4)	3 (2.0)
CNS3	0	0	0	0
Unknown	11 (11.7)	13 (11.6)	12 (9.4)	14 (9.2)

Abbreviations: BM = bone marrow; CNS = central nervous system; CSF = cerebrospinal fluid; ECOG = Eastern Cooperative Oncology Group; EMD = extramedullary disease; SD = standard deviation; SCT = stem cell transplantation; WBC = white blood cells.
[1] BM blast (%) was determined by morphology as the highest value from BM aspirate and trephine at screening.
[2] ECOG based on last non-missing value from screening period prior to leukapheresis.
[3] CNS-1 = No lymphoblasts in CSF regardless of WBC count; CNS-2 = WBC < 5/µL in CSF with presence of lymphoblasts; CNS-3 = WBC ≥ 5/µL in CSF with presence of lymphoblasts.
Data cut-off: 07-Feb-2024

Characteristics are broadly similar across the phases and cohorts of the study. Phase IIA is the main analysis cohort of the study.

For the 112 subjects enrolled into phase IIA:

Subjects had received between 1 and 6 prior therapies with a median of 2.
13 had disease that was refractory to all previous therapies
43 had received a stem cell transplant
58 had received blinatumomab or inotuzumab ozogamicin
21 had evidence of extramedullary disease prior to enrolment
ECOG status was 0 or 1

For the phase IIA cohort of 94 subjects who were administered product:

Subjects had received between 1 and 6 prior therapies with a median of 2.
12 had disease that was refractory to all previous therapies
36 had received a stem cell transplant
48 had received blinatumomab or inotuzumab ozogamicin
19 had evidence of extramedullary disease prior to enrolment
ECOG status was 0 or 1

The make-up of those infused is considered similar to those enrolled.

For 71 subjects in cohort IIA: lymphoblasts made up ≥5% of all nucleated cells in a bone marrow sample at lymphodepletion.

For the 127 subjects who were infused in the phase IB and all phase II cohorts:

13 had disease that was refractory to all previous therapies
56 had received a stem cell transplant
72 had received blinatumomab or inotuzumab ozogamicin
29 had evidence of extramedullary disease prior to enrolment
ECOG status was 0 or 1

It would have been preferred to have enrolled a higher racial mix.

The characteristic of the phase IIA and [phase IB & all phase II cohorts] appear broadly similar.

In other respects, the study population appears representative of adults with B-cell acute leukaemia.

Disease characteristics prior to lymphodepletion are summarised:

Table 9: Disease Characteristics Prior to Lymphodepleting Therapy (Phase Ib/Phase II, Infused Set)

	Phase II - Cohort A		Phase Ib and II	
	Infused (N=94)	Enrolled (N=112)	Infused (N=127)	Enrolled (N=153)
Bone marrow blasts (%) by morphology prior to lymphodepletion [1]				
n	94	94	127	127
Mean (SD)	45.1 (37.39)	45.1 (37.39)	43.4 (37.89)	43.4 (37.89)
Median	43.5	43.5	40.0	40.0
Q1 - Q3	5.0 - 85.6	5.0 - 85.6	3.0 - 85.6	3.0 - 85.6
Min - Max	0 - 100	0 - 100	0 - 100	0 - 100
Bone marrow blasts (%) by morphology prior to lymphodepletion categorized - n (%) [1]				
> 75%	30 (31.9)	30 (26.8)	40 (31.5)	40 (26.1)
> 20% - ≤ 75%	27 (28.7)	27 (24.1)	35 (27.6)	35 (22.9)
≥ 5% - ≤ 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)
Extramedullary disease status prior to lymphodepletion - n (%)				
Absent	75 (79.8)	91 (81.3)	100 (78.7)	123 (80.4)
Present	19 (20.2)	21 (18.8)	27 (21.3)	30 (19.6)
CNS	1 (1.1)	1 (0.9)	1 (0.8)	1 (0.7)
Mediastinal Lymph Node	2 (2.1)	2 (1.8)	3 (2.4)	3 (2.0)
Testis	1 (1.1)	1 (0.9)	1 (0.8)	1 (0.7)
Other	17 (18.1)	19 (17.0)	25 (19.7)	28 (18.3)
Neutrophil count (10^9/L) prior to lymphodepletion				
n	92	92	125	125
Mean (SD)	1.9 (2.10)	1.9 (2.10)	2.0 (2.22)	2.0 (2.22)
Median	1.3	1.3	1.4	1.4
Q1 - Q3	0.4 - 2.5	0.4 - 2.5	0.5 - 2.7	0.5 - 2.7
Min - Max	0 - 14	0 - 14	0 - 14	0 - 14
Neutrophil count (10^9/L) prior to lymphodepletion categorized - n (%)				
< 0.5	24 (25.5)	24 (21.4)	32 (25.2)	32 (20.9)
≥ 0.5	68 (72.3)	68 (60.7)	93 (73.2)	93 (60.8)
Missing	2 (2.1)	2 (1.8)	2 (1.6)	2 (1.3)
Platelet count (10^9/L) prior to lymphodepletion				
n	94	94	127	127
Mean (SD)	97.3 (83.50)	97.3 (83.50)	105.3 (88.66)	105.3 (88.66)
Median	83.5	83.5	89.0	89.0
Q1 - Q3	23.0 - 148.0	23.0 - 148.0	24.0 - 166.0	24.0 - 166.0
Min - Max	4 - 368	4 - 368	4 - 368	4 - 368
Platelet count (10^9/L) prior to lymphodepletion categorized - n (%)				
< 50	37 (39.4)	37 (33.0)	47 (37.0)	47 (30.7)
≥ 50	57 (60.6)	57 (50.9)	80 (63.0)	80 (52.3)
Cytogenetic risk groups for B ALL [2] - n (%)				
Good risk				
Hyperdiploidy	5 (5.3)	6 (5.4)	5 (3.9)	6 (3.9)
TEL-AML1	1 (1.1)	1 (0.9)	2 (1.6)	2 (1.3)
Poor risk				
Hypodiploidy	4 (4.3)	4 (3.6)	4 (3.1)	5 (3.3)
IL3-IGH	0	1 (0.9)	1 (0.8)	2 (1.3)
t(10;14)	1 (1.1)	1 (0.9)	1 (0.8)	1 (0.7)
BCR-ABL1-like	8 (8.5)	8 (7.1)	10 (7.9)	11 (7.2)
E2A-PBX1	1 (1.1)	1 (0.9)	1 (0.8)	1 (0.7)
Philadelphia chromosome-positive	25 (26.6)	26 (23.2)	36 (28.3)	39 (25.5)
MLL rearrangement	6 (6.4)	7 (6.3)	6 (4.7)	10 (6.5)
Del 17p	0	1 (0.9)	1 (0.8)	3 (2.0)
Other abnormality	37 (39.4)	47 (42.0)	41 (32.3)	55 (35.9)

Abbreviations: B ALL = B cell acute lymphoblastic leukemia; BM = bone marrow; CNS = central nervous system; Q = quartile; SD = standard deviation.
[1] BM blast (%) was determined by morphology as the highest value from BM aspirate and trephine
[2] Cytogenetic risk groups based on karyotype collected from screening to lymphodepletion period. If multiple karyotypes were recorded for the same patient, the latest record was used for the patient.
Data cut-off: 07-Feb-2024

Characteristics are broadly similar across the phases and cohorts of the study. Phase IIA is the main analysis cohort of the study.

For the 112 subjects enrolled into phase IIA:
26 returned a positive result for the Philadelphia chromosome
At lymphodepletion: 21 had extramedullary disease; 30 had >75% blasts in bone marrow; 27 had >20 to 75% bone marrow blasts and 37 had up to 20% bone marrow blasts.

For the phase IIA cohort of 94 subjects who were administered product:
25 returned a positive result for the Philadelphia chromosome
At lymphodepletion: 19 had extramedullary disease; 30 had >75% blasts in bone marrow; 27 had >20 to 75% bone marrow blasts and 37 had up to 20% bone marrow blasts.

The make-up of those infused is considered similar to those enrolled.

For the 127 subjects who were infused in the phase IB and all phase II cohorts:

36 returned a positive result for the Philadelphia chromosome
At lymphodepletion: 27 had extramedullary disease; 40 had >75% blasts in bone marrow; 35 had >20 to 75% bone marrow blasts and 52 had up to 20% bone marrow blasts.

The characteristic of the phase IIA and [phase IB & all phase II cohorts] appear broadly similar.

In other respects, the study population appears representative of adults with B-cell acute leukaemia.

Allowed Concomitant Medications / Therapies

- Palliative radiotherapy may be given concomitantly as clinically appropriate.
- Anti-microbial prophylaxis including antivirals may be given
- Approved Anti COVID-19 (SARS COV-2) treatments (both prophylaxis and anti-virals) may be given per institutional guidelines.
- Colony stimulating factors at physician's discretion
- Erythropoietin and transfusion of platelets and red cells.
- In Ph+ ALL patients who achieve CR after obe-cel infusion, a tyrosine kinase inhibitor may be resumed no earlier than 2 months after obe-cel infusion and after discussion with the medical monitor.
- Prophylaxis to cerebrospinal fluid may be given post- obe-cel infusion per investigator discretion in accordance with institutional guidelines yet should be avoided for at least 8 weeks after obe-cel infusion if possible.

Prohibited and Cautionary Therapies

- Herbal and homeopathic agents
- Corticosteroids and Immunosuppressant (except for managing treatment-related toxicity)

Bridging Therapy
Patients could receive bridging therapy as necessary between leukapheresis and one week prior to start of lymphodepleting treatment. The choice of bridging therapy was based on local practice except for the use of blinatumomab that is prohibited as a bridging therapy agent. Inotuzumab ozogamicin could have been used as bridging therapy with the implementation of protocol amendment version 6.

Blinatumomab (Blincyto, PLGB 13832/0018) is indicated as monotherapy for the treatment of adults with CD19 positive relapsed or refractory B-cell precursor acute lymphoblastic leukaemia.

Blincyto is a bi-specific antibody that binds to CD19 (same target as obe-cel) expressed on the surface of cells of B-lineage origin and CD3 expressed on the surface of T-cells; a cytolytic synapse is formed between the T-cell and the tumour cell and proteolytic enzymes are released to kill both proliferating and resting target cells.

Listing Blincyto as prohibited is acknowledged within a clinical trial setting.

Bridging therapies are summarised:

Table 11: Bridging Medications by Regimen by Study Phases (Phase Ib/Phase II, Infused Set)

	Phase Ib			Phase II				Phase Ib/ Phase II
	Cohort A (N=13) n (%)	Cohort B (N=3) n (%)	Total (N=16) n (%)	Cohort A (N=94) n (%)	Cohort B (N=10) n (%)	Cohort C (N=7) n (%)	Total (N=111) n (%)	Total (N=127) n (%)
Number of patients with any bridging medications	13 (100)	3 (100)	16 (100)	88 (93.6)	9 (90.0)	5 (71.4)	102 (91.9)	118 (92.9)
Chemo	10 (76.9)	2 (66.7)	12 (75.0)	59 (62.8)	5 (50.0)	4 (57.1)	68 (61.3)	80 (63.0)
Chemo + TKI	3 (23.1)	0	3 (18.8)	6 (6.4)	1 (10.0)	0	7 (6.3)	10 (7.9)
Chemo + Inotuzumab	0	0	0	8 (8.5)	0	1 (14.3)	9 (8.1)	9 (7.1)
Inotuzumab	0	0	0	9 (9.6)	0	0	9 (8.1)	9 (7.1)
TKI	0	1 (33.3)	1 (6.3)	3 (3.2)	3 (30.0)	0	6 (5.4)	7 (5.5)
Steroids	0	0	0	2 (2.1)	0	0	2 (1.8)	2 (1.6)
Other [1]	0	0	0	1 (1.1)	0	0	1 (0.9)	1 (0.8)

Abbreviations: Chemo = chemotherapy; TKI = tyrosine kinase inhibitor.
[1] Patient 0101US12046 received rituximab (see Listing 16.2.5.1).
Bridging medications were coded using WHODrug Global B3 202303.
Data cut-off: 07-Feb-2024

TKI: Tyrosine kinase inhibitor

Inotuzumab (inotuzumab ozogamicin, Besponsa) was permitted as bridging therapy.

Besponsa is an antibody-drug combination; the antibody binds to CD22-expressing tumour cells, the complex is internalised and the active product is released to promote cell cycle arrest and apoptotic cell death. Besponsa is indicated as monotherapy for the treatment of adults with relapsed or refractory CD22-positive B cell precursor acute lymphoblastic leukaemia.

Data for use of Besponsa as bridging therapy are shown:

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Table 14.2.27.1.5 Complete Remission with Disease Assessment by IRRC
By Bridging Therapy (With or Without Inotuzumab Ozogamicin)
Infused Set - Phase Ib and Phase II - All Cohorts

	Bridging with inotuzumab (N=18) n (%)	Bridging without inotuzumab (N=100) n (%)	No bridging (N=9) n (%)	Total (N=127) n (%)
Complete remission rate (CRR) - n (%)				
n (%) [1]	7 (38.9)	58 (58.0)	8 (88.9)	73 (57.5)
95% CI (%) [2]	(17.3, 64.3)	(47.7, 67.8)	(51.8, 99.7)	(48.4, 66.2)

Patient responses were based on the Overall Disease Status recorded on the "Overall Disease Response" page by Independent Response Review Committee (IRRC).
[1] Including patients who achieved best overall response of CR and prior to morphological relapse disease, SCT or other anticancer therapies for ALL.
[2] The 95% exact Clopper-Pearson CIs are displayed.

The above data represents those who were infused in all cohorts. There were 18 subjects who had 'bridging' with inotuzumab (inotuzumab ozogamicin, Besponsa).

Complete remission occurred in:

- 89% of subjects who did not undertake a bridging exercise.
- 58% of subjects who undertook a bridging exercise without Besponsa
- 39% of subjects who undertook a bridging exercise with Besponsa.

It is acknowledged that numbers of subjects are small and so any apparent pattern of response to the bridging exercise may be artefactual.

Intervention

Leukapheresis

Adequate washout of medications was observed as per protocol and testing for described infectious diseases in accord with the Human Tissue Act. Sites were responsible to conduct the procedure in accord with local guidelines.

Subjects underwent unstimulated leukapheresis in accord with a manual produced by the applicant; this is a day-case procedure to collect peripheral blood mononuclear cells.

A repeat leukapheresis procedure was permitted if collected material was found inadequate.

The applicant identifies the following risks associated with leukapheresis:

Table 10: Leukapheresis – Key Risks and Mitigation Strategy

Risks	Mitigation Strategy
Pain and bruising due to insertion of cannula/central venous access.	Experienced clinicians/nurses performing the procedure, analgesics to be used as needed for pain
Bacterial bloodstream infections associated with the insertion of access and return venous access devices.	The procedure will be carried out by trained and experienced personnel and risks will be minimised by strict adherence to aseptic measure.
Symptoms of hypocalcaemia e.g. muscle cramps due to chelation by anticoagulants used to prevent clotting.	Patients will be monitored for symptoms of hypocalcaemia, the rate of citrate infusion to the patient and duration of the procedure will be controlled by experienced personnel. Calcium supplements will be given as needed, according to local practice.

Enrolment occurred once leukapheresis material had been accepted for manufacture.

Pre-Conditioning Chemotherapy
Subjects had to meet eligibility requirements in the schedule of events to go ahead with pre-conditioning chemotherapy.

Disease burden was evaluated within 7 days of the start of the pre-conditioning regimen and determined the dosing schedule.

Exclusion Criteria for Starting Pre-Conditioning

Patients meeting any of the following exclusion criteria must not be given pre-conditioning or it must be delayed until they no longer meet these criteria:

- Severe intercurrent infection at the time of, or within 7 days of, scheduled pre-conditioning requiring systemic antimicrobials.
  Upon review by the physician, controlled severe infection may not be a reason to withhold pre-conditioning.
  The patient must not have received systemic antimicrobials for the treatment of a known or suspected infection within 48 hours before pre-conditioning chemotherapy (prophylactic use of antimicrobials is allowed).
- Requirement for supplementary oxygen at the time of scheduled pre-conditioning.
- Allogeneic transplant recipients with active significant acute GVHD overall Grade ≥II or moderate / severe chronic GVHD requiring systemic steroids at the time of scheduled pre-conditioning.
- Significant deterioration of renal or hepatic function
- New signs or symptoms of the central nervous system at any time after enrolment and prior to planned pre-conditioning

The pre-conditioning phase begins with administration of chemotherapy on Day -6 and ends with the beginning of treatment with obe-cel infusion on Day 1. Pre-conditioning is expected to increase the survival of CD19 CAR T cells

Patients received a lymphodepleting pre-conditioning treatment with cyclophosphamide for 2 days (starting Day -6) and fludarabine for 4 days (starting Day -6), timed to end 3 (±1) days but no less than 48 hours before obe-cel infusion.

Cyclophosphamide and fludarabine dosing are described below; fludarabine was administered first.

- Fludarabine 30 mg/m^2 followed by cyclophosphamide 500 mg/m^2 day 1 (Day -6)
- Fludarabine 30 mg/m^2 followed by cyclophosphamide 500 mg/m^2 day 2 (Day -5)
- Fludarabine 30 mg/m^2 (Day -4)
- Fludarabine 30 mg/m^2 (Day -3)

Fludarabine and cyclophosphamide were each administered by i.v. infusion over 30 minutes in accord with their respective SPCs and local guidance.

Fludarabine (PL 12375/0039) is indicated for the treatment of chronic lymphocytic leukaemia; the posology is 25 mg/m² body surface area given daily for 5 consecutive days; the dose is adjusted for those with renal or hepatic impairment or the elderly; administration is advised under supervision of an experienced physician.

Cyclophosphamide (PL 04416/1394 and associated numbers) is indicated for the treatment of acute lymphoblastic leukaemia; the posology (for bone marrow transplant) is 240 mg/m² body surface area given for 2 consecutive days; the dose is adjusted for those with renal or hepatic impairment or the elderly; administration is advised under supervision of an experienced physician.

The purpose of a pre-conditioning regimen is to provide sufficient suppression of the immune system to ensure engraftment and to provide niches in the host for the administered cells.

There are numerous low-intensity non-myeloablative conditioning regimens in current clinical practice; the applicant has chosen one such regimen (fludarabine and cyclophosphamide are known to be lympho-depleting); Section 4.2 of SmPC refers to the UK Public Assessment Report to describe the use of cyclophosphamide and fludarabine regimen as this is an off-label use.

The applicant provides a summary of the risks of the lymphodepletion regimen, as shown below.

Table 11: Pre-conditioning Chemotherapy – Key Risks and Mitigation Strategy

Risks	Mitigation Strategy
Myelosuppression and immunosuppression resulting in anaemia, neutropenia, thrombocytopenia, and lymphopenia, are the most common toxicities. In addition to being a manifestation of ALL, myelosuppression can be a toxicity of chemotherapy and also of CAR T cells treatment. Transient moderate to severe myelosuppression lasting up to 30 days is anticipated in this patient cohort. Bleeding, neutropenic fever, infections, and septic shock may occur and may sometimes be fatal. Herpes zoster and other viral reactivations may occur.	The FLU and CY chemotherapy given is milder than most chemotherapy treatment regimens for patients with r/r ALL and will be given only once (one cycle, given over 4 days). Anti-microbial prophylaxis may be given to prevent infections and patients should be monitored for cytomegalovirus, adenovirus and Epstein-Barr as per institution guidelines. If infections arise, they will be treated as per institutional guidelines. Blood, platelet and fresh frozen plasma transfusions will be given as per standard institutional guidelines. All sites have extensive expertise in managing these complications in patients with ALL and have on site intensive care unit support.
Cyclophosphamide associated toxicities (as per approved label), including but not limited to nausea/vomiting, haemorrhagic cystitis, myocarditis and myopericarditis and tamponade, pneumonitis and pulmonary fibrosis, and veno-occlusive liver disease may occur.	Given the low dose and short duration of treatment, these toxicities are unlikely. Patients will be given anti-emetic prophylaxis and hydration during lymphodepletion as per institutional policy. If haemorrhagic cystitis occurs, i.v. fluids and Mesna will be given. Other toxicities will be managed as per the standard institutional policy and by trained personnel.
Fludarabine is generally well tolerated: the most common side effects are lymphopenia and infection (see above). Neurotoxicity can occur but generally at higher doses. Other associated toxicities (as per the label) include, but are not limited to, autoimmune disorders, hepatic impairment, neurotoxicity, and renal impairment.	Given the low dose and short duration of treatment, these toxicities are unlikely. Toxicities will be managed as per the standard institutional policy and by trained personnel.

ALL = acute lymphoblastic leukaemia; CAR = chimeric antigen receptor; CY = cyclophosphamide; FLU = fludarabine; i.v.=intravenous.

Prior to administration, subjects underwent further assessments to ensure that they were still eligible to receive obe-cel.

<u>Exclusion Criteria for obe-cel Infusion</u>

- Severe intercurrent infection at the time of obe-cel infusion requiring systemic antimicrobials.

Upon review by the physician, controlled severe infection may not be a reason to withhold pre-conditioning.

- Requirement for supplementary oxygen at the time of scheduled obe-cel infusion.
- Patients with ≥Grade 3 pulmonary or cardiac toxicities following the first split dose will not receive the second split dose.
- Patients who develop obe-cel related ≥Grade 3 CRS and/or ≥Grade 2 ICANS following the first split dose will not receive the second split dose.

In the event a patient develops any other adverse event after receiving the first split dose of obe-cel preventing the administration of the second split dose, the infusion may be postponed beyond Day 10 (±2 days) up to Day 21 to allow for the resolution of the adverse event.

Premedication with paracetamol was permitted.

Patients will receive a total target dose of 410 x 10^6 CD19 CAR-positive T cells (±25%) on a schedule as shown below (Table 9):

Table 9: AUTO1 Dosing Regimen

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

BM = bone marrow; CAR = chimeric antigen receptor; CD = cluster of differentiation
*The blast count used to determine the dosing schedule will be based on analysis performed locally within 7 days prior to the start of the pre-conditioning, and by Investigator's assessment. All efforts should be made to have the bone marrow sample taken and analysed as close to the start of the pre-conditioning as possible. The % of blasts will be assessed as much as possible by morphology on both trephine and on the aspirate. In the event of discrepancies in the results, a conservative approach should be taken, and the highest blast count should be considered for split dose decision making. Once analysed locally, the BM aspirate smear slide will be sent to the Sponsor or third party laboratory for central storage should additional reading be required. In the event that the BM sample is not evaluable at baseline prior to dosing, the procedure must be repeated to determine disease burden on which dosing regimen is based. If the repeated sample is still not evaluable, a discussion with the medical monitor is warranted to select the appropriate dose.

The applicant presents a summary of risks associated with infusion of obe-cel:

Table 12: AUTO1 Infusion – Key Risks and Mitigation Strategy

Risks	Mitigation Strategy
Infusion reactions may occur with the infusion of AUTO1.	The product is autologous, and the risk is likely to be low. Patients may be pre-medicated with chlorpheniramine and paracetamol/acetaminophen. See Section 10.2.

Cytokine-release syndrome is a recognised toxicity associated with CAR T cell therapies. Clinical symptoms indicative of CRS includes culture negative fever, but may also include, myalgia, nausea/vomiting, tachycardia, hypoxia, hypotension, headache, confusion, tremor, and delirium. Potentially life-threatening complications of CRS may include: cardiac dysfunction, acute respiratory distress syndrome, renal and/or hepatic failure, and disseminated intravascular coagulation. The clinical features may overlap with macrophage activation syndrome.	Patients will be monitored for CRS and appropriate treatment given in the event of the occurrence (Section 10.4)
Neurotoxicity has been seen in patients with leukaemia after treatment with CAR T cell therapy and is now referred to as "Immune Effector Cell-associated Neurotoxicity Syndrome (ICANS)". The cause of neurotoxicity is not well-understood, although it is generally reported to be fully reversible. Although symptoms can vary the early manifestations of ICANS are often tremor, dysgraphia, mild difficulty with expressive speech especially naming objects, impaired attention, apraxia, and mild lethargy. Other symptoms can include confusion, depressed level of consciousness/encephalopathy, hallucinations, dysphasia, ataxia, apraxia, cranial nerve palsies, and seizures. Headache is a non-specific symptom, frequently occurring during fever or after chemotherapy, thus, headache alone is not a useful marker of ICANS. Expressive aphasia, on the other hand, appears to be a very specific symptom of ICANS.	The patient will be closely monitored for neurological signs and symptoms, and neuroimaging will be performed as appropriate. Appropriate treatment, including dexamethasone, may be given in the event of severe neurotoxicity, including cerebral oedema and seizures (Section 10.6).
Cytopenia (neutropenia, thrombocytopenia and anaemia) has been seen in patients with leukaemia after treatment with CAR T cell therapy, though is often confounded by the patient's prior treatments, disease state at the time of treatment and the pre AUTO1 lymphodepletion chemotherapy. The cytopenia may be prolonged but resolves in most individuals (Locke et al. 2019).	Patients should be supported according to local institution practice. Patients with low neutrophil counts will receive prophylactic antibiotics and antiviral medications if clinically appropriate and in accordance with local practice. All patients with fevers and neutropenia will have blood cultures drawn and broad-spectrum antibiotic coverage initiated promptly.
Tumour lysis syndrome (TLS) may occur on treatment with AUTO1 due to rapid killing of malignant cells in the context of a high tumour burden, but this is rarely seen after CD19 CAR T cell therapy.	In patients with high leukaemic burden allopurinol and i.v. fluids may be given. If TLS occurs, all sites have extensive experience in managing this complication and supportive care will be initiated rapidly as per standard institutional protocols (Section 10.7).

Risks	Mitigation Strategy
Hypogammaglobulinaemia Hypogammaglobulinaemia has been seen as a consequence of depletion of normal B cells by CD19 CAR T therapy. However, the degree and duration of this is likely to depend on the persistence of CD19 CAR T cells in the body and could last for months to years. Hypogammaglobulinaemia may occur because of depletion of normal B cells by AUTO1. This may potentially increase the risk of infections. The degree of hypogammaglobulinaemia and its duration are variable depending on the persistence of CAR T cells.	B cell recovery and Ig levels will be monitored regularly following AUTO1 infusion. Patients with recurrent and persistent severe hypogammaglobulinaemia will receive i.v. Ig replacement, according to institutional protocols (Section 10.8).
Immunogenicity Anti-CAR antibodies or anti-CAR T cell response could be neutralising; reduced efficacy is possible in patients who develop due to either neutralisation or enhanced clearance.	Evaluations to assess immunogenicity will be performed in this study as per schedule of assessment.
Insertional mutagenesis: Insertional mutagenesis leading to oncogenesis is a recognised safety concern of vector-based gene therapy. However, this has not been seen after transduction of terminally differentiated T cells and is considered a rare event. There are no reported cases of insertional mutagenesis in >200 patients treated with genetically modified T cells (including CAR T cells) over an extended period of follow-up (Scholler et al. 2012).	Patients will be monitored for secondary malignancy and survival in a long-term follow-up protocol for a total of 15 years in a separate long-term follow-up study (Section 8.10.4).
Risks associated with RCL: the vector backbone is a self-inactivating lentiviral vector. However, the theoretical risk exists that a recombination event may occur during vector or drug product manufacture that results in a RCL, which may be pathogenic in humans.	All vector lots and AUTO1 lots are tested for RCL prior to release. The risks of RCL formation is extremely low and to date, RCL has not been detected in any of the patients treated with lentiviral based CAR T cell therapy. Patients will be monitored for RCL by PCR during their scheduled follow-up visits. If a positive signal is confirmed, additional testing will be performed, and medical and research experts will be consulted for the optimal treatment approach should any complication arise.

CAR = chimeric antigen receptor; CD = cluster of differentiation; CRS = cytokine release syndrome; ICANS = Immune effector Cell-Associated Neurotoxicity Syndrome; Ig = immunoglobulin; i.v. = intravenous; PCR = polymerase chain reaction; RCL = replication competent lentivirus; TLS = tumour lysis syndrome.

The decision to administer the second split dose is made by the attending physician.

Patients were monitored for early onset of high-grade fever that is suspected to be CAR-related and evaluated for toxicity after infusion of the initial dose.

Patients with Grade 2 cytokine release syndrome and / or Grade 1 immune effector cell-associated neurotoxicity syndrome following the first split dose may receive the second dose on Day 10 (±2 days) up to Day 21 only if cytokine release syndrome has resolved to Grade 1 or less and immune effector cell-associated neurotoxicity syndrome has completely resolved.

Patients who develop obe-cel related ≥Grade 3 cytokine release syndrome and / or ≥Grade 2 immune effector cell-associated neurotoxicity syndrome following the first split dose will not receive the second split dose.

Patients with ≥Grade 3 pulmonary or cardiac toxicities following the first split dose will not receive the second split dose.

If the total target dose of 410 x 10^6 CD19 CAR-positive T cells cannot be manufactured, the first dose options will be kept as planned and the second dose will be reduced to package the remaining manufactured cells.

Timings to first obe-cel infusion are presented:

Table 12: Time from Informed Consent to First Obe-cel Infusion (Phase Ib/Phase II, Infused Set)

	Phase II Cohort A	Phase Ib and II All Cohorts
	Infused (N=94)	Infused (N=127)
Time from informed consent to enrollment (days)		
Mean (SD)	23.6 (23.37)	24.2 (21.89)
Median	16.0	17.0
Q1 - Q3	12.0 - 26.0	12.0 - 26.0
Min – Max	5 - 169	5 - 169
Time from informed consent to first obe-cel infusion (days)		
Mean (SD)	64.9 (28.14)	67.8 (30.73)
Median	56.5	61.0
Q1 - Q3	49.0 - 70.0	50.0 - 71.0
Min – Max	36 - 219	36 - 219
Time from enrollment to first obe-cel infusion (days)		
Mean (SD)	41.4 (13.77)	43.6 (19.79)
Median	37.0	38.0
Q1 - Q3	32.0 - 47.0	33.0 - 48.0
Min – Max	25 - 92	24 - 168

Abbreviations: BM = bone marrow; Q = quartile; SD = standard deviation.
Enrollment is defined as the point at which the patient meets all inclusion/exclusion criteria, and the patient's leukapheresate is accepted for manufacturing.
Data cut-off: 07-Feb-2024

For phase IIA subjects: time from enrolment to first infusion was 25 – 92 days (i.e. about 1 to 3 months). For all cohorts, the time taken was up to 168 days; this apparently long time interval presumably reflects a bedding-in process of the overall procedure.

Comparator
The study was conducted without an internal comparator; the applicant submits 2 technical reports as exercises in external comparisons.

Technical report 3964a: Technical Report for Indirect Treatment Comparisons of Obe-Cel Versus Brexu-Cel (brexucabtagene autoleucel, Tecartus) for the Treatment of R/R B-Cell ALL. Report dated 16 Jan 2024.

The report is a match-adjusted indirect (statistical comparison) comparison of (i) event-free survival, (ii) overall response rate and (iii) complete response based on data from study FELIX cohort IIA and study ZUMA-3; the applicant states that outcomes are similar.
The report also claims less evidence of cytokine release syndrome and immune effector cell-associated neurotoxicity syndrome in those who took part in study FELIX.

Technical report: External Control Arm Summary Report for a Prospectively Designed Non-interventional Study to Compare Obe-cel, A CAR T Cell Treatment Targeting CD19, With an External Control Arm in Adult Patients with Relapsed or Refractory B Cell Acute Lymphoblastic Leukaemia.
Report dated 18 Jan 2024.

The applicant presents several analyses using patient-level data in historical clinical trials with a propensity method to match patients to those in the FELIX study.

Outcomes
The main efficacy outcome of the applicant is overall remission rate for Cohort IIA infused patients (i.e. the Infused Set), defined as the proportion of patients achieving CR or CRi at any time post-infusion and as assessed by an Independent Response Review Committee.

Subjects were evaluated with the Response Criteria for Acute Lymphoblastic Leukaemia (National Comprehensive Cancer Network Guidelines, version 2, 2019) for documenting disease response as shown below:

Table 29: Overall Disease Response Criteria

Overall Disease Response Criteria	
Complete Remission (CR)*	The following criteria should be met within the same disease assessment: **Bone marrow:** • Trilineage haematopoiesis (TLH) • <5% blasts in bone marrow **Peripheral blood:** • No circulating lymphoblasts in peripheral blood and • Absolute neutrophil count (ANC) >1000/µL and • Platelet count >100,000/µL and • No platelet transfusions in the last 7 days and • No administration of short-acting Granulocyte colony-stimulating factor (G-CSF) and long-acting G-CSF in the last 3 and 14 days respectively **Extramedullary disease:** • No EM disease: e.g. no lymphadenopathy, splenomegaly, skin/gum infiltration, testicular mass, or central nervous system (CNS) involvement and • If additional assessments (e.g. CSF assessment by LP, CNS imaging, biopsy, etc.) are performed, results must show remission status
CR with incomplete recovery of counts (CRi)	Meets all criteria for CR except platelet count or ANC: • Recovery of platelets to ≤100,000/µL and/or • Recovery of absolute neutrophil count to <1000/µL

Table 29: Overall Disease Response Criteria

Overall Disease Response Criteria	
Relapsed ALL	Only in patients who previously achieved a CR or CRi and who have: • Reappearance of blasts in the blood or • Reappearance of lymphoblasts in bone marrow (≥ 5%)
	or • (Re-)appearance of any EM site after CR.
No response	Failure to meet the criteria for CR/CRi categories
Unknown	"Unknown" is 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.

ALL = acute lymphoblastic leukaemia; ANC = absolute neutrophil count; BM = bone marrow; CNS = central nervous system; CR = complete remission; CRi = complete remission with incomplete recovery of counts.

**Following initial establishment of response, patients should be assessed for recurrence of the disease starting at least 4 weeks after onset of CR/CRi. Patients will be considered continuing in CR/CRi if there is no clinical evidence of relapse as assessed by peripheral blood (% of blasts) and extramedullary disease assessment (physical exam and CNS symptom assessment). Invasive procedures including bone marrow assessments are not mandated after the initial achievement of CR or CRi unless clinical indicated. Please note, if additional assessments are performed (e.g. bone marrow, CSF assessment by LP, CNS imaging, biopsy, etc.), they need to support the remission status.*

Of note, assessment period (to have all components of disease assessments as part of the same overall response evaluation in each timepoint) is defined as having all efficacy assessments (e.g. bone marrow, blood counts, EM disease assessment) in a window of maximum 2 weeks.

The following response criteria were also used.

Table 30: Mediastinal Lymphomatous Extramedullary Disease* Response Classification At a Given Timepoint

Complete Remission (CR)	Complete resolution of lymphomatous mediastinal enlargement by CT scan with i.v. contrast. Note: post-treatment residual mass of any size is considered CR as long as it is PET negative.
Partial Remission (PR)	>50% decrease in the sum of the product of the greatest perpendicular diameters (SPD) of the mediastinal enlargement by CT scan with i.v. contrast. If PET scan was previously performed, the post-treatment PET must be positive in at least one previously involved site and no presence of PET avid new lesions (that is judged to be lymphomatous disease).
Progressive Disease (PD)	>25% increase in the SPD of the mediastinal enlargement by CT scan with i.v. contrast, or recurrence of mediastinal enlargement after achieving a CR or PR. If PET scan was previously performed, the PET-CT must show an overall increase of at least one of the previously identified lesion or PET-avid positivity in at least one new lesion (that is judged to be lymphomatous disease).
No Response (NR)	Failure to qualify for at least PR or PD.

** If the mediastinal disease is combined with B-ALL bone marrow involvement, Table 30 would be complementary to Table 29 for the overall disease response assessment (e.g. absence of EM mediastinal disease should meet the CR criteria specified in Table 30).*

Table 31: Isolated Extramedullary Disease* (Any Location, Except CNS and/or Mediastinal) Response Classification At a Given Timepoint

Complete Remission (CR)	Complete resolution of infiltration/enlargement by the gold standard technique/imaging** (depending on the EM disease location).
Partial Remission (PR)	>50% decrease in the infiltration/enlargement by PET-CT scan or the gold standard technique ** (if PET-CT is not considered the appropriate technique depending on the EM disease location).
Progressive Disease (PD)	>25% increase of infiltration/enlargement by PET-CT scan or the gold standard technique/imaging** (if PET-CT is not considered the appropriate technique depending on the EM disease location) or the appearance of a new lesion.
No Response (NR)	Failure to qualify for at least PR or PD.

** If EM disease is combined with B-ALL bone marrow involvement, Table 31 would be complementary to Table 29 for the overall disease response assessment (e.g. absence of EM disease should meet the CR criteria specified in Table 31).*

***A gold standard technique/imaging is defined as the best current available test for determining whether a patient does or does not have a disease and for determining the extension of the disease. Depending on the EM disease location, one or more gold standard tests should be performed as they could be complementary (per treating physician judgment).*

For the assessment of extramedullary disease, the CNS disease assessment should be performed according to Table 32 below.

Table 32 Response Criteria for CNS Disease

CNS remission	Achievement of no lymphoblast in cerebrospinal fluid (CSF) regardless of white blood cell (WBC) count
CNS relapse	Presence of lymphoblasts in CSF with WBC count ≥5/µL or clinical signs of CNS leukaemia such as facial nerve palsy, brain/eye involvement, or hypothalamic syndrome without another explanation.

CNS = central nervous system; CSF = cerebrospinal fluid; WBC = white blood cell.

Data for overall response rate (main outcome) are summarised with a comparison between the primary analysis (09-Jun-2023) and the latest cut-off date (07-Feb-2024):

Table 3: Overview of Remission Results in the FELIX Study with Disease Assessment by IRRC (Cohort IIA, Infused and Enrolled Set)

Parameter	09-Jun-2023 Cut-off		07-Feb-2024 Cut-off	
	Infused Set (N=94)	Enrolled Set (N=112)	Infused Set (N=94)	Enrolled Set (N=112)
ORR (= CR + CRi)				
n (%)	72 (76.6)	72 (64.3)	72 (76.6)	72 (64.3)
95% CI (%) [1]	66.7, 84.7	54.7, 73.1	(66.7, 84.7)	(54.7, 73.1)
p-value [2]	<0.0001	ND	<0.0001	ND
CR				
n (%)	52 (55.3)	55 (49.1)	52 (55.3)	55 (49.1)
95% CI (%) [1]	44.7, 65.6	39.5, 58.7	(44.7, 65.6)	(39.5, 58.7)
p-value [3]	<0.0001	ND	<0.0001	ND
MRD-negative ($<10^{-4}$) remission				
MRD-negative CR/CRi [4], n (%)	65 (90.3)	65 (90.3)	**64 (88.9)**	**64 (88.9)**

CI=confidence interval; CR=complete remission; CRi=complete remission with incomplete hematologic recovery; IRRC=Independent Response Review Committee; MRD=minimal residual disease; ND=not determined; ORR=overall remission rate.
[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/Flow Cytometry/PCR; percentage is based on the number of patients with best overall response of CR or CRi.
Changes compared to the 09-Jun-2023 cut-off date are indicated in **bold**.

Enrolled patients were those who met all inclusion / exclusion criteria and for whom leukapheresis material was accepted for manufacturing. CR was unchanged from the primary analysis.

Time to remission for **cohort IIA** is summarised in the following table:

Table 24: Time to Onset of Remission Assessed by IRRC 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)
Onset of CR or CRi (month)				
n	53	16	3	72
Mean (SD)	1.26 (1.005)	0.97 (0.048)	2.38 (2.104)	1.24 (0.968)
Median	0.95	0.95	1.35	0.95
Q1 - Q3	0.95 - 0.99	0.95 - 0.99	0.99 - 4.80	0.95 - 0.99
Min – Max	0.8 - 7.2	0.9 - 1.1	1.0 - 4.8	0.8 - 7.2
Onset of CR or CRi (Category) - n (%)				
Within M3 visit	51 (96.2)	16 (100)	2 (66.7)	69 (95.8)
After M3 But Within M6 visit	1 (1.9)	0	1 (33.3)	2 (2.8)
After M6 Visit	1 (1.9)	0	0	1 (1.4)
Onset of CR (month)				
n	41	9	2	52
Mean (SD)	2.60 (1.583)	1.88 (0.997)	3.91 (1.254)	2.53 (1.518)
Median	2.07	2.07	3.91	2.07
Q1 - Q3	1.84 - 3.02	0.99 - 2.14	3.02 - 4.80	1.43 - 3.02
Min – Max	0.9 - 7.2	1.0 - 3.5	3.0 - 4.8	0.9 - 7.2
Onset of CR (Category) - n (%)				
Within M3 visit	33 (80.5)	9 (100)	1 (50.0)	43 (82.7)
After M3 But Within M6 visit	7 (17.1)	0	1 (50.0)	8 (15.4)
After M6 Visit	1 (2.4)	0	0	1 (1.9)

BOR=Best overall response; BM=Bone marrow; CR=Complete remission; CRi=Complete remission with incomplete recovery of counts; EMD=Extramedullary disease; IRRC=Independent Response Review Committee; M=Month; Q=Quarter; SD=Standard deviation
Data cut-off: 09-June-2023

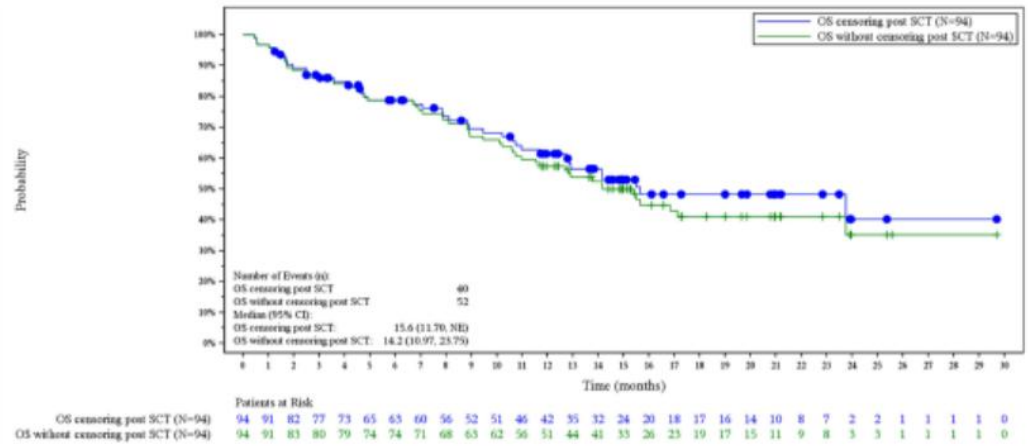
Almost all who achieved a form of remission did so within 3 months of exposure.
On an available case basis: complete remission occurred at between (about) 1 to 7 months; 83% were by month 3.

It is considered that information on overall survival has prime importance. Information is shown below:

Overall survival
44.7% of patients in Cohort IIA were alive (42/94) as of 07-Feb-2024 with median overall survival of (about) 14 months.

Overall survival for **cohort IIA** is displayed in the following figure:

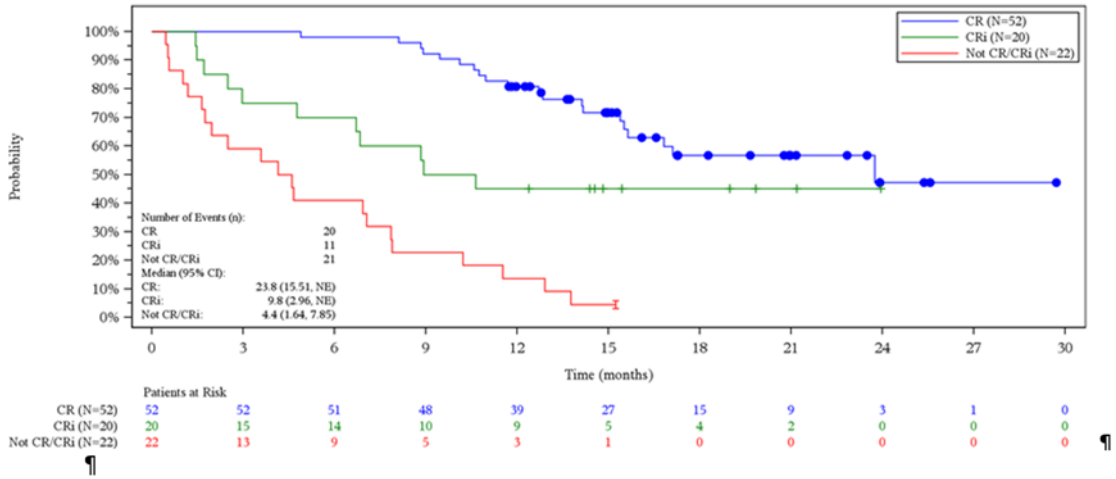
Figure 6: Kaplan-Meier Plot of Overall Survival With or Without Censoring Stem Cell Transplantation (Cohort IIA, Infused Set)



CI=confidence interval; NE=not estimable; SCT=stem cell transplantation.
Median with 95% CIs calculated from PROC LIFETEST output using method of Brookmeyer and Crowley, 1982.
Data cut-off: 07-Feb-2024.

The applicant also presents data on overall survival according to response status for cohort IIA, as shown in the following figure and table:

Figure: Kaplan-Meier Plot of Overall Survival Without Censoring SCT as Assessed by IRRC (Cohort IIA, Infused Set)



Abbreviations: CI = confidence interval; CR = complete remission; CRi = complete remission with incomplete hematologic recovery; IRRC = Independent Response Review Committee; NE = not estimable; SCT = stem cell transplantation.
Median with 95% CIs are calculated from PROC LIFETEST output method (Brookmeyer and Crowley 1982).
Cut off date: 07-Feb-2024.

Table: Overall Survival Without Censoring SCT By Best Overall Response with Disease Assessment by IRRC (Cohort IIA, Infused Set)

	CR (N=52) n (%)	**CRi (N=20) n (%)**	**Not CR/CRi (N=22) n (%)**	**Total (N=94) n (%)**
No. of patients in analysis[1]	52	20	22	94
No. of events - n (%)	20 (38.5)	11 (55.0)	21 (95.5)	52 (55.3)
Death	20 (38.5)	11 (55.0)	21 (95.5)	52 (55.3)
No. of censored observations - n (%)	32 (61.5)	9 (45.0)	1 (4.5)	42 (44.7)
Alive	32 (61.5)	9 (45.0)	1 (4.5)	42 (44.7)
Quartile Estimates (95% CI) [month][2]				
50th	23.75 (15.51, NE)	9.79 (2.96, NE)	4.37 (1.64, 7.85)	14.16 (10.97, 23.75)
Event-free probability estimate (95% CI)[3]				
6 months	98.1 (87.1, 99.7)	70.0 (45.1, 85.3)	40.9 (20.9, 60.1)	78.7 (69.0, 85.7)
12 months	80.8 (67.2, 89.2)	45.0 (23.1, 64.7)	13.6 (3.4, 30.9)	57.4 (46.8, 66.7)
18 months	56.7 (40.0, 70.4)	45.0 (23.1, 64.7)	NE	41.1 (30.0, 51.8)

Abbreviations: CI = confidence interval; CR = complete remission; CRi = complete remission with incomplete haematologic recovery; IRRC = Independent Response Review Committee; NE = not estimable; SCT = stem cell transplantation.

[1] The analysis includes all patients in the Infused Set – Cohort IIA.

[2] Percentiles with 95% CIs are calculated from PROC LIFETEST output method (Brookmeyer and Crowley 1982).

[3] % Event-free probability estimates are obtained from the Kaplan-Meier survival estimates, with 95% CIs estimated using Greenwood formula.

Cut off date: 07-Feb-2024.

It can be noted that the applicant has used the following definitions for the figure and table:

Complete remission:

- Bone marrow: trilineage haematopoiesis and <5% blasts in bone marrow
- Peripheral blood: no circulating lymphoblasts; neutrophil count >1000/µL; platelet count >100,000/µL and no platelet transfusions in last 7 days and no administration of granulocyte colony stimulating factor in last 3 days for short-acting GCSF products and 14 days for long-acting GCSF products.
- No extramedullary disease

Complete remission with incomplete recovery of counts:

- Meet all criteria for complete remission except: recovery of platelets to <=100,000 ul and / or recovery of neutrophil count to <1000 ul

The above figure and table are considered to be highly informative.

For cohort IIA, the infused set: 52/94 subjects show complete remission (CR); 20/94 show incomplete haematology response (CRi) and 22/94 show neither CR nor CRi.
It is viewed that:

- Those who show complete remission (about half of all subjects in the infused set) show 98% survival at month 6 and 81% survival at month 12; these overall survival data are considered most notable.
- Those who show incomplete haematology response (CRi) show 70% survival at month 6 and 45% survival at month 12; these subjects fare worse compared to the CR subgroup.
- Those who show neither CR nor CRi show 41% survival at month 6 and 14% survival at month 12; these subjects fare worst of all in terms of overall survival.

The above graph and table show a differential outcome related to response status; those who show complete remission (CR) fare better than those with incomplete haematology response (CRi) who in turn fare better than those with neither CR nor CRi. The differential survival based on response to exposure to product is considered consistent with efficacy and such efficacy is considered most notable in those with complete remission.

Overall survival data for those who achieve neither "CR nor CRi" in response to exposure to obe-cel are similar to the expectation of overall survival for those who would have been untreated.

It is considered that overall survival has paramount importance; data on "overall response rate", "duration of remission" and "event-free survival" are considered to be of secondary importance by comparison in a disease state where those who do not respond will most likely die within 12 months.

Information on obe-cel infusion for cohort IIA is provided in the following table:

Table 8: Obe-cel Infusion Summary (Cohort IIA, Infused Set)

Parameter	**Infused (N=94)**
Total CD19 CAR-positive T cells (10^6 cells)	
n	94
Median	410.0
Min - Max	10 - 480
Obe-cel split dose regimen - n (%)	
High tumor burden dosage regimen: 10×10^6 / 400×10^6 cells	57 (60.6)
Low tumor burden dosage regimen: 100×10^6 / 310×10^6 cells	37 (39.4)
Patient received both obe-cel doses - n (%)	88 (93.6)
Patient received only first obe-cel dose - n (%)	6 (6.4)
Patients receiving the target dose - n (%) [1]	85 (90.4)
Patients not receiving the target dose - n (%)	9 (9.6)

CAR=chimeric antigen receptor.
Infused set comprises of all patients who have received at least one infusion of obe-cel.
[1] Target dose was 410 × 10^6 CD19 CAR-positive T cells (±25%).

The above table shows that 57/94 (61%) of those infused were exposed to the high-burden posology and 37/94 (39%) were exposed to the low-burden posology.

88/94 (94%) received both doses; 6/94 received only the first dose.

85/94 (91%) received the target dose.

Compliance in terms of receiving the target dose is considered sufficiently high for all 94 subjects to be included in an assessment of outcome.

Other outcomes reported on are considered as supporting towards data on overall survival. Such supporting outcomes include duration of remission, event-free survival and quality of life assessments; these outcomes are displayed below:

Supporting outcomes

Analysis of duration of remission was conducted by including all patients in remission at any time post-infusion (CR or CRi as adjudicated by the IRRC) and assessing the time from first onset of remission to morphological relapse or death due to any reason with or without censoring of stem cell transplant or any other new anti-cancer therapies for B-cell acute lymphoblastic leukaemia.

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 a stem cell transplant or other non-protocol anti-cancer therapy then the duration of response was censored.

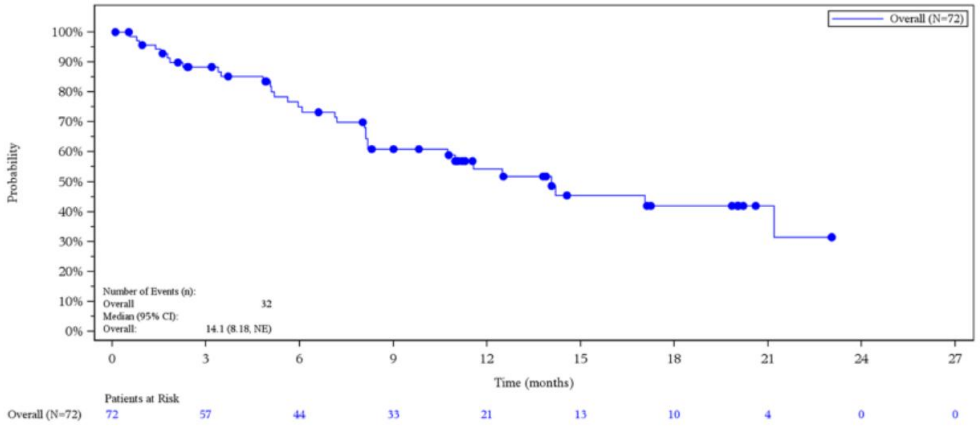
Data are presented in the following table and figure:

Table 4: Duration of Remission by IRRC With Censoring for SCT or Other New Non-protocol Anti-cancer Therapy (Cohort IIA, Infused and Enrolled Sets)

Parameter	09-Jun-2023 Cut-off		07-Feb-2024 Cut-off	
	All Infused (N=94)	Enrolled (N=112)	All Infused (N=94)	Enrolled (N=112)
No. of patients in analysis [1]	72	72	72	72
No. of events - n (%)	24 (33.3)	24 (33.3)	**32 (44.4)**	**32 (44.4)**
Morphological relapse	21 (29.2)	21 (29.2)	**28 (38.9)**	**28 (38.9)**
Death due to reason other than underlying cancer	3 (4.2)	3 (4.2)	**4 (5.6)**	**4 (5.6)**
No. of censored observations - n (%)	48 (66.7)	48 (66.7)	**40 (55.6)**	**40 (55.6)**
Ongoing without event	36 (50.0)	36 (50.0)	**26 (36.1)**	**26 (36.1)**
SCT	11 (15.3)	11 (15.3)	**12 (16.7)**	**12 (16.7)**
New non-protocol anti-cancer therapies other than SCT	1 (1.4)	1 (1.4)	**2 (2.8)**	**2 (2.8)**
Maximum follow-up (months)	20.0+	20.0+	**23.0+**	**24.2+**
Median follow-up (months) [2]	7.7	7.7	**13.8**	**13.8**
Quartile Estimates (month) [3]				
50th	11.56	12.48	**14.06**	**14.06**
95% CI, %	(8.11, NE)	(8.11, NE)	**(8.18, NE)**	**(8.18, NE)**
% Event-free probability estimate (95% CI) [4]				
At 6 months - %	73.5	76.5	**75.0**	**76.9**
95% CI	(59.2, 83.4)	(63.1, 85.5)	**(62.3, 83.9)**	**(64.5, 85.4)**
At 9 months - %	54.1	54.5	**60.9**	**60.8**
95% CI	(36.9, 68.5)	(37.4, 68.8)	**(47.3, 71.9)**	**(47.3, 71.9)**
At 12 months - %	49.2	50.3	**54.3**	**54.1**
95% CI	(31.2, 64.9)	(32.8, 65.5)	**(40.3, 66.3)**	**(40.1, 66.2)**

CI=confidence interval; CR=complete remission; CRi=complete remission with incomplete hematologic recovery; IRRC=Independent Response Review Committee; NE=not estimable; No.=Number; SCT=stem cell transplant.
[1] The analysis includes all patients who achieved a best overall response of CR or CRi post-obe-cel infusion for "All Infused" analysis and includes all patients who achieved a best overall response of CR or CRi post-enrollment for "Enrolled" analysis.
[2] Median follow-up is calculated using reverse KM method.
[3] Percentiles with 95% CIs are calculated from PROC LIFETEST output using method of Brookmeyer and Crowley, 1982.
[4] % Event-free probability estimates are obtained from the KM survival estimates, with 95% CIs estimated using Greenwood formula.
Changes compared to the 09-Jun-2023 cut-off date are indicated in **bold**.

Figure 5: Kaplan-Meier Plot of Duration of Remission by IRRC Censoring New Non-protocol Anticancer Therapies Including SCT (Cohort IIA, Infused Set)

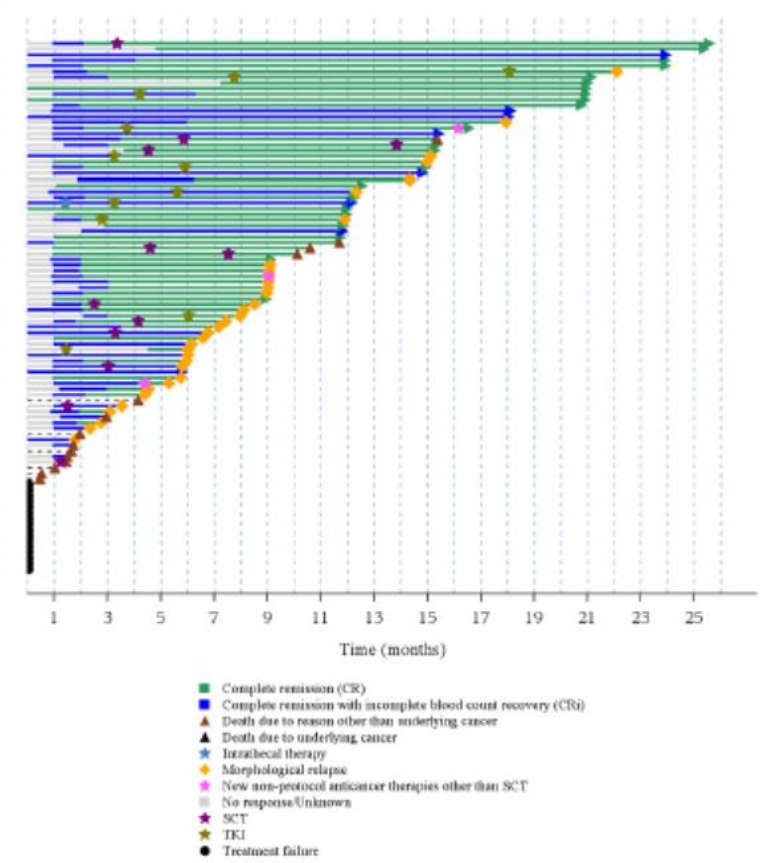


Abbreviations: CI = confidence interval; IRRC = Independent Response Review Committee; SCT = stem cell transplantation.
Time is relative to onset of remission; 1 month = 30.4375 days.
Data cut-off: 07-Feb-2024

Among the responding patients (N=72): the median time to response was 1 month (range 0.8-7.2 months) And with a median duration of response follow-up of 13.8 months, the estimated probability for being in remission after onset of remission was 75.0% (95% CI: 62.3, 83.9) at Month 6, 54.3% (95% CI: 40.3, 66.3) at Month 12 and 41.9% (95% CI: 27.1, 56.0) at Month 18. Median duration of response was 14.06 months (95% CI: 8.18, NE).

An analysis of individual patients' patterns of duration of response assessed by IRRC is provided in Figure 6, visualising durable remission for a high proportion of patients with r/r B ALL infused with obe-cel in Cohort IIA who achieved CR or CRi post-obe-cel infusion.

Figure 6: Swimmer Plot of Patients Infused with Obe-cel (Cohort IIA, Infused Set)

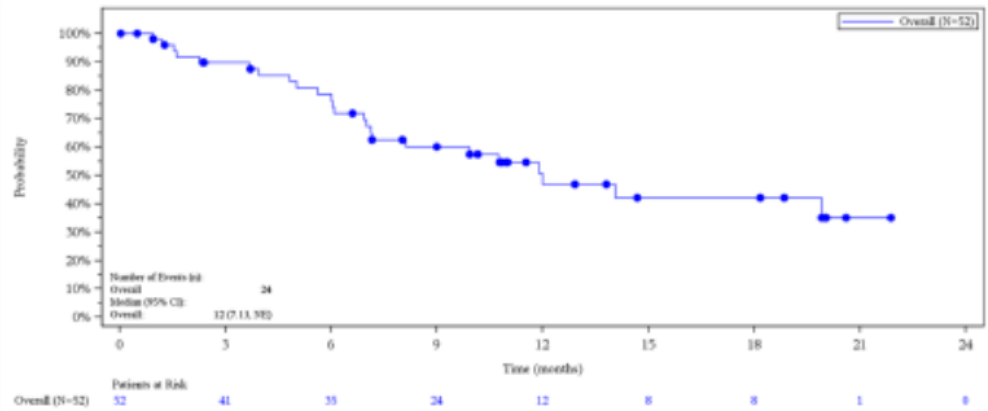


Abbreviations: CR = complete remission; CRi = complete remission with incomplete hematologic recovery; SCT = stem cell transplantation; TKI = tyrosine kinase inhibitor.
Data cut-off: 07-Feb-2024

Duration of Complete Remission

For patients infused with obe-cel who achieved a best overall response of complete remission by IRRC, the probability of remaining in complete remission at Month 6 after achieving of complete remission was 78.5% (95% CI: 63.7, 87.9) and at Month 12 was 46.8% (95% CI: 30.1, 61.8). With a median follow-up of 11.5 months, the median duration of complete remission was 11.99 months (95% CI: 7.13, NE) (Figure 7; Table 29).

Figure 7: Kaplan-Meier Plot of Duration of Complete Remission by IRRC Censoring New Non-Protocol Anticancer Therapies Including SCT (Cohort IIA, Infused Set)



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

Table 29: Duration of Complete Remission by IRRC Censoring New Non-Protocol Anticancer Therapies Including SCT by Disease Status at Lymphodepletion (Cohort IIA, Infused Set)

	≥5% Blast in BM (N=71) n (%)	<5% Blast in BM Without EMD (N=18) n (%)	<5% Blast in BM With EMD (N=5) n (%)	Total (N=94) n (%)
No. of patients in analysis [1]	41	9	2	52
No. of events - n (%)	20 (48.8)	4 (44.4)	0	24 (46.2)
Morphological relapse	20 (48.8)	3 (33.3)	0	23 (44.2)
Death due to reason other than underlying cancer	0	1 (11.1)	0	1 (1.9)
No. of censored observations - n (%)	21 (51.2)	5 (55.6)	2 (100)	28 (53.8)
Ongoing without event	12 (29.3)	5 (55.6)	1 (50.0)	18 (34.6)
SCT	7 (17.1)	0	1 (50.0)	8 (15.4)
New non-protocol anticancer therapies other than SCT	2 (4.9)	0	0	2 (3.8)
Min - Max follow-up (months)	0.0+ - 19.9+	3.7 - 21.9+	10.8+ - 20.6+	0.0+ - 21.9+
Median follow-up (months) [2]	11.5 (8.02, 14.69)	20.0 (10.15, NE)	15.7 (10.84, NE)	11.5 (10.15, 18.17)
Quartile Estimates (95% CI) (month) [3]				
75th	5.62 (1.61, 7.13)	10.74 (3.68, NE)	NE	6.05 (3.68, 7.16)
50th	9.92 (6.93, 19.91)	11.89 (3.68, NE)	NE	11.99 (7.13, NE)
25th	19.91 (14.06, NE)	NE	NE	NE
% Event-free probability estimate (95% CI) [4]				
3 months	86.7 (70.9, 94.2)	100.0 (NE, NE)	100.0 (NE, NE)	89.7 (77.0, 95.6)
6 months	74.7 (56.9, 86.0)	88.9 (43.3, 98.4)	100.0 (NE, NE)	78.5 (63.7, 87.9)
9 months	52.7 (34.6, 68.0)	77.8 (36.5, 93.9)	100.0 (NE, NE)	60.0 (44.2, 72.7)
12 months	43.5 (25.0, 60.7)	48.6 (12.8, 77.6)	100.0 (NE, NE)	46.8 (30.1, 61.8)
15 months	36.3 (17.3, 55.6)	48.6 (12.8, 77.6)	100.0 (NE, NE)	42.1 (25.1, 58.2)
18 months	36.3 (17.3, 55.6)	48.6 (12.8, 77.6)	100.0 (NE, NE)	42.1 (25.1, 58.2)
21 months	NE	48.6 (12.8, 77.6)	NE	35.1 (17.3, 53.5)
24 months	NE	NE	NE	NE

Abbreviations: BM = bone marrow; BOR = best overall response; CI = confidence interval; CR = complete remission; EMD = extramedullary disease; NE = not estimable; SCT = stem cell transplantation.
[1] The analysis includes all patients in the Infused Set - Phase II - Cohort A who achieved BOR of CR post-obe-cel infusion.
[2] Median follow-up is calculated using reverse Kaplan-Meier method.
[3] Percentiles with 95% CIs are calculated from PROC LIFETEST output method (Brookmeyer and Crowley 1982).
[4] % Event-free probability estimates are obtained from the Kaplan-Meier survival estimates, with 95% CIs estimated using Greenwood formula.
Data cut-off: 07-Feb-2024

The applicant has used the following definitions for complete remission for the figure and table above:

Complete remission:

- Bone marrow: trilineage haematopoiesis and <5% blasts in bone marrow
- Peripheral blood: no circulating lymphoblasts; neutrophil count >1000/µL; platelet count >100,000/µL and no platelet transfusions in last 7 days and no administration of granulocyte colony stimulating factor in last 3 days for short-acting GCSF products and 14 days for long-acting GCSF products.
- No extramedullary disease

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 owing to any cause. Event-free survival (and overall survival) data are presented in the following table for cohort IIA:

Table 5: Overview of Survival Results in FELIX (Cohort IIA, Infused and Enrolled Sets)

Efficacy parameter	09-Jun-2023 Cut-off		07-Feb-2024 Cut-off	
	Infused (N=94)	Enrolled (N=112)	Infused (N=94)	Enrolled (N=112)
Event-free survival [1]				
Patients with event, n (%)	46 (48.9)	63 (56.3)	**54 (57.4)**	**71 (63.4)**
Median EFS [95% CI] [2]	9.03 [6.01,14.32]	7.69 [4.34, 10.55]	**9.03 [6.14, 14.98]**	**8.18 [4.34, 12.12]**
6 months probability estimate (% [95% CI]) [3]	63.2 [52.1, 72.3]	57.4 [47.5, 66.0]	**63.8 [52.9, 72.8]**	**57.5 [47.7, 66.1]**
12 months probability estimate (% [95% CI]) [3]	41.9 [28.9, 54.3]	37.5 [26.4, 48.6]	**43.4 [32.4, 54.0]**	**40.7 [31.0, 50.2]**
Overall survival [4]				
Patients with event (death), n (%)	41 (43.6)	55 (49.1)	**52 (55.3)**	**66 (58.9)**
Median OS (95% CI) [2]	14.13 [10.12, 17.12]	11.73 [9.86, 16.76]	**14.16 [10.97, 23.75]**	**13.73 [11.01, 16.85]**
6 months probability estimate (% [95% CI]) [3]	78.6 [68.8, 85.6]	72.9 [63.6, 80.2]	**78.7 [69.0, 85.7]**	**73.0 [63.7, 80.3]**
12 months probability estimate (% [95% CI]) [3]	51.6 [38.7, 63.1]	48.7 [37.3, 59.1]	**57.4 [46.8, 66.7]**	**54.6 [44.8, 63.3]**

CI=confidence interval; EFS=event-free survival; KM=Kaplan-Meier; OS=overall survival.
[1] With censoring for SCT and other new anti-cancer therapy.
[2] Percentiles with 95% CIs are calculated from PROC LIFETEST output using method of Brookmeyer and Crowley, 1982.
[3] Probability estimates obtained from the KM survival estimates, with 95% CIs estimated using Greenwood formula.
[4] Without censoring for SCT.
Changes compared to the 09-Jun-2023 cut-off date are indicated in **bold**.

As of the data cut-off (07-Feb-2024):

54 of 94 patients (57.4%) infused with obe-cel in Cohort IIA had an event-free survival event (28 patients [29.8%] had morphological relapse, 16 patients [17.0%] had treatment failure, and 10 patients [10.6%] died due to reason other than their underlying disease).

26 patients (27.7%) were ongoing without an event and were censored for this analysis.

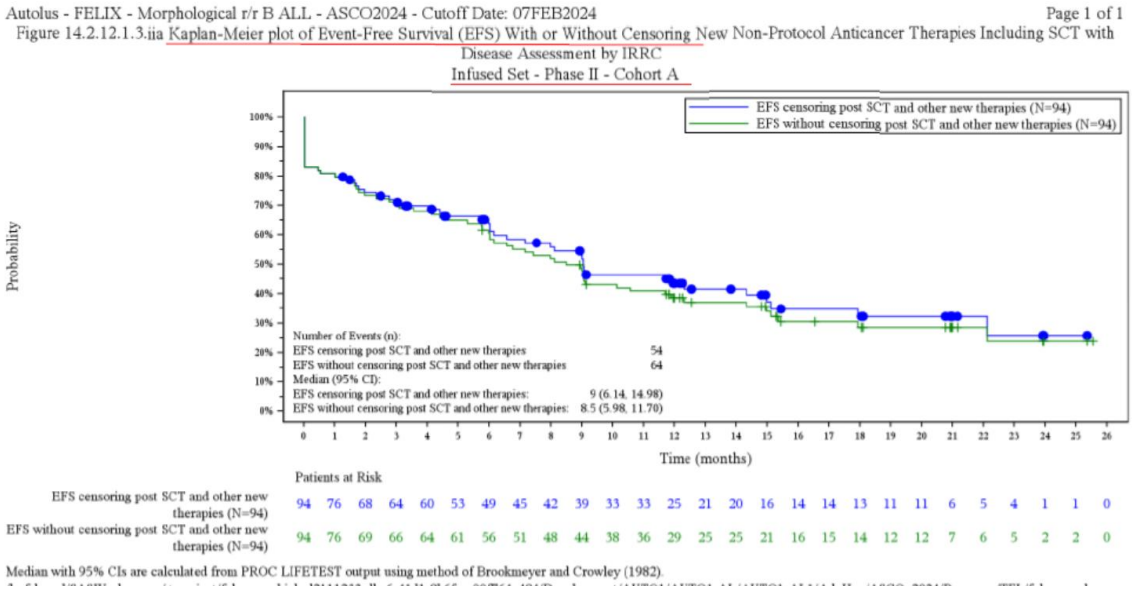
12 patients (12.8%) had stem cell transplant and were also censored for the analysis.

The estimated event-free probability was 63.8% (95% CI: 52.9, 72.8) at Month 6, 43.4% (95% CI: 32.4, 54.0) at Month 12 and 32.3% (95% CI: 21.1, 44.1) at Month 18.

With a median follow-up of 14.8 months, the median event-free survival was 9.03 months (95% CI: 6.14, 14.98)

Date on event-free survival are also presented in the following figure:

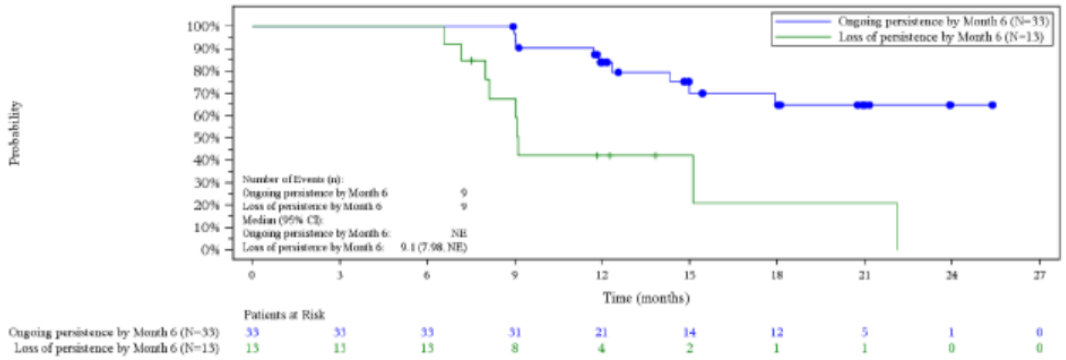
Data on event-free survival for cohort IIA with and without censoring are presented in figure form, as shown:



The figure above of event-free survival presented with and without censoring suggests that the outcome is similar irrespective of censoring status.

The long-term efficacy outcome for patients treated with obe-cel appears to be associated with persistence of CAR-T cells; 80.8% of patients in ongoing remission [at the Feb 2024 cut-off] have ongoing persistence of CAR-T cells. In order to understand the impact of persistence of CAR-T cells on long-term outcome, landmark analyses were performed among patients in Cohort IIA who were still in remission at 6 months, see Figure 7 on event-free survival:

Figure 7: Landmark Analysis: Kaplan-Meier Plot of Event-free Survival, Censoring New Non-Protocol Anti-cancer Therapies (Including Stem Cell Transplant) by Whether a Patient Had Ongoing CAR T Persistence at Month 6 – Infused Set, Cohort IIA



CI=confidence interval; NE=not estimable.
Time is relative to first obe-cel infusion; 1 month=30.4375 days.
Median follow-up is calculated using the reverse Kaplan-Meier method. Percentiles with 95% CI are calculated from PROC LIFETEST output using the method of Brookmeyer and Crowley, 1982. Percent event-free probability

estimates are obtained from the Kaplan-Meier survival estimates with 95% CI estimated using the Greenwood formula.
Data cut-off: 07-Feb-2024.

Data suggest persistence of CAR-T cells is associated with improved event-free survival.

The long-term efficacy seen in FELIX was achieved with obe-cel alone; 36% of patients treated with obe-cel in Cohort IIA continue in remission without non-protocol anticancer therapies (including stem cell transplant).

Of the 19.4% (14/72) of patients in Cohort IIA achieving remission after obe-cel treatment who proceeded to consolidation therapy (Table 4, see above):

- 12 patients proceeded to stem cell transplant. These 12 patients were all minimal residual disease-negative and most had CAR persistency prior to stem cell transplant. Among these 12, only 3 continue in remission. This suggests that depletion of the autologous CAR T cells as a consequence of the preparative regimen ahead of the subsequent allogeneic stem cell transplant may have impacted the remission in many of these patients.
- 2 patients received new non-protocol anti-cancer therapies other than stem cell transplant. Both patients relapsed afterwards.

Table 4: Duration of Remission by IRRC With Censoring for SCT or Other New Non-protocol Anti-cancer Therapy (Cohort IIA, Infused and Enrolled Sets)

	09-Jun-2023 Cut-off		07-Feb-2024 Cut-off	
Parameter	**All Infused (N=94)**	**Enrolled (N=112)**	**All Infused (N=94)**	**Enrolled (N=112)**
No. of patients in analysis [1]	72	72	72	72
No. of censored observations - n (%)	48 (66.7)	48 (66.7)	**40 (55.6)**	**40 (55.6)**
Ongoing without event	36 (50.0)	36 (50.0)	**26 (36.1)**	**26 (36.1)**
SCT	11 (15.3)	11 (15.3)	**12 (16.7)**	**12 (16.7)**
New non-protocol anti-cancer therapies other than SCT	1 (1.4)	1 (1.4)	**2 (2.8)**	**2 (2.8)**

CI=confidence interval; CR=complete remission; CRi=complete remission with incomplete hematologic recovery; IRRC=Independent Response Review Committee; NE=not estimable; No.=Number; SCT=stem cell transplant.

An extract of table 4 (to confirm numbers who went on to stem cell transplant and other anti-cancer therapies) is shown above:

Incidence of CD19-negative Relapses

CD19 status was determined in samples of bone marrow (local Investigator assessment) by flow cytometry.
As of the cut-off date (07-Feb-2024), 28 infused patients in Cohort IIA had relapsed (by IRRC assessment) prior to receiving any new non-protocol anticancer therapies (including stem cell transplant): 13 patients (46.4%) were CD19-negative, 12 patients (42.9%) were CD19-positive, and 3 patients (10.7%) had a mixed CD19 status (Table 34).

Table 34: CD19 Status at Relapse (Cohort IIA, Infused Set)

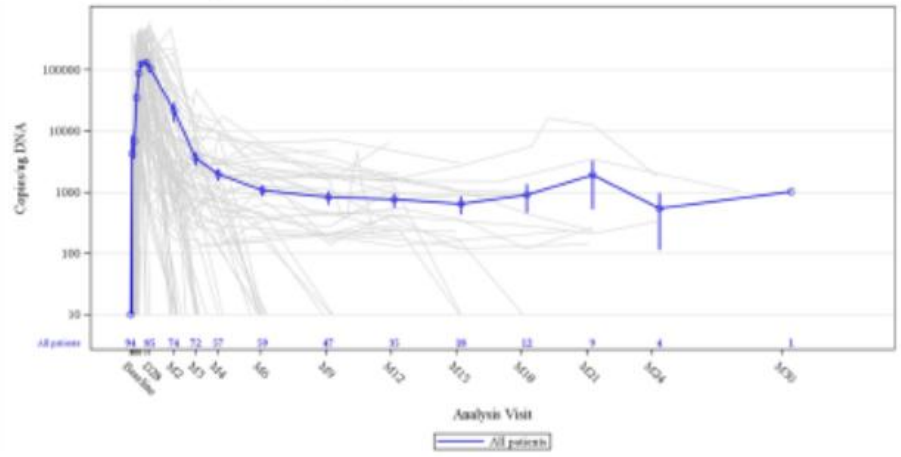
	Infused (N=94) n (%)
Relapse per IRRC assessment prior to new non-protocol anticancer therapies including SCT - n (%) [1]	28 (29.8)
CD19 status at relapse - n (%) [2]	
Positive	12 (42.9)
Negative	13 (46.4)
Mixed population	3 (10.7)

Abbreviations: IRRC = Independent Response Review Committee; SCT = stem cell transplantation.
CD19 status was based on local Investigator assessment. The CD19 result needed to be within ± 14 days of the relapse date by IRRC assessment.
[1] Percent based on the number of infused patients.
[2] Percent based on the number of relapsed patients.
Data cut-off: 07-Feb-2024

Results of subgroup analyses presented by the applicant are generally supportive towards the main analysis.

In addition:
Figure 2 presents the overall exposure to obe-cel over time in patients infused in Cohort IIA as of the latest cut-off date (07-Feb-2024):

Figure 2: CAR T Cell Pharmacokinetic Profile: Mean (SE) and Individual Concentration vs Time Profiles of Obe-cel Transgene Levels in Peripheral Blood (Cohort IIA, Infused Set)



CAR=chimeric antigen receptor; D=day; M=month; SE=standard error of the mean estimate.
The blue line indicates mean (± SE) concentration of transgene level in peripheral blood over time; gray lines indicate individual patient concentrations over time. Obe-cel transgene levels measured by droplet digital polymerase chain reaction.
Data cut-off: 07-Feb-2024.

There is prompt expansion followed by a decrease to a plateau.

Patient reported outcome tools.
The applicant collected data on (i) ECOG status, (ii) the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30) and (iii) the EuroQol. These tools and the data are presented below.

ECOG Performance Status

ECOG scores are summarised in the following table:

Appendix 2: Eastern Cooperative Oncology Group Performance Status Score

Grade	Eastern Cooperative Oncology Group Performance Status
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g. light house work, office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead

The applicant states:
Eastern Cooperative Oncology Group (ECOG)performance status was reported as Grade 3 or 4 on Day 28, primarily in patients with ≥ 5% blasts in the bone marrow at lymphodepletion (7 patients [8.3%] with Grade 3 and 2 patients [2.4%] with Grade 4 worsening of ECOG performance status).

3 patients (10.3%) in the subgroup of patients with < 5% blasts in the bone marrow without extramedullary disease had ECOG performance status Grade 3 on Day 28.

No Grade 3 or 4 events of ECOG performance status were observed at Month 6 (Table 14.3.7.1.1, as shown below).

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Table 14.3.7.1.1 ECOG Performance Status by Visit
By Disease status at Pre-conditioning
Safety Set - Phase Ib and Phase II - All Cohorts

Visit		Total (N=127) n (%)
Baseline	n	127
	Grade 0	48 (37.8)
	Grade 1	72 (56.7)
	Grade 2	7 (5.5)
	Grade 3	0
	Grade 4	0
	Grade 5	0
Day 28	n	119
	Grade 0	40 (33.6)
	Grade 1	57 (47.9)
	Grade 2	10 (8.4)
	Grade 3	10 (8.4)
	Grade 4	2 (1.7)
	Grade 5	0

BM = bone marrow; EMD = extramedullary disease.
"Prior to Enrollment" was defined as the last available measurement prior to enrollment.
"Prior to Pre-conditioning" was defined as the last available measurement after enrollment and prior to the start of pre-conditioning.
"Baseline" was defined as the last available measurement prior to the first dose of obe-cel infusion.

Table 14.3.7.1.1 ECOG Performance Status by Visit
By Disease status at Pre-conditioning
Safety Set - Phase Ib and Phase II - All Cohorts

Visit		Total (N=127) n (%)
Month 3	n	92
	Grade 0	41 (44.6)
	Grade 1	42 (45.7)
	Grade 2	6 (6.5)
	Grade 3	3 (3.3)
	Grade 4	0
	Grade 5	0
Month 6	n	74
	Grade 0	38 (51.4)
	Grade 1	33 (44.6)
	Grade 2	3 (4.1)
	Grade 3	0
	Grade 4	0
	Grade 5	0
Month 12	n	31
	Grade 0	19 (61.3)
	Grade 1	10 (32.3)
	Grade 2	2 (6.5)
	Grade 3	0
	Grade 4	0
	Grade 5	0
Month 18	n	10
	Grade 0	7 (70.0)
	Grade 1	3 (30.0)
	Grade 2	0
	Grade 3	0
	Grade 4	0
	Grade 5	0

Additional health-related quality of life measures will be collected prior to obe-cel infusion and periodically after obe-cel infusion as per the Schedule of Assessments. The instruments are the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30) and the EuroQol (EQ- 5D-5L and visual analog scale [VAS]).

Both questionnaires are widely used.

Interpretation will be based on published reference data and available thresholds of meaningful changes. Descriptive statistics (e.g. mean, median and frequency) and change from baseline of the summary scores for each post baseline time window of assessment will be summarised. Missing data will be noted on appropriate tables/listings.

Mixed-effect models may be explored to assess the change over time in the presence of missing data.

The Infused Set will be used for all analyses.

European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30)

COAT checklist for EORTC QLQ-C30

Name of COAT	EORTC QLQ-C30 Version 3.0 is the current standard version. To note that the applicant has not confirmed the version of the COAT used in this study.	
Existing COAT or novel?	existing	
Concept of interest	Single concept is not identified	
Conceptual framework	Number of items 30	Domains Complex array described on next page
Endpoint position	Within supportive end-points	
Has applicant submitted: • COAT sheet (or electronic image)? • Instructions given to patients? • training given to the interviewer?	To note that the applicant has not submitted the COAT, an instruction set or described if training was given.	
Administration mode	Not stated	
Response options	Combination of 1-4 and 1-7 Likert scales	
Recall period	The past week	
Scoring	Complex scoring system is described on next page	
Burden	30 questions per questionnaire attempt is considered to represent a high burden; a high drop-out may be anticipated	
How often completed during study	Baseline, month 1, month 3, month 6, month 9, month 12.	
Content validity	Not described by the applicant	
Reliability	Not described by the applicant	
Ability to detect change	Not described by the applicant	
Handling of missing data	The applicant states that a ‘mixed-effects model’ may be used to explore missing data.	

The applicant presents data by symptoms, functioning and global health scores from the EORTC QLQ-C30 questionnaire.

The following table extract is for the global health scores by disease status at lymphodepletion (the applicant also presents data by responder analysis i.e. responder v. non-responder). All tables presented by the applicant show a similar pattern to that of table 14.4.2.3.1.iia

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Table 14.4.2.3.1.iia Summary of EORTC QLQ-C30 Global Health Status and Change from Baseline
Safety Set - Phase II - Cohort A

	>=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)	
Parameter / Visit	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Global health status/QoL								
Baseline								
n	51		17		3		71	
Mean (SD)	59.64 (21.818)		65.20 (22.676)		58.33 (38.188)		60.92 (22.475)	
Median	58.33		66.67		50.00		58.33	
Q1 - Q3	41.67 - 75.00		50.00 - 83.33		25.00 - 100.00		50.00 - 83.33	
Min - Max	16.7 - 100.0		16.7 - 100.0		25.0 - 100.0		16.7 - 100.0	
Day 28								
n	46	36	15	14	5	3	66	53
Mean (SD)	56.34 (27.954)	-7.64 (33.117)	55.56 (27.936)	-11.31 (32.785)	76.67 (23.124)	19.44 (26.788)	57.70 (27.785)	-7.08 (32.865)
Median	58.33	0.00	58.33	-8.33	75.00	8.33	58.33	0.00
Q1 - Q3	33.33 - 75.00	-29.17 - 12.50	41.67 - 66.67	-16.67 - 16.67	58.33 - 100.00	0.00 - 50.00	41.67 - 75.00	-25.00 - 16.67
Min - Max	0.0 - 100.0	-83.3 - 66.7	0.0 - 100.0	-83.3 - 25.0	50.0 - 100.0	0.0 - 50.0	0.0 - 100.0	-83.3 - 66.7
Month 3								
n	40	27	16	15	4	2	60	44
Mean (SD)	76.04 (17.212)	9.88 (28.592)	76.04 (11.736)	8.89 (22.596)	58.33 (15.215)	20.83 (5.893)	74.86 (16.201)	10.04 (25.831)
Median	83.33	0.00	79.17	0.00	58.33	20.83	79.17	0.00
Q1 - Q3	66.67 - 83.33	-8.33 - 33.33	66.67 - 83.33	0.00 - 25.00	45.83 - 70.83	16.67 - 25.00	66.67 - 83.33	-4.17 - 25.00
Min - Max	33.3 - 100.0	-33.3 - 83.3	50.0 - 100.0	-33.3 - 50.0	41.7 - 75.0	16.7 - 25.0	33.3 - 100.0	-33.3 - 83.3
Month 6								
n	27	20	10	9	2	1	39	30
Mean (SD)	83.02 (16.583)	25.83 (27.023)	66.67 (32.632)	0.00 (34.106)	79.17 (17.678)	41.67 ( )	78.63 (22.360)	18.61 (31.002)
Median	83.33	20.83	70.83	0.00	79.17	41.67	83.33	16.67
Q1 - Q3	75.00 - 100.00	12.50 - 37.50	50.00 - 100.00	0.00 - 16.67	66.67 - 91.67	41.67 - 41.67	66.67 - 100.00	0.00 - 33.33
Min - Max	41.7 - 100.0	-16.7 - 83.3	0.0 - 100.0	-83.3 - 41.7	66.7 - 91.7	41.7 - 41.7	0.0 - 100.0	-83.3 - 83.3

	>=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)	
Parameter / Visit	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Global health status/QoL								
Month 9								
n	19	13	4	4	1	0	24	17
Mean (SD)	73.25 (22.323)	23.08 (26.604)	66.67 (22.567)	2.08 (37.500)	66.67 ( )		71.88 (21.537)	18.14 (29.644)
Median	83.33	25.00	75.00	12.50	66.67		83.33	25.00
Q1 - Q3	66.67 - 83.33	0.00 - 41.67	54.17 - 79.17	-25.00 - 29.17	66.67 - 66.67		66.67 - 83.33	0.00 - 33.33
Min - Max	0.0 - 100.0	-16.7 - 66.7	33.3 - 83.3	-50.0 - 33.3	66.7 - 66.7		0.0 - 100.0	-50.0 - 66.7
Month 12								
n	12	9	4	4	0	0	16	13
Mean (SD)	79.86 (22.879)	21.30 (36.351)	70.83 (15.957)	8.33 (28.868)			77.60 (21.239)	17.31 (33.586)
Median	87.50	25.00	75.00	8.33			83.33	25.00
Q1 - Q3	66.67 - 100.00	-8.33 - 41.67	58.33 - 83.33	-16.67 - 33.33			66.67 - 100.00	-16.67 - 33.33
Min - Max	33.3 - 100.0	-33.3 - 83.3	50.0 - 83.3	-16.7 - 33.3			33.3 - 100.0	-33.3 - 83.3

Improvement was defined as a >=10-point increase from baseline in global health status. Deterioration was defined as a >=10-point decrease from baseline in global health status.
The MID was defined as a >=10-point change in either direction.
"Baseline" was defined as the last available measurement prior to the first dose of obe-cel infusion.

Only 2 subjects have returned data for month 18.

The applicant states that: starting at Month 3, and in all subsequent months, average global health scores exceeded baseline scores to levels indicative of meaningful improvement and remained at that level throughout the 12 months.

Only 71 subjects out of total 94 appear to have submitted data at baseline; this falls to 53 subjects at month 1, 44 subjects at month 3, 30 subjects at month 6, 17 subjects at month 9 and 13 subjects at month 12 i.e. the applicant presents an available case analysis.

At baseline, the min observed score = 16.7 and the max observed score = 100.

By day 28: the min change score = -83.3 and the max change score = +66.7 i.e. some fare better and some fare worse.

The general pattern at day 28 persists to month 12 where the min change score = -33.3 and the max change score = +83.3 i.e. some fare better and some fare worse

It is not possible to concur with the applicant the scores indicate "meaningful improvement" to month 12.

EQ-5D-5L

The EQ-5D-5L assesses an adult subject's health status in a standardised way, is widely used in multiple diseases and consists of 2 parts: the EQ-5D-5L descriptive system and the EQ VAS.

The EQ-5D-5L descriptive system comprises 5 dimensions: mobility, self-care, usual activities, pain / discomfort and anxiety / depression.

The EQ-5D-5L descriptive system is expressed as an index score normalised to US or UK value sets.

The EQ VAS records the subject's self-rated health and can be used as a quantitative measure of health as judged by the individual respondents. For both components, higher values indicate better health status.

Studies of the EQ-5D-5L have shown that patients with transfusion-dependent β-thalassemia typically report near-normal health index scores despite their condition.

Results of the EQ-5D-L visual analogue tool are shown:

Table 38: Summary of EQ-5D-5L Questionnaire Visual Analogue Scale Results and Change from Baseline 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)	
Parameter / Visit	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Baseline								
n	50		17		3		70	
Mean (SD)	64.72 (21.449)		65.65 (22.550)		60.00 (36.056)		64.74 (21.988)	
Median	60.50		70.00		50.00		67.00	
Q1 - Q3	51.00 - 81.00		50.00 - 80.00		30.00 - 100.00		50.00 - 81.00	
Min - Max	20.0 - 100.0		25.0 - 100.0		30.0 - 100.0		20.0 - 100.0	
Day 28								
n	46	35	15	14	5	3	66	52
Mean (SD)	66.54 (25.381)	-1.91 (30.793)	63.87 (24.145)	-3.14 (33.768)	74.40 (26.482)	5.33 (22.480)	66.53 (24.922)	-1.83 (30.759)
Median	73.00	-1.00	69.00	-4.00	81.00	0.00	70.00	-1.50
Q1 - Q3	50.00 - 89.00	-25.00 - 17.00	41.00 - 81.00	-19.00 - 15.00	60.00 - 95.00	-14.00 - 30.00	50.00 - 89.00	-19.50 - 16.00
Min - Max	0.0 - 100.0	-72.0 - 70.0	10.0 - 100.0	-80.0 - 60.0	36.0 - 100.0	-14.0 - 30.0	0.0 - 100.0	-80.0 - 70.0
Month 6								
n	26	20	10	9	2	1	38	30
Mean (SD)	80.46 (15.324)	16.50 (23.719)	71.80 (25.871)	12.78 (33.951)	74.50 (6.364)	29.00 (NE)	77.87 (18.381)	15.80 (26.377)
Median	81.00	10.00	72.50	18.00	74.50	29.00	80.00	10.00
Q1 - Q3	70.00 - 91.00	2.00 - 25.00	65.00 - 90.00	5.00 - 40.00	70.00 - 79.00	29.00 - 29.00	70.00 - 91.00	4.00 - 30.00
Min - Max	46.0 - 100.0	-21.0 - 70.0	10.0 - 100.0	-66.0 - 48.0	70.0 - 79.0	29.0 - 29.0	10.0 - 100.0	-66.0 - 70.0
Month 12								
n	12	9	4	4	0	0	16	13
Mean (SD)	78.58 (26.103)	12.22 (37.292)	84.50 (9.469)	23.50 (24.283)			80.06 (22.904)	15.69 (33.225)
Median	88.00	10.00	87.50	18.50			88.00	10.00
Q1 - Q3	65.50 - 96.00	-10.00 - 34.00	78.00 - 91.00	4.50 - 42.50			70.50 - 92.00	2.00 - 34.00
Min - Max	9.0 - 100.0	-48.0 - 70.0	71.0 - 92.0	2.0 - 55.0			9.0 - 100.0	-48.0 - 70.0

BM = Bone marrow; EMD = Extramedullary disease; NE=Not estimable; Q=Quarter; SD=Standard deviation
Baseline was defined as the last available measurement prior to the first dose of obe-cel infusion.
EQ-5D-5L visual analog scale (VAS) recorded the respondent's self-rated health status on a graduated (0-100) scale, with higher scores for higher quality of life.BM = Bone marrow; EMD = Extramedullary disease.
Data cut-off: 09-June-2023

<u>The applicant states:</u>
In 70 patients infused with obe-cel in Cohort IIA with a CR or CRi and evaluable scores, the mean [SD] observed visual analogue scale score was 64.74 (SD 21.988) at baseline (last available measurement before obe-cel infusion).
The longitudinal trajectory of patients' visual analogue scale scores showed an expected reduction in health state from baseline to Day 28 (mean change of – 1.83 from baseline, Table 38) but not to a level indicating meaningful deterioration.
Starting at Month 3, and in all subsequent months, median scores exceeded baseline scores to levels indicative of meaningful improvement 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).

94 subjects were available to report on the EQ-5D-5L questionnaire yet only 70 are recorded at baseline; 52 subjects at day 28; 30 subjects at month 6; and 13 subjects at month 12. The applicant presents available case summaries in table 38 i.e. results are likely biased as a result of drop-outs / deaths.

Irrespective: data in table 38 for change from baseline show negative mins and positive maxs with a wide range of score i.e. some fare better and some fare worse.

It is not concurred that scores demonstrate 'meaningful improvement'.

Table 67: Hospitalizations Post-obe-cel Infusion by Disease Status at Lymphodepletion (Phase Ib/Phase II, Safety Set)

	≥ 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)
Hospitalization post-obe-cel [1]				
General hospitalization post-obe-cel	91 (100)	29 (100)	7 (100)	127 (100)
Duration of 1st hospitalization post-obe-cel infusion (days)				
n	91	29	7	127
Mean (SD)	27.3 (16.41)	19.6 (10.52)	19.6 (12.62)	25.1 (15.38)
Median	22.0	16.0	15.0	20.0
Min - Max	9 - 90	8 - 59	13 - 48	8 - 90
Patients re-admitted hospitalization - n (%) [2]	37 (40.7)	20 (69.0)	3 (42.9)	60 (47.2)
Total duration of hospitalization (days)				
n	91	29	7	127
Mean (SD)	40.5 (23.31)	43.8 (37.91)	31.0 (35.16)	40.7 (27.82)
Median	35.0	34.0	16.0	35.0
Min – Max	9 - 116	8 - 169	13 - 110	8 - 169
Duration of hospitalization within 28 days post-obe-cel infusion (days)				
n	91	29	7	127
Mean (SD)	22.5 (5.49)	18.6 (6.11)	16.7 (5.19)	21.3 (5.92)
Median	23.0	17.0	15.0	22.0
Min – Max	9 - 28	8 - 28	13 - 28	8 - 28
Patients admitted to ICU - n (%) [2]	18 (19.8)	1 (3.4)	1 (14.3)	20 (15.7)
Total duration of ICU stay (days) [2]				
n	18	1	1	20
Mean (SD)	9.4 (10.67)	20.0 ( )	26.0 ( )	10.8 (10.97)
Median	5.0	20.0	26.0	5.5
Min – Max	1 - 37	20 - 20	26 - 26	1 - 37
Initial Reason for ICU - n (%)				
Adverse event other than CRS/ICANS	11 (12.1)	1 (3.4)	1 (14.3)	13 (10.2)
ICANS	5 (5.5)	0	0	5 (3.9)
Technical/Social/Practical reasons	3 (3.3)	0	0	3 (2.4)
CRS	2 (2.2)	0	0	2 (1.6)
Disease progression	1 (1.1)	0	0	1 (0.8)

Abbreviations: BM = bone marrow; CRS = cytokine release syndrome; EMD = extramedullary disease; ICANS = immune effector cell-associated neurotoxicity syndrome; ICU = intensive care unit; SD = standard deviation.
[1] Hospitalization with admission or discharge after start of obe-cel were summarized. Percentage and summary below were based on N.
[2] Only patients admitted to ICU post-obe-cel were summarized. Duration of ICU stay for each hospitalization was calculated as the duration between first entry to ICU to last discharge from ICU during each hospitalization.
Data cut-off: 07-Feb-2024

The applicant presents data for all cohorts.

Subjects were admitted to hospital for between 8 and 169 days.
ICANS and CRS are noted as reasons for admission to an intensive care unit yet total numbers and percentages are small, as shown in the above table.

Summary of clinical efficacy

Design

The FELIX study is an on-going open-label, uncontrolled, non-randomised clinical study that has recruited adult subjects with relapsed or refractory CD19-positive B-cell acute lymphoblastic leukaemia.

The study is divided into 5 cohorts:

- Primary Cohort IA: Adults aged ≥18 years with B-cell acute lymphoblastic leukaemia

who had relapsed / refractory disease and ≥5% blasts in the bone marrow at screening.
- Exploratory Cohort IB: Adults aged ≥18 years with B-cell acute lymphoblastic leukaemia in morphological remission with minimal / measurable residual disease (≥10^{-4} and <5% blasts in the bone marrow at screening).

and

- Cohort IIA: Adults aged ≥18 years with B-cell acute lymphoblastic leukaemia who had relapsed / refractory disease and presence of ≥5% blasts in the bone marrow at screening.
- Cohort IIB: Adults aged ≥18 years with B-cell acute lymphoblastic leukaemia in ≥2nd complete response or "complete response with incomplete haematologic recovery" with minimal / measurable residual disease (≥10^{-3} and <5% blasts in the bone marrow at screening).
- Cohort IIC (exploratory cohort): Adults aged ≥18 years with B-cell acute lymphoblastic leukaemia with isolated extramedullary disease (including isolated central nervous system disease), with or without minimal / measurable residual disease.

Conduct

153 subjects have been enrolled into the FELIX study and 127 subjects have been administered obe-cel. The main analysis population of the applicant is cohort IIA:
Demographics of those enrolled into cohort IIA are similar to those infused. Thus:
For the 112 subjects enrolled into phase IIA: median age 49yrs (min 20yrs, max 81yrs); 65% subjects were >40yrs; 54% male; 77% White.
Cohort IIA is composed of 94 subjects: median age 50yrs (min 20yrs, max 81yrs); 67% subjects were >40yrs; 50% male; 74% White.

Disease characteristics of those enrolled into cohort IIA are similar to those infused. Thus:
For the 112 subjects enrolled into cohort IIA:

Subjects had received between 1 and 6 prior therapies with a median of 2; 13 had disease that was refractory to all previous therapies; 43 had received a stem cell transplant; 58 had received blinatumomab or inotuzumab ozogamicin; 45 had a complex karyotype and 25 returned a positive result for the Philadelphia chromosome. At lymphodepletion: 21 had extramedullary disease; 30 had >75% blasts in bone marrow; 27 had >20 to 75% bone marrow blasts and 37 had up to 20% bone marrow blasts (with 18 'not applicable').

18 subjects discontinued the study without receiving an obe-cel infusion – 11 subjects died before infusion, 5 did not receive the drug due to manufacturing issues, 1 subject had an adverse event and 1 subject discontinued due to physician's decision.

For the phase IIA cohort of 94 subjects who were administered product:
Subjects had received between 1 and 6 prior therapies with a median of 2; 12 subjects had disease that was refractory to all previous therapies; 36 subjects had received a stem cell transplant; 48 subjects had received blinatumomab or inotuzumab ozogamicin and 25 subjects returned a positive result for the Philadelphia chromosome.

At lymphodepletion: 19 had extramedullary disease; 30 had >75% blasts in bone marrow; 27 had >20 to 75% bone marrow blasts and 37 had up to 20% bone marrow blasts.

Subjects underwent leukapheresis to obtain material that was sent to a distant site for manufacture of obe-cel; bridging therapies were allowed.

A bone marrow assessment was available from a biopsy and / or aspirate sample obtained within 7 days prior to the commencement of the lymphodepleting chemotherapy. Prior to lymphodepletion: 19/94 had extramedullary disease; 30/94 had >75% blasts in bone marrow; 27/94 had >20 to 75% bone marrow blasts and 37/94 had up to 20% bone marrow blasts. Bone marrow assessment was used to determine the obe-cel dosage regimen based on tumour burden. Subjects underwent lymphodepletion (at day -6 to day -3 before exposure to obe-cel) with a regimen of fludarabine and cyclophosphamide. Cyclophosphamide and fludarabine dosing are described below; fludarabine was administered first.

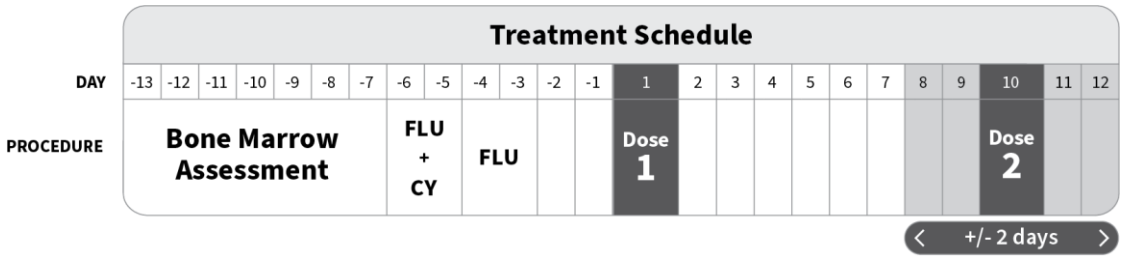
- Fludarabine 30 mg/m^2 followed by cyclophosphamide 500 mg/m^2 day 1 (Day -6)
- Fludarabine 30 mg/m^2 followed by cyclophosphamide 500 mg/m^2 day 2 (Day -5)
- Fludarabine 30 mg/m^2 (Day -4)
- Fludarabine 30 mg/m^2 (Day -3)

Obe-cel was administered as a split dose according to tumour load.

Low tumour burden regimen (bone marrow lymphoblasts make up ≤20% of total number of nucleated cells of bone marrow):
- Day 1: 100 x 10^6 cells administered via bag infusion
- Day 10 (±2days): 10 x 10^6 cells administered via syringe and 300 x 10^6 cells administered via bag infusion

High tumour burden regimen (bone marrow lymphoblasts make up >20% of total number of nucleated cells of bone marrow):
- Day 1: 10 x 10^6 cells administered via syringe
- Day 10 (±2days): 100 x 10^6 cells administered via bag infusion and 300 x 10^6 dose administered via bag infusion

The treatment schedule is summarised in the following diagram (administration of the second dose was delayed to up to 21 days if the recipient was experiencing significant toxicities):



CY=cyclophosphamide; FLU=fludarabine

The median time from leukapheresis to product release was 20 days (range: 17 to 43) and the median time from leukapheresis to obe-cel infusion was 36 days (range: 25 to 92).
For the 94 patients in the infused set, the median dose received was 410 × 10^6 CD19 CAR-positive viable T cells (range: 10 to 480 × 10^6).
85 patients (90.4%) received the total target dose of 410 × 10^6 CD19 CAR-positive viable T cells.

6 patients (6.4%) received the first dose only, primarily due to adverse events (3.2%), progressive disease (1.1%), manufacturing related issues (1.1%), and death (1.1%).

3 patients received a dose different to the target dose.

Outcomes and analysis

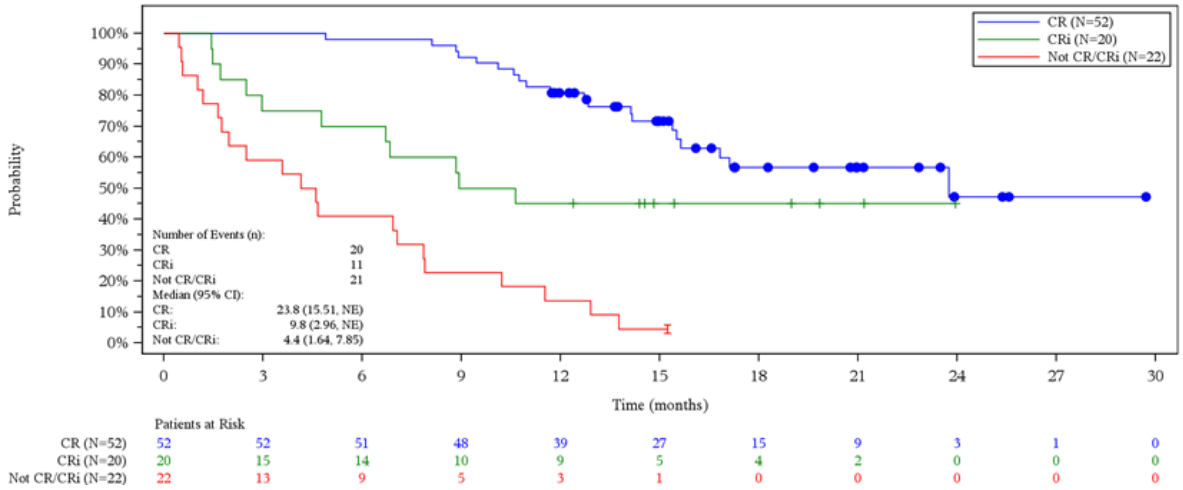
For cohort IIA, the infused set: 52/94 subjects show complete remission (CR); 20/94 show incomplete haematology response (CRi) and 22/94 show neither CR nor CRi.

- Those who show complete remission show 98% overall survival at month 6 and 81% overall survival at month 12; these overall survival data are considered most notable.
- Those who show incomplete haematology response (CRi) show 70% overall survival at month 6 and 45% overall survival at month 12; these subjects fare much worse compared to the CR subgroup.
- Those who show neither CR nor CRi show 41% overall survival at month 6 and 14% overall survival at month 12; these subjects fare worst of all in terms of overall survival.

94 subjects were infused with obe-cel; of these, 52 discontinued the study (50 died and 1 withdrew) and 42 are in ongoing follow-up.

Overall survival is summarised in the following figure and table:

Figure 1: Kaplan-Meier Plot of Overall Survival Without Censoring SCT as Assessed by IRRC (Cohort IIA, Infused Set)



Abbreviations: CI = confidence interval; CR = complete remission; CRi = complete remission with incomplete haematologic recovery; IRRC = Independent Response Review Committee; NE = not estimable; SCT = stem cell transplantation.

Median with 95% CIs are calculated from PROC LIFETEST output method.
Cut off date: 07-Feb-2024.

Table 2: Overall Survival Without Censoring SCT By Best Overall Response with Disease Assessment by IRRC (Cohort IIA, Infused Set)

	CR (N=52) n (%)	CRi (N=20) n (%)	Not CR/CRi (N=22) n (%)	Total (N=94) n (%)
No. of patients in analysis[1]	52	20	22	94
No. of events - n (%)	20 (38.5)	11 (55.0)	21 (95.5)	52 (55.3)
Death	20 (38.5)	11 (55.0)	21 (95.5)	52 (55.3)
No. of censored observations - n (%)	32 (61.5)	9 (45.0)	1 (4.5)	42 (44.7)
Alive	32 (61.5)	9 (45.0)	1 (4.5)	42 (44.7)
Quartile Estimates (95% CI) [month][2]				
50th	23.75 (15.51, NE)	9.79 (2.96, NE)	4.37 (1.64, 7.85)	14.16 (10.97, 23.75)
Event-free probability estimate (95% CI)[3]				
6 months	98.1 (87.1, 99.7)	70.0 (45.1, 85.3)	40.9 (20.9, 60.1)	78.7 (69.0, 85.7)
12 months	80.8 (67.2, 89.2)	45.0 (23.1, 64.7)	13.6 (3.4, 30.9)	57.4 (46.8, 66.7)
18 months	56.7 (40.0, 70.4)	45.0 (23.1, 64.7)	NE	41.1 (30.0, 51.8)

Abbreviations: CI = confidence interval; CR = complete remission; CRi = complete remission with incomplete haematologic recovery; IRRC = Independent Response Review Committee; NE = not estimable; SCT = stem cell transplantation.

[1] The analysis includes all patients in the Infused Set – Cohort IIA.

[2] Percentiles with 95% CIs are calculated from PROC LIFETEST output method.

[3] % Event-free probability estimates are obtained from the Kaplan-Meier survival estimates, with 95% CIs estimated using Greenwood formula.

Cut off date: 07-Feb-2024.

Overall conclusion on clinical efficacy

The study is presented as a sequence of treatments and so the primary efficacy population for this study is considered to be the “cohort IIA infused” population.

For the 52/94 subjects in cohort IIA who achieved complete remission (as defined by the applicant) the data on overall survival (81% at 12 months after exposure to obe-cel) are most notable.

Additional information on cohorts IIB and IIC of the FELIX study

In addition: the applicant has also submitted data for subjects in cohort IIB and IIC, as shown below

Table 1: Summary of Demographics in FELIX

	Phase II		
	Cohort A Infused n = 94	**Cohort B Infused n = 10**	**Cohort C Infused n = 7**
Age (years)			
N	94	10	7
Mean (SD)	48.3 (17.12)	49.4 (15.54)	34.4 (10.31)
Median	50.0	46.0	32.0
Q1 - Q3	33.0 - 62.0	39.0 - 63.0	26.0 - 39.0
Min - Max	20 - 81	26 - 73	23 - 54
Age (years) categorised – n (%)			
≥ 18 to ≤ 25	11 (11.7)	0	1 (14.3)
> 25 to < 40	20 (21.3)	3 (30.0)	5 (71.4)
≥ 40 to < 65	42 (44.7)	5 (50.0)	1 (14.3)
≥ 65	21 (22.3)	2 (20.0)	0
Age (years) categorised – n (%)			
< 65	73 (77.7)	8 (80.0)	7 (100)
≥ 65	21 (22.3)	2 (20.0)	0
≥ 65 to < 75	17 (18.1)	2 (20.0)	0
≥ 75 to < 85	4 (4.3)	0	0
≥ 85	0	0	0
Sex – n (%)			
Male	47 (50.0)	7 (70.0)	2 (28.6)
Female	47 (50.0)	3 (30.0)	5 (71.4)
Race – n (%)			
Asian	10 (10.6)	1 (10.0)	2 (28.6)
Black or African American	2 (2.1)	0	0
White	70 (74.5)	9 (90.0)	4 (57.1)
Unknown	12 (12.8)	0	1 (14.3)
Ethnicity – n (%)			

	Phase II		
	Cohort A Infused n = 94	**Cohort B Infused n = 10**	**Cohort C Infused n = 7**
Hispanic or Latino	29 (30.9)	2 (20.0)	3 (42.9)
Not Hispanic or Latino	58 (61.7)	8 (80.0)	3 (42.9)
Unknown	7 (7.4)	0	1 (14.3)
Country – n (%)			
United States	47 (50.0)	4 (40.0)	5 (71.4)
United Kingdom	36 (38.3)	5 (50.0)	2 (28.6)
Spain	11 (11.7)	1 (10.0)	0
Region – n (%)			
North America	47 (50.0)	4 (40.0)	5 (71.4)
Europe	47 (50.0)	6 (60.0)	2 (28.6)

Abbreviations: Q=quartile; SD=standard deviation.
Infused set comprises of all patients who have received at least one infusion of obe-cel.

Table 2: Disease Characteristics at Screening in FELIX

	Phase II		
	Cohort A Infused n = 94	**Cohort B Infused n = 10**	**Cohort C Infused n = 7**
Number of prior lines of therapy			
n	94	10	7
Mean (SD)	2.2 (1.08)	2.4 (0.70)	2.6 (0.79)
Median	2.0	2.5	2.0
Q1 - Q3	1.0 - 3.0	2.0 - 3.0	2.0 - 3.0
Min - Max	1 - 6	1 - 3	2 - 4
Number of prior lines of therapy categorised - n (%)			
1	29 (30.9)	1 (10.0)	0
2	36 (38.3)	4 (40.0)	4 (57.1)
3	17 (18.1)	5 (50.0)	2 (28.6)
≥ 4	12 (12.8)	0	1 (14.3)
Refractory to all prior lines of anti-cancer therapy – n (%)	12 (12.8)	1 (10.0)	0
Refractory to first line therapy – n (%)	24 (25.5)	2 (20.0)	3 (42.9)

	Phase II				
	Cohort A Infused n = 94	**Cohort B Infused n = 10**	**Cohort C Infused n = 7**		
Refractory to last prior line of therapy: – n (%)	51 (54.3)	4 (40.0)	2 (28.6)		
Relapsed to first line therapy within 12 months – n (%)	41 (43.6)	8 (80.0)	3 (42.9)		
Previous allogeneic stem cell transplantation – n (%)	36 (38.3)	7 (70.0)	4 (57.1)		
Previous blinatumomab – n (%)	33 (35.1)	5 (50.0)	6 (85.7)		
Previous inotuzumab ozogamicin – n (%)	30 (31.9)	3 (30.0)	2 (28.6)		
Previous blinatumomab and inotuzumab ozogamicin – n (%)	15 (16.0)	2 (20.0)	1 (14.3)		
Previous blinatumomab or inotuzumab ozogamicin – n (%)	48 (51.1)	6 (60.0)	7 (100)		
Bone marrow blasts (%) by morphology prior to enrolment [1]					
n	94	10	7		
Mean (SD)	53.4 (33.15)	1.6 (1.62)	0.7 (1.19)		
Median	58.9	1.5	0.0		
Q1 - Q3	20.0 - 86.0	0.0 - 2.0	0.0 - 1.6		
Min - Max	6 - 100	0 - 5	0 - 3		
Bone marrow blasts (%) by morphology prior to enrolment categorised – n (%) [1]					
> 75%	34 (36.2)	0	0		
> 20%-≤ 75%	32 (34.0)	0	0		
≥ 5%-≤ 20%	28 (29.8)	1 (10.0)	0		
< 5%	0	9 (90.0)	7 (100)		
Missing	0	0	0		
Bone marrow blasts (%) by morphology prior to enrolment categorised – n (%) [1]					
≤ 20%	28 (29.8)	10 (100)	7 (100)		
> 20%	66 (70.2)	0	0		
Extramedullary disease status prior to enrolment – n (%)					
Absent	75 (79.8)	10 (100)	0		
Present	19 (20.2)	0	7 (100)		
CNS	2 (2.1)	0	0		

	Phase II		
	Cohort A Infused n = 94	**Cohort B Infused n = 10**	**Cohort C Infused n = 7**
Mediastinal Lymph Node	2 (2.1)	0	0
Testis	1 (1.1)	0	0
Other	15 (16.0)	0	7 (100)
ECOG score [2] – n (%)			
0	35 (37.2)	5 (50.0)	4 (57.1)
1	58 (61.7)	5 (50.0)	3 (42.9)
2	0	0	0
> 2	0	0	0
Missing	1	0	0
CD19 status prior to enrolment (by flow cytometry) – n (%)			
Positive	94 (100)	10 (100)	7 (100)
Negative	0	0	0
Mixed population (positive + negative)	0	0	0
Unknown	0	0	0
CNS disease history – n (%) [3]			
CNS1	81 (86.2)	9 (90.0)	7 (100)
CNS2	2 (2.1)	0	0
CNS3	0	0	0
Unknown	11 (11.7)	1 (10.0)	0

Abbreviations: CNS=central nervous system; CSF=cerebrospinal fluid; ECOG=Eastern Cooperative Oncology Group; Q=quartile; SD=standard deviation; WBC=white blood cell(s).
[1] Bone marrow blast (%) was determined by morphology as the highest value from bone marrow aspirate and trephine at screening.
[2] ECOG based on last non-missing value from screening period prior to leukapheresis.
[3] CNS-1 = No lymphoblasts in CSF regardless of WBC count; CNS-2 = WBC < 5/µL in CSF with presence of lymphoblasts; CNS-3 = WBC ≥ 5/µL in CSF with presence of lymphoblasts.

Table 3: Disease Characteristics at the Time of Lymphodepleting Therapy in FELIX

	Phase II		
	Cohort A Infused n = 94	**Cohort B Infused n = 10**	**Cohort C Infused n = 7**
Patients who received pre-conditioning therapy – n (%)	94 (100)	10 (100)	7 (100)
Bone marrow blasts (%) by morphology prior to LD [1]			
n	94	10	7
Mean (SD)	45.1 (37.39)	18.8 (30.91)	30.9 (40.67)
Median	43.5	0.6	5.0

	Phase II			
	Cohort A Infused n = 94	**Cohort B Infused n = 10**	**Cohort C Infused n = 7**	
Q1 - Q3	5.0 - 85.6	0.0 - 35.0	1.0 - 80.0	
Min - Max	0 - 100	0 - 95	1 - 96	
Bone marrow blasts (%) by morphology prior to LD categorised – n (%) [1]				
≤ 20%	37 (39.4)	7 (70.0)	4 (57.1)	
> 20%	57 (60.6)	3 (30.0)	3 (42.9)	
Missing	0	0	0	
Bone marrow blasts (%) by morphology prior to LD categorised – n (%) [1]				
> 75%	30 (31.9)	1 (10.0)	2 (28.6)	
> 20%-≤ 75%	27 (28.7)	2 (20.0)	1 (14.3)	
≥ 5%-≤ 20%	14 (14.9)	1 (10.0)	1 (14.3)	
< 5%	23 (24.5)	6 (60.0)	3 (42.9)	
Missing	0	0	0	
Extramedullary disease status prior to LD – n (%)				
Absent	75 (79.8)	10 (100)	2 (28.6)	
Present	19 (20.2)	0	5 (71.4)	
CNS	1 (1.1)	0	0	
Mediastinal Lymph Node	2 (2.1)	0	1 (14.3)	
Testis	1 (1.1)	0	0	
Other	17 (18.1)	0	5 (71.4)	
Missing	0	0	0	
Karyotype				
Abnormal	66 (70.2)	6 (60.0)	2 (28.6)	
Normal	19 (20.2)	2 (20.0)	5 (71.4)	
Unknown	9 (9.6)	2 (20.0)	0	
Complex karyotype				
Yes	37 (39.4)	4 (40.0)	2 (28.6)	
No/Unknown	57 (60.6)	6 (60.0)	5 (71.4)	
Cytogenetic risk groups for B ALL [2] – n (%)				
Good risk				
Hyperdiploidy	5 (5.3)	0	0	
TEL-AML1	1 (1.1)	0	1 (14.3)	
Poor risk				
Hypodiploidy	4 (4.3)	0	0	
IL3-IGH	0	0	0	
t(10;14)	1 (1.1)	0	0	
BCR-ABL1-like	8 (8.5)	0	0	
E2A-PBX1	1 (1.1)	0	0	
Philadelphia chromosome-positive	25 (26.6)	6 (60.0)	1 (14.3)	
MLL rearrangement	6 (6.4)	0	0	
Del 17p	0	0	0	
Other abnormality	37 (39.4)	0	1 (14.3)	

Abbreviations: B ALL=B cell acute lymphoblastic leukaemia; CNS=central nervous system; LD=lymphodepletion; Q=quartile; SD=standard deviation.
[1] Bone marrow blast (%) was determined by morphology as the highest value from bone marrow aspirate and trephine.
[2] Cytogenetic risk groups based on karyotype collected from screening to pre-conditioning period. If multiple karyotypes were recorded for the same patient, the latest record was used for the patient.

Table 4: Time from Informed Consent to First Obe-cel Infusion in FELIX

	Phase II		
	Cohort A Infused n = 94	**Cohort B Infused n = 10**	**Cohort C Infused n = 7**
Time from informed consent to enrolment (days)			
n	94	10	7
Mean (SD)	23.6 (23.37)	38.1 (17.19)	26.9 (21.42)
Median	16.0	30.5	15.0
Q1 - Q3	12.0 - 26.0	27.0 - 45.0	13.0 - 50.0
Min - Max	5 - 169	21 - 80	13 - 65
Time from informed consent to first obe-cel infusion (days)			
n	94	10	7
Mean (SD)	64.9 (28.14)	91.0 (41.10)	78.9 (58.50)
Median	56.5	72.0	57.0
Q1 - Q3	49.0 - 70.0	64.0 - 112.0	49.0 - 75.0
Min - Max	36 - 219	57 - 189	49 - 210
Time from enrolment to first obe-cel infusion (days)			
n	94	10	7
Mean (SD)	41.4 (13.77)	52.9 (42.71)	52.0 (41.50)
Median	37.0	34.0	38.0
Q1 - Q3	32.0 - 47.0	32.0 - 64.0	34.0 - 46.0
Min - Max	25 - 92	29 - 168	25 - 145

Abbreviations: Q=quartile; SD=standard deviation.

Table 5: Obe-cel Exposure in FELIX

	Phase II				
	Cohort A Infused n = 94	**Cohort B Infused n = 10**	**Cohort C Infused n = 7**		
Obe-cel infusions completed/discontinued – n (%)	94 (100)	10 (100)	7 (100)		
Among patients who completed/discontinued obe-cel infusions [1]					
Calculated total CD19 CAR-positive T cells (10^6 cells)					
n	94	10	7		
Mean (SD)	376.0 (94.55)	407.2 (34.87)	409.9 (8.75)		
Median	410.0	409.5	414.0		
Q1 - Q3	405.0 - 413.0	407.0 - 412.0	407.0 - 414.0		
Min - Max	10 - 480	323 - 468	391 - 415		
Patient received both obe-cel doses	88 (93.6)	10 (100)	7 (100)		
Patient received only first obe-cel dose	6 (6.4)	0	0		
Patients receiving the target dose [2]	85 (90.4)	10 (100)	7 (100)		
Among patients who completed/discontinued obe-cel infusions [1]					
Patients not receiving the target dose	9 (9.6)	0	0		

Abbreviations: CAR=chimeric antigen receptor; CD=cluster of differentiation; Q=quartile; SD=standard deviation.

[1] All percentages below were based on number of patients who have completed or discontinued obe-cel infusions as the denominator.

[2] Target dose was 410 x 10^6 calculated CD19 CAR-positive T cells (± 25%).

Table 6: Study Follow-Up in FELIX

	Phase II			
	Cohort A Infused n = 94	**Cohort B Infused n = 10**	**Cohort C Infused n = 7**	
Duration from first obe-cel infusion to data cut-off date (months)				
n	94	10	7	
Mean (SD)	20.34 (4.765)	18.40 (6.448)	25.19 (1.716)	
Median	20.25	18.15	25.86	
Q1 - Q3	16.20 - 23.49	13.67 - 23.52	23.10 - 26.25	
Min - Max	12.7 - 29.8	8.6 - 28.7	22.6 - 27.2	
Duration from first AUTO1 infusion to data cut-off date categorised – n (%)				
< 3 months	0	0	0	
3 months to < 6 months	0	0	0	
6 months to < 12 months	0	2 (20.0)	0	
12 months to < 24 months	73 (77.7)	6 (60.0)	2 (28.6)	
≥ 24 months	21 (22.3)	2 (20.0)	5 (71.4)	

Abbreviations: Q=quartile; SD=standard deviation.
[1] Duration of survival follow-up = duration from first obe-cel infusion until the last contact date or date of death. 1 month = 30.4375 days.

Cohort IIB
There are 10 subjects in cohort IIB (subjects with minimal residual disease); mean age 50yrs (min 26yrs, max 73yrs); 70% male; 90% white; in receipt of 1 to 3 prior lines of therapy; 1 was refractory to all prior therapies, 8 had relapsed within 12 months of 1st line therapy, 7 had previous stem cell transplantation; 6 had previous blinatumomab or inotuzumab ozogamicin; none had extramedullary disease; ECOG score of 0 or 1; all 10 were CD19 positive. Note that 4/10 showed >5% blasts in bone marrow prior to lymphodepletion; 6/10 were positive for the Philadelphia chromosome.

The time from informed consent to the first infusion of obe-cel was between 57 to 189 days; all received the target dose; subjects have been followed for between 8 and 29 months.

There were regional differences in the method used to assess minimal residual disease i.e. (i) flow cytometry, (ii) the polymerase chain reaction and (iii) ClonoSEQ next generation sequencing leading to data as shown in the table below:

Table 1: Number of Patients with Evaluable MRD Response Data by Assay Type (Phase Ib and Phase II, All Cohorts, Infused Set)

	Phase Ib			Phase II				Phase Ib and Phase II
	Cohort A (N=13) n (%)	Cohort B (N=3) n (%)	Total (N=16) n (%)	Cohort A (N=94) n (%)	Cohort B (N=10) n (%)	Cohort C (N=7) n (%)	Total (N=111) n (%)	Total (N=127) n (%)
Flow cytometry	10 (76.9)	3 (100)	13 (81.3)	79 (84.0)	9 (90.0)	7 (100)	95 (85.6)	108 (85.0)
PCR	9 (69.2)	1 (33.3)	10 (62.5)	39 (41.5)	2 (20.0)	2 (28.6)	43 (38.7)	53 (41.7)
ClonoSEQ	4 (30.8)	2 (66.7)	6 (37.5)	70 (74.5)	6 (60.0)	2 (28.6)	78 (70.3)	84 (66.1)

Abbreviations: BM = bone marrow; MRD = minimal residual disease; PCR = polymerase chain reaction.
Note: patients may have multiple assay results depending on BM sample availability.

It would have been preferred for all such analyses to have been conducted in a central laboratory according to one acceptable method.
As a result, data have been viewed in a general sense only.

The applicant has submitted the following data on outcomes for subjects in cohort IIB:

Table 4: Per-patient Listing of Outcomes (Best Overall Response and Overall Survival) for Patients in Cohort IIB, Infused Set

Best Overall Response (IRRC)	Bone marrow status			Overall Survival (months)	Overall Survival Status
	Blast % at Screening	Blast % at LD	Best Status After Exposure to Obe-cel		
CR	2	0	CR MRD-neg	6.0	Alive
CR	5	0.5	CR MRD-neg	17.7	Alive
CR	2	40	CR MRD-neg	24.3	Alive
CR	1	0	CR MRD-neg	15.1	Alive
CR	0	0	CR MRD-neg	9.0	Alive
CR	0	95	CR MRD-neg	12.1	Alive
CR	0	35	CR MRD-neg	24.0	Alive
CR	1	0	CR MRD-neg	21.2	Alive
CR	3.4	0.6	CR MRD-neg	12.2	Alive
CRi	2	17	CRi without MRD results	1.7	Death

complete remission; CRi = complete remission with incomplete hematologic recovery;
Response Review Committee; LD = lymphodepletion; MRD = minimal residual disease;
= no response.

Cohort IIC
There are 7 subjects in cohort IIC (subjects with isolated extramedullary disease); mean age 34yrs 29% male; 57% white, 43% Latino; in receipt of 2 to 4 prior lines of therapy; none was refractory to all prior therapies, 3 had relapsed within 12 months of 1st line therapy, 4 had previous stem cell transplantation; all 7 had previous blinatumomab or inotuzumab ozogamicin; all 7 had extramedullary disease and recorded <5% blasts in the bone marrow; ECOG score of 0 or 1; all 7 were CD19 positive. Note that 4/7 showed >5% blasts in bone marrow and 2/7 had absent extramedullary disease prior to lymphodepletion; 1/7 was positive for the Philadelphia chromosome.

The time from informed consent to the first infusion of obe-cel was between 49 to 210 days; all received the target dose; subjects have been followed for between 22 and 28 months.

The applicant has submitted the following data on outcomes for subjects in cohort IIC:

Table 3: Per-patient Listing of Outcomes (Best Overall Response and Overall Survival) for Patients in Cohort IIC (Phase II, Infused Set)

Best EMD Response Post-obe-cel Infusion (IRRC)	Best Overall Response (IRRC)	Onset of Remission (IRRC)	Overall Survival (months)	Overall Survival Status
Absent	CR	Day 30	20.7	Alive
Absent	CR	Day 30	25.5	Alive
Absent	CRi	Day 59	25.6	Alive
Absent	CR	Day 60	24.2	Alive
Absent	CR	Day 28	25.0	Alive
Absent	NR [1]	-	23.1	Alive
Absent	CRi	Day 28	7.8	Death

Abbreviations: CR = complete remission; CRi = complete remission with incomplete hematologic recovery; EMD = extramedullary disease; IRRC = Independent Response Review Committee; NR = no response.

It is noted that subjects in cohort IIC already met the criteria for "CR" at study entry and so data on 'best overall response' and 'onset of remission' are not understood within context.
It is considered that radiological assessment of tumour mass, as described in the protocol for the FELIX study would be the informative outcome yet the applicant records this as 'absent' in all cases; this is regarded as a notable deficiency of study conduct.
Data on outcomes for subjects in cohort IIC are noted without additional comment.

IV.5 Clinical safety
The applicant describes the following analysis sets:

Screened Set
The Screened Set comprises all patients who have signed informed consent and who have been screened in the study.

Enrolled Set
The Enrolled Set comprises all patients who are enrolled in the study. Enrolment is defined as the point at which the patient meets all inclusion/exclusion criteria, and the patient's leukapheresis material is accepted for manufacturing.

Infused Set
The Infused Set comprises all patients who have received at least one infusion of obe-cel.

Target Dose Analysis Set
The Target Dose Analysis Set comprises all patients in the Infused Set who have received the target 410 x 10^6 total CAR-positive T cells. A patient will be considered to have received the target dose if the total received dose is within ±25% of 410 x 10^6 total CD19 CAR-positive T cells.

Safety Set
The Safety Set comprises all patients who have been enrolled and received at least one obe-cel infusion. For this study, the Safety Set is the same as the Infused Set and is the main analysis set for safety.

Safety reporting periods are described in the following table:

Table 4: Safety Reporting Periods

Period	Definition	Patients Included for Analysis
Screening Period	From the date of informed consent to the date prior to enrollment.	Screened Set
Bridging Period	From day of enrollment to the day before start of pre-conditioning therapy or the day before obe-cel infusion in case pre-conditioning therapy is not given.	Enrolled Set
Pre-Conditioning Period	From the start day of pre-conditioning therapy to the day before first obe-cel infusion, or to 30 days after last dose of pre-conditioning therapy for patients who didn't receive obe-cel infusion.	All patients in Enrolled Set who started pre-conditioning therapy
Post-Infusion Period	From the day of first obe-cel infusion to EoS	Safety Set

Data of the applicant on clinical safety is based on 153 subjects enrolled into the FELIX study. The applicant presents a comparison of those enrolled and those infused with product.

The Safety Set is the same as the Infused Set; there would not be particular objection to this analysis.
The applicant gives emphasis to the 153 subjects enrolled, the 127 subjects infused in all cohorts and the 94 subjects infused in cohort IIA.

Clinical safety
Demographics of the safety population
The applicant presents a comparison of those enrolled (153 off) and those infused (127) with product; subjects are presented by cohort, as shown:

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Table 14.1.2.1.4 Demographics

	Phase II - Cohort A			Phase Ib and II - All Cohorts	
	>= 5% blast in BM (N=71)	Infused (N=94)	Enrolled (N=112)	Infused (N=127)	Enrolled (N=153)
Age (years)					
n	71	94	112	127	153
Mean (SD)	49.7 (17.23)	48.3 (17.12)	47.9 (17.04)	47.1 (16.89)	46.7 (16.87)
Median	51.0	50.0	49.0	47.0	45.0
Q1 - Q3	36.0 - 64.0	33.0 - 62.0	33.5 - 62.5	33.0 - 60.0	32.0 - 60.0
Min - Max	20 - 81	20 - 81	20 - 81	20 - 81	20 - 81
Age (years) categorized - n (%)					
>=18 to <=25	8 (11.3)	11 (11.7)	13 (11.6)	14 (11.0)	16 (10.5)
>25 to <40	14 (19.7)	20 (21.3)	26 (23.2)	34 (26.8)	45 (29.4)
>=40 to <65	32 (45.1)	42 (44.7)	49 (43.8)	54 (42.5)	63 (41.2)
>=65	17 (23.9)	21 (22.3)	24 (21.4)	25 (19.7)	29 (19.0)
Age (years) categorized - n (%)					
<65	54 (76.1)	73 (77.7)	88 (78.6)	102 (80.3)	124 (81.0)
>=65	17 (23.9)	21 (22.3)	24 (21.4)	25 (19.7)	29 (19.0)
Sex - n (%)					
Male	36 (50.7)	47 (50.0)	60 (53.6)	66 (52.0)	82 (53.6)
Female	35 (49.3)	47 (50.0)	52 (46.4)	61 (48.0)	71 (46.4)
Race - n (%)					
Asian	8 (11.3)	10 (10.6)	11 (9.8)	16 (12.6)	17 (11.1)
Black or African American	2 (2.8)	2 (2.1)	2 (1.8)	2 (1.6)	3 (2.0)
White	51 (71.8)	70 (74.5)	86 (76.8)	94 (74.0)	117 (76.5)
Unknown	10 (14.1)	12 (12.8)	13 (11.6)	15 (11.8)	16 (10.5)
Ethnicity - n (%)					
Hispanic or Latino	23 (32.4)	29 (30.9)	33 (29.5)	38 (29.9)	44 (28.8)
Not Hispanic or Latino	43 (60.6)	58 (61.7)	72 (64.3)	80 (63.0)	100 (65.4)
Unknown	5 (7.0)	7 (7.4)	7 (6.3)	9 (7.1)	9 (5.9)
Country - n (%)					
United States	39 (54.9)	47 (50.0)	54 (48.2)	66 (52.0)	80 (52.3)
United Kingdom	26 (36.6)	36 (38.3)	42 (37.5)	49 (38.6)	56 (36.6)
Spain	6 (8.5)	11 (11.7)	16 (14.3)	12 (9.4)	17 (11.1)
Region - n (%)					
North America	39 (54.9)	47 (50.0)	54 (48.2)	66 (52.0)	80 (52.3)
Europe	32 (45.1)	47 (50.0)	58 (51.8)	61 (48.0)	73 (47.7)

Enrollment = All inclusion/exclusion criteria have been fulfilled and leukapheresate has been accepted for manufacturing.
Infused set comprises of all patients who have received at least one infusion of obe-cel.
BM = bone marrow.

- 153 subjects in the enrolled set: 54% male; median age 45yrs, min 20yrs, max 81yrs; 76% white, 11% Asian, 2% black.
- 127 subjects in the infused set: 52% male, median age 46yrs, min 20yrs, max 81yrs; 74% white, 13% Asian, 2% black.
- 94 subjects in cohort IIA: 54% male; median age 59yrs, min 29yrs, max 81yrs; 74% white, 11% Asian, 2% black

The main 'sets' are found to have similar demographics.

Disease Characteristics at Screening for the infused set are shown:

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Table 14.1.2.2.2 Disease Characteristics at Screening
By Study Phase and Cohort
Infused Set - Phase Ib and Phase II - All Cohorts

	Phase Ib			Phase II				
	Cohort A (N=13) n (%)	Cohort B (N=3) n (%)	Total (N=16) n (%)	Cohort A (N=94) n (%)	Cohort B (N=10) n (%)	Cohort C (N=7) n (%)	Total (N=111) n (%)	Total (N=127) n (%)
Number of prior lines of therapy								
n	13	3	16	94	10	7	111	127
Mean (SD)	3.0 (1.35)	3.3 (1.15)	3.1 (1.29)	2.2 (1.08)	2.4 (0.70)	2.6 (0.79)	2.2 (1.04)	2.3 (1.10)
Median	2.0	4.0	2.5	2.0	2.5	2.0	2.0	2.0
Q1 - Q3	2.0 - 4.0	2.0 - 4.0	2.0 - 4.0	1.0 - 3.0	2.0 - 3.0	2.0 - 3.0	1.0 - 3.0	2.0 - 3.0
Min - Max	2 - 6	2 - 4	2 - 6	1 - 6	1 - 3	2 - 4	1 - 6	1 - 6
Number of prior lines of therapy categorized - n (%)								
1	0	0	0	29 (30.9)	1 (10.0)	0	30 (27.0)	30 (23.6)
2	7 (53.8)	1 (33.3)	8 (50.0)	36 (38.3)	4 (40.0)	4 (57.1)	44 (39.6)	52 (40.9)
3	2 (15.4)	0	2 (12.5)	17 (18.1)	5 (50.0)	2 (28.6)	24 (21.6)	26 (20.5)
>=4	4 (30.8)	2 (66.7)	6 (37.5)	12 (12.8)	0	1 (14.3)	13 (11.7)	19 (15.0)
Refractory to all prior lines of anti-cancer therapy - n (%)	0	0	0	12 (12.8)	1 (10.0)	0	13 (11.7)	13 (10.2)
Refractory to first line therapy - n (%)	2 (15.4)	1 (33.3)	3 (18.8)	24 (25.5)	2 (20.0)	3 (42.9)	29 (26.1)	32 (25.2)

Refractory to last prior line of therapy: - n (%)	8 (61.5)	1 (33.3)	9 (56.3)	51 (54.3)	4 (40.0)	2 (28.6)	57 (51.4)	66 (52.0)
Relapsed to first line therapy within 12 months - n (%)	7 (53.8)	1 (33.3)	8 (50.0)	41 (43.6)	8 (80.0)	3 (42.9)	52 (46.8)	60 (47.2)
Previous Allogeneic Stem Cell Transplantation - n (%)	7 (53.8)	2 (66.7)	9 (56.3)	36 (38.3)	7 (70.0)	4 (57.1)	47 (42.3)	56 (44.1)
Previous blinatumomab - n (%)	7 (53.8)	2 (66.7)	9 (56.3)	33 (35.1)	5 (50.0)	6 (85.7)	44 (39.6)	53 (41.7)
Previous inotuzumab ozogamicin - n (%)	4 (30.8)	1 (33.3)	5 (31.3)	30 (31.9)	3 (30.0)	2 (28.6)	35 (31.5)	40 (31.5)
Previous blinatomumab and inotuzumab ozogamicin - n (%)	2 (15.4)	1 (33.3)	3 (18.8)	15 (16.0)	2 (20.0)	1 (14.3)	18 (16.2)	21 (16.5)
Previous blinatomumab or inotuzumab ozogamicin - n (%)	9 (69.2)	2 (66.7)	11 (68.8)	48 (51.1)	6 (60.0)	7 (100)	61 (55.0)	72 (56.7)
Bone marrow blasts (%) by morphology prior to enrollment [1]								
n	13	3	16	94	10	7	111	127
Mean (SD)	65.7 (28.36)	1.3 (1.15)	53.6 (36.29)	53.4 (33.15)	1.6 (1.62)	0.7 (1.19)	45.4 (35.85)	46.4 (35.86)
Median	80.0	2.0	56.6	58.9	1.5	0.0	37.0	40.0
Q1 - Q3	40.0 - 90.0	0.0 - 2.0	21.0 - 87.5	20.0 - 86.0	0.0 - 2.0	0.0 - 1.6	10.0 - 84.0	11.0 - 85.0
Min - Max	20 - 95	0 - 2	0 - 95	6 - 100	0 - 5	0 - 3	0 - 100	0 - 100
Bone marrow blasts (%) by morphology prior to enrollment categorized - n (%) [1]								
>75%	7 (53.8)	0	7 (43.8)	34 (36.2)	0	0	34 (30.6)	41 (32.3)
>20%-<=75%	5 (38.5)	0	5 (31.3)	32 (34.0)	0	0	32 (28.8)	37 (29.1)
>=5%-<=20%	1 (7.7)	0	1 (6.3)	28 (29.8)	1 (10.0)	0	29 (26.1)	30 (23.6)
<5%	0	3 (100)	3 (18.8)	0	9 (90.0)	7 (100)	16 (14.4)	19 (15.0)
Missing	0	0	0	0	0	0	0	0
Bone marrow blasts (%) by morphology prior to enrollment categorized - n (%) [1]								
<=20%	1 (7.7)	3 (100)	4 (25.0)	28 (29.8)	10 (100)	7 (100)	45 (40.5)	49 (38.6)
>20%	12 (92.3)	0	12 (75.0)	66 (70.2)	0	0	66 (59.5)	78 (61.4)
Extramedullary disease status prior to enrollment - n (%)								
Absent	10 (76.9)	3 (100)	13 (81.3)	75 (79.8)	10 (100)	0	85 (76.6)	98 (77.2)
Present	3 (23.1)	0	3 (18.8)	19 (20.2)	0	7 (100)	26 (23.4)	29 (22.8)
CNS	1 (7.7)	0	1 (6.3)	2 (2.1)	0	0	2 (1.8)	3 (2.4)
Mediastinal Lymph Node	0	0	0	2 (2.1)	0	0	2 (1.8)	2 (1.6)
Testis	0	0	0	1 (1.1)	0	0	1 (0.9)	1 (0.8)
Other	3 (23.1)	0	3 (18.8)	15 (16.0)	0	7 (100)	22 (19.8)	25 (19.7)
ECOG score [2] - n (%)								
0	4 (30.8)	2 (66.7)	6 (37.5)	35 (37.2)	5 (50.0)	4 (57.1)	44 (39.6)	50 (39.4)
1	9 (69.2)	1 (33.3)	10 (62.5)	58 (61.7)	5 (50.0)	3 (42.9)	66 (59.5)	76 (59.8)
2	0	0	0	0	0	0	0	0
>2	0	0	0	0	0	0	0	0
Missing	0	0	0	1	0	0	1	1
CD19 status prior to enrollment (by flow cytometry) - n (%)								
Positive	13 (100)	3 (100)	16 (100)	94 (100)	10 (100)	7 (100)	111 (100)	127 (100)
Negative	0	0	0	0	0	0	0	0
Mixed population (positive + negative)	0	0	0	0	0	0	0	0
Unknown	0	0	0	0	0	0	0	0

Table 14.1.2.2.2 Disease Characteristics at Screening
By Study Phase and Cohort
Infused Set - Phase Ib and Phase II - All Cohorts

	Phase Ib			Phase II				
	Cohort A (N=13) n (%)	Cohort B (N=3) n (%)	Total (N=16) n (%)	Cohort A (N=94) n (%)	Cohort B (N=10) n (%)	Cohort C (N=7) n (%)	Total (N=111) n (%)	Total (N=127) n (%)
CNS disease history - n (%) [3]								
CNS1	13 (100)	2 (66.7)	15 (93.8)	81 (86.2)	9 (90.0)	7 (100)	97 (87.4)	112 (88.2)
CNS2	0	1 (33.3)	1 (6.3)	2 (2.1)	0	0	2 (1.8)	3 (2.4)
CNS3	0	0	0	0	0	0	0	0
Unknown	0	0	0	11 (11.7)	1 (10.0)	0	12 (10.8)	12 (9.4)
Neutrophil count (10^9/L) prior to enrollment								
n	13	3	16	94	10	6	110	126
Mean (SD)	1.9 (2.83)	3.1 (1.70)	2.1 (2.65)	2.0 (1.91)	2.7 (1.53)	3.3 (1.25)	2.1 (1.87)	2.1 (1.97)
Median	0.5	2.2	1.0	1.4	2.4	3.3	1.8	1.6
Q1 - Q3	0.2 - 3.0	2.1 - 5.1	0.3 - 3.5	0.7 - 2.9	1.9 - 3.5	2.8 - 4.0	0.7 - 3.4	0.7 - 3.4
Min - Max	0 - 10	2 - 5	0 - 10	0 - 9	0 - 6	1 - 5	0 - 9	0 - 10
Neutrophil count (10^9/L) prior to enrollment categorized - n (%)								
<0.5	6 (46.2)	0	6 (37.5)	20 (21.3)	1 (10.0)	0	21 (18.9)	27 (21.3)
>=0.5	7 (53.8)	3 (100)	10 (62.5)	74 (78.7)	9 (90.0)	6 (85.7)	89 (80.2)	99 (78.0)
Missing	0	0	0	0	0	1 (14.3)	1 (0.9)	1 (0.8)
Platelet count (10^9/L) prior to enrollment								
n	13	3	16	94	10	7	111	127
Mean (SD)	64.7 (63.01)	130.0 (36.35)	76.9 (63.61)	99.3 (83.62)	173.0 (91.97)	175.1 (89.79)	110.7 (88.15)	106.5 (85.98)
Median	24.0	121.0	52.0	73.0	169.5	144.0	88.0	85.0
Q1 - Q3	17.0 - 130.0	99.0 - 170.0	19.0 - 133.5	40.0 - 133.0	104.0 - 254.0	125.0 - 268.0	43.0 - 169.0	39.0 - 148.0
Min - Max	16 - 196	99 - 170	16 - 196	1 - 451	35 - 306	40 - 292	1 - 451	1 - 451
Platelet count (10^9/L) prior to enrollment categorized - n (%)								
<50	8 (61.5)	0	8 (50.0)	33 (35.1)	1 (10.0)	1 (14.3)	35 (31.5)	43 (33.9)
>=50	5 (38.5)	3 (100)	8 (50.0)	61 (64.9)	9 (90.0)	6 (85.7)	76 (68.5)	84 (66.1)
Missing	0	0	0	0	0	0	0	0

[1] ECOG based on last non-missing value from screening period prior to leukapheresis.
[2] CNS-1 = No lymphoblasts in cerebrospinal fluid (CSF) regardless of WBC count; CNS-2 = WBC <5/mcL in CSF with presence of lymphoblasts; CNS-3 = WBC >= 5/mcL in CSF with presence of lymphoblasts.
[3] Bone marrow blast (%) was determined by morphology as the highest value from bone marrow aspirate and trephine at screening.

Table 14.1.2.2.4 Disease Characteristics at Screening

	Phase II - Cohort A		Phase Ib and II - All Cohorts	
	Infused (N=94)	Enrolled (N=112)	Infused (N=127)	Enrolled (N=153)
Number of prior lines of therapy				
n	94	112	127	153
Mean (SD)	2.2 (1.08)	2.2 (1.08)	2.3 (1.10)	2.3 (1.10)
Median	2.0	2.0	2.0	2.0
Q1 - Q3	1.0 - 3.0	1.0 - 3.0	2.0 - 3.0	2.0 - 3.0
Min - Max	1 - 6	1 - 6	1 - 6	1 - 6
Number of prior lines of therapy categorized - n (%)				
1	29 (30.9)	34 (30.4)	30 (23.6)	36 (23.5)
2	36 (38.3)	43 (38.4)	52 (40.9)	61 (39.9)
3	17 (18.1)	21 (18.8)	26 (20.5)	33 (21.6)
>=4	12 (12.8)	14 (12.5)	19 (15.0)	23 (15.0)
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)	66 (52.0)	79 (51.6)
Relapsed to first line therapy within 12 months - n (%)	41 (43.6)	52 (46.4)	60 (47.2)	75 (49.0)
Previous Allogeneic Stem Cell Transplantation - 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 blinatomumab and inotuzumab ozogamicin - n (%)	15 (16.0)	20 (17.9)	21 (16.5)	27 (17.6)
Previous blinatomumab or inotuzumab ozogamicin - n (%)	48 (51.1)	58 (51.8)	72 (56.7)	86 (56.2)
Bone marrow blasts (%) by morphology prior to enrollment [1]				
n	94	112	127	153
Mean (SD)	53.4 (33.15)	55.1 (32.43)	46.4 (35.86)	50.4 (35.43)
Median	58.9	61.0	40.0	52.0
Q1 - Q3	20.0 - 86.0	20.0 - 86.0	11.0 - 85.0	15.0 - 86.0
Min - Max	6 - 100	6 - 100	0 - 100	0 - 100
Bone marrow blasts (%) by morphology prior to enrollment categorized - n (%) [1]				
>75%	34 (36.2)	42 (37.5)	41 (32.3)	55 (35.9)
>20%-<=75%	32 (34.0)	40 (35.7)	37 (29.1)	47 (30.7)
>=5%-<=20%	28 (29.8)	30 (26.8)	30 (23.6)	32 (20.9)
<5%	0	0	19 (15.0)	19 (12.4)
Missing	0	0	0	0
Bone marrow blasts (%) by morphology prior to enrollment categorized - n (%) [1]				
<=20%	28 (29.8)	30 (26.8)	49 (38.6)	51 (33.3)
>20%	66 (70.2)	82 (73.2)	78 (61.4)	102 (66.7)
Extramedullary disease status prior to enrollment - n (%)				
Absent	75 (79.8)	91 (81.3)	98 (77.2)	121 (79.1)
Present	19 (20.2)	21 (18.8)	29 (22.8)	32 (20.9)
CNS	2 (2.1)	2 (1.8)	3 (2.4)	3 (2.0)
Mediastinal Lymph Node	2 (2.1)	2 (1.8)	2 (1.6)	2 (1.3)
Testis	1 (1.1)	1 (0.9)	1 (0.8)	1 (0.7)
Other	15 (16.0)	17 (15.2)	25 (19.7)	28 (18.3)
ECOG score [2] - n (%)				
0	35 (37.2)	39 (34.8)	50 (39.4)	58 (37.9)
1	58 (61.7)	72 (64.3)	76 (59.8)	94 (61.4)
2	0	0	0	0
>2	0	0	0	0
Missing	1	1	1	1
CD19 status prior to enrollment (by flow cytometry) - n (%)				
Positive	94 (100)	111 (99.1)	127 (100)	152 (99.3)
Negative	0	0	0	0
Mixed population (positive + negative)	0	1 (0.9)	0	1 (0.7)
Unknown	0	0	0	0
CNS disease history - n (%) [3]				
CNS1	81 (86.2)	97 (86.6)	112 (88.2)	136 (88.9)
CNS2	2 (2.1)	2 (1.8)	3 (2.4)	3 (2.0)
CNS3	0	0	0	0
Unknown	11 (11.7)	13 (11.6)	12 (9.4)	14 (9.2)

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Table 14.1.2.2.4 Disease Characteristics at Screening

	Phase II - Cohort A		Phase Ib and II - All Cohorts	
	Infused (N=94)	Enrolled (N=112)	Infused (N=127)	Enrolled (N=153)
Neutrophil count (10^9/L) prior to enrollment				
n	94	112	126	152
Mean (SD)	2.0 (1.91)	1.9 (2.13)	2.1 (1.97)	2.0 (2.16)
Median	1.4	1.2	1.6	1.4
Q1 - Q3	0.7 - 2.9	0.4 - 2.7	0.7 - 3.4	0.4 - 3.0
Min - Max	0 - 9	0 - 13	0 - 10	0 - 13
Neutrophil count (10^9/L) prior to enrollment categorized - n (%)				
<0.5	20 (21.3)	30 (26.8)	27 (21.3)	41 (26.8)
>=0.5	74 (78.7)	82 (73.2)	99 (78.0)	111 (72.5)
Missing	0	0	1 (0.8)	1 (0.7)
Platelet count (10^9/L) prior to enrollment				
n	94	112	127	153
Mean (SD)	99.3 (83.62)	93.4 (82.43)	106.5 (85.98)	97.9 (84.10)
Median	73.0	62.0	85.0	66.0
Q1 - Q3	40.0 - 133.0	34.5 - 131.0	39.0 - 148.0	34.0 - 137.0
Min - Max	1 - 451	1 - 451	1 - 451	1 - 451
Platelet count (10^9/L) prior to enrollment categorized - n (%)				
<50	33 (35.1)	45 (40.2)	43 (33.9)	61 (39.9)
>=50	61 (64.9)	67 (59.8)	84 (66.1)	92 (60.1)
Missing	0	0	0	0

BM = bone marrow; EMD = extramedullary disease.
[1] ECOG based on last non-missing value from screening period prior to leukapheresis.
[2] CNS-1 = No lymphoblasts in cerebrospinal fluid (CSF) regardless of WBC count; CNS-2 = WBC <5/mcL in CSF with presence of lymphoblasts; CNS-3 = WBC >= 5/mcL in CSF with presence of lymphoblasts.
[3] Bone marrow blast (%) was determined by morphology as the highest value from bone marrow aspirate and trephine at screening.

<u>Prior to enrolment:</u>

Enrolled set: n = 153; median of 2 prior lines of therapy; 10% refractory to all prior lines; 45% had previous stem cell transplant; median of 52% bone marrow blast cells; 21% with extramedullary disease; ECOG score 0 (38%) or 1 (61%); 99% CD19 status +ve; median neutrophil count (10^9/L) = 1.4; median platelet count (10^9/L) = 66.

Total infused set: n = 127; median of 2 prior lines of therapy; 10% refractory to all prior lines; 44% had previous stem cell transplant; median of 40% bone marrow blast cells; 23% with extramedullary disease; ECOG score 0 (39%) or 1 (60%); 100% CD19 status +ve; median neutrophil count (10^9/L) = 1.6; median platelet count (10^9/L) = 85.

Cohort IIA infused set: n = 94; median of 2 prior lines of therapy; 13% refractory to all prior lines; 38% had previous stem cell transplant; median of 59% bone marrow blast cells; 20% with extramedullary disease; ECOG score 0 (37%) or 1 (62%); 100% CD19 status +ve; median neutrophil count (10^9/L) = 1.4; median platelet count (10^9/L) = 73.

The make-ups of the above-described sets appear broadly similar (though noting that the bone marrow blast figure is higher in the cohort IIA set).

Disease Characteristics prior to pre-conditioning are shown:

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Table 14.1.2.3.3 Disease Characteristics Prior to Pre-conditioning

	Phase II - Cohort A		Phase Ib and II - All Cohorts	
M	Infused (N=94)	Enrolled (N=112)	Infused (N=127)	Enrolled (N=153)
Patients who received pre-conditioning therapy - n (%)	94 (100)	94 (83.9)	127 (100)	127 (83.0)
Bone marrow blasts (%) by morphology prior to pre-conditioning [1]				
n	94	94	127	127
Mean (SD)	45.1 (37.39)	45.1 (37.39)	43.4 (37.89)	43.4 (37.89)
Median	43.5	43.5	40.0	40.0
Q1 - Q3	5.0 - 85.6	5.0 - 85.6	3.0 - 85.6	3.0 - 85.6
Min - Max	0 - 100	0 - 100	0 - 100	0 - 100
Bone marrow blasts (%) by morphology prior to pre-conditioning categorized - n (%) [1]				
<=20%	37 (39.4)	37 (33.0)	52 (40.9)	52 (34.0)
>20%	57 (60.6)	57 (50.9)	75 (59.1)	75 (49.0)
Missing	0	18 (16.1)	0	26 (17.0)
Bone marrow blasts (%) by morphology prior to pre-conditioning categorized - n (%) [1]				
>75%	30 (31.9)	30 (26.8)	40 (31.5)	40 (26.1)
>20%-<=75%	27 (28.7)	27 (24.1)	35 (27.6)	35 (22.9)
>=5%-<=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)
Missing	0	18 (16.1)	0	26 (17.0)
Extramedullary disease status prior to pre-conditioning - n (%)				
Absent	75 (79.8)	91 (81.3)	100 (78.7)	123 (80.4)
Present	19 (20.2)	21 (18.8)	27 (21.3)	30 (19.6)
CNS	1 (1.1)	1 (0.9)	1 (0.8)	1 (0.7)
Mediastinal Lymph Node	2 (2.1)	2 (1.8)	3 (2.4)	3 (2.0)
Testis	1 (1.1)	1 (0.9)	1 (0.8)	1 (0.7)
Other	17 (18.1)	19 (17.0)	25 (19.7)	28 (18.3)
Missing	0	0	0	0
Neutrophil count (10^9/L) prior to pre-conditioning				
n	92	92	125	125
Mean (SD)	1.9 (2.10)	1.9 (2.10)	2.0 (2.22)	2.0 (2.22)
Median	1.3	1.3	1.4	1.4
Q1 - Q3	0.4 - 2.5	0.4 - 2.5	0.5 - 2.7	0.5 - 2.7
Min - Max	0 - 14	0 - 14	0 - 14	0 - 14
Neutrophil count (10^9/L) prior to pre-conditioning categorized - n (%)				
<0.5	24 (25.5)	24 (21.4)	32 (25.2)	32 (20.9)
>=0.5	68 (72.3)	68 (60.7)	93 (73.2)	93 (60.8)
Missing	2 (2.1)	2 (1.8)	2 (1.6)	2 (1.3)
Platelet count (10^9/L) prior to pre-conditioning				
n	94	94	127	127
Mean (SD)	97.3 (83.50)	97.3 (83.50)	105.3 (88.66)	105.3 (88.66)
Median	83.5	83.5	89.0	89.0
Q1 - Q3	23.0 - 148.0	23.0 - 148.0	24.0 - 166.0	24.0 - 166.0
Min - Max	4 - 368	4 - 368	4 - 368	4 - 368
Platelet count (10^9/L) prior to pre-conditioning categorized - n (%)				
<50	37 (39.4)	37 (33.0)	47 (37.0)	47 (30.7)
>=50	57 (60.6)	57 (50.9)	80 (63.0)	80 (52.3)
Missing	0	0	0	0
Karyotype				
Abnormal	66 (70.2)	78 (69.6)	83 (65.4)	100 (65.4)
Normal	19 (20.2)	20 (17.9)	31 (24.4)	34 (22.2)
Unknown	9 (9.6)	14 (12.5)	13 (10.2)	19 (12.4)
Complex karyotype				
Yes	37 (39.4)	45 (40.2)	51 (40.2)	63 (41.2)
No/Unknown	57 (60.6)	67 (59.8)	76 (59.8)	90 (58.8)

[1] Bone marrow blast (%) was determined by morphology as the highest value from bone marrow aspirate and trephine.
[2] Cytogenetic risk groups based on karyotype collected from screening to pre-conditioning period. If multiple karyotypes were recorded for the same patient, the latest record was used for the patient.

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Table 14.1.2.3.3 Disease Characteristics Prior to Pre-conditioning

	Phase II - Cohort A		Phase Ib and II - All Cohorts	
	Infused (N=94)	Enrolled (N=112)	Infused (N=127)	Enrolled (N=153)
Cytogenetic risk groups for B-ALL [2] - n (%)				
Good risk				
Hyperdiploidy	5 (5.3)	6 (5.4)	5 (3.9)	6 (3.9)
TEL-AML1	1 (1.1)	1 (0.9)	2 (1.6)	2 (1.3)
Poor risk				
Hypodiploidy	4 (4.3)	4 (3.6)	4 (3.1)	5 (3.3)
IL3-IGH	0	1 (0.9)	1 (0.8)	2 (1.3)
t(10;14)	1 (1.1)	1 (0.9)	1 (0.8)	1 (0.7)
BCR-ABL1-like	8 (8.5)	8 (7.1)	10 (7.9)	11 (7.2)
E2A-PBX1	1 (1.1)	1 (0.9)	1 (0.8)	1 (0.7)
Philadelphia chromosome-positive	25 (26.6)	26 (23.2)	36 (28.3)	39 (25.5)
MLL rearrangement	6 (6.4)	7 (6.3)	6 (4.7)	10 (6.5)
Del 17p	0	1 (0.9)	1 (0.8)	3 (2.0)
Other abnormality	37 (39.4)	47 (42.0)	41 (32.3)	55 (35.9)

[1] Bone marrow blast (%) was determined by morphology as the highest value from bone marrow aspirate and trephine.
[2] Cytogenetic risk groups based on karyotype collected from screening to pre-conditioning period. If multiple karyotypes were recorded for the same patient, the latest record was used for the patient.

Prior to pre-conditioning:
Enrolled set: n = 153; a median of 40% bone marrow blast cells; 20% extramedullary disease present; median neutrophil count (10^9/L) = 1.4; median platelet count (10^9/L) = 89; 22% normal karyotype; 41% complex karyotype; 26% Philadelphia chromosome-positive.

Total infused set: n = 127; a median of 40% bone marrow blast cells; 21% extramedullary disease present; median neutrophil count (10^9/L) = 1.4; median platelet count (10^9/L) = 89; 24% normal karyotype; 40% complex karyotype; 28% Philadelphia chromosome-positive.

Cohort IIA infused set: n = 94; a median of 44% bone marrow blast cells; 20% extramedullary disease present; median neutrophil count (10^9/L) = 1.3; median platelet count (10^9/L) = 84; 20% normal karyotype; 39% complex karyotype; 27% Philadelphia chromosome-positive.

The make-ups (including the detailed cytogenetic risk groups for B-ALL) of the above-described sets at pre-conditioning appear broadly similar (including the bone marrow blast figures).

The make-ups of the sets at (i) screening and (ii) prior to pre-conditioning appear broadly similar (noting change in the bone marrow blast figures for cohort IIA).

At the time of pre-conditioning: subjects in Cohort IIA would appear to be representative of all enlisted subjects; this is acceptable.

Procedures to collect safety data
An adverse event is defined as any untoward medical occurrence in a patient administered a medicinal product which does not necessarily have a causal relationship with the treatment.

An adverse reaction is any untoward and unintended responses to a medicinal product related to any dose administered. A causal relationship between a medicinal product and an adverse event is at least a reasonable possibility e.g. the relationship cannot be ruled out.

A serious adverse event is defined as an adverse event that (i) results in death, (ii) is life-threatening, (iii) requires in-patient hospitalisation or prolonged existing hospitalisation, (iv) results in persistent or significant disability / incapacity / congenital anomaly / birth defect or is (v) medically significant.

The following are adverse events of special interest (AESI) and will always be considered serious:

- Grade 3 to 5 cytokine release syndrome (CRS)
- Grade 3 to 5 immune effector cell-associated neurotoxicity syndrome (ICANS) (includes depressed level of consciousness, ataxia, seizures and cerebral oedema).
- Grade 3 to 5 infusion-related reaction to obe-cel.
- Any new malignancy.

Adverse events will be elicited at each study visit as indicated in the Schedule of Assessments and as clinically necessary.
Patients will be instructed to report any adverse events occurring between study visits to the study site.
Adverse events will be assessed for severity, relationship to study treatment, action taken,

outcome and whether the event meets criteria for a serious adverse event according to study guidelines.

The severity of adverse events will be graded according to the Common Terminology Criteria for Adverse Events (CTCAE) v5.0.

Adverse events that are not defined by the NCI CTCAE will be evaluated for severity according to the following scale (Table 27):

Table 27: Severity Grading of AEs Not Listed on the NCI CTCAE Grading System

Grade	Severity	
1	Mild	Transient or mild discomfort; no limitation in activity; no medical intervention/therapy required.
2	Moderate	Mild to moderate limitation in activity, some assistance may be needed; no or minimal medical intervention/therapy required.
3	Severe	Marked limitation in activity, some assistance usually required; medical intervention/therapy required, hospitalisation is possible.
4	Life-threatening	Extreme limitation in activity, significant assistance required; significant medical intervention/therapy required, hospitalisation or hospice care probable.
5	Fatal	Death because of this AE.

AE = adverse event; CTCAE = Common Terminology Criteria for Adverse Events; NCI = National Cancer Institute

Relationship of adverse events to treatment will be classed as: (i) not related, (ii) possibly related, (iii) probably related, (iv) definitely related.

The reporting period for all adverse events is described in Table 28:

Table 28: Reporting Period for All AEs

Reporting Period **From**: ICF signature **Until**: Month 6	**Reporting Period** **From**: Month 6 **Until**: End of Study/patient withdrawal OR, when patient starts a new anti-cancer therapy
Report the following: • All AEs • All SAEs	**Report the following:** • All AEs considered related to AUTO1 • All SAEs (regardless of relationship to AUTO1) • All AEs of special interest (regardless of relationship to AUTO1) (Section 12.3.6) • All AEs related to study procedures (BM assessments, lumbar punctures etc.) (regardless of relationship to AUTO1)
If at any time a patient starts a new anti-cancer therapy including HSCT, report the following: • All AEs considered related to AUTO1 • All AEs that result in the patient's death (regardless of relationship to AUTO1)	
N.B. Death due to disease progression is not considered an AE (see Section 12.1.6) but must be recorded on the death case report form in the EDC.	

AE = adverse event; BM = bone marrow; EDC = Electronic Data Capture; HSCT = haematopoietic stem cell transplantation; ICF = Informed consent form; SAE = serious adverse event.

Cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS) were graded according to the American Society for Transplantation and Cellular Therapy consensus grading.

Special safety topics included:

- Cytokine release syndrome (CRS)
- Immune effector cell-associated neurotoxicity syndrome (ICANS)
- Prolonged cytopenias
- Hemophagocytic lymphohistiocytosis (HLH) / macrophage activation syndrome (MAS)
- B cell aplasia and hypogammaglobulinemia
- Severe infections
- Tumour lysis syndrome
- Graft-versus-host disease
- Secondary malignancies
- Hypersensitivity reactions
- Antigenicity / immunogenicity

The Investigator should follow each adverse event until either:

- The adverse event has resolved to baseline
- The adverse event is assessed as stable by the Investigator
- Patient is lost to follow-up
- Patient withdraws consent
- Death
- Study completion

If the event is on-going at the completion of the study then the event will be followed until resolution or is assessed as stable by the Investigator or one of the following applies:

- Death
- Withdrawal of consent
- Patient lost to follow-up

Exposure to product

Overall Extent of Exposure (FELIX Study)

153 patients were enrolled (Enrolled Set) and 127 patients received at least one dose of obe-cel in the FELIX Study (Safety Set).

Most subjects in the Safety Set are from Cohort IIA (94/127; 74.0%); the contribution per cohort is summarised in Table 6.

Table 6: Summary of Patient Contribution per Cohort in FELIX (Phase Ib and Phase II, Safety Set)

Parameter	Cohort IA (N=13)	Cohort IB (N=3)	Cohort IIA (N=94)	Cohort IIB (N=10)	Cohort IIC (N=7)	Total (Safety Set) (N=127)
Patients infused, n (%) [1]	13 (10.2)	3 (2.4)	94 (74.0)	10 (7.9)	7 (5.5)	**127 (100)**
Patients ongoing, n (%) [1]	4 (3.1)	2 (1.6)	53 (4.2)	9 (7.1)	6 (4.7)	**74 (58.3)**
Median duration of follow-up, months	26.81	22.21	12.27	10.17	17.87	**13.47**
Min - Max	22.4 - 33.4	21.7 - 24.0	4.7 - 21.8	0.6 - 20.7	14.7 - 19.2	**0.6 - 33.4**
≥ 6 months, n (%) [1]	13 (10.2)	3 (2.4)	87 (68.5)	7 (5.5)	7 (5.5)	**117 (92.1)**
≥ 12 months, n (%) [1]	13 (10.2)	3 (2.4)	48 (3.8)	5 (3.9)	7 (5.5)	**76 (59.8)**

[1] Denominator is total number of patients in Safety Set (N=127).

Exposure to Bridging Therapy

Use of bridging therapy was based on Investigator's choice and local practice, except for the use of blinatumomab, which was prohibited as a bridging therapy agent. (92.9%, 118/127)

received bridging therapy, with chemotherapy being the most common bridging therapy used (see Table 7).

Table 7: Bridging Medications Utilized in FELIX Study (Phase Ib and Phase II, Safety Set)

Therapy	Infused (N=127) n (%)
Number of patients with any bridging medications	118 (92.9)
Chemotherapy	80 (63.0)
Chemotherapy + TKI	10 (7.9)
Chemotherapy + Inotuzumab	9 (7.1)
Inotuzumab	9 (7.1)
TKI	7 (5.5)
Steroids	2 (1.6)
Other	1 (0.8)

TKI=tyrosine kinase inhibitors.

Inotuzumab ozogamicin, either alone or in combination with chemotherapy, was administered to 14.2% (18/127) of patients.

Exposure to Lymphodepleting Therapy

All 127 patients (100%) received lymphodepletion therapy prior to obe-cel infusion.
The median dose of IV fludarabine was 120 mg/m2 (range 68 to 240 mg/m2)
The median dose of IV cyclophosphamide was 1,000 mg/m2 (range 700 to 2,000 mg/m2).

Exposure to Obe-cel Therapy

The target total dose of obe-cel was to be the same for all patients: 410 × 10^6 CD19 CAR-positive T cells (± 25% variance).

The median dose of obe-cel administered in the Safety Set was 410 × 10^6 CD19 CAR-positive T cells. Most subjects received both administrations (94.5%, 120/127); the target dose was achieved in 116/127 patients (91.3%) i.e. 11 subjects did not receive the target dose; refer to Table 8:

Table 8: Obe-cel Dosing in FELIX Study (Phase Ib and Phase II, Safety Set)

Parameter	Infused (N=127)
Total number of patients infused, n (%)	127 (100)
Total calculated CAR-positive T cells received (× 10^6 cells)	
n	127
Mean (SD)	379.9 (89.94)
Median	410.0
Q1 - Q3	405.0 - 413.0
Min – Max	10 - 480
Patient received both obe-cel doses, n (%)	120 (94.5)
Patient received only first obe-cel dose, n (%)	7 (5.5)
Reason for not receiving the second infusion, n (%)	
Adverse event	3 (2.4)
Progressive disease	2 (1.6)
Death	1 (0.8)
Manufacturing related issues	1 (0.8)
Patients receiving the target dose, n (%) [1]	116 (91.3)
Patients not receiving the target dose, n (%)	11 (8.7)

CAR=chimeric antigen receptor; SD=standard deviation.
[1] Target dose was 410 × 10^6 CD19 CAR-positive T cells (±25%).

There were 9 patients (9.6%, 9/94) in Cohort IIA who did not receive their target dose. In the 85 patients (90.4%, 85/94) who received the target total dose in Cohort IIA, the following remission rates were observed:

- Overall remission rate of 81.2% (69/85).
- Complete remission at any time of 61.2% (52/85).

7 patients did not receive their second dose in the Safety Set (Table 8). The reasons for not administering the second dose were adverse events (Grade 3 CRS or ICANS), rapid disease progression or disease-associated death.

In addition, there was inadequate dose manufactured for 1 patient.

9 patients had a delay in administration of their second dose beyond Day 12 (but no later than Day 21), all of whom were in Cohort IIA. In all cases, this delay was owing to the occurrence of adverse events delaying the administration of the second dose.

6/9 patients showed a complete response.

The CAR T cell expansion and persistency were not negatively impacted in those patients with delayed second dose. Overall, a delay of up to 21 days did not impact the response to treatment.

The protocol provides general advice on infection prophylaxis and support care for respiratory, cardiovascular, haematologic and neurologic body systems.

Pre- and Post-Infusion Supportive Therapy is summarised in the following table:

Table 16: Pre- and Post-infusion Medications

Medication	Dose	Administration	Pre-infusion	Post-infusion
Antihistamine	Chlorpheniramine (10 mg, 6 hourly). Refer to local prescribing information	i.v. – administer at least 30 minutes prior to study drug	Optional	Optional as clinically indicated
Antipyretic	Paracetamol/acetaminophen (1000 mg; 6 hourly). Refer to local prescribing information	Oral - administer at least 30 minutes prior to study drug	Yes	Optional as clinically indicated
Antiemetic	Ondansetron Refer to local prescribing information	i.v. - start infusion 30 minutes prior to study drug Oral - as clinically indicated	Optional	Optional as clinically indicated

i.v. = intravenous;

The applicant permitted Infusion Related Reactions to be managed by local guidelines (and provided recommendations).

Tumour Lysis Syndrome was managed by local guidelines with emphasis on fluid and electrolyte balance.

Management of hypogammaglobulinaemia associated with CAR-T therapy was according to local institutional practice.

Haemophagocytic lymphohistiocytosis and / or macrophage activation syndrome were diagnosed in the presence of a peak concentration of serum ferritin >10,000 ng/mL and any two of the following:

- NCI CTCAE Grade ≥3 increase in serum bilirubin concentration or increased serum activities of aspartate aminotransferase or alanine aminotransferase levels.
- NCI CTCAE Grade ≥3 oliguria or increase in serum creatinine concentration.
- NCI CTCAE Grade ≥3 pulmonary oedema.
- Presence of haemophagocytosis in bone marrow or organs based on histopathological assessment of cell morphology and / or detection of CD-68 (a marker on cell surfaces that identifies macrophages) by immunohistochemistry.

The applicant following guidelines of the American Society for Transplantation and Cellular Therapy on grading of cytokine release syndrome and neurological toxicity associated with CAR-T cells, published in 2019.

Management of cytokine release syndrome (CRS) is summarised in the following table / the attending physician may follow local guidelines:

Table 19: Management of CRS

CRS Grade (NCI CTCAE Version 5.0)	Treatment
Grade 1 Symptoms are not life-threatening and require symptomatic treatment only, e.g. fever, nausea, fatigue, headache, myalgia, and malaise or organ toxicity.	Supportive care per institutional standards including analgesics and antipyretics, assess and treat for neutropenic infections. Consider tocilizumab for persisting (>3 days) and refractory fever.
Grade 2 Symptoms require and respond to moderate intervention.	Supportive care including fluid substitution is recommended. Low-flow-oxygen (<40% fraction of inspired oxygen). Consider tocilizumab early if persistent fever of ≥39°C despite antipyretics for 10 hours. (Lee et al. 2014, Neelapu et al. 2018).
Grade 3 Symptoms require and respond to aggressive intervention.	Intensive care should be considered. Oxygen (flow ≥40% fraction of inspired oxygen). Vasopressors as needed (Table 20). Treat with tocilizumab See Table 20). Add siltuximab as necessary if not previously administered. Add steroids if unresponsive within 24 hours. CRS associated with MAS or haemophagocytosis may also be treated with anakinra, an IL-1 receptor antagonist (Shah et al. 2017). Also, consider anti-TNF antibodies as clinically appropriate (Table 20).
Grade 4 Life-threatening symptoms.	Intensive care. Treat with tocilizumab (see Table 20). Add siltuximab as necessary if not previously administered (Table 20). Treat with corticosteroids (Table 20). CRS associated with MAS or haemophagocytosis may also be treated with anakinra, an IL-1 receptor antagonist (Shah et al. 2017). Consider alternative agents such as anti-TNF, and other agents as appropriate.
Grade 5 Death.	Not applicable.

CRS = cytokine release syndrome; CTCAE = Common Terminology Criteria for Adverse Events; IL = interleukin; MAS = macrophage activation syndrome; NCI = National Cancer Institute; TNF = tumour necrosis factor.

Management of Immune Effector Cell-associated Neurotoxicity Syndrome (ICANS) is summarised in the following table / the attending physician may follow local guidelines:

Table 23: Management of ICANS

Grade	Management
Grade 1	Vigilant supportive care; aspiration precautions; i.v. hydration. Withhold oral intake of food, medicines, and fluids, and assess swallowing. Convert all oral medications and/or nutrition to i.v. if swallowing is impaired. **Start dexamethasone 10 mg every 6 hours or methylprednisolone 1 mg/kg every 12 hours.** Avoid medications that cause CNS depression. Low doses of lorazepam (0.25 to 0.5 mg i.v. every 8 hours) or haloperidol (0.5 mg i.v. every 6 hours) can be used, with careful monitoring, for agitated patients. Neurology consultation. Fundoscopic exam to assess for papilloedema. MRI of the brain with and without contrast; diagnostic lumbar puncture with measurement of opening pressure; MRI spine if the patient has focal peripheral neurological deficits; CT scan of the brain can be performed if MRI of the brain is not feasible. Daily 30-minute EEG until toxicity symptoms resolve; if no seizures are detected on EEG. Consider levetiracetam 750 mg every 12 hours (oral or i.v.) for a month for seizure prophylaxis. If EEG shows non-convulsive status epilepticus, treat as per algorithm (Table 24). Consider anti-IL-6 therapy if neurotoxicity is associated with concurrent CRS (Section 10.4). **Worsening**: treat as ≥Grade 2.
Grade 2	Supportive care and neurological work-up as indicated for Grade 1. Anti-IL-6 therapy if associated with concurrent CRS (Section 10.4). Dexamethasone 10 mg every 6 hours or methylprednisolone 1 mg/kg every 12 hours if refractory to anti-IL-6 therapy, or for neurotoxicity without concurrent CRS. Consider transferring patient to ICU if neurotoxicity is associated with Grade ≥2 CRS. **Worsening:** treat as Grade 3 to 4.

Grade	Management
Grade 3 neurologic toxicities, (with the exception of headaches, that last continuously for 24 hours or longer)	Supportive care and neurological work-up as indicated for Grade 1. ICU transfer is recommended Anti-IL-6 therapy if associated with concurrent CRS, as described for Grade 2 neurotoxicity and if not administered previously. Dexamethasone 10 mg every 6 hours or methylprednisolone 1 mg/kg every 12 hours if refractory to anti-IL-6 therapy, or for neurotoxicity without concurrent CRS; continue corticosteroids until improvement to Grade 1 neurotoxicity and then taper (Table 20). Stage 1 or 2 papilloedema with CSF opening pressure <20 mmHg should be treated as per algorithm (Table 25). Consider repeat neuroimaging (CT or MRI) every 2 to 3 days if patient has persistent Grade ≥3 neurotoxicity.
Grade 4 neurologic toxicity of any duration **Any generalised seizures**	Supportive care and neurological work-up as outlined for Grade 1 neurotoxicity. ICU monitoring; consider mechanical ventilation for airway protection. Anti-IL-6 therapy and repeat neuroimaging as described for Grade 3 neurotoxicity. High-dose corticosteroids continued until improvement to Grade 1 neurotoxicity and then taper; for example, methylprednisolone 1 g/day for 3 days, followed by rapid taper at 250 mg every 12 hours for 2 days, 125 mg every 12 hours for 2 days, and 60 mg every 12 hours for 2 days (Table 20). For convulsive status epilepticus, treat as per algorithm (Table 24). Stage ≥3 papilloedema, with a CSF opening pressure ≥20 mmHg or cerebral oedema, should be treated as per algorithm (Table 25). **Worsening:** May consider use of lymphodepleting drugs such as CY (Garfall et al. 2015) or other drugs (Klinger et al. 2016) if unresponsive to standard immunosuppressive therapies.

Adapted from (Neelapu et al. 2018).
AE = adverse event; CRS = cytokine release syndrome; CSF = cerebrospinal fluid; CT = computed tomography; EEG = electroencephalogram; ICU = intensive care unit; IL = interleukin; i.v. = intravenous; MRI = magnetic resonance imaging.

Subjects were monitored for signs and symptoms indicative of Immune-Related Adverse Events owing to On-Target but Off-Tumour Toxicity with special attention to lung, brain and eyes.

Overview of Adverse Events

As of the cut-off date of 07-Feb-2024, 81.9% patients (104/127 patients) experienced treatment-emergent adverse events of ≥Grade 3 (Table 6):

Table 6: Overview of Treatment-emergent Adverse Events Post-obe-cel (Safety Set)

Parameter	09-Jun-2023 Cut-off		07-Feb-2024 Cut-off	
	All Grades (N=127) n (%)	Grade ≥ 3 (N=127) n (%)	All Grades (N=127) n (%)	Grade ≥ 3 (N=127) n (%)
Overall				
Any TEAE	127 (100)	102 (80.3)	127 (100)	**104 (81.9)**
Any obe-cel-related TEAE	118 (92.9)	75 (59.1)	**119 (93.7)**	**77 (60.6)**
Any death	53 (41.7)	NA	**64 (50.4)**	NA
Any serious TEAE	77 (60.6)	66 (52.0)	**83 (65.4)**	**71 (55.9)**
Any obe-cel-related serious TEAE	50 (39.4)	41 (32.3)	50 (39.4)	**40 (31.5)**
TEAEs Associated with Significant Safety Topics				
CRS	87 (68.5)	3 (2.4)	87 (68.5)	3 (2.4)
ICANS	29 (22.8)	9 (7.1)	29 (22.8)	9 (7.1)
Prolonged cytopenia	Not applicable			
Severe infections	92 (72.4)	55 (43.3)	**99 (78.0)**	**66 (52.0)**
Non-COVID-19 infections	81 (63.8)	50 (39.4)	**90 (70.9)**	**57 (44.9)**
HLH / MAS	2 (1.6)	2 (1.6)	2 (1.6)	2 (1.6)
Hypogammaglobulinaemia	10 (7.9)	1 (0.8)	**12 (9.4)**	**2 (1.6)**
TLS	1 (0.8)	1 (0.8)	1 (0.8)	1 (0.8)
GvHD [1]	7 (5.5)	3 (2.4)	**8 (6.3)**	**5 (3.9)**
Secondary malignancies related to obe-cel [2]	0	0	**0**	**0**
Hypersensitivity reactions	0	0	0	0

COVID-19=coronavirus disease 2019; CRS=cytokine release syndrome; GvHD=graft versus host disease; HLH=hemophagocytic lymphohistiocytosis; ICANS=immune effector cell-associated neurotoxicity syndrome; MAS=macrophage activation syndrome; NA=not applicable; TEAE=treatment-emergent adverse event; TLS=tumor lysis syndrome.
Changes compared to the 09-Jun-2023 cut-off date are indicated in **bold**.
[1] Aggravation of GvHD, irrespective of prior history of an allogeneic SCT or receipt of an allogeneic SCT after obe-cel infusion.
[2] Three patients had TEAEs of malignancies, however none were confirmed as secondary malignancies and none were related to obe-cel.

At least one serious treatment emergent adverse event was experienced by 65.4% (83/127) of patients and 50.4% of patients (64/127) have discontinued from the study because of death.

The high percentage of serious adverse events and deaths may be understood within the context of a disease with an associated high mortality.

Deaths

Prior to obe-cel infusion, 14.4% patients (22/153) enrolled in Phase Ib and Phase II of the FELIX study died after enrolment but before receiving obe-cel. All 22 patients had morphological disease at screening.

As of the cut-off date of 07-Feb-2024, 50.4% (64/127) of patients died post-obe-cel infusion. The most common primary reasons reported for death remained progressive disease (45 patients) and treatment emergent adverse events (17 patients).

2 patients were reported to have died owing to adverse events suspected to be related to obe-cel treatment by the Investigator: 1 patient owing to neutropenic sepsis; and 1 patient owing to acute respiratory distress syndrome and immune effector cell-associated neurotoxicity

syndrome (ICANS).

The high mortality of (about) 50% after exposure to obe-cel is understood in the context of the natural history / poor prognosis for adults with B-cell acute lymphoblastic leukaemia

Other Serious Adverse Events

As of the cut-off date of 07-Feb-2024, 65.4% (83/127) patients experienced at least one serious adverse event of any grade post-obe-cel treatment.

The most common serious treatment emergent adverse event, regardless of relationship to study treatment, was febrile neutropenia (17/127, 13.4%). Other serious treatment emergent adverse events occurring in ≥5% of patients included COVID-19 and pyrexia.

The most common serious treatment emergent adverse events (≥5% of patients) suspected to be related to study treatment by the Investigator were immune effector cell-associated neurotoxicity syndrome (ICANS, 9.4%), cytokine release syndrome (CRS, 7.9%), febrile neutropenia (6.3%) and hyper-ferritinaemia (5.5%). Data are presented in the following table:

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Table 14.3.2.4.1 Serious Treatment Emergent Adverse Events Anytime Post Obe-cel Infusion, With Suspected Relationship to Obe-cel, by Preferred Term By Disease Status at Pre-Conditioning
Safety Set - Phase Ib and Phase II - All Cohorts

	>=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)	
Preferred Term	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 serious TEAE with suspected relationship to obe-cel	37 (40.7)	29 (31.9)	12 (41.4)	10 (34.5)	1 (14.3)	1 (14.3)	50 (39.4)	40 (31.5)
Immune effector cell-associated neurotoxicity syndrome	12 (13.2)	8 (8.8)	0	0	0	0	12 (9.4)	8 (6.3)
Cytokine release syndrome	8 (8.8)	3 (3.3)	2 (6.9)	0	0	0	10 (7.9)	3 (2.4)
Febrile neutropenia	4 (4.4)	4 (4.4)	3 (10.3)	3 (10.3)	1 (14.3)	1 (14.3)	8 (6.3)	8 (6.3)
Hyperferritinaemia	7 (7.7)	7 (7.7)	0	0	0	0	7 (5.5)	7 (5.5)
Bone marrow failure	2 (2.2)	2 (2.2)	1 (3.4)	1 (3.4)	0	0	3 (2.4)	3 (2.4)
Lower respiratory tract infection	3 (3.3)	1 (1.1)	0	0	0	0	3 (2.4)	1 (0.8)
Neutrophil count decreased	2 (2.2)	2 (2.2)	1 (3.4)	1 (3.4)	0	0	3 (2.4)	3 (2.4)
Pneumonia	2 (2.2)	2 (2.2)	1 (3.4)	1 (3.4)	0	0	3 (2.4)	3 (2.4)
Confusional state	2 (2.2)	1 (1.1)	0	0	0	0	2 (1.6)	1 (0.8)
Diarrhoea	0	0	2 (6.9)	1 (3.4)	0	0	2 (1.6)	1 (0.8)
Haemophagocytic lymphohistiocytosis	1 (1.1)	1 (1.1)	1 (3.4)	1 (3.4)	0	0	2 (1.6)	2 (1.6)
Leukopenia	2 (2.2)	2 (2.2)	0	0	0	0	2 (1.6)	2 (1.6)
Neurotoxicity	1 (1.1)	0	1 (3.4)	0	0	0	2 (1.6)	0
Neutropenia	1 (1.1)	1 (1.1)	1 (3.4)	1 (3.4)	0	0	2 (1.6)	2 (1.6)
Pyrexia	0	0	2 (6.9)	1 (3.4)	0	0	2 (1.6)	1 (0.8)
Sepsis	2 (2.2)	2 (2.2)	0	0	0	0	2 (1.6)	2 (1.6)
Thrombocytopenia	1 (1.1)	1 (1.1)	1 (3.4)	1 (3.4)	0	0	2 (1.6)	2 (1.6)
Anaemia	1 (1.1)	1 (1.1)	0	0	0	0	1 (0.8)	1 (0.8)
Anal abscess	0	0	1 (3.4)	1 (3.4)	0	0	1 (0.8)	1 (0.8)
COVID-19 pneumonia	0	0	1 (3.4)	1 (3.4)	0	0	1 (0.8)	1 (0.8)
Clostridium difficile infection	0	0	1 (3.4)	1 (3.4)	0	0	1 (0.8)	1 (0.8)
Coagulopathy	1 (1.1)	1 (1.1)	0	0	0	0	1 (0.8)	1 (0.8)
Cognitive disorder	1 (1.1)	1 (1.1)	0	0	0	0	1 (0.8)	1 (0.8)
Disseminated intravascular coagulation	1 (1.1)	1 (1.1)	0	0	0	0	1 (0.8)	1 (0.8)
Encephalopathy	1 (1.1)	1 (1.1)	0	0	0	0	1 (0.8)	1 (0.8)
Enterococcal sepsis	1 (1.1)	1 (1.1)	0	0	0	0	1 (0.8)	1 (0.8)
Fusarium infection	1 (1.1)	1 (1.1)	0	0	0	0	1 (0.8)	1 (0.8)
Hepatic infection	0	0	1 (3.4)	1 (3.4)	0	0	1 (0.8)	1 (0.8)
Hypotension	0	0	1 (3.4)	0	0	0	1 (0.8)	0
Hypoxia	1 (1.1)	1 (1.1)	0	0	0	0	1 (0.8)	1 (0.8)
Infection	1 (1.1)	1 (1.1)	0	0	0	0	1 (0.8)	1 (0.8)
Mental status changes	1 (1.1)	1 (1.1)	0	0	0	0	1 (0.8)	1 (0.8)
Myelodysplastic syndrome	0	0	1 (3.4)	1 (3.4)	0	0	1 (0.8)	1 (0.8)
Nausea	0	0	1 (3.4)	1 (3.4)	0	0	1 (0.8)	1 (0.8)
Neutropenic sepsis	1 (1.1)	1 (1.1)	0	0	0	0	1 (0.8)	1 (0.8)
Pancytopenia	1 (1.1)	1 (1.1)	0	0	0	0	1 (0.8)	1 (0.8)
Perineal cellulitis	1 (1.1)	1 (1.1)	0	0	0	0	1 (0.8)	1 (0.8)
Pharyngitis	0	0	1 (3.4)	1 (3.4)	0	0	1 (0.8)	1 (0.8)
Portal hypertension	1 (1.1)	1 (1.1)	0	0	0	0	1 (0.8)	1 (0.8)
Respiratory failure	1 (1.1)	1 (1.1)	0	0	0	0	1 (0.8)	1 (0.8)
Stenotrophomonas infection	1 (1.1)	1 (1.1)	0	0	0	0	1 (0.8)	1 (0.8)
Upper respiratory tract infection	1 (1.1)	1 (1.1)	0	0	0	0	1 (0.8)	1 (0.8)
Vomiting	0	0	1 (3.4)	1 (3.4)	0	0	1 (0.8)	1 (0.8)

BM = bone marrow; EMD = extramedullary disease.
Adverse events (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.

The nature and many forms of reported serious adverse events are not unexpected in the context of a CAR-T cell therapy.

Adverse Events Prior to Obe-cel Infusion

In the period after enrolment but prior to first obe-cel infusion, which includes the administration of bridging and lymphodepletion therapies, the majority of enrolled patients (Enrolled Set, N=153) experienced at least one adverse event (84.3%, 129/153) and the majority of patients had at least one adverse event ≥ Grade 3 (66.0%, 101/153). Data are summarised in table 12:

Table 12: Adverse Events in ≥ 10% of Patients (System Organ Class or Preferred Term) After Enrollment and Prior to Obe-cel Infusion (Phase Ib and Phase II, Enrolled Set)

System Organ Class Preferred Term	Enrolled (N=153)	
	All grades n (%)	Grade ≥ 3 n (%)
Number of patients with any adverse event after enrollment and prior to obe-cel infusion	**129 (84.3)**	**101 (66.0)**
Blood and lymphatic system disorders	59 (38.6)	55 (35.9)
Febrile neutropenia	31 (20.3)	30 (19.6)
Anaemia	23 (15.0)	20 (13.1)
Cardiac disorders	19 (12.4)	2 (1.3)
Gastrointestinal disorders	83 (54.2)	14 (9.2)
Nausea	42 (27.5)	1 (0.7)
Constipation	25 (16.3)	0
Vomiting	22 (14.4)	1 (0.7)
Diarrhoea	18 (11.8)	2 (1.3)
General disorders and administration site conditions	56 (36.6)	7 (4.6)
Pyrexia	28 (18.3)	3 (2.0)
Fatigue	22 (14.4)	0
Infections and infestations	66 (43.1)	43 (28.1)
Injury, poisoning and procedural complications	19 (12.4)	3 (2.0)
Investigations	46 (30.1)	33 (21.6)
Neutrophil count decreased	17 (11.1)	17 (11.1)
Platelet count decreased	15 (9.8)	13 (8.5)
White blood cell count decreased	14 (9.2)	14 (9.2)
Metabolism and nutrition disorders	48 (31.4)	12 (7.8)
Hypokalaemia	17 (11.1)	4 (2.6)
Musculoskeletal and connective tissue disorders	31 (20.3)	6 (3.9)
Nervous system disorders	31 (20.3)	5 (3.3)
Headache	21 (13.7)	1 (0.7)
Psychiatric disorders	20 (13.1)	1 (0.7)
Respiratory, thoracic and mediastinal disorders	39 (25.5)	7 (4.6)
Skin and subcutaneous tissue disorders	20 (13.1)	1 (0.7)
Vascular disorders	26 (17.0)	12 (7.8)

The nature of the adverse events prior to exposure to obe-cel is considered consistent with the underlying disease and medicinal products employed in bridging & lymphodepletion

Overall Treatment-emergent Adverse Event Profile After Obe-cel Infusion

An overview of data is presented:

Table 6: Overview of Treatment-emergent Adverse Events Post-obe-cel (Safety Set)

Parameter	09-Jun-2023 Cut-off		07-Feb-2024 Cut-off	
	All Grades (N=127) n (%)	Grade ≥ 3 (N=127) n (%)	All Grades (N=127) n (%)	Grade ≥ 3 (N=127) n (%)
Overall				
Any TEAE	127 (100)	102 (80.3)	127 (100)	**104 (81.9)**
Any obe-cel-related TEAE	118 (92.9)	75 (59.1)	**119 (93.7)**	**77 (60.6)**
Any death	53 (41.7)	NA	**64 (50.4)**	NA
Any serious TEAE	77 (60.6)	66 (52.0)	**83 (65.4)**	**71 (55.9)**
Any obe-cel-related serious TEAE	50 (39.4)	41 (32.3)	50 (39.4)	**40 (31.5)**
TEAEs Associated with Significant Safety Topics				
CRS	87 (68.5)	3 (2.4)	87 (68.5)	3 (2.4)
ICANS	29 (22.8)	9 (7.1)	29 (22.8)	9 (7.1)
Prolonged cytopenia	Not applicable			
Severe infections	92 (72.4)	55 (43.3)	**99 (78.0)**	**66 (52.0)**
Non-COVID-19 infections	81 (63.8)	50 (39.4)	**90 (70.9)**	**57 (44.9)**
HLH / MAS	2 (1.6)	2 (1.6)	2 (1.6)	2 (1.6)
Hypogammaglobulinaemia	10 (7.9)	1 (0.8)	**12 (9.4)**	**2 (1.6)**
TLS	1 (0.8)	1 (0.8)	1 (0.8)	1 (0.8)
GvHD [1]	7 (5.5)	3 (2.4)	**8 (6.3)**	**5 (3.9)**
Secondary malignancies related to obe-cel [2]	0	0	**0**	**0**
Hypersensitivity reactions	0	0	0	0

COVID-19=coronavirus disease 2019; CRS=cytokine release syndrome; GvHD=graft versus host disease; HLH=hemophagocytic lymphohistiocytosis; ICANS=immune effector cell-associated neurotoxicity syndrome; MAS=macrophage activation syndrome; NA=not applicable; TEAE=treatment-emergent adverse event; TLS=tumor lysis syndrome.
Changes compared to the 09-Jun-2023 cut-off date are indicated in **bold**.
[1] Aggravation of GvHD, irrespective of prior history of an allogeneic SCT or receipt of an allogeneic SCT after obe-cel infusion.
[2] Three patients had TEAEs of malignancies, however none were confirmed as secondary malignancies and none were related to obe-cel.

64/127 patients (50.4%) have discontinued from the study because of death.
40/127 subjects had an obe-cel related serious treatment emergent adverse event
77/127 subjects had an obe-cel related treatment emergent adverse event

The pattern of treatment emergent adverse events may be understood in the context of the underlying disease and exposure to obe-cel.

Common treatment emergent adverse events after obe-cel infusion

The most common treatment emergent adverse events (≥10% of patients) after obe-cel infusion and regardless of causality are presented in Table 7:

Table 7: 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)

Primary System Organ Class Preferred Term	09-Jun-2023 Cut-off		07-Feb-2024 Cut-off	
	All Grades (N=127) n (%)	Grade ≥3 (N=127) n (%)	All Grades (N=127) n (%)	Grade ≥3 (N=127) n (%)
Blood and lymphatic system disorders	76 (59.8)	65 (51.2)	76 (59.8)	65 (51.2)
Febrile neutropenia	31 (24.4)	30 (23.6)	31 (24.4)	30 (23.6)
Anaemia	29 (22.8)	25 (19.7)	**30 (23.6)**	**26 (20.5)**
Neutropenia	28 (22.0)	25 (19.7)	**29 (22.8)**	**26 (20.5)**
Thrombocytopenia	18 (14.2)	16 (12.6)	18 (14.2)	16 (12.6)
Cardiac disorders	20 (15.7)	2 (1.6)	20 (15.7)	2 (1.6)
Eye disorders	14 (11.0)	1 (0.8)	14 (11.0)	1 (0.8)
Gastrointestinal disorders	78 (61.4)	15 (11.8)	**79 (62.2)**	**17 (13.4)**
Nausea	33 (26.0)	3 (2.4)	33 (26.0)	3 (2.4)
Diarrhoea	31 (24.4)	1 (0.8)	**32 (25.2)**	**2 (1.6)**
Vomiting	21 (16.5)	1 (0.8)	21 (16.5)	1 (0.8)
Abdominal pain	16 (12.6)	2 (1.6)	16 (12.6)	2 (1.6)
Constipation	16 (12.6)	0	16 (12.6)	0
General disorders and administration site conditions	67 (52.8)	10 (7.9)	**66 (52.0)**	**9 (7.1)**
Pyrexia	36 (28.3)	2 (1.6)	**37 (29.1)**	2 (1.6)
Fatigue	24 (18.9)	2 (1.6)	24 (18.9)	2 (1.6)
Hepatobiliary disorders	13 (10.2)	7 (5.5)	**14 (11.0)**	**8 (6.3)**
Immune system disorders	90 (70.9)	9 (7.1)	**91 (71.7)**	**12 (9.4)**
Cytokine release syndrome	87 (68.5)	3 (2.4)	87 (68.5)	3 (2.4)
Infections and infestations	92 (72.4)	55 (43.3)	**99 (78.0)**	**66 (52.0)**
COVID-19	21 (16.5)	4 (3.1)	**23 (18.1)**	**8 (6.3)**
Injury, poisoning and procedural complications	23 (18.1)	3 (2.4)	23 (18.1)	3 (2.4)
Investigations	62 (48.8)	46 (36.2)	**64 (50.4)**	**48 (37.8)**
Neutrophil count decreased	24 (18.9)	24 (18.9)	**25 (19.7)**	**25 (19.7)**
Platelet count decreased	17 (13.4)	15 (11.8)	**18 (14.2)**	**16 (12.6)**
Alanine aminotransferase increased	15 (11.8)	6 (4.7)	15 (11.8)	6 (4.7)
Weight decreased	13 (10.2)	2 (1.6)	13 (10.2)	2 (1.6)
Metabolism and nutrition disorders	62 (48.8)	29 (22.8)	62 (48.8)	29 (22.8)
Hypokalaemia	27 (21.3)	8 (6.3)	27 (21.3)	8 (6.3)
Hyperferritinaemia	17 (13.4)	13 (10.2)	17 (13.4)	13 (10.2)
Decreased appetite	15 (11.8)	4 (3.1)	15 (11.8)	4 (3.1)
Hypomagnesaemia	14 (11.0)	0	14 (11.0)	0
Musculoskeletal and connective tissue disorders	48 (37.8)	5 (3.9)	**50 (39.4)**	**7 (5.5)**
Arthralgia	13 (10.2)	0	13 (10.2)	0
Nervous system disorders	73 (57.5)	13 (10.2)	73 (57.5)	13 (10.2)
Headache	30 (23.6)	0	30 (23.6)	0
Immune effector cell-associated neurotoxicity syndrome	29 (22.8)	9 (7.1)	29 (22.8)	9 (7.1)
Psychiatric disorders	35 (27.6)	6 (4.7)	35 (27.6)	6 (4.7)
Confusional state	16 (12.6)	3 (2.4)	16 (12.6)	3 (2.4)
Renal and urinary disorders	21 (16.5)	5 (3.9)	21 (16.5)	5 (3.9)
Respiratory, thoracic and mediastinal disorders	44 (34.6)	13 (10.2)	44 (34.6)	**14 (11.0)**
Cough	15 (11.8)	0	15 (11.8)	0
Skin and subcutaneous tissue disorders	30 (23.6)	1 (0.8)	30 (23.6)	1 (0.8)
Vascular disorders	40 (31.5)	10 (7.9)	40 (31.5)	10 (7.9)
Hypotension	28 (22.0)	6 (4.7)	28 (22.0)	6 (4.7)

COVID-19=coronavirus disease 2019.
Changes compared to the 09-Jun-2023 cut-off date are indicated in **bold**.

Treatment-related treatment emergent adverse events after obe-cel infusion

119 patients (93.7%) and 77 patients (60.6%) experienced TEAEs of any grade and ≥Grade 3, respectively, suspected to be related to obe-cel by the Investigator. Data are summarised in the following table:

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Table 14.3.1.5.1 Treatment Emergent Adverse Events Anytime Post Obe-cel Infusion, With Suspected Relationship to Obe-cel, by Preferred Term
By Disease Status at Pre-Conditioning
Safety Set - Phase Ib and Phase II - All Cohorts

	Total (N=127)	
Preferred Term	All grades n (%)	Grade >=3 n (%)
Number of patients with any TEAE with suspected relationship to obe-cel	119 (93.7)	77 (60.6)
Cytokine release syndrome	87 (68.5)	3 (2.4)
Immune effector cell-associated neurotoxicity syndrome	29 (22.8)	9 (7.1)
Pyrexia	27 (21.3)	1 (0.8)
Febrile neutropenia	20 (15.7)	20 (15.7)
Neutropenia	20 (15.7)	19 (15.0)
Anaemia	18 (14.2)	14 (11.0)
Headache	17 (13.4)	0
Hyperferritinaemia	17 (13.4)	13 (10.2)
Nausea	17 (13.4)	2 (1.6)
Neutrophil count decreased	17 (13.4)	17 (13.4)
Fatigue	16 (12.6)	1 (0.8)
Hypotension	16 (12.6)	2 (1.6)
Confusional state	14 (11.0)	3 (2.4)
Thrombocytopenia	14 (11.0)	12 (9.4)
Hypogammaglobulinaemia	11 (8.7)	2 (1.6)
Chills	10 (7.9)	0
Diarrhoea	10 (7.9)	2 (1.6)
Platelet count decreased	9 (7.1)	8 (6.3)
Sinus tachycardia	7 (5.5)	0
White blood cell count decreased	7 (5.5)	5 (3.9)
Alanine aminotransferase increased	6 (4.7)	3 (2.4)
Hypofibrinogenaemia	6 (4.7)	4 (3.1)
Leukopenia	6 (4.7)	4 (3.1)
Vomiting	6 (4.7)	1 (0.8)
B-cell aplasia	5 (3.9)	0
C-reactive protein increased	5 (3.9)	1 (0.8)
Hypoxia	5 (3.9)	3 (2.4)
Tremor	5 (3.9)	0
Arthralgia	4 (3.1)	0
Aspartate aminotransferase increased	4 (3.1)	3 (2.4)
Blood alkaline phosphatase increased	4 (3.1)	0
Hyperbilirubinaemia	4 (3.1)	2 (1.6)
Lower respiratory tract infection	4 (3.1)	2 (1.6)
Lymphopenia	4 (3.1)	2 (1.6)
Myalgia	4 (3.1)	0
Rash	4 (3.1)	1 (0.8)
Asthenia	3 (2.4)	1 (0.8)
Bone marrow failure	3 (2.4)	3 (2.4)
Bone pain	3 (2.4)	0
Cytomegalovirus infection reactivation	3 (2.4)	0
Decreased appetite	3 (2.4)	1 (0.8)
Disseminated intravascular coagulation	3 (2.4)	2 (1.6)
Dizziness	3 (2.4)	0
Oral candidiasis	3 (2.4)	0
Pain	3 (2.4)	0
Pain in extremity	3 (2.4)	0
Pancytopenia	3 (2.4)	2 (1.6)
Pneumonia	3 (2.4)	3 (2.4)
Stomatitis	3 (2.4)	1 (0.8)
Agitation	2 (1.6)	1 (0.8)
Blood lactate dehydrogenase increased	2 (1.6)	0
Coagulopathy	2 (1.6)	1 (0.8)
Constipation	2 (1.6)	0
Confusion	2 (1.6)	0
Depressed level of consciousness	2 (1.6)	1 (0.8)
Dysarthria	2 (1.6)	0
Dysgraphia	2 (1.6)	0
Enterococcal bacteraemia	2 (1.6)	1 (0.8)
Graft versus host disease	2 (1.6)	2 (1.6)
Haemophagocytic lymphohistiocytosis	2 (1.6)	2 (1.6)
Hypertriglyceridaemia	2 (1.6)	0
Interleukin-2 receptor increased	2 (1.6)	2 (1.6)
Malaise	2 (1.6)	0
Mental status changes	2 (1.6)	1 (0.8)
Neurotoxicity	2 (1.6)	0
Respiratory failure	2 (1.6)	2 (1.6)

Table 14.3.1.5.1 Treatment Emergent Adverse Events Anytime Post Obe-cel Infusion, With Suspected Relationship to Obe-cel, by Preferred Term
By Disease Status at Pre-Conditioning
Safety Set - Phase Ib and Phase II - All Cohorts

	Total (N=127)	
Preferred Term	All grades n (%)	Grade >=3 n (%)
Sepsis	2 (1.6)	2 (1.6)
Serum ferritin increased	2 (1.6)	1 (0.8)
Stenotrophomonas infection	2 (1.6)	1 (0.8)
Upper respiratory tract infection	2 (1.6)	1 (0.8)
Weight decreased	2 (1.6)	1 (0.8)
Abdominal pain	1 (0.8)	0
Abscess limb	1 (0.8)	0
Adrenal insufficiency	1 (0.8)	0
Anal abscess	1 (0.8)	1 (0.8)
Anal fissure	1 (0.8)	0
Angioedema	1 (0.8)	0
Anxiety	1 (0.8)	0
Aphasia	1 (0.8)	0
Arthropathy	1 (0.8)	0
Ascites	1 (0.8)	1 (0.8)
BK virus infection	1 (0.8)	0
Back pain	1 (0.8)	0
Bacteraemia	1 (0.8)	0
Balance disorder	1 (0.8)	0
Blood bilirubin increased	1 (0.8)	1 (0.8)
Blood fibrinogen decreased	1 (0.8)	1 (0.8)
Blood phosphorus decreased	1 (0.8)	1 (0.8)
Body temperature increased	1 (0.8)	0
Bradycardia	1 (0.8)	0
Bronchitis fungal	1 (0.8)	1 (0.8)
COVID-19	1 (0.8)	0
COVID-19 pneumonia	1 (0.8)	1 (0.8)
Cellulitis	1 (0.8)	0
Cerebral microhaemorrhage	1 (0.8)	0
Clostridium difficile infection	1 (0.8)	1 (0.8)
Cognitive disorder	1 (0.8)	1 (0.8)
Corynebacterium infection	1 (0.8)	0
Cough	1 (0.8)	0
Delirium	1 (0.8)	0
Depression	1 (0.8)	0
Disturbance in attention	1 (0.8)	0
Dry eye	1 (0.8)	0
Dyscalculia	1 (0.8)	0
Dyskinesia	1 (0.8)	0
Dyspnoea	1 (0.8)	1 (0.8)
Dysuria	1 (0.8)	0
Embolism	1 (0.8)	1 (0.8)
Encephalopathy	1 (0.8)	1 (0.8)
Enterococcal sepsis	1 (0.8)	1 (0.8)
Enterocolitis infectious	1 (0.8)	0
Eosinophilia	1 (0.8)	0
Epistaxis	1 (0.8)	0
Erythema	1 (0.8)	0
Facial asymmetry	1 (0.8)	0
Fall	1 (0.8)	0
Flushing	1 (0.8)	0
Fusarium infection	1 (0.8)	1 (0.8)
Gamma-glutamyltransferase increased	1 (0.8)	1 (0.8)
Haematotoxicity	1 (0.8)	1 (0.8)
Haematuria	1 (0.8)	0
Haemorrhage intracranial	1 (0.8)	0
Haemorrhoids	1 (0.8)	0
Hallucination	1 (0.8)	0
Hepatic infection	1 (0.8)	1 (0.8)
Hepatomegaly	1 (0.8)	0
Herpes zoster oticus	1 (0.8)	0
Hot flush	1 (0.8)	0
Hydrocephalus	1 (0.8)	1 (0.8)
Hyperglycaemia	1 (0.8)	1 (0.8)
Hyperhidrosis	1 (0.8)	0
Hypertension	1 (0.8)	0
Hypertransaminasaemia	1 (0.8)	1 (0.8)
Hypoalbuminaemia	1 (0.8)	0

Table 14.3.1.5.1 Treatment Emergent Adverse Events Anytime Post Obe-cel Infusion, With Suspected Relationship to Obe-cel, by Preferred Term
By Disease Status at Pre-Conditioning
Safety Set - Phase Ib and Phase II - All Cohorts

	Total (N=127)	
Preferred Term	All grades n (%)	Grade >=3 n (%)
Hypocalcaemia	1 (0.8)	0
Hypoglobulinaemia	1 (0.8)	0
Hypophagia	1 (0.8)	1 (0.8)
Hypophosphataemia	1 (0.8)	0
Hypothermia	1 (0.8)	0
Immune effector cell encephalopathy score	1 (0.8)	0
Incontinence	1 (0.8)	0
Infection	1 (0.8)	1 (0.8)
Influenza like illness	1 (0.8)	0
Infusion related reaction	1 (0.8)	0
Irritability	1 (0.8)	0
Left ventricular dysfunction	1 (0.8)	0
Lethargy	1 (0.8)	0
Lower respiratory tract infection fungal	1 (0.8)	0
Lymphocyte count decreased	1 (0.8)	1 (0.8)
Malnutrition	1 (0.8)	0
Memory impairment	1 (0.8)	0
Mental impairment	1 (0.8)	0
Muscle spasms	1 (0.8)	0
Myelodysplastic syndrome	1 (0.8)	1 (0.8)
Neutropenic sepsis	1 (0.8)	1 (0.8)
Night sweats	1 (0.8)	0
Nodule	1 (0.8)	0
Non-alcoholic steatohepatitis	1 (0.8)	0
Oedema peripheral	1 (0.8)	0
Oesophagitis	1 (0.8)	0
Orthostatic hypotension	1 (0.8)	0
Otitis media	1 (0.8)	0
Overlap syndrome	1 (0.8)	1 (0.8)
Palpitations	1 (0.8)	0
Panic attack	1 (0.8)	0
Paraesthesia	1 (0.8)	0
Parainfluenzae virus infection	1 (0.8)	1 (0.8)
Perineal cellulitis	1 (0.8)	1 (0.8)
Perseveration	1 (0.8)	0
Pharyngitis	1 (0.8)	1 (0.8)
Physical deconditioning	1 (0.8)	0
Pleuritic pain	1 (0.8)	0
Portal hypertension	1 (0.8)	1 (0.8)
Presyncope	1 (0.8)	0
Proctitis	1 (0.8)	0
Productive cough	1 (0.8)	0
Pruritus	1 (0.8)	0
Pseudomonas infection	1 (0.8)	0
Respiratory syncytial virus infection	1 (0.8)	0
Rhinovirus infection	1 (0.8)	0
Staphylococcal infection	1 (0.8)	1 (0.8)
Streptococcal bacteraemia	1 (0.8)	1 (0.8)
Systemic candida	1 (0.8)	0
Tachycardia	1 (0.8)	0
Taste disorder	1 (0.8)	0
Troponin T increased	1 (0.8)	0
Urinary tract infection	1 (0.8)	0
Vision blurred	1 (0.8)	0
Vulvovaginal discomfort	1 (0.8)	0
Vulvovaginal pruritus	1 (0.8)	0
Vulvovaginal rash	1 (0.8)	0
Wheezing	1 (0.8)	0

BM = bone marrow; EMD = extramedullary disease.
Adverse events (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.

The most commonly reported events in this category (≥10%) were cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS), irrespective of grade (68.5% [87/127] and 22.8% [29/127], respectively).

The most commonly reported events in this category (≥ 10%) with severity ≥Grade 3 were febrile neutropenia (15.7%), neutropenia (15.0%), neutrophil count decreased (13.4%) and anaemia (11.0%).

The pattern of treatment-emergent adverse events considered related to obe-cel is considered consistent with that expected for a CAR-T cell therapy.

Adverse events of special interest

Cytokine Release Syndrome (CRS)

As of 07-Feb-2024:

- 87/127 patients (68.5%) in the Safety Set experienced Cytokine Release Syndrome (CRS) of any grade post-obe-cel infusion.
- 3 patients (2.4%, 3/127) experienced Grade 3 Cytokine Release Syndrome (CRS)
- no patients experienced Grade 4 or 5 Cytokine Release Syndrome (CRS)

Overall, the median time to onset of Cytokine Release Syndrome (CRS) was 8 days (range: 1 to 23 days) with a median duration of 5 days (range: 1 to 21 days).

Of the 87 patients who experienced Cytokine Release Syndrome (CRS), most (56/87, 64%) experienced this after the first but prior to the second infusion of obe-cel.

Of the 87 patients who experienced Cytokine Release Syndrome (CRS), 80% (70 patients) had ≥5% blasts in their bone marrow at the time of lymphodepletion with 39% (34/87) presenting with >75% blast in their bone marrow.

With reference to table 5, below.
The median time to onset of cytokine release syndrome was 6 days after the first infusion and a median of 2 days after the second infusion.
For both first and second infusions, the event occurred up to 2 weeks after exposure.
The event lasted up to 21 days. 55% of subjects received anti-cytokine therapy.

Data on Cytokine Release Syndrome (CRS) are summarised in the following table:

Appendix 1 Table 5 Cytokine Release Syndrome Any Time Post-obe-cel Infusion (Phase Ib and Phase II, Safety Set)

	09-Jun-2023 Cut-off	07-Feb-2024 Cut-off
	All Patients (N=127)	All Patients (N=127)
CRS - n (%)	87 (68.5)	87 (68.5)
Maximum CRS grade - n (%)		
Grade 1	47 (37.0)	47 (37.0)
Grade 2	37 (29.1)	37 (29.1)
Grade 3	3 (2.4)	3 (2.4)
Grade 4	0	0
Grade 5	0	0
Time to onset of CRS (days) [1]		
N	87	87
Mean (SD)	7.8 (3.91)	7.8 (3.91)
Median	8.0	8.0
Q1 - Q3	4.0 - 10.0	4.0 - 10.0
Min – Max	1 - 23	1 - 23
Onset of CRS (days) categorized - n (%)		
After 1st obe-cel infusion and before 2nd obe-cel infusion	56 (44.1)	56 (44.1)
Time from 1st obe-cel infusion to onset of CRS (days) [1]		
N	56	56
Mean (SD)	5.8 (2.86)	5.8 (2.86)
Median	6.0	6.0
Q1 - Q3	3.0 - 8.5	3.0 - 8.5
Min – Max	1 - 10	1 - 10
After 2nd obe-cel infusion	31 (24.4)	31 (24.4)
Time from 2nd obe-cel infusion to onset of CRS (days) [2]		
N	31	31
Mean (SD)	2.7 (2.64)	2.7 (2.64)
Median	2.0	2.0
Q1 - Q3	1.0 - 3.0	1.0 - 3.0
Min - Max	1 - 14	1 - 14
Duration of CRS (days)		
n	87	87
Mean (SD)	5.6 (3.24)	**5.6 (3.28)**
Median	5.0	5.0
Q1 - Q3	3.0 - 7.0	3.0 - 7.0
Min - Max	1 - 21	1 - 21
Systemic anti-cytokine therapy given - n (%)	70 (55.1)	70 (55.1)
Tocilizumab	66 (52.0)	66 (52.0)
Corticosteroids	19 (15.0)	**20 (15.7)**
Other anti-cytokine therapy	9 (7.1)	**12 (9.4)**

CRS=cytokine release syndrome; Q=quartile; SD=standard deviation
CRS grading was based on ASTCT consensus grading (Lee et al, 2019).
[1] Time to onset (days)=[(Date of start of CRS - Date of first obe-cel infusion) + 1].
[2] Time to onset (days)=[(Date of start of CRS - Date of second obe-cel infusion) + 1].
Data cut-off: 07-Feb-2024.
Changes compared to the 09-Jun-2023 cut-off date are indicated in **bold**.

<u>Immune Effector Cell-associated Neurotoxicity Syndrome (ICANS)</u>
As of 07-Feb-2024:

- 29 patients (22.8%, 29/127) in the Safety Set experienced immune effector cell-associated neurotoxicity syndrome (ICANS).
- 7/127 patients (7.1%) experienced immune effector cell-associated neurotoxicity syndrome (ICANS) of Grade 3
- Grade 4 and Grade 5 [1 patient (0.8%) each].

Overall, the median time to onset for immune effector cell-associated neurotoxicity syndrome (ICANS) events was 12 days (range: 1 to 31 days) with a median duration of 8 days (range: 1 to 53 days).

Among the 29 patients who experienced immune effector cell-associated neurotoxicity syndrome (ICANS), 62% (18/29) experienced immune effector cell-associated neurotoxicity syndrome (ICANS) after the second infusion.

Of the 29 patients who experienced immune effector cell-associated neurotoxicity syndrome (ICANS), 90% (26 patients) had ≥5% blast in the bone marrow at lymphodepletion.

All 9 patients who experienced ≥Grade 3 immune effector cell-associated neurotoxicity syndrome (ICANS) had ≥5% blast in the bone marrow at lymphodepletion with 56% (5/9) presenting with >75% blasts in their bone marrow.

With reference to table 6, below.
The median time to onset of immune effector cell-associated neurotoxicity syndrome after the first infusion was 8 days (up to a maximum of 10 days)

The median time to onset of immune effector cell-associated neurotoxicity syndrome after the second infusion was 6.5 days (up to a maximum of 22 days)

The event lasted up to 53 days. 19% of subjects were administered anti-ICANS therapy, as described in the table.

Data are summarised in the following table:

Appendix 1 Table 6 ICANS Any Time Post-obe-cel Infusion (Phase Ib and Phase II, Safety Set)

	09-Jun-2023 Cut-off	07-Feb-2024 Cut-off
	All Patients (N=127)	All Patients (N=127)
ICANS - n (%)	29 (22.8)	29 (22.8)
Maximum ICANS grade - n (%)		
Grade 1	13 (10.2)	13 (10.2)
Grade 2	7 (5.5)	7 (5.5)
Grade 3	7 (5.5)	7 (5.5)
Grade 4	1 (0.8)	1 (0.8)
Grade 5	1 (0.8)	1 (0.8)
Time to onset of ICANS (days) [1]		
N	29	29
Mean (SD)	13.0 (7.65)	13.0 (7.65)
Median	12.0	12.0
Q1 - Q3	8.0 - 18.0	8.0 - 18.0
Min - Max	1 - 31	1 - 31
After 1st obe-cel infusion and before 2nd obe-cel infusion	11 (8.7)	11 (8.7)
N	11	11
Mean (SD)	5.6 (3.44)	5.6 (3.44)
Median	8.0	8.0
Q1 - Q3	2.0 - 8.0	2.0 - 8.0
Min - Max	1 - 10	1 - 10
After 2nd obe-cel infusion [2]	18 (14.2)	18 (14.2)
N	18	18
Mean (SD)	8.5 (5.50)	8.5 (5.50)
Median	6.5	6.5
Q1 - Q3	5.0 - 13.0	5.0 - 13.0
Min - Max	2 - 22	2 - 22
Duration of ICANS (days)		
N	29	29
Mean (SD)	11.9 (12.77)	11.9 (12.77)
Median	8.0	8.0
Q1 - Q3	4.0 - 13.0	4.0 - 13.0
Min - Max	1 - 53	1 - 53
Therapy given for ICANS - n (%)	24 (18.9)	24 (18.9)
Anti-epileptics	12 (9.4)	12 (9.4)
Corticosteroids	24 (18.9)	24 (18.9)
Other	8 (6.3)	**9 (7.1)**

ICANS=immune effector cell-associated neurotoxicity syndrome; Q=quartile; SD=standard deviation.
ICANS grading was based on ASTCT consensus grading (Lee et al, 2019).
[1] Time to onset (days) = [(Date of start of ICANS - Date of first obe-cel infusion) + 1].
[2] Time to onset (days) = [(Date of start of ICANS - Date of second obe-cel infusion) + 1]. Changes compared to the 09-Jun-2023 cut-off date are indicated in **bold**.

Prolonged Cytopenia

The FELIX study enrolled a heavily pre-treated population including a large proportion of patients having received previous allogeneic stem cell transplant. This can result in reduced bone marrow reserve that will affect the ability of subjects to maintain blood counts in the reference intervals. At enrolment, 34.6% of patients (44/127) had ≥Grade 3 neutropenia and 33.9% of patients (43/127) had ≥Grade 3 thrombocytopenia.

After lymphodepletion, 74.8% (95/127) showed ≥Grade 3 neutropenia and 40.9% (52/127) showed ≥Grade 3 thrombocytopenia.

It is acknowledged that the lymphodepletion regimen would exacerbate neutropenia and thrombocytopenia, as described by the applicant.

Grade ≥3 ongoing cytopenias at Day 28, month 2 and month 3 for those who achieved CR or CRi are shown in the following table:

Table 14.3.5.1.3 Grade 3 or 4 Neutropenia and Thrombocytopenia at Day 28, Month 2, or Month 3
Infused Set - Phase Ib and Phase II - All Cohorts
Patients Who Achieved BOR of CR or CRi After First Obe-cel Infusion per IRRC Assessment

	Patients Who Achieved CR or CRi (N=99)		
	At Day 28 n (%)	At Month 2 n (%)	At Month 3 n (%)
Grade 3 or 4 neutropenia or thrombocytopenia not resolved	68 (68.7)	32 (32.3)	20 (20.2)
Grade 4 neutropenia or thrombocytopenia not resolved	52 (52.5)	19 (19.2)	10 (10.1)
Grade 3 or 4 neutropenia not resolved	58 (58.6)	23 (23.2)	13 (13.1)
Grade 4 neutropenia not resolved	44 (44.4)	11 (11.1)	5 (5.1)
Grade 3 or 4 thrombocytopenia not resolved	48 (48.5)	20 (20.2)	11 (11.1)
Grade 4 thrombocytopenia not resolved	27 (27.3)	16 (16.2)	6 (6.1)

The above table suggests that the described cytopenias resolve over time (though persist in a notable percentage of subjects up to month 3).

Time to recovery to different thresholds (≥0.5 or ≥1 × 10^9/L for neutrophil count; ≥50 or ≥100 × 10^9/L for platelet count) are shown in the following table:

Appendix 1 Table 7 Time of Recovery to Neutrophil and Platelet Count in Responders (Phase Ib and Phase II, Safety Set)

	09-Jun-2023 Cut-off				07-Feb-2024 Cut-off			
	Neutrophils (×10^9/L)		Platelets (×10^9/L)		Neutrophils (×10^9/L)		Platelets (×10^9/L)	
	≥ 0.5	≥ 1.0	≥ 50	≥ 100	≥ 0.5	≥ 1.0	≥ 50	≥ 100
	(N=98)	(N=98)	(N=98)	(N=98)	(N=99)	(N=99)	(N=99)	(N=99)
No. of events - n (%)	93 (94.9)	92 (93.9)	91 (92.9)	80 (81.6)	**94 (94.9)**	**93 (93.9)**	**93 (93.9)**	**82 (82.8)**
No. of censored observations - n (%) [1]	5 (5.1)	6 (6.1)	7 (7.1)	18 (18.4)	5 (5.1)	6 (6.1)	**6 (6.1)**	**17 (17.2)**
Ongoing neutrophil count < 0.5 (10^9/L)	5 (5.1)	6 (6.1)	7 (7.1)	18 (18.4)	5 (5.1)	6 (6.1)	**6 (6.1)**	**17 (17.2)**
Min - Max follow-up (months)	0.0 - 4.3	0.0 - 6.2	0.0 - 12.1	0.0 - 18.2+	0.0 - 4.3	0.0 - 6.2	0.0 - 12.1	**0.0 - 24.0+**
Quartile Estimates (95% CI) (month) [2]								
25th	0.5 (0.4, 0.5)	0.7 (0.6, 0.9)	0.0 (NE, NE)	0.7 (0.0, 1.0)	0.5 (0.4, 0.5)	0.7 (0.6, 0.9)	0.0 (NE, NE)	0.7 (0.0, 1.0)
50th	0.7 (0.5, 0.9)	1.9 (1.0, 1.9)	0.7 (0.3, 1.8)	2.0 (1.9, 2.1)	0.7 (0.5, 0.9)	1.9 (1.0, 1.9)	0.7 (0.3, **1.7**)	2.0 (1.9, 2.1)
75th	1.9 (1.5, 2.1)	2.1 (2.0, 2.3)	2.0 (1.9, 2.3)	3.1 (2.1, 6.0)	1.9 (1.5, 2.1)	2.1 (2.0, 2.3)	2.0 (1.9, **2.1**)	3.1 (2.1, 6.0)
% Probability estimate of recovery (95% CI) [3]								
1 month	65.0 (55.5, 74.4)	45.5 (34.3, 54.0)	57.3 (47.7, 67.2)	36.0 (27.3, 46.4)	**65.4 (55.9, 74.7)**	**44.1 (34.9, 54.5)**	**57.7 (48.2, 67.5)**	**36.7 (28.0, 47.0)**
2 months	76.0 (67.0, 84.0)	59.8 (50.1, 69.7)	71.1 (61.9, 79.8)	47.0 (37.6, 57.6)	**76.2 (67.3, 84.2)**	**60.2 (50.6, 70.0)**	**71.4 (62.3, 80.0)**	**47.6 (38.1, 58.0)**
3 months	97.3 (91.8, 99.5)	89.1 (81.6, 94.6)	88.3 (80.6, 93.9)	70.7 (61.1, 79.7)	**97.4 (91.9, 99.5)**	**89.2 (81.8, 94.6)**	**88.4 (80.8, 94.0)**	**71.0 (61.5, 79.9)**
4 months	98.7 (93.7, 99.9)	96.4 (90.7, 99.0)	92.2 (85.2, 96.7)	78.0 (68.9, 86.0)	98.7 (93.7, 99.9)	96.4 (90.8, 99.0)	**92.3 (85.3, 96.7)**	**78.2 (69.2, 86.1)**
5 months	100.0 (NE, NE)	97.6 (92.4, 99.5)	93.5 (86.8, 97.5)	81.9 (73.1, 89.2)	100.0 (NE, NE)	97.6 (**92.5**, 99.5)	**93.6 (86.9, 97.5)**	**82.1 (73.3, 89.3)**
6 months		97.6 (92.4, 99.5)	95.1 (88.6, 98.5))	83.4 (74.6, 90.5)		97.6 (**92.5**, 99.5)	**94.8 (88.5, 98.3)**	**83.5 (74.8, 90.4)**
7 months		100.0 (NE, NE)	97.6 (90.4, 99.7)	88.4 (79.9, 94.4)		100.0 (NE, NE)	**96.6 (90.4, 99.2)**	**88.0 (79.7, 94.0)**
8 months			97.6 (90.4, 99.7)	88.4 (79.9, 94.4)			**96.6 (90.4, 99.2)**	**88.0 (79.7, 94.0)**
9 months			97.6 (90.4, 99.7)	88.4 (79.9, 94.4)			**96.6 (90.4, 99.2)**	**88.0 (79.7, 94.0)**
10 months			97.6 (90.4, 99.7)	90.7 (82.1, 96.2)			**96.6 (90.4, 99.2)**	**89.5 (81.4, 95.1)**
11 months			97.6 (90.4, 99.7)	90.7 (82.1, 96.2)			**96.6 (90.4, 99.2)**	**89.5 (81.4, 95.1)**
12 months			97.6 (90.4, 99.7)	90.7 (82.1, 96.2)			**98.3 (92.4, 99.8)**	**89.5 (81.4, 95.1)**
13 months			100.0 (NE, NE)	90.7 (82.1, 96.2)			100.0 (NE, NE)	**89.5 (81.4, 95.1)**
14 months				90.7 (82.1, 96.2)				**89.5 (81.4, 95.1)**
15 months				90.7 (82.1, 96.2)				**89.5 (81.4, 95.1)**
16 months				90.7 (82.1, 96.2)				**92.1 (83.6, 97.2)**
17 months				90.7 (82.1, 96.2)				**92.1 (83.6, 97.2)**
18 months				90.7 (82.1, 96.2)				**92.1 (83.6, 97.2)**
19 months				NE				**92.1 (83.6, 97.2)**

CI=confidence interval; NE=not estimable; KM=Kaplan-Meier.
Time of recovery was defined as the first day after 1st obe-cel infusion when absolute neutrophil/platelet reach the threshold. Time was relative to first obe-cel infusion; 1 month=30.4375 days.
[1] Patients with no laboratory result showing recovery were censored at the last laboratory assessment.
[2] Percentiles with 95% CIs were calculated from PROC LIFETEST output using method of Brookmeyer and Crowley, 1982.
[3] Greenwood formula was used for CIs of KM estimates.
Changes compared to the 09-Jun-2023 cut-off date are indicated in **bold**.

The proportion of responders post-obe-cel infusion with Grade 3 or 4 neutropenia decreased over time: 58.6% (58/99), 23.2% (23/99), and 13.1% (13/99) at Day 28, Month 2, and Month 3, respectively.

Corresponding values for Grade 3 or 4 thrombocytopenia were 48.5% (48/99), 20.2% (20/99), and 11.1% (11/99), respectively.

The median time to recovery (95% CI) to the lower thresholds was 0.7 months (0.5, 0.9) and 0.7 months (0.3, 1.7) for neutrophils and platelets, respectively, and to the higher thresholds was 1.9 months (1.0, 1.9) and 2.0 months (1.9, 2.1).

The associated Kaplan Meier probability of recovery at 6 months post-infusion illustrated the high chance of recovery, being 97.6% at the 1.0 × 10^9/L threshold for neutrophils (100% already reached at 5 months for the 0.5 × 10^9/L neutrophil threshold) and 94.8% and 83.5% for the 50 × 10^9/L and 100 × 10^9/L thresholds for platelets, respectively.

Infections
90/127 patients (70.9%) had any grade infection.

Most serious infections occurred within the first 3 months after obe-cel infusion, consistent with the established higher risk period following lymphodepletion. The applicant lays focus on infection rates that exclude COVID-19 infection events (the study was conducted during the covid pandemic).

The most common (≥5% of patients) non-COVID severe infection ≥Grade 3 were pneumonia (7.1%, 9/127) and sepsis (6.3%, 8/127).

Grade 3 non-COVID severe infections were reported for 35.4% (45/127) of patients.

Grade 4 and 5 non-COVID severe infections were reported for 4.7% (6/127) of patients each. There was 1 additional death since the 09-Jun-2023 primary analysis (septic shock); the remaining deaths were: 2 patients each for sepsis, neutropenic sepsis; 1 patient for abdominal infection. One event of neutropenic sepsis was possibly related to study treatment.

Infection, as described (and whether severe or serious), is a known association with CAR-T cell therapy and the underlying disease. The nature of the condition and the number of subjects affected may be understood and (though unfortunate) would not give rise to particular concern from a regulatory perspective.

To note that the applicant appears to conflate ‘severe’ and ‘serious’ though these have different meanings in a regulatory sense.

Hypogammaglobulinemia
12/127 patients (9.4%) in the Safety Set experienced at least 1 episode of any grade hypogammaglobulinemia during the study; 2 patients (1.6%) experienced Grade ≥ 3 hypogammaglobulinemia.

Graft-versus-host disease
During the FELIX study: 127 patients who were infused with at least one dose of obe-cel (Safety Set); 56/127 subjects had a history of previous allogeneic stem cell transplant. Graft-versus-host disease has been reported in 8 patients (6.2%) post obe-cel infusion by the data cut-off at 07-Feb-2024.

The applicant position is based on biologic plausibility, availability of data, likelihood of occurrence, potential severity, predictability of the event, time to onset in relation to administration of obe-cel, health status of the subject and persistence of CAR-T cells.

The applicant presents summary histories of the 8 subjects who have developed graft-versus-host disease during the timeline of the FELIX study. 6 subjects had received a stem-cell transplant prior to the FELIX study; 3 subjects received a stem cell transplant after the administration of obe-cel (1 subject received a stem cell transplant both before and after obe-cel infusion).

The applicant also reports on 1 subject who developed stomatitis on day 162 after obe-cel administration. The event was assessed as possibly related to obe-cel.

The applicant presents a table to summarise narratives:

Table 1: Summary of GvHD Case Narratives

HSCT prior to AUTO1	HSCT prior to AUTO1/Date (Study Day)	HSCT Type (HLA Match)	Hx of GVHD	First AUTO1 infusion	(Earliest) GVHD onset date (Study Day)	(Earliest) GVHD resolution date (Study Day)	Related to obe-cel	Persistence during GvHD (in blood, copies/µg DNA) date (Study Day) value	HSCT post-AUTO1/Date (Study Day)
No	N/A	N/A	N/A	05-Oct-2022	06-Mar-2023 (153)	N/A	Not related	No	02-Jan-2023 (90)
Yes	03-Mar-2022 (-264)	Matched related donor (MRD)	No data	22-Nov-2022	Jan-2023	23-May-2023 (183)	Unlikely	23-May-2023 (183) = 188	No
Yes	14-Oct-2021 (-277)	Double umbilical cord blood (UCB)	21-Feb-2022 to 2022	18-Jul-2022	14-Aug-2022 (28)	17-Oct-2022 (92)	Unlikely	15-Aug-2022 (29) = 1881	No
Yes	21-Sep-2021 (-175)	Matched unrelated donor (MUD)	No data (no Med Hx data)	15-Mar-2022	27-Mar-2022 (13)	14-Jun-2022 (92)	Related	29-Mar-2022 (15) = 28,075	No
Yes	08-Mar-2017 (-1469)	MUD	Nov-2020 to 20-Dec-2020	16-Mar-2021	25-Nov-2022 (620)	Jan-2023	Unlikely	13-Dec-2022 (638) = 563	No
Yes	20-Jun-2013 (-3262)	MRD	No data	26-May-2022	31-Jul-2022 (67)	28-Aug-2022 (95)	Unlikely	02-Aug-2022 (69) = 7993	No
No	N/A	N/A	N/A	18-Jul-2022	07-Apr-2023 (284)		Not related	Negative from day 71, no data beyond day 165	03-Mar-2023 (Day 229)
Yes	16-Oct-2020 (-578), first alloSCT	MUD	N/A	17-May-2022	08-Jul-2023 (Day 468)	N/A	Not related	Negative from day 106, no data beyond day 365	10-Nov-2022 (Day 178)

The applicant finds that only 1 subject experienced graft-versus-host disease that was assessed as definitely related to obe-cel; the episode occurred 13 days after administration of obe-cel and was associated with persistence of CAR-T cells.

The applicant states: Further evaluation beyond the limited number of patients in the FELIX study is needed to determine which patients who received prior SCT are at risk of developing any grade GvHD post-infusion. Aggravation of GvHD will be further characterised in patients who received prior SCT as part of routine post-marketing pharmacovigilance surveillance activities to determine if additional risk minimisation measures are required.
To note that, in the main, the applicant permitted the attending physician to manage adverse events of interest by following local guidelines / the applicant also provided tables of recommendations in its protocol to manage the named adverse events of interest.

Laboratory safety
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 9 with grading using the worst laboratory values post-obe-cel infusion.

Table 9: Grade 3 or 4 Laboratory Abnormalities Occurring in ≥ 10% of Patients After Obe-cel Infusion (Safety Set)

Laboratory Parameter	09-Jun-2023 Cut-off Infused (N=127) n (%)	07-Feb-2024 Cut-off Infused (N=127) n (%)
Hemoglobin (g/L) (Decreased)	82 (64.6)	**83 (65.4)**
Lymphocytes (10^9/L) (Decreased)	121 (95.3)	121 (95.3)
Neutrophils (10^9/L) (Decreased)	125 (98.4)	125 (98.4)
Platelets (10^9/L) (Decreased)	95 (74.8)	**98 (77.2)**
Leukocytes (10^9/L) (Decreased)	124 (97.6)	124 (97.6)
Alanine Aminotransferase (U/L) (Increased)	13 (10.2)	13 (10.2)
Aspartate Aminotransferase (U/L) (Increased)	13 (10.2)	13 (10.2)

Grading was based on the worst case of all post-baseline visits within the time range, including non-scheduled visits of a patient.
Changes compared to the 09-Jun-2023 cut-off date are indicated in **bold**.

Most patients had abnormal laboratory findings prior to obe-cel infusion as a result of the impact of lymphodepletion and the underlying clinical status of the patients treated with obe-cel.

Vital signs
Vital signs and physical findings were closely monitored in obe-cel infused patients in the FELIX Study, as a component of the standard of care in autologous transplantation during which fluctuations and abnormalities are usually observed. No abnormal changes to vital signs were observed. No clinically significant pattern was observed in physical functioning post obe-cel infusion

Immunogenicity
Refer to the Pharmacokinetic section of this PAR.

Additional aspects of safety
Adverse Drug Reactions
Events considered as adverse drug reactions for obe-cel as of the data cut-off of 07-Feb-2024 are presented in Table 10. These include:

- All non-laboratory treatment emergent adverse events that occurred in ≥10% of patients infused in the FELIX study (N=127), irrespective of causality.
- All abnormal laboratory findings of Grade 3 or 4 based on laboratory graded using CTCAE criteria (or Investigator assessment for hyperferritinaemia) and occurring in ≥ 10% of patients.
- Important adverse drug reactions that occurred in <10% of patients based on a case-by-case evaluation.

Table 10: Adverse Reactions Identified with Obe-cel in the FELIX Study (Safety Set)

System Organ Class Preferred Term	Frequency	09-Jun-2023 Cut-off		07-Feb-2024 Cut-off	
		Any Grade (N=127) (%)	≥ Grade 3 (N=127) (%)	Any Grade (N=127) (%)	≥ Grade 3 (N=127) (%)
Infections and infestations					
Infections - pathogen unspecified [a]	Very common	41	30	**45**	**32**
Bacterial infectious disorders [b]	Very common	25	11	**26**	11
COVID-19 [c]	Very common	18	5	**20**	**8**
Viral infectious disorders excluding COVID-19 [d]	Very common	15	3	**18**	**6**
Fungal infectious disorders [e]	Very common	12	4	**13**	**5**
Blood and lymphatic system disorders					
Neutropenia [f]	Very common	-	98	-	98
Leukopenia [g]	Very common	-	98	-	98
Lymphopenia [g]	Very common	-	95	-	95
Thrombocytopenia [g, y]	Very common	-	75	-	77
Anaemia [g]	Very common	-	65	-	65
Febrile neutropenia	Very common	24	24	24	24
Coagulopathy [h]	Very common	11	6	11	6
Immune system disorders					
Cytokine release syndrome	Very common	69	2	69	2
Hypogammaglobulinaemia	Common	8	1	**9**	**2**
Haemophagocytic lymphohistiocytosis	Common	2	2	2	2
Metabolism and nutrition disorders					
Decreased appetite	Very common	12	3	12	3
Psychiatric disorders					
Delirium [i]	Common	5	1	5	1
Nervous system disorders					
Headache	Very common	24	0	24	0
Immune effector cell-associated neurotoxicity syndrome	Very common	23	7	23	7
Encephalopathy [j]	Very common	20	5	20	5
Dizziness [k]	Very common	11	0	11	0
Tremor	Common	9	0	9	0
Cardiac disorders					
Tachycardia [l]	Very common	13	0	13	0
Arrhythmia [m]	Common	5	2	**6**	2
Cardiac failure [n]	Common	2	1	2	1
Palpitations	Common	2	1	2	1
Vascular disorders					
Hypotension [o]	Very common	24	5	24	5
Haemorrhage [p]	Very common	20	5	**21**	5
Respiratory, thoracic and mediastinal disorders					
Cough [q]	Very common	13	0	13	0

System Organ Class Preferred Term	Frequency	09-Jun-2023 Cut-off		07-Feb-2024 Cut-off	
		Any Grade (N=127) (%)	≥ Grade 3 (N=127) (%)	Any Grade (N=127) (%)	≥ Grade 3 (N=127) (%)
Gastrointestinal disorders					
Nausea	Very common	26	2	26	2
Diarrhoea	Very common	24	1	**25**	**2**
Vomiting	Very common	17	1	17	1
Abdominal pain [r]	Very common	15	2	15	2
Constipation	Very common	13	0	13	0
Stomatitis	Common	6	1	**7**	1
Skin and subcutaneous tissue disorders					
Rash [s]	Very common	15	1	15	1
Musculoskeletal and connective tissue disorders					
Musculoskeletal pain [t]	Very common	32	2	**31**	2
General disorders and administration site conditions					
Pyrexia	Very common	28	2	**29**	2
Pain [u]	Very common	28	2	28	2
Fatigue [v]	Very common	22	2	22	2
Oedema [w]	Very common	16	2	**15**	**1**
Chills	Common	9	0	9	0
Investigations					
Alanine aminotransferase increased [g]	Very common	-	10	-	10
Aspartate aminotransferase increased [g]	Very common	-	10	-	10
Hyperferritinaemia [g, x]	Very common	13	10	13	10
Weight decreased	Very common	10	2	10	2
Injury, poisoning and procedural complications					
Infusion related reaction	Common	3	0	3	0

Frequencies are defined as very common (≥ 1/10) or common (≥ 1/100 to < 1/10).

[a] Infections - pathogen unspecified includes abdominal infection, abscess limb, acute sinusitis, amniotic cavity infection, anal abscess, appendicitis, bacteraemia, brain abscess, endocarditis, enterocolitis infectious, fungaemia, gastroenteritis, gingivitis, hepatic infection, infection, lower respiratory tract infection, neutropenic sepsis, osteomyelitis, otitis externa, otitis media, perineal cellulitis, periorbital infection, peritonitis, pharyngitis, pneumonia, pyelonephritis, respiratory tract infection, sepsis, sinusitis, skin infection, tooth abscess, tooth infection, upper respiratory tract infection, urinary tract infection, urosepsis.

[b] Bacterial infectious disorders includes bacterial infection, Campylobacter gastroenteritis, cellulitis, Clostridium difficile infection, Corynebacterium infection, Corynebacterium sepsis, Enterococcal bacteraemia, Enterococcal infection, Enterococcal sepsis, Escherichia bacteraemia, Escherichia urinary tract infection, folliculitis, gastroenteritis bacterial, Granulicatella bacteraemia, Klebsiella infection, pneumonia Klebsiella, Pseudomonas infection, Staphylococcal bacteraemia, Staphylococcal infection, Stenotrophomonas bacteraemia, Stenotrophomonas infection, Streptococcal bacteraemia, urinary tract infection bacterial, Enterococcal urinary tract infection, Staphylococcal wound infection.

[c] COVID-19 includes COVID-19 and COVID-19 pneumonia.

[d] Viral infectious disorders excluding COVID-19 include adenovirus infection, BK virus infection, coronavirus infection, cytomegalovirus infection, cytomegalovirus infection reactivation, enterovirus infection, gastroenteritis norovirus, herpes zoster, herpes zoster oticus, human herpes virus 6 infection, influenza, oral herpes, parainfluenzae virus infection, polyomavirus viraemia, respiratory syncytial virus infection, rhinovirus infection, viral haemorrhagic cystitis.

[e] Fungal infectious disorders include bronchitis fungal, bronchopulmonary Aspergillosis, Candida infection, cutaneous mucormycosis, Fusarium infection, lower respiratory tract fungal infection, oral candidiasis, Pneumocystis jirovecii pneumonia, sinusitis fungal, systemic Candida, tinea cruris.

[f] Neutropenia includes neutropenia, neutrophil count decreased.

[g] Frequency based on Grade 3 or higher laboratory parameter.

[h] Coagulopathy includes blood fibrinogen decreased, coagulopathy, disseminated intravascular coagulation, hypofibrinogenaemia, international normalised ratio increased.

[i] Delirium includes agitation, delirium, disorientation, hallucination, irritability.

[j] Encephalopathy includes aphasia, cognitive disorder, confusional state, depressed level of consciousness, disturbance in attention, dysarthria, dysgraphia, encephalopathy, lethargy, memory impairment, mental status changes, posterior reversible encephalopathy syndrome, somnolence.

[k] Dizziness includes dizziness, presyncope.

[l] Tachycardia includes sinus tachycardia, tachycardia.

[m] Arrhythmia includes atrial fibrillation, bradycardia, electrocardiogram qt prolonged, sinus bradycardia.

[n] Cardiac failure includes ejection fraction decreased, left ventricular dysfunction.

[o] Hypotension includes hypotension, orthostatic hypotension.

[p] Haemorrhage includes anal haemorrhage, cerebral microhaemorrhage, contusion, epistaxis, gingival bleeding, hematoma, haematuria, haemorrhage intracranial, haemorrhoidal haemorrhage, haemorrhoids, intermenstrual bleeding, intra-abdominal haemorrhage, large intestinal haemorrhage, melaena, petechiae, subarachnoid haemorrhage, subdural haematoma, subdural haemorrhage, upper gastrointestinal haemorrhage, vaginal haemorrhage, wound haemorrhage.

[q] Cough includes cough, productive cough.

[r] Abdominal pain includes abdominal pain, abdominal pain upper.

[s] Rash includes catheter site erythema, drug eruption, erythema, pruritus, rash, rash macular, rash maculo-papular, urticaria, vulvovaginal rash.

[t] Musculoskeletal pain includes arthralgia, arthropathy, back pain, bone pain, musculoskeletal chest pain, musculoskeletal pain, myalgia, neck pain, non-cardiac chest pain.

[u] Pain includes catheter site pain, ear pain, eye pain, facial pain, flank pain, incision site pain, oropharyngeal pain, pain, pain in extremity, pain in jaw, pelvic pain, pleuritic pain, procedural pain, proctalgia, tension headache, toothache, urinary tract pain.

[v] Fatigue includes asthenia, fatigue, malaise.

[w] Oedema includes face oedema, generalised oedema, hypervolaemia, localised oedema, oedema peripheral, periorbital oedema, pharyngeal oedema, swelling face.

[x] Based on Investigator-reported grading.

[y] Thrombocytopenia includes platelet count decreased, thrombocytopenia.

Changes compared to the 09-Jun-2023 cut-off date are indicated in **bold**.

Summary of clinical safety

The analysis sets

The Safety Set comprises all patients who have been enrolled and received at least one obe-cel infusion. For this study, the Safety Set is the same as the Infused Set (all patients who have received at least one infusion of obe-cel) and is the main analysis set for safety.

153 subjects have been enrolled into the FELIX study; the Safety Set contains 127 adult subjects with relapsed / refractory B-cell acute lymphoblastic leukaemia. For these 127 subjects at enrolment: 52% were male; median age 46yrs, min 20yrs, max 81yrs; 74% white, 13% Asian, 2% black. Subjects had undergone a median of 2 prior lines of therapy; 10% were refractory to all prior lines; 44% had previous stem cell transplant; subjects had a median of 40% bone marrow blast cells; 23% with extramedullary disease; ECOG score 0 (39%) or 1 (60%); 100% CD19 status +ve; median neutrophil count (10^9/L) = 1.6; median platelet count (10^9/L) = 85.

Prior to preconditioning: subjects had a median of 40% bone marrow blast cells; 21% extramedullary disease present; median neutrophil count (10^9/L) = 1.4; median platelet count (10^9/L) = 89; 24% normal karyotype; 40% complex karyotype; 28% Philadelphia chromosome-positive.

The procedure

Subjects underwent leukapheresis to obtain material to be sent to the central manufacturing site. Bridging therapy was permitted and was based on local practice; chemotherapy was the most common form of bridging therapy in 118/127 subjects.

All subjects received fludarabine and cyclophosphamide as lymphodepletion therapy, as described.

Exposure

The target total dose of obe-cel was to be the same for all patients: 410 × 106 CD19 CAR-positive T cells (± 25% variance) administered as a split dose. The median dose of obe-cel administered in the Safety Set was 410 × 106 CD19 CAR-positive T cells.

Most subjects received both administrations (94.5%, 120/127); the target dose was achieved in 116/127 patients. Reasons for not administering the second dose were related to adverse events, rapid disease progression or disease-associated death.

9 patients had a delay in administration of their second dose until up to Day 21; this did not appear to affect the efficacy outcome.

Pre- and post-infusion therapies such as paracetamol were permitted.

Adverse events

As of the cut-off date of 07-Feb-2024:

104/127 patients experienced treatment-emergent adverse events of ≥Grade 3.

For the grade >3 adverse events:

- 77/127 subjects experienced an obe-cel related treatment emergent adverse event; such events were serious in 40/127 subjects.
- There were severe infections in 66/127 subjects; cytokine release syndrome in 3/127

subjects and immune effector cell-associated neurotoxicity syndrome in 9/127 subjects.

- 64/127 of patients died post-obe-cel infusion. The most common primary reasons reported for death remained progressive disease (45 patients). The deaths of 2 subjects were evaluated as related to exposure to obe-cel.
- 83/127 patients experienced at least one serious adverse event of any grade post-obe-cel treatment. 40/127 subjects had an obe-cel related serious treatment emergent adverse event.
- The most common serious treatment emergent adverse events (≥5% of patients) suspected to be related to study treatment by the Investigator were immune effector cell-associated neurotoxicity syndrome (ICANS, 9.4%), cytokine release syndrome (CRS, 7.9%), febrile neutropenia (6.3%) and hyper-ferritinaemia (5.5%).
- 119 patients experienced treatment emergent adverse events of any grade and that were suspected to be related to obe-cel by the Investigator.
- The most commonly reported events in this category (≥10%) were cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS), irrespective of grade (68.5% [87/127] and 22.8% [29/127], respectively).

Cytokine Release Syndrome

- The median time to onset of cytokine release syndrome was 6 days after the first infusion and a median of 2 days after the second infusion.
- For both first and second infusions, the event occurred up to 2 weeks after exposure.
- The event lasted up to 21 days. 55% of subjects received anti-cytokine therapy.

Immune effector cell-associated neurotoxicity syndrome

- The median time to onset of immune effector cell-associated neurotoxicity syndrome after the first infusion was 8 days (up to a maximum of 10 days)
- The median time to onset of immune effector cell-associated neurotoxicity syndrome after the second infusion was 6.5 days (up to a maximum of 22 days)
- The event lasted up to 53 days. 19% of subjects were administered anti-ICANS therapy

Infections

- 90/127 patients (70.9%) had any grade infection.
- Most serious infections occurred within the first 3 months after obe-cel infusion, consistent with the established higher risk period following lymphodepletion.
- The most common (≥5% of patients) non-COVID severe infection ≥Grade 3 were pneumonia (7.1%, 9/127) and sepsis (6.3%, 8/127).

Hypogammaglobulinemia

12/127 patients in the Safety Set experienced at least 1 episode of any grade hypogammaglobulinemia during the study.

Conclusion on clinical safety

At this stage of the procedure: there would not appear to be novel (novel for a CAR-T cell therapy) aspects of safety. Aspects of harm are considered to be amenable to clinical management.

IV.6 Risk Management Plan (RMP)

The applicant has submitted an RMP, in accordance with the requirements of Regulation 182 of The Human Medicines Regulation 2012, as amended. In addition to routine pharmacovigilance and risk minimisation measures, additional risk minimisation measures and additional pharmacovigilance activities have been proposed (see table below for the risk minimisation measures and pharmacovigilance activities for the important identified risks):

Important identified risk: Cytokine Release Syndrome (CRS)	
Evidence for linking the risk to the medicine	Cytokine release syndrome is a recognised toxicity with CAR T cell therapies and was reported in AUTO1-AL1 (FELIX) study. Clinical symptoms indicative of CRS includes culture-negative fever, but may also include myalgia, nausea/vomiting, tachycardia, hypoxia, hypotension, headache, confusion, tremor, and delirium. Potentially life-threatening complications of CRS may include cardiac dysfunction, acute respiratory distress syndrome, renal and/or hepatic failure, and disseminated intravascular coagulation (Brudno and Kochenderfer, 2016). CRS is considered an important identified risk due to its frequency and seriousness and the potential for severe outcomes if left untreated.
Risk factors and risk groups	Risk factors of CRS include tumour burden, intensity of lymphodepletion chemotherapy, CAR T cell dose, and thrombocytopenia (Siddiqi et al, 2017; Hay et al, 2017; Santomasso et al, 2018; Lee et al, 2015; Jia et al, 2019). The evaluation of the impact of disease burden at time of lymphodepletion on CRS highlighted its importance since the rate of CRS of any grade increased as the blasts in BM increased. In the AUTO1-AL1 (FELIX) study, across the 4 blast subgroups of <5%, ≥5% to ≤20%, >20% to ≤75%, >75% the percentage of subjects with CRS of any grade was 47.2%, 62.5%, 71.4% and 87.5%, respectively. This reinforced the importance of the split dose regimen with a lower first dose administered when blasts in BM are > 20% at lymphodepletion which is also associated with enhanced CAR T cell expansion post infusion. Subgroup analysis did not highlight any findings that would be unexpected and the key impact on safety appeared to be the disease burden in terms of blasts in BM at lymphodepletion.
Risk minimisation measures	Routine risk minimisation measures: SPC sections 4.4, 4.8 and corresponding PL section 4 Additional risk minimisation measures: 1. Risk minimisation control programme 2. Educational programme (HCP educational programme and Patient Card)

Important identified risk: Cytokine Release Syndrome (CRS)	
Additional pharmacovigilance activities	Additional pharmacovigilance activities: 1. AUTO1-LT2 long term study for post approval patients. 2. AUTO-LT1 long-term follow-up study for clinical trial patients. 3. AUTO1-AL1 study for clinical trial patients.

Important identified risk:	Immune effector Cell-Associated Neurotoxicity Syndrome (ICANS)
Evidence for linking the risk to the medicine	ICANS were reported in AUTO1-AL1 (FELIX) clinical trial and in patients treated with other CAR T therapies.
Risk groups or risk factors	Although no correlation has been observed between ICANS and CRS/MAS (Santomasso et al, 2018), ICANS appear to occur more frequently in the presence of severe CRS. Patients with a high disease burden, prior to treatment, higher peak CAR T expansion and early and higher elevations of serum cytokines may have a higher risk of neurotoxicity (Santomasso et al, 2018). Of note, patients can develop ICANS even after treatment of anti-IL6 therapy, after the resolution of CRS. In the FELIX study, the evaluation of the impact of disease burden at time of lymphodepletion also emphasized its importance for the risk of ICANS and showed an even more important impact of the fractionated split dosing regimen. The rate of ICANS of any grade increased across the 2 subgroups within each dosing bracket (8.3% and 25.0% in the <5% and ≥5% to ≤20% categories; 14.3% and 42.5% in the 20% to ≤75%, > 75% categories), whereas it can be seen that it decreased when moving across the dosing thresholds of ≤20% and > 20%. As described already for CRS, the relatively low rate of ICANS following AUCATZYL treatment is consistent with expectations based on the properties of AUCATZYL and the dosing regimen and makes this potential immunotoxicity consequence of therapy a much more manageable risk. Subgroup analysis did not highlight any findings that would be unexpected and the key impact on safety appeared to be the disease burden in terms of blasts in

Important identified risk:	**Immune effector Cell-Associated Neurotoxicity Syndrome (ICANS)**
	BM at lymphodepletion. Neurotoxicity may also be caused by fludarabine, but usually at higher doses than those being administered as part of lymphodepletion (Helton et al, 2013). Symptoms of fludarabine including objective weakness, agitation, confusion, seizures, visual disturbances, optic neuritis, optic neuropathy, blindness, and coma have been reported in CLL patients treated with multiple cycles of fludarabine (Fludarabine SPC, 2019).
Risk minimisation measures	Routine risk minimisation measures: SPC sections 4.4, 4.8 and corresponding PL sections 4 Additional risk minimisation measures: 1. Risk minimisation control programme. 2. Educational programme (HCP educational programme and Patient Card).
Additional pharmacovigilance activities	Additional pharmacovigilance activities: 1. AUTO1-LT2 long term study for post approval patients. 2. AUTO-LT1 long-term follow-up study for clinical trial patients. 3. AUTO1-AL1 study for clinical trial patients.

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

Important identified risk:	**Prolonged Cytopenia**
	1. AUTO1-LT2 long term study for post approval patients. 2. AUTO-LT1 long-term follow-up study for clinical trial patients. 3. AUTO1-AL1 study for clinical trial patients.

This is acceptable.

IV.7 Discussion on the clinical aspects

The grant of a marketing authorisation is recommended for this application.

V USER CONSULTATION

A text draft of the Patient Information Leaflet (PIL) was presented. A commitment to provide a mock-up and evidence of user consultation of the PIL to the MHRA prior to marketing was accepted.

VI OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The quality of the product is acceptable. The non-clinical and clinical data submitted have shown the positive benefit/risk of these product for the treatment of adult patients (≥18 years) with relapsed or refractory B cell precursor acute lymphoblastic leukaemia.

Aucatzyl has been authorised with the condition to perform further studies and/or to provide additional measures to minimise the risk. The Marketing Authorisation Holder shall complete, within the stated timeframe, the following measures:

Description	Due date
To confirm the long-term efficacy and safety of Aucatzyl in adult patients with relapsed and / or refractory B cell acute lymphoblastic leukaemia, the Marketing Authorisation Holder shall submit follow-up results of the FELIX clinical study. Interim report due 30/06/2026.	30/06/2029
Prior to the launch of AUCATZYL the Marketing Authorisation Holder (MAH) must agree the content and format of the Controlled distribution programme and educational materials with the MHRA. The MAH shall ensure that where AUCATZYL is marketed, all HCPs in the qualified treatment centres who are expected to use AUCATZYL are provided with the following educational material: - HCP educational material - Patient card	30/04/2030
In order to confirm the short and long-term safety and effectiveness of Aucatzyl in adult patients with relapsed or refractory B cell acute lymphoblastic leukaemia, the Marketing Authorization Holder shall 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 (obe-cel LT2). Interim reports due according to schedule in the RMP.	30/06/2044
It is a condition of this approval that the marketing authorisation holder (MAH) work with the MHRA to resolve to the satisfaction of the Department for the Environment, Food and Rural Affairs (Defra) any concerns it may have with this product, about deliberate release of a GMO into the environment. The aim is to resolve this by 1 December 2025.	01/12/2025

The following post-authorisation measures are recorded which should be fulfilled by the MAH by the dates shown.

Autolus commits to providing confirmatory stability data from patient	01/01/2027

derived retain material manufactured at The Nucleus according to the commercial process, as it may become available	
Autolus commits to characterising the ratio of empty: partial: full capsids in LV18970. and commits to execute this characterisation study and provide data post-approval	01/01/2027
Autolus commits to provide batch data from 30 commercial batches manufactured at The Nucleus when available post-authorisation	01/01/2027
Autolus commits to evaluating an alternative to the current Human AB serum, male, off the clot (BIOVT- GemBio, UK) post-approval (from Major Objection 1).	01/01/2027

The Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and labelling are satisfactory, and in line with current guidelines.

In accordance with legal requirements, the current approved UK versions of the SmPC and PIL for this product are available on the MHRA website.

TABLE OF CONTENT OF THE PAR UPDATE

Steps taken after the initial procedure with an influence on the Public Assessment Report (non-safety variations of clinical significance).

Please note that only non-safety variations of clinical significance are recorded below and in the annexes to this PAR. The assessment of safety variations where significant changes are made are recorded on the MHRA website or European Medicines Agency (EMA) website. Minor changes to the marketing authorisation are recorded in the current SmPC and/or PIL available on the MHRA website.

Application type	**Scope**	**Product information affected**	**Date of grant**	**Outcome**	**Assessment report attached Y/N**

Annex 1
Summary of fulfilment of the criteria for orphan drug designation

Product: Aucatzyl 410 × 106 cells dispersion for infusion
Active substance: obecabtagene autoleucel
Orphan Designation Number: PLGB 46113/0001/OD1
Background:

This application was evaluated for fulfilment of orphan designation criteria by the Commission on Human Medicines (CHM) and the designation criteria were considered fulfilled.

Orphan condition
The orphan condition is acute lymphoblastic leukaemia. This is acceptable.

Orphan indication
The orphan indication is for the treatment of adult patients (≥18 years) with relapsed or refractory B cell precursor acute lymphoblastic leukaemia.

Life threatening/ debilitating condition
Acute lymphoblastic leukaemia is characterised by the malignant transformation and proliferation of lymphoid progenitor cells in the blood and bone marrow, replacing 'normal' blood cells over time. This compromises the patient's haematopoietic and immune functions; infections and haemostatic complications owing to coagulopathy are the leading causes of morbidity and mortality in patients with acute lymphoblastic leukaemia.
It may be accepted that B-cell acute lymphoblastic leukaemia is seriously debilitating and life-threatening.

Prevalence of the Condition in Great Britain (GB)
Suitable evidence has been provided that demonstrates that, at the time of orphan designation, the condition is estimated to affect 1.04 in 10,000 people in GB. This does not exceed the upper limit of prevalence for orphan designation, which is 5 in 10,000 people in GB.

Existing methods of treatment
The following methods have been identified:

Table 1. Products approved in the UK for the treatment of acute lymphoblastic leukaemia

Class	INN (Product Name)	Approved Indication
Chemotherapy: vinca alkaloid (Induction, Maintenance)	Vincristine sulphate (generics)	Used either alone or in conjunction with other oncolytic drugs for the treatment of ALL.
Chemotherapy: anthracyclines (Induction)	Daunorubicin (Cerubidine, Daunoblastine)	Induction of remission in ALL and AML. Used in combination with other cytostatics.
	Doxorubicin (generics)	Treatment of ALL. Frequently used in combination chemotherapy regimens with other cytotoxic drugs.
	Idarubicin (Zavedos and generics)	For second line treatment of relapsed ALL.
Chemotherapy: alkylating agent (Induction)	Cyclophosphamide (Endoxan and generics)	Used alone or in combination with other chemotherapeutic agents, depending on the indication. Treatment of: • ALL • As conditioning for a BM transplantation, in the treatment of ALL.
	Ifosfamide	Treatment of malignant disease; used in combination with other cytotoxic drugs, radiotherapy and surgery.
Chemotherapy: antimetabolites (Induction, Consolidation)	Cytarabine (Cytosar and generics)	Alone or in combination for the induction of clinical remission and/or maintenance therapy in patients with ALL.
	Clofarabine (Evoltra and generics)	Treatment of ALL in paediatric patients who have relapsed or are refractory after receiving at least 2 prior regimens and where there is no other treatment option anticipated to result in a durable response.
	Nelarabine (Atriance)	Nelarabine is indicated for the treatment of patients with T ALL and T LBL whose disease has not responded to or has relapsed following treatment with at least 2 chemotherapy regimens.
	Tioguanine	Primarily, for the treatment of acute leukaemias especially acute myelogenous leukaemia and acute lymphoblastic leukaemia.
Chemotherapy (Induction, Consolidation)	Asparaginase (Spectrila, Kidrolase)	As a component of antineoplastic combination therapy for the treatment of ALL in paediatric patients from birth to 18 years and adults.
	Pegaspargase (Oncaspar)	As a component of antineoplastic combination therapy in ALL in paediatric patients from birth to 18 years, and adult patients.

Class	INN (Product Name)	Approved Indication
	Crisantaspase (Enrylaze, Erwinase)	As a component of a multi-agent chemotherapeutic regimen for the treatment of ALL in adult and paediatric patients (1 month and older) who developed hypersensitivity or silent inactivation to E. coli-derived asparaginase.
Chemotherapy: antimetabolites (Consolidation, Maintenance)	Methotrexate (Jylamvo and generics)	Maintenance treatment of ALL in adults, adolescents and children aged 3 years and over.
Chemotherapy: antimetabolites (Maintenance)	Mercaptopurine (Xaluprine)	Treatment of ALL in adults, adolescents and children.
Chemotherapy: alkylating agents (SCT conditioning)	Melphalan (Phelinun)	High dose of melphalan used alone or in combination with other cytotoxic medicinal products and/or total body irradiation for the treatment of ALL and AML. In combination with other cytotoxic medicinal products, as reduced intensity conditioning treatment prior to allo HSCT in malignant haematological diseases in adults.
	Treosulfan	In combination with fludarabine as part of conditioning treatment prior to alloHSCT in adult patients and in paediatric patients older than one month with malignant and non-malignant diseases.
TKIs	Glivec (imatinib) (and generics)	Treatment of adult patients with newly diagnosed Ph+ ALL integrated with chemotherapy, and adult patients with r/r Ph+ ALL as monotherapy.
	Sprycel (dasatinib) (and generics)	Treatment of adult patients with Ph+ ALL and lymphoid blast CML with resistance or intolerance to prior therapy.
	Iclusig (ponatinib)	Treatment of adult patients with Ph+ ALL who are resistant to dasatinib; who are intolerant to dasatinib and for whom subsequent treatment with imatinib is not clinically appropriate; or who have the T315I mutation.
Bispecific antibodies	Blincyto (blinatumomab)	As monotherapy, for the treatment of adults with CD19 positive r/r B-precursor ALL. Patients with Ph+ B-precursor ALL should have failed treatment with at least 2 TKIs and have no alternative treatment options. As monotherapy, for the treatment of adults with Ph- CD19+ B-precursor ALL in first or second CR with MRD greater than or equal to 0.1%.

Class	INN (Product Name)	Approved Indication
Antibody-Drug Conjugates	Besponsa (inotuzumab ozogamicin)	As monotherapy, for the treatment of adults with r/r CD22-positive B cell precursor ALL. Adult patients with Ph+ r/r B cell precursor ALL should have failed treatment with at least 1 TKI.
CAR T cell	Kymriah (tisagenlecleucel)	Treatment of young adult patients up to and including 25 years of age with B cell ALL that is refractory, in relapse post-transplant or in second or later relapse.
	Tecartus (brexucabtagene autoleucel)	Treatment of adult patients 26 years of age and above with r/r B cell precursor ALL.

Abbreviations: ALL = acute lymphoblastic leukaemia; allo HSCT = allogeneic haematopoietic stem cell transplantation; AML = acute myeloid leukaemia; BM = bone marrow; CAR = chimeric antigen receptor; CML = chronic myeloid leukaemia; CR = complete remission; MRD = minimal residual disease; MRP = mutual recognition procedure; Ph+ = Philadelphia -chromosome-positive; r/r = relapsed or refractory; SCT = stem cell transplantation; T ALL = T cell acute lymphoblastic leukaemia; T LBL = T cell lymphoblastic lymphoma; TKI = tyrosine kinase inhibitor.

Table 2 provides an overview of the medicinal products authorised in the UK for the therapeutic indication intended for Aucatzyl [treatment of adult patients (18 years and older) with relapsed / refractory B cell acute lymphoblastic leukaemia]:

Product Name (INN)	Approved Therapeutic Indication	Requirement of significant benefit demonstration
Chemotherapy for induction, consolidation and maintenance (see Table 14)	Treatment of ALL.	SOC chemotherapy does not fall into the same treatment line as proposed for obe-cel. Demonstrating significant benefit over SOC chemotherapy is therefore not necessitated for the maintenance of obe-cel orphan designation.
Glivec (imatinib) (and generics)	Treatment of adult patients with newly diagnosed Ph+ ALL integrated with chemotherapy and adult patients with r/r Ph+ ALL as monotherapy.	No significant benefit discussion is necessary as imatinib is only authorised for use in Ph+ ALL patients.
Sprycel (dasatinib) (and generics)	Treatment of adult patients with Ph+ ALL with resistance or intolerance to prior therapy.	No significant benefit discussion is necessary as dasatinib is only authorised for use in Ph+ ALL patients.
Iclusig (ponatinib)	Treatment of adult patients with Ph+ ALL who are resistant to dasatinib; who are intolerant to dasatinib and for whom subsequent treatment with imatinib is not clinically appropriate; or who have the T315I mutation.	No significant benefit discussion is necessary as ponatinib is only authorised for use in Ph+ ALL patients.

Blincyto (blinatumomab)	As monotherapy, for the treatment of adults with CD19+ r/r B ALL. Patients with Ph+ B ALL should have failed treatment with at least 2 TKIs and have no alternative treatment options. As monotherapy, for the treatment of adults with Ph- CD19+ B ALL in first or second CR with MRD greater than or equal to 0.1%.	Overlap between the approved indication for blinatumomab and proposed indication for obe-cel. A discussion on significant benefit is required.
Besponsa (inotuzumab ozogamicin)	As monotherapy, for the treatment of adults with r/r CD22+ B ALL. Adult patients with Ph+ r/r B ALL should have failed treatment with at least 1 TKI.	Overlap between the approved indication for blinatumomab and proposed indication for obe-cel. A discussion on significant benefit is applicable.
Kymriah (tisagenlecleucel)	Treatment of young adult patients up to and including 25 years of age with B cell ALL that is refractory, in relapse post-transplant or in second or later relapse.	Tisagenlecleucel is approved for the treatment of paediatric and young adult patients only. A discussion on significant benefit is not applicable.
Product Name (INN)	**Approved Therapeutic Indication**	**Requirement of significant benefit demonstration**
Tecartus (brexucabtagene autoleucel)	Treatment of adult patients 26 years of age and above with r/r B cell precursor ALL.	Overlap between the approved indication for brexucabtagene autoleucel and the proposed indication for obe-cel. A discussion on significant benefit is applicable.

Abbreviations: ALL = acute lymphoblastic leukaemia; EMA = European Medicines Agency; MRD = minimal residual disease; Ph+ = Philadelphia chromosome-positive; r/r = relapsed or refractory; SOC = standard of care; TKI = tyrosine kinase inhibitor.

Justification of significant benefit

Methods for the treatment of the orphan condition already exist in GB. Suitable justification has been provided that Aucatzyl provides a significant benefit to those affected by the condition as specified in the orphan indication.

By comparison to Blincyto and Besponsa, available clinical efficacy data suggest that Aucatzyl offers a clinically relevant advantage via better clinical efficacy / better clinical effect in the claimed indication.

By comparison to Tecartus, it may be accepted that Aucatzyl offers a clinically relevant advantage via improved safety by means of less serious and less frequent adverse reactions as exemplified by the immune-mediated toxicities i.e. cytokine release syndrome and immune effector cell associated neurotoxicity syndrome.

Improved safety may also be accepted by means of a treatment-sparing effect (less need for additional therapies) resulting from a higher persistence of cells of Aucatzyl in comparison to Tecartus.

It may be accepted that the applicant has demonstrated significant benefit in comparison to other (named) licensed products.

Conclusion on acceptability of orphan designation

The applicant has demonstrated fulfilment of the criteria for approval as an orphan medicinal product.

All medicines that gain an orphan marketing authorisation from the UK Licensing Authority are listed on its publicly available Orphan Register until the end of the market exclusivity period. The authorised orphan indication defines the scope of orphan market exclusivity.

Decision: Grant

Date: 25 April 2025