12 June 2025
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Committee for Orphan Medicinal Products

Orphan designation withdrawal assessment report

Aucatzyl (obecabtagene autoleucel)
Treatment of acute lymphoblastic leukaemia
EU/3/22/2605

Sponsor: Autolus GmbH

Note

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

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1. Product and administrative information

Product	
Designated active substances	Obecabtagene autoleucel
Other name	Aucatzyl
International Non-Proprietary Name	Obecabtagene autoleucel
Tradename	-
Orphan condition	Treatment of acute lymphoblastic leukaemia
Sponsor's details:	Autolus GmbH Im Schwarzenbach 4 Friedlingen 79576 Weil Am Rhein Baden-Wuerttemberg Germany
Orphan medicinal product designation procedural history	
Sponsor/applicant	Autolus GmbH
COMP opinion	17 March 2022
EC decision	13 April 2022
EC registration number	EU/3/22/2605
Marketing authorisation procedural history	
Rapporteur / Co-rapporteur	Berendina Maria van den Hoorn / Claire Beuneu
Applicant	Autolus GmbH
Application submission	8 February 2024
Procedure start	28 March 2024
Procedure number	EMA/H/C/005907
Invented name	Aucatzyl
Proposed therapeutic indication	Aucatzyl is indicated for the treatment of adult patients 26 years of age and above with relapsed or refractory (r/r) B cell precursor acute lymphoblastic leukaemia (B ALL). Further information on the product can be found in the European public assessment report (EPAR) on the Agency's website https://www.ema.europa.eu/en/medicines/human/EPAR/Aucatzyl
CHMP opinion	22 May 2025
COMP review of orphan medicinal product designation procedural history	
COMP rapporteurs	Karri Penttila / Jana Mazelova
Sponsor's report submission	20 January 2025
COMP discussion and adoption of list of questions	13-15 May 2025
Oral explanation	10 June 2025
Sponsor's removal request	11 June 2025

2. Grounds for the COMP opinion

The COMP opinion that was the basis for the initial orphan medicinal product designation in 2022 was based on the following grounds:

"Having examined the application, the COMP considered that the sponsor has established the following:

- the intention to treat the condition with the medicinal product containing obecabtagene autoleucel was considered justified based on preliminary clinical data showing high rate of responses in heavily pre-treated patients;
- the condition is chronically debilitating and life-threatening depending on the response to treatment, with acute leukaemic forms being fatal in a few weeks if left untreated. Symptoms include persistent fever, infections, anaemia, fatigue, breathlessness, bone and joint pain. The invasion of tumour cells in the bloodstream, the bone marrow and/or the lymphatic system result in lack of normal blood cells, bone marrow failure, and organ damage;
- the condition was estimated to be affecting approximately 1.4 in 10,000 persons in the European Union, at the time the application was made.

Thus, the requirements under Article 3(1)(a) of Regulation (EC) No 141/2000 on orphan medicinal products are fulfilled.

In addition, although satisfactory methods of treatment of the condition exist in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing obecabtagene autoleucel will be of significant benefit to those affected by the condition. The sponsor has provided preliminary clinical data that demonstrate high rate of responses in heavily pre-treated patients with relapsed/refractory acute lymphoblastic leukaemia. The Committee considered that this constitutes a clinically relevant advantage.

Thus, the requirement under Article 3(1)(b) of Regulation (EC) No 141/2000 on orphan medicinal products is fulfilled.

The COMP concludes that the requirements laid down in Article (3)(1) (a) and (b) of Regulation (EC) No 141/2000 on orphan medicinal products are cumulatively fulfilled. The COMP therefore recommends the designation of this medicinal product, containing obecabtagene autoleucel as an orphan medicinal product for the orphan condition: "treatment of acute lymphoblastic leukaemia".

3. Review of criteria for orphan designation

Article 3(1)(a) of Regulation (EC) No 141/2000

Intention to diagnose, prevent or treat a life-threatening or chronically debilitating condition affecting not more than five in 10 thousand people in the Community when the application is made

Condition

Acute lymphoblastic leukaemia (ALL) is a heterogeneous disease characterized by proliferation and accumulation of immature lymphoid cells in bone marrow, peripheral blood, lymphoid tissues, and other extra nodal sites (Rafei et al. 2019).

Typically, B cell precursor ALL (B ALL) is classified as either immature or mature. In approximately 87% of adult B ALL cases, the malignancy occurs in the immature B precursor cells (Moorman et al, 2010). B ALL is also classified based on the presence of the most frequent genetic aberration in ALL patients, the Philadelphia chromosome (Ph) translocation. This is present (denoted by Ph+) in approximately 20-30% of adult B ALL compared to only 5% of childhood B ALL.

Refractory ALL is characterized by poor sensitivity to commonly used chemotherapeutic drugs, a low clinical remission rate and a significantly shortened survival cycle (Schmid et al. 2006); relapse of ALL is defined as recurrence of the disease at any site after a period of complete remission (CR), either while still on or after completion of front-line therapy (Henze et al. 2013). Relapsed or refractory (r/r) disease is very common in adults and is associated with a significant mortality rate, with median survival of less than 1 year (Gökbuget et al. 2012; Maffini et al. 2019). Despite the recent approval of innovative immunotherapy treatments, the prognosis and outcome for adult patients with r/r B ALL is dismal and has remained unchanged during the last 2 to 3 decades (Malard and Mohty 2020; Hoelzer et al. 2024).

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

The approved therapeutic indication "treatment of adult patients 26 years of age and above with relapsed or refractory (r/r) B cell precursor acute lymphoblastic leukaemia (B ALL)" falls within the scope of the designated orphan condition "treatment of acute lymphoblastic leukaemia".

Intention to diagnose, prevent or treat

The medical plausibility has been confirmed by the positive benefit/risk assessment of the CHMP, see EPAR.

Chronically debilitating and/or life-threatening nature

The sponsor discussed the chronically debilitating and life-threatening nature of the condition.

ALL is a life-threatening and seriously debilitating malignant disease, characterized by the malignant transformation and proliferation of lymphoid progenitor cells in the blood and BM, replacing normal blood cells over time. This seriously compromises the patient's immune function, leading to infections, bleeding complications and anaemia. Moreover, the spread of lymphoblasts into any organ of the body (extramedullary disease [EMD]) makes the treatment and the prognosis even more challenging and contributes to the overall disease burden. If untreated, B ALL will progress rapidly and is generally fatal.

Whilst the cure rates and survival outcomes for paediatric patients with ALL have improved dramatically over the past several decades (SEER, 2023), adults have the poorest 5-year overall survival (OS) rates being 39.2% for patients between the ages of 40 and 64 and only 19.1% for patients ≥ 65 years of age. Thus, OS decreases substantially with increasing age, although there may also be a proportion of younger adults who are particularly challenging to treat as they are patients who were diagnosed at a younger age with a long history of multiple treatments and lack of durable remissions, so are less likely to respond to any additional salvage therapies (Trama et al, 2016). Indeed, in contrast to paediatric B ALL, the prognosis for adult B ALL has remained unchanged during

the last two to three decades with long-term (> 3 years) remission rates of approximately 40% (Paul et al, 2019). Adult patients with r/r disease are therefore common and is associated with a significant mortality rate, with median survival of less than one year (Gökbuget et al, 2012; Kantarjian et al, 2017; Aldoss et al, 2017).

The COMP has previously accepted that the clinical course of ALL is chronically debilitating and life-threatening depending on the response to treatment, with acute leukemic forms being fatal in a few weeks if left untreated. Symptoms include persistent fever, infections, anaemia, fatigue, breathlessness, bone and joint pain. The invasion of tumour cells in the bloodstream, the bone marrow and/or the lymphatic system results in lack of normal blood cells, bone marrow failure, and organ damage. The severe nature of ALL earlier acknowledged by the COMP remains acceptable for this procedure.

Number of people affected or at risk

The sponsor proposed a prevalence of 1.4 in 10,000 persons.

This was based on incidence data for leukaemia derived from the European Cancer Information System (ECIS) database. These data were used for an indirect comparison assuming an ALL proportion of 12.4.% of the total leukaemia population as published for 2017 (Dong et al. 2020). Estimated crude ALL incidence rate is 0.2 per 10,000 inhabitants.

The surveillance, epidemiology and end results (SEER) database provides long-term data on survival rates in yearly increments up to 10 years. These data allow a precise approximation of the real disease duration. The methodology applied below considers the average lifetime of the patients after diagnosis, and requires only a few assumptions, which are explained in the footnotes of the calculation Table 1.

Table 1. ALL estimated disease duration 2000-2020 (all ages)

Years after diagnosis	Average disease duration until death or cure [years]	Relative survival [%]	Death rate [%] [1]	Contribution to overall average disease duration [years] [2]
1	0.50	84.1	15.9	0.080
2	1.50	76.4	7.7	0.116
3	2.50	72.4	4.0	0.100
4	3.50	70.0	2.4	0.084
5	4.50	68.5	1.5	0.068
6	5.50	67.4	1.1	0.061
7	6.50	66.7	0.7	0.046
8	7.50	66.2	0.5	0.038
9	8.50	65.7	0.5	0.043
10	9.50	65.4	0.3	0.029
10+ [3]	10.00	65.4	65.4	6.540
Average disease duration [years]				7.201

Abbreviations: ALL = acute lymphoblastic leukemia.
[1] Calculated as difference in relative survival from previous year; for > 10 years, this corresponds to the cure rate.
[2] Calculated as the death rate x the average disease duration / 100.
[3] The estimate for group "10+" considers that the majority of these patients, in particular patients diagnosed and treated at an early stage, are permanently cured within the first 10 years after diagnosis.
Source: (SEER 2024b).

Based on the above calculations, the average disease duration is 7.2 years for ALL patients.

A summary of the point prevalence calculation is presented in Table 2.

Table 2. Calculation of point prevalence for the orphan condition ALL

Incidence per 10,000 in the EEA	**Duration (years)**	**Prevalence per 10,000 inhabitants**
0.2	7.2	1.4

Abbreviations: ALL = acute lymphoblastic leukemia; EEA = European Economic Area.

The COMP considered that the proposed figure seems to be an underestimate of the prevalence. The sponsor should provide the methods for estimating prevalence and, in addition, the sponsor should clarify if the reported proportion of ALL comprises both adult and pediatric patients.

Article 3(1)(b) of Regulation (EC) No 141/2000

Existence of no satisfactory methods of diagnosis prevention or treatment of the condition in question, or, if such methods exist, the medicinal product will be of significant benefit to those affected by the condition.

Existing methods

Table 3 provides an overview of all medicinal products authorized in the EU for the orphan indication, treatment of ALL.

Table 3. Products approved in the EU for the treatment of ALL

Class	**INN (Product Name)**	**Approval Pathway**	**Approved Indication**
Chemotherapy: vinca alkaloid (Induction, Maintenance)	Vincristine sulphate (generics)	MRP, National	Used either alone or in conjunction with other oncolytic drugs for the treatment of ALL.
Chemotherapy: anthracyclines (Induction)	Daunorubicin (Cerubidine, Daunoblastine)	MRP, National	Induction of remission in ALL and AML. Used in combination with other cytostatics.
	Doxorubicin (generics)	MRP, National	Treatment of ALL. Frequently used in combination chemotherapy regimens with other cytotoxic drugs.
	Idarubicin (Zavedos and generics)	MRP, National	For second line treatment of relapsed ALL.

Chemotherapy: alkylating agent (Induction)	Cyclophosphamide (Endoxan and generics)	MRP, National	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.
Chemotherapy: antimetabolites (Induction, Consolidation)	Cytarabine (Cytosar and generics)	MRP, National	Alone or in combination for the induction of clinical remission and/or maintenance therapy in patients with ALL.
	Clofarabine (Evoltra and generics)	Centralized, MRP	Treatment of ALL in pediatric 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)	Centralized	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.
Chemotherapy (Induction, Consolidation)	Asparaginase (Spectrila, Kidrolase)	Centralized, MRP	As a component of antineoplastic combination therapy for the treatment of ALL in pediatric patients from birth to 18 years and adults.
	Pegaspargase (Oncaspar)	Centralized	As a component of antineoplastic combination therapy in ALL in pediatric patients from birth to 18 years, and adult patients.
	Crisantaspase (Enrylaze, Erwinase)	Centralized, MRP	As a component of a multi-agent chemotherapeutic regimen for the treatment of ALL in adult and pediatric patients (1 month and older) who developed hypersensitivity or silent inactivation to E. coli-derived asparaginase.
Chemotherapy: antimetabolites (Consolidation, Maintenance)	Methotrexate (Jylamvo and generics)	Centralized, MRP	Maintenance treatment of ALL in adults, adolescents and children aged 3 years and over.
Chemotherapy: antimetabolites (Maintenance)	Mercaptopurine (Xaluprine)	Centralized	Treatment of ALL in adults, adolescents and children.

Chemotherapy: alkylating agents (SCT conditioning)	Melphalan (Phelinun)	Centralized	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 hematological diseases in adults.
TKIs	Glivec (imatinib) (and generics)	Centralized	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)	Centralized	Treatment of adult patients with Ph+ ALL and lymphoid blast CML with resistance or intolerance to prior therapy.
	Iclusig (ponatinib)	Centralized	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)	Centralized	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%.
Antibody-Drug Conjugates	Besponsa (inotuzumab ozogamicin)	Centralized	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)	Centralized	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)	Centralized	Treatment of adult patients 26 years of age and above with r/r B cell precursor ALL.

Abbreviations: ALL = acute lymphoblastic leukemia; allo HSCT = allogeneic hematopoietic stem cell transplantation; AML = acute myeloid leukemia; BM = bone marrow; CAR = chimeric antigen receptor; CML = chronic myeloid leukemia; 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 leukemia; T LBL = T cell lymphoblastic lymphoma; TKI = tyrosine kinase inhibitor.

Table 4 provides an overview of the medicinal products authorized in the EU for the therapeutic indication intended for obe-cel [treatment of adult patients (26 years and older) with r/r B-precursor ALL], including the reasoning if the therapy is identified as a comparator to demonstrate significant benefit or not.

Table 4. Identification of satisfactory treatment methods for the demonstration of significant benefit

Product Name (INN)	**Approved Therapeutic Indication**	**Requirement of significant benefit demonstration**
Chemotherapy for induction, consolidation and maintenance (see Table 2)	Treatment of ALL	Since the current indication for chemotherapy for induction, consolidation and maintenance is quite broad, these authorized treatments are considered as satisfactory methods
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 authorized 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 authorized 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 authorized 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.
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 approved indication for obe-cel.

Product Name (INN)	Approved Therapeutic Indication	Requirement of significant benefit demonstration
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 pediatric and young adult patients only.
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 approved indication for obe-cel.

Abbreviations: ALL = acute lymphoblastic leukemia; 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.

According to the above table, blinatumomab, inotuzumab ozogamicin and brexucabtagene autoleucel are considered as satisfactory methods for the treatment of the same patient population as obe-cel.

Significant benefit

The sponsor claimed significant benefit based on major contribution to patient care and improved efficacy.

The efficacy and safety of obecabtagene autoleucel is based on the results of the FELIX study, an open-label, multi-centre, single arm Phase Ib/II study of obecabtagene autoleucel in adult patients with r/r B ALL.

The primary outcome of Cohort IIA was the overall complete remission rate defined as proportion of patients achieving complete remission (CR) or complete remission with incomplete haematologic recovery (CRi) as assessed by an Independent Response Review Committee (IRRC) and the secondary outcomes included duration of remission (DOR), complete remission rate (CRR) and proportion of patients achieving minimal residual disease (MRD)-negative response.

Patients in the pivotal study were adults (≥ 18 years) with r/r CD19+ B ALL, presence of ≥ 5% blasts in BM at screening and confirmed CD19 expression after blinatumomab therapy. Patients with Philadelphia chromosome positive ALL were eligible if they were intolerant to or have failed 2 lines of any tyrosine kinase inhibitor (TKI) or one line of second-generation TKI, or if TKI therapy was contraindicated. Patients with prior CD19 targeted therapy other than blinatumomab were excluded.

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

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

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

	Infused set (N=94)	**Leukapheresed set (N=113)**
Median age, range (years)	50 (20 – 81)	49 (20 – 81)
Gender, n (M/F)	47M/47F	60M/52F
Race, n (%)		
Caucasian	70 (74.5)	86 (76.8)
Philadelphia chromosome positive status (BCR-ABL positive), n (%)	25 (26.6)	26 (23.2)
Median prior lines of treatment, n (range)	2 (1 – 6)	2 (1 – 6)
≥ 3 prior lines, n (%)	29 (30.9)	35 (31.3)
Refractory to last prior line of therapy, n (%)	51 (54.3)	59 (52.7)
Prior HSCT, n (%)	36 (38.3)	43 (38.4)
Prior blinatumomab, n (%)	34 (36.2)	41 (36.6)
Prior inotuzumab, n (%)	30 (31.9)	37 (32.7)
BM blast % at lymphodepletion, median (range)	41.1 (0 – 100)	41.1 (0 – 100)
BM blast % at lymphodepletion, n (%)		
> 75%	30 (31.9)	30 (26.5)
> 20% to 75%	27 (28.7)	27 (23.9)
5 to 20%	14 (14.9)	14 (12.4)
< 5%	23 (24.5)	23 (20.4)
N/A	0	18 (15.9)
Extramedullary disease at lymphodepletion, n (%)	19 (20.2)	21 (18.6)

ABL = Abelson murine leukaemia; BCR = breakpoint cluster region; BM = bone marrow; F = female
HSCT = haematopoietic stem cell transplantation; M = male; N/A = not applicable.

The primary efficacy analysis was evaluated in patients who received at least one infusion of Aucatzyl (infused set) in the pivotal Cohort IIA of the FELIX study. The median manufacturing time from leukapheresis receipt to product certification was 20 days (range: 17-43 days) and the median time from leukapheresis to obecabtagene autoleucel infusion was 35.5 days (range: 25-92 days). The median follow-up (duration from first infusion to data cut-off date of 07-Feb-2024) was 20.25 months (range: 13-30 months).

Table 6. Overview of key efficacy results in FELIX per IRRC assessment (cohort IIA, infused and enrolled set)

Parameter	**Infused Set (N = 94)**	**Enrolled Set (N = 112)**
BOR - n (%) [1]		
CR	52 (55.3)	55 (49.1)
CRi	20 (21.3)	17 (15.2)
ORR (= CR + CRi) - n (%)		
n (%)	72 (76.6)	72 (64.3)
95% CI (%) [2]	(66.7, 84.7)	(54.7, 73.1)
p-value	<0.0001 [7]	ND
CR rate - n (%)		
n (%)	52 (55.3)	55 (49.1)
95% CI (%) [2]	(44.7, 65.6)	(39.5, 58.7)
p-value	<0.0001 [8]	ND
MRD negativity (10-4) [3]		
Patients who achieved CR or CRi	N = 72	N = 72
n (%) [3]	64 (88.9%)	64 (88.9%)
95% CI (%) [2]	(79.3, 95.1)	(79.3, 95.1)
DOR [4]		
Median (95% CI)	14.1 (8.2, NE)	14.1 (8.2, NE)
6 months probability (95% CI) (%) [2]	75.0 (62.3, 83.9)	76.9 (64.5, 85.4)
12 months probability (95% CI) (%) [2]	54.3 (40.3, 66.3)	54.1 (40.1, 66.2)
EFS [4]		
Patients with event, n (%)	54 (57.4)	71 (63.4)
6 months probability (95% CI) (%) [5]	63.8 (52.9, 72.8)	57.5 (47.7, 66.1)
12 months probability (95% CI) (%) [5]	43.4 (32.4, 54.0)	40.7 (31.0, 50.2)
OS [6]		
Patients alive, n (%)	42 (44.7)	46 (41.1)
6 months probability (95% CI) (%) [5]	78.7 (69.0, 85.7)	73.0 (63.7, 80.3)
12 months probability (95% CI) (%) [5]	57.4 (46.8, 66.7)	54.6 (44.8, 63.3)

Abbreviations: BM = bone marrow; BOR = best overall remission; CI = confidence interval; CR = complete remission; CRi = complete remission with incomplete hematologic recovery; DOR = duration of remission; EFS = event-free survival; FACS = fluorescence-activated cell sorting; IRRC = Independent Response Review Committee; MRD = minimal residual disease; ND = not determined; NE = not estimable; NGS = next-generation sequencing; ORR = overall response rate; OS = overall survival; PCR = polymerase chain reaction; SCT = stem cell transplantation.
[1] BOR is defined as the best response achieved after obe-cel infusion (for infused analysis) or after enrollment (for all leukapheresed analysis) without initiation of any new non-protocol anti-cancer therapies.
[2] The 95% exact Clopper-Pearson CIs are displayed.
[3] Patients in remission by IRRC with MRD-negative BM by central ClonoSEQ NGS/PCR/FACS.
[4] With censoring for SCT and other new anti-cancer therapy.
[5] Percent event-free probability estimates are obtained from the Kaplan-Meier survival estimates, with 95% CIs estimated using Greenwood formula.
[6] Without censoring for SCT.
[7] Exact p-value testing H_{10}: ORR ≤ 40% in all infused patients.
[8] Exact p-value testing H_{20}: CR at any time ≤ 20% in all infused patients.
FELIX Data cut-off: 07-Feb-2024

Significant benefit of obe-cel over blinatumomab

The sponsor claims significant benefit of obe-cel over blinatumomab based on improved efficacy. Blinatumomab is a bispecific monoclonal antibody construct that enables CD3positive T cells to recognize and target CD19positive ALL blasts. Full approval for blinatumomab was granted based on the TOWER study, a multiinstitutional Phase III trial (Kantarjian et al. 2017). Adults with pretreated Ph- B cell precursor ALL were randomly assigned, in a 2:1 ratio, to receive either blinatumomab or SOC chemotherapy. The primary endpoint was OS.

Overall (405 patients in total), 271 patients received blinatumomab and 134 patients received SOC chemotherapy. The efficacy results of the FELIX study compared favorably to the results observed with blinatumomab in the TOWER study (Table 7). For FELIX, both the Infused Set and Enrolled Set are presented for the comparison to the intent-to-treat (ITT) population from TOWER; however, it should be noted that most of the randomized patients in TOWER (98.5%) received blinatumomab so the Infused Set from FELIX is considered the most comparable population. Regardless, results are consistently in favor of obe-cel, with higher CRR (by approximately 1.7-fold) and longer DOR and OS (by approximately 2-fold).

Table 7. Comparison of key efficacy data between FELIX and TOWER

Parameter	**Obe-cel (FELIX) [1] (Cohort IIA)**		**Blinatumomab (TOWER) (N = 271) [2] (ITT)**
	Infused Set (N = 94)	**Enrolled Set (N = 112)**	
Treated patients, n (%)	94 (100%)	94 (83.9%)	267 (98.5%)
Overall response rate/ overall clinical response (%) (95% CI)	CR/CRi: 76.6 (66.7, 84.7)	CR/CRi: 64.3 (54.7, 73.1)	CR/CRh/CRi: 43.9 (37.9, 50.0)
CR (%) (95% CI)	55.3 (44.7, 65.6)	49.1 (39.5, 58.7)	33.6 (28.0, 39.5)
Median DOR (months) [3] (95% CI)	14.06 (8.18, NE)	14.06 (8.18, NE)	7.3 (5.8, 9.9)
EFS [3] 6-month estimate (%) (95% CI)	63.8 (52.9, 72.8)	57.5 (47.7, 66.1)	30.7 (25.0, 36.5)
Median OS (months) [4] (95% CI)	14.16 (10.97, 23.75)	13.73 (11.01, 16.85)	7.7 (5.6, 9.6)

Abbreviations: CI = confidence interval; CR = complete response; CRh = complete remission with partial hematologic recovery; CRi = complete remission with incomplete hematologic recovery; DOR = duration of remission; EFS = event-free survival; ITT = intent-to-treat; NE = not estimable; OS = overall survival; SCT = stem cell transplantation.
[1] Median follow-up 20.25 months (range: 12.7 to 29.8).
[2] (Blincyto SmPC 2023).
[3] With censoring for SCT and other new anti-cancer therapy.
[4] Without censoring for SCT.
FELIX Data cut-off: 07-Feb-2024.

Similar to inotuzumab ozogamicin and in contrast to obe-cel, blinatumomab treatment is characterized by a relatively short median DOR (7.3 months) and a median OS of 7.7 months, although this is longer compared to the SOC chemotherapy arm (4.0 months) (Blincyto SmPC 2023). Similar to inotuzumab ozogamicin, due to the short DOR, blinatumomab mostly serves as a bridge to allogeneic SCT (Topp et al. 2015; Dombret et al. 2019).

Based on this indirect comparison, the sponsor concludes that the efficacy of obe-cel provides a significant benefit over blinatumomab for the treatment of r/r B precursor ALL based on the available clinical efficacy data from the FELIX and TOWER studies which demonstrate obe-cel provides a more

durable and deep remission, with significantly higher CRR (by approximately 1.7-fold) and longer DOR and OS (by approximately 2-fold).

COMP discussion

Based on the results presented above, the ORR is >20% larger in the obe-cel study compared to blinatumomab study, and median OS is approximately 13-14 months vs. 7.7 months, respectively. The sponsor did not compare the baseline characteristics of the studies to confirm whether the study populations would be comparable. However, the FELIX study included 33 patients in cohort IIA who received blinatumomab and 22 of these patients responded to treatment with obe-cel. The COMP considers that this could justify the significant benefit of obe-cel over blinatumomab.

Significant benefit of obe-cel over inotuzumab ozogamicin

Inotuzumab ozogamicin is an antibody-drug conjugate composed of a humanized antiCD22 monoclonal antibody conjugated to the cytotoxic agent calicheamicin. It binds with high affinity to CD22, a cell surface antigen expressed by > 90% of B cell blasts in nearly all patients with B cell ALL. Inotuzumab ozogamicin was approved on the basis of an open-label, international, multicenter, Phase III study (INO-VATE) in which patients were randomized to receive inotuzumab ozogamicin (N = 164) or Investigator's choice of chemotherapy (N = 162) (Kantarjian et al. 2016; Kantarjian et al. 2019).

The efficacy results between obe-cel in the FELIX study and inotuzumab ozogamicin in the INO-VATE study are compared in Table 8. For FELIX, both the Infused Set and Enrolled Set are presented in comparison to the ITT population from INO-VATE; however, it should be noted that all randomized patients in INO-VATE received inotuzumab ozogamicin so the Infused Set from FELIX is considered the most comparable population. According to the sponsor, results are consistently in favor of obe-cel.

Table 8. Comparison of key efficacy data between FELIX and INO-VATE

Parameter	**Obe-cel (FELIX) [1] (Cohort IIA)**		**Inotuzumab ozogamicin (INO-VATE) (N = 109 or 164) [2] (ITT)**
	Infused Set (N = 94)	**Enrolled Set (N = 112)**	
Treated patients, n (%)	94 (100%)	94 (83.9%)	164 (100%)
Overall response rate/ overall clinical response (%) (95% CI)	CR/CRi: 76.6 (66.7, 84.7)	CR/CRi: 64.3 (54.7, 73.1)	CR/CRi: 80.7 (72.1, 87.7)
CR (%) (95% CI)	55.3 (44.7, 65.6)	49.1 (39.5, 58.7)	35.8 (26.8, 45.5)
Median DOR (months) [3] (95% CI)	11.56 (8.08, 17.05)	-	3.7 (2.8, 4.6)
Median EFS/PFS (months) [3] (95% CI)	9.03 (EFS) (6.14, 14.98)	8.18 (EFS) [4.34, 12.12]	5.0 (PFS) (3.9, 5.8)
Median OS (months) [4] (95% CI)	14.16 (10.97, 23.75)	13.73 [11.01, 16.85]	7.7 (6.0, 9.2)

Abbreviations: CI = confidence interval; CR = complete response; CRi = complete remission with incomplete hematologic recovery; DOR = duration of remission; EFS = event-free survival; ITT = intent-to-treat; MRD = minimal residual disease; NE = not estimable; OS = overall survival; PFS = progression-free survival; SCT = stem cell transplantation.

[1] Median follow-up 20.25 months (range: 12.7 to 29.8).
[2] N=109 for CR/CRi and MRD negativity; N=164 for OS, PFS, and DOR (Besponsa SmPC 2022). All randomized patients received inotuzumab ozogamicin.
[3] For FELIX: without censoring for SCT and other new anti-cancer therapy; for inotuzumab ozogamicin: analysis with patients without remission being given a duration of zero and considered an event.
[4] Without censoring for SCT and other new anti-cancer therapy.
FELIX Data cut-off: 07-Feb-2024.

According to the sponsor, the main clinical value of inotuzumab ozogamicin is its use as a bridge to SCT, so a durable remission without further intervention was not observed (Kantarjian et al. 2019; Marks et al. 2019). Therefore, the significant benefit for obe-cel versus inotuzumab ozogamicin is based on the demonstrated ability to provide a more durable remission as evidenced by higher rate of CR and longer DOR, EFS and particularly OS. This is particularly relevant as the patients in INOVATE were less severely affected, with less prior lines of treatment than those in the FELIX study. In addition, inotuzumab ozogamicin is associated with hepatotoxicity. VOD/SOS was reported during or after treatment (including after post-HSCT follow-up) in 14.0% (23/164) of patients; among the 79 patients who proceeded to a subsequent HSCT, VOD/SOS was reported in 22.8% (18/79) of patients, with 5 of the 18 VOD/SOS events being fatal (Besponsa SmPC 2022).

The sponsor concludes that obe-cel provides a significant benefit over inotuzumab ozogamicin for the treatment of r/r B cell precursor ALL based on the available clinical efficacy data from the FELIX and INOVATE studies, with significantly longer DOR (by approximately 3-fold) and OS (by approximately 2-fold). Further, the safety profile of inotuzumab ozogamicin is characterized by the potential of severe hepatotoxicity, particularly after allogeneic HSCT, with an increased risk of post-transplant non-relapse mortality.

COMP discussion

Based on the on the point estimates presented above, the obe-cel resulted in numerically worse ORR results (80.7 in inotuzumab ozogamicin study versus 76.6 and 64.3 in obe-cel study). In terms of median OS, the results are in favour of obe-cel with approximately 13-14 months in obe-cel study compared to 7.7 months in inotuzumab ozogamicin study. The sponsor did not compare the baseline characteristics of the studies to confirm whether the study populations would be comparable.

However, the FELIX study included in Cohort IIA 30 patients who received inotuzumab ozogamicin and 20 of these patients responded to treatment with obe-cel. The COMP considers that this could justify the significant benefit of obe-cel over inotuzumab ozogamicin.

Significant benefit of obe-*cel over brexucabtagene autoleucel*

The sponsor claims significant benefit of obe-cel over brexucabtagene autoleucelbased on major contribution to patient care (MCPC) through:

a) a significant reduction in the immune-mediated toxicities and the associated high treatment burden and need for intensive care experienced by patients,

b) a significant number of patients experiencing a definitive long-lasting CAR T therapy without the need for SCT or other anti-cancer therapies.

Comparable overall efficacy despite differences in poor prognosis factors

The sponsor claims comparable efficacy between obe-cel over brexucabtagene autoleucel. The sponsor presented a comparison of baseline characteristics of FELIX and ZUMA-3 studies (Table 9). According to the sponsor, characteristics associated with poor prognostic factors were more common in the FELIX study. The median age in FELIX study was higher (50.0 years versus 40 years) with a higher proportion being ≥ 65 years (22% versus 15%), a larger proportion of patients were Hispanic or Latino

(31% versus 20%) and the proportion with EMD was also higher (20% versus 11%). Age, Hispanic ethnicity and EMD involvement are established negative prognostic characteristics associated with a more aggressive disease and poorer long-term survival (Bencomo-Alvarez et al. 2021; Gökbuget et al. 2024); and as such, a lower efficacy could be expected in obe-cel compared to brexucabtagene autoleucel.

Table 9. Patient baseline characteristics for FELIX and ZUMA-3

Parameter	**Obe-cel (FELIX) Infused Set (N = 94)**	**Brexucabtagene autoleucel (ZUMA-3) (N = 55) [1]**
Age, median (range) < 65 Years ≥ 65 Years	50 (20 – 81) 73 (77.7) 21 (22.3)	40 (19 - 84) 47 (85.5) 8 (14.5)
Hispanic or Latino, n (%)	29 (30.9)	11 (20.0)
Ph+ (BCR-ABL), n (%)	25 (26.6)	15 (27.3)
Median prior lines of therapy (range)	2 (1 – 6)	2 (1 – 8)
Number of prior lines of therapy, n (%) 1 2 3 ≥ 4	 29 (30.9) 36 (38.3) 17 (18.1) 12 (12.8)	 10 (18.2) 19 (34.5) 14 (25.5) 12 (21.8)
Refractory to all prior lines of anti-cancer therapy, n (%) Refractory to first-line therapy, n (%) Refractory to last prior line of therapy, n (%) Relapsed to first-line therapy within 12 months, n (%)	 12 (12.8) 24 (25.5) 51 (54.3) 41 (43.6)	 N/A 18 (32.7) N/A 16 (29.1)
BM blasts at screening, median (Q1 - Q3)	58.9 (20.0 – 86.0)	65 (24 – 87)
EMD at screening, n (%)	19 (20.2)	6 (10.9)

Abbreviations: BM = bone marrow; EMD = extramedullary disease; LD = lymphodepletion; N/A = not available; Ph+ = Philadelphia chromosome-positive; Q = quartile.
[1] (Shah, Ghobadi, et al. 2021; Tecartus EPAR 2022).
FELIX Data cut-off: 07 Feb 2024

Despite these differences in baseline characteristics, the rates of remission appeared comparable between obe-cel and brexucabtagene autoleucel (Table 10). Of note, and in line with the different product attributes of obe-cel compared to brexucabtagene autoleucel as described above, it is remarkable that there was a marked (by approximately 2-times) reduced rate of use of SCT or other anti-cancer therapies in patients who achieved a best overall response of CR or CRi with obe-cel compared with brexucabtagene autoleucel.

Table 10. Comparison of remission data from FELIX and ZUMA-3

Parameter	**Obe-cel (FELIX) (N = 94) (Infused Set, Cohort IIA)**	**Brexucabtagene autoleucel (ZUMA-3) (N = 55)**	
		[1]	**[2]**
Median follow-up (months) (Range, months)	20.25 (12.7 – 29.8)	16.4 (13.8 – 19.6)	26.8 (20.7 – 32.6)
Overall response rate (CR/CRi) n (%) (95% CI)	72/94 (76.6%) (66.7, 84.7)	39/55 (70.9%) (57.0, 82.0)	39/55 (70.9%)
CR n (%) (95% CI)	52/94 (55.3%) (44.7, 65.6)	31/55 (56.4%) (42.0, 70.0)	31/55 (56.4%)
Use of SCT or other anti-cancer therapy post-infusion among patients who achieved BOR of CR/CRi n (%)	14/72 (19.4%)	14/39 (35.9%)	16/39 (41.0%)
Duration of remission			
Median (months) (95% CI)	14.1 (8.2, NE)	12.8 (8.7, NE)	14.6 (9.4, NE)

Abbreviations: BOR = best overall response; CI = confidence interval; CR = complete remission; CRi = complete remission with incomplete hematologic recovery; NE = not estimable; SCT = stem cell transplantation.
[1] (Shah, Ghobadi, et al. 2021)
[2] (Shah et al. 2022)
FELIX Data cut-off: 07-Feb-2024

Efficacy results from the FELIX pivotal cohort IIA are thus clinically meaningful and compare favorably with the clinical performance of brexucabtagene autoleucel in ZUMA-3, despite the fact that a more difficult-to-treat patient population was enrolled in FELIX.

Differentiated design and CAR T kinetics profile of obe-cel

Obe-cel is a CD19-directed CAR T-cell therapy developed for the treatment of r/r B-ALL. It is structurally and functionally distinct from currently approved CD19 CAR T-cell therapies, such as brexucabtagene autoleucel, with the aim of addressing limitations related to long-term cell persistence and immune-mediated toxicities.

A key difference is the binding domain: while existing therapies, including brexucabtagene autoleucel, utilize a high-affinity FMC63-derived single-chain variable fragment (scFv), obe-cel incorporates an scFv from the CAT19 hybridoma. CAT19 exhibits approximately 40-fold lower affinity for CD19, attributable to a faster dissociation rate, while maintaining a similar association rate. This lower-affinity interaction may reduce sustained cell-to-cell contact and minimize mechanisms such as trogocytosis, which have been associated with potential loss of target antigen and off-tumor effects.

Obe-cel also differs in its intracellular signaling domains. It uses a hinge and transmembrane region derived from CD8α and includes a 4-1BB (CD137) co-stimulatory domain. In preclinical models, 4-1BB-based CARs have shown advantages over CD28-based CARs (as used in brexucabtagene autoleucel) in terms of proliferation, persistence, and reduced T-cell exhaustion under chronic stimulation. These properties may contribute to the longer-term persistence of CAR T cells in vivo.

In clinical evaluation, obe-cel demonstrated measurable expansion and persistence of CAR T cells in peripheral blood, as assessed by PCR detection of the CAR transgene. Data from the FELIX study showed a geometric mean peak transgene concentration of 114,982 copies/µg DNA, with a median time to peak of 14 days and an AUC from Day 0 to Day 28 of 1,138,188 copies/µg DNA·day. CAR T cells were detectable for up to 30 months post-infusion.

In contrast, published results from the ZUMA-3 trial evaluating brexucabtagene autoleucel reported CAR T-cell detection up to 6 months post-infusion. Comparative observations indicate that obe-cel achieved higher and more consistent expansion, and treatment responses were less variable with respect to expansion levels compared to brexucabtagene autoleucel (Table 11). This may suggest differences in pharmacokinetics or interaction with host immune environments, though direct comparisons should be interpreted with consideration of study design and patient population differences.

Table 11. Measures of CAR T expansion by complete remission status for obe-cel in comparison to brexucabtagene autoleucel

Parameter	**Obe-cel (FELIX Cohort IIA)**			**Brexucabtagene autoleucel (ZUMA-3 Phase II) [1]**		
	CR/CRi	**Not CR/CRi**	**Total**	**CR/CRi**	**Not CR/CRi**	**Total**
N	72	22	94	39	16	55
Peak or C_{max} [2]	C_{max} 117,381 (2,120 - 478,000)	C_{max} 107,465 (129 - 600,000)	C_{max} 114,982 (129 - 600,000)	Peak 56,862 (3,564 - 417, 150)	Peak 4,981.5 (0.0 – 323,190)	Peak 50,382 (0.0 - 417,150)
AUC_{0-28d} [3]	1,089,908 (17,900 - 6,730,000)	1,404,899 (176,00 - 7,230,000)	1,138,188 (17,900 - 7,230,000)	783,764 (46,551 - 5,317,893)	34,559 (0.0 - 4,437,796)	702,314 (0.0 - 5,317,893)

Abbreviations: AUC0-28d = area under the concentration-time curve from time zero to 28 days; Cmax = maximum (or peak) concentration; CR = complete response; CRi = complete remission with incomplete hematologic recovery; N/A = Not applicable.
[1] Tables 14.5.1.1.1 and 14.5.5.1.1 (Kite Pharma 2021).
[2] Cmax for obe-cel (copies/µg DNA; geometric mean [min - max]); peak for brexucabtagene autoleucel (copies/µg DNA; median [min – max]).
[3] obe-cel (copies/µg DNA·days, geometric mean [min – max]); brexucabtagene autoleucel (copies/µg DNA·days, median [min – max]).
FELIX Data cut-off: 07-Feb-2024

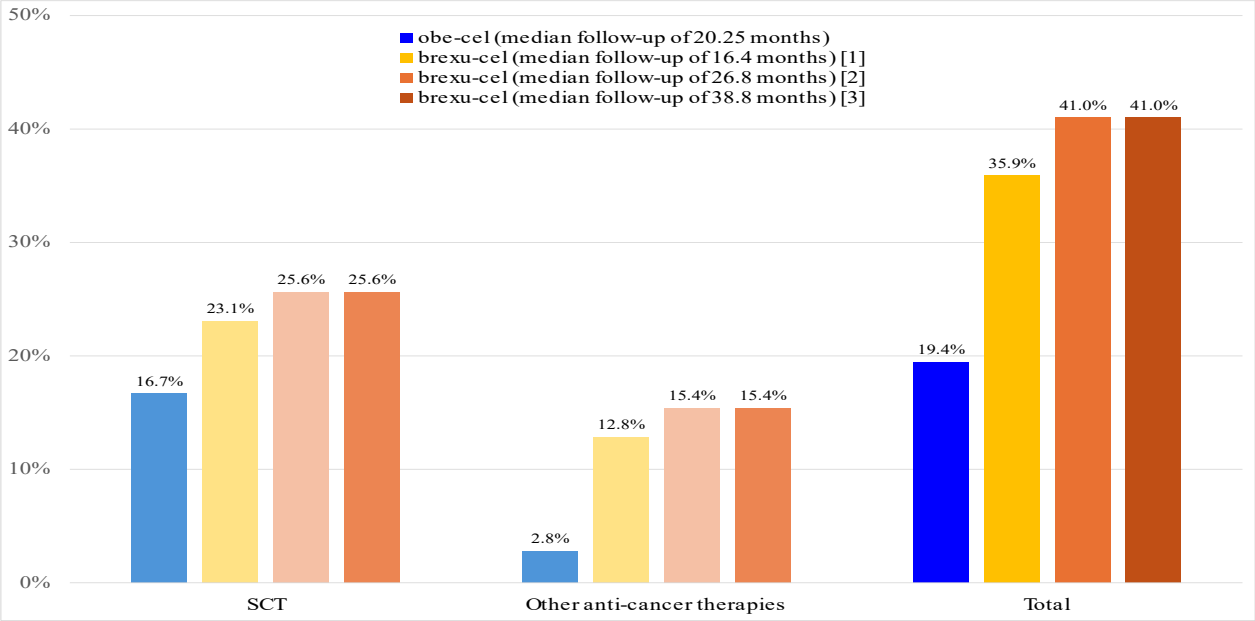
Definitive long-lasting CAR T therapy without additional therapies

The sponsor claims that obe-cel has demonstrated the potential to induce durable remissions in a subset of patients with r/r B-ALL without the need for subsequent anti-cancer therapies, including SCT. In the FELIX study (Cohort IIA), 36.1% (26/72) of patients were reported to be in ongoing remission without further anti-cancer treatment at a median follow-up of 20.25 months. Similarly, in the ALLCAR19 study, 41.2% (7/17) of patients remained in remission without additional therapy after a median follow-up of 36 months (Roddie et al. 2023). Among these patients, high rates of CAR T-cell persistence were observed: 80.8% (21/26) in FELIX and 87.5% (7/8) in ALLCAR19.

These outcomes were compared with data from the ZUMA-3 trial evaluating brexucabtagene autoleucel. At a median follow-up of 26.8 months, 15.4% (6/39) of responders remained in remission without further therapy; this decreased to 10.3% (4/39) at a 38.8-month follow-up (Shah et al. 2022; Hadjivassileva et al. 2023).

In addition, the application reports a lower rate of post-infusion use of SCT or other anti-cancer therapies among patients achieving CR or CRi following obe-cel. At the most recent data cut-off (7 February 2024), 19.4% (14/72) of such patients in FELIX had received further therapy, compared with 41.0% (16/39) of CR/CRi patients treated with brexucabtagene autoleucel in Phase II of the ZUMA-3 study (Figure 1).

Figure 1. Use of SCT or other anti-cancer therapies in patients who achieved best overall response of CR or CRi during FELIX or ZUMA-3



Abbreviations: brexu-cel = brexucabtagene autoleucel; CR = complete remission; CRi = complete remission with incomplete hematologic recovery; SCT = stem cell transplantation.
[1] (Shah, Ghobadi, et al. 2021)
[2] (Shah et al. 2022)
[3] (Hadjivassileva et al. 2023)
Source for obe-cel: FELIX Data cut-off 07-Feb-2024

The sponsor also suggests that these findings indicate that obe-cel may allow a proportion of patients to achieve sustained remission as a stand-alone treatment, reducing reliance on subsequent therapies such as SCT, which can carry additional risks and burdens. In this context, the capacity to maintain long-term disease control without further intervention is presented as a meaningful clinical attribute, potentially distinguishing obe-cel from therapies primarily used as a bridge to consolidation.

Reduced immune-mediated toxicities and associated consequences

The sponsor claims that obe-cel is associated with lower rates of immune-mediated toxicities—specifically CRS and ICANS—when compared to brexucabtagene autoleucel. The applicant attributes this difference to the distinct binding characteristics of obe-cel's CAR construct, notably its faster CD19 dissociation rate, as well as its tumor burden–adapted, fractionated dosing regimen.

In the FELIX study (cut-off: 7 February 2024), 68.5% (87/127) of patients experienced CRS of any grade after obe-cel infusion, with 2.4% (3/127) experiencing ≥ Grade 3 CRS. No Grade 4 or 5 CRS was reported. ICANS was observed in 22.8% of patients, with 7.1% experiencing Grade ≥ 3 events. By contrast, in the ZUMA-3 trial of brexucabtagene autoleucel, 89.1% (49/55) of patients experienced CRS of any grade, and 23.6% experienced CRS of Grade ≥ 3 (Shah et al. 2021). While ICANS was not graded by ASTCT criteria in ZUMA-3, real-world studies using ASTCT grading (ROCCA and CIBMTR) reported higher ICANS rates with brexucabtagene autoleucel: 55.9–47.8% of patients experienced

ICANS of any grade, and 31.4–23.9% had Grade ≥ 3 ICANS (Roloff et al. 2024; Bezerra et al. 2023). Despite a higher disease burden in the FELIX population, obe-cel was associated with lower rates of CRS and ICANS across both controlled and real-world comparisons.

Table 12. Comparative immunotoxicity of obe-cel and brexucabtagene autoleucel

		Obe-cel (FELIX) (N = 127)	**Brexucabtagene autoleucel**		
			ZUMA-3 [1] (N=55)	**Real-world use ROCCA (N=187) [2]**	**Real-world use CIBMTR (N=138) [3]**
CRS [4]	Any Grade	68.5%	89.1%	84.0%	81.2%
	≥ Grade 3 Grade 3 Grade 4 Grade 5	2.4% 2.4% 0 0	23.6% 12.7% 10.9% 0	10.7%	9.4%
ICANS [5]	Any Grade	22.8%	60.0%	55.9%	47.8%
	≥ Grade 3 Grade 3 Grade 4 Grade 5	7.1% 5.5% 0.8% 0.8%	25.5% 23.6% 0 1.8%	31.4%	23.9%

ASTCT = American Society for Transplantation and Cellular Therapy; CIBMTR = Center for International Blood and Marrow Transplant Research; CRS = cytokine release syndrome; ICANS = immune effector cell-associated neurotoxicity syndrome; ROCCA = Real-world Outcomes Collaborative of CAR-T in Adult ALL.
[1] Data for Phase II (Shah, Ghobadi, et al. 2021)
[2] (Roloff et al. 2024)
[3] (Bezerra et al. 2023)
[4] In ZUMA-3, CRS events were reported according to (Lee et al. 2014), which is considered reasonably similar to the subsequent ASTCT consensus grading for CRS (Lee et al. 2019) which was used in FELIX and in real-world reports.
[5] In ZUMA-3, 'ICANS' events were reported as 'neurological events' according to (Topp et al. 2015), which is considered reasonably similar to the subsequent ASTCT consensus grading for ICANS (Lee et al. 2019) which was used in FELIX and in real-world reports.
FELIX Data cut-off: 07-Feb-2024

Stratified analysis by bone marrow blast count at infusion showed that obe-cel consistently resulted in lower rates of ≥ Grade 3 CRS and ICANS compared to brexucabtagene autoleucel, regardless of disease burden. For example, in patients with high tumor burden (>20% for obe-cel; >25% for brexucabtagene autoleucel), the rate of ≥ Grade 3 CRS was 2.7% with obe-cel versus 27.5% with brexucabtagene autoleucel and the corresponding values for ICANS/neurotoxicity were 9.3% versus 25.0%, respectively.

A Matching-Adjusted Indirect Comparison (MAIC) was conducted by the sponsor to compare safety results between obe-cel (all infused patients, N=127) and brexucabtagene autoleucel (infused patients from ZUMA-3 Phase II, N=55) using the primary analysis cut-off of 09-Jun-2023. According to the sponsor, statistically significant reductions in the risk of ≥ Grade 3 CRS (87% reduction), immune-mediated neurotoxicity (77% reduction), and nervous system or psychiatric disorder AEs (63% reduction) were reported for obe-cel.

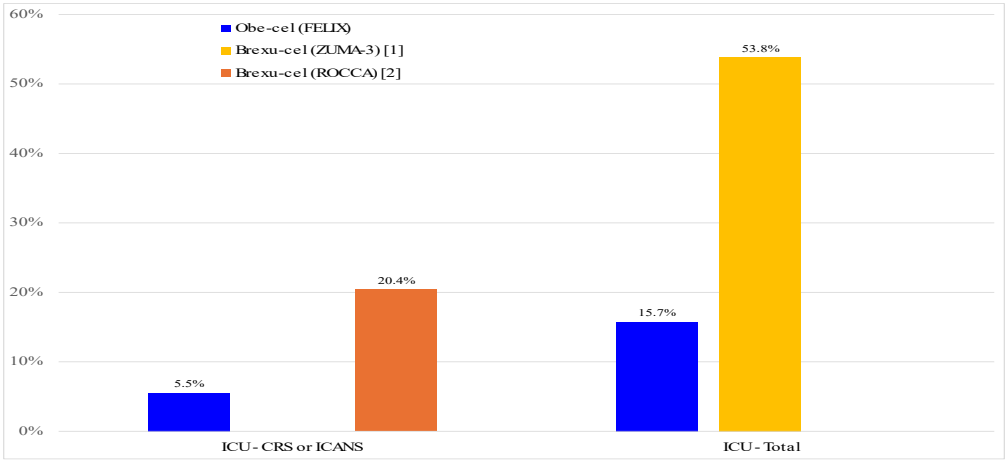
Table 13. Odds ratios for safety endpoints – obe-cel (FELIX cohort IIA) versus brexucabtagene autoleucel (ZUMA-3)

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

Abbreviations: CI = confidence interval; ESS = effective sample size; mITT = modified intent-to-treat; OR = odds ratio; SE = standard error.
OR < 1 is favorable for obe-cel and indicates lower odds of event. Results are considered statistically significant if the 95% CI does not include 1.
Source: obe-cel: FELIX Data cut-off 09-Jun-2023 cut-off; brexucabtagene autoleucel: ZUMA-3 (Shah, Ghobadi, et al. 2021).

From a healthcare resource utilization perspective, obe-cel was associated with a lower rate of intensive care unit (ICU) admissions. In FELIX, 15.7% of patients were transferred to ICU for any reason, and 5.5% specifically for CRS or ICANS. In contrast, 53.8% of patients in ZUMA-3 were admitted to ICU (Tecartus BLA 2021), and 20.4% in the ROCCA real-world study required ICU care for immunotoxicity (Kopmar et al. 2023), despite these cohorts generally having lower baseline disease burden.

Figure 2. ICU transfer rates after obe-cel or brexucabtagene autoleucel infusion



Abbreviations: brexu-cel = brexucabtagene autoleucel; CRS = cytokine release syndrome; ICANS = immune effector cell-associated neurotoxicity syndrome; ICU = intensive care unit; ROCCA = Real-world Outcomes Collaborative of CAR-T in Adult ALL.
[1] (Tecartus BLA 2021)
[2] (Kopmar et al. 2023) Real-world use, including patients with lower disease burden than FELIX
Source for obe-cel: FELIX Data cut-off 07-Feb-2024

While acknowledging the limitations of cross-trial comparisons, the applicant argues that the observed differences—particularly in rates of severe (Grade ≥ 3) toxicity and ICU transfer—are unlikely to be fully explained by differences in trial conduct or patient management and instead reflect underlying differences in product design and dosing strategy. Accordingly, the reduction in life-threatening immune-mediated events and decreased need for intensive care support are presented as important clinical benefits of obe-cel.

COMP discussion

The sponsor claims significant benefit of obe-cel over brexucabtagene autoleucel based on the MCPC. The COMP highlighted that a claim of major contribution to patient care may not be established in the absence of the demonstration of the product's equivalence in terms of efficacy, safety, and benefit/risk balance with the relevant authorised medicinal products. Reference is made, in this respect, to the 2016 "Commission notice on the application of Articles 3, 5 and 7 of Regulation (EC) No 141/2000 on orphan medicinal products" (available at: https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=OJ:JOC_2016_424_R_0003&from=EN).

There are several unclarities about the MAIC analysis and the sponsor is invited to address the following questions:

- The sponsor presents a MAIC, which is unanchored due to the single-arm designs of the chosen studies. What were the assumptions for the indirect comparison? Were all assumptions met? If not, what are the violations and what is the impact of the violations?
- Given that there are differences in patient characteristics, e.g. age and the number of prior lines of treatment across studies, are the differences properly reflected in the analysis?
- The presented MAIC show a reduction in the effective sample size (in Scenario 2 from 94 to 38 which is approx. 40% and in Scenario 1 from 94 to 61.6 which is approx. 66%). The sponsor is asked to comment on the validity of the comparisons, also in view of the underlying assumptions.
- The sponsor reports hazard ratios of around 0.8 for EFS. However, the Kaplan-Meier Curves (Figures 10, 12 of Annex 1 - MAIC report) show crossing/overlapping survival curves. Can the sponsor comment on how this translates into a significant benefit?
- No overall survival results are presented for the comparison against Tecartus.
- The sponsor states that "The efficacy and safety profiles and the overall positive benefit-risk balance of obe-cel can be considered as at least equivalent to brexucabtagene autoleucel". However, non-inferiority margins were not (pre-)specified or discussed.
- Please report the distribution of raw and standardised weights, if possible. Add a discussion on the impact of extreme weights (weights close to 0 or above 5) on the results, if applicable.

The following table serves as a template to present results from indirect comparisons (may be adjusted to add additional columns for different scenarios):

Table 14.

Baseline Variables	**Matching variable**	**Trial 1 Arm A (N =)**	**Trial 1, adjusted Arm A (ESS = n(%))**	**Trial 2 Arm B (N =)**
Variable 1 (continuous)	Yes	Mean (sd)	Mean (sd)	Mean (sd)
Variable 2 (categorical) Category 1 Category 2	Yes	n (%) n (%)	n (%) n (%)	n (%) n (%)
Variable 3	Yes	…	…	…
Variable 4	Yes			
Variable 5	No			
Variable 6	No			
Variable 7	No			
Variable 8	no			

In terms of the equivalent efficacy claim, the sponsor discussed the naïve comparisons of the baseline characteristic for studies FELIX and ZUMA-3. According to the sponsor, there were characteristics associated with poor prognostic factors that were more common in the FELIX study. The median age in FELIX was higher (50.0 years versus 40 years) with a higher proportion being ≥ 65 years (22% versus 15%) and a larger proportion of patients were Hispanic or Latino (31% versus 20%). However, the ZUMA-3 study included younger patients but with a higher number of prior lines of treatment. Regarding the remission rates, the sponsor claimed that despite the differences in baseline characteristics, the rates of remission appeared comparable between obe-cel and brexucabtagene autoleucel. The sponsor should further discuss whether the heavier pre-treatment of the ZUMA-3 study population has an impact on the outcome based on the naive indirect comparisons. The sponsor did not discuss the results of the MAIC analyses that were carried out for studies FELIX and ZUMA-3. However, the sponsor should comment on the MAIC analyses questions presented above.

In support of the safety claim, a MAIC was carried out by the sponsor to compare safety results between obe-cel and brexucabtagene autoleucel. This analysis focused on only three safety endpoints (cytokine release syndrome, immune-mediated neurotoxicity, and adverse events related to nervous system or psychiatric disorders) making it highly selective and not representative of the overall safety profile. Furthermore, the issues discussed above for the efficacy MAIC analysis are also relevant for the safety. In addition, due to the increased use of bispecific mAbs and CAR-T products, the management of both CRS and ICANS has considerably evolved and improved over recent years. Finally, differences between the studies such as differences in lymphodepleting regimen, longer persistence of obe-cel compared to brexu-cel, and different criteria used for the definition of neurotoxicity (Topp 2015 versus ASTCT 2019) introduce bias on the safety comparisons. The COMP considered that the claim of improved safety does not reflect the full safety profile of the products and the outcome of the treatment regardless of the safety concern. Given the limited experience with obe-cel, the claim of better safety in comparison to brexucabtagene autoleucel cannot be concluded on at present stage while no adequate quantification is possible.

Regarding the argument on definitive long-lasting CAR T therapy without additional therapies, these comparisons are not reliable, given the differences of the patient populations which were mentioned above. Moreover, the Kaplan-Meier plots for EFS presented in the MAIC analysis do not indicate any longer-lasting benefit of obe-cel versus brexu-cel.

The sponsor also claimed that obe-cel was associated with a lower rate of ICU admissions. However, no quality-of-life (QoL) data were provided to support the effect of a reduction in ICU rate in the QoL. Furthermore, the sponsor should provide additional information regarding the duration of ICU admission and the duration of hospitalization.

With regard to the limitations of naïve unadjusted indirect comparison and the real-world data limited to brexu-cel only, it was considered that these data could not suffice to establish the claimed differences in safety.

The COMP would like also to highlight that the MCPC claim should be assessed in relation to factors such as ease of self-administration e.g., when a new treatment enables ambulatory care rather than requiring hospital-based administration, or a significant improvement in convenience that reduces the treatment burden. Additionally, a meaningful enhancement in treatment adherence, due to a change in pharmaceutical form (such as a modified-release formulation), can also represent a MCPC. Based on this, the sponsor's argument regarding the reduced immune-mediated toxicities and associated consequences will be addressed as part of the broader safety evaluation.

4. COMP list of issues

- Prevalence

The sponsor is asked to provide the methods for estimating prevalence. Please clarify if the reported proportion of ALL comprises both adult and paediatric patients.

Significant benefit

The sponsor should address the issues identified regarding the MAIC analyses. In addition, the sponsor should provide additional justifications to support the claim of significant benefit of obecabtagene autoleucel over brexucabtagene autoleucel (Tecartus) in adult patients 26 years of age and above with relapsed or refractory B cell precursor acute lymphoblastic leukaemia.