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Applicant	Autolus Inc.
Established Name	Obecabtagene autoleucel (obe-cel)
(Proposed) Trade Name	AUCATZYL
Pharmacologic Class	CD19-directed genetically modified autologous T cell immunotherapy
Formulation(s)	Intravenous infusion
Dosing Regimen	A target total dose of 410×10^6 CD19 CAR-positive viable T cells
Indication(s)/Population(s)	Treatment of adult patients with relapsed or refractory B cell precursor acute lymphoblastic leukemia

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GLOSSARY

Abbreviation	Definition
AESI	Adverse event of special interest
ALL	Acute lymphoblastic leukemia
BLA	Biologics Licensure Application
BM	Bone marrow
BOR	Best overall response
CAR	Chimeric antigen receptor
CI	Confidence interval
CNS	Central nervous system
CR	Complete remission
CRi	Complete remission with incomplete recovery of counts
CRS	Cytokine release syndrome
DOCR	Duration of remission with a CR within 3 months
DOR	Duration of remission
DSMB	Data safety monitoring board
ECOG	Eastern Cooperative Oncology Group
EMD	Extramedullary disease
FDA	Food and Drug Administration
HSCT	Hematopoietic stem cell transplant
ICANS	Immune effector cell-associated neurotoxicity syndrome
IDMC	Independent data monitoring committee
IRRC	Independent response review committee
IND	Investigational new drug
KM	Kaplan-Meier
MRD	Minimal/measurable residual disease
NR	Not reached
ORR	Overall remission rate
OS	Overall survival
PFS	Progression-free survival
RMAT	Regenerative medicine advanced therapy
r/r	Relapsed or refractory
SAE	Serious adverse event
SAP	Statistical analysis plan
SCT	Stem cell transplant
SSC	Study steering committee
STD	Standard deviation
US	United States

1. EXECUTIVE SUMMARY

Obecabtagene autoleucel (obe-cel) is a CD19-directed genetically modified autologous T cell immunotherapy consisting of the patient's own T cells expressing an anti-CD19 chimeric antigen receptor (CAR). This Biologics License Application (BLA) seeks licensure of obe-cel for the treatment of adult patients with relapsed or refractory (r/r) B cell precursor acute lymphoblastic leukemia (ALL).

In support of this application, the Applicant submitted the safety and efficacy data from Study AUTO1-AL1 (referred as FELIX). Study FELIX is an open-label, multi-center, multi-national, single-arm Phase Ib/II study in adult patients with r/r B cell precursor ALL. There are two phases of the study, Phase Ib and Phase II. Phase Ib included Cohort IA and IB that provided feasibility for manufacturing and dosing as well as evaluation of safety and preliminary efficacy to enable progression to patient enrollment into the pivotal Phase II part of the study. The pivotal phase evaluated efficacy and safety of obe-cel and included 3 cohorts (Cohort IIA, IIB and IIC). A total of 153 patients were enrolled across all cohorts in both phases of the FELIX study. Of these enrolled patients, 100 patients in Cohort IA and Cohort IIA were infused with at least 1 dose of obe-cel, which is the basis for safety evaluation. Among the 94 patients infused in Cohort IIA, 65 patients received conforming product and had $\geq 5\%$ blasts in bone marrow (BM) subsequent to screening and prior to the start of the lymphodepletion therapy (referred as efficacy-evaluable set), which provides the primary source of efficacy evaluation for the product.

The pre-specified primary efficacy endpoint proposed by the Applicant was overall remission rate (ORR), defined as proportion of patients achieving complete remission (CR) or complete remission with incomplete recovery of counts (CRi) as assessed by an independent response review committee (IRRC) in all infused subjects in Cohort IIA. However, FDA's primary determination of efficacy was based on CR rate within 3 months since infusion by FDA adjudicated assessment in the efficacy-evaluable set in Cohort IIA, further supported by duration of remission with a CR within 3 months (DOCR), with a data cut-off date of September 13, 2023. The CR rate within 3 months was 41.5% (27/65; 95% confidence interval [CI]: 29.4%, 54.4%). The lower limit of the 95% exact Clopper-Pearson CI of 29.4% exceeded the pre-specified remission rate of 20%, a threshold under the null hypothesis. The median DOCR was 14.1 months (95% CI: 6.1, not reached [NR]) with a median follow-up time of 7.4 months. Per FDA clinical review team, DOCR of 6 months or greater is considered as clinically meaningful.

For safety evaluation (n=100), 62 subjects (62%) experienced at least one treatment emergent serious adverse event (SAE) post obe-cel treatment and Grade 3 or higher SAEs occurred in 54% of subjects. Regarding the adverse event of special interest (AESI), cytokine release syndrome (CRS) occurred most frequently in 75% and Grade 3 or higher CRS occurred in 3% of subjects. Neurologic toxicity occurred in 64% and Grade 3 or higher neurologic toxicity occurred in 12% of subjects. Fifty-two deaths (52.0%) occurred with most deaths (36) due to progressive disease.

Study FELIX Cohort IIA met the efficacy criterion for the CR rate within 3 months since infusion and demonstrated clinically meaningful durability of complete remission. Safety profile of obe-cel is similar to that of other marketed CAR-T treatments. The statistical analysis findings in this memo provide sufficient evidence to support the safety and effectiveness of obe-cel for the proposed indication.

2. CLINICAL AND REGULATORY BACKGROUND

2.1 Disease or Health-Related Condition(s) Studied

B cell precursor ALL is a serious, life-threatening, and debilitating malignant disease. It is characterized by the malignant transformation and proliferation of non-functional, clonal B-precursor cells in the BM leading to an abundance of lymphoblasts and suppression of normal hematopoiesis. Although most common in patients < 20 years of age, with peak incidence between 2 to 5 years, the incidence rises again after the age of approximately 50 years (Pui et al, 2008). While cure rates and survival outcomes for pediatric patients have improved dramatically, data from the Surveillance, Epidemiology and End Results (SEER) Program database demonstrates that adults have an increasing poorer outcome with increasing age (SEER, 2023) and the prognosis has remained unchanged over the last two to three decades with long-term (> 3 years) remission rates of approximately 40% (Paul et al, 2019). Relapsed and refractory disease in adult patients is therefore common and is associated with a significant mortality rate, with median overall survival of less than 1 year (Gökbüget et al, 2012; Kantarjian et al, 2016; Kantarjian et al, 2017; Aldoss et al, 2017).

2.2 Currently Available, Pharmacologically Unrelated Treatment(s)/Intervention(s) for the Proposed Indication(s)

Blinatumomab is a bispecific T cell engager first approved by the FDA in December 2014 based on the Phase 3 TOWER study. The median overall survival (OS) was 7.7 months in the blinatumomab groups versus 4.0 months in the chemotherapy group (Blincyto USPI, 2023). However, it has been reported that for those patients who received blinatumomab as a third line or later therapy, the median OS is only 5.1 months and the complete remission rates are considerably decreased (Cappell and Kochenderfer, 2021; Dombret et al, 2019). Inotuzumab ozogamicin is an antibody-drug conjugate that consists of a monoclonal anti-CD22 antibody bound to calicheamicin that was first approved by the FDA in August 2017 based on the INO-VATE study. Similar to blinatumomab, inotuzumab ozogamicin seems to act as a bridge to allogeneic hematopoietic stem cell transplant (HSCT), with patients who proceeded to HSCT having a considerably better OS than those who did not. Tisagenlecleucel (tisa-cel) is a CD19 CAR T cell therapy (4-1BB costimulatory domain) approved in August 2017 (adults up to 25 years) based on the ELIANA study. While robust anti-tumor responses have been observed, its use is associated with a high proportion of patients experiencing severe and potentially fatal or life-threatening toxicities (Grade \geq 3 cytokine release syndrome [CRS] reported in 48% and Grade \geq 3 neurotoxicity events were reported in 22% of patients; Kymriah USPI, 2023). Brexucabtagene autoleucel (brexu-cel) is a CD19 CAR T

cell therapy (CD28 costimulatory domain) approved in October 2021 based on the ZUMA-3 study. Similarly, while a high remission rate was observed, a high proportion of patients experienced serious toxicity (\geq Grade 3 CRS reported in 26% of patients and \geq Grade 3 neurologic toxicity in 35% of patients).

2.5 Summary of Pre- and Post-submission Regulatory Activity Related to the Submission

Table 1 summarizes the major pre- and post-submission regulatory activities associated with this BLA.

Table 1. Summary of major Pre- and Post-submission regulatory activities

Date	Submission
March 16, 2020	IND 19534 submitted
April 20, 2022	Granted Regenerative Medicine Advanced Therapy (RMAT) designation
August 17, 2022	Type B RMAT meeting. FDA stated that for CAR T cell treatments of r/r ALL, the efficacy endpoint that has been used for regulatory consideration is CR rate within 3 months after infusion.
September 28, 2023	Pre-BLA meeting
November 17, 2023	BLA received
January 16, 2024	BLA filed.
November 15, 2024	PDUFA Action Date

(Source: clinical overview; FDA reviewer's summary)

3. SUBMISSION QUALITY AND GOOD CLINICAL PRACTICES

3.1 Submission Quality and Completeness

The submission was adequately organized for conducting an in-depth and complete statistical review without unreasonable difficulty.

5. SOURCES OF CLINICAL DATA AND OTHER INFORMATION CONSIDERED IN THE REVIEW

5.1 Review Strategy

The primary source of evidence to support the efficacy of the proposed product comes from Cohort IIA of Study FELIX, while safety assessment is based on Cohort IA and Cohort IIA of Study FELIX.

5.2 BLA/IND Documents That Serve as the Basis for the Statistical Review

The basis of this statistical memo includes the review of clinical study reports and data sets submitted in modules 2 and 5 of BLA 125813/0 (original data) and BLA 125813/64 (FDA adjudicated data).

5.3 Table of Studies/Clinical Trials

Table 2 summarizes the clinical trials relevant to this BLA submission.

Table 2. Studies in the BLA application

Study code	Study population	Study design	# of subjects
FELIX (Cohort IIA: pivotal)	adult patients with r/r B cell ALL	Phase Ib/II single-arm, open-label study	153 enrolled, 127 treated across all cohorts for both phases; 94 treated in Cohort IIA
AUTO-LT1 (long-term follow-up)	Patients previously treated with autologous T cells genetically modified with viral vectors	Long-term follow-up study	Up to 500

(Source: Synopses of Individual Studies Table 1; FDA statistical reviewer's summary)

6. DISCUSSION OF INDIVIDUAL STUDIES/CLINICAL TRIALS

6.1 Study # FELIX

Note: This section would focus on all efficacy-evaluable subjects in Cohort IIA that constitutes the primary efficacy set for this application.

6.1.1 Objectives (Phase II)

Primary: To evaluate the efficacy of obe-cel (i.e., measured by CR rate within 3 months since infusion in Cohort IIA)

Secondary objectives included assessing safety, tolerability and efficacy of obe-cel (i.e., measured by DOCR, CR rate, ORR, duration of remission [DOR]), and evaluating the expansion and persistence of AUTO1.

6.1.2 Design Overview

Study FELIX is a Phase Ib/II, single-arm, open-label, multicenter clinical study to evaluate the safety and efficacy of obe-cel when administered to adult patients with r/r B cell precursor ALL. The study consists of a Phase Ib and a Phase II part. The main objectives of this study were to evaluate the safety profile of obe-cel in the Phase Ib part and to determine the clinical efficacy of obe-cel in adult patients with r/r B cell precursor ALL in the Phase II part. Cohort IA in Phase Ib and Cohort IIA in Phase II enrolled patients with morphological disease defined as $\geq 5\%$ blasts in the BM at screening. Cohort IB in Phase Ib and Cohort IIB in Phase II enrolled patients in morphological remission defined as $< 5\%$ BM blasts but with minimal/measurable residual disease (MRD). The primary source of efficacy assessment for obe-cel is based on data from subjects in Cohort IIA of Study FELIX.

6.1.3 Population

Key elements of eligibility criteria in Cohort IIA of the study are listed below.

- Eligible subjects were ≥ 18 years and must have diagnosis of refractory B cell ALL, first relapse following a remission lasting ≤ 12 months, r/r ALL after two or more prior lines of systemic therapy, or r/r ALL at least greater than 3 months after allogeneic stem cell transplantation.
- Must have disease burden of $\geq 5\%$ blasts in BM at screening.
- Excluded subjects with isolated extra medullary disease, active or serious infections requiring systemic antimicrobials for management, active graft versus host disease, history or presence of central nervous system (CNS) disorders, including CNS-2 disease with neurologic changes and CNS-3 disease irrespective of neurological changes.

6.1.4 Study Treatments or Agents Mandated by the Protocol

Treatment was administered in the in-patient setting and consisted of lymphodepleting chemotherapy (fludarabine 30 mg/m² iv daily on Days -6, -5, -4 and -3; cyclophosphamide 500 mg/m² iv on Days -6 and -5) followed by obe-cel as a split dose infusion with a target total dose of 410×10^6 CD19 CAR-positive viable T cells.

6.1.6 Sites and Centers

Thirty-four (34) sites including 23 sites in the US and 11 sites in Europe participated in the study.

6.1.7 Surveillance/Monitoring

An independent data monitoring committee (IDMC), consisting of two independent physicians and one statistician, was established by the Applicant and they reviewed serious safety events. The IDMC met during and/or at least before the end of the Phase Ib prior to opening Phase II, at the time of the interim analysis and every 6 months to review cumulative safety data during Phase II.

6.1.8 Endpoints and Criteria for Study Success (Cohort IIA)

The primary endpoint was CR rate within 3 months, defined as the proportion of subjects achieving complete remission within 3 months since infusion.

The study also included several secondary efficacy endpoints: CR rate, CRi rate, ORR, DOCR, DOR, proportion of subjects achieving MRD-negative CR/CRi, progression-free survival (PFS), and OS.

Reviewer's Note #1: The pre-specified primary efficacy endpoint proposed by the Applicant was overall remission rate (ORR). However, FDA clinical review team clearly stated in the study design stage that they did not agree with the proposed primary endpoint and instead, CR rate within the 3 months since infusion in the efficacy-evaluable set would be used for regulatory decision making. The Applicant agreed and added CR rate within 3 months as a key secondary endpoint and proposed to test the endpoint after ORR and CR rate at any time, hierarchically. In addition, during the review of the initial efficacy data submitted, FDA clinical review team identified inconsistencies in the implementation response adjudication, and requested the updated efficacy data based on

FDA adjudicated assessment. As such, the efficacy evaluation in this memo is based on CR rate within 3 months since infusion, further supported by DOCR, in efficacy-evaluable set determined by FDA adjudicated assessment.

6.1.9 Statistical Considerations & Statistical Analysis Plan (Cohort IIA)

Statistical hypothesis:

$H_0: p \leq 20\%$ vs. $H_1: p > 20\%$, where p is CR rate within 3 months since infusion.

Reviewer's Note #2: The Applicant provided the rationale for the assumed threshold of 20% for CR rate (at any time). This threshold of 20% lies in between the CR rate of blinatumomab (34%) and the CR rate achieved with standard-of-care chemotherapy (16%) for patients treated in the Phase 3 TOWER study (Kantarjian et al, 2017). However, the Applicant did not provide the rationale for the assumed CR rate (within 3 months since infusion) of 20% under null hypothesis. FDA clinical review team did not agree to the proposed null hypothesis of CR rate within 3 months of 20% and communicated to the sponsor at prior meetings that this would be a review issue given that it is lower than that observed with brexu-cel (52% (95% CI: 38%-66%)), and not substantially greater than for blinatumomab (34% (95% CI: 28%-40%)). However, based on the review of the totality of the data, the potential benefit of obe-cel is considered adequate given its safety profile¹.

Analysis populations:

- *Enrolled Set:* all subjects who were enrolled and underwent leukapheresis.
- *Infused Set:* all subjects who received at least one infusion of obe-cel. For this study, infused set in Cohort A for both phases was the primary analysis set for safety.
- *Efficacy-evaluable Set:* all subjects in the infused set who received conforming product and had $\geq 5\%$ blasts in BM subsequent to screening and prior to the start of the lymphodepletion therapy. For this study, efficacy-evaluable set in Cohort IIA was the primary analysis set for efficacy.

Statistical methods:

The primary efficacy analyses were conducted in the efficacy-evaluable set in Cohort IIA. For the primary analysis, FDA adjudicated assessment of disease status was used.

Primary endpoint

The primary efficacy endpoint, CR rate within 3 months, was calculated along with the 2-sided 95% exact Clopper-Pearson CI.

Secondary endpoints

For time-to-event endpoints, the Kaplan-Meier (KM) method was used to estimate the median along with the 95% CI. The reverse KM method was used to estimate the median follow-up time with the 95% CI. For binary endpoints, the number and proportion of subjects who were evaluated as CR and CRi were tabulated.

¹ FDA clinical review memo

Interim analyses:

One futility and one efficacy interim analysis was planned in Cohort IIA. The futility interim analysis took place when 17 patients had been treated with obe-cel and had either discontinued or reached the Day 28 follow-up visit. The results showed that the Bayesian posterior predictive probability of claiming success at the end of the study was >10%. Therefore, the study steering committee (SSC) endorsed the continuation of the study. A pre-planned interim analysis for efficacy was performed when the first 50 patients had received obe-cel infusion and had been followed for 3 months or discontinued from the study before the Month 3 visit. The study met its pre-specified primary endpoint ORR (proposed by Applicant) at the interim analysis.

Reviewer's Note #3: The interim analysis (both futility and efficacy) was based on ORR instead of FDA's recommended primary endpoint of CR rate within 3 months since infusion. The study was not stopped upon interim analysis despite meeting the Applicant's primary endpoint ORR. All patients treated with obe-cel are being followed-up according to the protocol requirements. The initial BLA submission was based on data as of the pre-specified primary analysis, triggered when at least 90 patients in Cohort IIA had reached 6 months follow-up after obe-cel infusion or discontinued prior to this. The data cutoff was Jun 9, 2023. However, FDA clinical review team decided to use the 3-month updated data (cutoff date of September 13, 2023) in order to incorporate more subjects with longer follow-up data.

Sample size and power calculation:

In the protocol and statistical analysis plan (SAP), the sample size and power calculation was based on the Applicant's proposed primary endpoint ORR and key secondary endpoint CR rate at any time. A sample size of 90 subjects in Cohort IIA (infused set) was calculated to provide ~95% power to exclude a 40% ORR if the true rate was 60% at a one-sided alpha level of 0.025, and ~89% power to exclude a 20% CR rate if the true rate was 35% at a one-sided alpha level of 0.025.

No formal sample size and power calculation was performed based on CR rate within 3 months since infusion, the primary efficacy endpoint recommended by the FDA.

Sensitivity and supplemental analyses:

- Sensitivity analyses of the primary and secondary efficacy endpoints were performed based on the remission determined by IRRC
- Supplemental efficacy analyses were performed based on enrolled subjects

Subgroup analyses:

Subgroup analyses included but not limited to the following based on the patient's baseline status:

- Age group: ≥ 18 to <40, ≥ 40 to <65 years, ≥ 65 years
- Sex: male, female
- Race: Asian, Black or African American, White, other
- Ethnicity: Hispanic or Latino, Not Hispanic or Latino, unknown

- Region: North America, Europe
- Baseline extramedullary disease (EMD) disease presence: Yes, No
- Baseline blasts in BM (%): <5 , ≥ 5 to ≤ 20 , >20 to ≤ 75 , >75
- Number of prior lines of therapy: 1, 2, 3, >3

Note: Subgroup analyses only was performed if at least 5 patients were present in each subgroup. Some grouping of classes was considered if there were too few patients in the subgroups.

Missing data:

Subjects who did not meet the criteria for a CR within 3 months after infusion were considered as non-responders. For assessment of DOCR or DOR, 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.

6.1.10 Study Population and Disposition

6.1.10.1 Populations Enrolled/Analyzed

A total of 153 patients were enrolled across all cohorts in both phases of the FELIX study and 112 subjects were enrolled and underwent leukapheresis in Cohort IIA. Of these 112 enrolled patients, 94 (83.9%) patients were infused with at least 1 dose of obe-cel. Of 94 subjects, 65 (58.0%) subjects received conforming product and had $\geq 5\%$ blasts in BM subsequent to screening and prior to the start of the lymphodepletion therapy that constituted the primary efficacy set. Table 3 summarizes the study analysis sets in Cohort IIA.

Table 3. Analysis sets (Cohort IIA)

Analysis Set	N (%)
Enrolled	112
Infused	94 (83.9%)
Efficacy-evaluable	65 (58.0%)

(Source: FDA statistical reviewer's summary)

6.1.10.1.1 Demographics

Table 4 shows the demographic information for subjects in the enrolled set and efficacy-evaluable set, respectively, in Cohort IIA. Subjects' demographics were generally similar between the two analysis sets.

Table 4. Demographics in the enrolled and efficacy-evaluable sets (Cohort IIA)

	Enrolled set, n=112	Efficacy-evaluable set, n=65
Age (years)		
Mean (STD)	47.9 (17.0)	49.2 (16.6)
Median (min, max)	49 (20, 81)	51 (20, 77)
Sex n (%)		
Female	52 (46.4%)	35 (53.8%)
Male	60 (53.6%)	30 (46.2%)
Race n (%)		
White	86 (76.8%)	47 (72.3%)
Black or African American	2 (1.8%)	1 (1.5%)
Asian	11 (9.8%)	8 (12.3%)
Unknown	13 (11.6%)	9 (13.8%)
Ethnicity n (%)		
Hispanic or Latino	33 (29.5%)	21 (32.3%)
Not Hispanic or Latino	72 (64.3%)	40 (61.5%)
Not reported	7 (6.2%)	4 (6.2%)
Geographical Region		
North America	54 (48.2%)	34 (52.3%)
Europe	58 (51.8%)	31 (47.7%)

(Source: FDA statistical reviewer's summary)

6.1.10.1.2 Medical/Behavioral Characterization of the Enrolled Population

Table 5 shows the baseline characteristics for subjects in the enrolled set and efficacy-evaluable set, respectively, in Cohort IIA. There were no outstanding differences with respect to subject baseline characteristics between the two analysis sets.

Table 5. Baseline characteristics in the enrolled and efficacy-evaluable sets (Cohort IIA)

	Enrolled set, n=112	Efficacy-evaluable set, n=65
Number of prior lines of therapy, n (%)		
1	34 (30.4%)	20 (30.8%)
2	43 (38.4%)	26 (40.0%)
3	21 (18.8%)	10 (15.4%)
4+	14 (12.4%)	9 (13.8%)
BM blasts (%) by morphology prior to enrollment		
Mean (STD)	53.2 (32.6)	51.7 (32.6)
Median (min, max)	55.7 (6, 100)	52 (6, 100)
EMD status prior to enrollment, n (%)		
absent	91 (81.2%)	52 (80.0%)
present	21 (18.8%)	13 (20.0%)
ECOG score, n (%)		
0	39 (34.8%)	21 (32.3%)
1	72 (64.3%)	43 (66.2%)
2+	0	0
missing	1 (0.9%)	1 (1.5%)

BM = Bone marrow; EMD = Extramedullary disease; ECOG = Eastern Cooperative Oncology Group

(Source: FDA statistical reviewer's summary)

6.1.10.1.3 Subject Disposition

At the time of the data cutoff date September 13, 2023, among the 112 enrolled subjects in Cohort IIA, 18 (16%) subjects discontinued without receiving the cell infusion due to the following reasons: death (n=11), adverse event (n=1), physician decision (n=1), and manufacturing failure (n=5). Out of the 65 efficacy-evaluable subjects in Cohort IIA, 30 were still ongoing and 35 had discontinued. Among the 35 subjects who discontinued, the most frequent reason was due to death (n=32).

6.1.11 Efficacy Analyses

6.1.11.1 Analyses of Primary Endpoint

The FDA's primary efficacy evaluation was based on CR rate within 3 months since infusion per FDA adjudicated assessment.

In the efficacy-evaluable set of 65 subjects in Cohort IIA, 27 subjects (41.5%; 95% CI: [29.4%, 54.4%]) had a CR within 3 months since infusion, as determined by FDA adjudicated assessment. The lower limit of the 95% exact Clopper-Pearson CI for CR rate within 3 months was 29.4% which is above the pre-specified null hypothesis rate of 20%.

FDA also performed the sensitivity analysis based on IRRC. Additionally, the supportive analysis in the enrolled set were summarized (Table 6). The lower limit of the 95% exact Clopper-Pearson CI for CR rate within 3 months in all sets are above the pre-specified null hypothesis rate of 20%.

Table 6. Summary of CR rate within 3 months since infusion (Cohort IIA)

Parameter	Enrolled set, n=112	Efficacy-evaluable set, n=65
FDA adjudicated assessment		
CR within 3 months	40 (35.7%)	27 (41.5%)
CI	(26.9%, 45.3%)	(29.4%, 54.4%)
IRRC		
CR within 3 months	43 (38.4%)	30 (46.2%)
CI	(29.4%, 48.1%)	(33.7%, 59.0%)

(Source: FDA statistical reviewer's analysis)

6.1.11.2 Analyses of Secondary Endpoints

Best of response (BOR)

Table 7 below summarizes the BOR results in Cohort IIA including CR and CRi per FDA adjudicated assessment and IRRC in the enrolled set and efficacy-evaluable set, respectively. In the efficacy-evaluable set per FDA adjudicated assessment, a total of 41 subjects had a BOR of CR or CRi. Among these 41 subjects, 33 subjects had a BOR of CR and 8 subjects had a BOR of CRi.

Table 7. Summary of CR, CRi and ORR by FDA adjudicated assessment/ IRRC (Cohort IIA)

Parameter	Enrolled set, n=112	Efficacy-evaluable set, n=65
FDA adjudicated assessment		
CR	46 (41.1%)	33 (50.8%)
CRi	14 (12.5%)	8 (12.3%)
ORR (CR+CRi)	60 (53.6%)	41 (63.1%)
CI for ORR	(43.9%, 63.0%)	(50.2%, 74.7%)
IRRC		
CR	55 (49.1%)	37 (56.9%)
CRi	17 (15.2%)	12 (18.5%)
ORR (CR+CRi)	72 (64.3%)	49 (75.4%)
CI for ORR	(54.7%, 73.1%)	(63.1%, 85.2%)

(Source: FDA statistical reviewer's analysis)

DOCR

Table 8 summarizes the DOCR results for subjects in the efficacy-evaluable set per FDA adjudicated assessment in Cohort IIA.

Table 8. DOCR results in the efficacy-evaluable set per FDA adjudicated assessment (Cohort IIA)

Number of subjects who had a BOR of CR, n ^a	27
Number of events, n (%)	11 (40.8%)
Morphological relapse	11 (40.8%)
Censored, n (%)	16 (59.2%)
Ongoing without events	10 (37.0%)
Stem cell transplant (SCT)	6 (22.2%)
DOCR (months)	
median	14.1
95% CI	(6.1, NR)
range	(0.5+, 21.2)
Median follow-up time (months)	7.4
Percentage of subjects with response duration (%) ^b	
≥ 6 months	76.6
≥ 12 months	50.2
≥ 18 months	33.4

a CR within 3 months since infusion

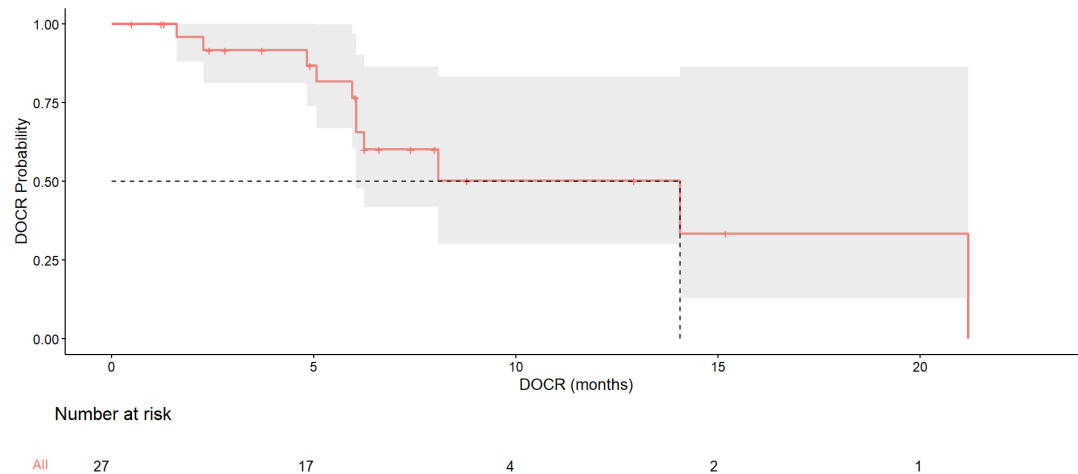
b The estimated percentage of subjects with response duration ≥ 6, ≥ 12, and ≥ 18 months was presented with 95% CIs using the KM method.

(Source: FDA statistical reviewer's analysis)

For analysis of DOCR per FDA adjudicated assessment, the overall median was 14.1 months with a lower 95% limit of 6.1 months and an unattainable upper limit. The median follow-up time was 7.4 months. For analysis per IRRC, the overall median of DOCR was 8.2 months with a lower 95% limit of 8.0 months and an unattainable upper

limit. Figure 1 below shows the Kaplan-Meier curve of DOCR per FDA adjudicated assessment.

Figure 1. Kaplan-Meier curves of DOCR per FDA adjudicated assessment (Cohort IIA)

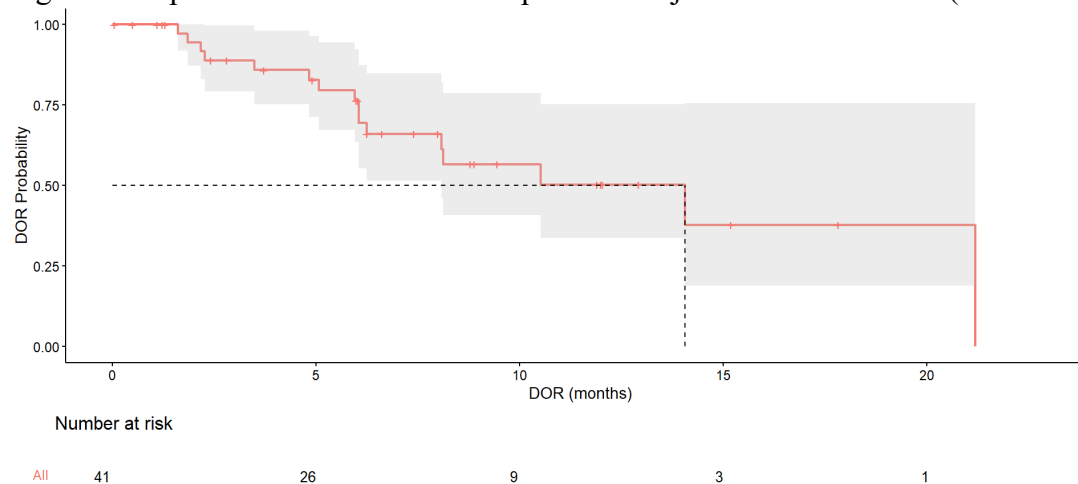


(Source: FDA statistical reviewer's analysis)

DOR

For analysis of DOR per FDA adjudicated assessment, the overall median was 14.1 months with a lower 95% limit of 8.1 months and an unattainable upper limit. The median follow-up time was 8.8 months. For analysis per IRRC, the overall median of DOR was 12.5 months with a lower 95% limit of 8.1 months and an unattainable upper limit. Figure 2 below shows the Kaplan-Meier curve of DOR per FDA adjudicated assessment.

Figure 2. Kaplan-Meier curves of DOR per FDA adjudicated assessment (Cohort IIA)

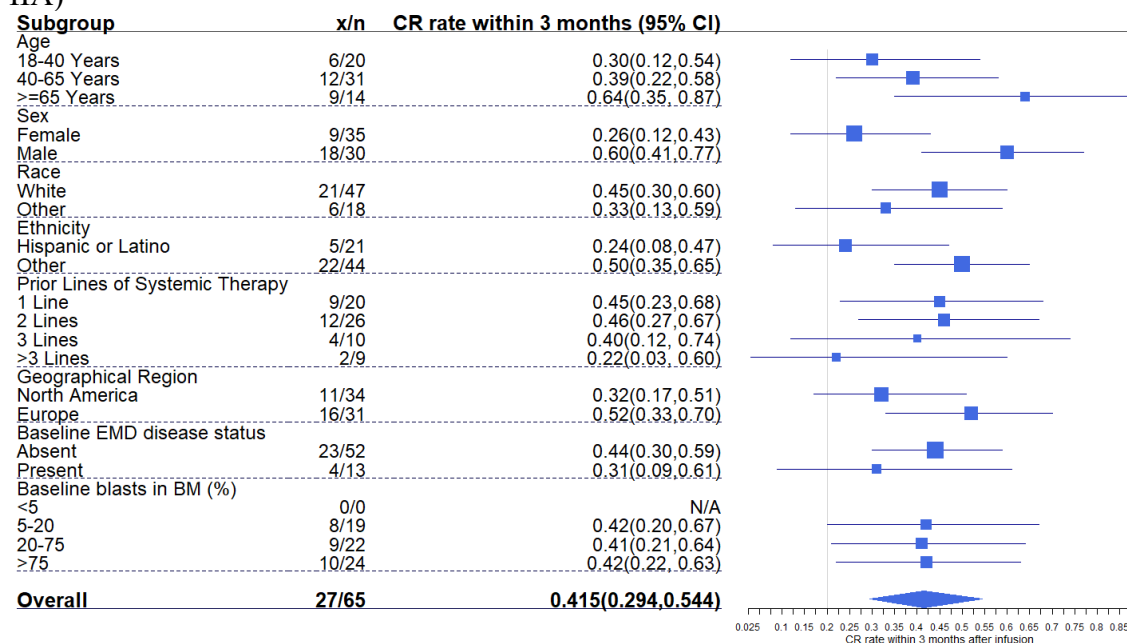


(Source: FDA statistical reviewer's analysis)

6.1.11.3 Subpopulation Analyses

Figure 3 shows the forest plot of CR rate within 3 months since infusion in the efficacy-evaluable set for subjects in Cohort IIA by some key baseline characteristics. The CR rate over subpopulations in general trends in the favorable direction. No outstanding discrepancies are noted.

Figure 3. Forest plot of CR rate within 3 months since infusion by subgroups (Cohort IIA)



(Source: FDA statistical reviewer's analysis)

6.1.11.4 Dropouts and/or Discontinuations

Table 9 summarizes subjects with discontinuations from the study. The reasons for dropouts and discontinuations included deaths, progressive disease and content withdrawal. Among the 65 efficacy-evaluable subjects in Cohort IIA, 35 (53.8%) subjects discontinued from the study.

Table 9. Subjects with discontinuations (Cohort IIA)

Status	Efficacy-evaluable, n=65 n (%)
Subjects discontinued from study	35 (53.8%)
Primary reason for discontinuation from study	
Death	32 (49.2%)
Progressive disease	1 (1.5%)
Withdrawal by subject	2 (3.1%)

(Source: FDA reviewer's summary)

6.1.12 Safety Analyses

This section summarizes safety results of Study FELIX (Cohort IA and Cohort IIA) for subjects who received at least one dose of obe-cel.

6.1.12.1 Methods

Descriptive statistics were used to summarize safety data. The analysis set for safety included treated subjects in Cohort IA and Cohort IIA (n=100).

6.1.12.3 Deaths

Among the 100 treated subjects, 52 (52.0%) subjects died post the cell infusion. Of these 52 deaths, 36 deaths were due to progressive disease, 14 deaths were due to adverse events and 2 deaths were due to other reasons.

6.1.12.4 Nonfatal Serious Adverse Events (SAEs)

Among 100 subjects in the safety analysis set, treatment emergent SAEs occurred in 62% and Grade 3 or higher SAEs occurred in 54% of subjects. Most common SAEs included infections-pathogen unspecified (24%), febrile neutropenia (13%), immune effector cell-associated neurotoxicity syndrome (ICANS, 11%) and CRS (10%). See FDA clinical review memo for details.

6.1.12.5 Adverse Events of Special Interest (AESI)

Among 100 subjects in the safety analysis set, CRS occurred most frequently in 75% and Grade 3 or higher CRS occurred in 3% of subjects. Neurologic toxicity occurred in 64% and Grade 3 or higher neurologic toxicity occurred in 12% of subjects. The most common symptoms of neurologic toxicity (> 5%) included ICANS (38%), headache (34%), encephalopathy (33%), dizziness (22%), tremor (13%), anxiety (9%), insomnia (9%), and delirium (8%). See FDA clinical review memo for details.

10. CONCLUSIONS

10.1 Statistical Issues and Collective Evidence

Obecabtagene autoleucel (obe-cel) is a CD19-directed genetically modified autologous T cell immunotherapy consisting of the patient's own T cells expressing an anti-CD19 CAR. This BLA seeks licensure of obe-cel for the treatment of adult patients with r/r B cell precursor ALL.

The primary source of evidence to support the efficacy of this application is the Cohort IIA (Phase II part) of Study FELIX, a single-arm, open-label, multi-cohort, multicenter, multi-national Phase Ib/II study. A total of 153 patients were enrolled across all cohorts in both phases. Of these enrolled patients, 100 patients from Cohort IA and Cohort IIA were infused with at least 1 dose of obe-cel, which is the basis for safety assessment. Among the 94 treated patients in Cohort IIA, 65 patients received conforming product and had $\geq 5\%$ blasts in BM subsequent to screening and prior to the start of the lymphodepletion therapy (referred as efficacy-evaluable set), which provides the primary source of efficacy assessment for the product.

FDA evaluates efficacy based on CR rate within 3 months since infusion, further supported by DOCR, in the efficacy-evaluable set in Cohort IIA determined by FDA adjudicated assessment. The CR rate within 3 months since infusion was 41.5% (27/65; 95% CI: 29.4%, 54.4%). The lower limit of the 95% exact Clopper-Pearson CI of 29.4% exceeded the pre-specified remission rate of 20%, a threshold under the null hypothesis. The median DOCR was 14.1 months (95% CI: 6.1, NR) with a median follow-up time of 7.4 months. Per FDA clinical review team, DOCR of 6 months or greater is considered as clinically meaningful.

For safety evaluation (n=100), 62 subjects (62%) experienced at least one treatment emergent SAE post obe-cel treatment and Grade 3 or higher SAEs occurred in 54% of subjects. Regarding the AESI, CRS occurred most frequently in 75% and Grade 3 or higher CRS occurred in 3% of subjects. Neurologic toxicity occurred in 64% and Grade 3 or higher neurologic toxicity occurred in 12% of subjects. Fifty-two deaths (52.0%) occurred with most deaths (36) due to progressive disease.

10.2 Conclusions and Recommendations

Study FELIX Cohort IIA met the efficacy criterion for the CR rate within 3 months since infusion and demonstrated clinically meaningful durability of complete remission (DOCR). Safety results of obe-cel are similar to those of other marketed CAR-T treatments. The statistical analysis results in this review memo provide sufficient evidence to support the safety and effectiveness of obe-cel for the proposed indication.