

BLA Clinical Review and Evaluation

Disclaimer: In this document, the sections labeled as “Data” and “The Applicant’s Position” are completed by the Applicant, which do not necessarily reflect the positions of the FDA.

Application Type	Original BLA
Application Number(s)	125813/0
Priority or Standard	Standard
Submit Date(s)	17 Nov 2023
Received Date(s)	17 Nov 2023
PDUFA Goal Date	16 Nov 2024
Division/Office	DCEH/OCE/OTP
Review Completion Date	November 7, 2024
Established/Proper Name	obecabtagene autoleucel (obe-cel)
Brand/Proprietary Name	AUCATZYL
Pharmacologic Class	CD19-directed, genetically-modified autologous T cell immunotherapy
Applicant	Autolus Inc
Formulation(s)	Cryopreserved injection containing genetically modified autologous T cells in phosphate-buffered saline (PBS) human serum albumin (HSA), ethylenediaminetetraacetic acid (EDTA) and 7.5% dimethyl sulfoxide (DMSO), and supplied in patient-specific infusion bag(s)
Route(s) of Administration	Intravenous (IV)
Dosing Regimen	Split dose infusion with a total recommended dose of 410×10^6 CAR-positive viable T cells administered on Day 1 and Day 10 (± 2 days) as determined by patient bone marrow blast assessment, and preceded by fludarabine and cyclophosphamide conditioning chemotherapy
Applicant Proposed Indication(s)/Population(s)	For the treatment of adult patients (18 years and over) with relapsed or refractory (r/r) B cell precursor acute lymphoblastic leukemia (B ALL)
Recommendation on Regulatory Action	Traditional approval
Recommended Indication(s)/Population(s) (if applicable)	For the treatment of adults with relapsed or refractory B-cell precursor acute lymphoblastic leukemia (ALL)
Orphan Drug Designation	Yes

Table of Contents

Reviewers of the BLA Review and Evaluation	9
Additional Reviewers of Application	9
Glossary	10
1 Executive Summary.....	13
1.1. Product Introduction	13
1.2. Conclusions on the Substantial Evidence of Effectiveness.....	13
1.3. Benefit-Risk Assessment.....	17
1.4. Patient Experience Data	20
2 Therapeutic Context	20
2.1. Analysis of Condition	20
2.2. Analysis of Current Treatment Options	21
3 Regulatory Background.....	27
3.1. U.S. Regulatory Actions and Marketing History	27
3.2. Summary of Presubmission/Submission Regulatory Activity.....	27
4 Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety.....	31
4.1. Office of Compliance and Biologics Quality	31
4.2. Product Quality.....	32
4.3. Devices and Companion Diagnostic Issues	32
5 Summary of Nonclinical Pharmacology/Toxicology Findings	32
6 Clinical Pharmacology.....	35
6.1. Expansion and Persistency.....	35
6.2. Factors Influencing Pharmacokinetics	36
6.3. Pharmacodynamics.....	36
6.4. Dose-Exposure.....	37
7 Sources of Clinical Data.....	39
7.1. Table of Clinical Studies	39

7.2.	Review Strategy	42
8	Statistical and Clinical Evaluation.....	43
8.1.	Review of Relevant Individual Trials Used to Support Efficacy	43
8.1.1.	AUTO1-AL1 (FELIX)	43
8.1.2.	Study Results	53
8.1.3.	Integrated Review of Effectiveness	92
8.1.4.	Assessment of Efficacy Across Trials.....	94
8.1.5.	Integrated Assessment of Effectiveness	95
8.2.	Review of Safety	95
8.2.1.	Safety Review Approach.....	95
8.2.2.	Review of the Safety Database	97
8.2.3.	Adequacy of Applicant’s Clinical Safety Assessments.....	101
8.2.4.	Safety Results	102
8.2.5.	Analysis of Submission-Specific Safety Issues.....	137
8.2.6.	Clinical Outcome Assessment Analyses Informing Safety/Tolerability	138
8.2.7.	Safety Analyses by Demographic Subgroups	139
8.2.8.	Specific Safety Studies/Clinical Trials.....	145
8.2.9.	Additional Safety Explorations.....	146
8.2.10.	Safety in the Postmarket Setting.....	147
8.2.11.	Integrated Assessment of Safety.....	147
	SUMMARY AND CONCLUSIONS	148
8.3.	Statistical Issues.....	148
8.4.	Conclusions and Recommendations	148
9	Advisory Committee Meeting and Other External Consultations	151
10	Pediatrics	152
11	Labeling Recommendations.....	153
12	Risk Evaluation and Mitigation Strategies.....	155
13	Postmarketing Requirements and Commitment	156
14	Chief, Malignant Hematology Branch	157

BLA 125813/0 Clinical Review and Evaluation
AUCATZYL (obecabtagene autoleucel)

15	Division Director (DCEH)	158
16	Oncology Center of Excellence Signatory.....	159
17	Director, Office of Clinical Evaluation	160
18	Appendices	161
18.1.	References	161
18.2.	Financial Disclosure.....	164
18.3.	List of FDA Group Terms and Preferred Terms Used in This Review	166
18.4.	Schedule of Assessments per Protocol.....	170
18.5.	Overall Disease Response Criteria (Protocol V.1 to V.4).....	173
18.6.	Overall Disease Response Criteria (Protocol V.5 Onward)	174

Applicant Table of Tables

Applicant Table 1	Novel Targeted Agents and Immunotherapeutics Approved for the Treatment of Recurrent/Refractory B-cell Precursor Acute Lymphocytic Leukemia	23
Applicant Table 2	Key Regulatory Interactions with the FDA	28
Applicant Table 3	Listing of Clinical Trials Relevant to this BLA	40
Applicant Table 4	2-Step Obe-Cel Dose Regimen Based on Bone Marrow Blast Counts at Lymphodepletion	45
Applicant Table 5	Primary and Secondary Endpoints	48
Applicant Table 6	Summary of Demographics at Screening and Lymphodepletion – FELIX Study	60
Applicant Table 7	Disease Characteristics at Screening and Lymphodepletion – FELIX Study ..	62
Applicant Table 8	Overview of Remission Results with Disease Assessment by IRRC (Cohort IIA, Infused and Enrolled Set) – FELIX Study	68
Applicant Table 9	Duration of Remission by IRRC With Censoring for SCT or Other New Non-Protocol Anti-Cancer Therapy (Cohort IIA, Infused Set) – FELIX Study	82
Applicant Table 10	Event-Free Survival with Censoring for SCT and Other New Non-Protocol Anti-Cancer Therapy (Cohort IIA, Infused Set) – FELIX Study	84
Applicant Table 11	Overall Survival Without Censoring for SCT (Cohort IIA, Infused Set) – FELIX Study	85
Applicant Table 12	Obe-cel Exposure (Phase Ib and Phase II, Safety Set) – FELIX Study.....	97
Applicant Table 13	Deaths Any Time After Obe-cel Infusion (Phase Ib and Phase II, Safety Set) – FELIX Study	104
Applicant Table 14	Treatment Emergent SAEs Occurring in ≥ 5% Patients (Any Grade) Any Time Post Obe-cel Infusion, Regardless of Relationship to Obe-cel, by Preferred Term (Phase Ib and Phase II, Safety Set) – FELIX Study	106
Applicant Table 15	Treatment Emergent SAEs Occurring in ≥ 2% Patients (Any Grade) Any Time Post Obe-cel Infusion, with Suspected Relationship to Obe-cel, by Preferred Term (Phase Ib and Phase II, Safety Set) – FELIX Study.....	107
Applicant Table 16	Overview of Treatment Emergent Adverse Events Anytime Post Obe-cel Infusion (Phase Ib and Phase II, Safety Set) – FELIX Study	110
Applicant Table 17	Treatment Emergent Adverse Events in ≥10% of Patients in Any System Organ Class (All Grades) and Preferred Term (All Grades), Any Time Post Obe-cel Infusion, Regardless of Relationship to Obe-cel (Phase Ib and Phase II, Safety Set) – FELIX Study	112
Applicant Table 18	Treatment Emergent Adverse Events in More Than 10% of Patients (All Grades) Any Time Post Obe-cel Infusion, with Suspected Relationship to Obe-cel by the Investigator, by Preferred Term and Maximum Grade (Phase Ib and Phase II, Safety Set) – FELIX Study	115
Applicant Table 19	Overview of Other Significant Treatment Emergent Adverse Events by Group Term (Phase Ib and Phase II, Safety Set) – FELIX Study	119
Applicant Table 20	Grade 3 or 4 Laboratory Abnormalities Occurring in ≥ 10% of Patients After Obe-cel Infusion (Safety Set) – FELIX Study	136
Applicant Table 21	Summary of Analysis of Safety by Subgroup – FELIX Study	140

FDA Table of Tables

FDA Table 1. Approved Agents With Indication(s) Relevant to the Treatment of Relapsed or Refractory B-cell Precursor Acute Lymphoblastic Leukemia	25
FDA Table 2. Summary of Treatment Armamentarium (Novel Targeted Agents) Relevant to the Proposed Indication	27
FDA Table 3. Clinical Information Requests.....	30
FDA Table 4. FDA BLA Amendments, Clinical and Other Relevant Review Disciplines	30
FDA Table 5. FDA Bioresearch Monitoring Inspection Summary.....	54
FDA Table 6. FELIX: Key Analysis Population Sets*	56
FDA Table 7. Disposition of the Primary Efficacy Population	56
FDA Table 8. Summary of Administration Errors, Applicant's Root Cause/Comments/Mitigation	58
FDA Table 9. Demographic Characteristics, Efficacy and Safety Population.....	60
FDA Table 10. Disease Characteristics at Screening and Lymphodepletion, Efficacy Analysis Set and Safety Analysis Set	64
FDA Table 11. Bridging Therapies Received by Patients Included in Primary Efficacy Analysis ...	66
FDA Table 12. Efficacy Results Per FDA's Adjudication.....	75
FDA Table 13. Efficacy Results Per FDA's Adjudication#	76
FDA Table 14. Patient Level Listing of Best Overall Response, Onset of Remission, and Onset of CR, per IRRC and FDA for the Primary Efficacy Population.....	77
FDA Table 15. Efficacy Results (Duration of Complete Remission) Per FDA's Adjudication.....	86
FDA Table 16. Obe-cel Exposure, Safety Analysis Set.....	98
FDA Table 17. Demographic Characteristics, Safety Analysis Set	99
FDA Table 18. Baseline Disease Characteristics, Safety Population.....	100
FDA Table 19. Summary of FDA Adjudicated Fatal Adverse Reaction, Safety Analysis Set.....	105
FDA Table 20. Treatment-Emergent Serious Adverse Events.....	108
FDA Table 21. Treatment-Emergent Adverse Events Occurring in $\geq 10\%$, Safety Analysis Set ...	116
FDA Table 22. Summary of Adverse Events of Special Interest, Safety Analysis Set.....	119
FDA Table 23. CRS Incidence, Safety Analysis Set (N=100).....	121
FDA Table 24. Neurologic Toxicity* Incidence, Safety Analysis Set (N=100)	124
FDA Table 25. Prolonged Cytopenias, All Responders*.....	128
FDA Table 26. Infections, Safety Analysis Set	130
FDA Table 27. Medication Use, Safety Analysis Set.....	133
FDA Table 28. Grade 3 or 4 Laboratory Abnormalities, Safety Analysis Set	137
FDA Table 29. Treatment-Emergent Adverse Events by Age Group in $\geq 10\%$, Safety Analysis Set	142
FDA Table 30. Treatment-Emergent Adverse Events by Sex in $\geq 10\%$, Safety Analysis Set	143
FDA Table 31. Treatment-Emergent Adverse Events by Race in $\geq 10\%$, Safety Analysis Set	143
FDA Table 32. Treatment-Emergent Adverse Events by Ethnicity* in $\geq 10\%$, Safety Analysis Set	144
FDA Table 33. Summary of Adverse Events and Adverse Events of Special Interest Incidence per Cohort	145

FDA Table 34. Summary of Significant Labeling Changes	153
FDA Table 35. Efficacy Results Per FDA’s Adjudication.....	154
FDA Table 36. Covered Clinical Study: FELIX.....	165
FDA Table 37. FDA Grouped Terms Used for FDA Analyses of Adverse Events, N=100 (FELIX Study).....	166
FDA Table 38. Schedule of Assessments Per Protocol.....	170
FDA Table 39. Overall Disease Response Criteria for Protocol V.1 to V.4.....	173
FDA Table 40. Overall Disease Response Criteria for Protocol V.5	174

Applicant Table of Figures

Applicant Figure 1	Trial Design	44
Applicant Figure 2	Hypothesis Testing Hierarchy for Cohort IIA.....	50
Applicant Figure 3	Swimmer Plot of Patients Achieving CR After 3 Months or CRi Ongoing (Cohort IIA, Infused Set) – FELIX Study	70
Applicant Figure 4	Landmark Analysis: Kaplan-Meier Plot of Event-Free Survival by Best Overall Response of CR or CRi At 3 Months (Cohort IIA, Infused Set) – FELIX Study	71
Applicant Figure 5	Forest Plot for Subgroup Analysis of ORR (Cohort IIA, Infused Set) – FELIX Study	72
Applicant Figure 6	Forest Plot for Subgroup Analysis of CR (Cohort IIA, Infused Set) – FELIX Study	73
Applicant Figure 7	Kaplan-Meier Plot of Duration of Remission by IRRC With Censoring for SCT or Other New Non-Protocol Anti-Cancer Therapy (Cohort IIA, Infused Set) – FELIX Study.....	81
Applicant Figure 8	Kaplan-Meier Plot of Event-free Survival by IRRC With Censoring for SCT or Other New Non-Protocol Anti-Cancer Therapy (Cohort IIA, Infused Set) – FELIX Study	83
Applicant Figure 9	Overall Survival Without Censoring for SCT (Cohort IIA, Infused Set) – FELIX Study	85
Applicant Figure 10	Median (Q1, Q3) Laboratory Values over Time for A) Neutrophil Count; B) Platelet Count – Phases Ib and II, All Cohorts (Safety Set) – FELIX Study	126

FDA Table of Figures

FDA Figure 1. Disposition of Patients (Phase 1b/2)	56
FDA Figure 2. Kaplan-Meier Curves of Duration of CR* per FDA-Adjudicated Assessment.....	87
FDA Figure 3. Kaplan-Meier Curves of Duration of OCR At Anytime per FDA-Adjudicated Assessment	88
FDA Figure 4. Kaplan-Meier Curves of Duration of OCR (CR vs. CRi) Within 3 Months per FDA- Adjudicated Assessment	88
FDA Figure 5. Forest Plot of Complete Remission Rate Within 3 Months of Obe-cel Infusion by Subgroups in the Primary Efficacy Population	92

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Abbreviations: APLB, Advertising and Promotional Labeling Branch; BIMO, bioresearch monitoring; CDRH, Center for Devices and Radiological Health; CMC, Chemistry, Manufacturing, and Controls; DBSQC, Division of Biological Standards and Product Quality; DCEH, Division of Clinical Evaluation Hematology; DMPQ, Division of Manufacturing and Product Quality; MHB, Malignant Hematology Branch; MORE, Medical Oncology Review and Evaluation; OBPV, Office of Biostatistics and Pharmacovigilance; OCBQ, Office of Compliance and Biologics Quality; OCE, Oncology Center of Excellence; OCE*, Office of Clinical Evaluation; OMEPRM, Office of Medication Error Prevention and Risk Management RPM, Regulatory Project Manager.

Glossary

4-1BB	cluster of differentiation 137 (TNF-receptor superfamily 9)
ADR	adverse drug reaction
AE	adverse event
AESI	adverse event of special interest
ALL	acute lymphoblastic leukemia
AML	acute myeloid leukemia
ANC	absolute neutrophil count
ASTCT	American Society for Transplantation and Cellular Therapy
AUC	area under the curve
B ALL	B-cell precursor acute lymphoblastic leukemia
BCMA	B cell maturation antigen
BIMO	bioresearch monitoring
BLA	Biologics License Application
BM	bone marrow
BOR	best overall response
brexu-cel	brexucabtagene autoleucel
CAT	CD19 CAR (expressed in obe-cel)
CAR	chimeric antigen receptor
CD	cluster of differentiation
CD19 CAR	CAR directed against CD19
CDRH	Center for Devices and Radiological Health
CFR	Code of Federal Regulations
COVID-19	coronavirus disease 2019
CI	confidence interval
C _{max}	maximum concentration
CNS	central nervous system
COA	clinical outcome assessment
CR	complete remission
CRh	complete remission with partial hematologic recovery
CRi	complete remission with incomplete recovery of counts
CRS	cytokine release syndrome

BLA 125813/0 Clinical Review and Evaluation
AUCATZYL (obecabtagene autoleucel)

CSF	cerebrospinal fluid
CTCAE	Common Terminology Criteria for Adverse Events
DMEPA	Division of Medication Error Prevention and Analysis
DOCR	duration of complete remission
DOR	duration of remission
DSP	Dose Schedule Planner
EFS	event-free survival
EMD	extramedullary disease
FDA	Food and Drug Administration
(b) (4)	CD19 ScFv
GCP	Good Clinical Practice
GCSF	granulocyte-colony stimulating factor
GvHD	graft-versus-host disease
GT	grouped term
HF	human factors
HLH	hemophagocytic lymphohistiocytosis
HSCT	hematopoietic stem cell transplantation
ICANS	immune effector cell-associated neurotoxicity syndrome
ICH	International Conference for Harmonisation
IPD	important protocol deviation
IRRC	Independent Response Review Committee
ITT	intent-to-treat
IVIG	intravenous immunoglobulin
KM	Kaplan Meier
LD	lymphodepletion (pre-conditioning)
MAS	macrophage activation syndrome
MDS	myelodysplastic syndrome
MedDRA	Medical Dictionary for Regulatory Activities
MRD	minimal residual disease
NCCN	National Comprehensive Cancer Network
(b) (4)	
NT	neurologic toxicity
obe-cel	obecabtagene autoleucel
OCE	Oncology Center of Excellence
OCR	overall complete remission

BLA 125813/0 Clinical Review and Evaluation
AUCATZYL (obecabtagene autoleucel)

OOS	out of specification
ORR	overall remission rate
OS	overall survival
(b) (4)	
Ph+	Philadelphia chromosome translocation present
Ph-	Philadelphia chromosome translocation negative
PD	pharmacodynamics
PK	pharmacokinetics
PMR	postmarketing requirement
PRO	patient-reported outcome
PROM	premature rupture of membranes
PT	preferred term
r/r	relapsed or refractory
REMS	risk evaluation and mitigation strategy
RfIC	Release for Infusion Certificate
RFS	relapse-free survival
RMAT	Regenerative Medicine Advanced Therapy
scFv	single-chain variable fragment
SAE	serious adverse event
SAP	statistical analysis plan
SCT	stem cell transplantation
SOC	system organ class
TEAE	treatment-emergent adverse event
TKI	tyrosine kinase inhibitor
TLS	tumor lysis syndrome
USPI	United States Prescribing Information
WBC	white blood cell

1 Executive Summary

1.1. Product Introduction

On November 17, 2023, Autolus Inc (the Applicant) submitted a Biologics License Application (BLA), seeking approval of AUCATZYL (obecabtagene autoleucel, hereafter referred to as obe-cel), for the treatment of adult patients (18 years and over) with relapsed or refractory (r/r) B cell precursor acute lymphoblastic leukemia (B ALL)

Obe-cel is an autologous chimeric antigen receptor (CAR) T-cell product that is transduced with the (b) (4) lentiviral vector to express an anti-CD19 CAR. The CAR in obe-cel is constructed using the cluster of differentiation 137 (4-1BB) co-stimulatory domain. Obe-cel also contains non-transduced autologous T cells and non-T cells. Obe-cel mimics physiologic T-cell activation, enabling CAR T-cell expansion and long-term persistency.

1.2. Conclusions on the Substantial Evidence of Effectiveness

To support the proposed indication, the Applicant submitted safety and efficacy data from the clinical study, FELIX (NCT04404660) Phase 1b/2 (Cohort A), as well as supplemental data from Cohort B and Cohort C.

FELIX is an open-label, multicenter, single-arm study that evaluates obe-cel for the treatment of adults with r/r B ALL. Cohort A included patients with r/r B ALL with $\geq 5\%$ blasts in the bone marrow at screening; Cohort B included patients with r/r B ALL in morphological remission with minimum residual disease (MRD)-positive disease, and Cohort C included patients with r/r B ALL with isolated extramedullary disease (EMD). Patients were required to meet the following key eligibility criteria: adults with refractory B ALL, first relapse following a remission lasting ≤ 12 months, r/r B ALL after two or more prior lines of systemic therapy, or r/r B ALL at least greater than 3 months after allogeneic stem cell transplantation (SCT) and had disease burden of $\geq 5\%$ blasts in bone marrow at screening. Patients were excluded if they had isolated EMD, active or serious infections, active graft versus host disease, and history or presence of central nervous system (CNS) disorders. Patients in FELIX received obe-cel following lymphodepletion with cyclophosphamide and fludarabine. During product manufacturing, patients were allowed to receive bridging therapy at the discretion of the investigator.

The primary efficacy endpoint in FELIX is the overall complete remission (OCR) rate at any time following obe-cel infusion, defined as the combined rate of complete remission (CR) and CR with incomplete hematological recovery (CRi) per independent response review committee (IRRC). Key secondary efficacy endpoints include duration of remission (DOR) and CR within 3 months following obe-cel infusion. The primary efficacy analysis population consists of patients enrolled in Phase 2 (Cohort A), who had $\geq 5\%$ bone marrow blasts prior to lymphodepletion (LD) and who received at least one infusion of conforming obe-cell. The primary safety analysis

population consists of patients enrolled in Phase 1b (Cohort A) and Phase 2 (Cohort A) of FELIX, and who received at least one infusion of conforming obe-cel.

Efficacy

As of the data cutoff date of September 13, 2023, a total of 65 patients comprised the primary efficacy analysis set. FELIX demonstrated an OCR rate of 41 patients (63% (95% confidence interval [CI]: 50, 75)). For the key secondary efficacy endpoints, FELIX demonstrated the following results: Duration of OCR (CR + CRi) at any time: median of 14.1 months (95% CI: 6.2, not reached [NR]), CR rate within 3 months of obe-cel infusion of 27 patients (42% (95% CI: 29, 54), and duration of CR within 3 months: median of 14.1 months (95% CI: 6.1, NR). The manufacturing failure rate for obe-cel was 5%.

Safety

A total of 100 patients enrolled in the Phase 1b and Phase 2 (Cohort A) portion of FELIX who were treated with at least one dose of obe-cel conforming product as of the data cutoff date of September 13, 2023, were analyzed for safety. All patients experienced treatment-emergent adverse events (TEAEs) and Grade 3 or higher TEAEs occurred in 81% of patients. The most common non-laboratory adverse reactions (incidence \geq 20%) included: cytokine release syndrome (CRS), infections - pathogen unspecified, musculoskeletal pain, viral infections, fever, nausea, bacterial infectious disorders, diarrhea, febrile neutropenia, immune effector cell-associated neurotoxicity syndrome (ICANS), hypotension, pain, fatigue, headache, encephalopathy, and hemorrhage. The most common Grade 3 or 4 laboratory abnormalities included: lymphopenia, leukopenia, neutropenia, anemia, and thrombocytopenia.

Serious adverse events (SAEs) occurred in 62% of patients and Grade 3 or higher SAEs occurred in 54% of patients. Most common SAEs included infections-pathogen unspecified, febrile neutropenia, CRS, and fever.

Any grade CRS occurred in 75% and any grade neurologic toxicity occurred in 64% of patients. Grade 3 or higher adverse events of special interest (AESIs) included: non-COVID infections (41%), prolonged cytopenias (34% in the 41 responders), neurologic toxicity (12%), CRS (3%), and hemophagocytic lymphohistiocytosis/macrophage activation syndrome (HLH/MAS; 2%).

Among the 52 patients from the safety population who died during the study, 9 patients had fatal adverse reactions which included infections (sepsis, pneumonia, peritonitis), ascites, pulmonary embolism, acute respiratory distress syndrome, HLH/MAS, and ICANS.

Two cases of secondary malignancies occurred during this study (one acute myeloid leukemia and one basal cell carcinoma); based on available data, a causal relationship is not apparent.

The safety profile of obe-cel appears generally consistent with approved CAR T cell products, with no new safety signals identified. The risks of obe-cel, including CRS and neurologic toxicity

are serious, life-threatening, and can be fatal. These risks can be adequately mitigated through product labeling. Given the extensive experience gained in diagnosing and managing these risks across products in the class, the review team determined that the safe and effective use of obe-cel for the indicated population can be assured without a risk evaluation and mitigation strategy (REMS) for CRS and neurologic toxicity. Of note, currently approved CD19 and B cell maturation antigen (BCMA)-CAR T cell therapies are available under REMS due to risk of CRS and neurologic toxicities. Insertional mutagenesis and subsequent development of T cell malignancies remain a risk for CD19 and BCMA CAR T cell products approved for the treatment of hematologic malignancies. Accordingly, although no cases of T Cell malignancies were reported in FELIX study, product labeling describes this risk. Additionally, a postmarketing long-term follow-up registry study will be required to further characterize this risk.

Recommendation

FELIX study represents an adequate and well-controlled study that provides substantial evidence of effectiveness based on complete remission rate within 3 months and durability of remission in patients with r/r B ALL in the context of an acceptable safety profile in support of a traditional approval. Given the life-threatening nature of the disease in the indicated population, the adverse reactions of CRS and neurologic toxicity, if managed appropriately, represent toxicities that are acceptable from a benefit-risk perspective in the intended population. Efficacy and safety data from the patients treated on FELIX Phase 1b Cohort A demonstrated similar outcomes to the primary results. In addition, B ALL has a well understood pathophysiology; the mechanism of action of obe-cel in B-ALL treatment is due to its binding with CD19, an antigen universally expressed on B ALL blasts leading to tumor lysis. In vitro pharmacology studies of co-culture of obe-cel with cell lines expressing CD19 resulted in target-specific killing, secretion of pro-inflammatory-associated cytokines, and proliferation. In vivo pharmacology studies in a systemic human tumor xenograft mouse model demonstrated that obe-cel resulted in significant reduction in tumor burden. The supportive data from the additional cohorts and the mechanism of action of obe-cel serve as confirmatory evidence to substantiate the results from one adequate and well-controlled trial to demonstrate substantial evidence of effectiveness.

Thus, the overall benefit-risk profile supports a traditional approval of obe-cel in adults with r/r B ALL.

Although FELIX was designed with overall complete remission rate at any time as the primary efficacy endpoint, FDA considers complete remission rate at 3 months to be the main efficacy outcome measure for this BLA. FDA considers a CR within 3 months from start of therapy, as assessed by IRRC to reflect a clinical benefit for patients with r/r B ALL treated with CAR T cell therapies. Accordingly, the Agency has previously accepted durable complete remission rate at 3 months to support traditional approval for drugs and biological products to treat B ALL;

durable CR represents recovery of adequate blood counts to protect against infection, prevent bleeding, and avoid transfusions, which denote clinical benefit.

The review team considers the high CR and durable remission rate observed in FELIX and the additional supportive evidence provided in the BLA, to represent substantial evidence of the effectiveness of obe-cel in the indicated population.

The recommended obe-cel dosing is a split dose infusion to be administered on Day 1 and Day 10 (± 2 days) at a total dose of 410×10^6 CD19 CAR-positive viable T cells. Dose to be administered is determined by the patient's bone marrow (BM) blast assessment prior to LD.

1.3. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

The benefit-risk assessment for obe-cel for the indicated population is based on the results of Study FELIX, a Phase 1b/2, single-arm, open-label, multicenter, multiregional (U.S., United Kingdom, and Spain) trial of obe-cel in adults with r/r B ALL. A total of 65 patients from Phase 2 Cohort A constituted the efficacy analysis population. The primary efficacy endpoint is the overall complete remission (OCR) rate (CR+CRi) at any time following obe-cel infusion, per independent response review committee. Key secondary efficacy endpoints include DOR and CR within 3 months following obe-cel infusion.

The totality of the data from Study FELIX demonstrates a favorable benefit-risk for obe-cel as treatment for adults with r/r B ALL.

Efficacy: Study FELIX Phase 2 Cohort A demonstrates substantial evidence of effectiveness of obe-cel based on CR rate within 3 months of obe-cel infusion of 27 patients (42% (95% CI: 29, 54), supported by OCR rate at any time of 41 patients 63% (95% CI: 50, 75), and duration of OCR with median of 14.1 months (95% CI: 8.1, not reached).

Safety: The risks of obe-cel are associated with its mechanism of action. The major risks include CRS and ICANS, which can be life threatening or fatal. Some patients may develop prolonged cytopenia, HLH/MAS, hypersensitivity reactions, and secondary malignancies. Infections may occur, which could result in a fatal outcome. Patients should be evaluated for infection and managed with broad-spectrum antibiotics, fluids and other supportive care, as medically indicated. B cell aplasia and resultant hypogammaglobulinemia may predispose patients to infections and requires monitoring and intervention. These risks may be managed with appropriate monitoring and treatment strategies. These adverse events represent toxicities that are acceptable from a benefit-risk perspective in the intended population.

Overall benefit-risk assessment:

Obe-cel has a favorable benefit-risk profile in adults with r/r B ALL. Based on complete remission rate supported by durability of remission, obe-cel represents a meaningful clinical benefit for the indicated population, and therefore supports a traditional approval.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	<ul style="list-style-type: none"> Patients with r/r B ALL do not survive without treatment. Long-term survival is <1% for patients with r/r B ALL. 5-year overall survival (OS) rates for adults are low at approximately 20% to 40%. 	<ul style="list-style-type: none"> R/r B ALL is a fatal disease.
Current Treatment Options	<ul style="list-style-type: none"> Treatment approach includes the use of several antineoplastic agents given in varying doses and schedules, HSCT, and novel therapeutic agents (e.g., blinatumomab or inotuzumab), which do not induce long-term remission and are dependent on HSCT. Brexucabtagene autoleucel (brexu-cel) is a CD19 CAR T that is approved for the same indication. Remission rates using current available therapy are low <10% with single agents and 25 to 46% with combination chemotherapy, and even with allogeneic HSCT, survival is only about 35%. Duration of first CR, age, white blood cell count at diagnosis, refractoriness to prior therapy, number of relapses, and subsequent HSCT are known prognostic factors for survival after salvage chemotherapy. 	<ul style="list-style-type: none"> B ALL after second or subsequent relapse or refractory to initial induction chemotherapy is highly resistant to salvage chemotherapy based on prior exposure to standard of care chemotherapy and HSCT. R/r B ALL has a poor prognosis with standard of care therapy including SCT; prognosis is influenced by disease biology, patient characteristics, and prior therapy. r/r B ALL in adults represent unmet medical need. Patients may benefit from a one-time treatment option.
Benefit	<ul style="list-style-type: none"> FELIX Study included a total of 65 efficacy evaluable patients with r/r B ALL. The CR rate within 3 months was 41.5% [95% CI: 29.4, 54.4]; median duration of CR was 14.1 months (95% CI: 6.1, NR). 	<ul style="list-style-type: none"> The evidence for clinical benefit for r/r B ALL in adults is compelling based on CR rate and DOR.
Risk and Risk Management	<ul style="list-style-type: none"> Cytokine release syndrome (CRS) is a serious adverse event which is included in the USPI Boxed Warning. At the first sign of CRS, patients should be immediately evaluated for hospitalization and treatment with supportive care should be instituted. Healthcare providers administering obe-cel should have immediate access to medications and resuscitative 	<ul style="list-style-type: none"> The evidence indicates that the risk of obe-cel, while substantial, does not outweigh the benefit in adults with r/r pre-B ALL. The risks associated with obe-cel warrant

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	<p>equipment to manage CRS.</p> <p>Additional serious adverse events include neurologic toxicity including immune effector cell associated neurotoxicity syndrome (ICANS), prolonged cytopenias, infections, hypogammaglobulinemia, HLH/MAS, and hypersensitivity reactions.</p> <ul style="list-style-type: none"> • Healthcare providers administering obe-cel should have immediate access to medications and resuscitative equipment to manage ICANS. • There is a theoretical risk for secondary malignancy with this genetically modified immunotherapy based on the potential for replication competent retrovirus due to the lentiviral vector and the insertional mutagenesis. However, no such cases occurred by the data cut-off date in this study. 	<p>boxed warnings for CRS and ICANS and a long-term follow-up study.</p> <ul style="list-style-type: none"> • The PMR study will follow 500 recipients of the commercial product for 15 years for secondary malignancy and other safety signals. • The evidence suggests that the risks of obe-cel do not outweigh the benefit in adult patients with r/r B ALL. • The risks of obe-cel, including CRS and neurologic toxicity are serious, life-threatening, and can be fatal. These risks can be adequately mitigated through product labeling. Given the extensive experience gained in diagnosing and managing these risks across products in the class, the safe and effective use of obe-cel for the indicated population can be assured without a risk evaluation and mitigation strategy (REMS) for CRS and neurologic toxicity.

1.4. Patient Experience Data

Patient Experience Data Relevant to this Application (check all that apply)

Check if Submitted	Type of Data	Section Where Discussed, if Applicable
<input checked="" type="checkbox"/>	Patient-reported outcome	Section 8.1.2
<input type="checkbox"/>	Observer-reported outcome	
<input type="checkbox"/>	Clinician-reported outcome	
<input type="checkbox"/>	Performance outcome	
<input type="checkbox"/>	Patient-focused drug development meeting summary	
<input type="checkbox"/>	FDA Patient Listening Session	
<input type="checkbox"/>	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel)	
<input type="checkbox"/>	Observational survey studies	
<input type="checkbox"/>	Natural history studies	
<input type="checkbox"/>	Patient preference studies	
<input type="checkbox"/>	Other: (please specify)	
<input type="checkbox"/>	If no patient experience data were submitted by Applicant, indicate here.	
Check if Considered	Type of Data	Section Where Discussed, if Applicable
<input type="checkbox"/>	Perspectives shared at patient stakeholder meeting	
<input type="checkbox"/>	Patient-focused drug development meeting summary report	
<input type="checkbox"/>	FDA Patient Listening Session	
<input type="checkbox"/>	Other stakeholder meeting summary report	
<input type="checkbox"/>	Observational survey studies	
<input type="checkbox"/>	Other: (please specify)	

Reviewer comment: Because FELIX study was a single-arm trial with no comparator, the patient-reported outcome (PRO) data are descriptive and were not considered for regulatory decision making.

2 Therapeutic Context

2.1. Analysis of Condition

The Applicant's Position:

B cell precursor acute lymphoblastic leukemia (B 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 bone marrow (BM) leading to an abundance of lymphoblasts (frequently referred to as ‘blasts’) and suppression of normal hematopoiesis. Over time, this over-production of lymphoblasts leads to an insufficient production of all normal blood cells. This seriously compromises the patient’s immune function, leading to infections, bleeding complications, and anemia. 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 ([Aldoss et al. 2022](#)). If untreated, B ALL will progress rapidly and is generally fatal within weeks.

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](#)). This is explained by older adult patients diagnosed with relapsed or refractory (r/r) B ALL tending to have disease with intrinsic unfavorable biology, more comorbidities, and a reduced ability to tolerate standard chemotherapy regimens ([Terwilliger and Abdul-Hay, 2017](#)). In addition, there are younger adult r/r B ALL patients, 20% diagnosed at age < 40 years, who, although may have had positive outcomes when initially treated using chemotherapy regimens, are now more difficult to salvage as they have failed multiple prior treatments including prior hematopoietic stem cell transplant (SCT) so have a long history of lack of durable remissions and are less likely to respond to any additional salvage therapies.

Relapsed or refractory B ALL in adult patients is therefore common, difficult to treat, and is associated with a significant mortality rate, with median overall survival of less than 1 year ([Gökbuget et al, 2012](#); [Kantarjian et al, 2016](#); [Kantarjian et al, 2017](#); [Aldoss et al, 2017](#)).

The FDA’s Assessment:

FDA agrees with the Applicant’s statement that adults with r/r ALL have an unfavorable prognosis, which is influenced by disease biology, patient characteristics, and prior therapy. Duration of first CR, age, white blood cell counts at diagnosis, refractoriness to prior therapy, number of relapses, and subsequent hematopoietic stem cell transplantation (HSCT) are known prognostic factors for survival outcomes (Gokbuget et al. 2012; Gokbuget et al. 2016).

2.2. Analysis of Current Treatment Options

There remains a high unmet need for a therapy that offers robust efficacy while minimizing the potential for serious and life-threatening side effects in this difficult-to-treat adult r/r B ALL

population. A better-tolerated therapy that delivers clinically meaningful and durable efficacy, would serve this unmet need.

[Applicant Table 1](#) summarizes the targeted agents and immunotherapies currently approved for r/r B ALL which highlights the remaining unmet need:

Blinatumomab is a bispecific T cell engager first approved by the United States Food and Drug Administration (FDA) in Dec-2014 based on the phase 3 TOWER study. The available data suggests the role of blinatumomab in r/r B ALL treatment, due to a short durability of remission, is primarily to act as a bridge to SCT; patients who achieve a response to blinatumomab but who do not proceed to SCT had a worse prognosis compared with those who underwent SCT. In the TOWER study, among the 38 patients who achieved remission and underwent allogeneic SCT, 10 patients (26%) died during the median follow-up of 206 days, highlighting the limitations of survival following SCT ([Saygin et al, 2016](#); [Kantarjian et al, 2017](#)).

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 Aug-2017 based on the INO-VATE study. Like blinatumomab, inotuzumab ozogamicin primarily acts as a bridge to SCT due to the limited duration of remission, with patients who proceeded to SCT having a considerably better overall survival (OS) than those who did not. A significant decrease in remission rate was observed when this therapy was used as a third line therapy rather than a second line therapy (66.1% versus 77.8%; [Kantarjian et al, 2019](#)).

Tisagenlecleucel (tisa-cel) is a CD19 chimeric antigen receptor (CAR) T cell therapy (4-1BB costimulatory domain) approved in Aug-2017 (including 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.

Brexucabtagene autoleucel (brexu-cel) is a CD19 CAR T cell therapy (CD28 costimulatory domain) approved in Oct-2021 based on the ZUMA-3 study. While a high remission rate was observed in this pivotal study, a high proportion of patients experienced serious toxicity (\geq Grade 3 CRS reported in 26% of patients and \geq Grade 3 neurological toxicity in 35% of patients). Other clinically important adverse reactions included hemophagocytic lymphohistiocytosis (HLH) (4%) and seizure (8%) (Tecartus USPI, 2023). It is noteworthy that the challenging adverse event (AE) profile of brexu-cel has been highlighted during real-world use of brexu-cel in 25 US centers as part of the Real World Outcomes Collaborative of CAR T-cell Therapy in Adult ALL Study [ROCCA], N=152 infused. The overall rates of Cytokine Release Syndrome (CRS) and Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS) in ROCCA were 88% and 56%, respectively. The rate of Grade 3-4 CRS and ICANS was 9% and 31%, respectively, despite 43% patients having a low disease burden and not having morphological disease at apheresis (23% minimal residual disease [MRD] only, 15% MRD-negative) ([Roloff et al, 2023](#)).

Applicant Table 1 Novel Targeted Agents and Immunotherapeutics Approved for the Treatment of Recurrent/Refractory B-cell Precursor Acute Lymphocytic Leukemia

Product Name (s)	Relevant Indication	Year of Approval And Type of Approval	Dosing/ Administration	Efficacy Information	Important Safety and Tolerability Issues	Other Comments
FDA Approved Treatments for r/r B-cell precursor ALL						
Blinatumomab (CD19-directed CD3 T cell engager)	Treatment of r/r B ALL in adults and children.	Initial Accelerated approval*: 2014 Full approval: 2017	2 cycles of Blincyto for induction followed by 3 cycles for consolidation and up to 4 cycles of continued therapy	TOWER: Phase III, randomized, open-label, multi-center study of Blincyto compared to SOC chemotherapy ORR (CR/CRh): 42% (95% CI: 37, 49) CR within 3 months: 34% (95% CI: 28, 40) DOR (CR+CRh): 5.9 months (range: 0.13-16.5) Patients who received blinatumomab as a third line or later therapy, the median OS is only 5.1 months and the CR rate 39.5% (versus 51.0% in first salvage therapy) (Dombret et al, 2019; Cappell and Kochenderfer, 2021).	CRS: • Grade ≥ 3: 3% of patients Neurological Toxicity: • Grade ≥ 3: 13% of patients [Blincyto USPI, 2023 Amgen]	TOWER: CD19 naive patient population; patients who achieve a response to blinatumomab but who do not proceed to SCT had a worse prognosis compared with those who underwent SCT (Kantarjian 2017)
Inotuzumab ozogamicin (CD22-directed antibody-drug conjugate (ADC))	Treatment of adults with r/r B ALL	Full approval: 2017	Dependent on response to treatment. See Besponsa USPI [2] for details. (Besponsa USPI, 2017 Pfizer) .	INO-VATE ALL: Phase III, randomized, open-label, multi-center study of inotuzumab ozogamicin vs Investigator's choice of chemotherapy ORR (CR/CRI): 80.7% (95% CI: 72.1, 87.7) CR: 35.8% (95% CI: 26.8, 45.5) DOR (CR+CRI): 5.4 months (95% CI: 4.2, 8.0) Remission rate when used as a third line	Hepatotoxicity, including life-threatening hepatic VOD: 14% of patients Increased risk of post SCT non-relapse mortality rate (Besponsa USPI, 2017 Pfizer)	Ino-Vate: CD22 naive patient population; patients who proceeded to SCT have considerably better OS than those who do not; The risk of VOD was greater in patients who underwent SCT after inotuzumab ozogamicin

BLA 125813/0 Clinical Review and Evaluation
AUCATZYL (obecabtagene autoleucel)

				therapy rather than a second line therapy (66.1% versus 77.8%).(Kantarjian 2017)		treatment
Tisagenlecleucel (CD19-directed CAR T cell immunotherapy, 4-1BB costimulatory domain)	Treatment of pediatric and young adult patients up to 25 years of age with B ALL refractory or in second or later relapse.	Full approval: 2017	For patients 50 kg or less: 0.2 to 5.0×10^6 CAR-positive viable T cells per kg body weight intravenously. For patients above 50 kg: 0.1 to 2.5×10^8 total CAR-positive viable T cells (non-weight based) intravenously.	ELIANA: Phase II, single arm, open-label, multi-center study ORR (CR/CRi): 83% (95% CI: 71, 91) CR within 3 months: 63% DOR: Not reached (95% CI: 7.5, NE)	CRS: • Grade ≥ 3 : 48% of patients. Neurological Toxicity: • Grade ≥ 3 : 22% of patients [Kymriah USPI, Novartis]	CD19-naïve patients with no prior use of blinatumomab, only 10% were primary refractory; high proportion of patients experienced severe, potentially fatal toxicities
Brexucabtagene autoleucel (CD19-directed CAR T cell immunotherapy, CD28 costimulatory domain)	Treatment of adult patients with r/r B ALL	Full Approval (r/r MCL): 2020 Supplemental Approval (r/r B ALL, 2021)	Single infusion of 1×10^6 CAR positive viable T cells per kg body weight, with a maximum of 1×10^8 CAR-positive viable T cells.	ZUMA-3: Phase I/II single arm, open-label, multi-center study ORR (CR/CRi): 64.8% (95% CI: 51, 77) CR within 3 months: 51.9% (95% CI: 37.8, 65.7) DOR (CR): 13.6 months (95% CI: 9.4, NE)	CRS: • Grade ≥ 3 : 26% of patients Neurological Toxicity: • Grade ≥ 3 : 35% of patients [Tecartus USPI, 2023 Kite]	r/r B ALL with morphological disease in the bone marrow (>5% blasts) at study entry; high proportion of patients experienced serious toxicity

ALL = Acute lymphoblastic leukemia; Blin = Blinatumomab; CAR = chimeric antigen receptor; CD19 = Cluster of differentiation 19 (B-Lymphocyte Surface Antigen B4); CR = Complete remission; CRh = Complete remission with partial hematologic recovery; CRi = Complete remission with incomplete count recovery; CRS = Cytokine release syndrome; HLH/MAS = Haemophagocytic lymphohistiocytosis /macrophage activation syndrome; MCL = Mantle cell lymphoma; mDOR = Median duration of remission; mOS = Median overall survival; MRD-ve =Minimal residual disease-negative; r/r = Relapsed/refractory; SCT = Stem cell transplant; SOC = Standard of care; USPI = United States Prescribing Information; VOD = veno-occlusive disease.

The FDA's Assessment:

To add to the Applicant's analysis of available therapies in the r/r B ALL setting, [FDA Table 1](#) lists all the drugs with FDA approval for r/r Philadelphia (Ph)-positive or Ph-negative precursor B-cell ALL.

FDA Table 1. Approved Agents With Indication(s) Relevant to the Treatment of Relapsed or Refractory B-cell Precursor Acute Lymphoblastic Leukemia

Agent	Excerpted Indication
Asparaginase (E. coli)	Indicated as a component of a multi-agent chemotherapeutic regimen for the treatment of patients with ALL.
Asparaginase (Erwinia)	Indicated as a component of a multi-agent chemotherapeutic regimen for the treatment of patients with ALL who have developed hypersensitivity to E. coli-derived asparaginase.
Blinatumomab	Treatment of relapsed or refractory CD19-positive B ALL in adults and children.
Brexucabtagene autoleucel	Treatment of adult patients with relapsed or refractory B ALL.
Clofarabine*	Treatment of pediatric patients 1 to 21 years old with relapsed or refractory acute lymphoblastic leukemia after at least two prior regimens.
Cyclophosphamide	Cyclophosphamide, although effective alone in susceptible malignancies, is more frequently used concurrently or sequentially with other antineoplastic drugs. The following malignancies are often susceptible to cyclophosphamide treatment: acute lymphoblastic (stem-cell) leukemia in children.
Cytarabine	Useful in the treatment of acute lymphocytic leukemia.
Daunorubicin	In combination with other approved anticancer drugs is indicated for remission induction in acute lymphocytic leukemia of children and adults.
Dasatinib	Treatment of adults with Ph+ ALL resistant to or intolerant of prior therapy.
Dexamethasone	For palliative management of leukemias and lymphomas in adults, acute leukemia of childhood.
Doxorubicin	To produce regression in disseminated neoplastic conditions such as acute lymphoblastic leukemia.
Imatinib	Treatment of adult patients with relapsed or refractory Ph+ ALL; in combination with chemotherapy for first line treatment of pediatric patients with newly diagnosed Ph+ ALL.
Inotuzumab ozogamicin#	Treatment of relapsed or refractory CD22-positive B ALL in adult and pediatric patients 1 year and older.
Mercaptopurine	For maintenance therapy of acute lymphatic (lymphocytic, lymphoblastic) leukemia as part of a combination regimen.
Methotrexate	Used in maintenance therapy in combination with other chemotherapeutic agents.
Methylprednisolone	For palliative management of leukemias and lymphomas in adults, acute leukemia of childhood.

BLA 125813/0 Clinical Review and Evaluation
AUCATZYL (obecabtagene autoleucel)

Agent	Excerpted Indication
Pegasparaginase	Indicated as a component of a multi-agent chemotherapeutic regimen for the treatment of patients with ALL and hypersensitivity to native forms of L-asparaginase.
Ponatinib	ALL that is Ph+ and has the T315I mutation.
Prednisone	For palliative management of leukemias and lymphomas in adults, acute leukemia of childhood.
Teniposide	In combination with other approved anticancer agents, is indicated for induction therapy in patients with refractory childhood acute lymphoblastic leukemia.
Tisagenlecleucel	Treatment of patients up to 25 years of age with B ALL that is refractory or in second or later relapse.
Vincristine	Indicated in acute leukemia.
Vincristine sulfate liposome	Treatment of adult patients with Ph- ALL in second or greater relapse or whose disease has progressed following two or more anti-leukemia therapies.

Source: FDA Reviewer

*Accelerated approval only

#The pediatric indication was approved in 2024

Abbreviations: ALL, acute lymphoblastic leukemia; B ALL, B-cell Precursor Acute Lymphoblastic Leukemia; Ph+, Philadelphia chromosome-positive; Ph-, Philadelphia chromosome-negative.

[FDA Table 2](#) provides a summary of CR rates achieved with conventional combination chemotherapy or single-agent use of approved targeted therapies for adults and children with ALL (O'Leary et al. 2019). Duration of first CR, age, white blood cell count at diagnosis, and number of relapses are known prognostic factors for reinduction of remission (Gokbuget et al. 2012; Gokbuget et al. 2016). Notably, the definition of CR across clinical studies is based on general clinical practice guidelines and varies across the study groups or centers.

FDA Table 2. Summary of Treatment Armamentarium (Novel Targeted Agents) Relevant to the Proposed Indication

Agent	Population	Number of Patients Efficacy Evaluable	
		[Enrolled]	% CR (95% CI)
Clofarabine	Children	61	12% (5%, 22%)
Vincristine liposome	Adults	65	5% (1%, 13%)
Blinatumomab	Children and Adults	70	17% (9%, 28%)
		185	32% (26%, 40%)
		271	34% (28%, 40%)
Inotuzumab ozogamicin	Adults	109	36% (27%, 46%)
	Children	53	42% (28%, 56%)
Tisagenlecleucel	Children and young adults	63 [78]	63% (50%, 75%)
			[51% (40%, 63%)]
Brexucabtagene autoleucel	Adults	54 [71]	52% (38%, 66%)
			[41% (29%, 53%)]
Combination chemotherapy	Children Salvage 2	108	44% (35%, 54%)
	Salvage ≥3	121	19% (12%, 27%)
Combination chemotherapy	Adults Salvage 2	275	21% (16%, 26%)
	Salvage 3	125	11% (6%, 18%)
Allogeneic HSCT (Pavlu et al. 2017)	Adults	84	79% (68%, 87%)

Source: FDA Reviewer (Adapted from O'Leary et al. 2019)

Abbreviations: CR, complete remission; HSCT, hematopoietic stem cell transplant.

3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

The Applicant's Position:

Obecabtagene autoleucel (obe-cel) has not previously been approved for marketing by any regulatory authority.

The FDA's Assessment:

FDA agrees.

3.2. Summary of Presubmission/Submission Regulatory Activity

The Applicant's Position:

The development program of obe-cel was conducted in conjunction with advice from regulatory agencies. This included a pre-IND meeting with the FDA, as well as meetings conducted under Regenerative Medicine Advanced Therapy Designation, and European Medicines Evaluation Agency (EMA) scientific where advice was obtained.

The final protocol and analysis for the pivotal AUTO-AL1 study (hereafter referred to as FELIX) incorporated the suggestions from the FDA from Type B clinical meetings as well as input from EMA during scientific advice procedures. In addition, a pre-Biologics License Application (BLA) meeting was held with the FDA in September 2023 to discuss the filing strategy for obe-cel. Obe-cel was granted orphan drug designation (ODD [ODD #19-7083]) status on 04-Nov-2019 for the treatment of B ALL and regenerative medicine advanced therapy (RMAT) designation on 20-Apr-2022.

The key regulatory interactions between the Agency and the Applicant are summarized in [Applicant Table 2](#).

Applicant Table 2 Key Regulatory Interactions with the FDA

Interaction Type	Date	Meeting ID CRMTS #
Pre-IND advice on quality, non-clinical and clinical development aspects	Aug-2019	11916
Regenerative Medicine Advanced Therapy (RMAT) designation granted	Apr-2022	N/A
Type B multidisciplinary RMAT meeting on Chemistry, Manufacturing, and Controls (CMC), non-clinical, clinical and regulatory obe-cel development aspects to support a BLA submission	Jul-2022	14149
Type B meeting on the estimands framework applicable to the pivotal FELIX study	Sep-2022	14303
Type B meeting on quality development aspects	May-2023	14810
Type B meeting on REMS	Jul-2023	15026
Type B pre-BLA meeting	Sep-2023	15185

The FDA's Assessment:

Development of obe-cel for treatment of r/r ALL was conducted under IND 19534. A summary of the regulatory actions and key interactions with FDA regarding obe-cel development is provided in [Applicant Table 2](#) above.

Key Regulatory Advice

As the Applicant did not submit a request for Special Protocol Assessment, there were no formal agreements on size and design of the pivotal trial. FDA provided the following advice to the Applicant during formal meetings:

- The Applicant submitted an initial request for Regenerative Medicine Advanced Therapy (RMAT) designation based on clinical data from the Phase 1 ALLCAR19 study (NCT02935257). FDA denied the initial RMAT designation on the basis that the clinical data from the ALLCAR19 were generated using obe-cel drug product manufactured

using Process (b) (4) and data demonstrating comparability to Process (b) (4) process, used in FELIX study) was not submitted.

- The Applicant re-submitted an RMAT designation request on February 28, 2022, with clinical data from 17 patients in Phase 2 Cohort A of the FELIX study infused with obe-cel DP manufactured by Process (b) (4). RMAT designation was granted on April 20, 2022. FDA noted that any patients enrolled in FELIX and treated with out of specification (OOS) obe-cel will not be included in the efficacy assessment.
- The FELIX Phase 1b/2 study design is considered adequate to evaluate the efficacy and safety of obe-cel. However, supportive data from the literature from Study ALLCAR19 are not sufficient for regulatory consideration. [Initial RMAT meeting]
- Advice that regulatory decision-making will be based on the proportion of patients with CR within 3 months of infusion of obe-cel. [Meeting on estimands framework]
- Recommendation to use CR rate within 3 months as the primary endpoint and to prioritize CR rate within 3 months in the hierarchical testing sequence. In addition, time-to-event endpoints, such as relapse-free survival (RFS) and event-free survival (EFS), cannot be interpreted in a single-arm trial. [Meeting on estimands framework]
- FDA communicated that the hypothesis testing for CR within 3 months will not be sufficient to demonstrate a favorable benefit-risk for obe-cel. FDA noted that the CR rate reported for brexu-cel is 52% with 95% CI 38-66. If the Applicant excludes close to only 15% as indicated in H03, the benefit-risk may be inadequate in the context of available therapy in the U.S. FDA recommended that the Applicant revises the hypothesis for CR within 3 months to exclude at least 35% to 40% CR within 3 months and to adjust the sample size and power calculation accordingly. [Meeting on estimands framework]
- Recommendation to not submit a breakthrough designation request as the FELIX study results do not demonstrate a substantial improvement over available therapy on a clinically significant endpoint. [pre-BLA]
- Agreement that FELIX study is appropriate for BLA submission and that the data to support the BLA approval will be a review issue. [pre-BLA]
- The Applicant proposed a hierarchical testing for OCR followed by CR at any time followed by CR within 3 months. FDA recommended that the final study protocol and statistical analysis plan (SAP) submitted to support the BLA submission be consistent and revised to incorporate FDA feedback on the formal testing of the endpoint of the proportion of patients achieving CR within 3 months. [pre-BLA]
- The Applicant proposed to submit the Day 120 safety update to the BLA at an earlier time by Day 30 of the BLA submission. The update will include additional 3 months of follow-up for efficacy and safety. [Pre-BLA]
- If MRD data are proposed to be included in labeling, all assay information per the MRD guidance (including assay validation and individual test results) should be submitted to the BLA. [Pre-BLA]

The IRs to the Applicant from the clinical review team are found in [FDA Table 3](#) below.

BLA 125813/0 Clinical Review and Evaluation
AUCATZYL (obecabtagene autoleucel)

FDA Table 3. Clinical Information Requests

Clinical Information Request	Date of Request
Clinical IR #1	11/29/2023
Clinical IR #2	12/22/2023
Clinical IR #3	1/3/2024
Clinical IR #4	1/19/2024
Clinical IR #5	1/24/2024
Clinical IR #6	1/30/2024
Clinical IR #7	2/9/2024
Clinical IR #8	3/1/2024
Clinical IR #9	3/7/2024
Clinical IR #10	4/5/2024
Clinical IR #11	8/2/2024
Clinical IR #12	9/6/2024
Clinical IR#13	10/7/2024

Source: FDA Clinical Reviewer

The BLA clinical review covered the original BLA submission and the following amendments:

FDA Table 4. FDA BLA Amendments, Clinical and Other Relevant Review Disciplines

Sequence Number	Date of Submission	Amendment Description
0001	11/17/2023	Original BLA submission
0002	12/6/2023	Response to Clinical IR #1 to clarify certain parameters in several datasets
0003	12/15/2023	Day 30 Safety Update Report (in lieu of the Day 120 safety update), addendum to the Summary of Clinical Efficacy, updated narratives and updated USPI, to include 3 additional months of follow-up.
0004	12/15/2023	Pharmacovigilance plan (PVP) (Non-REMS)
0007	1/2/2024	Response to Clinical IR #2: Resubmission of the annotated CRF in the correct location, clarification regarding report of BM blasts based on morphology vs. (b) (4), and data on platelet transfusion.
0009	1/10/2024	Application orientation meeting and dataset walkthrough material
0010	1/11/2024	Response to Clinical IR #3: data on GCSF use, clarification regarding transfusions and incorrect lab values for hemoglobin
0011	1/16/2024	Assessment Aid
0012	1/16/2024	Response to Epidemiology IR#2: clarification on REMS
0013	1/25/2024	Response to Epidemiology IR#3: Submission of LTFU protocol synopsis, clarification regarding “potential” risk of GvHD, and revised PVP.
0014	1/25/2024	Response to Clinical IR #4: Clarification regarding BM blasts, response assessment outside the allowed visit window, and response to MRD inquiry.
0016	1/29/2024	Response to Clinical IR #5: Day 30 narratives with hyperlinks.
0018	2/2/2024	Partial response to Clinical IR #6: MRD data, and all patients’ narratives with hyperlinks.
0020	2/14/2024	Partial response to Clinical IR #7: CNS and EMD info
0022	2/23/2024	Final response to Clinical IRs #4, 6, 7: Updated efficacy data to include disease assessments based on BMA and BMBx morphology (not by (b) (4)), and updated responses based on 2022 NCCN definition of response (CRi vs. CRh, vs. MLFS)

Sequence Number	Date of Submission	Amendment Description
0025	3/4/2024	Response to Clinical IR #8: Clarification on datasets for LD and CT scan findings for EMD evaluation.
0026	3/5/2024	Response to Division of Medication Error Prevention and Analysis (DMEPA) IR#1 regarding root causes for medication administration error and mitigation strategies
0027	3/18/2024	Response to Clinical IR #9: Updated efficacy responses based on 2022 NCCN definition considering complete disease assessment and platelet and GCSF administration. Updated datasets for BM morphological assessments (FAPRSP and ADSLSP).
0030	4/9/2024	Response to Clinical IR #10: Clarification on efficacy responses and blasts prior to LD for several patients.
0046	7/30/2024	Response to OBPV IR#6: Rationale for proposing a revised pharmacovigilance plan (PVP) to modify the important potential risk of “GvHD” to “Aggravation of GvHD”
0053	8/14/2024	Response and follow-up to OBPV IR#5 regarding algorithm testing for secondary malignancies
0058	8/30/2024	Response to Clinical IR #11: Response to FDA’s adjudication, however, the updated datasets were not submitted.
0064	9/9/2024	Response to Clinical IR #12: Submission of updated efficacy and safety datasets based on FDA’s adjudication: ADSLFDA1, ADAEFDA, ADEFFDA, and ADTTEFDA. The Applicant also submitted ADEFSP and ADTTESP efficacy datasets reflecting FDA’s adjudication and Applicant’s assessment taking into account FDA’s definition of CRi, without mandating additional procedure to ensure all disease assessment components are performed at the same time.
0069	9/20/2024	Applicant’s position in response to FDA’s assessment of efficacy
0079	10-8-2024	Response to Clinical Pharmacology IR #1: Submission of updated PK data/analyses based on FDA adjudicated safety and primary efficacy population
0080	10/10/2024	Response to Clinical IR #13: Submission of updated ADLB dataset to reflect laboratory abnormalities considering baseline values to be prior to lymphodepletion (rather than prior to obe-cel treatment).

Source: FDA Clinical Reviewer

Abbreviations: BM, bone marrow; CNS, central nervous system; CRF, case report form; CRh, complete remission with partial hematologic recovery; CRi, complete remission with incomplete recovery of counts; EMD, extramedullary disease; GCSF, granulocyte-colony stimulating factor; GvHD, graft versus host disease; IR, information request; LD, lymphodepletion; LTFU, long-term follow-up; MRD, major residual disease; NCCN, National Comprehensive Cancer Network; OBPV, Office of Biostatistics and Pharmacovigilance; PK, pharmacokinetics; REMS, Risk Evaluation and Mitigation Strategy; USPI, United States Prescribing Information

4 Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Compliance and Biologics Quality

There were no concerns during the pre-license inspections per the OCBQ Review team.

4.2. Product Quality

The chemistry, manufacturing, and control (CMC) review team concludes that the manufacturing process, along with associated test methods and control measures, can produce a pharmaceutical product of consistent quality.

4.3. Devices and Companion Diagnostic Issues

The FDA's Assessment:

The Applicant is not seeking to include in labeling a description of the MRD testing results from the FELIX study. In this study, MRD was measured by (b) (4). The Center for Devices and Radiological Health (CDRH) Reviewer noted that the submission did not include sufficient data to establish the analytical validity of the assay for the level of MRD needed to support labeling.¹

5 Summary of Nonclinical Pharmacology/Toxicology Findings

The Applicant's Position:

Nonclinical pharmacokinetic studies (absorption, distribution, metabolism, excretion and in vitro drug-drug interaction) were not conducted, in agreement with the Agency because obe-cel is an autologous human cell therapy product and there is no pharmacologically relevant non-human species for such testing. The CD19 scFv (CAT) used in the CAR construct does not cross-react with murine homologs. Therefore, conventional nonclinical toxicology studies normally applicable in small molecule drug development would yield relevant information for a complex biological product such as CAR T cells and were not performed in agreement with the Agency (Meeting info).

The nonclinical program therefore focused on verifying specificity and anti-tumor potency.

Biophysical characterization of the CAT binding domain used in obe-cel showed that the molecule engaged its target, CD19, with a lower affinity and a faster disengagement than CD19 ScFv (single-chain variable fragment; (b) (4)), the binding domain described by [Imai et al, 2004](#) and reported to be used in other approved CD19 CAR T products, such as axicabtagene ciloleucel, tisa-cel and brexu-cel.

Although other CAR T-cell therapies also target the CD19 pathway, they have different mechanisms of action. The design of brexu-cel, for example, includes a CD28 co-stimulatory domain and the (b) (4) binder to CD19 which is a high affinity binder of CD19 with a slow off-

¹ See BLA 125813/0 Consult Review, dated July 5, 2024.

rate ([Cappell and Kochenderfer, 2021](#)). Brexu-cel has a short persistency in patients with B ALL ([Shah et al, 2021](#)).

Obe-cel is constructed using the 4-1BB costimulatory domain with the novel low affinity CAT binder, CD19 (CAT) CAR. The unique mechanism of action of obe-cel provides a fast off-rate of $3.1 \times 10^{-3} \text{ s}^{-1}$ resulting in a shorter half-life of interaction of 3.7 minutes compared with other binders used in approved CD19 CAR T-cell therapies (e.g. 2.8 hours for the (b) (4) binding domain in tisa-cel) ([Ghorashian et al, 2019](#)). The short interaction between obe-cel with CD19 positive target cells mimics physiological T cell activation and may result in reduced cytokine release and immunotoxicity while preserving robust CAR T expansion and persistency. In synergy with the split dose regimen, this modality of short interaction is intended to attain an improved safety profile. Indeed, this, as well as durability of response and persistency of CAR-T cells, was demonstrated in clinical Phase I studies in both pediatric and adult patients with r/r B ALL ([Ghorashian et al, 2019](#); [Roddie et al, 2021](#); [Roddie et al, 2023](#)).

In vitro studies have demonstrated that CD19 (CAT) CAR T cells proliferate and produce soluble mediators with cytolytic activity when co-cultured with cells expressing CD19. In submitted studies, cytotoxicity and the release of the cytokine TNF- α were statistically significantly greater with T cells expressing CD19 (CAT) CAR T than those expressing the CD19 (b) (4) CAR.

In vivo efficacy studies using a leukemia tumor xenograft mouse model showed tumor control in mice treated with CD19 (CAT) CAR T cells compared to the control group (non-transduced T cells). The tumor burden was lower in the mice treated with CD19 (CAT) CAR T cells compared with those treated with CD19 (b) (4) CAR T cells. At termination of the experiment, mice treated with CD19 (CAT) CAR T cells had a statistically significantly higher absolute number of circulating CAR T cells than those treated with CD19 (b) (4) CAR T cells.

The CD19 scFv (CAT) used in the CAR construct does not cross-react with murine homologs. Therefore, on-target toxicities, like CRS or ICANS, cannot be adequately characterized in animal models.

In accordance with ICH S9 guidance, carcinogenicity studies are not warranted to support products intended to treat advanced cancer and hence such studies were not conducted for obe-cel. The lentiviral vector used to produce obe-cel is based on a SIN vector that lacks viral promoter and enhancer activity in the 3' long terminal repeat, thus limiting the effects of the viral sequences on flanking genes ([Zufferey et al, 1998](#)). No evidence of insertional mutagenesis-induced leukemogenesis or associated long-term toxicities have been observed in cell and gene therapy trials that involve genetic modification of either hematopoietic stem cells or non-dividing T cells, however, in accordance with Health Authority recommendations and guidelines, and to minimize possible insertional mutagenesis, a limit of 5 or fewer vector copies per transduced cell is implemented for final product release of obe-cel.

In accordance with ICH S6 (R1) and ICH S2 (R1) guidance, genotoxicity studies routinely conducted for pharmaceuticals are deemed not appropriate for biotechnology products and hence such studies have not been conducted for obe-cel.

Developmental toxicology studies were not conducted.

A GLP tissue cross reactivity study was undertaken in a panel of 42 different frozen human tissues and blood smears. No unexpected tissue cross reactivity was observed.

Overall, the nonclinical pharmacology and toxicology studies provide experimental evidence that treatment with obe-cel had not only the potential to be efficacious in the treatment of ALL but may confer advantages over other CD19 CAR T cell products approved for this indication.

Additional information on the nonclinical program is provided in Module 2.4, Nonclinical Overview.

The safety of obe-cel is further elucidated in the obe-cel clinical development program, which will also include the long-term follow-up of patients in clinical studies for 15 years.

The FDA's Assessment:

There were no nonclinical deficiencies identified in the pharmacology/toxicology studies. The nonclinical data provided in this BLA submission support the approval of this licensure application. Refer to FDA pharmacology/toxicology review memo for this BLA. To summarize:

In vitro pharmacology studies compared Autolus' CD19-CAR (referred to as CAT19 for nonclinical studies) component of obe-cel to a reference CD19-CAR (referred to as (b) (4) for nonclinical studies). Results showed that co-culture of obe-cel with cell lines expressing CD19 resulted in target-specific killing, secretion of pro-inflammatory-associated cytokines, and proliferation. In comparison to (b) (4) CAR T cells, obe-cel showed significantly greater cytolytic and proliferative capacity.

In vivo pharmacology studies in a systemic human tumor xenograft mouse model demonstrated that a single intravenous administration of obe-cel at a dose level of 2.5×10^6 CAR T cells/animal resulted in significant reduction in tumor burden on Day 12 post-administration compared to mice administered either (b) (4) CAR T cells or non-transduced T cells.

The potential for off-target binding of the CD19-targeted CAT19 scFv binding domain was evaluated for tissue cross reactivity (TCR) against a panel of 42 different frozen human tissues and blood smears. No off-target TCR was observed, and CAT19 binding to CD19 was consistent with the expected distribution of B cells in lymphoid organs.

Conventional toxicology, genotoxicity, and carcinogenicity studies were not performed for obe-cel. No animal reproductive and developmental toxicity studies were conducted for obe-cel, which is acceptable based on the product characteristics.

Reviewer comment: *The preclinical data support the MOA of obe-cel.*

6 Clinical Pharmacology

The Applicant's Position:

The clinical development of obe-cel is based on the pivotal FELIX Phase Ib/II study, which evaluated the safety and efficacy, as well as pharmacokinetics (PK) and pharmacodynamics (PD) of obe-cel following a split-dose infusion that is adapted to disease burden at LD administered on Day 1 and Day 10 (± 2 days) with a total target dose of 410×10^6 CAR-positive viable T cells in adult patients with r/r B ALL. Patients with a high tumor burden ($>20\%$ blasts in bone marrow [BM] at LD) receive a 10×10^6 cell infusion dose on Day 1 and a 400×10^6 cell infusion dose on Day 10 (± 2 days). Patients with a low tumor burden ($\leq 20\%$ blasts in BM within 7 days prior to LD) receive a 100×10^6 cell infusion dose on Day 1 and a 310×10^6 infusion dose on Day 10 (± 2 days) ([Applicant Table 4](#)).

The dosing regimen for obe-cel was primarily based on the initial proof-of-concept study, ALLCAR19 (NCT02935257; [Roddie et al, 2021](#); [Roddie et al, 2023](#)), the benefit of which was confirmed by data in the pivotal FELIX study. Overall, and notwithstanding the inherent design properties of obe-cel, such a fractionated dosing paradigm was introduced to FELIX to minimize the immunotoxicity risk known in CAR T cell therapy, particularly in light of multiple findings in the literature suggesting that administering a single high dose to r/r adult B ALL patients with higher disease burden might lead to excessive immunotoxicity ([Davila et al, 2014](#); [Lee et al, 2015](#); [Turtle et al, 2016](#); [Frey et al, 2019](#)). Additionally, the separation into 2 dose administrations permits the management of the immunotoxicity, or delay or omission of the second dose if significant immunotoxicity develops after the first dose.

Refer to Module 2.7.3 Summary of Clinical Efficacy, Section 4.1 for further details on dosing rationale.

Key features of the FELIX study ([Section 8.1.1](#)), including study design, target patient population, objectives and endpoints as well as statistical considerations, were discussed with the FDA and with the Scientific Advice Working Party/Committee for Medicinal Products for Human Use in the European Union.

Clinical pharmacology data are provided in Module 2.7.2, Summary of Clinical Pharmacology and the AUTO1-AL1 PK/PD Report.

6.1. Expansion and Persistency

Overall, across all infused patients in Cohort IIA of the FELIX study, the pivotal cohort, a rapid and robust expansion of CAR T cells followed by persistency was observed, as quantified through the detection of the obe-cel transgene of the CAR T cells using (b) (4) in peripheral blood and BM following infusion with a median peak expansion being observed at Day 14. This expansion was observed regardless of remission status (complete

remission (CR)/complete remission with incomplete recovery of counts (CRi) vs non-CR/CRi) and was driven by tumor burden (Module 2.7.2, Summary of Clinical Pharmacology, Section 1.3).

As of data cut 13-Sep-2023, of those patients who have ongoing remission, 78.1% (25/32) had ongoing CAR T persistency at the last assessment (Module 2.7.3, Summary of Clinical Efficacy Addendum – Day 30 Update, Section 2.4).

The initial proof-of-concept ALLCAR19 study in which patients were treated with obe-cel using the same fractionated split dose regimen, and which had the opportunity for longer-term follow-up were in line with the PK findings of the FELIX study. The PK profile also demonstrated robust expansion and durable persistency, with all 7 patients in ongoing remission, without additional new therapies, having measurable CAR T cells; the median duration that CAR T cells were still measurable in the blood after infusion was 320 days.

6.2. Factors Influencing Pharmacokinetics

Patients with high disease burden had an increased CAR T cell expansion compared to those with low disease burden. The CAR T cell expansion parameters, maximum concentration (C_{max}) and area under the curve (AUC_{0-28d}), increased progressively as disease burden increased from < 5%, $\geq 5\%$ to $\leq 20\%$, $>20\%$ to $\leq 75\%$ and $>75\%$ BM blasts, respectively (Module 2.7.2, Summary of Clinical Pharmacology, Section 1.4). Generally, EMD is indicative of a higher disease burden in patients with B ALL, and CAR expansion was higher in patients with EMD when compared with patients without EMD. The incidence of CRS and ICANS was higher in the patients with higher disease burden at baseline and at lymphodepletion (LD) and increasing C_{max} and AUC_{0-28d} correlated with an increased odds ratio (OR) of developing CRS or ICANS.

The influence of tocilizumab or corticosteroids on obe-cel PK cannot be ascertained directly because both are generally administered for the treatment of CRS and/or ICANS. Tocilizumab nor corticosteroids appeared to have a direct impact on CAR T cell expansion or persistency, and associated differences in expansion are unlikely to be causal but more likely reflected their use in patients with high disease burden, consistent with other CAR T cell products ([Gardner et al. 2019](#); [Stein et al, 2019](#)).

Previous lines of therapy(ies) and/or response to previous therapy(ies) had a negligible impact on PK parameters.

No apparent differences in CAR T cell persistency were observed across all analyzed subgroups, including patients with and without EMD.

6.3. Pharmacodynamics

In the Infused Set (Cohort IIA, N=94), B cell aplasia was observed in most responding patients and correlated with ongoing CAR T cell persistency.

Overall, small increases in cytokine levels were observed post-infusion by Day 28, with a higher level in patients with CRS and ICANS, as expected. Like other CD19 CAR T cell products, increases

in cytokines overall are expected from the mode of action of obe-cel (Module 2.7.2, Summary of Clinical Pharmacology, Section 1.7). However, when compared to other CD19 CAR T cell products that use the (b) (4) binder, patients treated with obe-cel in the FELIX study had a lower level of cytokines, such as IL-6, consistent with the unique obe-cel binder and the split dose regimen adapted to the disease burden of each patient.

6.4. Dose-Exposure

Most patients (88.3%) infused with obe-cel in Cohort IIA received the total target dose of 410×10^6 cells. The number of patients who did not receive the target dose as per protocol (n=11) is small, and the reasons for not receiving the target dose are heterogenous, therefore it is not feasible to draw firm conclusions on target dose-efficacy or dose-safety relationships.

The dose-exposure relationship needs to be interpreted in the context of tumor burden because it is well established in the literature that a higher tumor burden prior to CAR-T treatment is associated with greater CAR T expansion, more cytokine production and in turn higher rates of immune-mediated toxicities such as CRS and ICANS ([Hay et al, 2017](#); [Santomasso et al, 2019](#)). In the FELIX study that obe-cel CAR T expansion increased with increasing bone marrow blasts prior to lymphodepletion, as discussed in [Section 6.2](#).

Patients who received an initial infusion dose of 10×10^6 cells (high tumor burden regimen; > 20% blasts in BM at LD) had a numerically higher expansion of CAR T cells with a later peak compared to patients who received an initial infusion dose of 100×10^6 cells (low tumor burden regimen; ≤ 20% blasts in BM at LD), suggesting that tumor burden is the main driver of the expansion (Module 2.7.2, Summary of Clinical Pharmacology, Section 1.5).

Despite a numerically higher CAR T cell expansion, the overall response rate (ORR=[CR/CRi]) is numerically lower in patients receiving a first dose of 10×10^6 cells (high tumor burden regimen) compared to those who received a first split dose of 100×10^6 cells (low disease burden regimen), being 75.0% and 87.5%, respectively. The numerically lower ORR is likely a consequence of the higher tumor burden, in line with the expectation that patients with a high disease burden are more difficult to treat.

In terms of expansion-safety relationship, increasing C_{max} and AUC_{0-28d} correlates with an increased OR of developing CRS or ICANS.

Taken together, these data suggest that tumor burden, rather than the number of CAR T cells infused at the first dose of obe-cel, is a major driver for a larger expansion, which in turn may lead to the onset of CRS and ICANS. High disease burden also impacts response to obe-cel and suggests that patients with high disease burden are more difficult to treat. Importantly, despite the robust expansion observed following obe-cel infusion, the incidence of ≥ Grade 3 CRS and ICANS remains low ([Section 8.2.5](#)).

The FDA's Assessment:

Below is a summary of obe-cel pharmacokinetics/pharmacodynamics (PK/PD) data per the Clinical Pharmacology Reviewer:

The clinical pharmacology review focused on Phase 1b Cohort A and Phase 2 Cohort A and for patients who received conforming obe-cel at the target dose of $410 \times 10^6 \pm 25\%$ CAR-positive T cells (N=90).

After administration, obe-cel exhibited a rapid expansion, followed by contraction and persistence. Patients who received obe-cel per the >20% tumor burden regimen (i.e., an initial infusion of 10×10^6 CAR+ T cells, followed by a subsequent infusion of 400×10^6) had higher obe-cel exposure compared to patients who received obe-cel per the $\leq 20\%$ tumor burden regimen (i.e., an initial infusion of 100×10^6 CAR+ T cells, followed by a subsequent infusion of 310×10^6 CAR+ T cells). For both dosing regimens, median T_{max} was achieved after the second obe-cel infusion at Day 14 (Range: Day 2 – Day 55). Persistency of obe-cel was observed up to 36.5 months and 18 months in peripheral blood and bone marrow, respectively. High inter-subject variability was observed for the obe-cel expansion including maximum concentration (C_{max}) and area under the curve (AUC). Tumor burden blasts of >20% appeared to be associated with higher obe-cel expansion.

No evident association was found between obe-cel exposure and efficacy responses: OCR and duration of remission. Compared to patients without CRS, patients who experienced any grade of CRS had 6.8-fold and 5.0-fold higher geometric mean AUC_{0-28d} and C_{max}, respectively. Compared to patients without ICANS, patients who experienced any grade of ICANS had 2.9-fold and 3.3-fold higher geometric mean AUC_{0-28d} and C_{max}, respectively.

B cell aplasia was observed in most patients after infusion of obe-cel. In Phase 2 Cohort A, 93 % of treated patients had B cell aplasia at Month 3 and 80% of patients had B cell aplasia at Month 6 following obe-cel infusion. B cell aplasia appeared to be resolved slowly over time. Serum levels of cytokines such as IL-2, IL-5, IL-6, IL-7, IL-8, IL-10, IL-15, TNF- α , IFN- γ , and granulocyte-macrophage colony-stimulating factors were evaluated. Cytokines levels reach a peak concentration within the first month post infusion and reverted to baseline levels by Month 3. IgG levels were lower than normal clinical range at $37.3 \mu\text{mol/L}$ at baseline and remained low until Month 12 at interim data cutoff date (June 9, 2023).

In Study FELIX all cohorts, 11 out of 127 (8.7%) patients who received obe-cel treatment, tested positive for humoral immunogenicity at baseline. All but one patient test negative post-infusion. One patient with pre-existing antibodies had positive humoral immunogenicity at Day 28 of post-infusion. However, the anti-drug antibodies (ADA) titers in this patient were substantially lower post-infusion. After administration of obe-cel, 2 out of 127 (1.6) patients were positive for humoral immunogenicity at Month 3 post-infusion. Positive cellular immunogenicity findings observed in 3 out of 75 (4%) patients at the Month 3 visit (IFN- γ).

Humoral and cellular immune responses against obe-cel did not show significant impact on clinical outcomes.

No evaluable subjects were positive for replication-competent lentivirus (RCL) testing at the time of interim data cutoff date (June 9, 2023)

***Reviewer Comment:** The analyses performed by the Clinical Pharmacology Reviewer were based on the updated analysis per FDA’s adjudication of efficacy and safety.*

7 Sources of Clinical Data

7.1. Table of Clinical Studies

Data:

A pivotal study was initiated in 2020, which is the basis of the submitted BLA (FELIX study; NCT04404660) ([Applicant Table 3](#)).

The primary and important secondary endpoints were met in the FELIX study ([Section 8.1.2](#)).

Applicant Table 3 Listing of Clinical Trials Relevant to this BLA

Trial Identity	NCT no.	Trial Design	Regimen/ schedule/ route [1]	Study Endpoints	Treatment Duration/ Follow Up	No. of patients enrolled	Study Population	No. of Centers and Countries
Studies to Support Efficacy and Safety								
AUTO1- AL1 (FELIX); ongoing	NCT04404660	Phase Ib/II, single-arm, open-label, multi-center	<p>Split dose infusion adapted to tumor burden of AUTO-1 (obe-cel) on Day 1 and Day 10 (± 2 days).</p> <p>Patients with $>20\%$ blasts in BM at LD receive a 10×10^6 cell infusion on Day 1 and a 400×10^6 cell infusion on Day 10 (± 2 days).</p> <p>Patients with $\leq 20\%$ blasts in BM at LD receive a 100×10^6 cell infusion on Day 1 and a 310×10^6 infusion on Day 10 (± 2 days).</p>	<p>Primary efficacy for Cohort A in Phase II (Cohort IIA): ORR (CR + CRi)</p> <p>Selected secondary efficacy for Cohort IIA:</p> <ul style="list-style-type: none"> • CR any time • CR within 3 months • DOR <p>Primary safety: Safety and tolerability of AUTO1 (obe-cel) as assessed by AEs, SAEs, other significant AEs in all treated patients</p> <p>PK: The expansion and persistency of AUTO1 (obe-cel)</p> <p>Quality: The feasibility of manufacturing and administering AUTO1 (obe-cel)</p>	<p>Split dose infusion adapted to tumor burden administered on Day 1 and Day 10 (± 2 days).</p> <p>Subjects followed up until the EOS (last patient last visit [expected to be at Month 24])</p> <p>Once last patient completed 24 months or discontinued (FELIX study completed), long-term extension follow up of up to 15 years post-infusion</p>	153 (approx. 145 planned) 127 treated	<p>Adults aged ≥ 18 years with r/r B ALL</p> <ul style="list-style-type: none"> • Cohort A: morphological disease ($\geq 5\%$ blasts in BM at screening) • Cohort B: morphological remission ($<5\%$ blasts in BM at screening), but MRD-positive at Screening [2] • Cohort C: isolated EMD at screening, with or without MRD <p>Cohorts A and B were enrolled in Phase Ib and Phase II of the study, Cohort C was only enrolled in Phase II.</p>	34 centers, 3 countries (US, Spain and UK)

BLA 125813/0 Clinical Review and Evaluation
AUCATZYL (obecabtagene autoleucel)

Supportive Studies from the Literature								
ALLCAR19 (academic- led proof- of- concept study); ongoing	NCT02935257	Phase I multi-center, non-randomized, open label	<p>Split dose infusion of AUTO-1 (obe-cel) on Day 0 and Day 9 [3]</p> <p>Patients with >20% blasts in BM receive a 10×10^6 cell infusion on Day 0 and a 400×10^6 cell infusion on Day 9.</p> <p>Patients with $\leq 20\%$ blasts in BM receive a 100×10^6 cell infusion on Day 0 and a 310×10^6 infusion on Day 9 (± 2 days).</p>	<p>Primary:</p> <p>Toxicity evaluated by the incidence of grade 3-5 toxicity causally related to the AUTO-1 [Time Frame: 28 days]</p> <p>Feasibility of manufacturing CD19CAR T-cells evaluated by the number of AUTO-1 products generated [Time Frame: 30 days]</p> <p>Secondary:</p> <p>AUTO-1 expansion and persistence</p> <p>ORR (CR + CRi), EFS, OS</p>	Split dose infusion administered on Day 1 and Day 9.	r/r B ALL cohort: 25 enrolled 20 treated (as of 15-Sep-2022)	Patients aged ≥ 16 years with r/r B ALL (median 3 lines previous therapy)	3 centers in the UK

Abbreviations: AE = Adverse event; B ALL = B cell acute lymphocytic leukemia; BM = Bone marrow; CNS = Central nervous system; CR = Complete remission; CRi = Complete remission with incomplete recovery of blood counts; DOR = Duration of remission; EFS = Event free survival; EMD = Extramedullary disease; EOS = End of study; LD = lymphodepletion; MRD = Minimal residual disease; obe-cel = Obecabtagene autoleucel; OS = Overall survival; PK = pharmacokinetics; UK = United Kingdom; US = United States of America.

[1] Regimen, schedule, route in proposed USPI.

[2] The MRD-negative definition for Cohort B was $\geq 10^{-4}$ and < 5% blasts in the BM for Phase Ib and $\geq 10^{-3}$ and < 5% blasts in the BM for Phase II). In addition, patients in Phase II had to be \geq second CR or CRi.

[3] ALLCAR19 used a split dose infusion regimen with the same interval length between doses used in FELIX.

The FDA's Assessment:

FDA agrees with the Applicant listing of the FELIX study which is relevant to this submission. However, the results from Study ALLCAR19 were not considered in the BLA review. FDA informed the Applicant during the type B initial RMAT meeting that for a BLA submission: (1) trials to support efficacy must have used the to-be-marketed formulation (or one established as comparable), (2) the Applicant must have the right of reference to all submitted efficacy data, and (3) patient-level datasets must be included with the BLA submission. Literature results alone are not sufficient for regulatory consideration.

7.2. Review Strategy

The FDA's Assessment:

FELIX Study served as the primary basis for the clinical review. The key material used in the review of the efficacy and safety includes:

- BLA 125813/0 submission
- Prior regulatory history
- Applicant's response to the review team's several IRs
- Proposed labeling
- Relevant published literature
- Safety and efficacy analyses were performed using JMP 17.2 (SAS Institute, Inc.) and Medical Dictionary for Regulatory Activities (MedDRA) Adverse Events Diagnostic (MAED) v4.2 (FDA, Silver Spring, MD).

The original BLA submission was based on a data cutoff date of June 9, 2023. On Day 30 of the BLA submission, the Applicant submitted updated efficacy and safety data and updated proposed United States Prescribing Information (USPI) as per new data cut-off date of September 13, 2023. The later data cut-off date of September 13, 2023, was used for all FDA analyses as it reflected longer follow-up.

Efficacy:

The determination of efficacy was based primarily on the analysis of data submitted for the 65 patients who were enrolled and treated in FELIX Phase 2 Cohort A study and who had documented morphologic disease (BM blast $\geq 5\%$) at baseline post-bridging therapy. FDA efficacy-evaluable population excluded six patients who received OOS (i.e., non-conforming) products. Data from the remainder of the patients treated on FELIX Phase 1b Cohort A and Cohort B and Phase 2 Cohort B and Cohort C are supportive.

Safety:

The safety analysis set included all patients who received at least one infusion of obe-cel at a target dose of 410×10^6 anti-CD19 CAR T cells, which is the proposed dose. The safety analysis set consisted of 100 patients (13 patients from the Phase 1b Cohort A portion of the study and 87 patients from the Phase 2 Cohort A) who received the conforming product (7 patients were excluded who received OOS products). Data from the remainder of the patients in Phase 1b Cohort B and Phase 2 Cohort B and Cohort C are supportive. Details of the approach to the review of safety are described in Section [8.2.1](#).

8 Statistical and Clinical Evaluation

8.1. Review of Relevant Individual Trials Used to Support Efficacy

8.1.1. AUTO1-AL1 (FELIX)

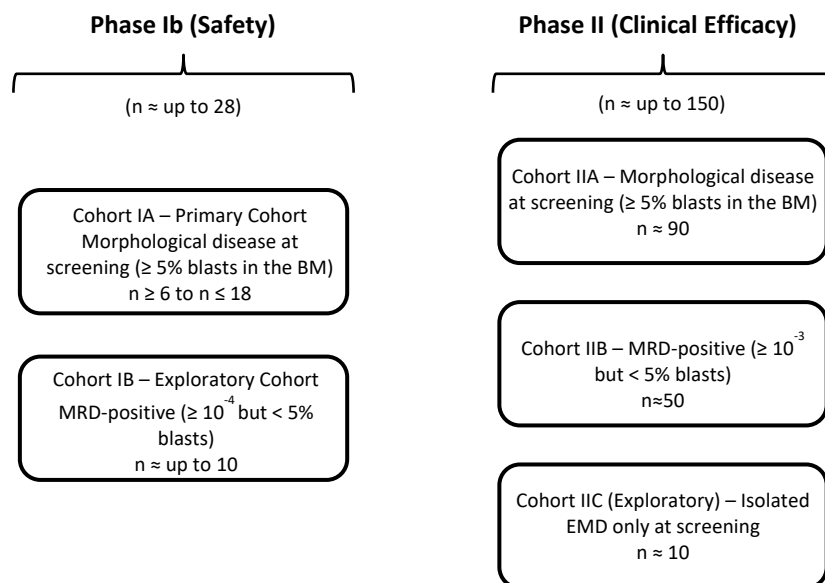
The original BLA was based on a data cutoff date of 09-Jun-2023. This Clinical Assessment Aid and all data presented within, unless otherwise specified, reflect the aggregated data obtained as of the 13-Sep-2023 data cut-off date.

The remission data in the 09-Jun-2023 and 13-Sep-2023 data is the same. The updated data provided more mature data (an additional 3-month follow-up) for time to event outcomes such as duration of remission (DOR), event-free survival (EFS) and overall survival (OS).

The Applicant's Description:

The FELIX study is a single-arm, open-label, multi-center, multi-national, Phase Ib/II study in adult patients with r/r B ALL (Module 2.7.3 Summary of Clinical Efficacy, Section 1.3.2). Long-term follow-up of patients in the study is ongoing. In the study there are 2 phases (Phase Ib and II) and 3 cohorts of patients with different disease characteristics (Cohorts A, B and C), [Applicant Figure 1](#). Cohort A in Phase II (referred to as Cohort IIA) is the pivotal cohort on which efficacy of obe-cel is based.

Applicant Figure 1 Trial Design



Lymphodepletion: Fludarabine / cyclophosphamide (Days -6, -5, -4, -3)

Obe-cel treatment: All patients were to receive the target dose of 410×10^6 CD19 CAR-positive T cells, administered as a split dose, based on disease burden.

BM = Bone marrow; EMD = Extra medullary disease; MRD = Minimal residual disease

Phase Ib was comprised of 2 cohorts (Cohort IA and IB; [Applicant Figure 1](#)) designed to assess the feasibility of manufacturing and dosing of obe-cel in a multi-center setting and provide data to enable initiation of the pivotal phase of the study, Phase II, which evaluated efficacy and safety of obe-cel in 3 cohorts (Cohort IIA, IIB and IIC).

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

The LD conditioning regimen aimed to enhance treatment efficacy by eliminating regulatory T cells and increasing access of the CD19 CAR T cells to activating cytokines, thus increasing CAR T cell survival and likelihood of anti-tumor efficacy.

The total target dose of obe-cel for patients in all cohorts was 410×10^6 CD19 CAR-positive T cells, which was administered using the split dosing regimen based on the patient's tumor burden (% blasts in BM at LD), as shown in [Applicant Table 4](#) and described in [Section 6](#).

Applicant Table 4 2-Step Obe-Cel Dose Regimen Based on Bone Marrow Blast Counts at Lymphodepletion

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

BM = Bone marrow; CAR = Chimeric antigen receptor.

Patients with Grade 2 CRS and/or Grade 1 ICANS following the first split dose may have received the second dose on Day 10 (± 2 days) up to Day 21, only if CRS had resolved to Grade 1 or less and ICANS had completely resolved. A second split dose was not administered if ≥ Grade 3 CRS, ≥ Grade 2 ICANS and/or ≥ Grade 3 pulmonary or cardiac toxicities were observed following the first split dose.

One futility and one interim efficacy analysis were pre-planned and have been performed for Cohort IIA. The primary analysis occurred when at least 90 patients in Cohort IIA had been followed up for at least 6 months post obe-cel infusion or discontinued from the study. Clinical efficacy of obe-cel has been demonstrated on data from 94 patients who received at least one dose of obe-cel in Cohort IIA and were followed up for at least 6 months or discontinued early.

The FDA's Assessment:

FELIX is a Phase 1b/2 open-label, multicenter, multiregional (U.S. United Kingdom, and Spain) single-arm study evaluating the safety and efficacy of obe-cel in adults with r/r B ALL.

Eligibility: Eligible patients were 18 years of age or older with r/r B ALL, defined as one of the following: primary refractory disease, first relapse if first remission was ≤12 months, r/r disease after 2 or more lines of systemic therapy, or r/r disease after allogeneic stem cell transplant (allo SCT) provided the patient was at least 3 months after transplant at the time of enrollment, without active GvHD, and off of systemic steroids or other immunosuppressive medications for at least 4 weeks prior to enrollment. Patients in Cohorts A from Phase 1b and 2 were required to have morphological disease in the BM (≥5% blasts) at the time of screening.

Patients with Philadelphia chromosome (Ph)+ disease were eligible if they were intolerant to or had failed two lines of any tyrosine kinase inhibitor (TKI) or one line of second generation TKI, or if TKI therapy is contraindicated. In patients previously treated with blinatumomab, CD19 tumor expression on blasts must have been documented after completion of the most recent prior line of therapy. Patients with CNS-1 disease (no detectable leukemia in the cerebrospinal fluid [CSF]) and those with CNS-2 disease (defined as detectable cerebrospinal blast cells in a sample of CSF with <5 white blood cells [WBCs] per mm³) without clinically evident neurological changes were eligible to participate in the study. Patients with CNS-2 disease with neurological changes and patients with CNS-3 disease (defined as detectable cerebrospinal blast cells in a

sample of CSF with ≥ 5 WBC per mm^3) with or without neurological changes were excluded. Patients with B ALL with isolated EMD were excluded from Cohorts A and B in the Phase 1b and 2 study.

Treatment: FDA agrees with the Applicant's description of treatment. Patients were enrolled in the study when they underwent leukapheresis. Patients received a split dose infusion of obe-cel based on disease burden prior to LD (bone marrow assessment to be performed within 7 days prior to LD). The main analyses of efficacy and safety are based on outcomes following obe-cel treatment.

Monitoring: Efficacy, PK/PD, safety, and biomarker assessments are provided in the Schedule of assessment [FDA Table 38](#) in Section [18.4](#).

For efficacy, patients were to be evaluated for disease response by performing bone marrow, peripheral blood and EMD assessments at the times indicated in the schedule of assessments (see [FDA Table 38](#)). Disease response was evaluated by an IRRC using the overall disease response classification as shown in [FDA Table 40](#) in Section [18.6](#) and included assessments of peripheral blood, bone marrow evaluations, as well as imaging for patients with known non-CNS EMD at baseline. Following initial establishment of response (CR or CRi), patients should be assessed for recurrence of the disease starting at least 4 weeks after onset of CR/CRi. Patients were considered continuing in CR/CRi if there was no clinical evidence of relapse as assessed by peripheral blood (percent of blasts) and EMD assessment (physical exam and CNS symptom assessment). Invasive procedures, including bone marrow assessments, were not mandated after the initial achievement of CR or CRi unless clinically indicated. If additional assessments were performed (e.g., bone marrow, CSF assessment by LP, CNS imaging, biopsy, etc.), they needed to support the remission status.

Patients were to be hospitalized for 10 days following the first obe-cel infusion (or longer if necessary), for monitoring and management of CRS, tumor lysis syndrome (TLS), and neurotoxicity. Once discharged, patients were instructed to monitor for signs and symptoms of fever or change in neurological behavior for 4 weeks after the first obe-cel infusion, and then at the investigator's discretion. Safety assessments included monitoring of AEs and concomitant medications, clinical laboratory analyses, vital signs measurements, neurological assessments, electrocardiogram, echocardiogram, physical examinations, and testing for replication competent lentiviruses (RCL) and antibodies to the anti-CD19 CAR. All patients were eligible to be enrolled onto a separate long-term follow-up to monitor for AESIs including secondary malignancies and insertional mutagenesis.

Schedule of Efficacy Assessments: Patients were to be evaluated for first disease response assessment at the end of Month 1 following first obe-cel infusion, then as per the Schedule of Assessments (see Appendix Section [18.4](#)). The assessment period for efficacy (to have all components of disease assessments as part of the same overall response evaluation in each timepoint) is defined as having all efficacy assessments (e.g., bone marrow morphology, blood

counts, EMD assessment) in a window of ± 2 weeks. If patients achieve initial response defined as either CR or CRi, additional assessments did not mandate to have all components of disease assessments to be performed during a specific window.

Study Efficacy Endpoints

The Applicant's Description:

The primary and secondary endpoints of the pivotal Cohort IIA are summarized in [Applicant Table 5](#) and detailed in Module 2.7.3 Summary of Clinical Efficacy, Section 1.3.5. The disease response was assessed by an Independent Response Review Committee (IRRC) and based on the ALL response criteria adapted from the National Comprehensive Cancer Network (NCCN) guidelines ([NCCN Guidelines, 2019](#)) and agreed with IRRC prior to the start of the pivotal cohort.

The primary efficacy endpoint for the pivotal Cohort IIA is overall remission rate (ORR [CR = CRi]). The Applicant acknowledges that the proportion of patients with CR within 3 months of obe-cel infusion is important for regulatory decision making, therefore the Sponsor has formally tested this endpoint along with ORR and CR at any time, as outlined in the statistical analysis plan section.

Applicant Table 5 Primary and Secondary Endpoints

Primary
ORR defined as proportion of patients achieving CR or CRi as assessed by an IRRC.
Secondary
CR at any time post obe-cel infusion as assessed by an IRRC
CR within 3 months post obe-cel infusion as assessed by an IRRC
Proportion of patients achieving MRD-negative remission in BM at 10^{-4} level
DOR, defined as duration from the date of achieving CR/CRi post obe-cel infusion to the date of relapse or death due to any reason
DOCR, defined as duration from the date of achieving CR post obe-cel infusion to the date of relapse or death due to any reason
EFS, defined as duration from first obe-cel infusion to the earliest of treatment failure, relapse, or death [1]
OS calculated from the date of first obe-cel infusion to the date of death. Patients still alive were censored at the date of last contact (clinic visit or telephone contact).
BOR as assessed by the Investigators
Proportion of patients undergoing SCT prior to leukemia relapse
Proportion of patients in CR/CRi without SCTs or other subsequent therapies at 6, 12 and 24 months following obe-cel infusion
Frequency and severity of AEs and SAEs
Proportion of enrolled patients for whom an obe-cel product can be manufactured and administered
Detection of CAR T cells measured by (b) (4) in the peripheral blood and BM following obe-cel infusion
Depletion of circulating B cells assessed by (b) (4) in the peripheral blood
Changes over time in symptom, functioning and quality of life scores in the EQ-5D and EORTC instruments
Frequency and duration of hospitalization and/or critical care support to manage obe-cel related toxicity

AE=Adverse event; BOR=Best overall response; BM=Bone marrow; CAR=Chimeric antigen receptor; CR=Complete remission; CRi=Complete remission with incomplete recovery of blood counts; DOCR=Duration of complete remission; DOR=Duration of remission; EFS=Event-free survival; EQ-5D-5L= EuroQoL 5 dimension 5 level; EORTC=European Organisation for Research and Treatment of Cancer; IRRC=Independent Response Review Committee; MRD=Minimal residual disease; ORR=Overall response rate; OS=Overall survival; (b) (4) ; SAE=Serious adverse event; SCT=Stem cell transplantation.;

[1] Progression Free Survival (PFS) is also included in the SAP; however, the definition is synonymous with EFS and so only EFS is presented.

The final design and analysis of the endpoints in the FELIX study are outlined in the FELIX clinical study protocol, version 9.0.

The FDA's Assessment:

For the purposes of regulatory decision-making, FDA has accepted CR within 3 months from infusion of CAR T cell therapy and durability as a measure of clinical benefit. The endpoint was prespecified as a key secondary endpoint in the protocol with hierarchical testing. See Section 8.1.3 for further discussion.

Statistical Analysis Plan and Amendments

The Applicant's Description:

The initial version of the statistical analysis plan (SAP) for the FELIX study was finalized 20 Dec-2019. The SAP was amended in Dec-2020 to align with FELIX protocol, version 5.0, and again in Feb-2022 to align with FELIX protocol, version 7.0. Regulatory consultation was sought during the Type B Regenerative Medicine Advanced Therapy (RMAT) Multidisciplinary Meeting with FDA in Jul-2022, followed by a Type B written response on estimands received in Sep- and Oct-2022.

Based on the feedback received, the pre-planned interim efficacy analysis was documented in the Efficacy Interim and Primary Analysis SAP, version 1.0 (dated 26-Oct-2022). Subsequently the additional details of the primary analysis for the FELIX clinical study report included in the BLA and the Day 30 Update was documented in the Efficacy Interim and Primary Analysis SAP, version 2.0 (dated 28-Jul-2023), together with the SCE SAP (version 1.0, dated 22-Feb-2023).

The statistical analysis plans and amendments outlined above were reflected in the FELIX protocol version 9.0.

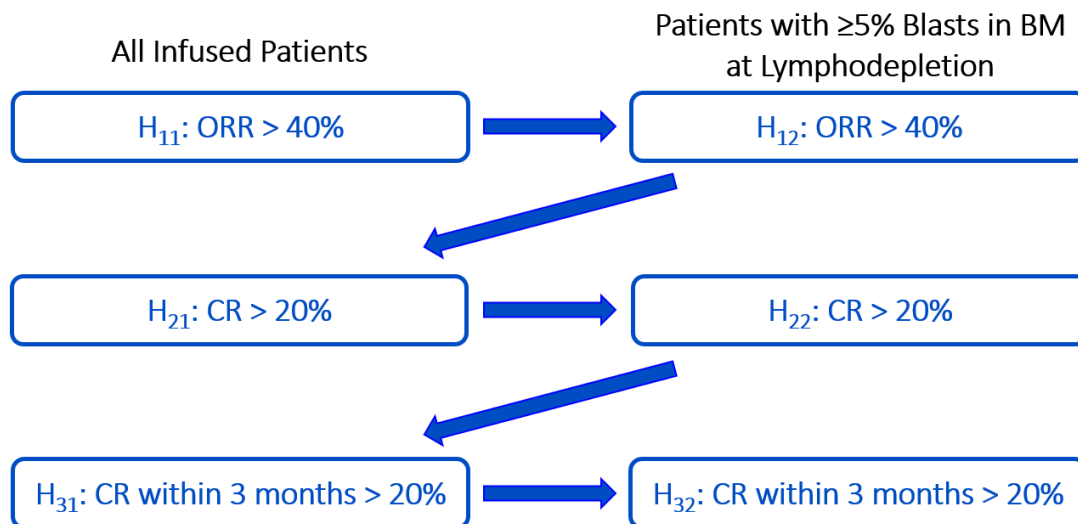
Because of the uniqueness of autologous CAR T manufacturing period prior to treatment, multiple analysis sets are defined for the FELIX study to evaluate the results, including:

- The Enrolled Set comprises all patients who are enrolled in the study (i.e. meets all inclusion/exclusion criteria, leukapheresate is accepted for manufacturing), and will be used for the intent to treat (ITT) analysis.
- The Infused Set comprises all patients who have received at least one infusion of obe-cel, and will be used to evaluate the treatment effect after obe-cel infusion.
- Following FDA recommendation, results were also presented for the sub-population of patients with $\geq 5\%$ blast in BM at lymphodepletion.

The focus of the efficacy summary is the Infused set and the important subpopulation of patients with $\geq 5\%$ blast in BM at lymphodepletion in Cohort IIA, following the discussion with FDA. The primary efficacy endpoint and two secondary endpoints were tested hierarchically at a one-sided 2.5% level of significance for 3 endpoints (ORR, CR, and CR within 3 months) in these 2 populations ([Applicant Figure 2](#))

Pooled analyses from other cohorts and phases were included as supportive analysis, particularly those patients with $\geq 5\%$ blast in bone marrow at lymphodepletion from any cohorts in both Phase Ib and Phase II.

Applicant Figure 2 Hypothesis Testing Hierarchy for Cohort IIA



Sample Size and Power Estimation for Overall Response Rate

In the Phase III TOWER study of blinatumomab versus standard of care chemotherapy the ORR (CR/ complete remission with partial hematologic recovery [CRh]) within 3 months of starting treatment was 42% [95% CI 37 to 49] and that of standard of care chemotherapy was 20% [95% CI 14 to 28] ([Blincyto USPI, 2017](#)).

Considering this, the primary efficacy analysis for Cohort IIA was performed by testing whether the ORR is $\leq 40\%$ against the alternative hypothesis that ORR is $> 40\%$ at an overall one-sided 2.5% level of significance.

The 94 patients in the Infused Set provide $> 94\%$ power to demonstrate statistical significance at a one-sided 2.5% level of significance, if the underlying ORR is 60%.

Sample Size and Power Estimation for Complete Response

An important secondary efficacy analysis for the FELIX Study Cohort IIA was performed by testing whether the CR rate after obe-cel infusion is $\leq 20\%$ against the alternative hypothesis that CR rate is $> 20\%$ at an overall one-sided 2.5% level of significance. Considering a heterogenous and heavily pretreated patient population in the FELIX study, the threshold of 20% is both relevant and clinically meaningful for endpoints of CR at any time and CR within 3 months. This threshold of 20% lies in between the CR rate of blinatumomab (34%) and the CR rate achieved with SOC chemotherapy (16%) for patients treated in the Phase 3 TOWER study ([Kantarjian et al, 2017](#)). The 94 patients in the Infused Set will provide $> 88\%$ power to demonstrate statistical significance with an overall one-sided 2.5% level of significance, if the underlying CR rate is 35%.

The FDA's Assessment:

FDA considers the question of interest as whether LD + CAR T cells ("the treatment") is effective in the treatment of patients with r/r B ALL. The population and treatment plan should allow isolation of the effect of LD chemo + CAR T cells in a single-arm trial; patients who receive bridging therapy may respond prior to receiving CAR T cells and therefore, FDA's primary efficacy population comprises patients who had evidence of disease (i.e., BM blasts >5%) prior to LD not at enrollment and were treated with obe-cel. If prior bridging therapy were included, it would constitute an additional component in a combination therapy and a randomized trial would be required to determine the treatment effect of LD chemo + CAR T cells. Therefore, the population of interest for the primary analysis is patients who were treated with at least one administration of obe-cel and who had >5% blasts in the BM at start of LD chemotherapy (not at enrollment).

The interim analysis (both futility and efficacy) was based on OCR instead of FDA's recommended primary endpoint of CR rate within 3 months. However, the study was not stopped upon interim analysis. All patients treated with obe-cel continued to be followed-up according to the protocol requirements. The BLA submission was based on data as of the pre-specified primary analysis that was triggered when at least 90 patients in Cohort 2A had reached 6 months follow-up after obe-cel infusion or discontinued prior. The data cutoff was Jun 9, 2023. However, FDA agreed to use the 3-month updated data (cutoff date of September 13, 2023) in order to incorporate longer follow-up data.

Data Quality and Integrity

The Applicant's Position:

All data were collected via an electronic case report form (CRF) system, and source document verification of CRF data was performed at regular intervals during the study. Protocol adherence, accuracy, and consistency of study conduct and data collection with respect to local regulations was confirmed. Investigators assured cooperation and compliance with the monitoring visits. Site audits were to include an inspection of the facility(ies); review of subject and study-related records; and compliance with protocol requirements, ICH/GCP, and applicable regulatory policies. Additional information is provided in Module 5.3.5.2 - FELIX Interim Clinical Study Report, Section 10.2.

The FDA's Assessment:

For the purposes of disease, BM morphology is used for assessing the blast percentage and not (b) (4). The review team noted that some BM results were not performed by morphology. FDA requested that the Applicant resubmit the FAPRSP and ADSLSP datasets to include the data elements based on BM aspirate and trephine biopsy at all time points for all

study patients. The updated data are based on the information obtained from the source reports and not from the case report forms.

Reviewer comment: All BM assessments (a total of 737 timepoints) reported for all infused patients as of the data cutoff date of September 13, 2023, (SN0003, 15-Dec-2023) were reviewed and corrections were made for the identified discrepancies. Such discrepancies include: (b) (4) results reported as morphology results, BM aspirate results reported as BM trephine results, or vice versa. Based on the Applicant's response to IR and updated datasets which corrected the discrepancies, there was no impact on conclusions due to the errors in entering (b) (4) results rather than morphology results for the BM blast percentage.

After FDA's adjudication of all efficacy and safety data, FDA requested that the Applicant submit new datasets that reflect FDA's adjudication (e.g., FDA efficacy and safety population, adjudicated responses, fatal adverse reactions, AEs per FDA grouped terms, PK/PD data, etc.). See [FDA Table 4](#) in Section [3.2](#) for details on the submitted datasets. The FDA-adjudicated responses and safety were used for FDA's analyses of efficacy and safety respectively.

Protocol Amendments

The Applicant's Description:

The original protocol was dated 04 November 2019. Changes to amendments earlier than protocol version 3.0 were made prior to the enrollment of any patients in FELIX. All patients in the pivotal Cohort IIA were consented to participate in the study after protocol version 6.0.

The major changes across 9 versions of the FELIX protocol were:

- Added health care resource utilization for the management of obe-cel related toxicity (Version 3.0)
- Patients with > Grade 3 toxicity involving heart and lungs excluded from study and stopping criteria revised (Version 4.0)
- New cohort (Cohort IB) of patients in morphological remission with MRD-positive disease ($\geq 10^{-4}$ and >5% blasts in BM) was included in Phase Ib to assess safety of obe-el and gather early data in this patient population (Version 5.0)
- Central laboratory testing for B cell aplasia and modify the management of bridging therapy (allowance of inotuzumab ozogamicin) (Version 6.0)
- Cohort IIB was expanded to include more patients with MRD-positive disease and Cohort IIC was added specifically for patients, B ALL with isolated EMD (including isolated CNS disease), and 50 patient efficacy interim analysis for Cohort IIA was added (Version 7.0)

- Phase II (Cohort IIB) (b) (4) screening cut-off for MRD-positive definition changed from 10^{-4} to 10^{-3} and central (b) (4) testing at enrollment was mandated per FDA request (Version 8.0)
- Hypothesis testing added with addition of 2 secondary endpoints for Cohort IIA, CR (any time) and CR within 3 months, DOCR added as a secondary efficacy endpoint and RFS removed from analysis (Version 9.0)

The FDA's Assessment:

FDA agrees. See Section [8.1.1](#) regarding the definition of CRi which was revised in protocol V.5.

8.1.2. Study Results

Compliance with Good Clinical Practices

Data:

Autolus' Quality Assurance group conducted 5 compliance audits of investigator sites during the study. Site audit certificates are provided in the FELIX study report submitted with the BLA.

The Applicant's Position:

The FELIX study conducted in the AUTO-1/obe-cel B ALL development program met International Council for Harmonisation (ICH) Good Clinical Practice (GCP) guidelines. For studies conducted under a US investigational new drug application, investigators were required to ensure adherence to the basic principles of GCP as outlined in US Code of Federal Regulations (CFR) Title 21, Part 312 (21CFR312), as well as other local legislation.

The FDA's Assessment:

The submission was adequately organized and integrated to accommodate the conduct of a complete clinical review without unreasonable difficulty.

Bioresearch Monitoring (BIMO) inspection assignments were issued for four clinical investigator study sites (two foreign sites and two domestic sites) that participated in the conduct of FELIX study. The sites were selected based upon Applicant-reported deaths, AEs, protocol deviations, number of patients enrolled, and previous BIMO inspection histories.

Overall, the inspections verified the data reported in the BLA, including but not limited to patient eligibility, protocol deviations, study drug administration, primary efficacy endpoint, and adverse events for all patients enrolled at the inspected clinical sites. No Form FDA 483 was issued for four sites. No significant BIMO inspectional findings were noted. The below [FDA Table 5](#) summarizes site information and outcomes from the BIMO inspections.

FDA Table 5. FDA Bioresearch Monitoring Inspection Summary

Site ID	Firm Name and Location	FDA Form 483 Issued	Final Inspection Classification
GB01	Claire Roddie, PhD, FRCPath, MRCP, MBChB University College London Hospital NHS Foundation Trust 235 Euston Road London, England, United Kingdom, NW1 2BU	No	No Action Indicated (NAI)
GBO6	Eleni Tholouli, MD, PhD, FRCPath, MRCP, MBChB The Manchester University NHS Foundation Trust Manchester Royal Infirmary, Oxford Road Manchester, England, United Kingdom M13 9WL	No	NAI
US17	Paul Shaughnessy, MD TTI-Methodist (Texas Transplant Institute) 8026 Floyed Curl Drive San Antonio, Texas 78229	No	NAI
US11	Karamjeet Sandhu, MD City of Hope National Medical Center 1500 East Duarte Road Duarte, California 91010	No	NAI

Source: FDA BIMO Reviewer

Financial Disclosure

The Applicant's Position:

Autolus has adequately disclosed financial interests/arrangements with clinical investigators in accordance with the regulatory guidance. Financial certification and disclosure information was submitted under Financial Certification and Disclosure for investigators involved in FELIX study. Additional details are provided in the FELIX clinical study report.

The FDA's Assessment:

See Section [18.2](#) for details.

Patient Disposition

Data:

A total of 217 adult patients with r/r B ALL were screened, and 153 patients were enrolled in the FELIX study at 34 sites across the United States (23 sites), Spain (3 sites) and the United Kingdom (8 sites). Thirty-two of these sites screened at least 1 patient, 31 sites enrolled at least 1 patient, and 30 sites dosed at least 1 patient.

A total of 153 patients were enrolled across all cohorts in both phases of the FELIX study. Of these enrolled patients, 127 (83.0%) patients were infused with at least 1 dose of obe-cel (all cohorts and both Phase Ib and Phase II), who are the focus of the safety evaluation, and 94 patients were infused in Cohort IIA, who are the focus of the efficacy evaluation.

Twenty-six patients (17.0%) were not infused. Reasons for not receiving any dose of obe-cel included death (15 patients, 9.8%), manufacturing related issues (7 patients, 4.6%), AE (2 patients, 1.3%), physician decision and progressive disease (1 patient each, 0.7%).

A total of 59 of 127 infused patients (38.6%) in all cohorts discontinued from the study after infusion as of 13-Sep-2023, most of them due to death (56 patients, 36.6%). A high proportion of these deaths occurred due to progressive disease (40 patients). One patient (0.8%) withdrew from the study, and another patient (0.8%) recorded as “other” on the CRF discontinued due to progressive disease.

Of 112 patients enrolled in the pivotal Cohort IIA, 94 patients (83.9%) received at least 1 infusion of obe-cel. Eighteen patients (16.1%) were not infused. Reasons for not receiving an obe-cel infusion included death (11 patients, 9.8%), manufacturing related issues (5 patients, 4.5%), AE and physician decision (1 patient each, 0.9%). Forty-seven patients (42.0) discontinued the study after infusion. Reasons included death (44 patients, 39.3%; most of them [31 patients] due to progressive disease, withdrawal by patient (1 patient, 0.9%) and “other” (1 patient, 0.9%, see paragraph above).

There is approximately 50% of infused patients in Cohort IIA ongoing in the study as of 13-Sep-2023 data cut off. The overall median duration of follow-up from the first infusion was 15.43 months (range 7.9 to 24.9 months) for patients in Cohort IIA. Sixty-nine percent of patients in Cohort IIA had a follow-up time of ≥ 12 months. Across all cohorts and both phases of the study, the median duration of follow-up is 16.62 months (range 3.7 to 36.6 months)

For further details see 2.7.3 Summary of Clinical Efficacy, Addendum – Day 30 Update, Section 2.2 and Module 2.7.3 Summary of Clinical Efficacy Addendum – Day 30 Update, Section 2.1.

The FDA’s Assessment:

Summary of FDA analysis population sets is presented in [FDA Table 6](#) below. The primary efficacy population included patients from the Phase 2 Cohort A portion of FELIX study who had evidence of morphologic disease ($>5\%$ blasts in BM) at baseline prior to LD and who received at least one infusion of obe-cel. The safety analysis set included patients from the Phase 1b Cohort A and Phase 2 Cohort A who were treated with at least one obe-cel infusion. Patients who received out of specification obe-cel (i.e., non-conforming products) were excluded from the primary efficacy and safety population but were included in the all leukapheresed population (i.e., ITT analysis). Specifically, 6 out of 71 patients from the Applicant’s efficacy population (Phase 2 Cohort A) and 7 out of 107 patients (from Phase 1b/2 Cohorts A) were excluded from FDA’s analysis.

At the time of the data cutoff date of September 13, 2023, out of the 65 efficacy-evaluable patients in Cohort 2A, 30 were still ongoing and 35 had discontinued. Among the 35 patients who discontinued, the most frequent reason was due to death (n=32).

FDA Table 6. FELIX: Key Analysis Population Sets*

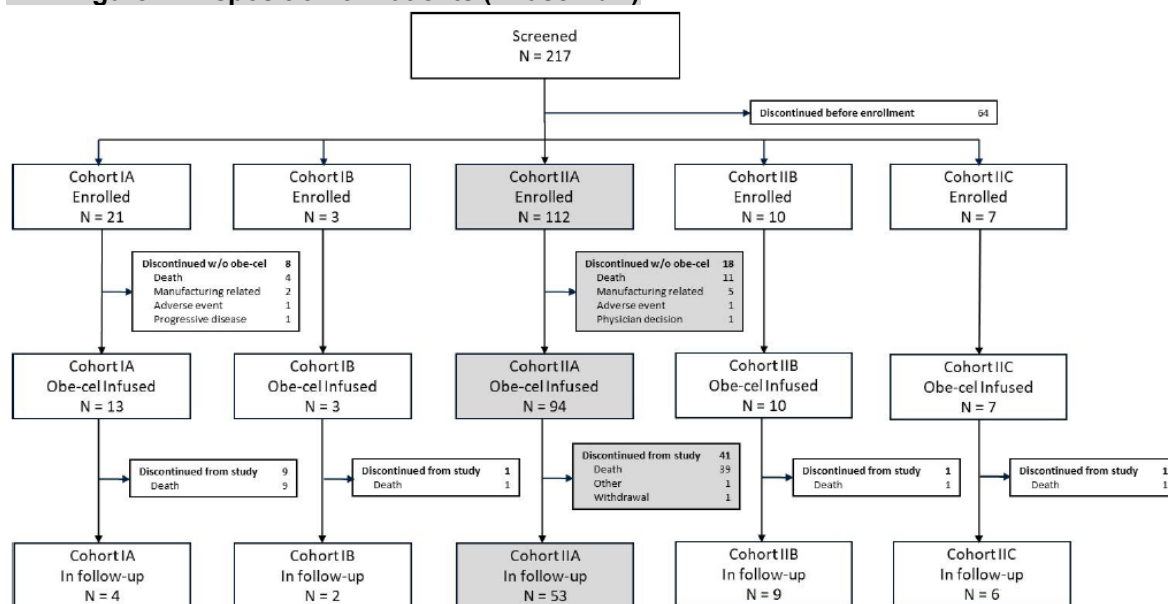
Population	Number of Patients (Phase/Cohort)
All leukapheresed population/full analysis set	112 (Phase 2/Cohort A)
Primary efficacy population	65 (Phase 2/Cohort A)
Safety analysis set	100 (13 in Phase 1b/Cohort A, 87 in Phase 2 Cohort A)

Source: FDA Analysis

*FDA primary efficacy and safety populations excluded patients who received out of specification obe-cel

The overall disposition of all patients is depicted in [FDA Figure 1](#) below.

FDA Figure 1. Disposition of Patients (Phase 1b/2)



Source: CSR Page 49

Enrolled = All inclusion/exclusion criteria were met AND the patient's leukapheresate was accepted for manufacturing.

Cohort A: Adults with r/r B ALL who have $\geq 5\%$ blasts in BM at screening.

Cohort B: Adults with r/r B ALL in morphological remission with minimal residual disease at screening (Cohort IB: $\geq 10^{-4}$ and $< 5\%$ blasts in the BM; Cohort IIB: $\geq 10^{-3}$ by central (b) (4) testing and $< 5\%$ blasts in the BM).

Cohort C: Adults with r/r B ALL with isolated extramedullary disease at screening.

Data cutoff: June 9, 2023.

[FDA Table 7](#) summarizes patients with discontinuations from the study. The reasons for dropouts and discontinuations included deaths, progressive disease, and patient withdrawal. Among the 65 efficacy-evaluable patients, 35 (53.8%) patients discontinued the study.

FDA Table 7. Disposition of the Primary Efficacy Population

Status	Efficacy-Evaluable N=65 n (%)
Patients discontinued from study	35 (53.8%)
Primary reason for discontinuation from study	-
Death	32 (49.2%)
Progressive disease	1 (1.5%)
Withdrawal by patient	2 (3.1%)

Source: FDA Analysis

See Section 8.2 regarding patients' disposition of the safety analysis set.

Reviewer comment: *The number of patients enrolled and treated with obe-cel is sufficient to evaluate the efficacy and safety of this treatment in adults with r/r B ALL.*

Protocol Violations/Deviations

Data:

An important protocol deviation (IPD) is one that could have a significant effect on the patient's safety, rights, or welfare and/or on the integrity of the study data and required the Investigator to notify the Sponsor and the appropriate IEC/IRB as soon as possible or as per local requirements. Twenty patients enrolled in FELIX had at least 1 IPD. Most of the IPDs were related to study assessments and procedure compliance (8 patients) and eligibility criteria (4 patients) (Module 5.3.5.2 - FELIX Interim Clinical Study Report, Section 10.2). The types of important deviations included:

- Related to study assessments and procedure compliance (8 patients)
- Related to eligibility criteria (4 patients)
- Related to dosing and administration errors or compromised bag – incorrect or partial dose (3 patients)
- Related to visit compliance – missed Visit or assessment (3 patients)
- Related to prohibitive medication or treatment - steroid use (2 patients)
- Related to AE/serious adverse event (SAE)/Other significant AE assessment – second infusion obe-cel after reported ICAN (1 patient)
- Related to AE/SAE/Other significant AE assessment management – coronavirus 2019 disease (COVID-19) related (1 patient)

The Applicant's Position:

No protocol deviation met the criteria for a serious breach or led to exclusion from analysis.

The FDA's Assessment:

Due to the important protocol deviation (IPD) of dosing errors, the review team consulted the Division of Medication Error Prevention and Analysis 2 (DMEPA 2) in the Office of Medication Error Prevention and Risk Management (OMEPRM) and the Office of Surveillance and Epidemiology (OSE) within the Center for Drug Evaluation and Research (CDER). The review team requested that DMEPA evaluate the administration section of the proposed USPI and comment on whether a use-related risk analysis (URRA) or human factors (HF) study is needed

to identify, evaluate, and minimize the potential for medication errors. [FDA Table 8](#) below provides the summary of the dosing errors, root cause, and mitigations implemented by the Applicant.

FDA Table 8. Summary of Administration Errors, Applicant's Root Cause/Comments/Mitigation

Description of Error	Applicant's Root Cause	Applicant's Mitigation During Study	Applicant's Comments	Applicant's Mitigations implemented within the BLA for commercialization.
Administered 10 mL of obe-cel instead of 1.3 mL (10 million cells) at first dose. Second dose not administered due to AE (Grade 3 CRS)	Ineffective internal communication and lack of process adherence by the clinical site that led to misinterpretation of instructions by site staff associated with extraction of 10 million cells rather than a volume of 10 mL	Several actions for the clinical site and Autolus were implemented, including updates to documentation and training of staff.	Higher first dose, CRS G3 and no second dose as per protocol. Patient achieved CRi but had disease progression and died.	Split infusion bags will have color coded labels specific to bag configuration. A patient batch specific Release for Infusion Certificate (RfIC) and Dose Schedule Planner (DSP) will assist with determination of the dose regimen and volumes to be administered. The RfIC includes information on <ul style="list-style-type: none"> The specific volume to be administered via syringe for the 10 x 10⁶ dose. Bag configuration for each dose, including details on the number of bag(s), serial number(s), the volume per bag, and number of CD19 CAR-positive cells in each bag.
Site administered 10 mL of obe-cel rather than 10 million cells at first dose (i.e., higher dose)			Higher first dose, low grade CRS and ICANS but CR achieved (and still ongoing at M18)	
Full of 10 million dose bags infused at second dose, but dose impact low.	Misinterpretation of instructions by site staff; full bag of 10 million cell dose infused at second dose.	Dose deviation occurred at the second dose (377 vs. 310 x 10 ⁶ cells) and was recorded as a protocol deviation. No further occurrences were observed.	Higher second dose, however remained within target range.	The DSP allows HCPs to plan for the number and type of bag(s) required for each dose, and volume to be administered via syringe, depending on the dose regimen to be administered (high or low). A 'red box' caution is prominent in the DSP, referring the HCP to the RfIC to obtain the volume to be administered via syringe for the 10 x 10 ⁶ doses. Furthermore, 2 signatures are required on DSP to confirm accuracy of volume to be infused. Both the RfIC and DSP will be provided in the shipper and via Autolus's Scheduling Portal. The USPI (Section 2.2 Administration) provides clear instruction on use of the RfIC and DSP to plan for AUCATZYL administration.

Source: FDA analysis, DMEPA Consult

Abbreviations: AE, adverse event; CAR, chimeric antigen receptor; CRS, cytokine release syndrome; CRi, complete remission with incomplete recovery of blood counts; DSP, Dose Schedule Planner; HCP, health care professionals; ICANS, immune effector cell-associated neurotoxicity syndrome; RfIC, Release for Infusion Certificate; USPI, United States Prescribing Information.

DMEPA provided recommendations to revise the USPI, Release for Infusion Certificate (RfIC), and Dose Schedule Planner (DSP), to minimize the potential for medication errors with the to-be-marketed product. Summary of DMEPA recommendations is provided below:

- Revising Section 2.3 "Infusion Instructions" of the USPI to clarify that the volume to be administered for the 10 x 10⁶ dose is via syringe.
- Including a statement in the Infusion Bag Label to alert healthcare providers of the patient-specific volume to be administered via syringe.

- Adding the same color coding, used to differentiate the infusion bags in the DSP, to the RfIC.
- Revising the presentation of information in the RfIC for better clarity
- Adding syringe vs. bag graphics in the DSP and relocating the red warning box to improve prominence.
- Adding second signature box to the DSP form for another healthcare provider to check the dose and sign prior to dose administration.

DMEPA recommended that these changes be implemented without submitting HF validation study results for Agency review.

Reviewer comment: *The review team agreed with DMEPA recommendation to mitigate the risk of dosing errors.*

The Reviewer recommended that BIMO inspect the clinical sites with the most IPDs. The reviewer agrees that the IPDs did not impact the interpretation of study results.

Demographic Characteristics

The demographic characteristics of patients enrolled in the pivotal FELIX study is provided in [Applicant Table 6](#).

In the pivotal Cohort IIA for efficacy (Infused Set, n=94), the median age was 50 years (range: 20 - 81). Twenty-one patients (22.3%) infused with obe-cel were ≥ 65 years old. Sex was equally distributed (53.6% male/46.4% female), most of the patients were white (76.5%) and about a third of the study population was of Hispanic or Latino ethnicity (28.8%). The demographics of patients with $\geq 5\%$ Blast in BM at Lymphodepletion were not markedly different than that of the Cohort IIA Infused Set. ([Applicant Table 6](#)).

Applicant Table 6 Summary of Demographics at Screening and Lymphodepletion – FELIX Study

	Phase II - Cohort A			Phase Ib and II - All Cohorts	
	≥ 5% Blast in BM at Lymphodepletion (N=71)	Infused (N=94)	Enrolled (N=112)	Infused (N=127)	Enrolled (N=153)
Age (years)					
Mean (SD)	49.7 (17.23)	48.3 (17.12)	47.9 (17.04)	47.1 (16.89)	46.7 (16.87)
Median	51.0	50.0	49.0	47.0	45.0
Q1 - Q3	36.0 - 64.0	33.0 - 62.0	33.5 - 62.5	33.0 - 60.0	32.0 - 60.0
Min - Max	20 - 81	20 - 81	20 - 81	20 - 81	20 - 81
Age (years) categorized - n (%)					
≥ 18 to ≤ 25	8 (11.3)	11 (11.7)	13 (11.6)	14 (11.0)	16 (10.5)
> 25 to < 40	14 (19.7)	20 (21.3)	26 (23.2)	34 (26.8)	45 (29.4)
≥ 40 to < 65	32 (45.1)	42 (44.7)	49 (43.8)	54 (42.5)	63 (41.2)
≥ 65	17 (23.9)	21 (22.3)	24 (21.4)	25 (19.7)	29 (19.0)
Sex - n (%)					
Male	36 (50.7)	47 (50.0)	60 (53.6)	66 (52.0)	82 (53.6)
Female	35 (49.3)	47 (50.0)	52 (46.4)	61 (48.0)	71 (46.4)
Race - n (%)					
Asian	8 (11.3)	10 (10.6)	11 (9.8)	16 (12.6)	17 (11.1)
Black or African American	2 (2.8)	2 (2.1)	2 (1.8)	2 (1.6)	3 (2.0)
White	51 (71.8)	70 (74.5)	86 (76.8)	94 (74.0)	117 (76.5)
Unknown	10 (14.1)	12 (12.8)	13 (11.6)	15 (11.8)	16 (10.5)
Ethnicity - n (%)					
Hispanic or Latino	23 (32.4)	29 (30.9)	33 (29.5)	38 (29.9)	44 (28.8)
Not Hispanic or Latino	43 (60.6)	58 (61.7)	72 (64.3)	80 (63.0)	100 (65.4)
Unknown	5 (7.0)	7 (7.4)	7 (6.3)	9 (7.1)	9 (5.9)
Country - n (%)					
United States	39 (54.9)	47 (50.0)	54 (48.2)	66 (52.0)	80 (52.3)
United Kingdom	26 (36.6)	36 (38.3)	42 (37.5)	49 (38.6)	56 (36.6)
Spain	6 (8.5)	11 (11.7)	16 (14.3)	12 (9.4)	17 (11.1)

BM=Bone marrow; Q=Quarter; SD=Standard deviation

Enrollment = All inclusion/exclusion criteria have been fulfilled and leukapheresate has been accepted for manufacturing.

Infused set comprises of all patients who have received at least 1 infusion of obe-cel.

Data cut-off: 13-Sep-2023.

Source: BLA D30 Update - Table 14.1.2.1.4.

The FDA's Assessment:

In addition to the Applicant's table of demographics above, demographic characteristics displayed in [FDA Table 9](#) below include those for the 65 patients and 100 patients who were included in FDA's primary efficacy and safety analysis sets, respectively.

FDA Table 9. Demographic Characteristics, Efficacy and Safety Population

Demographic Characteristic	Efficacy Population (N=65)	Safety Population (N=100)
Age (years)		
Mean (SD)	49 (16.5)	48 (16.5)
Median	51.0	49.5
Min-max	20-77	20-77

Demographic Characteristic	Efficacy Population (N=65)	Safety Population (N=100)
Age (years) categorized, n (%)		
≥18 to <65	51 (78)	80 (80)
≥65	14 (22)	20 (20)
Sex, n (%)		
Female	35 (54)	50 (50)
Male	30 (46)	50 (50)
Race, n (%)		
Asian	8 (12)	12 (12)
Black or African American	1 (1.5)	1 (1)
White	47 (72)	75 (75)
Unknown	9 (14)	12 (12)
Ethnicity, n (%)		
Hispanic or Latino	21 (32)	30 (30)
Not Hispanic or Latino	40 (62)	63 (63)
Unknown	4 (6)	7 (7)
Country, n (%)		
United States	34 (52)	50 (50)
United Kingdom	25 (38)	39 (39)
Spain	6 (9)	11 (11)

Source: FDA Analysis, ADSL, ADSLFDA, ADSLFDA1 datasets

Reviewer comment: The overall demographics of the study population are reasonably representative of the patient population of adults with B ALL in the U.S., except for the equal percentage of female and male patients in the study, whereas B ALL occurs slightly more frequently in males than females. Furthermore, although the incidence of B ALL is three times higher in White than Black or African American people, there is limited representation of Black/African American race (n=1) in the study.

FDA's primary efficacy analysis population and the all leukapheresed population are the two efficacy populations likely to provide the most useful information to prescribers, and as such are the two populations for which disease response results will be included in the product label. The Reviewer does not agree with the Applicant's proposal to include information on all patients who were infused with obe-cel in the efficacy section of the USPI because several patients may respond to bridging therapy which may confound the efficacy results.

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

In the pivotal Cohort IIA for efficacy (n=94), a high proportion of patients were refractory to the last prior line of therapy (51 patients, 54.3%) (Module 2.7.3 Summary of Clinical Efficacy Addendum – Day 30 Update, Section 2.2; Module 2.7.3 Summary of Clinical Efficacy, Section 2.1.2). Patients had received a median of 2 prior lines of anticancer therapy (range: 1- 6). Sixty-five patients (69.1%) had ≥ 2 lines and 12.8% had ≥ 4 lines of prior therapy, 35.1% patients had received prior blinatumomab, 31.9% prior inotuzumab ozogamicin, 16.0% prior blinatumomab and inotuzumab ozogamicin, and 38.3% of patients had prior SCT. Of patients in Cohort IIA, 35.1% patients > 75% blasts in the BM at screening. No patient had < 5% BM blasts at

screening, per the eligibility criteria for Cohort IIA. Nineteen patients (20.2%) had EMD at screening ([Applicant Table 7](#)).

As expected, with adult patients with r/r B ALL, there were changes in disease status between screening and LD. Specifically in the subset of patients in Cohort IIA with $\geq 5\%$ blasts in BM at both screening and LD (N=71), there was a general shift to patients having a higher blast count at LD compared to screening, meaning this subset not only maintained morphological disease, but also worsened in general despite receiving bridging therapies, 35.28% [25/71] of patients had $> 75\%$ blasts in BM at screening compared to 43.7% [31/71] at LD. These patients are practically refractory to all treatment options including bridging therapies and are considered the most difficult to treat patients.

Applicant Table 7 Disease Characteristics at Screening and Lymphodepletion – FELIX Study

Parameter	Phase II - Cohort A			Phase Ib and II - All Cohorts	
	$\geq 5\%$ blasts in BM at LD (N=71)	Infused (N=94)	Enrolled (N=112)	Infused (N=127)	Enrolled (N=153)
Prior Therapies					
Refractory to all prior lines of anti-cancer therapy - n (%)	11 (15.5)	12 (12.8)	13 (11.6)	13 (10.2)	15 (9.8)
Refractory to first line therapy - n (%)	20 (28.2)	24 (25.5)	28 (25.0)	32 (25.2)	37 (24.2)
Refractory to last prior line of therapy: - n (%)	38 (53.5)	51 (54.3)	59 (52.7)	67 (52.8)	80 (52.3)
Relapsed to first line therapy within 12 months - n (%)	34 (47.9)	41 (43.6)	52 (46.4)	60 (47.2)	75 (49.0)
Number of prior lines of therapy					
Median	2.0	2.0	2.0	2.0	2.0
Min - Max	1 - 6	1 - 6	1 - 6	1 - 6	1 - 6
Number of prior lines of therapy categorized - n (%)					
1	23 (32.4)	29 (30.9)	34 (30.4)	30 (23.6)	36 (23.5)
2	27 (38.0)	36 (38.3)	43 (38.4)	53 (41.7)	62 (40.5)
3	12 (16.9)	17 (18.1)	21 (18.8)	25 (19.7)	32 (20.9)
≥ 4	9 (12.7)	12 (12.8)	14 (12.5)	19 (15.0)	23 (15.0)
Previous alloSCT - n (%)	22 (31.0)	36 (38.3)	43 (38.4)	56 (44.1)	69 (45.1)
Previous blinatumomab - n (%)	26 (36.6)	33 (35.1)	41 (36.6)	53 (41.7)	64 (41.8)
Previous inotuzumab ozogamicin - n (%)	23 (32.4)	30 (31.9)	37 (33.0)	40 (31.5)	49 (32.0)
Previous blinatumomab and inotuzumab ozogamicin - n (%)	11 (15.5)	15 (16.0)	20 (17.9)	21 (16.5)	27 (17.6)
Previous blinatumomab or inotuzumab ozogamicin - n (%)	38 (53.5)	48 (51.1)	58 (51.8)	72 (56.7)	86 (56.2)
Cytogenetics					
Complex karyotype	24 (33.8)	37 (39.4)	45 (40.2)	51 (40.2)	63 (41.2)
Philadelphia-chromosome positive B-ALL - n (%)	18 (25.4)	25 (26.6)	26 (23.2)	36 (28.3)	39 (25.5)
Disease Characteristics at Screening					
EMD Present - n (%)	13 (18.3)	19 (20.2)	21 (18.8)	29 (22.8)	32 (20.9)

Parameter	Phase II - Cohort A			Phase Ib and II - All Cohorts	
	≥ 5% blasts in BM at LD (N=71)	Infused (N=94)	Enrolled (N=112)	Infused (N=127)	Enrolled (N=153)
BM blasts (%)					
Median	47.0	49.5	55.7	36.0	47.0
Min – Max	6-100	6-100	6-100	0-100	0-100
BM blasts by morphology categorized - n (%) [1]					
>75%	25 (35.2)	33 (35.1)	41 (36.6)	40 (31.5)	54 (35.3)
>20% to ≤ 75%	25 (35.2)	32 (34.0)	40 (35.7)	37 (29.1)	47 (30.7)
≥5% to ≤ 20%	21 (29.6)	29 (30.9)	31 (27.7)	30 (23.6)	32 (20.9)
<5%	0	0	0	20 (15.7)	20 (13.1)
Disease Characteristics at Lymphodepletion					
EMD Present – n (%)	14 (19.7)	19 (20.2)	21 (18.8)	27 (21.3)	30 (19.6)
BM blasts (%)					
Median	65.0	41.1	41.1	40.0	40.0
Min – Max	5-100	0-100	0-100	0-100	0-100
BM blasts by morphology categorized - n (%) [1]					
>75%	31 (43.7)	31 (33.0)	31 (27.7)	40 (31.5)	40 (26.1)
>20% to ≤ 75%	26 (36.6)	26 (27.7)	26 (23.2)	35 (27.6)	35 (22.9)
≥5% to ≤20%	14 (19.7)	14 (14.9)	14 (12.5)	16 (12.6)	16 (10.5)
<5%	0	23 (24.5)	23 (20.5)	36 (28.3)	36 (23.5)

alloSCT = Allogeneic stem cell therapy; B-ALL = B-cell acute lymphoblastic leukemia; BM = Bone marrow; EMD = Extramedullary disease; LD = Lymphodepletion

[1] Bone marrow blast (%) was determined by morphology as the highest value from bone marrow aspirate and trephine.

Data cut-off: 13-Sep-2023.

Source: BLA D30 Update - Table 14.1.2.2.4.

The Applicant's Position:

The FELIX study enrolled an adult r/r B ALL patient population that is representative of the real-world US population. This included patients with a wide spectrum of disease burden as well as patients who are typically more difficult to treat such as young adults (< 40 years) as well as older patients (≥ 65 years), different ethnicities including Hispanics, patients with high disease burden, presence of EMD, complex karyotype, Ph+, and refractory to many lines of prior therapy. Despite this, robust and clinically meaningful efficacy was observed, with an acceptable and manageable safety profile.

The FDA's Assessment:

See [FDA Table 10](#) below for details of baseline disease characteristics for FDA's primary efficacy and safety populations in FELIX study.

FDA Table 10. Disease Characteristics at Screening and Lymphodepletion, Efficacy Analysis Set and Safety Analysis Set

Disease Characteristics	Efficacy Analysis Set (N=65)	Safety Analysis Set (N=100)
Prior therapies, n (%)	-	-
Refractory to all prior lines of anti-cancer therapy	8 (12.3)	9 (9.0)
Refractory to first line therapy	17 (26.2)	23 (23.0)
Refractory to last prior line of therapy	35 (53.8)	56 (56.0)
Relapsed to first line therapy within 12 months	32 (49.2)	46 (46.0)
Number of prior lines of therapy	-	-
Median	2.0	2.0
Min-max	1-6	1-6
Number of prior lines of therapy categorized, n (%)	-	-
1	20 (30.8)	26 (26.0)
2	26 (40.0)	42 (42.0)
3	10 (15.4)	17 (17.0)
≥4	9 (13.8)	15 (15.0)
Previous therapy used, n (%)	-	-
Previous allo SCT	22 (33.8)	42 (42.0)
Previous blinatumomab	23 (35.4)	36 (36.0)
Previous inotuzumab ozogamicin	22 (33.8)	33 (33.0)
Previous blinatumomab and inotuzumab ozogamicin	10 (15.4)	16 (16.0)
Previous blinatumomab or inotuzumab ozogamicin	35 (53.8)	53 (53.0)
Cytogenetics, n (%)	-	-
Complex karyotype	23 (35.4)	43 (43.0)
Philadelphia-chromosome positive B ALL	17 (26.2)	28 (28.0)
Disease characteristics at screening	-	-
EMD present, n (%)	13 (20.0)	21 (21.0)
BM blasts (%)	-	-
Median	52.0	58.9
Min-max	6-100	6-100
BM blasts by morphology categorized, n (%) [1]	-	-
>75%	24 (36.9)	39 (39.0)
>20% to ≤ 75%	22 (33.8)	33 (33.0)
≥5% to ≤ 20%	19 (29.2)	28 (28.0)
<5%	0	0
Disease characteristics at lymphodepletion	-	-
EMD present, n (%)	13 (20.0)	20 (20.0)
BM blasts (%)	-	-
Median	65.0	43.0
Min-max	5-100	0-100
BM blasts by morphology categorized, n (%) [1]	-	-
>75%	29 (44.6)	35 (35.0)
>20% to ≤ 75%	23 (35.4)	28 (28.0)
≥5% to ≤ 20%	13 (20.0)	13 (13.0)
<5%	0	24 (24.0)

Source: FDA Analysis, ADSL dataset

Abbreviations: B ALL, B-cell precursor acute lymphoblastic leukemia; BM, bone marrow; EMD, extramedullary disease; SCT, stem cell transplant

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Data:

Bridging Medications

Bridging therapy was based on Investigator choice. In the pivotal Cohort IIA for efficacy, 88 of the 94 patients infused with obe-cel (93.6%) received bridging therapy after leukapheresis until 1 week prior to LD, most of them chemotherapy alone or in combination with TKI (65 patients, 69.1%). Inotuzumab ozogamicin alone or in combination with chemotherapy was administered to 17 patients (18.1%) in Cohort IIA (Module 2.7.3 Summary of Clinical Efficacy, Section 2.1.3, BLA D30 Update -Table 14.1.1.1.1).

Lymphodepletion

All 127 patients infused with obe-cel in Phase Ib and Phase II (Safety Set) had received LD treatment with fludarabine and cyclophosphamide. The median fludarabine total dose was 120 mg/m² (range 68 to 240) and the median cyclophosphamide total dose was 1000 mg/m² (range: 700 - 2000) (Module 2.7.3 Summary of Clinical Efficacy, Section 2.1.3, BLA D30 Update - Table 14.1.4.3.1).

Obe-cel Compliance (Dose)

In the Safety Set, 94.5% (120/127) patients received both doses of obe-cel, and 91.3% (116/127) of infused patients received the target dose of 410×10^6 CD19 CAR-positive T cells (Module 2.7.3 Summary of Clinical Efficacy, Section, 4.3.2.2).

There were 3% (4/127) of patients who received a higher than intended dose at first infusion. All 4 patients had a high tumor burden and should have received a 10×10^6 first dose but received a dose between 68 and 103×10^6 CAR-positive viable T cells. CRS, ICANS, and HLH were observed in these patients. Three out of these 4 patients achieved CR or CRi post obe-cel infusion.

Concomitant Medications

Of the 127 patients in the Safety Set, 126 (99.2%) received concomitant medications with a start or end date on or after obe-cel infusion. The most frequently administered medications by ATC class were Nucleosides and Nucleotides Excluding Reverse Transcriptase Inhibitor (93.7% patients), Triazole and Tetrazole Derivatives (86.6% patients), Anilides (80.3% patients), Preparations Inhibiting Uric Acid Production (77.2%), Proton Pump Inhibitors (72.4% patients), Serotonin (5HT3) Antagonists (70.1% patients), and Combinations of Sulfonamides and Trimethoprim Including Derivatives (68.5% patients) (BLA D30 Update - Table 14.1.5.3.1).

Rescue Medications

CRS

In the Safety Set, 55.1% (70/127) patients were administered medications or therapy for the treatment of CRS (Module 2.7.4 Summary of Clinical Safety, Section 2.1.5.1, BLA D30 Update - Table 14.3.4.3.1). Concomitant medications provided to patients with CRS in the Safety Set

included tocilizumab 52.0% (66/127), corticosteroids 15.7% (20/127) or other anti-cytokine therapy 9.4% (12/127). In patients with $\geq 5\%$ blast in BM at LD, 61.5% (56/91) patients were treated using tocilizumab, 19.8% (18/91) patients with treated using corticosteroids, and 9.9% (9/91) treated using other anti-cytokine therapy for CRS.

No patients with CRS were treated with siltuximab.

ICANS

In the Safety Set, 18.9% (24/127) patients were administered medications or therapy for the treatment of ICANS (Module 2.7.3 Summary of Clinical Safety, Section 2.1.5.2, BLA D30 Update - Table 14.2.4.4.1). Concomitant medications provided to patients with ICANS in the Safety Set included anti-epileptics 9.4% (12/127), corticosteroids 18.9% (24/127) or other therapy 7.1% (9/127). In patients with $\geq 5\%$ blast in BM at LD, 12.1% (11/91) patients were treated using anti-epileptics, 24.2% (22/91) patients with treated using corticosteroids, and 8.8% (8/91) treated using other therapy for ICANS.

Stem Cell Transplant or Other Non-protocol Anticancer Therapies After obe-cel Infusion

In the Cohort IIA Infused Set, 11.7% (11/94) patients proceeded to SCT after obe-cel infusion while in remission (Module 2.7.3 D30 Safety Update Report – Day 30 Update, Table 2). In patients with $\geq 5\%$ blast in BM at LD who received at least 1 obe-cel infusion, 12.7% (9/71) proceeded to SCT after obe-cel infusion while in remission. One patient (1.1%) proceeded to a non-protocol anticancer therapy other than SCT while in remission. This patient had $\geq 5\%$ blast in BM at LD.

The FDA's Assessment:

Bridging therapy was administered to 59 of 65 (91%) patients in FDA's efficacy population.

FDA Table 11. Bridging Therapies Received by Patients Included in Primary Efficacy Analysis

Type of Bridging Therapy	Efficacy Analysis Set (N=65) n (%)
Vincristine	40 (62)
Dexamethasone	27 (42)
Methotrexate	22 (34)
Cytarabine	19 (29)
Cyclophosphamide	14 (22)
Mercaptopurine	7 (1)
Inotuzumab ozogamicin	6 (9)
Fludarabine	5 (8)
Ponatinib	3 (5)
Prednisone	3 (5)
Daunorubicin	2 (3)
Venetoclax	2 (3)
Clofarabine	1 (1.5)
Cytosine	1 (1.5)
Etoposide	1 (1.5)
Hydrocortisone	1 (1.5)
Hydrocortisone sodium succinate	1 (1.5)
Hydroxycarbamide	1 (1.5)

Type of Bridging Therapy	Efficacy Analysis Set (N=65) n (%)
Mesna	1 (1.5)
Prednisolone	1 (1.5)
Rituximab	1 (1.5)
Vincristine sulfate	1 (1.5)

Source: FDA Analysis, ADSL, ADCM datasets of FELIX study

Reviewer comment: Bridging therapy was based on Investigator choice. All patients were required to repeat bone marrow assessment prior to LD to determine disease status and the obe-cel dosing regimen to be administered.

Concomitant medications provided to patients with CRS in the safety set included tocilizumab in 55%, corticosteroids in 16%, and other anti-cytokine therapy in 10%. Concomitant medication provided for the treatment of ICANS (not all neurologic toxicity) included anti-epileptics in 10%, corticosteroids in 21%, and other therapy in 8%.

Reviewer comment: Concomitant medication usage is as expected for this patient population. For information on dosing errors, see section above Protocol Violations/Deviations.

Efficacy Results – Primary Endpoint, ORR

Data:

Overall remission rate (ORR) was the primary efficacy endpoint in the FELIX study, defined as the proportion of patients achieving CR or CRi, at any time post-infusion, as assessed by an IRRC.

The patients infused in Cohort IIA (N=94), all of whom had morphological disease at screening ($\geq 5\%$ blasts in BM) are considered to be the best representative of patients who would be candidates for obe-cel treatment in a real-world clinical setting since the initial clinical decision to treat with obe-cel is at the time of screening/leukapheresis rather than at time of LD (Module 2.7.3 Summary of Clinical Efficacy Addendum – Day 30 Update, Section 2.3.1.1). Obe-cel treatment induced a clinically meaningful remission rate in this difficult to treat adult r/r B ALL population, ORR was 76.6% (95% CI: 66.7, 84.7; $p < 0.0001$) ([Applicant Table 8](#)).

Among the subpopulation of patients in Cohort IIA who received obe-cel and had $\geq 5\%$ blasts in the BM at screening and LD, ORR was 74.6% (95% CI: 62.9, 84.2; $p < 0.0001$) ([Applicant Table 8](#)). The result is similar compared to the Infused set and represents clinically meaningful benefit.

Applicant Table 8 Overview of Remission Results with Disease Assessment by IRRC (Cohort IIA, Infused and Enrolled Set) – FELIX Study

Parameter	Infused Set		Enrolled Set (N=112)
	≥5% blasts in BM at LD (N=71)	Total (N=94)	
ORR (= CR + CRi) - n (%)			
n (%)	53 (74.6)	72 (76.6)	72 (64.3)
95% CI (%) [1]	(62.9, 84.2)	(66.7, 84.7)	(54.7, 73.1)
p-value [4]	<0.0001	<0.0001	
CR - n (%)			
n (%)	41 (57.7)	52 (55.3)	55 (49.1)
95% CI (%) [2]	(45.4, 69.4)	(44.7, 65.6)	(39.5, 58.7)
p-value [5]	<0.0001	<0.0001	
CR within 3 months - n (%) [3]			
n (%)	33 (46.5)	43 (45.7)	43 (38.4)
95% CI (%) [2]	(34.5, 58.7)	(35.4, 56.3)	(29.4, 48.1)
p-value [6]	<0.0001	<0.0001	
DOR			
Median (95% CI)	11.56 (8.08, NE)	12.48 (8.11, NE)	12.48 (8.18, NE)
6 months probability	71.5	75.9	78.0
95% CI (%) [2]	(55.7, 82.5)	(63.1, 84.8)	(65.6, 86.4)

BOR = Best overall response; CI = confidence interval; CR = Complete remission; CRi = CR with incomplete recovery of counts; IRRC = Independent Response Review Committee; ORR = Overall remission rate.

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 anticancer therapies.

[1] Including patients who achieved BOR of CR or CRi after obe-cel infusion (Infused Set) or enrollment (Enrolled Set).

[2] The 95% exact Clopper-Pearson CIs are displayed.

[3] Includes all infused patients who achieved BOR of CR within or after 3 months post obe-cel infusion.

[4] Exact p-value testing H10: ORR ≤ 40% vs H11 and H12: ORR > 40% in all infused patients and patients with ≥5% blast in BM at lymphodepletion, respectively.

[5] Exact p-value testing H20: CR at any time ≤ 20% vs H21 and H22: CR at any time > 20% in all infused patients and patients with ≥5% blast in BM at pre- conditioning, respectively.

[6] Exact p-value testing H30: CR within 3 months ≤ 20% vs H31 and H32: CR within 3 months > 20% in all infused patients and patients with ≥5% blast in BM at lymphodepletion, respectively.

Data cut-off: 13-Sep-2023.

Source: BLA D30 Update – Table 14.2.1.4.1.iiia, 14.2.1.2.1.iiia, 14.2.2.1.1.iiia, 14.2.3.1.1.iiia, 14.2.3.4.1.iiia, 14.2.3.4.2.iiia, Table 14.2.7.2.1.iiia, 14.2.7.2.17.iiia.

The ORR was 76.6% of patients (72/94) following obe-cel infusion in Cohort IIA (95% CI: 66.7, 84.7; p<0.0001), despite the r/r B ALL population having a poor prognosis and that the FELIX study enrolled significant proportions of patients with known difficult-to-treat characteristics. This included 33.0% (31/94) of patients with > 75% blasts in BM at LD, 20.2% (19/94) of patients with EMD, 30.9% (29/94) of Hispanic/Latino ethnicity, 26.6% (25/94) with Ph+ karyotype, 30.9% (29/94) having had at least 3 lines of prior therapy, 54.3% (51/94) being refractory to their most recent therapy, and 38.3% (36/94) having had received prior SCT. Therefore, the remission rate was both compelling and clinically meaningful.

In the subset of patients who had ≥ 5% BM blasts at both screening and LD in Cohort IIA (N=71), the ORR remained high at 74.6% (53/71) of patients (95% CI: 62.9, 84.2; p<0.0001) ([Applicant](#)

[Table 8](#)). This subset included a higher proportion of patients with > 75% blasts in BM at LD than the overall infused population (43.7% and 33.0%, respectively; [Applicant Table 7](#)).

Efficacy Results – Secondary Endpoints

Complete remission (CR) was achieved in many patients infused with obe-cel (55.3%, 52/94 [95% CI: 44.7, 65.6]; $p < 0.0001$) and it occurred within 3 months for 45.7% (43/94 [95% CI: 35.4, 56.3]; $p < 0.0001$) of patients (Module 2.7.3 Summary of Clinical Efficacy Addendum – Day 30 Update, Section 2.3.1.1 and Module 2.7.3 Summary of Clinical Efficacy Sections 2.1.4.2 to 2.1.4.6).

Among the 72 patients in Cohort IIA who achieved remission (CR or CRi), 69 patients had evaluable samples for either (b) (4)

determination of MRD to 10^{-4} level, and 94.2% (65/69) achieved MRD-negative remission to 10^{-4} level.

In the subset of patients who had $\geq 5\%$ BM blasts at both screening and LD in Cohort IIA (N=71), there were high rates of CR and CR within 3 months: 57.7% (41/71 [95% CI: 45.4, 69.4]; $p < 0.0001$) and 46.5% (33/71 [95% CI: 34.5, 58.7; $p < 0.0001$]), respectively.

Therefore, in patients with $\geq 5\%$ BM blasts both at screening and LD, remission rates were both compelling and clinically meaningful.

Patients in the Enrolled Set (N=112), which includes all patients regardless of whether they received obe-cel infusion or not, still had meaningful remission rates (e.g. ORR of 64.3%, [72/112]). The lower rate of remission observed reflects that 16.1% of patients (18/112) of the enrolled patients did not receive obe-cel treatment ([Applicant Table 8](#)).

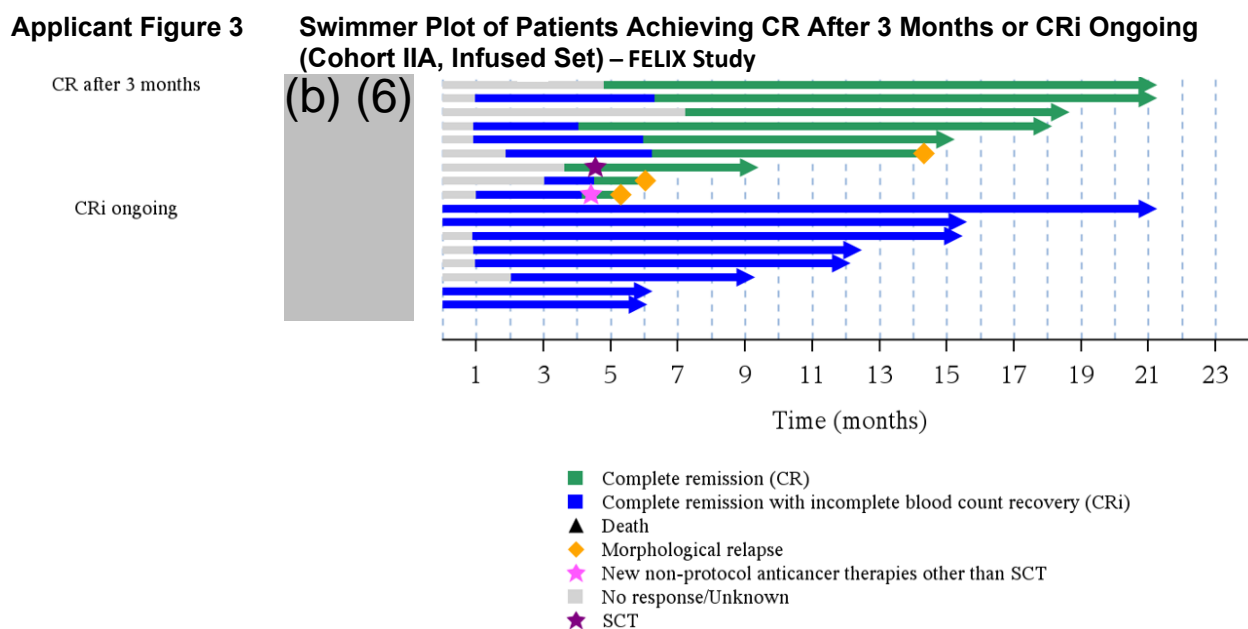
Conversely, in the subset of patients who received the total target dose in Cohort IIA of obe-cel (N=85), a numerically higher ORR of 81.2% (69/85) was observed, with 61.2% (52/85) achieving CR and 50.6% (43/85) achieving CR within 3 months.

In addition, a pooled analysis across all of Cohort A (Phase Ib and Phase II) and across All Cohorts yielded robust remission rates, including in the subset with $\geq 5\%$ of blasts in BM at LD (i.e. morphological disease at both screening and LD).

Patients Who Achieved CR After 3 Months or Have Ongoing CRi

Of those patients in Cohort IIA who achieved remission after obe-cel infusion (N=72), 23.6% of the responders (17/72) achieved CR after 3 months or had CRi ongoing as of the 13-Sep-2023 cutoff (Module 2.7.3 Summary of Clinical Efficacy, Addendum - D30 Update, Section 2.3.1.1). As depicted in [Applicant Figure 3](#), there were 9 patients who achieved CR after 3 months and 8 patients who had CRi ongoing as of the latest data cut. All these 17 patients achieved MRD-negative remission with the vast majority is still in ongoing remission with longest follow-up at 21 months without new anti-cancer therapies ([Applicant Figure 3](#)), indicating clinically meaningful durability.

As presented in [Section 8.2](#), there was no additional safety risk associated with achieving CR more than 3 months post-infusion or an ongoing CRi.



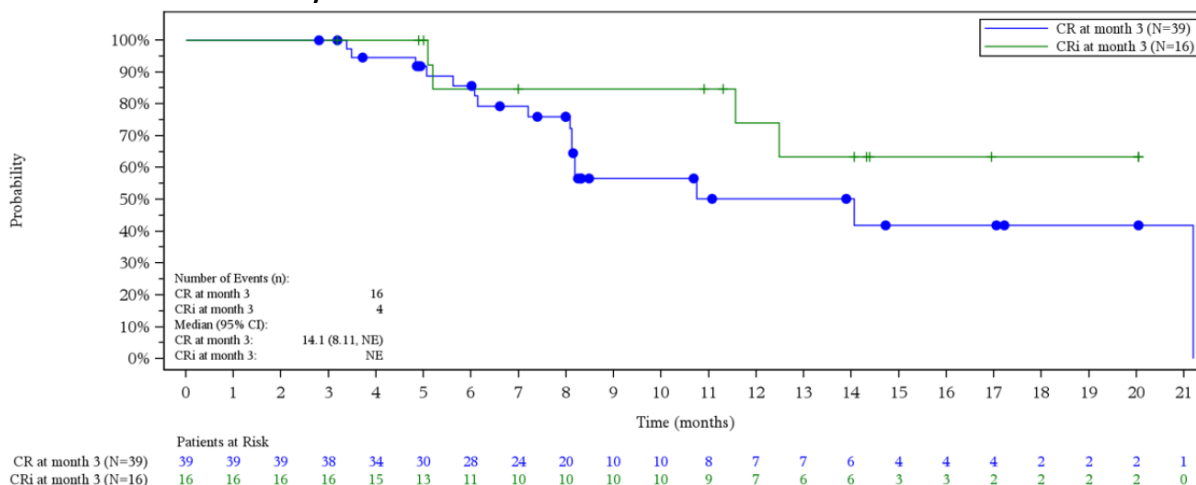
Note: Patients with CRi ongoing are those who have never achieved CR and are ongoing in CRi without SCT or other new non-protocol anti-cancer therapy.

Data cut-off: 13-Sep-2023.

Source: BLA D30 Update - Figure 14.2.1.1.2.ia.

To understand the impact of whether there was a difference in the durability of obe-cel's treatment effect depending on whether a patient achieved CR or CRi within 3 months, a landmark analysis of EFS beyond 3 months was conducted. Among all patients who were still in remission beyond 3 months (CR or CRi), EFS was summarized by whether it was CR or CRi at 3 months. This analysis showed that no clear trend for differentiation was observed between patients who had achieved CR versus CRi by 3 months ([Applicant Figure 4](#)).

Applicant Figure 4 Landmark Analysis: Kaplan-Meier Plot of Event-Free Survival by Best Overall Response of CR or CRi At 3 Months (Cohort IIA, Infused Set) – FELIX Study



Data cut-off: 13-Sep-2023.

Source: BLA D30 Update - Figure 14.2.22.1.iaa

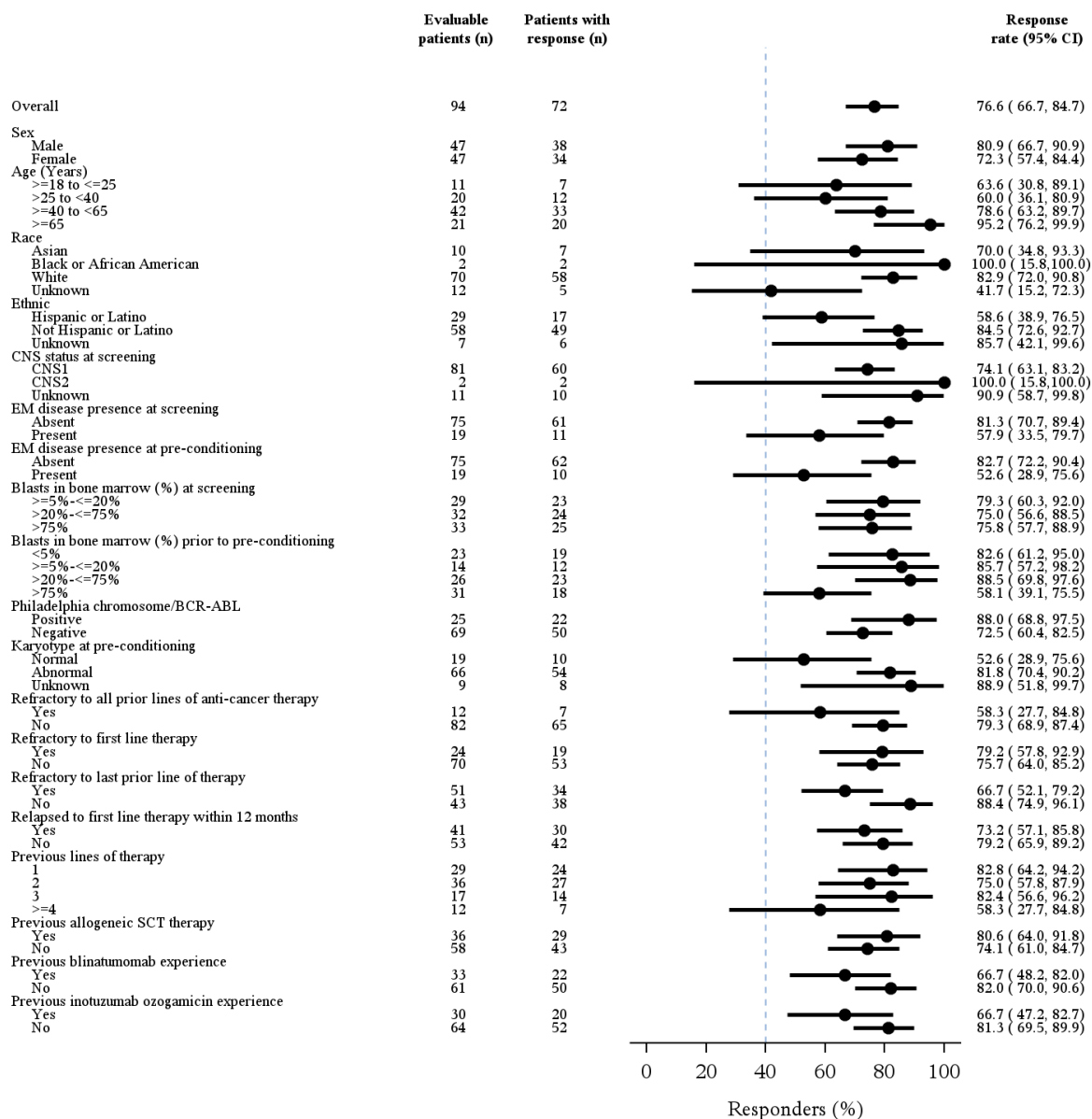
Refer to Module 2.7.3 Summary of Clinical Efficacy Addendum – Day 30 Update, Section 2.3.1.1 and Module 2.7.3 Summary of Clinical Efficacy Section 2.1.4.7 for further discussion.

Efficacy in Subgroups

The FELIX study included a broad range of patients that is representative of the real-world adult r/r B ALL population, including those typically associated with a poor prognosis or poorer outcome with other treatments for B ALL e.g. Hispanic ethnicity, younger adults (< 40 years), older age, Ph+, high disease burden based on blasts in BM, presence of EMD.

The primary efficacy endpoint, ORR, was assessed over a broad range of subgroups for patients in Cohort IIA using the data cutoff of 09-Jun-2023. This included demographic parameters, disease status parameters and different prior anti-cancer therapy parameters (Module 2.7.3 Summary of Clinical Efficacy, Section 2.1.4.13). The output is presented in a Forest plot in [Applicant Figure 5](#), which provides the response rate and 95% CI for all subgroups, with reference to the pre-defined threshold of response of 40% of patients. Regardless of subgroup, evidence of efficacy is clearly observed, which supports the use of obe-cel in wide range of patients, including those patients who are typically difficult to manage.

Subgroup analyses have also been performed for the secondary endpoint of CR at any time ([Applicant Figure 6](#)), and CR within 3 months (Module 2.7.3 Summary of Clinical Efficacy, Section 2.1.4.13), with reference to the threshold of response rate of 20%. A treatment effect is observed across the spectrum of typically difficult-to-treat subgroups.

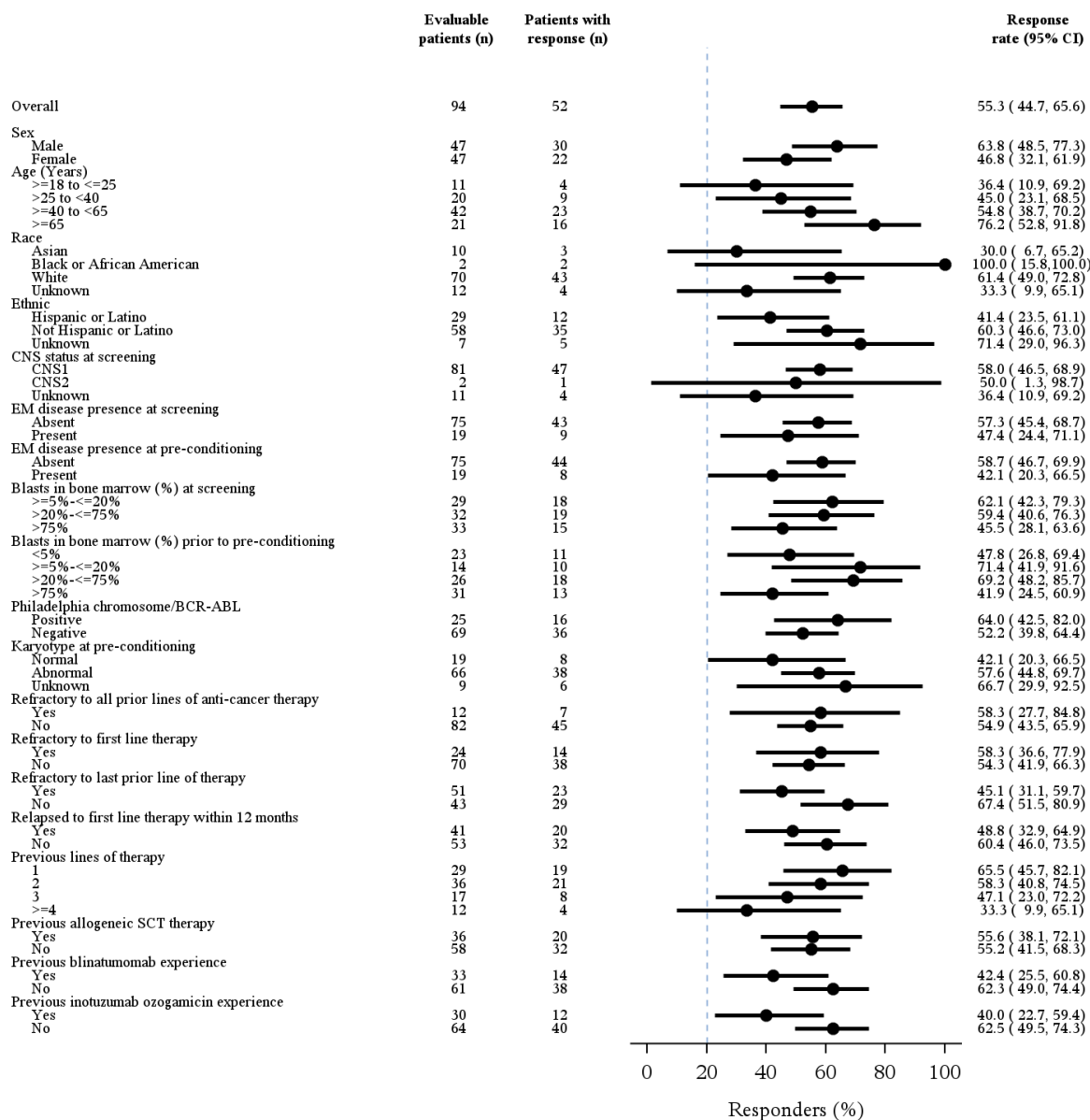
Applicant Figure 5 Forest Plot for Subgroup Analysis of ORR (Cohort IIA, Infused Set) – FELIX Study

CNS = Central nervous system; EM = Extramedullary; SCT= hematopoietic stem cell transplant.

The dotted reference line represents the pre-specified null hypothesis of ORR (40%).

Data cut-off: 09-Jun-2023.

Source: FELIX Interim Clinical Study Report Figure 14.2.21.1.1.ii.a.

Applicant Figure 6 Forest Plot for Subgroup Analysis of CR (Cohort IIA, Infused Set) – FELIX Study

CNS = Central nervous system; EM = Extramedullary.

The dotted reference line represents the pre-specified null hypothesis of CR (20%).

Data cut-off: 09-Jun-2023.

Source: FELIX Interim Clinical Study Report - Figure 14.2.21.2.1.ii.a.

The Applicant's Position

The primary and secondary endpoints were met in the FELIX study.

Based on patients infused in Cohort IIA (N=94), all of whom had morphological disease at screening ($\geq 5\%$ blasts in BM), obe-cel treatment induced a robust and clinically meaningful remission in this difficult to treat population. This was also demonstrated in the subpopulation of patients who had $\geq 5\%$ blasts in BM at both screening and LD. This is supported by statistical

significance being reached for all 6 hypotheses tested (< 0.0001). Moreso, the extensive subgroup analysis highlights the ability of obe-cel to achieve clinically meaningful responses across the clinically relevant target population.

The FDA's Assessment:

Efficacy-Evaluable Population

The efficacy-evaluable population consisted of 65 patients who were enrolled and treated in FELIX Phase 2 Cohort A study and who had documented disease (bone marrow blast $\geq 5\%$) at baseline post-bridging therapy and prior to LD. The efficacy-evaluable population excluded six patients from the Applicant's efficacy population because they received OOS (i.e., non-conforming) products (Patients IDs: (b) (6))

Notably, the definition of CRi at the time of initial protocol submission was based on version 2.2019 NCCN guidelines. Thus, CRi was defined as meeting all criteria for CR except recovery of either platelets $\leq 100,000/\mu\text{L}$ or absolute neutrophil count (ANC) $< 1000/\mu\text{L}$. In protocol V.5, the protocol was revised to define CRi as meeting all criteria for CR except recovery of platelets and/or ANC. See [FDA Table 39](#) and [FDA Table 40](#) in Sections [18.5](#) and [18.6](#). No justification was provided for this protocol change. Traditionally, FDA has defined CRi as meeting all criteria for CR except recovery of either platelets or ANC. Therefore, FDA did not use the protocol V5 criteria for CRi definition. For FDA's analysis, patients who were responders by achieving initial CRi, and then on subsequent disease assessments achieved CR per IRRC will not be considered to have achieved CR unless their disease assessments included all components (complete blood count, BM, EMD) performed within the prespecified window (± 14 days).

To facilitate FDA's review and adjudication of efficacy results, the Applicant submitted summary tables which identified all patients from Phase 1b/2 cohorts A, B & C who received short or long-acting granulocyte-colony stimulating factor (GCSF), eltrombopag, romiplostim, or platelet transfusions prior to any disease assessment.

FDA's Assessment of Efficacy:

FDA's primary efficacy evaluation was based on CR within 3 months of obe-cel infusion supported by duration of CR (DOCR) per FDA-adjudicated assessment. See [FDA Table 12](#) which also includes the results of the primary efficacy and key secondary efficacy endpoints per protocol, OCR (CR+CRi) rate at any time, and the duration of OCR at any time; respectively.

FDA Table 12. Efficacy Results Per FDA's Adjudication

Endpoint	Efficacy Evaluable N=65 n (%)	All Leukapheresed N=112 n (%)
Complete remission (within 3 months) rate		
n (%)	27 (42%)	40 (36%)
[95% CI]	(29%, 54%)	(27%, 45%)
Duration (months), median [95% CI]	14.1 (6.1, NR)	14.1 (6.2, NR)
(Range in months)	(0.5+, 21.2)	(0.5+, 21.2)
Overall complete remission (at anytime) rate*		
n (%)	41 (63%)	60 (54%)
[95% CI]	(50%, 75%)	(44%, 63%)
Duration (months), median [95% CI]	14.1 (6.2, NR)	14.1 (8.1, NR)
(Range in months)	(0.03+, 21.2)	(0.03+, 21.2)

Source: FDA Analysis, ADSLFDA, ADSLFDA1, ADEFFDA, and ADTTEFDA datasets.

*Rate of Overall Complete Remission "At Anytime" includes Complete Remission and Complete Remission with incomplete hematologic recovery "At Anytime".

Abbreviation: CI, confidence interval; NR, not reached.

Reviewer comment: Of note, CR within 3 months includes CR achieved up to Study Day 106 since the protocol allowed for time window of ± 14 days for disease response assessments.

As expected, the primary reason for the lower remission rates and delayed onset of remission per FDA's adjudication compared to the Applicant's results are likely due to the limitation of the study design with the lack of performing BM or EMD assessments at the time of achieving peripheral blood count recovery.

The Applicant provided two additional datasets (ADEFSP and ADTESP) reflecting FDA's adjudication and Applicant's assessment of first CR taking into account FDA's definition of CRi, without mandating additional procedures (BM aspiration/biopsy and/or EMD) to be performed at the same time as the peripheral blood assessments ([FDA Table 13](#)).

For regulatory decision making, all compartment response assessments (peripheral blood, bone marrow, and EMD) should be performed at the same time (\pm prespecified window) for confirmation of a CR.

FDA Table 13. Efficacy Results Per FDA's Adjudication[#]

Endpoint	Efficacy Evaluable N=65 n (%)	All Leukapheresed N=112 n (%)
Complete remission (within 3 months) rate		
n (%)	30 (46%)	43 (38%)
[95% CI]	(34%, 59%)	(29%, 48%)
Duration (months), median [95% CI]	8.1 (6.8, NR)	10.7 (7.1, NR)
(Range in months)	(0.5+, 21.2)	(0.5+, 21.2)
Overall complete remission (at anytime) rate*		
n (%)	43 (66%)	65 (58%)
[95% CI]	(53%, 77%)	(48%, 67%)
Duration (months), median [95% CI]	14.1 (8.1, NR)	14.1 (8.1, NR)
(Range in months)	(0.03+, 21.2)	(0.03+, 21.2)

Source: FDA Analysis, ADEFSP and ADTESP datasets

[#]Without mandating all disease assessments components prior to achieving first CR

*Rate of Overall Complete Remission "At Anytime" includes Complete Remission and Complete Remission with incomplete hematologic recovery "At Anytime".

Details of FDA Adjudication of Efficacy:

Based on review of all data for the primary efficacy population, FDA readjudicated the following:

- FDA downgraded the results of the overall response assessment for eight responses:
 - IRRC: 37 responses (25 CR and 12 CRi)
 - FDA: 29 responses (21 CR and 8 CRi)
- Onset of remission (CR +CRi) at any time was delayed for 24 patients
- Onset of CR at any time was delayed for 11 patients
- Onset of CR within 3 months of obe-cel infusion was delayed for one patient
 - One patient whose CR was considered within 3 months per IRRC but delayed to Day 182 per FDA adjudication.

[FDA Table 14](#) provides a summary of patient level listing of best overall response (BOR), onset of remission (CR or CRi), and onset of CR per IRRC and per FDA for the primary efficacy population.

Patient level listing of efficacy adjudication for of all patients from the Phase 1b/2 cohorts A, B & C is included in the Applicant's response to IR submitted under SN0022 and SN 0027, and the corresponding updated efficacy datasets submitted under SN0064.

FDA Table 14. Patient Level Listing of Best Overall Response, Onset of Remission, and Onset of CR, per IRRC and FDA for the Primary Efficacy Population

Patient ID	BOR per IRRC	BOR Per FDA	Onset of Remission Study Day Per IRRC	Onset of Remission Study Day Per FDA	Onset of CR Per IRRC	Onset of CR Per FDA	FDA Adjudication
(b) (6)	CR	CR	29	92	92	92	MLFS on D29 due to GCSF and Plts. Because D29 was considered by IRRC and Applicant a response (CRi), BM were not mandated per protocol to be performed afterwards. Blood count recovery on D70 but no BM done. CR at first full assessment after blood count recovery on D92.
	CR	CR	30	94	92	94	MLFS on D30. Blood count recovery on D70 but no BM done. CR at first full assessment after blood count recovery on D94.
	CRi	CRi	24	56	-	-	MLFS on D24. CRi based on blood count recovery and full assessment on D56.
	CR	CR	30	126	126	126	MLFS on D30. GCSF and platelets prior to earlier disease assessments. CR based on blood count recovery and full assessment on D126.
	CRi	MLFS	62	-	-	-	No morphological disease but patient had sustained low platelet counts and intermittent neutrophil recovery with GCSF administration.
	CR	CRi	29	97	192	No CR	MLFS on D29. CRi on Day 97. Blood count recovery on D192 but no BM done. BM done on D159, 275, 374, and 512. No blasts.
	CR	CR	28	28	63	91	CRi on D25. No BM on Day 63. BM on D91
	CR	CR	28	91	182	182	MLFS on D28. CRi based on blood count recovery and full assessment on D91. CR on D182.
	CR	CRi	29	29	66	No CR	No BM on D66. BM on D92 but low ANC and platelet. Relapse on D134.
	CR	CR	29	29	68	92	No BM on D 68. BM on Day 92.
	CRi	MLFS	29	-	-	-	MLFS on D29. Patient died due to AE on D52.
	CR	CR	28	182	123	543	MLFS on D28. Blood count recovery on D63 but no BM done. No BM done at Day 123. CRi based on first full disease assessment with only platelet recovery on Day 182.
	CRi	MLFS	30	-	-	-	MLFS on D30 and relapsed on D71.
	CR	CR	36	90	90	90	MLFS on D36. Blood count recovery on D57 but no BM done. CR based on blood count recovery and full assessment on D90.

Patient ID	BOR per IIRC	BOR Per FDA	Onset of Remission Study Day Per IIRC	Onset of Remission Study Day Per FDA	Onset of CR Per IIRC	Onset of CR Per FDA	FDA Adjudication
(b) (6)	CR	CR	29	99	64	99	MLFS on D29. Blood count recovery on D64 but no BM done. CR based on blood count recovery and full assessment on D99.
	CR	CR	29	29	61	99	No BM on D61. BM and EMD exam on D99.
	CRi	MLFS	37	-	-	-	MLFS on D37. Patient died due to AE on D90.
	CRi	MLFS	36	-	-	-	MLFS on D36 then immediate started conditioning for SCT. Patient died on D44.
	CR	CR	30	93	59	93	MLFS on D30. Blood count recovery on D59 but no BM done. CR based on blood count recovery and full assessment on D93.
	CR	CR	29	92	92	92	MLFS on D29. CR based on blood count recovery and full assessment on D92.
	CR	CR	29	59	59	59	MLFS on D29: ANC 0.98 and platelet 86.
	CRi	MLFS	29	-	-	-	MLFS on D29. Blood count recovery on D130 but no BM done. No full disease assessment done at any subsequent visits.
	CRi	MLFS	29	-	-	-	MLFS on D29. Patient died due to AE on D45.
	CR	CR	28	62	62	62	MLFS on D28. CR based on blood count recovery and full assessment on D62.
	CRi	CRi	28	85	-	-	MLFS on D28. Blood count recovery on D57 but no BM done. CRi based on blood count recovery and full assessment achieved on D85.
	CR	CR	26	97	61	182	MLFS on D26. Blood count recovery on D61 but no BM done. CR based on blood count recovery and full assessment achieved on D182.
	CR	CR	28	96	63	96	MLFS on D28. Blood count recovery on D63 but no BM done. CR based on blood count recovery and full assessment achieved on D96.
	CR	CRi	29	29	56	No CR	D29 CRi. D56 blood count recovered but no BM. Relapse on D84.
	CR	CR	30	90	55	90	MLFS on D30. Blood count recovery on D55 but no BM done. CR based on blood count recovery and full assessment achieved on D90.

Patient ID	BOR per IRRC	BOR Per FDA	Onset of Remission Study Day Per IRRC	Onset of Remission Study Day Per FDA	Onset of CR Per IRRC	Onset of CR Per FDA	FDA Adjudication
(b) (6)	CR	CR	29	106	106	106	MLFS on D29. CR based on blood count recovery and full assessment on D106.
	CR	No Response	110	-	110	No CR	No disease in BM and blood since Day 29 but EMD remission initially not confirmed by PET/CT. Although CR on D110 upon additional EMD assessed by PET/CT but bi BM, so can't adjudicate CR. Allo HSCT on D128.
	CRi	CRi	29	60	-	-	MLFS on D29. CRi based on blood count recovery and full assessment on D60. No full blood count recovery prior to patient proceeded to Allo SCT on D92.
	CRi	CRi	30	122	-	-	Day 30 MLFS. No BM until D122 which should be CRi ANC 0.3, platelet183.
	CR	CR	57	190	190	190	No disease in BM and blood since Day 28 but EMD remission initially not confirmed by PET/CT. Blood count recovery on Day 125 but no BM done. CR based on blood count recovery and full assessment achieved on D190.
	CR	CR	220	290	220	290	No disease in BM and blood since Day 27 but EMD remission initially not confirmed by PET/CT. Day 220 EMD assessed by PET/CT but no BM done. CR based on full assessment on D290.
	CR	CR	27	86	63	86	D27 is MLFS not CRi (ANC 600 and platelet 97). BM done on D27 and then D86. CR is not until D86 when BM was done.
	CRi	CRi	27	97	-	-	MLFS on D27. CRi based on blood count recovery and full assessment on D97. CR never achieved.

Source: FDA Analysis, ADEFIRC, ADRS, ADSLFDA1 datasets

Abbreviations: AE, adverse event; ANC, absolute neutrophil count; BM, bone marrow; BOR, best overall response; CR, complete remission; CRi, complete remission with incomplete recovery of counts; CT, computed tomography; EMD, extramedullary disease; GCSF, granulocyte-colony stimulating factor; IRRC, Independent Response Review Committee; MLFS, morphologic leukemia-free state; PET, positron emission tomography; SCT, stem cell transplant

Reviewer comment: *The primary endpoint of the study of OCR at any time was met. The CR within 3 months and OCR rates at any time after treatment with obe-cel in FELIX study did not change substantially by FDA's adjudication, which resulted in exclusion of 6 patients from the primary efficacy population (who received OOS product), reclassification of disease response from response to no response for 8 patients, reclassification from CR within 3 months for one patient, and delay in onset of CR for 11 patients.*

Efficacy Results – Other Relevant Secondary Endpoints

Duration of Remission (DOR)

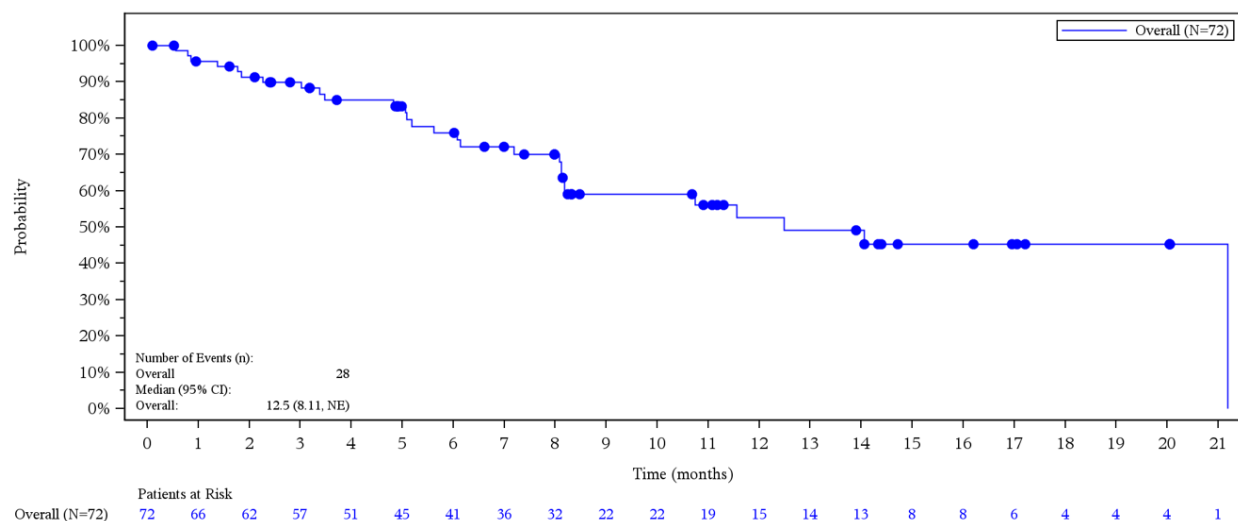
Data:

All patients in remission at any time post-infusion (CR or CRi by IRRC) were included in the DOR analysis and time from first onset of remission to morphological relapse or death due to any reason was assessed, with censoring of SCT or any other B ALL new anti-cancer therapies.

As of 13-Sep-2023 cut off, in Cohort IIA a large proportion of patients are still ongoing in remission without an event (44.4%, 32/72). The estimated median DOR (95% CI) is 12.48 months (8.11, NE) in these patients ([Applicant Figure 7](#); Module 2.7.3 Summary of Clinical Efficacy, Addendum - D30 Update, Section 2.3.1.2). The probability of ongoing remission at 6 months after remission onset is evidenced by a Kaplan Meier (KM) probability estimate of 75.9% (95% CI: 63.1, 84.8) in all infused patients. The KM probability estimate (95% CI) at 9 months after remission onset was 59.0% (44.5, 70.9). Timepoints beyond 9 months after remission onset are not considered mature enough for reliable interpretation given that the median duration of follow-up using reverse KM method is estimated at 10.7 months.

In the subset of infused patients with $\geq 5\%$ blasts in BM at LD in Cohort IIA, durable remission was observed, with 37.7% (20/53) patients in ongoing remission without relapse, death, or use of SCT/other non-protocol therapies ([Applicant Table 9](#)). The estimated median DOR (95% CI) in this subset with censoring of SCT/other new non-protocol anti-cancer therapies, was 11.56 months (8.08, NE). The KM probability estimate (95% CI) was 71.5% (55.7, 82.5) at 6 months after remission onset and 52.4% (35.1, 67.2) at 9 months after remission onset.

Applicant Figure 7 Kaplan-Meier Plot of Duration of Remission by IRRC With Censoring for SCT or Other New Non-Protocol Anti-Cancer Therapy (Cohort IIA, Infused Set) – FELIX Study



CI = Confidence interval; CR = Complete remission; CRi = Complete remission with incomplete hematologic recovery; IRRC = Independent Response Review Committee; SCT = Stem cell transplantation

Time is relative to onset of remission; 1 month=30.4375 days.

Median with 95% CIs are calculated from PROC LIFETEST output using method of Brookmeyer and Crowley (1982).

The analysis includes all patients who achieved a best overall response of CR or CRi post obe-cel infusion.

Data cut-off: 13-Sep-2023.

Source: BLA D30 Update - Figure 14.2.7.1.1.ia.

Applicant Table 9 Duration of Remission by IRRC With Censoring for SCT or Other New Non-Protocol Anti-Cancer Therapy (Cohort IIA, Infused Set) – FELIX Study

Parameter	≥ 5% Blast in BM at LD (N=71)	All Infused (N=94)
No. of patients in analysis [1]	53	72
No. of events - n (%)	23 (43.4)	28 (38.9)
Morphological relapse	20 (37.7)	24 (33.3)
Death due to reason other than underlying cancer	3 (5.7)	4 (5.6)
No. of censored observations - n (%)	30 (56.6)	44 (61.1)
Ongoing without event	20 (37.7)	32 (44.4)
SCT	9 (17.0)	11 (15.3)
New non-protocol anticancer therapies other than SCT	1 (1.9)	1 (1.4)
Maximum follow-up (months)	21.2+	21.2+
Median follow-up (months) [2]	10.9	10.7
Quartile Estimates (month) [3]		
50 th	11.56	12.48
95% CI, %	(8.08, NE)	(8.11, NE)
% Event-free probability estimate (95% CI) [4]		
At 6 months	71.5	75.9
95% CI, %	(55.7, 82.5)	(63.1, 84.8)
At 9 months	52.4	59.0
95% CI, %	(35.1, 67.2)	(44.5, 70.9)

BM = Bone marrow; CR = Complete remission; CRi = Complete remission with incomplete hematologic recovery; IRRC = Independent Response Review Committee; LD = Lymphodepletion; NE = Not estimable; No. = Number; SCT = Stem cell transplantation

[1] The analysis includes all patients in the Infused Set who achieved a best overall response of CR or CRi post obe-cel infusion.

[2] Median follow-up is calculated using reverse KM method.

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

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

Data cut-off: 13-Sep-2023.

Source: BLA D30 Update - Table 14.2.7.2.1.iiia.

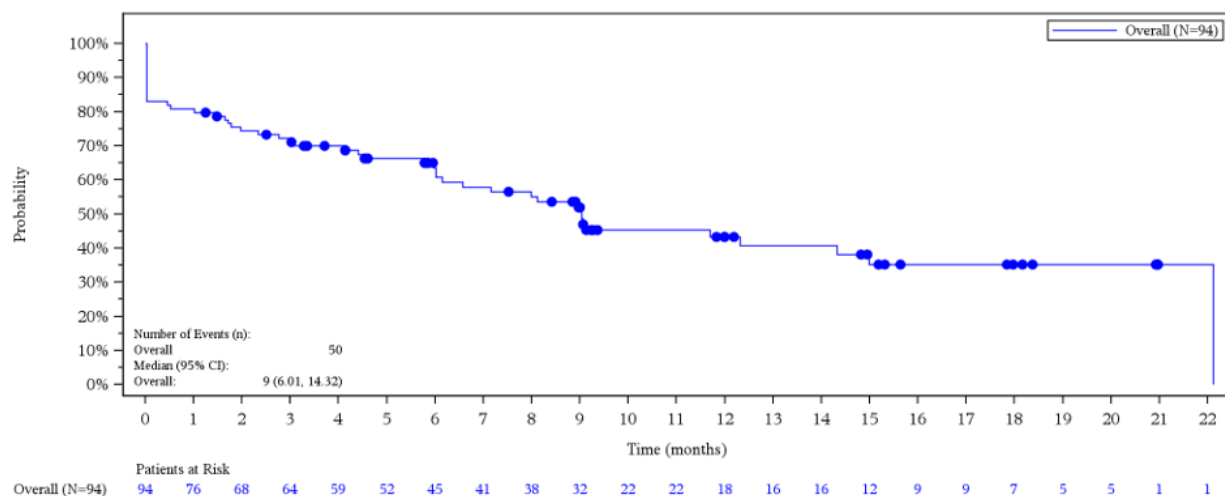
Event Free Survival (EFS)

As of 13-Sep-2023, just over a third of all infused patients in Cohort IIA (34%, 32/94) were surviving in ongoing remission, without use of new non-protocol anti-cancer therapy, including SCT (Module 2.7.3 Summary of Clinical Efficacy, Addendum - D30 Update, Section 2.3.1.3.)

The KM probability estimate for EFS (95% CI) at 6 months post obe-cel infusion, with censoring for SCT or other new non-protocol anti-cancer therapies, was 63.6% (52.1, 72.3) in Cohort IIA ([Applicant Figure 8](#), [Applicant Table 10](#)). The KM probability estimate for EFS (95% CI) at 9 months post obe-cel infusion was 52.0% (40.6, 62.3).

For the subset of patients (N=71) who had ≥ 5% blast in BM at both time of screening and prior to start of LD, the corresponding KM probability value (95% CI) for EFS at 6 months post obe-cel infusion was 58.9% (46.2, 69.7) and at 9 months was 49.0% (35.9, 60.9) ([Applicant Table 10](#)).

Applicant Figure 8 **Kaplan-Meier Plot of Event-free Survival by IRRC With Censoring for SCT or Other New Non-Protocol Anti-Cancer Therapy (Cohort IIA, Infused Set) – FELIX Study**



CI = Confidence interval; IRRC = Independent Response Review Committee; SCT = Stem cell transplantation.

Time is relative to first obe-cel infusion; 1 month=30.4375 days.

Median with 95% CIs are calculated from PROC LIFETEST output using method of Brookmeyer and Crowley (1982).

Data cut-off: 13-Sep-2023.

Source: BLA D30 Update - Figure 14.2.12.1.1.iiia.

Applicant Table 10 Event-Free Survival with Censoring for SCT and Other New Non-Protocol Anti-Cancer Therapy (Cohort IIA, Infused Set) – FELIX Study

Parameter	≥ 5% Blast in BM at LD (N=71)	All Infused (N=94)
Number of patients in analysis	71	94
Number patients with event, n (%)	41 (57.7)	50 (53.2)
Morphological relapse	20 (28.2)	24 (25.5)
Treatment failure	14 (19.7)	16 (17.0)
Death	7 (9.9)	10 (10.6)
Number of patients censored, n (%)	30 (42.3)	44 (46.8)
Ongoing with no event	20 (28.2)	32 (34.0)
SCT	9 (12.7)	11 (11.7)
Other new non-protocol anti-cancer therapy	1 (1.4)	1 (1.1)
Maximum follow-up (months)	22.1	22.1
Median follow-up (months) [2]	11.8	11.8
Quartile Estimate (95% CI) (month) [2]		
50th	8.97 (5.75, 12.32)	9.03 (6.01, 14.32)
% EFS probability estimate (95% CI) [3]		
At 6 months	58.9 (46.2, 69.7)	63.6 (52.7, 72.6)
At 9 months	49.0 (35.9, 60.9)	52.0 (40.6, 62.3)

BM = Bone marrow; CI = Confidence interval; EF = Event-free; EFS = Event-free survival; LD = Lymphodepletion; SCT = Stem cell therapy

[1] With censoring for SCT and other new non-protocol anti-cancer therapy.

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

[3] Percent event-free probability estimates are obtained from the KM survival estimates, with 95% CIs estimated using Greenwood formula.

Data cut-off: 13-Sep-2023.

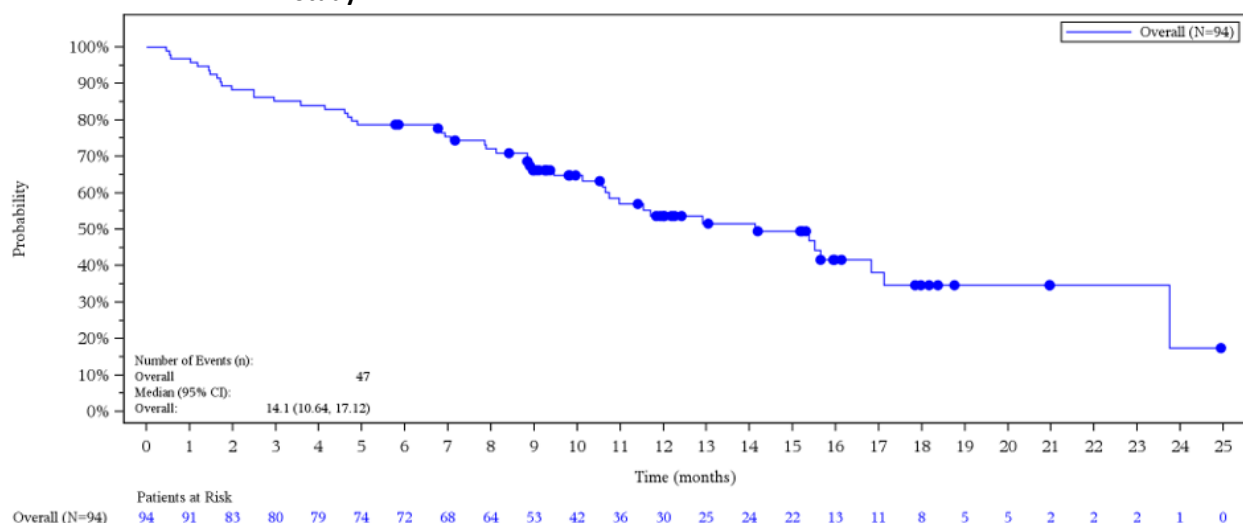
Source: BLA D30 Update - Table 14.2.12.2.2.iiia.

Overall Survival

As of 13-Sep-2023, a high proportion of patients in Cohort IIA are still alive (50.0%, 47/94)(Module 2.7.3 Summary of Clinical Efficacy, Addendum - D30 Update, Section 2.3.1.4).

For a long-term endpoint such as OS the data values should be interpreted with caution. Nevertheless, the KM probability estimate (95% CI) for OS at 6 months in Cohort IIA was 78.7% (69.0, 85.7). The KM probability estimate for OS (95% CI) at 9 months post obe-cel infusion was 66.2% (55.6, 74.9) ([Applicant Figure 9](#)).

In the subset with ≥ 5% blasts at LD (N=71) the KM probability estimate for OS at 6 months post obe-cel infusion was 77.5% (95% CI: 65.9, 85.5) and at 9 months 65.4% (95% CI: 52.9, 75.3) ([Applicant Table 11](#)).

Applicant Figure 9 Overall Survival Without Censoring for SCT (Cohort IIA, Infused Set) – FELIX Study

CI = Confidence interval; SCT = Stem cell transplant.

Time is relative to first obo-cel infusion; 1 month=30.4375 days.

Median with 95% CIs are calculated from PROC LIFETEST output using method of Brookmeyer and Crowley (1982).

Data cut-off: 13-Sep-2023.

Source: BLA D30 Update - Figure 14.2.16.1.1.iiia.

Applicant Table 11 Overall Survival Without Censoring for SCT (Cohort IIA, Infused Set) – FELIX Study

Parameter	≥ 5% Blast in BM at LD (N=71)	All Infused (N=94)
Number of patients in analysis	71	94
Number patients with event (death), n (%)	38 (53.5)	47 (50.0)
Number of patients censored (alive), n (%)	33 (46.5)	47 (50.0)
Quartile Estimate (95% CI) (month) [2]		
50th	14.13 (10.12, 16.82)	14.13 (10.64, 17.12)
% EF probability estimate (95% CI) [3]		
At 6 months	77.5 (65.9, 85.5)	78.7 (69.0, 85.7)
At 9 months	65.4 (52.9, 75.3)	66.2 (55.6, 74.9)

BM = Bone marrow; EF = Event-free; LD = Lymphodepletion; OS = Overall survival; SCT = Stem cell therapy

[1] Without censoring for SCT

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

[3] Percent event-free probability estimates are obtained from the KM survival estimates, with 95% CIs estimated using Greenwood formula.

Data cut-off: 13-Sep-2023.

Source: BLA D30 Update - Table 14.2.16.2.1.iiia.

The Applicant's Position:

FELIX results have demonstrated clinically meaningful and durable remission following obo-cel infusion in adult patients with r/r B ALL. The median duration of follow-up in the FELIX study is shorter than the current median DOR and OS, therefore the median DOR and OS and point estimates beyond median follow up should be interpreted with caution.

Long-term efficacy of obe-cel is supported by the large proportion of responders (44.4%; 32/72) in Cohort IIA who are still in ongoing in remission and did not require any additional non-protocol anti-cancer therapies, including SCT. Furthermore, persistency of CAR T cells was observed in 78.1% of these patients.

As of the 13-Sep-2023 data cut-off date, the longest duration of survival follow-up in the FELIX study was 24.9 months in Cohort IIA and 36.5 months in all cohorts.

Long term efficacy data following obe-cel treatment from the ALLCAR19 study, which has enrolled a comparable population to the FELIX study and used the same obe-cel infusion regimen, supports the long-term efficacy of obe-cel. Thirty-five percent (7/20) of patients were reported in ongoing CR without SCT or other new anti-cancer therapies (representing 41.2% of responding patients [7/17]), with a median of 36 months follow-up; all these patients still had detectable CAR T cells. Given the similarities between the studies, it is expected that data from the FELIX study would align with the observed long-term efficacy in the ALLCAR19 study.

Taken as a whole, the efficacy results from the primary, secondary and subgroup analyses provided demonstrate clinically relevant and durable remission following obe-cel infusion in adult patients with r/r B ALL, including difficult-to-treat patients with high disease burden, multiple lines of prior treatment, and other predictors of poor prognosis.

The FDA's Assessment:

Duration of CR within 3 months

[FDA Table 15](#) summarizes the Duration of CR within 3 months results in the efficacy-evaluable population per FDA adjudication.

FDA Table 15. Efficacy Results (Duration of Complete Remission) Per FDA's Adjudication

Number of Patients Who Had a BOR of CR Within 3 Months		N=27
Number of events, n (%)		11 (40.8)
Morphological relapse		11 (40.8)
Censored, n (%)		16 (59.2)
Ongoing without events		10 (37.0)
SCT		6 (22.2)
Duration of CR (months)		-
Median		14.1
95% CI		(6.1, NR)
Range		(0.5+, 21.2)
Median follow-up time (months)		7.4
Percentage of patients with remission duration n (%)*		-
≥6 months		15 (55.6)
≥12 months		4 (14.8)
≥18 months		1 (3.7)

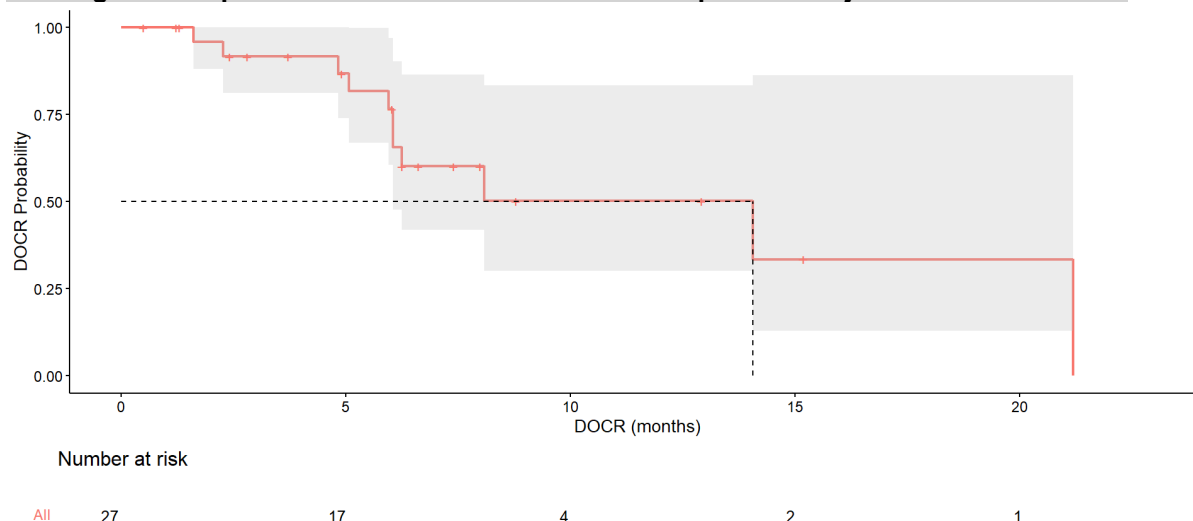
Source: FDA statistical reviewer's analysis

*The estimated percentage of patients with remission duration of ≥ 6, ≥ 12, and ≥ 18 months is presented using the observed duration of remission (not with 95% CIs using the KM method).

Abbreviations: BOR, best overall response; CR, complete remission; NR, not reached; SCT, stem cell transplant

[FDA Figure 2](#) below shows the Kaplan-Meier (KM) curve of Duration of CR per FDA adjudicated assessment.

FDA Figure 2. Kaplan-Meier Curves of Duration of CR* per FDA-Adjudicated Assessment



Source: FDA statistical reviewer's analysis

*For patients achieving CR within 3 months of obe-cel infusion

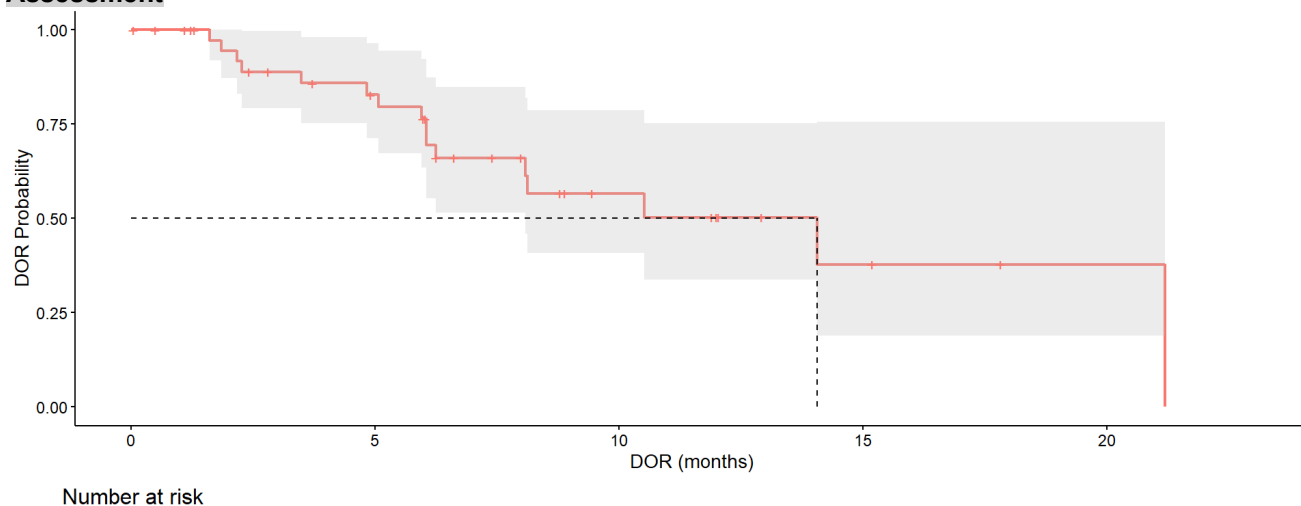
Abbreviations: CR, complete remission; DOCR, duration of complete remission

Duration of Overall Complete Remission At Anytime

For analysis of duration of OCR at any time (which includes CR and CRi), per FDA adjudicated assessment, see [FDA Figure 3](#) below which shows the KM curve.

Among patients in the efficacy evaluable population who achieved a best response of CR "At Anytime" (N=33; 51%), the median duration for remission was 14.1 months (95% CI: 6.1, NR). Among patients in the efficacy evaluable population in whom best response was CRi "At Anytime" (N=8; 12%), the median duration of remission was 10.5 months (95% CI: 1.8, NR).

FDA Figure 3. Kaplan-Meier Curves of Duration of OCR At Anytime per FDA-Adjudicated Assessment



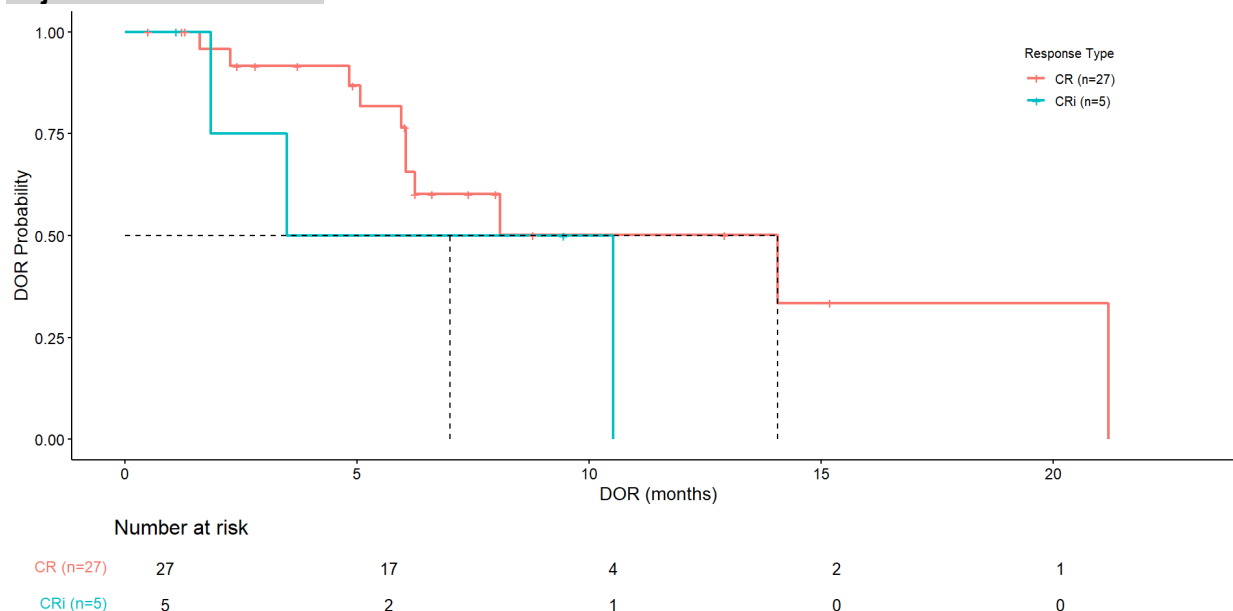
Source: FDA statistical reviewer's analysis

DOR in the graph refers to the duration of OCR

Abbreviations: OCR, overall complete remission which includes complete remission and complete remission with incomplete hematologic recovery, at any time; DOR, duration of remission.

[FDA Figure 4](#) below shows the KM curve of duration of remission within 3 months of obe-cel infusion, for patients who achieved BOR of CR vs. CRi, per FDA adjudicated assessment.

FDA Figure 4. Kaplan-Meier Curves of Duration of OCR (CR vs. CRi) Within 3 Months per FDA-Adjudicated Assessment



Source: FDA Statistical Reviewer

Abbreviations: CR, complete remission; CRi, complete remission with incomplete hematologic recovery; DOR, duration of remission

MRD

The Applicant included MRD data in BLA submission in the ADZB dataset. MRD was measured by either (b) (4)

The Applicant claimed that the (b) (4) MRD assay has been validated to a Laboratory Developed Test in two laboratories, (b) (4)

Per the Applicant, the assay is validated to assess MRD in bone-marrow aspirate specimens from patients with a prior diagnosis of B-ALL by (b) (4). The Applicant submitted additional information regarding the MRD assay under the original BLA submission SN0001, as well as in response to clinical information requests #4 and #6 submitted under SN 0014 and SN 0018; respectively. The Review team consulted CDRH to evaluate if the (b) (4)

MRD assay has been appropriately analytically validated for the proposed cut-off point (<0.01%) to provide a reliable answer in determining MRD as an efficacy endpoint in the FELIX study.

CDRH review team concluded that the (b) (4) MRD assay is not analytically validated for the proposed cut-off point. Therefore MRD results were not considered during this BLA.

Reviewer comment: The Applicant stated in response to the IR mentioned above that they do not propose to include MRD data in the USPI.

Dose/Dose Response

Data:

As discussed in [Section 6.4](#), most patients (88.3%) infused with obe-cel in Cohort IIA received the total target dose of 410×10^6 cells. The number of patients who did not receive the target dose as per protocol (n=11) is small, and the reasons for not receiving the target dose are heterogeneous, therefore it is not feasible to draw firm conclusions on dose-efficacy or dose-safety relationships.

Dose-Exposure, Exposure-Efficacy and Exposure-Safety analyses described in [Section 6.4](#) suggested that the CAR T expansion, efficacy, and safety was associated with disease burden prior to lymphodepletion.

The FDA's Assessment:

All 27 patients who achieved CR within 3 months received obe-cel at a total target dose of 410×10^6 CAR T cells ($\pm 25\%$). The median (range) was $410 (318 \text{ to } 416) \times 10^6$ CAR T cells. Of the 41 patients who achieved a BOR of OCR, the median (range) of obe-cel dose was $409 (68 \text{ to } 416) \times 10^6$ CAR T cells (2 patients received a dose of 68 and 94×10^6 CAR T cells, respectively). Five of 24 patients who were non-responders received a dose less than the total target dose (range: $10 \text{ to } 240 \times 10^6$ CAR T cells).

Reviewer comment: It is not possible to draw conclusion on dose-efficacy relationship due to the small number of patients who received lower than the target total dose during the study. The review team agrees that the proposed total target dose of 410×10^6 CAR T cells is adequate.

Durability of Remission

The Applicant's Position:

A durable and clinically meaningful remission following obe-cel infusion was observed in the FELIX study (refer to [DOR](#) and [EFS](#) results in Section 8.1.2) and further supported by results from the ALLCAR19 study with a median follow-up of 36 months ([Section 8.1.4](#)).

The FDA's Assessment:

Refer to description of DOR per FDA's adjudication in the section above.

Reviewer comment: *The Applicant's analyses of time to event endpoints such as EFS and overall survival (OS) from single-arm studies are difficult to interpret due to lack of a comparator and randomization. Therefore, these analyses are considered exploratory and do not support regulatory decision making.*

Persistence of Effect

The Applicant's Position:

A persistent clinical effect has been demonstrated in the FELIX study as of the 13-Sep-2023 cutoff date as shown by the analyses provided ([DOR](#) and [EFS](#) results in Section 8.1.2) and including persistency of CAR T cells ([Section 6.1](#)). Of note, among patients with ongoing remission without new anti-cancer therapies including SCT, 78.1% (25/32) had CAR T cell persistency at last follow-up. This is consistent with results from the ALLCAR19 study where a median follow-up of 36 months is available ([Section 8.1.4](#)).

The FDA's Assessment:

See [Section 6.1](#) and the clinical pharmacology review memo regarding analysis of CAR T cell persistence.

Efficacy Results – Secondary or exploratory COA (PRO) endpoints

The Applicant's Position:

A secondary objective of the FELIX study was to evaluate changes over time in responders in patient-reported outcome (PRO) measures assessing symptoms, functioning, and overall quality of life (QoL) using the non-disease specific EQ-5D-5L and VAS, and symptom, functioning, and Global Health Status (GHS) scores from the cancer-specific European Organization for Research and Treatment of Cancer Quality of Life questionnaire – Core 30 (EORTC QLQ-C30) (Module 2.7.3 Summary of Clinical Efficacy, Section 2.1.4.12).

In 70 patients infused with obe-cel in Cohort IIA with a CR or CRi and evaluable scores, as of the 09-Jun-2023 data cut off, the mean (standard deviation [SD]) observed VAS Score was 64.74 (21.988) at baseline (last score before obe-cel infusion). The mean score at Day 28 was 66.53

(24.922). Starting at Month 3, and in all subsequent months, median scores exceeded baseline scores to levels indicative of meaningful improvement and remained higher than baseline throughout the 12 months (mean VAS Scores 77.87 and 80.06 on at Month 6 and 12, respectively). GHS scores obtained from the EORTC QLQ-C30 questionnaire exceeded baseline scores to levels indicative of meaningful improvement starting at Month 3, and in all subsequent months, average GHS scores remained at that level throughout the 12 months.

The FDA's Assessment:

FELIX study was a single-arm open-label study. PROs in open label studies may be impacted by patients' knowledge of the treatment received. Moreover, no placebo group was present in the study to assess any potential advantage in PROs. Results of any exploratory analysis conducted by the Applicant should be interpreted with caution.

Although the Applicant proposed to include PRO measures as a secondary endpoint, the Applicant did not submit the PRO instruments for FDA's review by the clinical outcome assessment team. FDA considers the analyses of PRO data from FELIX to be exploratory and not suitable to support regulatory decision-making.

Additional Analyses Conducted on the Individual Trial

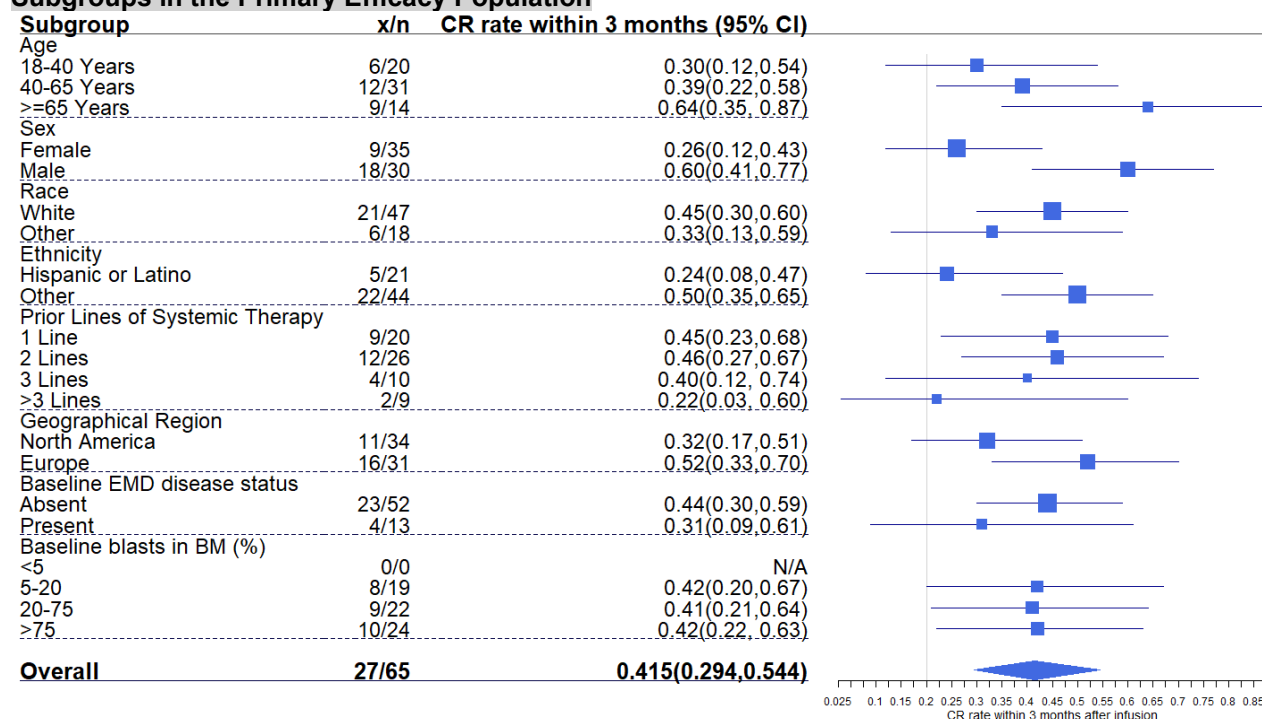
The Applicant's Position:

Subgroup analyses by demographics and disease characteristics were performed in the pivotal FELIX study as described in [Subgroups](#) in Section 8.1.2.

The FDA's Assessment:

[FDA Figure 5](#) shows the forest plot of CR rate within 3 months of obe-cel infusion in the efficacy-evaluable population by key baseline characteristics.

Although the lower limit of the 95% exact Clopper-Pearson confidence interval for CR rate within 3 months since infusion is below the null hypothesis rate of 20% in some subgroups, it is not possible to draw definitive conclusions due to the small sample size in these subgroups. Notably, male patients appear to have double the remission rate of female patients and patients treated in the U.S. had higher remission than those treated in Europe; however, definitive conclusions cannot be drawn due to sample size constraints.

FDA Figure 5. Forest Plot of Complete Remission Rate Within 3 Months of Obe-cel Infusion by Subgroups in the Primary Efficacy Population

Source: FDA statistical reviewer's analysis

Abbreviations: BM, bone marrow; CR, complete remission; EMD, extramedullary disease.

Reviewer comment: Given the small number of patients in these exploratory subgroup analyses, the results of the presented analyses are considered hypothesis generating, and thus definitive conclusions cannot be made about these results.

8.1.3. Integrated Review of Effectiveness

The FDA's Assessment:

Methods

The Applicant proposed the indication "for treatment of adult patients with relapsed or refractory B-cell precursor acute lymphoblastic leukemia (ALL)".

To support the proposed indication, the Applicant submitted efficacy data from one adequate and well controlled study FELIX (Phase 2 Cohort A). The Applicant also included data from additional cohorts (specifically from Phase 1 Cohort A), nonclinical and PK studies as confirmatory evidence. Notably, although FELIX included multiple cohorts, because it was one study, the Applicant did not submit an integrated summary of effectiveness.

Although FELIX was designed with OCR rate at any time as the primary efficacy endpoint, FDA considers CR rate within 3 months from start of therapy to reflect a clinical benefit for patients with r/r B ALL treated with CAR T cell therapies.

In general, responses to induction chemotherapy are expected to occur within 42 days from the start of therapy for treatment of acute leukemia. Delay in count recovery has been observed after CAR T-cell treatments, but the risks from prolonged cytopenias could at least partially negate the clinical benefit. Accordingly, the Agency has previously accepted durable complete remission rate at 3 months to support traditional approval for drugs and biological products to treat B ALL.^{2, 3} Durable CR represents recovery of adequate blood counts to protect against infection, prevent bleeding, and avoid transfusions, which denote clinical benefit.

In addition, B ALL has a well understood pathophysiology; and the preclinical studies provided information on the mechanism of action of obecel which targets CD19. Specifically, the in vitro pharmacology studies resulted in target-specific killing, secretion of pro-inflammatory-associated cytokines, and proliferation. Furthermore, In vivo pharmacology studies demonstrated that obe-cel resulted in significant reduction in tumor burden.

Endpoints

The Applicant reported that in FELIX Phase 2 Cohort A, OCR was achieved in 76.6% (95% CI: 66.7, 84.7) of the 94 patients treated with obe-cel who had morphological disease at screening ($\geq 5\%$ blasts in BM). Among the subpopulation of patients who received obe-cel and had $\geq 5\%$ blasts in the BM at screening and LD, OCR was 74.6% (95% CI: 62.9, 84.2). Since the lower bound of the 95% CI exceed the prespecified limit of 40%, the Applicant concluded that the primary objective was met.

Limiting the efficacy-evaluable population to those patients who received obe-cel, had evidence of disease prior to LD, and who received conforming products, using FDA-adjudicated responses, FDA identified an OCR (including CR and CRi) at any time in 41 (63.1%; 95% CI (50.2, 74.7) of 65 patients and confirmed that the primary objective of the study was met.

FELIX demonstrated a CR rate within 3 months of 42% (95% CI: 29, 54) and median duration of remission of 14.1 months (95% CI: 6.1, NR). The median duration of OCR at any time was 14.1 months (95% CI: 6.2, NR). A treatment effect was observed across the subpopulation analyses.

In FELIX Phase 1 Cohort A, 21 patients were enrolled and 13 patients were treated with obe-cel.

CR rate within 3 months was achieved in 31% (95% CI: 9, 61) of patients, and the OCR at anytime in 54% (95% CI: 25, 81). Because the Phase 1 study was hypothesis-generating and not an adequate and well-controlled trial, the review team recommends including only the outcomes from Phase 2 in labeling.

Reviewer comment: *The same FDA adjudication that was used in the primary analysis was applied when analyzing the efficacy results from the Phase 1 Cohort A.*

² US Prescribing Information for Kymriah, available at <https://www.fda.gov/media/107296/download?attachment>.

³ US Prescribing Information for Tecartus, available at <https://www.fda.gov/media/140409/download?attachment>.

Although the rate of remission was similar to that of the primary efficacy population, definitive conclusions cannot be made to the small sample size and therefore wide 95% CI.

The protocol and SAP listed multiple secondary endpoints including CR with MRD $<10^{-4}$. Because the CDRH review team determined that the MRD assay used in FELIX was not analytically valid for the $<10^{-4}$ cutoff (see Section 4.3), the review team concluded that the MRD data from FELIX are not sufficient to support a labeling claim for obe-cel.

Reviewer comment: *FDA did not agree to the proposed null hypothesis of CR rate within 3 months of 20% and communicated to the Applicant 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 profile.*

Overall, the observed rate and duration of complete remission within 3 months of obe-cel infusion in this relapsed refractory B ALL population demonstrates clinical benefit and constitutes substantial evidence of obe-cel effectiveness. In addition, the supportive data from the additional cohort and the mechanism of action of obe-cel serve as confirmatory evidence to substantiate the results from one adequate and well-controlled trial to demonstrate substantial evidence of effectiveness.

8.1.4. Assessment of Efficacy Across Trials

The Applicant's Position:

The academic-led, proof-of-concept ALLCAR19 study provided important safety and efficacy data to support the initiation of the pivotal FELIX study. Like the FELIX study, ALLCAR19 evaluated a real-world patient population.

In the ALLCAR19 study, 20 adult patients with r/r B ALL received obe-cel which was administered with the same 2-step regimen adapted to tumor burden (Roddie et al, 2021). The efficacy outcomes in the ALLCAR19 study are consistent with the efficacy outcomes in the pivotal FELIX study, although a longer duration of follow-up is available. As of last publication (Roddie et al, 2023), the median follow-up was 36 months and 40% (8/20) of patients infused the obe-cel were in ongoing remission, 7 of whom had not received SCT or other new anti-cancer therapies (representing 41.2% [7/17] of patients who achieved remission, all of whom had CAR T cell persistency).

In view of the similarity in patient population, dosing, and PK profile it is anticipated that the FELIX study will continue to show similar results.

The FDA's Assessment:

The data from FELIX Study are sufficient to evaluate the effectiveness of obe-cel.

ALLCAR19 is an academic-led study which provided proof-of-concept to support the initiation of FELIX Study. The investigational product in ALLCAR19 was manufactured using a different manufacturing process than obe-cel in FELIX and the Applicant did not provide comparability data to support the efficacy review. The clinical information from literature regarding Study ALLCAR19 have potential limitations given the difference in the study endpoints which were related to safety and dosing. Therefore the data from ALLCAR19 are considered supportive and were not reviewed for regulatory consideration.

8.1.5. Integrated Assessment of Effectiveness

The Applicant's Position:

This BLA is based on efficacy results from the pivotal FELIX study only, therefore, this section is not applicable.

The FDA's Assessment:

The efficacy data from FELIX Study Phase 2 Cohort A formed the basis for efficacy claims. Supportive data from Phase 1 Cohort A and the nonclinical data supporting obe-cel mechanism of action are considered confirmatory evidence.

Overall, the results of FDA's analysis of FELIX Study showed a 42% rate of CR within 3 months of infusion of obe-cel with a lower bound of 29.4% in the pivotal Phase 2 Cohort A, a duration of CR that is estimated to exceed 6 months for more than half the patients, and similar outcomes in the subgroup of patients in the Phase 1 Cohort A portion of the study. A treatment effect was observed across the subpopulation analyses. This is concluded to be substantial evidence of the effectiveness of obe-cel for treatment of adult patients with r/r B ALL.

8.2. Review of Safety

8.2.1. Safety Review Approach

Data:

The safety profile of obe-cel in the treatment of r/r B ALL is primarily based on safety data from all patients who have received at least one dose of obe-cel in the FELIX study (N=127), so includes all cohorts and both phases of the study, providing the most comprehensive evaluation over the longest duration of follow-up.

Safety was assessed in all patients receiving obe-cel by physical examination, vital signs, oxygen saturation and weight, neurocognitive assessment, Eastern Cooperative Oncology Group (ECOG) performance status, clinical laboratory tests, AE and SAE monitoring and concomitant medication usage (Module 2.7.4 Summary of Clinical Safety, Section 1.1.3).

Any clinically relevant changes occurring during the study had to be recorded in the AE section of the eCRF according to the safety reporting requirements. All AEs and SAEs were to be reported from the time of screening (ICF signature) to Month 6. From Month 6 to the end of study /patient

withdrawal, all AEs considered related to obe-cel, all other significant AEs, all AEs related to study procedures (e.g. BM assessments, lumbar punctures) regardless of relationship to obe-cel and all SAEs were to be reported. If a patient started new anticancer therapy or underwent hematopoietic SCT, only AEs that were considered related to obe-cel were to be reported. Adverse events were followed until resolution, assessed stable by the Investigator, patient lost to follow-up, withdrawal of consent, death, or study completion.

The safety data presented within this Clinical Assessment Aid reflect the aggregated data obtained as of the 13-Sep-2023 data cut-off date (Module 5.3.5.2, Safety Update Report).

The FDA's Assessment:

FELIX Study formed the basis for the primary safety review. The primary safety population included all 100 patients from Phase 1b Cohort A and Phase 2 Cohort A who received at least one dose of obe-cel conforming product. Because the treatment regimen was similar between the Phase 1b and Phase 2, safety analyses were pooled and displayed for all 100 patients.

FDA excluded patients who received obe-cel in Cohorts B and C from the primary safety population, to not underestimate safety outcomes as the safety profile of patients with B ALL who have bone marrow blasts of $\geq 5\%$ is different than in patients who are in morphological remission and have only MRD-positive disease or those who have isolated extramedullary disease. Data from Cohorts B and C were considered supportive.

The primary safety review was based on the data submitted on Day 30 with the data cutoff date of September 13, 2023.

The administration of obe-cel is preceded by LD consisting of cyclophosphamide and fludarabine; therefore, the safety assessment evaluated the entire treatment regimen, including LD and obe-cel. Additionally, patients may receive other concomitant medications, which may potentially confound the casualty of AEs occurring after obe-cel administration. During the safety review, adverse drug reactions were defined as TEAEs, treatment-emergent SAEs, and AESIs with onset or worsening after the start of obe-cel infusion, regardless of perceived relationship and causality with the investigational product.

The Applicant reported AEs of organ systems by preferred terms, which may underestimate the incidence of some AEs; therefore, the FDA grouped the preferred terms that represented the same pathophysiologic process in order to minimize such underestimation. The grouping practice used to analyze the AEs is consistent with the approach used for marketing applications of similar class of products. All grade AEs were counted by maximum toxicity grade (i.e., multiple incidences of the same AE in one patient are counted once at the worst grade for this patient).

Reviewer comment: *The Patient IDs of the patients who received OOS products in the Phase 1b/2 Cohorts A who were excluded from FDA's safety population are: (b) (6)*

(this patient had baseline blasts $< 5\%$ prior to LD).

8.2.2. Review of the Safety Database

Overall Exposure

Data:

Bridging Therapy

Most of the 127 patients in the Safety Set (118 patients, 92.9%) received bridging therapy after leukapheresis until 1 week prior to LD. Bridging therapy was based on Investigator's choice and primarily included chemotherapy alone or chemotherapy with TKI (90 patients, 70.9%). Inotuzumab ozogamicin alone or in combination with chemotherapy was administered to 18 of 127 infused patients (14.2%) (Module 2.7.4 Summary of Clinical Safety, Section 1.2.2; BLA D30 Update -Table 14.1.4.1.1).

Lymphodepletion Treatment

All 127 patients infused with obe-cel in Phase Ib and Phase II (Safety Set) received LD treatment with fludarabine and cyclophosphamide. The median fludarabine total dose was 120 mg/m² (range 68 to 240) and the median cyclophosphamide total dose was 1000 mg/m² (range: 700 - 2000) (Module 2.7.4 Summary of Clinical Safety, Section 1.2.3; BLA D30 Update -Table 14.1.4.3.1).

Extent of Exposure to Obe-cel Therapy

Of all 127 patients in Phase Ib and Phase II who completed or discontinued infusion with obe-cel, 11 patients did not receive the target dose of 410×10^6 CD19 CAR-positive T cells ($\pm 25\%$), 7 of them received the first dose only ([Applicant Table 12](#)) (Module 2.7.4 Summary of Clinical Safety, Section 1.2.4). Eight patients received lower or higher than planned first or second doses of obe-cel and 9 patients had the second split dose delayed but still received the target dose within the protocol defined range.

Applicant Table 12 Obe-cel Exposure (Phase Ib and Phase II, Safety Set) – FELIX Study

Phase Ib and II - All Cohorts

	Infused (N=127)
Total calculated CAR-positive T cells received (10^6 cells) [1]	
Mean (SD)	379.9 (89.94)
Median	410.0
Q1 - Q3	405.0 - 413.0
Min - Max	10 - 480
Patient received both obe-cel doses	120 (94.5)
Patient received only first obe-cel dose	7 (5.5)
Patients receiving the target dose [2]	116 (91.3)
Patients not receiving the target dose	11 (8.7)

CAR=Chimeric antigen receptor; Q=Quarter; SD=Standard deviation

Infused set comprises of all patients who have received at least 1 infusion of obe-cel.

Disease burden was determined by the % bone marrow blast by morphological assessment prior to the start of lymphodepletion therapies. Patients with low disease burden ($\leq 20\%$ blasts) at lymphodepletion received 100×10^6 CD19 CAR-

positive T cells on first dose and 310×10^6 CD19 CAR-positive T cells on second dose. Patients with high disease burden ($> 20\%$ blasts) at lymphodepletion 10×10^6 CD19 CAR-positive T cells on first dose and 400×10^6 CD19 CAR-positive T cells on second dose.

[1] All percentages below were based on number of patients who have completed or discontinued obe-cel infusions as the denominator.

[2] Target dose is 410×10^6 CD19 CAR-positive T cells (+/-25%).

Data cut-off: 13-Sep-2023.

Source: BLA D30 Update – Table 14.1.4.4.4.

A total of 9 patients received their second dose after the protocol pre-specified Day 10 ± 2 days due to the occurrence of AE (range: Day 13 - Day 21). No patient had the second split dose infusion beyond the protocol allowed Day 21.

In the overall population of infused patients in Phase Ib and Phase II, the median time from screening (i.e. providing informed consent) to enrollment (i.e. leukapheresis) was 17 days (range: 5 - 169), the median time from informed consent to first obe-cel infusion was 61 days (range: 36 - 219), and the median time from enrollment (leukapheresate accepted by manufacturing) to first obe-cel infusion was 38 days (range: 33 - 48 days). These medians were similar in Cohort IIA and in the subgroup of patients with $\geq 5\%$ blasts at LD.

The FDA's Assessment:

[FDA Table 16](#) provides a summary of obe-cel exposure in the safety analysis set.

FDA Table 16. Obe-cel Exposure, Safety Analysis Set

Exposure	Safety Analysis Set (N=100)
Total calculated CAR-positive T cells received (10^6 cells)	-
Mean (SD)	376 (98.5)
Median	410.0
Q1-Q3	406.0-413.0
Min-max	10-480
Patient received both obe-cel doses	93 (93.0)
Patient received only first obe-cel dose	7 (7.0)
Patients receiving the target dose	90 (90.0)
Patients not receiving the target dose	10 (10.0)

Source: FDA Analysis, ADSL, ADSLFDA1, ADEX datasets

Abbreviations: CAR, chimeric antigen receptor; SD, standard deviation

Reviewer comment: Overall, exposure to obe-cel was within the target planned in the study protocol and is adequate to support characterization of the safety profile of obe-cel.

Relevant characteristics of the safety population:

The Applicant's Position:

The demographic characteristics of the Safety Set are presented in [Section 8.1.2](#).

The FDA's Assessment:

Demographics characteristics for patients in the safety analysis set are presented in [FDA Table 17](#) below. The median age was 49.5 years (Range: 20 to 77 years old) with equal male and female representation. White and non-Hispanic were the predominant race and ethnic groups, and half the patients were treated in the U.S.

FDA Table 17. Demographic Characteristics, Safety Analysis Set

Demographic Group	Safety Population N=100
Age	-
<65	80
≥65	20
Mean (SD)	48.0 (16.5)
Median (Range)	49.5 (20–77)
Sex	-
Female	50
Male	50
Race	-
White	75
Asian	12
Unknown	12
Native Hawaiian or Other Pacific Islander	0
American Indian or Alaska Native	0
Black African or African American	1
Ethnicity	-
Not Hispanic or Latino	63
Hispanic or Latino	30
Unknown	7
Country	-
USA	50
GBR	39
Spain	11

Source: FDA analysis, ADSL dataset

Abbreviations: GBR, Great Britain; SD, standard deviation; USA, United States of America

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)The Applicant's Position:

Baseline characteristics of the Safety Set is presented in [Section 8.1.2](#).

The FDA's Assessment:

Baseline disease characteristics are displayed in [FDA Table 18](#) below.

FDA Table 18. Baseline Disease Characteristics, Safety Population

Parameter	Safety Analysis Set (N=100)
Prior therapies	
Refractory to all prior lines of anti-cancer therapy, n (%)	9 (9.0)
Refractory to first line therapy, n (%)	23 (23.0)
Refractory to last prior line of therapy, n (%)	56 (56.0)
Relapsed to first line therapy within 12 months, n (%)	46 (46.0)
Number of prior lines of therapy	
Median	2.0
Min-max	1-6
Number of prior lines of therapy categorized, n (%)	
1	26 (26.0)
2	42 (42.0)
3	17 (17.0)
≥4	15 (15.0)
Previous alloSCT, n (%)	42 (42.0)
Previous blinatumomab, n (%)	36 (36.0)
Previous inotuzumab ozogamicin, n (%)	33 (33.0)
Previous blinatumomab and inotuzumab ozogamicin, n (%)	16 (16.0)
Previous blinatumomab or inotuzumab ozogamicin, n (%)	53 (53.0)
Cytogenetics	
Complex karyotype	43 (43.0)
Philadelphia-chromosome positive B ALL, n (%)	28 (28.0)
Disease characteristics at screening	
EMD present, n (%)	21 (21.0)
BM blasts (%)	
Median	58.9
Min-max	6-100
BM blasts by morphology categorized, n (%)	
>75%	39 (39.0)
>20% to ≤75%	33 (33.0)
≥5% to ≤20%	28 (28.0)
<5%	0
Disease characteristics at lymphodepletion	
EMD present, n (%)	20 (20.0)
BM blasts (%)	
Median	43.0
Min-max	0-100
BM blasts by morphology categorized, n (%)	
>75%	35 (35.0)
>20% to ≤ 75%	28 (28.0)
≥5% to ≤20%	13 (13.0)
<5%	24 (24.0)

Source: FDA analysis, ADSL dataset

Abbreviations: B ALL, B-cell precursor acute lymphoblastic leukemia; BM, bone marrow; EMD, extramedullary disease; SCT, stem cell transplant

Adequacy of the safety database:The Applicant's Position:

The size of the safety database for FELIX, a total of n = 127 patients, is considered adequate to support the benefit/risk assessment for treatment with obe-cel in adult (18 years or older) patients with r/r B ALL and adequately represents the target patient population.

The FDA's Assessment:

The FDA concurs with the Applicant that the safety database (N=100) is considered adequate to identify most common AEs, support benefit-risk assessment, and represent the target patient population of adults with r/r B ALL.

8.2.3. Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

The Applicant's Position:

No issues relating to safety data integrity or quality in the FELIX study were identified.

The FDA's Assessment:

After FDA's adjudication of safety data, FDA requested that the Applicant submits updated datasets that reflect FDA's adjudication and analysis population. The Applicant submitted the updated datasets (ADSLFDA1, ADAEFDA, and ADLB). ADAEFDA included FDA grouped terms (GTs).

Categorization of Adverse Event

The Applicant's Position:

Treatment-emergent adverse events (TEAEs), hereafter referred to as AEs, were defined as AEs with an onset on or after the first obe-cel infusion. AEs were coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 26.0, and the severity of AEs was graded using the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.

AEs that could potentially be significant for the treatment of B ALL following CAR T cell therapy included important identified risks (CRS, ICANS, prolonged cytopenias, HLH/MAS, hypogammaglobulinaemia, severe infections) and important potential risks (tumor lysis syndrome (TLS), antigenicity/immunogenicity, graft-versus-host disease (GvHD), secondary malignancies, hypersensitivity reactions, overdose/medication error).

The severity of AEs was assessed using the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (NCI CTCAE) V5.0.

Cytokine release syndrome (CRS) and Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS) were graded according to the American Society for Transplantation and Cellular Therapy (ASTCT) consensus grading ([Lee et al, 2019](#))

Other AEs that are not defined by these grading systems were evaluated for severity using a scale of mild, moderate, severe, life-threatening, and fatal, which was mapped to an allocated Grade 1 through to Grade 5. As ICANS can present with multiple signs and symptoms (e.g. confusion, aphasia, encephalopathy, seizure), ICANS was reported as an AE with the appropriate grading in the eCRF. In addition, AEs associated with ICANS were recorded separately with the appropriate CTCAE grading as applicable.

The FDA's Assessment:

FDA requested that the Applicant submits updated ADAE dataset to reflect FDA's adjudication of neurologic toxicity which is broader definition than ICANS and includes all AEs under the nervous and psychiatric system organ class (SOCs).

Several AEs are presented, throughout the review memo, as GTs as defined by FDA. The complete list of FDA grouped terms for all TEAEs is presented in Section [18.3](#). Unless otherwise specified, all analyses and tables in FDA's assessment sections were generated by the FDA review team.

Note that the terms AEs and TEAEs are used interchangeably in this review except when discussing adverse events that occurred during the leukapheresis or chemotherapy conditioning periods where the AEs were considered not treatment-emergent.

Routine Clinical Test

The Applicant's Position:

Routine clinical safety assessments included clinical laboratory analyses, vital signs measurements, electrocardiograms (ECGs), and physical examinations. Specialty tests were conducted for antibodies to obe-cel.

The FDA's Assessment:

See schedule of assessments in [FDA Table 38](#) in Section [18.4](#). Overall, the schedule of testing in FELIX is considered adequate for the assessment of safety.

8.2.4. Safety Results

Deaths

Data:

Deaths Prior to Obe-cel Infusion

Of 153 patients enrolled in Phase Ib and Phase II of the FELIX study, 22 patients (14.4%) died after enrollment but prior to obe-cel infusion. All 22 patients had morphological disease at screening (Cohort A; $\geq 5\%$ blasts in the BM), 8 patients died in Phase Ib and 14 patients in Phase II of the study.

The most common reasons for death after enrollment but before obe-cel infusion were progressive disease (11 patients, 7.2%) and AEs (10 patients, 6.5%). Additional information is provided in Module 2.7.4 Summary of Clinical Safety, Section 2.1.1.

Deaths After Obe-cel Infusion

A total of 59 of 127 patients in the Safety Set (41.7%) died at any time post obe-cel treatment ([Applicant Table 13](#)). Most of these 59 patients (44 patients, 74.6%) had $\geq 5\%$ blasts in BM at the time of LD.

Within 30 days post obe-cel infusion, 5 patients (3.9%) died (3 due to progressive disease and 2 due to AE [sepsis and cerebrovascular accident]). None of these early deaths were suspected to be related to obe-cel.

The primary reason for deaths at any time post obe-cel infusion was progressive disease (40 of 127 patients, 31.5%). The second most common reason for death was AE (16 patients, 12.6%). Of the 16 patients who died due to AEs, 2 patients (1.6%) experienced a total of 3 fatal TEAEs that were suspected to be related to obe-cel treatment (acute respiratory distress syndrome, ICANS and neutropenic sepsis). The other 14 deaths (11.0%) were not suspected to be related to obe-cel treatment. For 3 patients, reasons were recorded as 'other' (see footnote to below the table for more information).

Applicant Table 13 Deaths Any Time After Obe-cel Infusion (Phase Ib and Phase II, Safety Set) – FELIX Study

Parameter Preferred term	Total (N=127) n (%)
Deaths at any time post obe-cel infusion	59 (46.5)
Deaths within 30 days after post obe-cel infusion	5 (3.9)
Primary reason of death at any time post obe-cel infusion	
Progressive Disease	40 (31.5)
Adverse Event	16 (12.6)
By relationship to obe-cel	
Related	2 (1.6)
Acute respiratory distress syndrome	1 (0.8)
ICANS	1 (0.8)
Neutropenic sepsis	1 (0.8)
Not related	14 (11.0)
Multiple organ dysfunction syndrome	3 (2.4)
Respiratory failure	2 (1.6)
Sepsis	2 (1.6)
Abdominal infection	1 (0.8)
Acute myeloid leukaemia	1 (0.8)
Acute respiratory failure	1 (0.8)
Ascites	1 (0.8)
Cerebrovascular accident	1 (0.8)
Neutropenic sepsis	1 (0.8)
Polyserositis	1 (0.8)
Status epilepticus	1 (0.8)
Other [1]	3 (2.4)

ICANS= Immune effector cell-associated neurotoxicity syndrome; MedDRA = Medical Dictionary for Regulatory Activities.

[1] Investigator supplemental information clarified that the cause of death of one patient was steroid refractory GvHD and sepsis due to second allogeneic SCT in MRD-negative remission at Day 140 post obe-cel treatment and was not related to obe-cel (also being more than 6 months post T cell treatment it was not qualified as an AE by site). Another patient died due to graft-versus-host disease (GvHD) and septic shock on Day 468. This was not reported as an AE because it occurred post second allogeneic transplant. The third patient, died on Day 288 due to multi-organ failure and septic shock in the context of relapsed disease, having received another CAR T product (UCART22) on Day 205, and therefore not reported as an AE in the FELIX study. Adverse events (AEs) were coded using MedDRA 26.0.

Data cut-off: 13-Sep-2023.

Source: BLA D30 Update – Table 14.3.3.1.3.

Most patients died either without achieving CR or CRi (22 of 59 patients, 17.3%) or while in relapse after having achieved CR or CRi (24 of 59 patients, 18.1%).

Seven patients (5.5%) died while in remission with no subsequent therapies received due to AEs not related to obe-cel treatment. Another 7 patients (5.5%) died after achieving remission and after having received subsequent therapies. These deaths were deemed unrelated to obe-cel treatment by the Investigator.

Additional information is provided in BLA D30 Safety Update Report, Section 3.1.2.

The FDA's Assessment:

Among the 52 patients from the safety population who died during the study, the Applicant states that 36 patients died of progression of disease, 14 patients died of AE, and 2 patients died of other causes. Moreover, the Applicant states that fatal adverse drug reactions (ADRs) occurred in only two patients (due to neutropenic sepsis and acute respiratory distress syndrome and ICANS). However, based on FDA's review of all narratives and data files, FDA identified a total of nine patients (all from Phase 2 Cohort A) who experienced ADRs since the relatedness of the fatal outcome of these AEs to the investigational product or the treatment regimen (which is inclusive of the LD) cannot be excluded. The ADRs include infections (sepsis, pneumonia, peritonitis), ascites, pulmonary embolism, acute respiratory distress syndrome, HLH/MAS, and ICANS. [FDA Table 19](#) summarizes FDA's adjudication of the root cause of death events.

FDA Table 19. Summary of FDA Adjudicated Fatal Adverse Reaction, Safety Analysis Set

Patient Identifier	Age (years)	Sex	Death Study Day	Applicant's Cause of Death	FDA Adjudication: Adverse Drug Reaction
(b) (6)	57	F	14	AE	Acute pulmonary thromboembolism and cerebrovascular accident.
	64	F	16	AE	Sepsis. Pneumonia and fungal sinusitis on Day 15.
	68	M	31	AE	Sepsis, pneumonia, acute respiratory failure and multiorgan failure.
	49	F	44	AE	Bacteremia Day 17-32. MLFS on D 27. Conditioning for HSCT Day 38-43. However, neutropenic sepsis on Day 44. HSCT was planned due to cytopenia which is related to the study treatment.
	60	F	50	AE	Abdominal infection, large intestine perforation, and peritonitis
	70	F	52	AE	Neutropenic sepsis (ICANS on Day 11 which was ongoing per ADAEONGO at the time of death)
	37	F	60	AE	HLH/MAS Day 41 and sepsis. Peritonitis on Day 59.
	62	F	90	AE	Ascites on Day 33. Bacteremia on Day 34, 45, 57 and CMV viremia on Day 57, and fungemia on Day 69 and 71.
	57	M	356	AE	Idiopathic ascites on Day 260 (based on Day 30 update), and bacteremia on Day 281-290.

Source: FDA analysis. ADSL, ADSLFDA, ADSLFDA1, ADAE datasets, Narratives, and Case Report Forms.

Abbreviations: AE, adverse event; CMV, cytomegalovirus; F, female; HLH, hemophagocytic lymphohistiocytosis; HSCT, hematopoietic stem cell transplant; ICANS, immune effector cell-associated neurotoxicity syndrome; M, male; MAS, macrophage activation syndrome; MLFS, morphologic leukemia-free state

Reviewer comment: The Applicant submitted updated ADSLFDA1 dataset which includes a flag to indicate the nine patients whom FDA considers having died due to an ADR that is considered at least possibly likely to be related to the treatment regimen they received during the study. The review team recommend including this information in section 6 of the USPI.

Serious Adverse Events

Data:

A total of 80 patients in the Safety Set (63.0%) experienced at least one SAE post obe-cel treatment ([Applicant Table 14](#)). Most frequent ($\geq 5\%$ of patients) SAEs of any grade reported were febrile neutropenia (13.4%), ICANS (9.4%), CRS (7.9%), pyrexia (7.1%), COVID-19 (6.3%), sepsis and hyperferritinemia (5.5% each). Most frequent ($\geq 3\%$ of patients) Grade ≥ 3 SAEs reported were febrile neutropenia (12.6%), ICANS (6.3%), sepsis and hyperferritinemia (5.5% each), and COVID-19 (3.9% each).

For the SAE of CRS, 3 (2.4%) patients were reported to have experienced a \geq Grade 3 serious event. For the SAE of ICANS, 9 (7.1%) of patients were reported to have experienced a \geq Grade 3 serious event.

Applicant Table 14 **Treatment Emergent SAEs Occurring in $\geq 5\%$ Patients (Any Grade) Any Time Post Obe-cel Infusion, Regardless of Relationship to Obe-cel, by Preferred Term (Phase Ib and Phase II, Safety Set) – FELIX Study**

Preferred Term	Total (N=127)	
	All grades n (%)	\geq Grade 3 n (%)
Number of patients with any serious TEAE	80 (63.0)	68 (53.5)
Febrile neutropenia	17 (13.4)	16 (12.6))
ICANS	12 (9.4)	8 (6.3)
Cytokine release syndrome	10 (7.9)	3 (2.4)
Pyrexia	9 (7.1)	3 (2.4)
Hyperferritinaemia	7 (5.5)	7 (5.5)
Sepsis	7 (5.5)	7 (5.5)

MedDRA = Medical Dictionary for Regulatory Activities; TEAE=Treatment emergent adverse event.

Adverse events (AEs) were coded using MedDRA 26.0. TEAE was defined as any AE with onset during the post-infusion period. Preferred terms were presented in descending order of counts in the column of "All grades" under "Total". Multiple AEs were counted only once per patient for each preferred term.

Data cutoff: 13-Sep-2023.

Source: BLA D30 Update – Table 14.3.2.2.1.

A total of 50 patients in the Safety Set (39.4%) experienced at least one SAE with suspected relatedness to obe-cel post infusion ([Applicant Table 15](#)). The most frequent ($\geq 2\%$ of patients) SAEs of any grade with suspected relationship to obe-cel were ICANS (9.4%), CRS (7.9%), febrile neutropenia (6.3%), hyperferritinemia (5.5%), and bone marrow failure, neutropenia, neutrophil count decreased and pneumonia (2.4% each). The vast majority occurred in patients with $\geq 5\%$ blasts in BM at the time of LD.

Additional information is provided in BLA D30 Safety Update Report, Section 3.1.3.

Applicant Table 15 Treatment Emergent SAEs Occurring in $\geq 2\%$ Patients (Any Grade) Any Time Post Obe-cel Infusion, with Suspected Relationship to Obe-cel, by Preferred Term (Phase Ib and Phase II, Safety Set) – FELIX Study

Preferred Term	Total (N=127)	
	All grades n (%)	Grade ≥ 3 n (%)
Number of patients with any serious TEAE with suspected relationship to obe-cel	50 (39.4)	41 (32.3)
Immune effector cell-associated neurotoxicity syndrome	12 (9.4)	8 (6.3)
Cytokine release syndrome	10 (7.9)	3 (2.4)
Febrile neutropenia	8 (6.3)	8 (6.3)
Hyperferritinaemia	7 (5.5)	7 (5.5)
Bone marrow failure	3 (2.4)	3 (2.4)
Neutropenia	3 (2.4)	3 (2.4)
Neutrophil count decreased	3 (2.4)	3 (2.4)
Pneumonia	3 (2.4)	3 (2.4)

CTCAE = Common Terminology Criteria for Adverse Events; MedDRA = Medical Dictionary for Regulatory Activities; NCI = National Cancer Institute; TEAE=Treatment emergent adverse event.

Adverse events (AEs) were coded using MedDRA 26.0. TEAE was defined as any AE with onset during the post-infusion period. AE severity was graded according to NCI's CTCAE V5.0. Grade 1 = Mild; Grade 2 = Moderate; Grade 3 = Severe; Grade 4 = Life-threatening consequences; Grade 5 = Fatal.

Preferred terms were presented in descending order of counts in the column of "All grades" under "Total". Multiple AEs were counted only once per patient for each preferred term.

Data cut-off: 13-Sep-2023.

Source: BLA D30 Update –Table 14.3.1.5.1.

The Applicant's Position:

The frequency of \geq Grade 3 CRS and ICANS was notably low, in line with the expected lower immune-mediated toxicity with obe-cel, which has inherent properties reducing the risk of such events coupled with the 2-step infusion adapted to tumor burden. The rate is lower than those reported in the pivotal trials of CD19 CAR T products already approved for treatment of r/r B ALL.

Many of the SAEs reported in the pivotal FELIX study were not unexpected. The SAEs reported are not uncommon in the r/r B ALL adult patient population being studied. The percent of patients experiencing any grade SAE, 60.6% (77/127), and \geq Grade 3 SAE, 52.0% (66/127), are generally lower than those reported in the pivotal studies for the already approved CD19 CAR T products for the treatment of r/r B ALL brexu-cel and tisa-cel.

The FDA's Assessment:

An SAE was defined as an AE that met at least one of the following serious criteria:

- Fatal
- Life-threatening (places the patient at immediate risk of death)
- Requires patient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Congenital anomaly/birth defect

- Other medically important serious event

Among 100 patients in the safety analysis set, SAEs occurred in 62% and Grade 3 or higher SAEs occurred in 54% of patients. Most common SAEs included infections - pathogen unspecified, febrile neutropenia, CRS, and Fever.

See [FDA Table 20](#) for details of all grade and Grade ≥ 3 SAE.

FDA Table 20. Treatment-Emergent Serious Adverse Events

SAEs	All Grades (N=100) (%)
Infections - pathogen unspecified	24
Febrile neutropenia	13
Immune effector cell-associated neurotoxicity syndrome	11
Cytokine release syndrome	10
Viral infections	9
Neutropenia	7
Fever	6
Hyperferritinaemia	6
Bacterial infections	5
Encephalopathy	4
Fungal infections	4
Hemorrhage	4
Respiratory failure	4
Hypotension	3
Thrombocytopenia	3
Anaemia	2
Ascites	2
Haemophagocytic lymphohistiocytosis	2
Hypoxia	2
Leukopenia	2
Pancytopenia	2
Thrombosis	2
Acute myeloid leukaemia	1
Basal cell carcinoma	1
Bone marrow failure	1
Cerebrovascular accident	1
Coagulopathy	1
Diarrhoea	1
Dizziness	1
Fatigue	1
Femoral neck fracture	1
Headache	1
Large intestine perforation	1
Multiple organ dysfunction syndrome	1
Musculoskeletal pain	1
Neurotoxicity	1
Oesophagitis	1
Pancreatitis	1
Pleural effusion	1
Polyserositis	1
Portal hypertension	1

SAEs	All Grades (N=100) (%)
Premature delivery	1
Preterm premature rupture of membranes	1
Rash	1
Second primary malignancy	1
Seizure	1
Vomiting	1

Source: FDA analysis. **ADSL, ADSLFDA1, ADAE datasets.**

Abbreviations: SAE, serious adverse event

Reviewer comment: *Serious viral infections excluding COVID 19 occurred in 1% of patients.*

Treatment Emergent Adverse Events and Adverse Reactions

Applicant Data:

Overall TEAE Profile

All adult patients with r/r B ALL treated with obe-cel in the Safety Set experienced at least one AE any time post obe-cel infusion (i.e. at least one treatment emergent adverse event [TEAE]), and the majority of patients experienced at least 1 \geq Grade 3 (103 patients, 81.1%) ([Applicant Table 16](#)).

Within 3 months of obe-cel infusion, all patients experienced at least 1 TEAE and approximately 49.6% of patients experienced at least 1 serious TEAE. Serious TEAEs in 33.9% of patients were suspected to be related to obe-cel treatment.

More than 3 months after obe-cel infusion, 48.0% of patients experienced TEAEs, 24.4% patients had serious TEAEs and 7.9% patients had serious TEAEs suspected to be related to obe-cel treatment.

Additional information is provided in BLA D30 Safety Update Report, Section 3.1.

Applicant Table 16 Overview of Treatment Emergent Adverse Events Anytime Post Obe-cel Infusion (Phase Ib and Phase II, Safety Set) – FELIX Study

	Total (N=127) n (%)
Any TEAE	127 (100)
Grade 3 or higher TEAE	103 (81.1)
Any obe-cel-related TEAE	119 (93.7)
Obe-cel-related ≥ Grade 3 TEAE	77 (60.6)
Deaths	59 (46.5)
Any serious TEAE	80 (63.0)
Any obe-cel-related serious TEAE	50 (39.4)

CTCAE = Common Terminology Criteria for Adverse Events; MedDRA = Medical Dictionary for Regulatory Activities; NCI = National Cancer Institute; TEAE=Treatment emergent adverse event

Adverse events (AEs) were coded using MedDRA 26.0. TEAE was defined as any AE with onset during the post-infusion period. AE severity was graded according to NCI's CTCAE V5.0. Grade 1 = Mild; Grade 2 = Moderate; Grade 3 = Severe; Grade 4 = Life-threatening consequences; Grade 5 = Fatal.

Data cut-off: 13-Sep-2023.

Source: D30 Update – Table 14.3.1.1.1, 14.3.3.1.3.

Adverse Events After Enrollment and Prior to Obe-cel Treatment

Overall, AE types and frequencies occurring during the period after enrollment but prior to the first obe-cel infusion were as expected for bridging and lymphodepleting chemotherapies administered in the target patient population and the underlying disease of the patients. A total of 129 patients (84.3%) experienced at least one AE in the Enrolled Set (N=153). Adverse events of the following SOCs were most commonly reported: gastrointestinal disorders (83 patients with at least one AE, 54.2%), infections and infestations (66 patients, 43.1%), blood and lymphatic system disorders (59 patients, 38.6%), general disorders and administration site conditions (56 patients, 36.6%), metabolism and nutrition disorders (48 patients, 31.4%), investigations (mostly abnormal lab test results; 46 patients, 30.1%), respiratory, thoracic and mediastinal disorders (39 patients, 25.5%), and musculoskeletal and connective tissue disorders and nervous system disorders (31 patients, 20.3% each).

Adverse events ≥ Grade 3 occurring most frequently in patients after enrollment but prior to LD included febrile neutropenia (30 patients, 19.6%), anemia (20 patients, 13.1%), and neutrophil count decreased (17 patients, 11.1%).

A total of 70 patients (45.8%) experienced at least one SAE after enrollment but prior to obe-cel infusion. Serious adverse events experienced most frequently (≥ 5% patients with at least one SAE of any grade) were febrile neutropenia (21 patients, 13.7%), and pyrexia (8 patients, 5.2%).

Additional information is provided in Module 2.7.4 Summary of Clinical Safety, Section 2.1.1.

Adverse Events After Obe-cel Treatment

The most common SOC in which AES of any grade were reported in $\geq 10\%$ of patients in the Safety Set or individual PTs occurring in $\geq 10\%$ of patients in the Safety Set (n=127) are summarized in [Applicant Table 17](#).

The most common SOC in the Safety Set, with at least one TEAE of any grade reported, were Infections and infestations (94 patients, 74%), Immune system disorders (90 patients, 70.9%), GI disorders (79 patients, 62.2%), Blood and lymphatic system disorders (76 patients, 59.8%), Nervous system disorders (73 patients, 57.5%), and General disorders and administration site conditions (67 patients, 52.8%). The TEAE profile by SOC was similar in the overall population to that in the subset with $\geq 5\%$ blast in BM at LD.

Common individual PTs post obo-cel infusion are summarized in [Applicant Table 17](#). The most frequently observed any grade TEAEs by PT included CRS (87 patients, 68.5%), pyrexia (37 patients, 29.1%), nausea (33 patients, 26.0%), diarrhea (32 patients, 25.2%), febrile neutropenia (31 patients, 24.4% each), anemia (30 patients, 23.6%), headache (30 patients, 23.6%), neutropenia (29 patients, 22.8%), ICANS (29 patients, 22.8% each), hypotension (28 patients, 22.0%), , and hypokalemia (27 patients, 21.3%). The most frequently observed ($\geq 10\%$) Grade ≥ 3 TEAEs by PT included febrile neutropenia (30 patients, 23.6%), anemia and neutropenia (26 patients, 20.5% each), neutrophil count decreased (25 patients, 19.7%), thrombocytopenia and platelet count decreased (16 patients, 12.6% each), and hyperferritinemia (13 patients, 10.2%).

Additional information is provided in BLA D30 Safety Update Report, Section 3.1.1.1 and Section 3.1.1.2.

Applicant Table 17 Treatment Emergent Adverse Events in ≥10% of Patients in Any System Organ Class (All Grades) and Preferred Term (All Grades), Any Time Post Obe-cel Infusion, Regardless of Relationship to Obe-cel (Phase Ib and Phase II, Safety Set) – FELIX Study

Primary System Organ Class Preferred Term	Total (N=127)	
	All grades n (%)	Grade ≥ 3 n (%)
Number of patients with any TEAE	127 (100)	102 (80.3)
Blood and lymphatic system disorders	76 (59.8)	65 (51.2)
Febrile neutropenia	31 (24.4)	30 (23.6)
Anaemia	30 (23.6)	26 (20.5)
Neutropenia	29 (22.8)	26 (20.5)
Thrombocytopenia	18 (14.2)	16 (12.6)
Cardiac disorders	20 (15.7)	2 (1.6)
Eye disorders	14 (11.0)	1 (0.8)
Gastrointestinal disorders	79 (62.2)	17 (13.4)
Nausea	33 (26.0)	3 (2.4)
Diarrhoea	32 (25.2)	2 (1.6)
Vomiting	21 (16.5)	1 (0.8)
Abdominal pain	16 (12.6)	2 (1.6)
Constipation	16 (12.6)	0
General disorders and administration site conditions	67 (52.8)	10 (7.9)
Pyrexia	37 (29.1)	3 (2.4)
Fatigue	24 (18.9)	2 (1.6)
Hepatobiliary disorders	13 (10.2)	7 (5.5)
Immune system disorders	90 (70.9)	10 (7.9)
Cytokine release syndrome	87 (68.5)	3 (2.4)
Infections and infestations	94 (74.0)	58 (45.7)
COVID-19	22 (17.3)	5 (3.9)
Injury, poisoning and procedural complications	23 (18.1)	3 (2.4)
Investigations	64 (50.4)	48 (37.8)
Neutrophil count decreased	25 (19.7)	25 (19.7)
Platelet count decreased	18 (14.2)	16 (12.6)
Alanine aminotransferase increased	15 (11.8)	6 (4.7)
Weight decreased	13 (10.2)	2 (1.6)
Metabolism and nutrition disorders	62 (48.8)	29 (22.8)
Hypokalaemia	27 (21.3)	8 (6.3)
Hyperferritinaemia	17 (13.4)	13 (10.2)
Decreased appetite	15 (11.8)	4 (3.1)
Hypomagnesaemia	14 (11.0)	0
Musculoskeletal and connective tissue disorders	48 (37.8)	5 (3.9)
Arthralgia	13 (10.2)	0
Nervous system disorders	73 (57.5)	13 (10.2)
Headache	30 (23.6)	0
Immune effector cell-associated neurotoxicity syndrome	29 (22.8)	9 (7.1)
Psychiatric disorders	35 (27.6)	6 (4.7)
Confusional state	16 (12.6)	3 (2.4)
Renal and urinary disorders	21 (16.5)	5 (3.9)
Respiratory, thoracic and mediastinal disorders	44 (34.6)	13 (10.2)
Cough	15 (11.8)	0

Primary System Organ Class Preferred Term	Total (N=127)	
	All grades n (%)	Grade ≥ 3 n (%)
Skin and subcutaneous tissue disorders	30 (23.6)	1 (0.8)
Vascular disorders	40 (31.5)	10 (7.9)
Hypotension	28 (22.0)	6 (4.7)

MedDRA = Medical Dictionary for Regulatory Activities.

Adverse events (AEs) were coded using MedDRA 26.0. TEAE was defined as any AE with onset during the post-infusion period.

Data cut-off: 13-Sep-2023.

Source: BLA D30 Update – Table 14.3.1.2.1.

Treatment Emergent Adverse Events Suspected to be Related to Obe-cel Treatment

Almost all patients (119 patients, 93.7%) reported at least one TEAE suspected to be related to obe-cel by the Investigator ([Applicant Table 18](#)). The most frequently observed ($\geq 10\%$) TEAEs of any grade suspected to be related to obe-cel were, by PT, CRS (87 patients, 68.5%), ICANS (29 patients, 22.8%), pyrexia (27 patients, 21.3%), febrile neutropenia and neutropenia (20 patients, 15.7% each). The most frequently observed ($\geq 10\%$) Grade ≥ 3 TEAEs suspected to be related to obe-cel included febrile neutropenia (20 patients, 15.7%), neutropenia (19 patients, 15%), neutrophil count decreased (17 patients, 13.4%), anemia (14 patients, 11.0%), and hyperferritinemia (13 patients, 10.2%).

Additional information is provided in BLA D30 Safety Update Report, Section 3.1.1.3.

Treatment Emergent Adverse Events Suspected to be Related to Obe-cel Occurring Within Three Months of Obe-cel Infusion

The most common ($\geq 15\%$) TEAEs of any grade with suspected relationship to obe-cel occurring within 3 months after obe-cel infusion included, by PT, CRS (87 patients, 68.5%), ICANS (28 patients, 22.0%), pyrexia (25 patients, 19.7%), and neutropenia (20 patients, 15.7%). The most common ($\geq 10\%$) Grade ≥ 3 TEAEs with suspected relationship to obe-cel occurring within 3 months after obe-cel infusion included neutropenia (19 patients, 15.0%), febrile neutropenia (18 patients, 14.2%), neutrophil count decreased (16 patients, 12.6%), anemia (14 patients, 11.0%), and hyperferritinemia (13 patients, 10.2%).

Treatment Emergent Adverse Events Suspected to be Related to Obe-cel Occurring More Than Three Months After Obe-cel Infusion

TEAEs with suspected relationship to obe-cel occurring more than 3 months after obe-cel infusion were rare and included ($\geq 2\%$), by PT, anemia, neutropenia, neutrophil count decreased, platelet count decreased (each in 4 patients, 3.1%), lymphopenia, and thrombocytopenia (3 patients, 2.4%). Most of these AEs were from the SOC blood and lymphatic system disorders, were \geq Grade 3, and expected due to the underlying disease and/or LD.

Applicant Table 18 Treatment Emergent Adverse Events in More Than 10% of Patients (All Grades) Any Time Post Obe-cel Infusion, with Suspected Relationship to Obe-cel by the Investigator, by Preferred Term and Maximum Grade (Phase Ib and Phase II, Safety Set) – FELIX Study

Preferred Term	Total (N=127)	
	All grades n (%)	Grade ≥ 3 n (%)
Number of patients with any TEAE with suspected relationship to obe-cel	119 (93.7)	77 (60.6)
Cytokine release syndrome	87 (68.5)	3 (2.4)
Immune effector cell-associated neurotoxicity syndrome	29 (22.8)	9 (7.1)
Pyrexia	27 (21.3)	1 (0.8)
Febrile neutropenia	20 (15.7)	20 (15.7)
Neutropenia	20 (15.7)	19 (15.0)
Anaemia	18 (14.2)	14 (11.0)
Neutrophil count decreased	17 (13.4)	17 (13.4)
Hyperferritinaemia	17 (13.4)	13 (10.2)
Nausea	17 (13.4)	2 (1.6)
Headache	17 (13.4)	0
Fatigue	16 (12.6)	1 (0.8)
Hypotension	16 (12.6)	2 (1.6)
Thrombocytopenia	14 (11.0)	12 (9.4)
Confusional state	14 (11.0)	3 (2.4)

CTCAE = Common Terminology Criteria for Adverse Events; MedDRA = Medical Dictionary for Regulatory Activities; NCI = National Cancer Institute; TEAE = Treatment emergent adverse event.

Adverse events (AEs) were coded using MedDRA 26.0. TEAE was defined as any AE with onset during the post-infusion period. AE severity was graded according to NCI's CTCAE V5.0. Grade 1 = Mild; Grade 2 = Moderate; Grade 3 = Severe; Grade 4 = Life-threatening consequences; Grade 5 = Fatal.

Preferred terms were presented in descending order of counts in the column of "All grades" under "Total". Multiple AEs were counted only once per patient for each preferred term.

Data cut-off: 13-Sep-2023.

Source: BLA D30 Update – Table 14.3.1.5.1.

The FDA's Assessment:

Overall summary of all TEAEs (based on SOC) occurring in $\geq 10\%$ of patients is listed in [FDA Table 21](#). Most common (non-laboratory) AEs with incidence $\geq 20\%$ were: CRS, infections - pathogen unspecified, musculoskeletal pain, viral infections, fever, nausea, bacterial infectious disorders, diarrhea, febrile neutropenia, ICANS, hypotension, pain, fatigue, headache, encephalopathy, and hemorrhage. See [FDA Table 21](#).

FDA Table 21. Treatment-Emergent Adverse Events Occurring in $\geq 10\%$, Safety Analysis Set

Adverse Event	All Grades (N=100) n (%)	\geq Grade 3 (N=100) N (%)
Number of patients with any TEAE	100 (100.0)	81 (81.0)
Blood and lymphatic system disorders	67 (67.0)	59 (59.0)
Neutropenia	42 (42.0)	39 (39.0)
Thrombocytopenia	30 (30.0)	27 (27.0)
Febrile neutropenia	26 (26.0)	26 (26.0)
Anaemia	23 (23.0)	20 (20.0)
Leukopenia	12 (12.0)	11 (11.0)
Coagulopathy	10 (10.0)	6 (6.0)
Cardiac disorders	16 (16.0)	2 (2.0)
Tachycardia	12 (12.0)	0 (0.0)
Gastrointestinal disorders	60 (60.0)	9 (9.0)
Nausea	29 (29.0)	2 (2.0)
Diarrhoea	26 (26.0)	0 (0.0)
Vomiting	18 (18.0)	0 (0.0)
Abdominal pain	16 (16.0)	1 (1.0)
Constipation	11 (11.0)	0 (0.0)
General disorders and administration site conditions	60 (60.0)	7 (7.0)
Fever	29 (29.0)	1 (1.0)
Pain	23 (23.0)	0 (0.0)
Fatigue	22 (22.0)	3 (3.0)
Edema	12 (12.0)	0 (0.0)
Chills	11 (11.0)	0 (0.0)
Hepatobiliary disorders	11 (11.0)	6 (6.0)
Immune system disorders	78 (78.0)	9 (9.0)
Cytokine release syndrome	75 (75.0)	3 (3.0)
Hypogammaglobulinaemia	10 (10.0)	2 (2.0)
Infections and infestations	76 (76.0)	46 (46.0)
Infections - pathogen unspecified	44 (44.0)	31 (31.0)
Viral infections*	32 (32.0)	7 (7.0)
Bacterial infections	26 (26.0)	11 (11.0)
Fungal infections	15 (15.0)	5 (5.0)
Injury, poisoning and procedural complications	14 (14.0)	2 (2.0)
Investigations	31 (31.0)	12 (12.0)
Amenotransferase increased	14 (14.0)	4 (4.0)
Weight decreased	11 (11.0)	2 (2.0)
Metabolism and nutrition disorders	51 (51.0)	26 (26.0)
Hypokalaemia	23 (23.0)	8 (8.0)
Hyperferritinaemia	18 (18.0)	13 (13.0)
Decreased appetite	13 (13.0)	3 (3.0)
Hypomagnesaemia	12 (12.0)	0 (0.0)

Adverse Event	All Grades (N=100) n (%)	≥ Grade 3 (N=100) N (%)
Musculoskeletal and connective tissue disorders	38 (38.0)	5 (5.0)
Musculoskeletal pain	36 (36.0)	4 (4.0)
Nervous system disorders	59 (59.0)	12 (12.0)
Immune effector cell-associated neurotoxicity syndrome	24 (24.0)	7 (7.0)
Headache	22 (22.0)	0 (0.0)
Encephalopathy	21 (21.0)	4 (4.0)
Dizziness	14 (14.0)	0 (0.0)
Psychiatric disorders	19 (19.0)	1 (1.0)
Renal and urinary disorders	14 (14.0)	5 (5.0)
Respiratory, thoracic, and mediastinal disorders	30 (30.0)	10 (10.0)
Cough	14 (14.0)	0 (0.0)
Skin and subcutaneous tissue disorders	23 (23.0)	1 (1.0)
Rash	17 (17.0)	1 (1.0)
Vascular disorders	46 (46.0)	10 (10.0)
Hypotension	23 (23.0)	4 (4.0)
Hemorrhage	20 (20.0)	4 (4.0)

Source: FDA analysis. ADSL, ADSL FDA1, ADAE datasets.

*Viral infections excluding COVID-19 occurred in 16%. COVID-19 occurred in 18% of patients.

Abbreviations: TEAE, treatment-emergent adverse event

[FDA Table 21](#) above will serve as the basis for the ADR table of the USPI. The laboratory abnormalities incidence will be presented in a separate table that is derived from the ADLB dataset and not from the ADAEFDA dataset since the ADLB is more accurate and will capture all treatment-emergent laboratory abnormalities rather than just the ones recorded as AEs.

Other clinically important adverse reactions that occurred in <10% of patients treated with obe-cel include the following:

- *Cardiac disorders*: Arrhythmia (5%), cardiac failure (1%), palpitations (2%).
- *Endocrine disorders*: Adrenal insufficiency (2%).
- *Eye disorders*: Visual impairment (2%).
- *Gastrointestinal disorders*: Stomatitis (5%), ascites (4%).
- *Immune system disorders*: HLH/MAS (2%), graft-versus-host disease (GvHD) (4%).
- *Injury, poisoning and procedural complications*: Infusion-related reaction (2%).
- *Nervous system and psychiatric disorders*: Tremor (8%), motor dysfunction (6%) delirium (5%), seizure (2%).
- *Renal disorders*: Renal impairment (7%).
- *Respiratory disorders*: Respiratory failure (8%), pleural effusion (4%).
- *Skin and subcutaneous tissue disorders*: Skin ulcer (2%).
- *Vascular disorders*: Thrombosis (5%).

Reviewer comment: The overall AEs noted after obe-cel treatment are consistent with those seen with other anti-CD19 CAR-T products and are considered of acceptable severity given patients' advanced stage of the disease. No new safety signal was observed.

Although the AEs are presented by SOC, some GTs include more than one SOC. For example: encephalopathy includes nervous system disorders and psychiatric disorders SOCs. We placed these group term AEs under the SOC with most representation in the data for that AE and/or clinically most appropriate (e.g., encephalopathy and dizziness under nervous system disorders SOC).

For analyses of infection by pathogen, we included the grouped term (e.g., bacterial, viral, etc.) which was based on the AE high level group term.

Infections and cytopenias are also known risks from LD and pre-existing conditions as discussed below (in analyses of the conditioning chemotherapy period in the AESI discussion).

A separate analysis was performed to identify the incidence of AEs during the leukapheresis and conditioning chemotherapy periods respectively. See details below.

Leukapheresis period

This period was defined from the day of leukapheresis until the day before the start of LD for patients intended to receive obe-cel at a dose of 410×10^6 cells. Among the 100 patients in the safety analysis set, any AE occurred in 90%, Grade ≥ 3 AEs in 69%, and SAEs in 43% of patients.

LD Chemotherapy period:

The period was defined from the first of LD administration until Day 0 (the day prior to obe-cel infusion). Among the 100 patients in the safety analysis set, any AE occurred in 75%, Grade ≥ 3 AEs in 33%, and SAEs in 3% of patients. Most common AEs included nausea, fever, neutropenia, constipation, anemia, and leukopenia.

Reviewer comment: *As expected, increased AEs that are related to chemotherapy side effects such as nausea, fever, and cytopenia was observed in the LD period.*

Bridging chemotherapy period:

After leukapheresis, bridging therapy was administered to patients while awaiting product manufacturing at the discretion of the treating investigator. Any AE occurred in 79, Grade ≥ 3 AEs in 55, and SAEs in 41 patients.

Reviewer comment: *Because of the small number of patients who did not receive bridging therapy, detailed analysis to compare these patients to those who received it was not performed. However, the overall safety profile of patients who received bridging therapy was similar to those who did not.*

Other Significant Treatment Emergent Adverse Events

All safety topics that have been considered as identified or potential risks following obo-cel treatment have been evaluated and no unexpected findings were observed. No new, important risks were identified when compared with approved CAR T therapies.

An overall summary is provided in [Applicant Table 19](#) pertaining to protocol-specified other significant TEAEs that could potentially be significant for the treatment of B ALL following CAR T cell therapy and each topic is further discussed in the subsequent sections.

Additional information is provided in BLA D30 Safety Update Report, Section 3.1.4.

Applicant Table 19 Overview of Other Significant Treatment Emergent Adverse Events by Group Term (Phase Ib and Phase II, Safety Set) – FELIX Study

Significant TEAE	All grades n (%)	Grade 3 n (%)	Grade 4 n (%)	Grade 5 n (%)	≥ Grade 3 n (%)
CRS	87 (68.5)	3 (2.4)	0	0	3 (2.4)
ICANS	29 (22.8)	7 (5.5)	1 (0.8)	1 (0.8)	9 (7.1)
Prolonged cytopenia	see Cytopenias below				
HLH/MAS	2 (1.6)	1 (0.8)	1 (0.8)	0	2 (1.6)
Hypogammaglobulinaemia	12 (9.4)	2 (1.6)	0	0	2 (1.6)
Severe infections	94 (74.0)	48 (37.8)	5 (3.9)	5 (3.9)	58 (45.7)
TLS	1 (0.8)	1 (0.8)	0	0	1 (0.8)
GvHD	7 (5.5)	3 (2.4)	0	0	3 (2.4)
Secondary malignancies [1]	0	0	0	0	0
Hypersensitivity [2]	0	0	0	0	0

CRS = Cytokine release syndrome; CTCAE = Common Terminology Criteria for Adverse Events; GvHD = Graft versus host disease; HLH/MAS = Lymphohistiocytosis/macrophage activation syndrome; ICANS=Immune effector cell-associated neurotoxicity syndrome; MedDRA = Medical Dictionary for Regulatory Activities; NCI = National Cancer Institute; TEAE = Treatment emergent adverse event; TLS = Tumor lysis syndrome.

Adverse events (AEs) were coded using MedDRA 26.0. TEAE was defined as any AE with onset during the post-infusion period. AE severity was graded according to NCI's CTCAE V5.0. Grade 1 = Mild; Grade 2 = Moderate; Grade 3 = Severe; Grade 4 = Life-threatening consequences; Grade 5 = Fatal.

Multiple TEAEs were counted only once per patient for each preferred term by maximum grade level.

[1] Source table includes 2 patients with malignancies, neither of which were considered secondary malignancies (2.7.4 – Section 2.1.5.9).

[2] Note that the source table does not include events of hypersensitivity as none were reported.

Data cut-off: 13-Sep-2023.

Source: BLA D30 Update – Tables 14.3.4.1.1, 14.3.4.2.1, 14.3.4.6.1 and 14.3.4.6.14.

The FDA's Assessment:

A summary of AESIs is provided in [FDA Table 22](#) below for the safety analysis set. More details are provided below.

FDA Table 22. Summary of Adverse Events of Special Interest, Safety Analysis Set

Adverse Event	N	Safety Analysis Set (N=100) n (%)
Cytokine release syndrome		
Any grade	100	75 (75.0)
Grade 3 or higher	100	3 (3.0)

Adverse Event	N	Safety Analysis Set (N=100) n (%)
Neurologic toxicity	-	-
Any grade	100	64 (64.0)
Grade 3 or higher	100	12 (12.0)
Prolonged Grade 3 or higher cytopenias*	-	-
Any cytopenia, unresolved by Day 30	41	29 (71)
Any cytopenia, unresolved by Day 60	41	11 (27)
Neutropenia, unresolved by Day 30	41	27 (66)
Neutropenia, unresolved by Day 60	41	7 (17)
Thrombocytopenia, unresolved by Day 30	41	22 (54)
Thrombocytopenia, unresolved by Day 60	41	6 (15)
Hypogammaglobulinaemia	-	-
Any grade	100	10 (10.0)
Grade 3 or higher	100	2 (2.0)
Infections, non-COVID	-	-
Any infections	100	67 (67.0)
Grade 3 or Higher	100	41 (41.0)
Haemophagocytic lymphohistiocytosis	-	-
Any grade	100	2 (2.0)
Grade 3 or higher	100	2 (2.0)

Source: FDA Analysis. ADSL, ADAEFDA

*Prolonged Cytopenia population (responders, N=41) identified as those from Efficacy Population (N=65) who achieve CR or CRi.

Reviewer comment: No new safety signals have been identified compared to similar products within the same class.

Cytokine Release Syndrome (CRS)

Cytokine release syndrome (CRS) is a recognized toxicity with CAR T cell therapies. A total of 87 patients (68.5%, 87/127, [Applicant Table 19](#)) experienced CRS of any grade post obe-cel infusion (criteria for CRS per [Lee et al, 2019](#)). Only 3 patients (2.4%, 3/127) experienced Grade 3 CRS (all in patients with $\geq 5\%$ blasts in BM at LD; none experienced Grade 4 or 5). This is included as an adverse drug reaction (ADR) for obe-cel of the proposed United States Prescribing Information (USPI) and covered in the Warnings and Precautions section.

Of the 87 patients who experienced CRS, the majority (56/87) experienced this after the first but prior to the second infusion of obe-cel. The overall median duration of CRS was 5.0 days (range 1 to 21 days). The median time to onset of CRS of any grade was 8.0 days following the first infusion (range 1 to 23 days) and the median duration of CRS was 5.0 days (range 1 to 21 days). The primary treatment for CRS was tocilizumab (66/87), with patients also receiving corticosteroids (19/87) and other anti-cytokine therapies (9/87).

In the FELIX study, both CD19 CAR T cell expansion ([Section 6.2](#)) and probability of CRS were impacted by disease burden. The most robust expansions of CAR T cells after obe-cel infusions occurred in the patient subset with a higher disease burden. Likewise, the percentage of patients experiencing CRS of any grade increased as the blasts in BM increased. Across 4 subgroups, $< 5\%$, $\geq 5\%$ to $\leq 20\%$, $> 20\%$ to $\leq 75\%$, and $> 75\%$ blasts in BM, the percentage of patients with CRS of any grade was 47.2%, 62.5%, 71.4% and 87.5%, respectively, even though patients with $\geq 20\%$

blasts in BM received a lower oxe-cel dose at first infusion. These trends reinforce the advantages of the split dose regimen, in that the low first dose in patients with > 20% BM blasts at LD may initially limit the CAR T cell expansion, and hence avoid excessive expansion which would increase the risk of immunotoxicity in such patients. This in turn would be expected to limit cytokine release and subsequent incidence of higher-grade CRS in response to CAR T cell expansion, as was observed.

The low rate of \geq Grade 3 CRS is fully consistent with the low cytokine levels observed following oxe-cel treatment, which is derived from inherent design properties of oxe-cel, and the positive impact of the dosing regimen on the underlying expansion of CAR T cells. As such, CRS becomes a more manageable potential consequence of oxe-cel treatment without diminishing the efficacy of oxe-cel.

Additional information is provided in Module 2.7.4 Summary of Clinical Safety, Section 2.1.5.1; BLA D30 Update – Table 14.3.4.3.1.

The FDA's Assessment:

CRS grading was based on American Society for Transplantation and Cellular Therapy (ASTCT) consensus grading (Lee et al. 2019), and the CRS events were graded using the Common Terminology Criteria for Adverse Events (CTCAE) criteria. Among 100 patients in the safety analysis set, CRS was reported in 75% including Grade 3 CRS in 3% of patients. There were no Grade 4 or 5 reported. The median time to onset of CRS was 8 days (range: 1 to 23 days) with a median duration of 5 days (range: 1 to 21 days). Sixty-eight percent of patients (51 of 75) experienced CRS after the first infusion but prior to the second infusion of oxe-cel, with a median time to onset of 6 days (range: 1 to 10 days). Patients who had baseline BM blasts >20% had an overall CRS rate of 83% compared to 63% in patients with baseline BM blasts of \leq 20%.

Key manifestations of CRS included fever (100%), hypotension (35%), and hypoxia (19%). There were no Grade 4 or fatal cases of CRS.

See [FDA Table 23](#) for details on CRS incidence: overall, after 1st and after 2nd oxe-cel infusion, and based on baseline bone marrow blasts.

The primary treatment for CRS was tocilizumab (73%; 55 of 75), with patients also receiving corticosteroids (21%; 16 of 75) or other anti-cytokine therapy (13%; 10 of 75).

FDA Table 23. CRS Incidence, Safety Analysis Set (N=100)

Category Severity	N	n (%)	Mean Time to Onset*	Median Time to Onset* (Min, Max)	Mean Duration*	Median Duration* (Min, Max)
Overall						
All grades	100	75 (75.0)	7.6	8 (1, 23)	5.7	5 (1, 21)
Grade 3 or higher [#]	100	3 (3.0)	8.0	9 (3, 12)	5.7	6 (5, 6)
After 1st Infusion [%]						
All grades	100	51 (51.0)	5.7	6 (1, 10)	5.1	5 (1, 21)
Grade 3 or higher	100	2 (2.0)	6.0	6 (3, 9)	5.0	5 (4, 6)

Category Severity	N	n (%)	Mean Time to Onset*	Median Time to Onset* (Min, Max)	Mean Duration*	Median Duration* (Min, Max)
After 2nd Infusion						
All grades	100	37 (37.0)	3.6	2 (1, 16)	4.6	5 (1, 12)
Grade 3 or higher	100	1 (1.0)	3.0	3 (3, 3)	5.0	5 (5, 5)
Baseline bone marrow blasts >20%						
All grades	63	52 (82.5)	7.7	9 (1, 13)	5.9	6 (1, 14)
Grade 3 or higher	63	2 (3.2)	6.0	6 (3, 9)	6.0	6 (6, 6)
Baseline bone marrow blasts ≤20%						
All grades	37	23 (62.2)	7.3	6 (1, 23)	5.4	5 (1, 21)
Grade 3 or higher	37	1 (2.7)	12.0	12 (12, 12)	5.0	5 (5, 5)

Source FDA Analysis. ADSLFDA1, ADAEFDA, ADCRS datasets.

* in days

#There were no Grade 4 or 5 cases of CRS.

%For Category = After 1st Infusion, analysis only includes events beginning before 2nd infusion (although resolution might occur after 2nd infusion).

Abbreviations: CRS, cytokine release syndrome

Reviewer comment: The overall incidence of CRS was similar to other approved CAR T cell products for the indication of r/r B ALL; however, the incidence of Grade ≥ 3 was notably lower. However, rates of AEs across trials can reflect differences in many factors and as such, comparisons should be interpreted with caution.

Immune Effector Cell-associated Neurotoxicity Syndrome and Neurotoxicity

The FELIX study was designed prospectively to assess ICANS as defined by the ASTCT consensus grading criteria., (Lee et al, 2019). ICANS is included as an ADR proposed obe-cel USPI and is covered in the Warnings and Precautions section of the proposed USPI.

A total of 22.8% of patients (29/127) experienced ICANS of any grade (Applicant Table 19). There were 7.1% (9/127) of patients who experienced ICANS of ≥ Grade 3 (7 patients Grade 3, 1 patient Grade 4, and 1 patient Grade 5). All patients who experienced ICANS events of ≥ Grade 3 occurred in patients with ≥ 5% blasts in BM at LD. Of those who experienced ICANS, most (18/29) experienced ICANS onset after the second infusion of obe-cel. The median duration of ICANS was 8.0 days (range 1 to 53 days).

The median time to onset of ICANS after the first obe-cel infusion was 12.0 days (range 1 to 31 days) and the median duration of ICANS was 8.0 days (range 1 to 53 days). The percentage of patients experiencing ICANS (any grade) was 8.3%, 25.0%, 14.3% and 42.5% in the < 5%, ≥ 5% to ≤ 20%, > 20% to ≤ 75% and > 75% blast in BM subgroups, respectively.

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

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

As with CRS, the relatively low rate of \geq Grade 3 ICANS following obe-cel treatment is consistent with expectations based on the properties of obe-cel and dosing regimen and makes this a potential immunotoxicity consequence of therapy a much more manageable risk.

Additional information is provided in Module 2.7.4. Summary of Clinical Safety, Section 2.1.5.2; BLA D30 Update – Table 14.3.4.4.1)

The FDA's Assessment:

The Applicant's definition of neurologic toxicity (NT) only included ICANS. FDA disagreed with this definition as it underestimates the true incidence of NT. FDA defines NT more broadly to include all events under MedDRA SOC of psychiatric disorders and nervous system disorders. In addition, the Reviewer searched for other AEs under other SOC's (e.g., general disorders, eye/ear disorders, respiratory disorders, etc.) that were not classified as NT and that could overlap with other neurologic events to see if they need to be included in FDA's NT definition. The information on NT in the USPI is based on FDA's definition.

Among the 100 patients in the safety analysis set, NT (including ICANS) were reported in 64% of patients, including Grade ≥ 3 in 12%. The median time to onset of NT was 10 days (range: 1 to 246 days) with a median duration of 13 days (range: 1 to 904 days). Fifty-five percent of patients (35 of 64) experienced NT after the first infusion but prior the second infusion of obe-cel, with a median time to onset of 6 days (range: 1 to 11). The most common symptoms ($>5\%$) included, ICANS (38%), headache (34%), encephalopathy (33%), dizziness (22%), tremor (13%), anxiety (9%), insomnia (9%), and delirium (8%).

See [FDA Table 24](#) for details on NT incidence: overall, after 1st and after 2nd obe-cel infusion, and based on baseline bone marrow blasts.

ICANS:

ICANS events occurred in 24% (24 of 100) of patients, including Grade ≥ 3 in 7% (7 of 100). Of the 24 patients who experienced ICANS, 33% (8 of 24) experienced an onset after the first obe-cel infusion but prior the second infusion.

The median time to onset for ICANS events was 8 days (range: 1 to 10 days) after the first infusion and 6.5 days (range: 2 to 22 days) after the second infusion, with a median duration of 8.5 days (range: 1 to 53 days).

Eighty-eight percent (21 of 24) of patients received treatment for ICANS. All treated patients received high-dose corticosteroids and 42% (10 of 24) of patients received anti-epileptics prophylactically.

FDA Table 24. Neurologic Toxicity* Incidence, Safety Analysis Set (N=100)

Category Severity	N	n (%)	Mean Time to Onset*	Median Time to Onset* (Min, Max)	Mean Duration*	Median Duration* (Min, Max)
Overall						
All grades	100	64 (64.0)	18.3	10 (1, 246)	58.6	13 (1, 904)
Grade 3 or higher	100	12 (12.0)	20.9	11 (1, 113)	24.3	12 (5, 62)
Grade 5	100	2 (2.0)	10.5	10.5 (10, 11)	33.5	33.5 (5, 62)
After 1st Infusion [#]						
All grades	100	35 (35.0)	5.8	6 (1, 11)	42.3	4 (1, 904)
Grade 3 or higher	100	3 (3.0)	5.0	4 (1, 10)	22.7	10 (5, 53)
Grade 5	100	1 (1.0)	10.0	10 (10, 10)	5.0	5 (5, 5)
After 2nd Infusion						
All grades	100	46 (46.0)	23.6	12 (1, 237)	49.6	12.5 (1, 349)
Grade 3 or higher	100	9 (9.0)	19.6	7 (1, 104)	24.0	11 (4, 59)
Grade 5	100	1 (1.0)	6.0	6 (6, 6)	59.0	59 (59, 59)
Baseline bone marrow blasts >20%						
All grades	63	44 (69.8)	15.5	10 (1, 113)	61.3	13 (1, 904)
Grade 3 or higher	63	9 (14.3)	21.6	10 (1, 113)	21.9	11 (5, 54)
Grade 5	63	1 (1.6)	10.0	10 (10, 10)	5.0	5 (5, 5)
Baseline bone marrow blasts ≤20%						
All grades	37	20 (54.1)	24.5	11 (2, 246)	52.7	11.5 (1, 337)
Grade 3 or higher	37	3 (8.1)	19.0	18 (11, 28)	31.3	24 (8, 62)
Grade 5	37	1 (2.7)	11.0	11 (11, 11)	62.0	62 (62, 62)

Source: FDA analysis, ADSL, ADSLFDA, ADSLFDA1, ADICANS datasets

%Neurologic toxicity includes* all cases where AESOC in (Nervous system disorders, Psychiatric disorders)

* in days

[#]For Category = After 1st Infusion, analysis only includes events beginning before 2nd infusion (although resolution might occur after 2nd infusion).

Reviewer comment: FDA requested that the Applicant updates the following datasets (ADAEFDA, ADSL, ADSLFDA) based on FDA adjudication and definition of NT.

As with CRS, the incidence of Grade ≥3 NT was notably lower when compared to other approved CAR T cell products for the indication of r/r B ALL. However, rates of AEs across trials can reflect differences in many factors and as such, comparisons should be interpreted with caution.

Cytopenias/Prolonged Cytopenias

Cytopenias that are more prolonged than would be expected after lymphodepleting chemotherapy have been observed in several CAR T cell studies ([Locke et al, 2019](#)). Cytopenias occurring after CAR-T infusion invariably manifest early (< 30 days), some are prolonged (30 to 90 days), and sometimes they persist or occur late (> 90 days) ([Jain et al, 2023](#)).

There was a significant proportion of patients who were severely cytopenic at enrollment in the FELIX study, with 34.6% of patients (44/127) having ≥ Grade 3 neutropenia and 33.9% (43/127) having ≥ Grade 3 thrombocytopenia based on the last available laboratory result. This may be

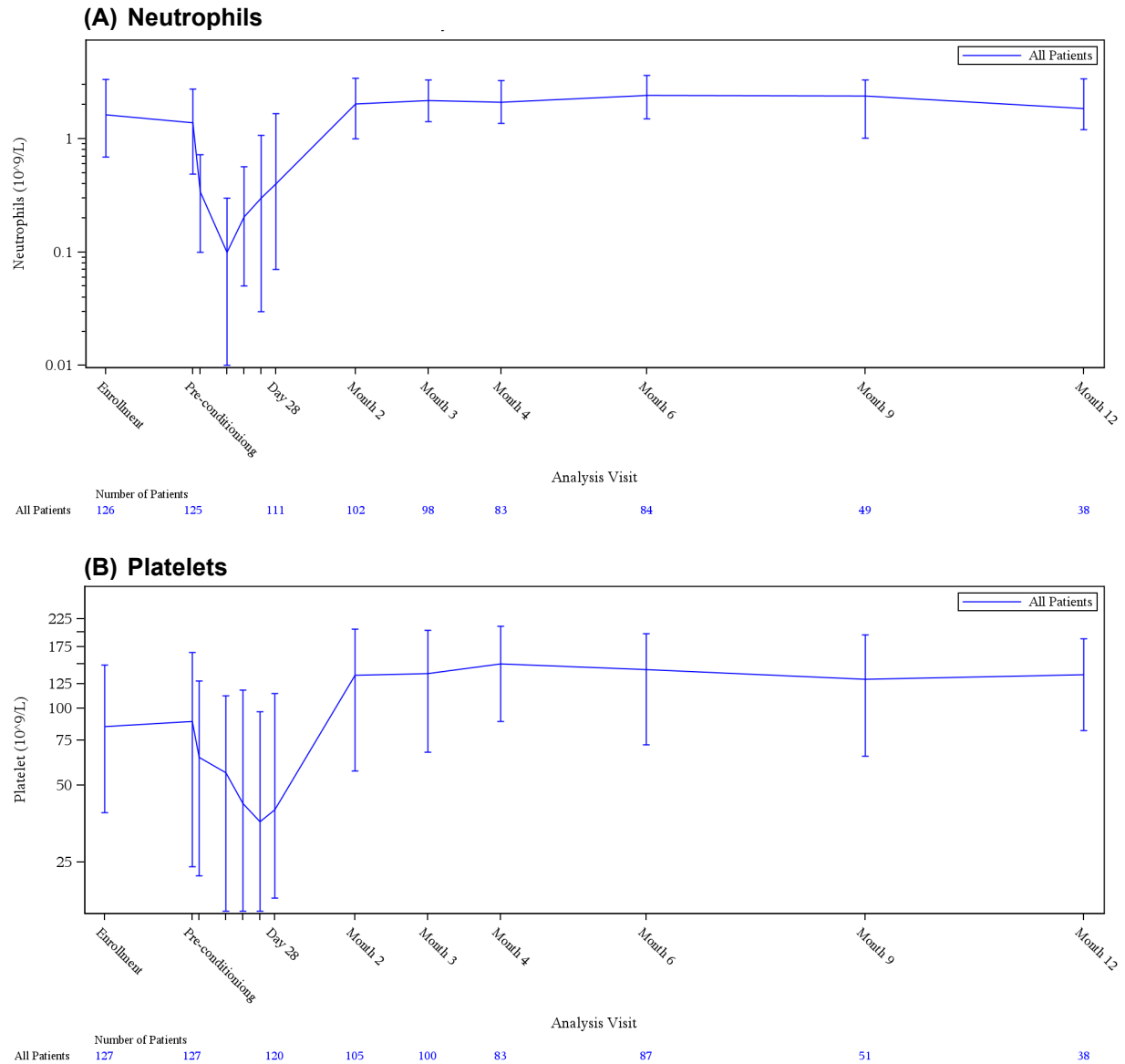
reflecting that the study included a proportion of patients who have already received many prior treatments, including SCT, so may have limited BM reserves for correction of cytopenia under any circumstances.

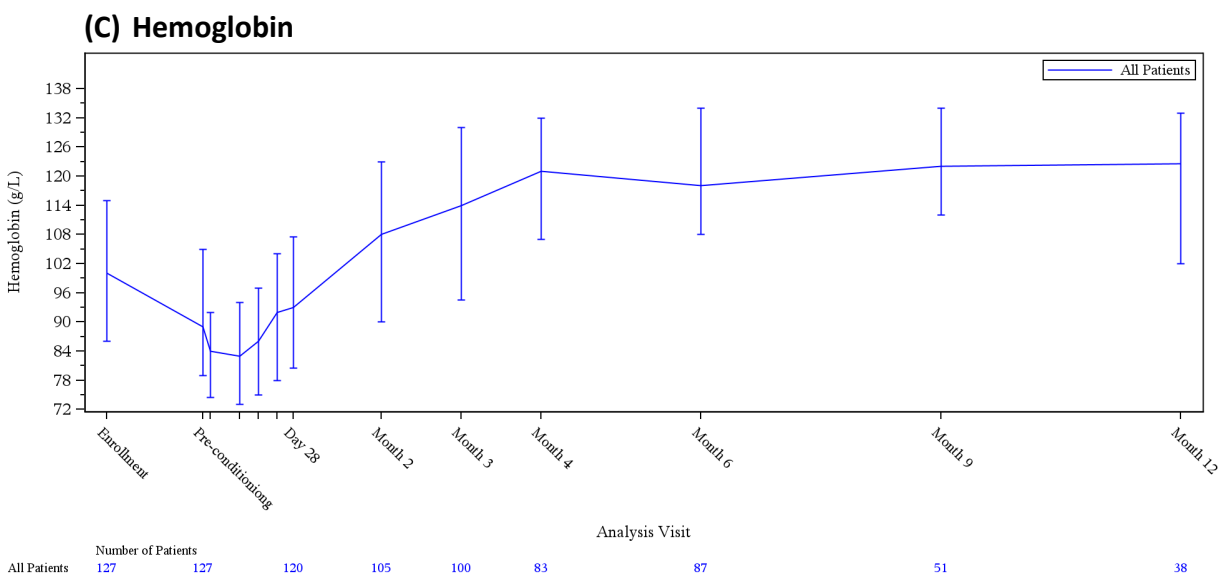
After LD therapy and obe-cel infusion, in laboratory tests conducted within 30 days after the obe-cel infusion, 124 of 127 patients (97.6%) in the Safety Set experienced at least one report of \geq Grade 3 neutropenia, 88 patients (69.3%) had \geq Grade 3 thrombocytopenia, and 78 patients (61.4%) had \geq Grade 3 anaemia.

Across the overall population treated with obe-cel, the impact of LD followed by recovery is illustrated for the absolute neutrophil and platelet counts over time in [Applicant Figure 10](#)

Additional information is provided in D30 Safety Update Report, Section 3.1.4.3; Module 2.7.4, Section 2.1.5.3.

Applicant Figure 10 Median (Q1, Q3) Laboratory Values over Time for A) Neutrophil Count; B) Platelet Count – Phases Ib and II, All Cohorts (Safety Set) – FELIX Study





Pre-conditioning was defined as the last available measurement prior to the start of lymphodepletion.

Data cut-off: 13-Sep-2023.

BLA D30 Update – Figures 14.3.6.4.4, 14.3.6.4.5, and FELIX CSR Figure 14.3.6.4.1.

A detailed evaluation of recovery from cytopenia was performed in patients who achieved remission (Best Overall Response [BOR] of CR or CRi, N=98) (2.7.4 - Section 2.1.5.3). As expected, the proportion of responders post obo-cel infusion with Grade 3 or 4 neutropenia gradually decreased with time, being 59.2% (58/98), 23.5% (23/98), and 13.3% (13/98) at Day 28, Month 2, and Month 3, respectively, and the corresponding values for Grade 3 or 4 thrombocytopenia were 49.0% (48/98), 20.4% (20/98), and 11.2% (11/98). However, no patient in remission had neutropenia ($< 1 \times 10^9/\text{L}$ neutrophil count) for more than 6 months and only 7 patients had thrombocytopenia ($< 100 \times 10^9/\text{L}$ platelet count) lasting longer than 6 months. All 7 of the patients who experienced thrombocytopenia for longer than 6 months had been heavily pre-treated, with 6/7 patients having received prior SCT and the remaining patient having received 3 lines of prior therapy. Such patients may have reduced BM reserve after multiple prior lines of ALL therapies and may have an inability to fully recover platelets over time; notably, none of these 7 patients had any bleeding events reported and only minimal platelet transfusion requirements.

Time to recovery in responders to different thresholds (≥ 0.5 or $\geq 1 \times 10^9/\text{L}$ for neutrophil count; ≥ 50 or $\geq 100 \times 10^9/\text{L}$ for platelet count) has been evaluated. The median time to recovery (95% CI) to the lower thresholds was 0.7 months (0.5, 0.9) and 0.7 months (0.3, 1.8) for neutrophils and platelets, respectively, and the corresponding times to recovery for the higher thresholds were 1.9 months (1.0, 1.9) and 2.0 months (1.9, 2.1). The associated KM probability of recovery at 6 months post infusion presented the high chance of recovery, being 97.6% at the $1.0 \times 10^9/\text{L}$ threshold for neutrophils (already reached 100% at 5 months for $0.5 \times 10^9/\text{L}$ threshold for neutrophils), and for the $50 \times 10^9/\text{L}$ and $100 \times 10^9/\text{L}$ thresholds for platelets it was 95.1% and 83.4%, respectively.

For prolonged neutropenia, all patients with any infection \geq Grade 3 after Month 3 post-infusion were reviewed, and the overall infection rate is as would be expected for an adult r/r B ALL

population in remission. In addition, all 17 patients who converted to CR after Month 3 or had CRi ongoing as of the cut-off date were reviewed and no additional infection risk is observed in this group of patients that can be directly associated with a low neutrophil count due to obe-cel administration. Regarding prolonged thrombocytopenia, there were no bleeding events \geq Grade 3 observed beyond Month 3 (the only 2 cases of \geq Grade 3 bleeding occurred within 3 months post obe-cel infusion).

The FDA's Assessment:

See [FDA Table 25](#) below which lists the incidence of cytopenias (including anemia, neutropenia, and thrombocytopenia) in all responders in the primary efficacy population lasting through Day 30 and Day 60 after Obe-cel treatment.

FDA Table 25. Prolonged Cytopenias, All Responders*

	All Responders (N=41) n (%)
Prolonged Cytopenias, Grade 3 or Higher	
Any prolonged cytopenias, unresolved by Day 30	29 (71)
Neutropenia	27 (66)
Thrombocytopenia	22 (54)
Any prolonged cytopenias, unresolved by Day 60	11 (27)
Neutropenia	7 (17)
Thrombocytopenia	6 (15)

Source: FDA analysis. ADSL, ADSL FDA1, ADLB datasets.

Any Cytopenia includes Neutropenia, Anaemia, Thrombocytopenia>.

*Prolonged Cytopenia population (responders, N=41) identified as those from Efficacy Population (N=65) who achieve CR or CRi.

Reviewer comment: *The Applicant proposed to include results of cytopenias not resolving by Day 30 and by Day 90 following obe-cel infusion in the USPI. The Reviewer recommends including prolonged cytopenias not resolved by Day 60 rather than by Day 90 as this is more informative to the prescriber.*

Hemophagocytic Lymphohistiocytosis/Macrophage Activation Syndrome

Applicant's Position :

In approximately 1% of cases, CRS after CAR T cell therapy has been reported to evolve into CAR T cell related HLH / MAS which has a high mortality ([Thompson et al, 2022](#)).

Diagnostic criteria for CAR T cell-related HLH/MAS in the FELIX study were based on a peak serum ferritin measurement of $> 10,000$ ng/mL and subsequent development of at least two of the following findings ([Neelapu et al, 2018](#)):

- Grade ≥ 3 increase in serum bilirubin, aspartate aminotransferase, or alanine aminotransferase levels
- Grade ≥ 3 oliguria or increase in serum creatinine levels
- Grade ≥ 3 pulmonary oedema
- Presence of haemophagocytosis in BM or organs based on histopathological assessment of cell morphology and/or CD68 IHC

As of the cut-off date, a total of 2 patients (1.6%, 2/127) experienced HLH/MAS. One patient (0.8%, 1/127) experienced Grade 3 HLH with onset at Day 22 post-infusion and although the patient recovered from HLH, the patient subsequently died due to progressive disease. The other patient experienced Grade 4 HLH with onset on Day 41 post-infusion and died due to sepsis with ongoing HLH that had not resolved.

Additional information is provided in Module 2.7.4 Summary of Clinical Safety, Section 2.1.5.4; BLA D30 Update – Table 14.3.4.1.1.

The FDA's Assessment:

FDA agrees with the Applicant's description of the 2 (out of 100) patients who experienced HLH/MAS.

Severe Infections

Most infections occur soon after infusion and may occur for several reasons, including lymphodepleting or antecedent chemotherapy, CAR T cell-mediated B cell aplasia or plasma cell depletion, prolonged cytopenias, corticosteroid treatment, or as a consequence of the underlying malignancy itself ([Thompson et al, 2022](#)).

Since this study was conducted during the COVID-19 pandemic there was an impact on the infection rate, particularly the viral infection rate. Therefore, the focus for infection rates is excluding COVID-19 infection events.

The percentage of patients with non-COVID severe infections (\geq Grade 3) was 39.4% (50/127), ([Applicant Table 19](#)); if COVID-19 infections are also included then the rate is 43.3% of patients (55/127). The lower rate is driven by infections in the viral disorders high level term (HLT) with \geq Grade 3 non-COVID viral disorders of 3.1% (4/127), compared to 7.9% (10/127) if COVID-19 is included.

The most common severe infection PTs (\geq 5% of patients) were pneumonia (7.1%, 9/127) and sepsis (6.3%, 8/127). A total of 5 patients (3.9%) died with infections which was due to sepsis (2 patients), neutropenic sepsis (2 patients) and abdominal infection (1 patient). The patient with neutropenic sepsis was related to study treatment (Investigator and Sponsor).

As would be expected, the analysis of infections by neutrophil count at LD ($< 0.5 \times 10^9$ versus $\geq 0.5 \times 10^9$) showed a higher percentage of patients in the lower neutrophil category with TEAEs \geq Grade 3 in the Infection System Organ Class (SOC) (59.4% [19/32] versus 38.7% [36/93]). This same pattern was observed for bacterial, fungal infections and viral infections, although the latter would be impacted by COVID-19 viral infections.

Also, in line with expectations was that more patients had severe non-COVID infections (\geq Grade 3) within 3 months of obe-cel infusion (28.3%, 36/127) compared to after 3 months post obe-cel infusion (15.0%, 19/127). Of note, Grade \geq 3 bacterial infections were observed in only 2.4% (3/127) of subjects after 3 months post obe-cel infusion.

Additional information is provided in D30 Safety Update Report, Section 3.1.4.6; Module 2.7.4, Section 2.1.5.6.

The FDA's Assessment:

See [FDA Table 26](#) regarding the incidence of infections in the safety analysis set.

FDA Table 26. Infections, Safety Analysis Set

Adverse Event	Any Grade (N=100) n (%)	Grade 3 or Higher (N=100) n (%)
Infections and infestations	76 (76.0)	46 (46.0)
Infections - pathogen unspecified	44 (44.0)	31 (31.0)
Viral infections	32 (32.0)	7 (7.0)
Bacterial infections	26 (26.0)	11 (11.0)
Fungal infections	15 (15.0)	5 (5.0)

Source: FDA Analysis, ADSL, ADAE, ADAEFDA datasets.

B Cell Aplasia and HypogammaglobulinemiaThe Applicant's Position:

B cell aplasia is an expected on-target effect of obe-cel and as such B cell aplasia is either a pharmacodynamic marker of functional CAR T cell persistency or is due to pre-existing B -ALL therapies and the pharmacodynamic analysis on B cell aplasia is presented in [Section 6.3](#).

More than a third of patients (34.6%, 44/127) were receiving IVIG at the time of LD, prior to obe-cel infusion.

Hypogammaglobulinemia, is caused by B cell aplasia and is a reported potential risk of CAR T cell therapy, usually with a late manifestation ([Thompson et al, 2022](#)). The TEAE of hypogammaglobulinemia has been reported in a total of 10 patients (7.9%, 10/127) at any grade and regardless of causality. One patient (0.8%, 1/127) experienced Grade 3 hypogammaglobulinemia which started more than 9 months after obe-cel infusion, after prior reporting of low immunoglobulin G (IgG) levels and treatment using intravenous immunoglobulin (IVIG); the patient experienced a Clostridium difficile infection and IVIG therapy was ceased.

Additional information is provided in D30 Safety Update Report, Section 3.1.4.5; Module 2.7.4, Section 2.1.5.5.

The FDA's Assessment:

Hypogammaglobulinemia was reported in 10% (10 of 100) of patients including 2 cases (2%) of Grade 3 hypogammaglobulinemia.

Tumor Lysis SyndromeThe Applicant's Position:

This is a potentially life threatening or fatal complication of patients or treatment which comprises of a constellation of laboratory findings such as hyperuricemia, hyperkalemia, hyperphosphatemia, and hypocalcemia, however with the manifestation of clinical complications such as seizures, acute renal failure, and cardiac dysrhythmias. The syndrome is called clinical tumor lysis syndrome (TLS).

There was 1 patient (0.8%, 1/127) who experienced TLS (Grade 3). This event occurred post new anti-cancer therapy and is considered not related to obe-cel.

Additional information is provided in D30 Safety Update Report, Section 3.1.4.7; Module 2.7.4, Section 2.1.5.7.

The FDA's Assessment:

FDA agrees.

Graft Versus Host Disease

The Applicant's Position:

The occurrence of graft versus host disease (GvHD) may be an expected consequence of obe-cel treatment in patients who have had prior allogeneic SCT.

A total of 7 patients (5.5%, 7/127) have reported GvHD post obe-cel infusion. Of these 7 patients, 6 had received prior SCT before entering the study without further SCT post-infusion. The remaining patient received SCT post obe-cel treatment (Day 90) and subsequently experienced GvHD (Day 153).

There were 3 patients (2.4%) with Grade 3 GvHD reported:

- 1 patient experienced Grade 3 GvHD of the skin
- 1 patient experienced Grade 3 GvHD with the location not specified, but also developed GvHD of the skin and GI tract, both with Grade < 3
- 1 patient experienced Grade 3 GvHD of the GI tract and Grade 3 GvHD of the liver, as well as GvHD Grade 1 of the skin

Additional information is provided in D30 Safety Update Report, Section 3.1.4.8; Module 2.7.4, Section 2.1.5.8.

The FDA's Assessment:

GvHD occurred in 4% (4 of 100) patients in the safety analysis set.

Secondary Malignancies

The Applicant's Position:

There were no patients identified with secondary malignancy causally related to obe-cel. There were 2 patients flagged as having potential secondary malignancies, or malignancies other than B ALL, post obe-cel infusion. One patient had acute myeloid leukemia (AML) reported post obe-cel infusion and 1 patient had basal cell carcinoma reported. Each patient was medically reviewed in detail and these cases were not considered to be secondary malignancies associated with obe-cel treatment in view of pre-existing conditions and confounding circumstances.

Additional information is provided in D30 Safety Update Report, Section 3.1.4.9; Module 2.7.4, Section 2.1.5.9.

The FDA's Assessment:

FDA agrees. Details on the patient who developed acute myeloid leukemia (AML) is listed below.

Patient (b) (6) was a 58-year-old female who was initially diagnosed with B ALL and was subsequently treated with obe-cel. The patient had the following genetic abnormalities at the time of B ALL diagnosis: KMT2A (11q23) rearrangement resulting in t(4;11), and a point mutation DNMT3A R882H. The patient had received two prior lines of therapies for ALL. Additionally, the patient had a suspected diagnosis of myelodysplastic syndrome (MDS) prior to obe-cel treatment. Day 29 disease assessment demonstrated CRi. However, there were molecular abnormalities by FISH compatible with MDS. The bone marrow findings were consistent with secondary treatment-related AML with monocytic differentiation. Subsequently, the patient developed treatment-related AML on Day 44 and died on Day 45 due to acute encephalopathy with focal weakness in the left side followed by right side secondary to AML. No autopsy was performed. The investigator and the Applicant considered the event not related to obe-cel treatment. No information regarding CAR transgene testing on BM was provided. Given the pre-existing clinical suspicion for MDS and pre-existing genetic abnormality (DNMT3A mutation) associated with development of MDS, the review team agrees with Applicant's assessment that it is unlikely that this event was related to obe-cel.

Hypersensitivity Reactions

The Applicant's Position:

As obe-cel is an autologous product, it would not be expected to induce a hypersensitivity reaction. However, obe-cel also contains dimethyl sulfoxide (DMSO) as an excipient, which could also trigger a hypersensitivity reaction.

No hypersensitivity reaction has been reported in the FELIX study after obe-cel infusion. The PTs used were to capture hypersensitivity reactions were hypersensitivity, type I hypersensitivity, type IV hypersensitivity reaction, type II hypersensitivity, infusion site hypersensitivity, administration site hypersensitivity, and infusion-related hypersensitivity reaction.

Additional information is provided in D30 Safety Update Report, Section 3.1.4.10; Module 2.7.4, Section 2.1.5.10.

The FDA's Assessment:

FDA concurs with the Applicant's assessment.

Antigenicity and Immunogenicity

Since obe-cel is an autologous therapy, a high rate of immune reactions is not expected.

Cellular immunogenicity data is discussed in the AUTO1-AL1 PK/PD Report, Section 9. In summary, of those patients for whom results are available (N=75), there were 3 patients (4.0%, 3/75) with a positive immunogenicity test at approximately 3 months after obe-cel infusion. All 3 patients achieved CR, all experienced CRS (< Grade 3) and 1 patient experienced ICANS (Grade

3) all of which resolved within approximately 1 month. These safety events are therefore unlikely related to a cellular immunogenicity signal.

Humoral immunogenicity data is provided in a separate Humoral Immunogenicity Report.

The FDA's Assessment:

The humoral immunogenicity of obe-cel was measured using an assay for the detection of anti-drug antibodies against obe-cel. In the FELIX overall safety population (from Phase 1b/2 cohorts A/B/C), 8.7% (11 of 127) of patients tested positive for anti-CD19 CAR antibodies pre-infusion. Treatment induced anti-CD19 CAR antibodies were detected in 1.6% (2 of 127) of patients. There is no evidence that the presence of pre-existing or post-infusion anti-CD19 CAR antibodies impact the effectiveness, safety, initial expansion, and persistency of obe-cel.

The cellular immunogenicity of obe-cel was measured using an assay for the detection of T cell responses, measured by the production of interferon gamma (IFN γ) to the full length anti-CD19 CAR. For patients whom results were available, 4% (3 of 75) of patients tested positive in the cellular immunogenicity readout (IFN γ) post-infusion. There is no evidence that the cellular immunogenicity impacts the kinetics of initial expansion and persistence of obe-cel, or the safety or effectiveness of obe-cel.

Concomitant Medications/Procedures

The Applicant's Position:

See [Section 8.1.2](#), Concomitant Medications

Of the 127 patients in the Safety Set, 126 (99.2%) received concomitant medications with a start or end date on or after obe-cel infusion. The most frequently administered medications by ATC class were Nucleosides and Nucleotides Excluding Reverse Transcriptase Inhibitor (93.7% patients), Triazole and Tetrazole Derivatives (86.6% patients), Anilides (80.3% patients), Preparations Inhibiting Uric Acid Production (77.2%), Proton Pump Inhibitors (72.4% patients), Serotonin (5HT₃) Antagonists (70.1% patients), and Combinations of Sulfonamides and Trimethoprim Including Derivatives (68.5% patients) (BLA D30 Update - Table 14.1.5.3.1).

Rescue Medications

The FDA's Assessment:

Most common concomitant medications ($\geq 20\%$) are presented in [FDA Table 27](#) below.

FDA Table 27. Medication Use, Safety Analysis Set

Medication Category	Medication	N=100 %
Nucleosides and nucleotides excl. Reverse transcriptase inhibitors	Aciclovir	89
Serotonin (5ht ₃) antagonists	Ondansetron	83
Anilides	Paracetamol	82
Preparations inhibiting uric acid production	Allopurinol	82

Medication Category	Medication	N=100 %
Combinations of sulfonamides and trimethoprim, incl. Derivatives	Sulfamethoxazole; trimethoprim	72
Other antiepileptics	Levetiracetam	64
Other blood products	Platelets, human blood	60
Interleukin inhibitors	Tocilizumab	59
Solutions affecting the electrolyte balance	Sodium chloride	47
Triazole and tetrazole derivatives	Posaconazole	47
Other blood products	Red blood cells	45
Glucocorticoids	Dexamethasone	43
Fluoroquinolones	Levofloxacin	41
Triazole and tetrazole derivatives	Fluconazole	40
Benzodiazepine derivatives	Lorazepam	39
Sulfonamides, plain	Furosemide	39
Carbapenems	Meropenem	38
Solutions affecting the electrolyte balance	Potassium chloride	38
Colony stimulating factors	Filgrastim	37
Combinations of penicillins, incl. Beta-lactamase inhibitors	Piperacillin sodium;tazobactam sodium	37
Solutions affecting the electrolyte balance	Magnesium sulfate	36
Aminoalkyl ethers	Diphenhydramine	35
Fluoroquinolones	Ciprofloxacin	35
Glycopeptide antibacterials	Vancomycin	35
Folic acid and derivatives	Folic acid	33
Proton pump inhibitors	Omeprazole	32
Heparin group	Enoxaparin	31
Bile acids and derivatives	Ursodeoxycholic acid	30
Propulsives	Metoclopramide	30
Fourth-generation cephalosporins	Cefepime	29
Potassium	Potassium chloride	28
H2-receptor antagonists	Famotidine	26
Substituted alkylamines	Chlorphenamine	25
Electrolyte solutions	Calcium gluconate	24
Other agents against amoebiasis and other protozoal diseases	Atovaquone	23
Other agents against leishmaniasis and trypanosomiasis	Pentamidine	23
Natural opium alkaloids	Oxycodone	22
Proton pump inhibitors	Pantoprazole	22
Selective beta-2-adrenoreceptor agonists	Salbutamol	20

Source: FDA Analysis, ADCM dataset

Dropouts and/or Discontinuations Due to Adverse Effects

Data:

Obe-cel is administered as 2 infusions, on Day 1 and Day 10 (\pm 2 days). In the Safety Set, 94.5% (120/127) patients received both obe-cel infusions, whereas 5.5% (7/127) patients received only the first infusion. Three patients (2.4%) did not receive the second infusion due to an AE.

Additional information is provided in Module 2.7.4, Section 1.2.4; BLA D30 Update – BLA D30 Table 14.1.4.4.4.

The FDA's Assessment:

FDA concurs with the Applicant's assessment.

Dose Interruption/Reduction Due to Adverse Effects

Data:

There were no interruptions or reductions during infusions due to an AE. A total of 9 patients received their second dose after Day 10 ± 2 days, but within the protocol-specified period of up to Day 21, due to the occurrence of an AE (range: Day 13 - 21)(Module 2.7.4 Summary of Clinical Safety, Section 1.2.4).

The FDA's Assessment:

A total of seven patients (7%) received only one of the planned two obe-cel infusions, three of whom received less than the planned target dose. A total of five patients received their second dose after Day 10 ± 2 days, but within the protocol-specified period of up to Day 21, due to the occurrence of an AE (range: Day 13 to 21).

Laboratory Findings

Laboratory values, where possible, were graded as the worse value obtained within the period specified using CTCAE grading.

Data:

A summary of all common Grade 3 or 4 laboratory abnormalities graded per CTCAE criteria (occurring in ≥ 10% of patients) is presented in [Applicant Table 20](#) which reflects the worst laboratory results post obe-cel infusion. As discussed above, most patients had abnormal laboratory findings prior to obe-cel infusion because of the impact of LD and the underlying clinical status of the patients treated with obe-cel.

Additional information is provided in D30 Safety Update Report, Section 4.1; Module 2.7.4, Section 3.

Applicant Table 20 Grade 3 or 4 Laboratory Abnormalities Occurring in ≥ 10% of Patients After Obe-cel Infusion (Safety Set) – FELIX Study

Laboratory Parameter	Total (N=127) n (%)
Hemoglobin (g/L) (Decreased)	82 (64.6)
Lymphocytes (10 ⁹ /L) (Decreased)	121 (95.3)
Neutrophils (10 ⁹ /L) (Decreased)	125 (98.4)
Platelets (10 ⁹ /L) (Decreased)	95 (74.8)
Leukocytes (10 ⁹ /L) (Decreased)	124 (97.6)
Alanine Aminotransferase (U/L) (Increased)	13 (10.2)
Aspartate Aminotransferase (U/L) (Increased)	13 (10.2)

The percentage in the table was based on N.

Grading was based on the worst case of all post-baseline visits within the time range, including non-scheduled visits of a patient.

Data cutoff 13-Sep-2023.

BLA D30 Update – Tables 14.3.6.4.4 and 14.3.6.4.5.

The FDA's Assessment:

Analysis of biochemistry and hematology laboratory abnormality parameters is presented in [FDA Table 28](#) below. The last value on or prior to the start date of LD is considered as baseline value, and abnormalities occurring or worsening after the start date of LD are considered as treatment-emergent laboratory abnormalities. Laboratory tests were graded according to CTCAE (V5.0).

The most common Grade 3 or 4 laboratory abnormalities included lymphopenia, leukopenia, neutropenia, anemia, and thrombocytopenia.

FDA Table 28. Grade 3 or 4 Laboratory Abnormalities, Safety Analysis Set

Category	Parameter	Worsen to Grade 3 or 4
Biochemistry		-
	Alkaline Phosphatase (Increase)	5/100 (5.0)
	Alanine Aminotransferase (Increase)	9/100 (9.0)
	Aspartate Aminotransferase (Increase)	10/99 (10.1)
	Bilirubin (Increase)	5/100 (5.0)
	Creatinine (Increase)	1/100 (1.0)
	Urate (Increase)	0
Hematology		-
	Hemoglobin (Decrease)	43/100 (43.0)
	Hemoglobin (Increase)	1/100 (1.0)
	Lymphocytes (Decrease)	90/100 (90.0)
	Lymphocytes (Increase)	3/100 (3.0)
	Neutrophils (Decrease)	72/100 (72.0)
	Platelets (Decrease)	48/100 (48.0)
	Leukocytes (Decrease)	87/100 (87.0)
	Leukocytes (Increase)	1/100 (1.0)

Source: FDA analysis, ADSLFDA, ADLBFDA

Baseline value was the last available result on or prior to start date of lymphodepletion.

The denominator used for calculation of each lab abnormality frequency included patients with baseline and at least one post treatment value available.

Reviewer comment: In response to IR, the Applicant submitted updated laboratory dataset ADLBFDA, which follows the same structure as the original ADLB dataset submitted in the BLA (SN0001) and BLA Day 30 update (SN0003), except that the last value on or prior to the start date of lymphodepletion (instead of the first obe-cel infusion) is now considered as baseline.

Vital Signs

The Applicant's Position:

Vital signs and physical findings were closely monitored in obe-cel infused patients in the FELIX study, as a component of the standard of care in autologous transplantation, during which fluctuations and abnormalities are usually observed. No clinically significant pattern was observed in vital signs or physical functioning post obe-cel infusion.

Additional information is provided in D30 Safety Update Report, Section 4.2; Module 2.7.4, Section 4.1.

The FDA's Assessment:

FDA concurs with the Applicant's assessment.

8.2.5. Analysis of Submission-Specific Safety Issues

The Applicant's Position:

Specific safety issues observed in the FELIX study are summarized in [Section 8.2.4](#). No new safety signals were identified in the analysis of the adult patients with r/r B ALL in FELIX. Data regarding known safety issues associated with this class of therapy (CAR T) has been provided and no new

safety signals specific to obe-cel have been identified. On the contrary, obe-cel when administered using the split dose regimen adapted to disease burden, resulted in low rates of \geq Grade 3 CRS (3/127, 2.4%) and ICANS (9/127, 7.1%).

The types of AEs that have been reported for adult patients with B ALL studies were generally observed in FELIX. As in other CAR T studies, the incidence of CRS and neurologic AEs in observed in FELIX and were generally comparable or lower to those observed in other CAR T studies, with a notably lower incidence of Grade 3 or higher CRS and ICANS than observed in other studies assessing CD19 CAR T products. A reduced potential for toxicity is likely attributable to the unique lower affinity design of the CD19 binding domain of obe-cel resulting in shorter cell-cell contact, as well as the split dose regimen adapted to tumor burden at time of LD.

There was a significant proportion of patients who were severely cytopenic at enrollment in the FELIX study, with 34.6% of patients (44/127) having \geq Grade 3 neutropenia and 33.9% (43/127) having \geq Grade 3 thrombocytopenia, which may reflect that patients who were enrolled had already failed several prior lines of treatment and had a limited remaining BM reserve. The proportion of responders post obe-cel infusion with Grade 3 or 4 neutropenia or thrombocytopenia gradually decreased with time, and no patient in remission had neutropenia ($< 1 \times 10^9$ /L neutrophil count) for more than 6 months and only 7 patients, who had had prior SCT or received more than 3 lines of prior therapy, had thrombocytopenia ($< 100 \times 10^9$ /L platelet count) lasting longer than 6 months. The analysis of infections by neutrophil count at LD ($< 0.5 \times 10^9$ versus $\geq 0.5 \times 10^9$) showed a higher percentage of patients in the lower neutrophil category with TEAEs \geq Grade 3 in the Infection SOC.

The FDA's Assessment:

FDA agrees that no new safety signals specific to obe-cel were identified during the review. although cross trial comparisons are limited, the safety profile of obe-cel appears generally consistent with that of other approved CAR T cell products. Rates of AEs across trials can reflect differences in many factors and as such, comparisons should be interpreted with caution.

8.2.6. Clinical Outcome Assessment Analyses Informing Safety/Tolerability

The Applicant's Position:

No information was included in this submission regarding COA to inform on safety of obe-cel.

The FDA's Assessment:

FDA agrees that no information was included in this submission regarding clinical outcome assessment (COA) to inform safety of obe-cel.

8.2.7. **Safety Analyses by Demographic Subgroups**

Data:

Several subgroup analyses have been performed, both in which the overall TEAE profile has been evaluated and, for selected adverse events of specific interest (such as CRS and ICANS), more detailed analysis has been performed. For disease characteristics, this was evaluated by status at screening and at LD. A summary of analyses for demographic parameters and disease characteristics is provided in [Applicant Table 21](#).

Applicant Table 21 Summary of Analysis of Safety by Subgroup – FELIX Study

Subgroup	Summary
Demographic Parameters	
Sex	No apparent differences in the safety profile of female and male patients.
Age group	Generally similar safety profile across 3 age groups (≥ 18 to < 40 , ≥ 40 to < 65 , and ≥ 65 years of age). Any grade ICANS were more frequently reported in patients ≥ 65 years of age than in the younger population, which can be expected considering the general health and the comorbidities in the older patient population.
Ethnicity	Generally similar safety profile for Hispanic or Latino ethnicity and non-Hispanic non-Latino ethnicity.
Race	Small numbers of Black or African American and Asian groups. No apparent differences in safety profile between these groups.
Disease Characteristics	
Blasts in BM at LD	<p>CRS and ICANS of any grade was highest in the subgroup with $> 75\%$ blasts in BM. Across blast subgroups of $< 5\%$, $\geq 5\%$ to $\leq 20\%$, $> 20\%$ to $\leq 75\%$, and $> 75\%$, the percentage of patients with CRS was 47.2% (17/36 patients), 62.5% (10/16 patients), 71.4% (25/35 patients), and 87.5% (35/40 patients), respectively, whereas for ICANS the corresponding percentages were 8.3% (3/36 patients), 25.0% (4/16 patients), 14.3% (5/35 patients) and 42.5% (17/40 patients).</p> <p>Supportive of the fractionated 2-step dosing regimen based on blasts in BM at LD (lower first dose if $> 20\%$ blasts vs $\leq 20\%$ blasts (See Section 6); a minimal difference in CRS \geq Grade 3 was observed in patients in the $> 20\%$ blast subgroup (2.7%, 2/75 patients) compared to the $\leq 20\%$ blast subgroup (1.9%, 1/52 patients), and a modest difference was observed in ICANS \geq Grade 3 (9.3% [7/75 patients] versus 3.8% [2/52 patients]). This indicates a positive influence of the dose regimen for obe-cel.</p>
EMD at LD	As expected, there was a trend towards more patients with EMD at LD having ICANS (any grade, and \geq Grade 3) than patients without EMD at LD.
Philadelphia chromosome (Ph) / BCR-ABL status	Higher frequency of ICANS (any grade), serious TEAE and obe-cel related serious TEAE in patients with Ph-negative status than in patients with Ph-positive status.
Prior ALL Therapy	
Prior lines of therapy	Generally similar safety profile across the subgroups of patients who had received 1 to ≥ 4 prior lines of anti-cancer therapy.
Prior allogeneic SCT	Generally similar safety profile across the subgroups of patients with or without prior allogeneic SCT.
Prior blina experience	As expected, patients who received prior blina than patients who did not receive prior blina had more ICANS (any grade, and \geq Grade 3).

Subgroup	Summary
Prior blina or ino experience	Generally similar safety profile across the subgroups of patients who had received or had not received prior ino therapy.
Prior blina and ino experience	As with blina alone, and as expected, patients who received prior blina and ino had higher ICANS rates (any grade, and \geq Grade 3) than patients who did not receive prior blina and ino.
Refractory to all prior lines of therapy	A higher proportion of patients who were not refractory to all prior lines of therapy than those who were refractory to all prior lines of therapy experienced ICANS (any grade, and \geq Grade 3), serious TEAEs and obe-cel related \geq Grade 3 TEAEs.
Refractory to 1 st prior line of therapy	A higher proportion of patients who were not refractory to 1 st prior line of therapy than those who were refractory to 1 st prior line of therapy experienced ICANS (any grade, and \geq Grade 3), CRS (any grade, and \geq Grade 3), serious TEAEs and obe-cel related \geq Grade 3 TEAE.
Refractory to last prior line of therapy	Generally similar safety profile across the subgroups of patients who were refractory or not refractory to last prior lines of therapy.
Relapsed to 1 st prior line of therapy within 12 months	As expected, a higher proportion of patients who relapsed to 1 st prior therapy within 12 months than patients who did not, had ICANS (any grade, and \geq Grade 3) and CRS (any grade, and \geq Grade 3).

BM=Bone marrow; CRS=Cytokine release syndrome; blina=Blinatumomab; EMD=Extramedullary disease; ICANS=Immune effector cell-associated neurotoxicity syndrome; ino=Inotuzumab ozogamycin; LD=Lymphodepletion; SCT=Stem cell transplantation; TEAE=Treatment emergent adverse event.

Source: Module 2.7.4, Table 24

The FDA's Assessment:

The following subgroups were used for analysis of TEAEs:

- Age group (<65 years/≥65 years)
- Sex (male/female)
- Race (White or Caucasian/Black or African American/Asian/American Indian or Alaska Native/Native Hawaiian or Other Pacific Islander)
- Ethnicity (Hispanic or Latino/Non-Hispanic or Latino)

See [FDA Table 29](#), [FDA Table 30](#), [FDA Table 31](#), and [FDA Table 32](#) below for the TEAEs per age group, sex, race, and ethnicity, respectively.

FDA considers these analyses to be exploratory in a small single-arm study and, therefore, definitive conclusions cannot be made.

FDA Table 29. Treatment-Emergent Adverse Events by Age Group in ≥10%, Safety Analysis Set

TEAE	<65 Years	≥65 Years	Risk Difference
	(N=80) n (%)	(N=20) n (%)	
Musculoskeletal pain	32 (40)	4 (20)	-20
Infections - pathogen unspecified	38 (48)	6 (30)	-18
Nausea	26 (33)	3 (15)	-18
Pain	21 (26)	2 (10)	-16
Leukopenia	12 (15)	0 (0)	-15
Abdominal pain	15 (19)	1 (5)	-14
Hypotension	20 (25)	3 (15)	-10
Fatigue	16 (20)	6 (30)	10
Hypomagnesaemia	8 (10)	4 (20)	10
Weight decreased	7 (9)	4 (20)	11
Delirium	2 (3)	3 (15)	13
Thrombocytopenia	22 (28)	8 (40)	13
Amenotransferase increased	9 (11)	5 (25)	14
Fever	21 (26)	8 (40)	14
Hypokalaemia	16 (20)	7 (35)	15
Hemorrhage	13 (16)	7 (35)	19
Neutropenia	30 (38)	12 (60)	23
Immune effector cell-associated neurotoxicity syndrome	14 (18)	10 (50)	33

Source: FDA Analysis, ADSL, ADSL FDA1, ADAEFDA datasets.

Events listed for those where the absolute risk difference is ≥10% in magnitude.

Abbreviations: TEAE, treatment-emergent adverse event

FDA Table 30. Treatment-Emergent Adverse Events by Sex in ≥10%, Safety Analysis Set

TEAEs	Male (N=50) n (%)	Female (N=50) n (%)	Risk Difference
Viral infections	21 (42)	11 (22)	-20
Chills	9 (18)	2 (4)	-14
Bacterial infections	16 (32)	10 (20)	-12
Hypocalcaemia	6 (12)	1 (2)	-10
Pain	14 (28)	9 (18)	-10
Anaemia	9 (18)	14 (28)	10
Cytokine release syndrome	35 (70)	40 (80)	10
Fever	12 (24)	17 (34)	10
Hypertension	1 (2)	6 (12)	10
Rash	6 (12)	11 (22)	10
Diarrhoea	10 (20)	16 (32)	12
Infections - pathogen unspecified	19 (38)	25 (50)	12
Leukopenia	3 (6)	9 (18)	12
Vomiting	6 (12)	12 (24)	12
Hyperferritinaemia	5 (10)	13 (26)	16

Source: FDA Analysis, ADSL, ADSLFDA1, ADAEFDA datasets.

Events listed for those where the absolute risk difference is ≥10% in magnitude.

Abbreviations: TEAE, treatment-emergent adverse event

FDA Table 31. Treatment-Emergent Adverse Events by Race in ≥10%, Safety Analysis Set

TEAE	Asian (N=12) n (%)	Black or African American (N=1) n (%)	White (N=75) n (%)	Unknown (N=12) n (%)
Cytokine release syndrome	9 (75)	0 (0)	54 (72)	12 (100)
Infections - pathogen unspecified	5 (42)	0 (0)	33 (44)	6 (50)
Neutropenia	3 (25)	0 (0)	34 (45)	5 (42)
Musculoskeletal pain	4 (33)	0 (0)	24 (32)	8 (67)
Viral infections	3 (25)	1 (100)	25 (33)	3 (25)
Thrombocytopenia	2 (17)	0 (0)	25 (33)	3 (25)
Fever	4 (33)	0 (0)	22 (29)	3 (25)
Nausea	4 (33)	0 (0)	21 (28)	4 (33)
Bacterial infections	6 (50)	0 (0)	16 (21)	4 (33)
Diarrhoea	4 (33)	0 (0)	18 (24)	4 (33)
Febrile neutropenia	2 (17)	0 (0)	20 (27)	4 (33)
Immune effector cell-associated neurotoxicity syndrome	2 (17)	0 (0)	18 (24)	4 (33)
Anaemia	3 (25)	0 (0)	18 (24)	2 (17)
Hypokalaemia	5 (42)	0 (0)	15 (20)	3 (25)
Hypotension	5 (42)	0 (0)	12 (16)	6 (50)
Pain	3 (25)	0 (0)	17 (23)	3 (25)
Fatigue	2 (17)	0 (0)	16 (21)	4 (33)
Headache	3 (25)	0 (0)	15 (20)	4 (33)
Encephalopathy	1 (8)	0 (0)	15 (20)	5 (42)
Hemorrhage	3 (25)	0 (0)	14 (19)	3 (25)
Hyperferritinaemia	2 (17)	0 (0)	15 (20)	1 (8)
Vomiting	2 (17)	0 (0)	13 (17)	3 (25)
Rash	0 (0)	0 (0)	12 (16)	5 (42)
Abdominal pain	1 (8)	0 (0)	13 (17)	2 (17)
Fungal infections	2 (17)	0 (0)	11 (15)	2 (17)

	Asian (N=12) n (%)	Black or African American (N=1) n (%)	White (N=75) n (%)	Unknown (N=12) n (%)
TEAE				
Amenotransferase increased	1 (8)	0 (0)	10 (13)	3 (25)
Cough	0 (0)	0 (0)	13 (17)	1 (8)
Dizziness	0 (0)	0 (0)	11 (15)	3 (25)
Decreased appetite	1 (8)	0 (0)	10 (13)	2 (17)
Edema	1 (8)	0 (0)	7 (9)	4 (33)
Hypomagnesaemia	2 (17)	0 (0)	8 (11)	2 (17)
Leukopenia	1 (8)	0 (0)	10 (13)	1 (8)
Tachycardia	1 (8)	0 (0)	8 (11)	3 (25)
Chills	0 (0)	0 (0)	10 (13)	1 (8)
Constipation	0 (0)	0 (0)	9 (12)	2 (17)
Weight decreased	0 (0)	0 (0)	9 (12)	2 (17)
Coagulopathy	1 (8)	0 (0)	6 (8)	3 (25)
Hypogammaglobulinaemia	1 (8)	0 (0)	7 (9)	2 (17)
Blood alkaline phosphatase increased	1 (8)	0 (0)	6 (8)	2 (17)
Hypophosphataemia	1 (8)	0 (0)	6 (8)	2 (17)
Hyperbilirubinaemia	1 (8)	0 (0)	5 (7)	2 (17)
Hypocalcaemia	1 (8)	0 (0)	3 (4)	3 (25)
Renal impairment	1 (8)	0 (0)	3 (4)	3 (25)
Motor dysfunction	0 (0)	0 (0)	4 (5)	2 (17)
Hyperglycaemia	1 (8)	0 (0)	2 (3)	2 (17)
Abdominal distension	0 (0)	0 (0)	0 (0)	2 (17)
Palpitations	0 (0)	0 (0)	0 (0)	2 (17)

Source: FDA Analysis, ADSL, ADSLFDA1, ADAEFDA datasets.

Abbreviations: TEAE, treatment-emergent adverse event

FDA Table 32. Treatment-Emergent Adverse Events by Ethnicity* in ≥10%, Safety Analysis Set

	Hispanic or Latino (N=30) n (%)	Not Hispanic or Latino (N=63) n (%)	Risk Difference
FDA Grouping Term			
Musculoskeletal pain	16 (53)	19 (30)	-23
Infections - pathogen unspecified	17 (57)	25 (40)	-17
Encephalopathy	10 (33)	11 (17)	-16
Hyperglycaemia	4 (13)	1 (2)	-12
Hyperferritinaemia	8 (27)	10 (16)	-11
Edema	6 (20)	6 (10)	-10
Coagulopathy	5 (17)	4 (6)	-10
Cytokine release syndrome	25 (83)	46 (73)	-10
Anxiety	4 (13)	2 (3)	-10
C-reactive protein increased	4 (13)	2 (3)	-10
Motor dysfunction	4 (13)	2 (3)	-10
Headache	4 (13)	15 (24)	10
Hemorrhage	4 (13)	15 (24)	10
Cough	2 (7)	11 (17)	11

FDA Grouping Term	Hispanic or Latino	Not Hispanic or Latino	Risk Difference
	(N=30) n (%)	(N=63) n (%)	
Fever	6 (20)	21 (33)	13
Thrombocytopenia	6 (20)	23 (37)	17
Diarrhoea	5 (17)	21 (33)	17
Nausea	4 (13)	22 (35)	22

Source: FDA Analysis, ADSL, ADSLFDA1, ADAEFDA datasets.

Events listed for those where the absolute risk difference is $\geq 10\%$ in magnitude.

*Seven patients with Unknown Ethnicity were not included in the analysis

Abbreviations: TEAE, treatment-emergent adverse event

FDA also analyzed TEAEs and CRS and NT per cohorts. See summary in [FDA Table 33](#) below.

FDA Table 33. Summary of Adverse Events and Adverse Events of Special Interest Incidence per Cohort

Category	Cohort A (N=107)* n (%)	Cohort B (N=13) n (%)	Cohort C (N=7) n (%)	Total (N=127) n (%)
Any AE	107 (100.0)	13 (100.0)	7 (100.0)	127 (100.0)
Any SAE	67 (62.6)	9 (69.2)	4 (57.1)	80 (63.0)
Grade 3 or higher AE	86 (80.4)	10 (76.9)	7 (100.0)	103 (81.1)
Grade 3 or higher SAE	57 (53.3)	7 (53.8)	4 (57.1)	68 (53.5)
All Grade CRS	79 (73.8)	5 (38.5)	3 (42.9)	87 (68.5)
Grade 3 or higher CRS	3 (2.80)	0	0	3 (2.4)
Any Grade NT	82 (76.6)	8 (61.5)	5 (71.4)	96 (75.6)
Grade 3 or higher NT	15 (14.0)	2 (15.4)	0	17 (13.4)

Source: FDA Analysis, ADSL, ADAE datasets

*Cohort A include the 7 patients who received nonconforming obe-cel

Abbreviations: AE, adverse event; CRS, cytokine release syndrome; NT, neurologic toxicity; SAE, serious adverse event

Reviewer comment: The overall incidence of AEs was comparable among all cohorts, however definitive conclusions cannot be made due to the small number of patients treated in Cohorts B and C. Notably, All grade CRS occurred at higher rate (in 74%) of patients from Cohort A compared with patients in Cohort B (39%) and Cohort C (43%).

8.2.8. Specific Safety Studies/Clinical Trials

The Applicant's Position:

No specific studies were conducted to evaluate safety concerns.

The FDA's Assessment:

FDA agrees that no other studies were conducted to evaluate safety of obe-cel.

8.2.9. Additional Safety Explorations

Human Carcinogenicity or Tumor Development

The Applicant's Position:

Secondary malignancies are a potential risk associated with obe-cel and CAR T therapies in general. As of the data cutoff date (13-Sep-2023), no secondary malignancies were causally attributed to obe-cel treatment [Section 8.2.4 – Secondary Malignancies](#).

The FDA's Assessment:

FDA concurs with the Applicant.

Human Reproduction and Pregnancy

The Applicant's Position:

There is very limited available data with obe-cel use in pregnant women. No animal reproductive and developmental toxicity studies have been conducted with obe-cel to assess whether it can cause fetal harm when administered to a pregnant woman. One pregnancy was reported in the FELIX study. The patient became pregnant approximately 6 months after obe-cel infusions and had a premature delivery Day 430. The mother and child are followed at an outside institution and reported to be doing well.

It is not known whether obe-cel has the potential to be transferred to the fetus. Obe-cel is not recommended for women who are pregnant.

Sexually active females of reproductive potential should have a negative pregnancy test before starting treatment with obe-cel.

Additional information is provided in Module 2.7.4, Section 5.4.

The FDA's Assessment:

The one pregnancy occurred in a 20-year-old White female patient with r/r B ALL (b) (6). The patient achieved CRi on Day 57, followed by a conversion to CR on Day 190 (Month 6). Shortly after, the patient became pregnant. Other SAEs the patient experienced included urinary tract infection (Day 367), febrile neutropenia (Day 408), and pyelonephritis (Day 408). On Day 430, the patient was hospitalized with Grade 3 SAEs of amniotic cavity infection that caused preterm premature rupture of membranes (PROM) and premature delivery.

On admission, the patient was 30 weeks and 6 days pregnant. She underwent a Caesarean section for delivery of a healthy male infant, weighing 1.64 kg. The infant's Apgar score at 1 minute was 7 and at 5 minutes was 8. The infant had respiratory distress at birth and was admitted to the neonatal intensive care unit for intubation. A feeding tube was also inserted. The infant was discharged.

Reviewer comment: *The Reviewer recommends including information on the one case of pregnancy with PROM/preterm delivery in Section 8.1 of the USPI.*

Pediatrics and Assessment of Effects on Growth (If applicable)

The Applicant's Position

Pediatric patients (<18 year of age) were ineligible to participate in the FELIX study. The targeted indication is r/r B ALL in adults (≥ 18 years of age). A study evaluating obe-cel use in pediatric patients is ongoing.

The FDA's Assessment:

FDA concurs with the Applicant. See Section [10](#) for details on the pediatric postmarketing requirement (PMR) study.

8.2.10. Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

The Applicant's Position:

Obe-cel is not currently approved for marketing by any regulatory authority. No safety data identified in real world post-market experience is available.

The FDA's Assessment:

FDA agrees with the Applicant.

Expectations on Safety in the Postmarket Setting

The Applicant's Position:

The patient population studied in the pivotal FELIX study is reflective of a real-world clinical population of adults seeking treatment for r/r B ALL. The safety data collected in the FELIX study is expected to closely align with safety data collected postmarket.

The FDA's Assessment:

FDA agrees with the Applicant's Position.

8.2.11. Integrated Assessment of Safety

The Applicant's Position

Only the pivotal FELIX study is presented to support the safety of obe-cel in the treatment of adults with r/r B ALL. However, the safety profile of obe-cel in the ALLCAR19 study ([Roddie et al](#),

2021) is consistent with that obtained in FELIX and shows the consistency of the favorable and manageable safety profile of obe-cel across both studies.

The FDA's Assessment:

Results from ALLCAR19 study were not considered during the review. No patient level data were included in the submission.

SUMMARY AND CONCLUSIONS

8.3. Statistical Issues

The FDA's Assessment:

No statistical issues have been identified in this submission.

8.4. Conclusions and Recommendations

The FDA's Assessment:

The primary evidence of effectiveness comes from FELIX Study. This is an open-label, multicenter, international, single-arm Phase 1b/2 trial evaluating the safety and efficacy obe-cel in adults with r/r B ALL. Patients underwent leukapheresis at enrollment. During manufacturing, patients were to receive bridging therapy at the discretion of the investigator. All patients were then treated with LD chemotherapy followed by obe-cel as a split dose infusion on Day 1 and Day 10 (\pm) with a total target dose of 410×10^6 CD19 CAR-positive viable T cells.

Efficacy

As of the data cutoff date of September 13, 2023, 112 patients were enrolled in the Phase 2 Cohort A portion of the study. Among the remaining 94 patients who received at least one infusion of obe-cel, 65 patients had $\geq 5\%$ blasts in the bone marrow after screening and prior to the start of the lymphodepletion therapy, and received a conforming product, qualifying them as efficacy-evaluable patients. Manufacturing failure was observed in 5% of patients.

The prespecified primary endpoint, as defined by the Applicant, was OCR rate defined as the combined rate of CR + CRi, as determined by central review. Using FDA-adjudicated results, the study met the bounds for the primary objective.

FDA has accepted CR with durability for determination of clinical benefit for regulatory decision-making. Additionally, since the clinical benefit is based on recovery of adequate blood counts to protect against infection and avoidance of blood product transfusions, the precedents of other approved CAR T cell products for r/r B ALL set response by 3 months from infusion as the timing for assessment of the endpoint.

The CR rate within 3 months of infusion of obe-cel was 41.5% (95% CI: 29.4%, 54.4%). The median time to CR was 87 days (range: 28 to 106 days). The duration of CR was estimated to exceed 6 months for more than half the patients. A treatment effect was observed across the subpopulations. This is concluded to be substantial evidence of the effectiveness of obe-cel for treatment of adult patients with r/r B ALL.

The overall results of a high CR with durable remission in a heavily pretreated population of adults with r/r ALL despite the small sample size denotes clinical benefit in the indicated population and therefore supports a traditional approval. The observed results with a single agent treatment with obe-cel indicate that obe-cel not only acutely treats the r/r B ALL but has persistence that allows for a durable remission.

The recommended obe-cel dosing is a split dose infusion to be administered on Day 1 and Day 10 (± 2 days) at total dose of 410×10^6 CD19 CAR-positive viable T cells. Dose to be administered is determined by the patient bone marrow blast assessment prior to LD.

Safety

The safety analysis set included all 100 patients from Phase 1b Cohort A and Phase 2 Cohort A who were treated with at least one dose of obe-cel conforming product.

In summary:

- Among the 52 patients from the safety population who died during the study, 9 patients had fatal adverse reactions which included infections (sepsis, pneumonia, peritonitis), ascites, pulmonary embolism, acute respiratory distress syndrome, HLH/MAS, and ICANS.
- SAEs occurred in 62% of patients and Grade 3 or higher SAEs occurred in 54% of patients. Most common SAEs included infections - pathogen unspecified, febrile neutropenia, CRS, and fever.
- All patients experienced TEAEs and Grade 3 or higher TEAEs occurred in 81% of patients.
- The most common non-laboratory adverse reactions (incidence $\geq 20\%$) included: CRS, infections - pathogen unspecified, musculoskeletal pain, viral infections, fever, nausea, bacterial infectious disorders, diarrhea, febrile neutropenia, ICANS, hypotension, pain, fatigue, headache, encephalopathy, and hemorrhage.
- The most common Grade 3 or 4 laboratory abnormalities included: lymphopenia, leukopenia, neutropenia, anemia, and thrombocytopenia.
- Any grade CRS occurred in 75%, and any grade NT occurred in 64% of patients.
- Grade 3 or higher AESI included: non-COVID infections (41%), prolonged cytopenias (34% in the 41 responders), NT (12%), CRS (3%), and HLH/MAS (2%).

No new safety signals were identified in this submission. CRS and neurologic toxicity associated with obe-cel therapy are serious, life-threatening, and can be fatal. Treatment strategies to mitigate these AEs as implemented in the study permit the benefits of treatment to outweigh these risks. None of the secondary malignancies during this study was attributed to the study product but concern for insertional mutagenesis and secondary malignancies remain. Due to

the lack of long-term safety data in the BLA, a postmarketing long-term follow-up registry study will be required.

The safety profile of obe-cel is consistent with the safety profile of approved CAR T cell therapies. There are established guidelines to manage CAR T associated immune toxicities including CRS, ICANS, and HLH/MAS. Given that six autologous CAR T therapies targeting CD19 and BCMA are currently approved for treatment of hematological malignancies, the medical hematology/oncology and cellular therapy community has extensive experience diagnosing and managing these acute and serious toxicities. Therefore, a REMS is not required to ensure safe and effective use of obe-cel for the indicated population.

In summary, the FELIX study represents an adequate and well controlled study that provided substantial evidence of effectiveness in the context of an acceptable safety profile, and therefore supports a traditional approval of obe-cel for treatment of adults with r/r B ALL.

The review team recommends granting a traditional approval for obe-cel for the treatment of adults with r/r B ALL. The review team recommends approval for obe-cel without REMS.

X

X

Primary Clinical Reviewer

MORE Team Lead

X

MHB Clinical Team Lead

9 Advisory Committee Meeting and Other External Consultations

The FDA's Assessment:

This application was not presented at an Advisory Committee meeting or to external consultants because it did not raise significant efficacy or safety issues for the proposed indication.

10 Pediatrics

The Applicant's Position:

Obe-cel was granted Orphan Drug Designation on 4-Nov 2019 for the following indication: treatment of r/r B ALL.

Autolus received agreement on an initial Pediatric Study Plan (iPSP) for obe-cel with the FDA, wherein Autolus requested a waiver for the pediatric population < 1 year of age and a deferral of submission of results of the planned AUTO1-PY1 pediatric study (≥1 to <18 years).

Pediatric subjects were excluded from the FELIX study.

A study of obe-cel treatment in pediatric r/r B ALL patients (AUTO1-PY1) is ongoing.

The FDA's Assessment:

FDA concurs with the Applicant's position.

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable.

The Applicant is required to conduct a molecularly targeted pediatric cancer investigation to evaluate dosing, pharmacokinetics, safety, and antitumor activity of obe-cel following lymphodepletion with fludarabine and cyclophosphamide in patients 1 year to less than 17 years of age who have relapsed refractory (r/r) B-cell acute lymphoblastic leukemia and r/r aggressive mature B-cell non-Hodgkin lymphoma.

The study will be conducted according to the following schedule:

- Final Protocol Submission: Completed
- Study Completion: September 2027
- Final Report Submission: March 2028

FDA is granting a partial waiver for patients less than 1 year of age is because necessary studies were deemed impossible or highly impracticable due to rarity of r/r B ALL in pediatric patients. FDA is granting a deferral to conduct the molecularly targeted pediatric cancer investigations in patients ≥1 to <17 years of age, to allow access to adult patients because the product is ready for approval in adults. The Applicant has already submitted the protocol to the IND, and the study is ongoing. This application was reviewed at the oncology subcommittee of PeRC on August 28, 2024.

11 Labeling Recommendations

Data:

This section is not applicable as this is an original BLA.

The FDA's Assessment

Several revisions were made to the Applicant's proposed USPI. See [FDA Table 34](#) below.

FDA Table 34. Summary of Significant Labeling Changes

Section	Applicant's Proposed Labeling	FDA's Proposed Labeling
Boxed Warning	Included REMS	Requirement for REMS was omitted. Risk for T cell malignancies was added consistent with USPI for other products in the same class
Section 1: Indication and Usage	For the treatment of adult patients (18 years and over) with relapsed or refractory (r/r) B cell precursor acute lymphoblastic leukemia (B ALL)	Revised the indication to simplify: For the treatment of adults with relapsed or refractory (r/r) B-cell precursor acute lymphoblastic leukemia (B ALL).
Section 2: Dosage and Administration	Guidelines for management of CRS and ICANS included in section 2.	Management of CRS and ICANS was removed as it is not required in the label and is based on current medical practice. Infusion bag configuration with color codes was added for clarity in dose administration.
Section 5: Warning and Precautions	Included REMS	Removed reference to REMS.
Section 6: Adverse Reactions (Safety)	The safety results included all subjects treated in FELIX study.	Revised the safety population to the 100 patients who were treated in Cohorts A with conforming products. The information in this section was revised based on the current labeling practice for concise presentation of data and to remove redundant information. Limited the group terms in the footnotes under the adverse reaction Table to only include AEs from the warning in precautions that were reported under more than one system organ class (e.g., encephalopathy)

Section	Applicant's Proposed Labeling	FDA's Proposed Labeling
Section 14: Clinical Studies (Efficacy)	Efficacy results from FELIX per IRRC were included. Efficacy population included all infused subjects with obe-cel.	Revised the efficacy population to the 65 patients who had evidence of disease following bridging and prior to LD who received the conforming product and displayed the results per FDA-adjudication.
Section 17: Patient Counseling Information		This section was revised for clarity, use of command language, and to include important risks listed in section 5 (Warning and Precautions).
Medication Guide		Revised to ensure inclusion of important safety concerns stated in the USPI with the use of obe-cel.

Source: FDA Clinical Reviewer and Associate Director of Labeling

The review team recommends displaying the following efficacy data in Section 14 of the USPI

FDA Table 35. Efficacy Results Per FDA's Adjudication

Endpoint	Efficacy Evaluable N=65 n (%)	All Leukapheresed N=112 n (%)
Complete remission (within 3 months) rate		
n (%)	27 (42%)	40 (36%)
[95% CI]	(29%, 54%)	(27%, 45%)
Duration (months), median [95% CI]	14.1 (6.1, NR)	14.1 (6.2, NR)
(Range in months)	(0.5+, 21.2)	(0.5+, 21.2)
Overall complete remission (at anytime) rate*		
n (%)	41 (63%)	60 (54%)
[95% CI]	(50%, 75%)	(44%, 63%)
Duration (months), median [95% CI]	14.1 (6.2, NR)	14.1 (8.1, NR)
(Range in months)	(0.03+, 21.2)	(0.03+, 21.2)

Source: FDA Analysis, ADSLFDA, ADSLFDA1, ADEFFDA, and ADTTEFDA datasets.

*Rate of Overall Complete Remission "At Anytime" includes Complete Remission and Complete Remission with incomplete hematologic recovery "At Anytime".

Abbreviation: CI, confidence interval; NR, not reached.

Among patients in the efficacy evaluable population who achieved a best response of complete remission "At Anytime" (N=33; 51%), the median duration for remission was 14.1 months (95% confidence interval [CI]: 6.1, not reached [NR]). Among patients in the efficacy evaluable population in whom best response was complete remission with incomplete hematologic recovery "At Anytime" (N=8; 12%), the median duration of remission was 10.5 months (95% CI: 1.8, NR).

12 Risk Evaluation and Mitigation Strategies

The FDA's Assessment:

The clinical review team determined that a REMS was not required to ensure safe and effective use of obe-cel for the indicated population. The review team made this determination given the consistency of the safety profile with approved CAR T cell therapies, and the established management guidelines and extensive experience of the medical hematology/oncology community in managing immune-mediated adverse reactions, including those associated with CAR T cellular therapies like obe-cel. Recommendations for the safe and effective use of obe-cel, including monitoring for immune-related adverse events, are provided in the USPI as well as in the patient medication guide.

13 Postmarketing Requirements and Commitment

The FDA's Assessment:

The pharmacovigilance plan (PVP) includes a long-term, prospective, non-interventional PMR registry study in patients treated with Obe-cel.

The Applicant will complete a post-marketing, prospective, multi-center, observational study to assess and characterize the risk of secondary malignancies and the long-term safety following treatment with obe-cel (Study AUTO1-LT2). The study will include at least 500 adult patients with relapsed or refractory B-cell precursor acute lymphoblastic leukemia; each enrolled patient will be followed for 15 years after product administration.

The Applicant will conduct this study according to the following schedule:

- Protocol Submission: December 16, 2024
- Study Completion Date: June 30, 2044

14 Chief, Malignant Hematology Branch

X

15 Division Director (DCEH)

X

16 Oncology Center of Excellence Signatory

This application was reviewed by the Oncology Center of Excellence (OCE) per the OCE Intercenter Agreement. My signature below represents an approval recommendation for the clinical portion of this application.

X

17 Director, Office of Clinical Evaluation

X

18 Appendices

18.1. References

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18.2. Financial Disclosure

The Applicant's Position:

Autolus, has adequately disclosed financial interests/arrangements with clinical investigators in accordance with the regulatory guidance. Financial disclosure information was submitted under Financial Certification and Disclosure for investigators involved in FELIX.

The FDA's Assessment:

The Applicant employed appropriate risk-reduction strategies to minimize bias and adequately investigated individuals who did not provide financial disclosure information (N=7). Neither the disclosed significant payments nor the missing disclosures are likely to have negatively impacted the integrity of FELIX study conduct or findings. See [FDA Table 36](#) for details.

FDA Table 36. Covered Clinical Study: FELIX

Was a list of clinical investigators provided:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request list from Applicant)
Total number of investigators identified: <u>720</u>		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): <u>0</u>		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): <u>2</u>		
<p>If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)):</p> <p>Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: <u>0</u></p> <p>Significant payments of other sorts: <u>0</u></p> <p>Proprietary interest in the product tested held by investigator: <u>0</u></p> <p>Significant equity interest held by investigator in study: <u>2</u></p> <p>Sponsor of covered study: <u>0</u></p>		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) _____		
Is an attachment provided with the reason:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request explanation from Applicant)

18.3. List of FDA Group Terms and Preferred Terms Used in This Review

FDA Table 37. FDA Grouped Terms Used for FDA Analyses of Adverse Events, N=100 (FELIX Study)

FDAGT	AEDECOD
Abdominal pain	Abdominal pain Abdominal pain upper
Amenotransferase increased	Alanine aminotransferase increased Aspartate aminotransferase increased
	Hypertransaminasaemia
Arrhythmia	Atrial fibrillation Electrocardiogram QT prolonged Sinus bradycardia
Bacterial infections	Bacterial infection Campylobacter gastroenteritis Cellulitis Clostridium difficile infection Corynebacterium infection Corynebacterium sepsis Enterococcal bacteraemia Enterococcal sepsis Escherichia urinary tract infection Folliculitis Gastroenteritis bacterial Klebsiella infection Pneumonia klebsiella Pseudomonas infection Staphylococcal bacteraemia Staphylococcal infection Stenotrophomonas infection Streptococcal bacteraemia Urinary tract infection bacterial Urinary tract infection enterococcal Wound infection staphylococcal
Coagulopathy	Blood fibrinogen decreased Coagulopathy Disseminated intravascular coagulation Hypofibrinogenaemia International normalised ratio increased
Cough	Cough Productive cough Upper-airway cough syndrome
Delirium	Agitation Brain fog Delirium Disorientation Irritability
Edema	Face oedema Hypervolaemia Localised oedema Oedema peripheral Swelling face

FDAGT	AEDECOD
Encephalopathy	Aphasia Cognitive disorder Confusional state Depressed level of consciousness Disturbance in attention Dysarthria Dysgraphia Encephalopathy Lethargy Memory impairment Mental impairment Mental status changes Somnolence
Fatigue	Asthenia Fatigue Malaise
Fungal infections	Aspergillus test positive Bronchitis fungal Candida infection Cutaneous mucormycosis Fusarium infection Lower respiratory tract infection fungal Oral candidiasis Pneumocystis jirovecii pneumonia Sinusitis fungal Systemic candida
Graft versus host disease	Graft versus host disease Graft versus host disease in gastrointestinal tract Graft versus host disease in skin
Headache	Headache Tension headache
Hemorrhage	Cerebral microhaemorrhage Contusion Epistaxis Gingival bleeding Haematoma Haematuria Haemorrhoids Intra-abdominal haemorrhage Melaena Petechiae Subarachnoid haemorrhage Subdural haematoma Subdural haemorrhage Upper gastrointestinal haemorrhage Vaginal haemorrhage Wound haemorrhage
Hyperbilirubinaemia	Blood bilirubin increased Hyperbilirubinaemia
Hyperferritinaemia	Hyperferritinaemia Serum ferritin increased
Hypertension	Blood pressure increased Hypertension

FDAGT	AEDECOD
Hypomagnesaemia	Blood magnesium decreased Hypomagnesaemia
Hypophosphataemia	Blood phosphorus decreased Hypophosphataemia
Hypotension	Hypotension Orthostatic hypotension
Infections - pathogen unspecified	Abdominal infection Abscess limb Acute sinusitis Amniotic cavity infection Anal abscess Appendicitis Bacteraemia Brain abscess CNS ventriculitis Device related bacteraemia Device related infection Endocarditis Enterocolitis infectious Gastroenteritis Gingivitis Hepatic infection Infection Lower respiratory tract infection Neutropenic sepsis Osteomyelitis Otitis externa Otitis media Perineal cellulitis Peritonitis Pneumonia Pyelonephritis Respiratory tract infection Sepsis Sinusitis Skin infection Tooth abscess Tooth infection Upper respiratory tract infection Urinary tract infection Urosepsis
Leukopenia	Leukopenia White blood cell count decreased
Motor dysfunction	Muscle spasms Muscular weakness

FDAGT	AEDECOD
Musculoskeletal pain	Arthralgia Arthropathy Back pain Bone pain Limb discomfort Musculoskeletal chest pain Musculoskeletal pain Myalgia Neck pain Non-cardiac chest pain Pain in extremity
Neutropenia	Neutropenia Neutrophil count decreased
Pain	Catheter site pain Ear pain Eye pain Facial pain Incision site pain Lip pain Oropharyngeal pain Pain Pain in jaw Pleuritic pain Procedural pain Proctalgia Sinus pain Toothache Urinary tract pain
Rash	Blister Dermatitis exfoliative generalised Drug eruption Erythema Pruritus Purpura Rash Rash macular Rash maculo-papular Urticaria Vulvovaginal rash
Renal impairment	Acute kidney injury Anuria Blood creatinine increased Chronic kidney disease Urine output decreased
Respiratory failure	Acute respiratory failure Respiratory failure
Seizure	Seizure Status epilepticus
Tachycardia	Sinus tachycardia Tachycardia
Thrombocytopenia	Platelet count decreased Thrombocytopenia

FDAGT	AEDECOD
Thrombosis	Deep vein thrombosis Jugular vein thrombosis Pulmonary embolism
Viral infections	COVID-19 COVID-19 pneumonia Coronavirus infection Cytomegalovirus infection Cytomegalovirus infection reactivation Enterovirus infection Enterovirus test positive Gastroenteritis norovirus Human rhinovirus test positive Influenza JC polyomavirus test positive Respiratory syncytial virus infection Respirovirus test positive Rhinovirus infection

FDAGT and AEDECOD pairs come selectively from Treatment-emergent Adverse Events in the ADAEFDA dataset, as experienced by patients in the Safety Analysis Set (N=100).

18.4. Schedule of Assessments per Protocol

FDA Table 38. Schedule of Assessments Per Protocol

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

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

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

AE = adverse event; AESI = adverse event of special interest; ALL = acute lymphoblastic leukaemia; ALT = alanine aminotransferase; AST = aspartate aminotransferase; CAR = chimeric antigen receptor; CD = cluster of differentiation; CNS = central nervous system; CR = complete remission; CRi = complete remission with incomplete count recovery; CRS = cytokine release syndrome; CSF = cerebrospinal fluid; CT = computed tomography; D/d = day; ECOG = Eastern Cooperative Oncology Group; ECHO = echocardiogram; eCRF = electronic case report form; EORTC = European Organization for Research and Treatment of Cancer; EM = extramedullary; EQ-SD-SL = EuroQol; FDG = fluorodeoxyglucose; Hep = hepatitis; HIV = human immunodeficiency virus; HTLV = human T-cell lymphotropic virus; ICANS = Immune effector Cell-Associated Neurotoxicity Syndrome; ICE = Immune effector Cell-Associated Encephalopathy; IFN- γ = interferon gamma; Ig(G) = immunoglobulin (G); IL = interleukin; LDH = lactate dehydrogenase; LVEF = left ventricular ejection fraction; MRD = minimal residual disease; MUGA = multigated acquisition scan; O₂ = oxygen; (b) (4) = redacted; PET = positron emission tomography; QLQ-C30 = Quality of Life Questionnaire; RCL = replication competent lentivirus; SAE = serious adverse event; TNF- α = tumour necrosis factor alpha.

*: The end of the treatment phase is defined as 1 Month (Day 28 \pm 2 days) post first AUTO1 infusion.

** The End of Study visit is to be performed upon completion of all study visits or in case of early withdrawal.

X^{DA, D7 etc}: Test/Assessments to be performed on a particular day of the schedule rather than systematically at every visit. Please refer to the number to determine the day of assessment.

*: In the event a patient is unable to attend clinic for protocol specified visits for any reason (e.g. Covid-19 outbreak), some visits may be conducted by a home health care provider selected by the Sponsor. Wherever feasible, the home health care provider may perform safety assessments in lieu of clinic visits at the protocol specified visits as per local and institutional guidelines (please refer to Schedule of Assessments 2 and 3).

[1] Enrolment:	Enrolment confirmed once all incl./excl. criteria have been fulfilled and leukapheresis has been accepted by the manufacturing facility.
[2] Demographics:	Race/ethnicity, height, age, and gender will be collected.
[3] Eligibility criteria:	Selected eligibility criteria will be re-assessed prior to pre-conditioning on Day -6 and prior to AUTO1 infusion. Please refer to Sections 6.3 and 6.4. Central (b) (4) testing is required for screening in Cohort IIB.
[4] Medical/ALL history:	Clinically significant diseases, surgeries, cancer history (including prior cancer therapies and procedures) and prior medications. Record disease status at last assessment and complications since last assessments.
[5] Prior/Concomitant Medication:	Prior to Day -6 and after Day 60 only concomitant medications relevant to study related procedures or prophylaxis or AUTO1 treatment will be recorded. Any medication the patient is receiving on Day -6 must be recorded. After the 24-month observation period in the efficacy and safety follow-up or in the safety and survival follow-up, only intravenous Ig and therapeutic steroids will be recorded.
[6] Survival status:	All enrolled patients will be followed up for survival. If a visit is skipped where survival status is required or if the time point does not align with a scheduled visit, the information can be obtained over the phone.
[7] Performance status:	Performance status will be assessed by using ECOG.
[8] Physical examination:	Complete physical examination including neurological examination to be performed at screening and Day -6 then focused examination as appropriate at following visits.
[9] Neurocognitive assessment:	Two baseline measurements (ICE scale, Section 10.6) to be taken (Day-6 and prior to AUTO1 infusion) and then in the event of any neurological symptom.
[10] Vital signs and O ₂ saturation:	Temperature, systolic and diastolic blood pressure, pulse rate, respiratory rate and oxygen saturation will be performed. On dosing days, perform vital signs immediately prior to AUTO1 infusion and then hourly (\approx 15 minutes) for 4 hours post infusion, and thereafter monitored as per hospital policy but no less than daily during hospital stay. Clinically significant abnormalities will be recorded as AEs. Once discharged, the patient or the patient's caregiver should continue to monitor the patient's temperature daily for the first 28 days after the first AUTO1 infusion.
[11] ECHO or MUGA:	ECHO or MUGA will be performed only in patients with history of coronary artery disease or cardiovascular disease or those with history of low LVEF and to be repeated if clinically indicated. The same method should be used for a patient throughout the study as much as possible.
[12] Haematology:	Haemoglobin, platelet count, and white blood cell count with differential (neutrophils, monocytes and lymphocytes). This is performed daily during admission as standard care and results from the indicated time points will be recorded in the electronic case report form (eCRF).
[13] Biochemistry:	AST/ALT, alkaline phosphatase, LDH, total bilirubin, urea/blood urea nitrogen, creatinine, uric acid. Glomerular filtration rate should be calculated at screening as per the institutional preferred method. The results from the indicated time points will be recorded in the eCRF. These tests are generally performed daily during admission as part of standard care. All tests must be performed prior to AUTO1 infusion on dosing days.
[14] Coagulation:	Prothrombin time, international normalised ratio, activated partial thromboplastin time, fibrinogen after baseline assessment may be repeated if patient experiences severe CRS.
[15] Infectious disease screen:	Must be performed within 30 days prior to leukapheresis and must be confirmed negative then repeated on the day of leukapheresis (or within 7 days after the leukapheresis). HIV-1 and HIV-2, Hep B virus, Hep C virus, HTLV-1, HTLV-2, Syphilis and other pathogens (per local requirements).
[16] Pregnancy test:	Serum β -human chorionic gonadotropin or urine pregnancy testing for women of childbearing potential.
[17] Adverse events:	Adverse events will be collected on an ongoing basis throughout the study. Please refer to eCRF completion guidelines. After month 6, all SAEs, AESI and ONLY non-serious AEs that are deemed related to AUTO1 treatment or study related procedure will be collected. Please refer to Section 12 of the protocol for reporting requirements.
[18] Pre-conditioning regimen:	The pre-conditioning regimen will include Cyclophosphamide 500 mg/m ² and Fludarabine 30 mg/m ² at the indicated time points.
[19] Antimicrobial prophylaxis:	Patients should receive Pneumocystis prophylaxis with trimethoprim-sulfamethoxazole or suitable alternative agents, and either acyclovir or valacyclovir for herpes virus prophylaxis from the start of conditioning chemotherapy until at least 3 to 6 months post AUTO1 infusion or longer as per institutional guidelines. Additional anti-microbial (e.g. ciprofloxacin) and anti-fungal prophylaxis should be given as per institutional practice. Consider starting antimicrobial prophylaxis from the time of leukapheresis. Patients should be monitored for cytomegalovirus, adenovirus and Epstein-Barr at least 6 months post AUTO1 infusion or longer as per institution guidelines for allogeneic stem cell transplant.
[20] AUTO1 infusion:	AUTO1 will be administered as a split dose for a target dose of 410×10^6 CD19 CAR-positive T cells. The first AUTO1 infusion will take place on Day 1 followed by the second infusion on Day 10 (\pm 2 days). Of note, in the event of adverse event preventing the administration of the 2 nd split dose, the infusion can be delayed beyond Day 10 (\pm 2 days) up to Day 21 to allow the adverse event to resolve. Please refer to Section 6.4 of the protocol for information. The fractionation of the dose is driven by the patient's disease burden. Patients with low disease burden, defined as $\leq 20\%$ blasts in the bone marrow performed within 7 days of the start of the pre-conditioning (assessed by morphology), will receive a first dose of 100×10^6 CD19 CAR-positive T cells and a second dose of 310×10^6 CD19 CAR-positive T cells; while patients with high disease burden, defined as $>20\%$ blasts in the bone marrow performed within 7 days of the start of the pre-conditioning (assessed by morphology), will receive a first dose of 10×10^6 CD19 CAR-positive T cells and a second dose of 400×10^6 CD19 CAR-positive T cells.
[21] Bone Marrow	Analysis performed centrally: For all patients, at each disease assessment visit requiring a BM aspirate/biopsy as specified in the Schedule of Assessments, the first BM aspirate sample draw should be sent for central (b) (4) (MRD testing by (b) (4)). Please note: the (b) (4) MRD assay requires a baseline calibration using a bone marrow sample containing leukaemic blasts. For Phase IIA, this is either from the patient at screening, Day-6 or a historical sample. For Phase IIB, due to the low disease burden at screening, we require both a screening sample for MRD (b) (4) testing as well as a historical sample for calibration. Please see Section 9.2.1. Furthermore, additional BM aspirate samples (unscheduled visits) for disease status assessment should be collected and sent for assessment centrally of immunophenotyping and MRD (b) (4) if: <ul style="list-style-type: none"> - A patient is not in CR/CRi at M1 then the assessment is required at the 1st time of clinical evidence of CR observed by peripheral blood and EM disease assessment (physical examination and CNS symptoms). - At any time, if morphological or molecular relapse is suspected post AUTO1 infusion. - A patient in CR/CRi (independently of the MRD status) starts a new treatment for ALL, a BM sample should be collected prior to beginning the new therapy. - A safety event occurs.

Analysis performed locally: The disease burden defined as the % of blasts in the BM will be assessed by morphology on both trephine and aspirate whenever possible. Trephine will be performed as per Investigator clinical judgment. The bone marrow aspirate smear slide may be sent to the Sponsor or third-party laboratory for central storage should additional reading be required. The first screening assessment for morphology can be collected locally or at the referring institution and reports should be available, including leukaemic blasts CD19 expression levels. A copy of the BM aspirate/trephine analysis report will be provided to the Sponsor as part of the eligibility package.

<p>[22] Bone Marrow cytogenetics: [23] CSF examination:</p>	<p>Prior to the initiation of the pre-conditioning, the sample must be taken and analysed within 7 days of the start of the pre-conditioning start. All efforts should be made to have the bone marrow sample taken as close to the start of the pre-conditioning, as possible. The leukaemic blast count and/or MRD status used to determine the dosing schedule will be based on analysis performed locally and Investigator's assessment. In the event that the bone marrow sample is not evaluable at baseline prior to dosing, the procedure must be repeated to determine disease burden on which dosing regimen is based. If the repeated sample is still not evaluable, a discussion with the medical monitor is warranted to select the appropriate dose. Please refer to the laboratory manual for further details.</p>
<p>[24] Imaging:</p>	<p>To be performed locally at screening and at relapse. White blood cells, presence or absence of lymphoblasts. The screening assessment can be performed at the referring institution and reports should be available.</p> <ul style="list-style-type: none"> All patients will be assessed for CNS disease by CSF examination at screening and if clinically indicated. For patients with CNS disease between screening and AUTO1 treatment, CSF examination to be repeated at Day 28 to confirm disease response. Additional samples to be collected at disease relapse and where possible during or after a neurological event. For patients without CNS disease between screening and AUTO1 treatment a CSF examination at Day28 and subsequent visits is not required to confirm response, but can be collected at relapse or after a neurological event.
<p>[25] Biomarkers:</p>	<p>Imaging for EM disease is to be conducted for all patients at screening with known or suspected EM disease. After screening, to be repeated only for patients with EM disease at screening or based on clinical indication. In the event of suspected EM disease, CT of the neck/chest/abdomen/pelvis with intravenous contrast, FDG-PET/CT, imaging, magnetic resonance angiography, ultrasonography or appropriate physical measurements should be performed to assess response and should be repeated if clinically indicated after CR has been confirmed. The same imaging modality/physical measurements should be used thereafter. For patients included in Cohort IIC with EM disease only, imaging will be performed at screening.</p>
<p>[26] RCL Testing</p>	<p>Additional samples will be collected at relapse and may be collected in case of safety events or as clinically indicated. In the event CAR T persistence is lost at any point, an additional sample may be taken ad hoc for confirmation visit if required. Please refer to the laboratory manual. The serum cytokine profile analysis will include IL-2, IL-5, IL-6, IL-7, IL-8, IL-10, IL-15, TNF-α, IFN-γ, and granulocyte-macrophage colony-stimulating factors [GM-CSF].</p>
<p>[27] Insertional Mutagenesis</p>	<p>B cell aplasia will be assessed at a Central Laboratory ^{(b)(4)} (based assay) using the peripheral blood samples at the time points indicated. If all results are negative during the first year post first AUTO1 infusion, the subsequent sample will be collected and stored in case further follow-up analysis may be required. After 24 months, sample for RCL testing will be collected annually until the end of the study.</p>

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

Source :FELIX Study Protocol

18.5. Overall Disease Response Criteria (Protocol V.1 to V.4)

FDA Table 39. Overall Disease Response Criteria for Protocol V.1 to V.4

Overall Disease Response Criteria	
Complete response (CR)	<ul style="list-style-type: none"> <5% blasts in bone marrow No circulating lymphoblasts in peripheral blood Absolute neutrophil count (ANC) >1000/μL Platelet count >100,000/μL No EM disease: e.g. no lymphadenopathy, splenomegaly, skin/gum infiltration, testicular mass, or central nervous system (CNS) involvement No recurrence for 4 weeks
CR with incomplete recovery of counts (CRi)	<p>Meets all criteria for CR except platelet count or ANC</p> <ul style="list-style-type: none"> Recovery of platelets to \leq100,000/μL Recovery of absolute neutrophil count to <1000/μL
Relapsed ALL	Reappearance of blasts in the blood or BM (\geq 5% blasts) or EM site after CR.
No response	Failure to meet the criteria for any response categories

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

Source: FELIX Study Protocol

18.6. Overall Disease Response Criteria (Protocol V.5 Onward)

FDA Table 40. Overall Disease Response Criteria for Protocol V.5

Overall Disease Response Criteria	
Complete Remission (CR)*	<p>The following criteria should be met within the same disease assessment:</p> <p>Bone marrow:</p> <ul style="list-style-type: none"> • Trilineage haematopoiesis (TLH) • <5% blasts in bone marrow <p>Peripheral blood:</p> <ul style="list-style-type: none"> • No circulating lymphoblasts in peripheral blood <p>and</p> <ul style="list-style-type: none"> • Absolute neutrophil count (ANC) >1000/μL <p>and</p> <ul style="list-style-type: none"> • Platelet count >100,000/μL <p>and</p> <ul style="list-style-type: none"> • No platelet transfusions in the last 7 days • No administration of short-acting Granulocyte colony-stimulating factor (G-CSF) and long-acting G-CSF in the last 3 and 14 days respectively <p>Extramedullary disease:</p> <ul style="list-style-type: none"> • No EM disease: e.g. no lymphadenopathy, splenomegaly, skin/gum infiltration, testicular mass, or central nervous system (CNS) involvement <p>and</p> <ul style="list-style-type: none"> • If additional assessments (e.g. CSF assessment by LP, CNS imaging, biopsy, etc.) are performed, results must show remission status
CR with incomplete recovery of counts (CRi)	<p>Meets all criteria for CR except platelet count or ANC:</p> <ul style="list-style-type: none"> • Recovery of platelets to \leq100,000/μL <p>and/or</p> <ul style="list-style-type: none"> • Recovery of absolute neutrophil count to <1000/μL
Relapsed ALL	<p>Only in patients who previously achieved a CR or CRi and who have:</p> <ul style="list-style-type: none"> • Reappearance of blasts in the blood <p>or</p> <ul style="list-style-type: none"> • Reappearance of lymphoblasts in bone marrow (\geq 5%)
	<p>or</p> <ul style="list-style-type: none"> • (Re-)appearance of any EM site after CR.
No response	Failure to meet the criteria for CR/CRi categories
Unknown	<p>“Unknown” is assigned when the response assessment is not performed, or it is incomplete, indeterminate, within the respective time frame related to a given timepoint.</p> <p>Note: any evidence of relapse should determine relapsed disease with the relapsed component alone.</p>

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

Source: FELIX Study Protocol