Summary Basis for Regulatory Action

Date:	November 7, 2024
From:	Andrew Timmons, PhD, Review Committee Chair, OTP/OGT
BLA STN:	125813/0
Applicant:	Autolus Inc.
Submission Receipt Date:	November 17, 2023
PDUFA Action Due Date:	November 16, 2024
Proper Name:	obecabtagene autoleucel (obe-cel)
Proprietary Name:	AUCATZYL
Indication:	Treatment of adults with relapsed or refractory B-cell precursor acute lymphoblastic leukemia (B ALL).

***** PDUFA=Prescription Drug User Fee Act

Recommended Action: The Review Committee recommends approval of this product.

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Director, Office of Clinical Evaluation

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Director, Office of Compliance and Biologics Quality

Discipline Reviews	Reviewer / Consultant - Office/Division
CMC • CMC Product (Product Office and OCBQ/DBSQC) • Facilities review (OCBQ/DMPQ) • Establishment Inspection Report (OCBQ/DMPQ and Product Office) • QC, Test Methods, Product Quality (OCBQ/DBSQC)	Andrew Timmons, PhD, CBER/OTP/OGT Jessica Chery, PhD, CBER/OTP/OGT Anurag Sharma, PhD, CBER/OTP/OGT Timothy Kamaldinov, PhD, CBER/OTP/OGT Kula Jha, PhD, CBER/OCBQ/DMPQ Kathleen Jones, PhD, CBER/OCBQ/MRB1 Alicia Howard, PhD, CBER/OCBQ/DBSQC CAPT Simleen Kaur, MSc, CBER/OCBQ/DBSQC George Kastanis, MS, CBER/OCBQ/DBSQC Kouassi Ayikoe, PhD, CBER/OCBQ/DBSQC
Pre-License Inspection	Kula Jha, PhD, CBER/OCBQ/DMPQ Kathleen Jones, PhD, CBER/OCBQ/DMPQ Andrew Timmons, PhD, CBER/OTP/OGT Jessica Chery, PhD, CBER/OTP/OGT
Clinical • Clinical (Product Office) • Postmarketing safety Pharmacovigilance review (OBPV/DE) • BIMO	Najat Bouchkouj, MD, CBER/OTP/OCE Upendra Mahat, MD, CBER/OTP/OCE Deborah Thompson, MD, MSPH, CBER/OBPV/DPV Char-Dell Edwards, MS, CBER/OCBQ/DIS
Statistical • Clinical data (OBPV/DB) • Non-clinical data	Harry Houghton, MS, CBER/OBPV/DB Cong Wang, PhD, CBER/OBPV/DB
Non-clinical/Pharmacology/Toxicology • Toxicology (Product Office) • Developmental toxicology (Product Office) • Animal pharmacology	Kate Dabirsiaghi, VMD, CBER/OTP/OPT
Clinical Pharmacology	Xiaofei Wang, PhD, CBER/OTP/OCE/DCEGM
Labeling • Promotional (OCBQ/APLB) • Container/carton • Proprietary Name Review	Afsah Amin, MD, MPH, CBER/OTP/OCE Danielle Bauman, MPH, CBER/OTP/ORMRR Oluchi Elekwachi, PharmD, MPH, CBER/OCBQ/DCM/APLB CAPT Teresa Vu, CBER/OCBQ/DCM/APLB
Other Reviewers • Consults	Donna Przepiorka, MD, PhD, CDER/OND/OOD/DHMI

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1. Introduction

Autolus Inc. submitted a biologics license application (BLA), STN 125813/0, for licensure of obecabtagene autoleucel (obe-cel) with the proprietary name AUCATZYL. AUCATZYL is indicated for the treatment of adults with relapsed or refractory B cell precursor acute lymphoblastic leukemia (B ALL).

AUCATZYL consists of autologous T cells that have been genetically modified via transduction with the (b) (4) lentiviral vector (LVV), which equips transduced cells with a constitutively expressed chimeric antigen receptor (CAR) that targets human CD19. AUCATZYL uses a novel CD19-binding single chain variable fragment (scFv) derived from the murine (b) (4) antibody, which imparts AUCATZYL with

different binding kinetics relative to other currently approved CD19-directed CAR T cell therapies. AUCATZYL is supplied frozen in three distinct bag configurations. Each bag configuration contains differing volumes of the same (b) (4) drug product (DP), which consists of a cellular suspension at a defined density (10×10^6 cells per mL). The recommended AUCATZYL 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 CAR+ viable T cells.

AUCATZYL is generated from autologous apheresis material at the Nucleus, an Autolus-owned manufacturing facility located in Stevenage, UK. AUCATZYL is manufactured by isolation and transduction of T cells with the (b) (4) LVV. Following lymphodepleting chemotherapy and AUCATZYL infusion, the transduced T cells help to reconstitute the patient's T cell repertoire with T cells exhibiting cytolytic activity towards CD19 positive cells.

This document summarizes the basis for approval of AUCATZYL. A single-arm, open-label, multicenter study (FELIX, Cohort A) provides the primary evidence of safety and effectiveness for the treatment of adults with r/r B ALL. The recommendation for approval is based on rate and duration of complete remission within 3 months after AUCATZYL infusion. The major risks of AUCATZYL include cytokine release syndrome (CRS), immune effector cell-associated neurotoxicity syndrome (ICANS), prolonged cytopenia, infections, hypogammaglobulinemia, hemophagocytic lymphohistiocytosis/ macrophage activation syndrome (HLH/MAS), hypersensitivity reactions, and secondary malignancies.

Autolus Inc. has provided substantial evidence of effectiveness based on a single, adequate and well controlled clinical trial supported by clinical data from additional cohorts in FELIX Study, nonclinical studies and pharmacokinetic (PK) studies. The review team recommends approval of this BLA with nine post-marketing commitments (PMCs) related to product quality and two post-marketing requirements (PMRs) (one related to pediatric study requirements and one related to safety).

2. Background

B-cell acute lymphoblastic leukemia (B ALL) is a serious and life-threatening malignant disease. It is characterized by malignant transformation and clonal B-precursor cells in the bone marrow (BM), pancytopenia and resultant clinical complications including infections, bleeding, and anemia. B ALL is most common in patients < 20 years of age with peak incidence between 2 to 5 years. The incidence rises again after the age of 50 years.

Standard treatment of r/r B ALL includes a combination of chemotherapy, targeted therapy, and hematopoietic stem cell transplantation (HSCT). Targeted therapies include 1) tyrosine kinase inhibitors for Philadelphia chromosome positive disease, 2) blinatumomab (a bispecific T-cell engager antibody that targets CD19 and CD3), 3) inotuzumab ozogamicin (an antibody-drug conjugate that targets CD22), and 4) tisagenlecleucel and bexucabtagene autoleucel (autologous CD19 CAR T cell therapies). Although the outcome of B ALL has significantly improved with the use of

risk adapted multiagent chemotherapy, the relapsed refractory B ALL, particularly in adults continues to have poor prognosis.

Regulatory history of AUCATZYL development is provided in **Table 1**.

Table 1. Regulatory History

Regulatory Events / Milestones	Date
1. Pre-IND meeting (PTS# PS004946)	August 12, 2019
2. IND submission (IND 19534)	March 16, 2020
3. Regenerative Medicine Adv. Therapy (RMAT) granted	April 21, 2022
4. Orphan Drug designation granted	November 4, 2019
5. Pre-BLA meeting	September 28, 2023
6. BLA 125813/0 submission	November 17, 2023
7. BLA filed	January 16, 2024
8. Mid-Cycle communication	May 13, 2024
9. Late-Cycle meeting	August 2, 2024
10. Action Due Date	November 16, 2024

3. Chemistry, Manufacturing, and Controls (CMC)

This BLA provides an adequate description of the manufacturing process and characterization of AUCATZYL. The CMC review team concludes that the manufacturing process, along with associated test methods and control measures, can produce a pharmaceutical product of consistent quality.

a. Product Quality

AUCATZYL is generated from T cells isolated from autologous apheresis material. Prior to manufacture, apheresis material is collected and shipped at (b) (4)

AUCATZYL drug product. The (b) (4) AUCATZYL drug product is filled into (b) (4) infusion bags, depending on the volume required to achieve the intended dose of 410×10^6 viable CAR+ cells/mL. Following fill of the infusion bags, (b) (4) AUCATZYL drug product is filled into (b) (4) for quality control testing. (b) (4) cryobags are cryopreserved in a (b) (4) vapor phase of liquid nitrogen prior for storage until shipment to the treatment site. The total manufacturing process occurs over a (b) (4) period, with no hold steps.

(b) (4)

Manufacturing Control Strategy

To maintain consistency in the manufacture of AUCATZL, Autolus Inc. employs a multi-faceted control strategy. Raw materials, reagents, and manufacturing consumables each have defined quality attributes which must be confirmed prior to use in manufacturing. In the manufacture of both the (b) (4) LVV and AUCATZYL, multiple in-process controls are defined. Further, critical process parameters and critical quality attributes of AUCATZYL were defined through process characterization and validation studies. All lot release tests for the (b) (4) LVV and AUCATZYL DP are appropriately validated, and product specifications are adequate to ensure product quality and consistency.

Autolus Inc. uses both a validated electronic system and paper-based tracking procedure to maintain the chain of identity (COI) and chain of custody (COC) throughout the accessioning of apheresis material, AUCATZYL manufacture, storage, and shipment to treatment sites. The COC/COI procedures were evaluated as part of BLA review, as well as during the pre-licensing inspection of the Nucleus facility. The COC/COI procedures adequately ensure traceability of AUCATZYL throughout manufacture.

Comparability Assessments

AUCATZYL intended for commercial distribution in the United States will be manufactured at the Nucleus facility in Stevenage, UK. The Nucleus is a newly established, Autolus-owned facility for the manufacture of AUCATZYL. However, all lots of AUCATZYL generated for the FELIX clinical study were produced at the Cell and Gene Therapy 'Catapult' manufacturing center in Stevenage, UK. To support that the Nucleus facility generated drug products with comparable quality attributes compared to the Catapult facility, Autolus Inc. provided the results of a comprehensive split-apheresis comparability study. All parameters evaluated in the comparability study met their prospective equivalence acceptance criteria (EAC) and demonstrate that the Nucleus can generate AUCATZYL lots which are comparable to those used to generate the clinical data supporting the safety and efficacy.

A second comparability report was provided by Autolus Inc. to justify a manufacturing change in the (b) (4) used to generate the (b) (4) . For commercial manufacture, (b) (4) will be generated using (b) (4) sourced from (b) (4) located in (b) (4) . Throughout the FELIX clinical study, (b) (4) was generated

using (b) (4) sourced from (b) (4) located in (b) (4)
The comparability study provided demonstrated that the use of (b) (4) did not compromise the quality attributes of the (b) (4) LVV.

PMRs/PMCs

Nine PMCs were included as part of the approval of AUCATZYL, all of which were related to CMC information.

- Five PMCs are related to the analytical control of (b) (4) manufacture and reflect commitments to provide additional validation data to further support the robustness, accuracy, and specificity of certain impurity assays.
- One PMC pertains to the repeat performance of container closure integrity testing (CCIT) for the (b) (4) using an alternative positive control relative to what is currently provided in the BLA.
- One PMC pertains to the re-evaluation of a (b) (4) release specification once additional manufacturing experience has been obtained in a commercial setting.
- Two PMCs pertain to the AUCATZYL (b) (4) assay. Specifically, Autolus Inc. will provide a supplemental assay validation to further support the accuracy and precision of the (b) (4) assay in lots with (b) (4) CAR frequencies. Additionally, Autolus Inc. will establish a procedure for (b) (4) between "in-use" and "new" lots of the CAR-detecting antibody.

b. Testing Specifications

The analytical methods and their validations and/or qualifications were reviewed for the AUCATZYL drug product. These were found to be adequate for their intended use.

AUCATZYL specifications are shown in **Table 2.**

Table 2 – Commercial AUCATZYL Release Specifications

Quality Attribute	Analytical Procedure	Acceptance Criteria
General	Appearance by Visual Inspection for Color	Colorless to pale yellow
General	Appearance by Visual Inspection for Clarity	Very opalescent
General	Visual Inspection for Visible Particles	Essentially free from visible foreign particles
Identity	CD19 CAR Expression by (b) (4)	Detected
Quantity	Number of CD19 CAR-positive T cells by (b) (4)	410 $\times 10^6$ ± 25%
Quantity	Cell Viability upon thaw by (b) (4)	(b) (4)
Purity	(b) (4)	(b) (4)
Safety	(b) (4)	(b) (4)
Quantity	CD19 CAR Expression by (b) (4)	(b) (4)
Potency	CD19-specific (b) (4)	(b) (4)
Safety	Sterility by (b) (4)	No growth
Safety	Endotoxin Detection by (b) (4)	(b) (4)
Safety	Mycoplasma Detection by (b) (4)	Negative
Safety	Replication Competent Lentivirus (RCL) Detection by (b) (4)	(b) (4)

c. CBER Lot Release

CBER Lot Release, including the submission of product samples to CBER, is not required. The basis for this decision is that AUCATZYL is an autologous product; as such, each lot will treat a single patient. Failure of a single lot will have minimal potential impact on public health.

d. Facilities Review / Inspection

Facility information and data provided in the BLA were reviewed by CBER and found to be sufficient and acceptable. The facilities involved in the manufacture of AUCATZYL along with activities performed and inspectional histories are listed in the table below in **Table 3.**

Table 3 – Facility Information

Name/Address	FEI Number	DUNS Number	Inspection/ Waiver	Justification /Results
Autolus Limited Marshgate, Stevenage, Hertfordshire, United Kingdom SG1 1FR Manufacture, labeling, packaging, and storage, release and stability testing of drug substance and drug product	3015674982	229442484	Inspection	PLI CBER/DMPQ Apr 2024 VAI
(b) (4) Manufacture, labeling, packaging, and storage, release and stability testing of LVV	(b) (4)	(b) (4)	Waiver	PLI CBER/DMPQ (b) (4) VAI

Pre-License Inspection (PLI); Voluntary Action Indicated (VAI); Lentiviral Vector (LVV)

CBER/DMPQ performed a PLI of Autolus Limited facility located at Stevenage, UK, from April 22 - 30, 2024. A Form FDA 483, Inspectional Observations, was issued at the end of the inspection. All inspectional issues were resolved, and the inspection was classified as VAI.

CBER/DMPQ performed a PLI inspection of (b) (4) A Form FDA 483, Inspectional Observations, was issued at the end of the inspection. All inspectional issues were resolved, and the inspection was classified as VAI.

e. Container/Closure System

The AUCATZYL container closure system consists of a primary, secondary, and tertiary packaging system. The primary package container consists of a sterile, single-use (b) (4) bag manufactured by (b) (4). The (b) (4) Freezing Bags are 510(k) cleared (No. (b) (4) in the USA and are constructed from (b) (4) The bags include ports, a filling line, and protective caps. (b) (4) performed the container closure integrity testing at its (b) (4) facility, employing a (b) (4) test method; all acceptance criteria were met.

The secondary package container consists of an aluminum cassette ((b) (4)) with a U-shaped felt insert (b) (4) . The tertiary package is a (b) (4) which consists of a (b) (4) sleeve with four separate compartmental inserts of appropriate dimensions to contain the aluminum cassettes. Filled (b) (4) bags are placed in (b) (4) overwrap, which is heat sealed before the overwrapped bags are (b) (4) cryopreservation. Following initial cryopreservation, frozen (b) (4) bags are placed inside felt-lined aluminum cassettes for long-term storage in the vapor phase of liquid nitrogen. When requested by a treatment center, the aluminum cassettes are retrieved from long term storage and are loaded into a (b) (4) for shipment. AUCATZYL is shipped in a qualified liquid nitrogen shipper.

f. Environmental Assessment

The BLA included a request for categorical exclusion from an Environmental Assessment under 21 CFR 25.31. The FDA concluded that this request is justified, and no extraordinary circumstances exist that would require an environmental assessment.

4. Nonclinical Pharmacology/Toxicology

In vitro pharmacology studies compared Autolus Inc.'s 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.

5. Clinical Pharmacology

The clinical pharmacology data in the current BLA derives from an open-label, multi-center, multi-national, single-arm Phase 1b/2 study in adults with r/r B ALL (Study FELIX, AUTO-AL1). The clinical pharmacology review focused on the Phase II Cohort IIA and Phase 1B Cohort A portions of the study, for patients who received conforming product at the target dose of 410×10^6 ± 25% CAR+ viable T cells (N=90).

After administration, AUCATZYL exhibited a rapid expansion, followed by contraction and persistence. Patients with >20% bone marrow blasts who received a CAR T cell regimen consisting of $10/400\times10^6$ CAR+ T cells (i.e., an initial infusion of 10×10^6 CAR+ T cells, followed by a subsequent infusion of 400×10^6CAR+ T cells), had higher AUCATZYL exposure compared to patients with ≤20% bone marrow blasts who received $100/310\times10^6$ CAR+ T cells 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 Tmax was achieved at Day 14 (Range: Day 2 – Day 55). Persistency of AUCATZYL was observed up to 36.5 months and 18 months in peripheral blood and bone marrow, respectively. High inter-patient variability was observed for the AUCATZYL expansion including Cmax and AUC. Higher tumor burden (bone marrow blast percentage) appeared to be associated with higher AUCATZYL expansion.

No association between AUCATZYL exposure and tumor responses was identified. Compared to patients without CRS, patients who experienced any grade of CRS had 6.8-fold and 5.0-fold higher geometric mean $AUC_{0\text{-}28d}$ and Cmax of AUCZTZYL, respectively. Compared to patients without ICANS, patients who experienced any grade of ICANS had 2.9-fold and 3.3-fold higher geometric mean $AUC_{0\text{-}28d}$ and Cmax of AUCATZYL, respectively.

B cell aplasia was observed in most patients after treatment with AUCATZYL. In Cohort IIA, 93.1% of treated patients had B cell aplasia at Month 3 and 80% patients had B cell aplasia at Month 6. B cell aplasia appeared to resolve 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. Cytokine 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 µmol/L (mean) at baseline and remained low until Month 12 at interim data cutoff date (June 09, 2023).

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

in 3 out of 75 (4%) patients at the Month 3 visit. Humoral and cellular immune responses against AUCATZAL did not show significant impact on clinical outcomes based on available data. Due to the small sample size, the definitive conclusion cannot be drawn.

Based on data cutoff date of June 09, 2023, there was no identified positive result for replication-competent lentivirus testing in evaluable patients treated with AUCATZYL in the safety follow up.

6. Clinical/Statistical

The clinical review team recommends granting traditional approval for AUCATZYL for the treatment of adults with r/r B ALL.

g. Clinical Program

The primary evidence of effectiveness of AUCATZYL in the indicated population comes from patients with r/r B ALL dosed in the Phase 2 Cohort A portion of FELIX, which is a Phase 1b/2, single-arm, open-label, multicenter, multiregional (U.S., United Kingdom, and Spain) study. FELIX included 3 cohorts of B ALL: 1) Cohort A: patients with ≥ 5% blasts in the bone marrow at screening; 2) Cohort B: patients in morphological remission with minimum residual disease (MRD)-positive disease, and 3) Cohort C: patients with isolated extramedullary disease (EMD). The primary efficacy endpoint in FELIX was the overall complete remission (OCR) rate at any time following AUCATZYL infusion, defined as the combined rate of complete remission (CR) and CR with incomplete hematological recovery (CRi) per independent response review committee. Key secondary efficacy endpoints included duration of remission (DOR) and CR within 3 months following AUCATZYL infusion.

At enrollment, patients underwent leukapheresis, received lymphodepletion (LD) with fludarabine and cyclophosphamide, followed by AUCATZYL which was administered as a split dose infusion on Day 1 and Day 10 (± 2 days) at a total dose of 410×10^6 CD19 CAR-positive viable T cells. Dose was determined by the patient's bone marrow blast assessment prior to LD. During product manufacturing, patients were allowed to receive bridging therapy at the discretion of the investigator.

Among the 112 patients who were enrolled in FELIX Phase 2 Cohort A, 94 patients received AUCATZYL. The manufacturing failure rate for AUCATZYL was 5%.

The FDA's primary efficacy evaluable population included 65 patients enrolled in FELIX Phase 2 (Cohort A), who had ≥ 5% bone marrow blasts prior to LD and who received at least one infusion of conforming AUCATZYL. For the primary efficacy evaluable population, the median age was 51 years (range: 20 to 77 years); 54% were female, 72% were White, 12% were Asian and 2% was Black or African American. Twenty-one patients (32%) were of Hispanic or Latino ethnicity. Fifty four percent were refractory to the last prior line of therapy, and 49% relapsed to first-line therapy within 12 months. The median number of prior lines of therapy was 2 (range: 1 to 6). Fifty-nine patients (91%) received bridging therapy between leukapheresis and lymphodepleting chemotherapy.

Efficacy Results:

FELIX study demonstrated a complete remission rate within 3 months of 42% (95% CI: 29, 54) and median duration of remission of 14.1 months (95% CI: 6.1, not reached [NR]). The overall complete remission rate at any time, OCR (including CR and CR with incomplete hematologic recovery) was 63% (95% CI: 50, 75), and the median duration of OCR at any time was 14.1 months (95% CI: 6.2, NR).

The observed rate and duration of complete remission within 3 months of AUCATZYL infusion in this relapsed refractory B ALL population denotes clinical benefit and constitutes substantial evidence of AUCATZYL's effectiveness.

Efficacy data from the patients treated on FELIX Phase 1b Cohort A demonstrated similar outcomes to the primary results.

h. Bioresearch Monitoring (BIMO) – Clinical/Statistical/Pharmacovigilance

Bioresearch Monitoring (BIMO) inspection assignments were issued for four Clinical Investigator (CI) study sites (two foreign sites and two domestic sites) that participated in the conduct of FELIX Study. The inspections did not reveal substantiative issues that impact the data submitted in this original BLA.

i. Pediatrics

Autolus Inc. has an agreed initial pediatric study plan with FDA, dated January 6, 2023. Autolus Inc. requested a partial waiver of the pediatric assessment for the pediatric population under 1 year of age and requested a deferral of submission of the pediatric assessment for the pediatric population aged 1 to < 17 years old at the time of BLA submission. The partial waiver request is based on the grounds that the necessary studies in these pediatric subsets are impossible or highly impracticable (section 505B(a)(4)(B)(i) of the Act). The deferral request is based on the grounds that the product is ready for approval for use in adults before pediatric studies are complete (section 505B(a)(3)(A)(i) of the Act).

AUCATZYL has been granted orphan drug designation (ODD #19-7083) for the treatment of B ALL on Nov 4, 2019.

In accordance with the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), as amended by the FDA Reauthorization Act of 2017 (FDARA), because the molecular target "CD19" is relevant to the growth or progression of pediatric cancer, Autolus Inc. is required to conduct a molecularly targeted pediatric cancer investigation to evaluate dosing, pharmacokinetics, safety, and antitumor activity of AUCATZYL in patients 1 year to less than 17 years of age who have r/r B ALL and r/r aggressive mature B-cell non-Hodgkin lymphoma.

The study will be conducted according to the following schedule: 1) Final Protocol Submission: Completed, 2) Study Completion: September 2027, and 3) Final Report Submission: March 2028

j. Other Special Populations

AUCATZYL has not been studied in other special populations.

7. Safety and Pharmacovigilance

Safety

The safety analysis is based on safety assessments conducted starting at the time patients began the treatment regimen, which included LD followed by AUCATZYL. Risks related to the entire treatment regimen were evaluated during this assessment.

The primary safety analysis population consists of 100 patients who were enrolled in Phase 1b (Cohort A) and Phase 2 (Cohort A) of FELIX, and who received at least one infusion of conforming AUCATZYL.

All 100 patients experienced treatment-emergent AEs (TEAEs); Grade 3 or higher TEAES occurred in 81% of patients. The most common non-laboratory adverse reactions (incidence ≥ 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.

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 HLH/MAS (2%).

Among the 52 patients from the safety population who died during the study, nine 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 with AUCATZL is not apparent.

Overall, the safety profile of AUCATZYL appears generally consistent with approved CAR T cell products, with no new safety signals identified. The risks of AUCATZYL, 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 AUCATZYL 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 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-directed 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.

Pharmacovigilance Plan (PVP)

The PVP includes Autolus Inc.'s assessment of important identified and potential risks and missing information based on data collected from the nonclinical and clinical development program for AUCATZYL in the treatment of B cell precursor ALL, including safety concerns associated with gene therapy. Autolus Inc. will conduct routine pharmacovigilance in accordance with 21 CFR 600.80 and enhanced pharmacovigilance for secondary malignancies and the risk of overdose/medication dosing errors. Enhanced pharmacovigilance will include expedited (15-day) reporting of secondary malignancies (regardless of seriousness or label status) following licensure. Autolus Inc. will also provide a safety assessment of secondary malignancies, and specifically T cell malignancies, in periodic safety reports. For 3-years post-licensure, Autolus Inc. will provide aggregate safety assessments for the risk of overdose/medication dosing errors in their periodic safety reports. Furthermore, Autolus Inc. will collect additional details for cases of CRS and neurologic toxicities using a Targeted Data Questionnaire.

In addition to routine and enhanced pharmacovigilance, the postmarketing safety monitoring of AUCATZYL will include a 15-year long term follow-up (LTFU) observational safety study (AUTO1-LT2), as a postmarketing requirement (PMR) under 505(o) of the Federal Food, Drug, and Cosmetic Act (FDCA), to assess the serious risk of secondary malignancies following administration of AUCATZYL. This study will enroll 500 adult patients with relapsed or refractory B cell precursor ALL.

Additionally, Autolus Inc. will conduct LTFU of clinical trial participants in ongoing study AUTO-LT1. The above LTFU studies are in alignment with FDA Guidance Long Term Follow-up After Administration of Human Gene Therapy Products (January 2020) available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/long-term-follow-after-administration-human-gene-therapy-products.

The PMR protocol AUTO1-LT2 design and data analysis plan will be finalized with Autolus Inc. post-licensure. Of note, an algorithm to assess for insertional oncogenesis for cases of secondary malignancies including insertion site analysis (ISA), will be agreed upon. FDA will review the final study protocol upon submission to ensure that FDA recommendations on study methods were appropriately incorporated.

8. Labeling

The proposed proprietary name, AUCATZYL, was reviewed by the Advertising and Promotional Labeling Branch (APLB) on February 8, 2024, and was found acceptable. CBER communicated the acceptability of the proprietary name to Autolus Inc. on February 15, 2024.

The Advertising and Promotional Labeling Branch (APLB) reviewed the proposed USPI, and package and container labels received on November 1, 2024. The APLB comments are provided in the review memorandum dated November 4, 2024.

Boxed Warning, Warnings and Precautions

Risk mitigation strategies will be instituted in the United States Prescribing Information (USPI) through a Boxed Warning for cytokine release syndrome (CRS), ICANS and T cell malignancies, and Warnings and Precautions section for CRS, neurologic toxicities, prolonged cytopenia, infections, hypogammaglobulinemia, HLH/MAS, hypersensitivity reactions and secondary malignancies.

9. Advisory Committee Meeting

This BLA was not referred to the Cellular, Tissue, and Gene Therapies Advisory Committee because the information submitted, including the clinical study design and trial results, did not raise concerns or controversial issues that would have benefited from an advisory committee discussion.

10. Other Relevant Regulatory Issues

AUCATZYL was granted an Orphan Drug designation and a Regenerative Medicine Advanced Therapy (RMAT) designation. The BLA was reviewed under standard review.

11. Recommendations and Benefit/Risk Assessment

a. Recommended Regulatory Action

The review team recommends granting traditional approval to AUCATZYL for the treatment of adults with relapsed or refractory B-cell precursor acute lymphoblastic leukemia (ALL). The basis for the recommendation is the complete remission rate within 3 months of AUCATZYL infusion supported by durability of remission and an acceptable risk profile for the intended population.

Although FELIX study was designed with overall complete remission rate at any time as the primary efficacy endpoint, FDA considers rate and duration of complete remission within 3 months as clinical benefit in the indicated population, and therefore were considered as the main efficacy outcome measure for this BLA. FDA 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.

b. Benefit/Risk Assessment

FELIX study represents an adequate and well-controlled investigation that provides substantial evidence of effectiveness of AUCATZYL 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. The magnitude and durability of complete remission rate within 3 months of AUCATZYL infusion denotes clinical benefit in the indicated population and therefore supports 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. Efficacy and safety data from patients treated on FELIX Phase 1b Cohort A and Cohort B, and from Phase 2 Cohort B and Cohort C demonstrates similar outcomes to the primary results. In addition, B ALL has a well understood pathophysiology; the mechanism of action of AUCATZYL in B ALL treatment is due to its binding with CD19, an antigen universally expressed on B ALL blasts leading to tumor lysis. The supportive data from the additional cohorts of FELIX and the mechanism of action of AUCATZYL serve as confirmatory evidence to substantiate the results from one adequate and well-controlled trial to demonstrate substantial evidence of effectiveness.

Risk mitigation strategies will be instituted in the USPI through a Boxed Warning for CRS, ICANS and T cell malignancies, and Warnings and Precautions section for CRS, neurologic toxicities, prolonged cytopenia, infections, hypogammaglobulinemia, HLH/MAS, hypersensitivity reactions and for secondary malignancies.

The recommended AUCATZYL 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 blast assessment prior to LD (> 20% or ≤ 20%).

The overall benefit-risk profile of AUCATZYL supports traditional approval for the treatment of adults with r/r B ALL.

c. Recommendation for Post-marketing Activities

1. Conduct a molecularly targeted pediatric cancer investigation to evaluate dosing, pharmacokinetics, safety, and antitumor activity of AUCATZYL 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.

   Final Protocol Submission: Completed
   Study Completion: September 2027
   Final Report Submission: March 2028

Autolus Inc. will conduct routine and enhanced pharmacovigilance activities as outlined in the Pharmacovigilance Plan, and the following safety study as a PMR under section 505(o) of the Federal Food, Drug, and Cosmetic Act, to assess the serious risk of secondary malignancies:

2. Autolus Inc. 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 AUCATZYL (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. We acknowledge the timetable you submitted on February 22, 2024, which states that you will conduct this study according to the following schedule:

Protocol Submission: December 16, 2024
Study Completion Date: June 30, 2044
Final Report Submission: June 30, 2045

Autolus Inc. has agreed to the following chemistry, manufacturing, and controls post-marketing commitments:

3. Autolus Inc. commits to conducing an additional product-specific requalification of the LVV adventitious agents test using a sample withdrawn from the (b) (4) The final qualification study report will be submitted as a PMC by March 31, 2025.

   Final Study Report Submission: March 31, 2025

4. Autolus Inc. commits to providing a supplemental assay validation of the AUCATZYL (b) (4) assay, which evaluates the accuracy and linearity of the (b) (4) assay at (b) (4) CD19 CAR frequencies. The final study report will be submitted as a PMC by May 31, 2025

   Final Study Report Submission: May 31, 2025

5. Autolus Inc. commits to establishing a procedure for (b) (4) between “in-use” and “new” lots of the (b) (4) antibody lots used for the (b) (4) and (b) (4) (AUCATZYL) release assays. The protocol used for analytical (b) (4) will be submitted by June 30, 2025.

   Protocol Submission: June 30, 2025

6. Autolus Inc. commits to providing a reassessment of the acceptance criterion for the (b) (4) ” assay following the manufacture of (b) (4) additional lots of commercial (b) (4) vector.

   Final study report submission: December 31, 2025

7. Autolus Inc. commits to providing a supplemental validation study report evaluating the robustness of the (b) (4) assay performed as part of the (b) (4) release test.

   Final study report submission: March 31, 2025

Autolus Inc. has agreed to the manufacturing and product quality post-marketing commitment:

8. Autolus Inc. commits to execute a new container closure integrity testing (CCIT) study for the (b) (4) LVV (b) (4) using a validated (b) (4) analysis method and a positive control with an established sensitivity [i.e., minimum critical leak defect (size) that can be reliably detected] in accordance with (b) (4) The final study report will be submitted as a PMC - Final Study Report by December 31, 2024.

   Final Study Report Submission: December 31, 2024

Autolus Inc. has also agreed to the biological standards and quality control post-marketing commitments:

9. Autolus Inc. commits to evaluating specificity and accuracy (b) (4) LVV purified final product at a concentration within the range of the assay to determine assay interference caused by the presence of LVV in the formulation matrix.

   Final Validation Study Report Submission: June 30, 2025

10. Autolus Inc. commits to evaluating specificity and accuracy (b) (4) LVV purified final product at a concentration within the range of the assay to demonstrate any assay interference caused by the presence of LVV in the formulation matrix.

    Final Validation Study Report Submission: June 30, 2025

11. Autolus Inc. commits to evaluating specificity and accuracy (b) (4) LVV purified final product at a concentration within the range of the assay to demonstrate any assay interference caused by the presence of LVV in the formulation matrix.

    Final Validation Study Report Submission: June 30, 2025

Document History / Concurrence Page

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History:

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