



**Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research (CBER)
Office of Biostatistics and Pharmacovigilance (OBPV)
Division of Pharmacovigilance (DPV)**

PHARMACOVIGILANCE ORIGINAL BLA MEMORANDUM

From: Deborah Thompson, MD, MSPH
Medical Officer, Pharmacovigilance Branch 3
(PB3), DPV, OBPV, CBER, FDA

To: Andrew Timmons
Chair of the Review Committee
Office of Therapeutic Products (OTP)

Through: Kerry Welsh, MD, PhD
Branch Chief, PB3

Meghna Alimchandani, MD
Deputy Director, DPV
OBPV, CBER, FDA

Subject: Review of Pharmacovigilance Plan

Sponsor: Autolus Inc.

Product: Obecabtagene autoleucel (obe-cel)

Application Type / Number BLA 125813/0

Proposed Indication Treatment of adult patients with relapsed or refractory B-cell precursor acute lymphoblastic leukemia (ALL)

Submission Date: November 17, 2023

Action Due Date: November 16, 2024

1 OBJECTIVE

The purpose of this review is to assess the adequacy of the sponsor's pharmacovigilance plan (PVP) submitted under the original BLA 125813/0 based on the safety profile of obecabtagene autoleucel (obe-cel; AUCATZYL). Our review will determine whether any safety-related studies such as Postmarketing Requirements (PMRs) are warranted, or if there will be any safety-related agreed upon studies as Postmarketing Commitments (PMCs), or if Risk Evaluation and Mitigation Strategies (REMS) are required for obe-cel, should the indication for this product be approved. Please refer to the Appendix for the complete list of materials reviewed for this memorandum.

2 BACKGROUND

Acute lymphoblastic leukemias (ALL) are malignancies classified based on B cell or T cell lineage. ALL has an estimated worldwide annual incidence of 1 to 5 cases per 100,000 population with >60% of cases being of B cell lineage. (Advani) Most cases occur in children <6 years of age although there is a second peak incidence in adults >60 years of age. (Advani) B cell ALL is a malignancy of immature B cells with clinical manifestations that can include anemia, neutropenia, and/or thrombocytopenia with symptoms of fatigue, infections, easy bruising or bleeding, bone pain, arthralgias, fevers, night sweats, and/or unintentional weight loss. (Advani) B cell ALL is associated with peripheral blood smear, bone marrow biopsy, and tissue biopsy specimens that show small to medium-sized lymphoblasts with uniform appearance and scant cytoplasm. (Advani) Lymphoblasts of B cell ALL are positive for CD19, cytoplasmic CD79a, and cytoplasmic CD22 antigens. (Advani) Obe-cel uses the patient's own T cells that are modified to express an anti-CD19 chimeric antigen receptor (CAR) which then binds to CD19-expressing target cells and results in anti-tumor activity and killing of CD19-expressing target cells.

3 PRODUCT INFORMATION

3.1 Product Description

Per the sponsor's draft U.S. package insert (USPI) Section 11, obe-cel is a "CD-19-directed genetically modified autologous anti-CD19 (CAT) CAR-positive T cell immunotherapy" that is "prepared from the patient's own peripheral blood mononuclear cells." The patient's cells are collected via leukapheresis and then "the mononuclear cells are enriched for T cells, activated, and transduced with a replication-incompetent lentiviral vector that contains the CD19 CAR transgene." The transduced T cells are expanded in cell culture, prepared as the drug product, and then infused intravenously back into the patient. The "anti-CD19 (CAT) CAR positive T-cells can recognize and eliminate CD19-expressing target cells." The product contains phosphate-buffered saline (PBS) human serum albumin (HAS), ethylenediaminetetraacetic acid (EDTA), and 7.5% dimethyl sulfoxide (DMSO).

Obe-cel is proposed as a split dose infusion on Day 1 and Day 10; the dose to be administered will be determined by the patient bone marrow blast assessment (i.e., low disease burden of $\leq 20\%$ blasts in bone marrow at lymphodepletion or high disease

burden of >20% blasts in bone marrow at lymphodepletion). The proposed USPI indicates that “a delay to the second dose may be required to manage toxicities” and provides a table specifying “dosage modifications intended to reduce the risk of adverse reactions.”

3.2 Proposed Indication

The sponsor’s proposed indication statement as submitted to the original BLA 125813/0 is “treatment of adult patients (18 years and over) with relapsed or refractory B cell precursor acute lymphoblastic leukemia (ALL).” OBPV defers to the product office on the final language for the indication statement. Please see the final version of the package insert submitted by the sponsor for the final agreed-upon indication after FDA review.

4 PERTINENT REGULATORY HISTORY

This is an original BLA submission, and no patients have been treated with obe-cel in the postmarket/commercial setting. Current FDA approved CD19-directed CAR T cell therapies include tisagenlecleucel (Kymriah), axicabtagene ciloleucel (Yescarta), Breyanzi (lisocabtagene maraleucel), and brexucabtagene autoleucel (Tecartus). The currently approved CD-19 directed CAR T cell therapies all have REMS to mitigate the risks of cytokine release syndrome (CRS) and neurologic toxicities (NT) and PMR safety studies to assess the long-term safety and risk of secondary malignancies following product administration.

5 DESCRIPTION OF OBE-CEL CLINICAL TRIAL SAFETY DATABASE

5.1 Clinical studies

The clinical study safety data reviewed are from the Clinical Overview and Summary of Clinical Safety submitted to STN 125813/0. OBPV defers to the product office on final review of the clinical database, including safety and efficacy outcomes, which will inform the final language in the USPI. Below is our *focused* review of the sponsor data initially submitted to the BLA, to inform decisions pertaining to pharmacovigilance planning, should this BLA 125813/0 be approved. Please refer to the package insert for the final clinical safety data.

The sponsor submitted data from the pivotal study AUTO1-AL1 (FELIX study), which is a single-arm, open-label, multi-center Phase Ib/II study assessing the safety and efficacy of obe-cel in three Phase II patient cohorts:

- Cohort IIA: Adults ≥18 years with relapsed/refractory (r/r) B ALL who have ≥5% blasts in bone marrow (BM) at screening
- Cohort IIB: Adults ≥18 years with r/r B ALL in morphologic remission but minimal residual disease (MRD) detected at screening
- Cohort IIC (exploratory): Adults ≥18 years with r/r B ALL with isolated extramedullary disease (EMD) at screening, with or without MRD

The AUTO1-AL1 study is being conducted in the U.S., Spain, and United Kingdom. Following lymphodepletion with fludarabine and cyclophosphamide, study treatment

includes two split infusions of obe-cel on Day 1 and Day 10 (+/- 2 days) for a total dose of 410×10^6 CD19 CAR-positive T cells. The second dose of obe-cel could be delayed or not given depending on the occurrence and severity of adverse events (AEs) following the first dose. A total of 127 individuals received at least one dose of obe-cel in study AUTO1-AL1 as of June 9, 2023 (data cut-off), including 94 individuals in cohort IIA. Most (94.5%) participants received two doses, including 93.6% of participants in Cohort IIA; three participants did not receive the second dose due to Grade 3 CRS or immune effector cell-associated neurotoxicity syndrome (ICANS). The overall median duration of follow-up is 13.5 months for all cohorts and 12.3 months for Cohort IIA. Individuals are followed for 24 months post-obe-cel treatment and then may enter a long-term follow-up (LTFU; 15 years) study AUTO-LT1 (see memo Section 6.2).

5.2 Adverse events: Clinical Study AUTO1-AL1

i) Most common AEs: Among the 127 participants who received at least one dose of obe-cel, CRS was the most common AE (n=87, 68.5%). AEs occurring in $\geq 10\%$ of study participants are shown in Table 1.

Table 1: Adverse Events Occurring in $\geq 10\%$ of Participants Following Obe-cel Infusion (as of data cut-off June 9, 2023)*

Primary System Organ Class Preferred Term	All grades n (%)	Grade ≥ 3 n (%)
Number of patients with any treatment emergent AE (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	29 (22.8)	25 (19.7)
Neutropenia	28 (22.0)	25 (19.7)
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	78 (61.4)	15 (11.8)
Nausea	33 (26.0)	3 (2.4)
Diarrhoea	31 (24.4)	1 (0.8)
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	36 (28.3)	2 (1.6)
Fatigue	24 (18.9)	2 (1.6)
Hepatobiliary disorders	13 (10.2)	7 (5.5)
Immune system disorders	90 (70.9)	9 (7.1)
Cytokine release syndrome	87 (68.5)	3 (2.4)

Infections and infestations	92 (72.4)	55 (43.3)
COVID-19	21 (16.5)	4 (3.1)
Injury, poisoning and procedural complications	23 (18.1)	3 (2.4)
Investigations	62 (48.8)	46 (36.2)
Neutrophil count decreased	24 (18.9)	24 (18.9)
Platelet count decreased	17 (13.4)	15 (11.8)
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
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)

* Excerpted from Table 10, Summary of Clinical Safety, STN 125813/0, Module 2.7.4

ii) Serious AEs (SAEs): SAEs occurred in most participants (n=77, 60.6%), including 66 (52.0%) participants who experienced SAEs of Grade ≥ 3 . The most common SAEs ($\geq 5\%$) included febrile neutropenia (n=15, 11.8%), ICANS (n=12, 9.4%), CRS (n=10, 7.9%), pyrexia (n=8, 6.3%), hyperferritinemia (n=7, 5.5%), and sepsis (n=7, 5.5%).

iii) Deaths: Fifty-three (41.7%) participants died following obe-cel infusion, including five (3.9%) participants who died within 30 days post-obe-cel infusion (as of the June 9, 2023 data cut-off). Among the 53 participants who died, the majority (n=37, 69.8%) experienced progressive disease. Two deaths were considered by investigators as related to obe-cel: one participant (subject (b) (6)) who died due to neutropenic

sepsis on Day 51 post-obe-cel infusion and one participant who died due to acute respiratory distress syndrome (ARDS) with ongoing ICANS on Day 54. Thirteen participants who died experienced AEs that were not considered related to obe-cel by investigators: multiple organ dysfunction syndrome (n=3), respiratory failure (n=2), sepsis (n=2), abdominal infection (n=1), acute myeloid leukemia (AML, n=1; see adverse events of special interest [AESI] section below for details), acute respiratory failure (n=1), cerebrovascular accident (n=1; autopsy revealed acute pulmonary thromboembolism as the cause of death), neutropenic sepsis (n=1; died Day 44 following hospitalization on Days 38-43 for stem cell transplant [SCT] conditioning chemotherapy), polyserositis (n=1), and status epilepticus (n=1). One additional participant died due to steroid refractory graft versus host disease (GvHD) and sepsis due to a second allogeneic SCT in minimal residual disease (MRD)-negative remission at Day 140 post-obe-cel treatment which was considered not related by study investigators.

iv) Adverse events of special interest (AESIs): The sponsor provided a summary of “other significant safety topics,” which included CRS (n=87, 68.5%), ICANS (n=29, 22.8%), infections (n=92, 72.4%), GvHD (n=7, 5.5%, including six participants who received SCT prior to obe-cel and one participant who received SCT post-obe-cel treatment with subsequent GvHD), hemophagocytic lymphohistiocytosis/macrophage activation syndrome (HLH/MAS; n=2, 1.6%), hypogammaglobulinemia (n=10, 7.9%), tumor lysis syndrome (TLS; n=1, 0.8%), and hypersensitivity reactions (n=0). The median time to onset of CRS was 8 days post-infusion of the first dose (range=1-23 days) with a median duration of 5 days (range=1-21 days); there were no Grade 4 or 5 CRS events. The median time to onset of ICANS was 12 days post-infusion of the first dose (range=1-31 days) with a median duration of 8 days (range=1-53 days). One participant experienced Grade 4 ICANS following the second dose of obe-cel after having experienced Grade 1 ICANS after the first dose. One participant experienced Grade 5 ICANS following the second dose after having experienced Grade 1 ICANS after the first dose (same participant as described in the death section above who died due to ARDS with ongoing ICANS on Day 54).

The sponsor indicates there were no patients identified with secondary malignancies due to insertional mutagenesis or replication competent lentivirus (RCL). There was one case of AML post-obe-cel infusion in a 58-year-old female with a history of breast cancer and suspected ongoing myelodysplastic syndrome (MDS) who on Day 29 had “molecular abnormalities by fluorescence in situ hybridization (FISH) which were pre-existing and compatible with persistent background myelodysplastic syndrome (MDS);” “bone marrow findings were consistent with secondary, treatment-related AML with monocytic differentiation post breast cancer treatment in 2019.” This individual died on Day 45 due to encephalopathy caused by AML; the investigator and sponsor assessed the event as not related to obe-cel. In addition, a 67-year-old female experienced basal cell carcinoma of the skin on Day 513 post-obe-cel infusion which was assessed by the investigator and sponsor as not related to obe-cel.

In addition, the sponsor assessed recovery of cytopenia post-obe-cel infusion and reported progressively lower percentages of participants with Grade 3 or 4 neutropenia or thrombocytopenia over time among participants who achieved remission after obe-cel infusion (n=98): 69.4% at Day 28, 32.7% at Month 2, and 20.4% at Month 3. Among participants who achieved remission, none were reported to have neutropenia $<1 \times 10^9/L$ that lasted >6 months. Seven participants had thrombocytopenia $<100 \times 10^9/L$ that lasted for >6 months; no bleeding events were reported for these seven participants.

The sponsor commented that viral reactivation is a theoretical risk and that individuals with a positive test for human immunodeficiency (HIV) or active hepatitis B or C virus were excluded from clinical trial participation. In addition, immunization with live viral vaccines was not allowed ≤ 4 weeks prior to leukapheresis in the clinical study and was not recommended for at least six weeks before the start of lymphodepleting chemotherapy, during treatment with obe-cel, or until immune recovery following obe-cel infusion.

Furthermore, the sponsor reported that there is limited available data on use of obe-cel in pregnant women; the sponsor's proposed USPI indicates that obe-cel is not recommended in pregnancy and that pregnancy status should be verified before treatment and should be negative. One participant in the AUTO1-AL1 study became pregnant 6-months following obe-cel infusion and was subsequently hospitalized with Grade 3 AEs of urinary tract infection, febrile neutropenia, and pyelonephritis. On Day 430, at 30 weeks and 6 days gestation, she was hospitalized with Grade 3 SAEs of amniotic cavity infection which led to preterm rupture of membranes and premature delivery via Caesarian section. The male infant initially showed respiratory distress and was admitted to the neonatal intensive care unit (NICU) for intubation; he was subsequently discharged.

v. 30-Day Safety Update Report: The sponsor submitted a 30-day safety update report with a data cut-off of September 13, 2023. No additional participants were treated with obe-cel since the original BLA submission (total n=127). The median duration of follow-up after obe-cel infusion was 16.6 months (range=3.7-36.6 months), including 126 (99.2%) participants with ≥ 6 months of follow-up and 93 (73.2%) participants with ≥ 12 months of follow-up. Among AEs occurring in $\geq 10\%$ of participants, there were the following additional \geq Grade 3 AEs since the primary data cut-off: anemia (1), neutropenia (1), diarrhea (1), pyrexia (1), COVID-19 (1), neutrophil count decreased (1), and platelet count decreased (1). Among SAEs that occurred in $\geq 5\%$ of participants following obe-cel infusion, there were two additional SAEs of febrile neutropenia, and one additional SAE each of COVID-19 and pyrexia.

Among AESIs, there were two additional participants with an AE of hypogammaglobulinemia (one with Grade 3 AE) and three additional participants with severe infections (\geq Grade 3; one event each of lower respiratory tract infection, *pneumocystis jirovecii* pneumonia, and COVID-19). There were also two participants with previous \geq Grade 3 infections who experienced new \geq Grade 3 infections (one

participant with secondary bacteremia due to central line bloodstream infection and one participant with a device-related infection and central nervous system ventriculitis). There were no new AEs of CRS, ICANS, HLH/MAS, TLS, GvHD, secondary malignancies, or hypersensitivity.

Among the six additional deaths, three were due to progressive disease, two were due to reasons recorded as “other” (one participant died on Day 468 due to GvHD and septic shock post-second allogeneic bone marrow transplant and one participant died on Day 288 due to multi-organ failure and septic shock while experiencing relapsed disease), and one death was due to an AE of idiopathic ascites (participant died on Day 356). The sponsor reported that none of the additional deaths were considered related to obe-cel.

Reviewer comment: Overall, the safety profile of obe-cel appears consistent with the known safety profile of CD-19 directed CAR T cell therapies, including the known risks of CRS, neurologic toxicities and ICANS, prolonged cytopenias, HLH/MAS, hypogammaglobulinemia, and infections. The sponsor reported that clinical trial data did not identify secondary malignancies due to insertional oncogenesis or RCL.

6 SPONSOR’S PHARMACOVIGILANCE PLAN

The sponsor submitted a PVP (dated November 6, 2023) and revised PVPs (dated January 2024, May 2024, July 2024, and August 2024) proposing routine pharmacovigilance (PV), including a targeted data questionnaire (TDQ) for CRS and neurologic toxicities, a postmarketing registry study (Study AUTO1-LT2), and a LTFU study (AUTO-LT1) for clinical trial participants (Table 2). There is also an ongoing long-term safety extension study for pediatric individuals who were treated with obe-cel in clinical trials (AUTO1-PY1). In addition, in the initial PVP submissions, the sponsor proposed a REMS for the known serious risks of CRS and ICANS.

Table 2. Summary of Sponsor’s Pharmacovigilance Plan*

Type of Concern	Safety Concern	Proposed Action
Important identified risk	Cytokine release syndrome (CRS)	<u>Routine PV Activities</u> Adverse event reporting, Monthly signal detection, Bi-annual (every 6 months) Periodic Benefit Risk Evaluation Reports (PBRERs), literature surveillance, CRS Targeted Data Questionnaire (TDQ) <u>Additional PV Activities</u> Study AUTO-LT1, ongoing long-term safety extension study Study AUTO1-LT2, postmarketing LTFU of patients treated with Aucatzyl

Important identified risk	Neurologic toxicities	<u>Routine PV Activities</u> Adverse event reporting, Monthly signal detection, Bi-annual (every 6 months) PBRERs, literature surveillance, neurologic toxicities TDQ <u>Additional PV Activities</u> Study AUTO-LT1, ongoing long-term safety extension study Study AUTO1-LT2, postmarketing LTFU of patients treated with Aucatzyl
Important identified risk	Prolonged cytopenias	<u>Routine PV Activities</u> Adverse event reporting, Monthly signal detection, Bi-annual (every 6 months) PBRERs, literature surveillance <u>Additional PV Activities</u> Study AUTO-LT1, ongoing long-term safety extension Study AUTO1-LT2, postmarketing LTFU of patients treated with Aucatzyl
Important identified risk	Haemophagocytic lymphohistiocytosis /macrophage activation syndrome (HLH/MAS)	<u>Routine PV Activities</u> Adverse event reporting, Monthly signal detection, Bi-annual (every 6 months) PBRERs, literature surveillance <u>Additional PV Activities</u> Study AUTO-LT1, ongoing long-term safety extension Study AUTO1-LT2, postmarketing LTFU of patients treated with Aucatzyl
Important identified risk	Hypogammaglobulinemia	<u>Routine PV Activities</u> Adverse event reporting, Monthly signal detection, Bi-annual (every 6 months) PBRERs, literature surveillance <u>Additional PV Activities</u> Study AUTO-LT1, ongoing long-term safety extension Study AUTO1-LT2, postmarketing LTFU of patients treated with Aucatzyl
Important identified risk	Severe infections	<u>Routine PV Activities</u> Adverse event reporting, Monthly signal detection, Bi-annual (every 6 months) PBRERs, literature surveillance

		<u>Additional PV Activities</u> Study AUTO-LT1, ongoing long-term safety extension Study AUTO1-LT2, postmarketing LTFU of patients treated with Aucatzyl
Important potential risk	Tumor lysis syndrome (TLS)	<u>Routine PV Activities</u> Adverse event reporting, Monthly signal detection, Bi-annual (every 6 months) PBRERs, literature surveillance <u>Additional PV Activities</u> None
Important potential risk	Antigenicity and immunogenicity	<u>Routine PV Activities</u> Adverse event reporting, Monthly signal detection, Bi-annual (every 6 months) PBRERs, literature surveillance <u>Additional PV Activities</u> Study AUTO-LT1, ongoing long-term safety extension Study AUTO1-LT2, postmarketing LTFU of patients treated with Aucatzyl
Important potential risk	Aggravation of Graft versus Host Disease (GvHD)	<u>Routine PV Activities</u> Adverse event reporting, Monthly signal detection, Bi-annual (every 6 months) PBRERs, literature surveillance <u>Additional PV Activities</u> Study AUTO-LT1, ongoing long-term safety extension Study AUTO1-LT2, postmarketing LTFU of patients treated with Aucatzyl
Important potential risk	Secondary malignancy	<u>Routine PV Activities</u> Adverse event reporting, Monthly signal detection, Bi-annual (every 6 months) PBRERs, literature surveillance <u>Additional PV Activities</u> Study AUTO-LT1, ongoing long-term safety extension Testing of blood/tumor samples in consented patients who received Aucatzyl Study AUTO1-LT2, postmarketing LTFU of patients treated with Aucatzyl

Important potential risk	Gene vector related risks	<u>Routine PV Activities</u> Adverse event reporting, Monthly signal detection, Bi-annual (every 6 months) PBRERs, literature surveillance <u>Additional PV Activities</u> Study AUTO-LT1, ongoing long-term safety extension Testing of blood/tumor samples in consented patients who received Aucatzyl Study AUTO1-LT2, postmarketing LTFU of patients treated with Aucatzyl
Important potential risk	Hypersensitivity reactions	<u>Routine PV Activities</u> Adverse event reporting, Monthly signal detection, Bi-annual (every 6 months) PBRERs, literature surveillance <u>Additional PV Activities</u> None
Important potential risk	Overdose/medication errors	<u>Routine PV Activities</u> Adverse event reporting, Monthly signal detection, Bi-annual (every 6 months) PBRERs, literature surveillance <u>Additional PV Activities</u> None
Missing information	Pregnancy and lactation	<u>Routine PV Activities</u> Adverse event reporting, Monthly signal detection, Bi-annual (every 6 months) PBRERs, literature surveillance <u>Additional PV Activities</u> Study AUTO-LT1, ongoing long-term safety extension Study AUTO1-LT2, postmarketing LTFU of patients treated with Aucatzyl
Missing information	Safety in pediatric population	<u>Routine PV Activities</u> Adverse event reporting, Monthly signal detection, Bi-annual (every 6 months) PBRERs, literature surveillance <u>Additional PV Activities</u> Study AUTO1-PY1, patients will be rolled over into AUTO-LT1, ongoing long-term safety extension

Missing information	Long-term safety	<u>Routine PV Activities</u> Adverse event reporting, Monthly signal detection, Bi-annual (every 6 months) PBRERs, literature surveillance <u>Additional PV Activities</u> Study AUTO-LT1, ongoing long-term safety extension Study AUTO1-LT2, postmarketing LTFU of patients treated with Aucatzyl
Missing information	New occurrence or exacerbation of an autoimmune disorder	<u>Routine PV Activities</u> Adverse event reporting, Monthly signal detection, Bi-annual (every 6 months) PBRERs, literature surveillance <u>Additional PV Activities</u> Study AUTO-LT1, ongoing long-term safety extension Study AUTO1-LT2, postmarketing LTFU of patients treated with Aucatzyl

*Adapted from Tables 1 and 4, Pharmacovigilance Plan (August 2024), STN 125813/0.50, Module 1.16.

6.1 Enhanced Pharmacovigilance

The sponsor proposes to collect additional details for cases of CRS and neurologic toxicities using a Targeted Data Questionnaire and indicates that the data collected will aid in better understanding these AEs and can lead to more effective management and prevention strategies. Of note, in addition, FDA will require enhanced pharmacovigilance for secondary malignancies.

6.2 Safety-related Postmarketing Studies

Postmarketing Study (AUTO1-LT2)

The sponsor submitted a protocol synopsis for study AUTO1-LT2 entitled “Prospective, international, non-interventional study to assess long-term safety and effectiveness of adult patients with relapsed or refractory B-cell acute lymphoblastic leukemia receiving Aucatzyl® treatment.” The study objectives are as follows:

Primary objective:

- To characterize the long-term safety of Aucatzyl, including secondary malignancies

Secondary objectives:

Safety assessments:

- To determine the causes of death after Aucatzyl administration
- To evaluate rate of complications, secondary malignancies, CRS, ICANS, and serious infections post-Aucatzyl treatment
- To evaluate pregnancy outcomes

Effectiveness assessments:

- To evaluate the effectiveness of Aucatzyl in terms of overall response rate (ORR)
- To determine the duration of response (DoR) post-Aucatzyl administration
- To determine the event-free survival (EFS) post-Aucatzyl treatment
- To determine the overall survival (OS) post-Aucatzyl treatment
- Incidence and outcomes after subsequent allogeneic stem cell transplantation

The study will use secondary data available in established registries and will collect data from 500 adults diagnosed with r/r B ALL and treated with Aucatzyl in the global postmarketing setting. Individuals who received product within approved product specifications or out of specification but released at physician request will be eligible. The study will include a minimum 5-year recruitment period followed by a 15-year follow-up period. If a secondary malignancy is suspected, the sponsor “should be contacted to obtain instructions on collection and transfer of tumor tissue sample for testing in a separate process of this non-interventional study.” The study will use descriptive statistics for categorical and continuous variables and Kaplan-Meier curves to illustrate time-to-event data. The sponsor will receive quarterly safety data from the registries for the first 3-years and then annually thereafter. The sponsor “will provide a yearly report to the Health Authorities.”

The sponsor proposed the following key study milestones:

- FDA approval of study protocol: approximately 1-2 months after approval
- EMA/PRAC approval of study protocol: approximately 9 months after EC approval
- UK approval of study protocol: approximately 9 months after MHRA approval
- Protocol registration EU PAS registry: 2-weeks after PRAC approval
- Start of data collection: U.S. and Europe 2025, UK 2026
- End of data collection: 2046/47
- Study duration: approximately 20 years

Reviewer comment: An AUTO1-LT2 protocol synopsis was submitted with the IR response to DPV IR #3 (STN 125813/0.12). Please see a summary of IRs and IR responses below, which include revised study milestone dates.

As required by regulations under Section 901 of the Food and Drug Administration Amendments Act (FDAAA) and as described in CBER SOPP 8415: Procedures for Developing Postmarketing Requirements and Commitments, a Sentinel sufficiency assessment was conducted to determine the sufficiency (i.e., capability) of the CBER Sentinel program to identify a serious risk of secondary malignancy associated with the use of obecabtagene autoleucel. The CBER Biologics Effectiveness and Safety (BEST)

Program is not sufficient to identify the serious risk of secondary malignancy since 15 years of follow-up, and collection of clinical samples and laboratory testing is needed; this is not feasible in available databases.

Sentinel insufficiency serves as a justification for requiring a safety-related postmarketing study under Section 901, Title IX of FDAAA. Therefore, the sponsor will be required to conduct a PMR safety study under FDAAA Title IX to identify the serious risk of secondary malignancy after treatment with obe-cel. The PMR will be conducted for 15 years in accordance with the FDA Guidance for Industry: Long Term Follow-Up After Administration of Human Gene Therapy Products (January 2020).

OBPV/DPV presented the PMR to the CBER SWG on July 25, 2024 and received SWG concurrence for requiring a PMR safety study to assess the serious risk of secondary malignancy following administration of obe-cel. The sponsor was notified on September 16, 2024 that the registry study will be a PMR. The sponsor was asked to submit interim summaries on the status of study AUTO1-LT2 in their periodic safety update reports (see DPV IR #5 summarized below).

Long-Term Follow-Up Study for Clinical Trial Participants (Study AUTO-LT1)

The sponsor provided a study synopsis for an ongoing LTFU study in clinical trial participants who received autologous T cells genetically modified with viral vectors to express CARs. The primary study objective is to monitor the long-term safety of the investigational product, including the incidence of treatment-related SAEs, new malignancies, and other AESIs. Secondary objectives are to monitor survival, B-cell/T-cell aplasia, clinical efficacy, CAR transgene persistence, emergence of replication competent retroviruses (RCR) or RCL, and the risk of insertional mutagenesis. If a new malignancy occurs, insertion site analysis (ISA) will be performed to determine if insertional mutagenesis could have been a potential cause or contributor to the new malignancy. Assessment of CAR transgene persistence will include the proportion of individuals with detectable vector copy number in peripheral blood for up to 15 years following the first AUTO CAR T cell therapy infusion. The study will include up to 500 individuals with up to 15 years of follow-up. Safety monitoring will occur every 3 months for the first year, every 6 months for the next 4 years, and then annually for the following 10 years.

Reviewer comment: *OBPV defers to OTP for review of this LTFU study (AUTO-LT1) for clinical trial participants.*

The following IRs were sent regarding the sponsor's PVP, including the sponsor's proposed postmarketing LTFU study and REMS:

DPV IR #1

We note that the Pharmacovigilance Plan (PVP) for obe-cel was submitted in Module 1.16.2.2 Draft REMS. Please submit the PVP under Module 1.16.1 Risk Management (Non-REMS).

Reviewer comment: The sponsor's IR response STN 125813/0.3 (sequence 0004) included submission of the PVP under Module 1.16.1 (Non-REMS) as requested.

DPV IR #2

We are reviewing your BLA submission for obecabtagene autoleucel (obe-cel; BLA 125813/0) and have the following information request (IR) regarding your proposed Risk Evaluation and Mitigation Strategy (REMS).

1. REMS Goal #3 in the proposed REMS Document states, "Ensuring patient safety through FACT institutional quality and educational programs for healthcare providers (HCPs) on the management of the risks of CRS and ICANS and training specific to AUCATZYL's unique product characteristics." Please provide example screenshots of FACT training on the identification and management of adverse events following CAR T cell product administration, including for cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS).

*Reviewer comment: The sponsor's IR response (STN 125813/0.10, sequence 0012) revised the wording for REMS Goal #3 clarify "Ensuring patient safety through FACT-**required** institutional quality and educational programs..." The IR response reiterated that "obe-cel will only be available through the Aucatzyl REMS program via a controlled distribution system at treatment centers that are accredited under the FACT-JACIE standards with Immune Effector Cellular (ICE) capabilities" and provided information about FACT accreditation and education requirements, including a copy of the Hematopoietic Cellular Therapy Accreditation Manual (Eighth Edition 8.2). The IR response also reiterated the obe-cel specific training and tools included in the proposed REMS.*

DPV IR #3

We are reviewing your BLA submission for obecabtagene autoleucel (obe-cel; BLA 125813/0) and have the following comments and questions regarding your proposed Pharmacovigilance Plan (PVP).

1. The PVP includes Study AUTO-LT1, an ongoing long-term follow-up (LTFU) study to assess the incidence of serious adverse events related to AUTO CAR T-cell therapy, including new malignancies, in individuals who received the CAR T-cell therapy in clinical trials. In your PVP, please include your proposed protocol synopsis for a postmarketing observational study for 15-year follow up of patients who would receive the commercial product in the postmarketing setting, should this product be approved. Please see FDA Guidance *Long Term Follow-up After Administration of Human Gene Therapy Products* (2020) available at <https://www.fda.gov/media/113768/download>. The safety outcomes for the 15-year postmarketing study should include assessment of the long-term safety of obe-cel, including the occurrence of secondary malignancies, in individuals who would receive the product in the postmarket setting, should the BLA be approved.

2. We note that "Secondary malignancy" is listed as an important potential risk in the PVP. If a patient develops a secondary malignancy in the postmarket setting, please describe your plans for collection and testing of clinical specimens (e.g., whole blood, bone marrow, and/or tissue biopsy of tumor and non-tumor) for vector copy number, presence of CAR transgene, and integration site analysis (ISA) to assess for possible insertional oncogenesis and to evaluate the potential causal role of obe-cel. Also, please describe your plans for testing for replication competent lentivirus (RCL) in the postmarket setting, should this BLA be approved.
3. The PVP lists "gene vector related risks" as an important potential risk. Please clarify and describe what is meant by "gene vector related risks." Please specify if gene vector related risks include the potential risks of insertional oncogenesis and/or generation of RCL. Please describe your plans for long term monitoring for gene vector related risks in the postmarket setting, should this BLA be approved.
4. In the PVP, Section 4 "Summary of Safety Concerns and Planned Pharmacovigilance Activities," please clarify and provide details for what is meant by "Long term follow up scheme for patients treated with Aucatzyl."
5. We note that the Summary of Clinical Safety (page 48) indicates that the occurrence of graft versus host disease (GvHD) may be an "expected consequence" of obe-cel in individuals who have had prior allogeneic stem cell transplant (SCT). The draft USPI also lists GvHD as an adverse reaction. Please provide rationale for why GvHD is considered an important potential risk rather than an important identified risk in the PVP.
6. The PVP lists antigenicity and immunogenicity as an important potential risk but does not provide details regarding this safety concern and/or specific adverse events that will be monitored. The Summary of Clinical Safety (page 49) indicates that three patients had a positive immunogenicity test at approximately 3-months after obe-cel infusion and that all three patients achieved CR, all experienced CRS (<Grade 3), and one patient experienced ICANS (Grade 3). The Summary of Clinical Safety indicates that these safety events were unlikely related to a cellular immunogenicity signal. Please describe the potential safety concerns regarding antigenicity and immunogenicity and adverse events that will be monitored in the postmarket setting, should this BLA be approved.
7. The PVP lists Study AUTO-PY1 as an "ongoing long-term safety extension." Please clarify if the LTFU of participants from clinical study AUTO-PY1 is being conducted as part of the interventional clinical study protocol or under a separate LTFU study protocol.

Reviewer comment: The sponsor's IR response (STN 125813/0.12) included a protocol synopsis for study AUTO1-LT2, a prospective, non-interventional study to assess the long-term safety and efficacy of obe-cel in individuals treated in the postmarket setting. The IR response also indicated that if a secondary malignancy occurs, the sponsor will "recommend to the reporting physician to request consent from the patient to collect blood, bone marrow and/or tumor and non-tumor samples to enable testing for replication competent lentivirus (RCL), vector copy number (VCN), CAR T cell persistence and integration site analysis (ISA)"; results will be reported to the Agency.

In addition, the IR response clarified that “gene vector-related risks” include the important potential risks of insertional oncogenesis and generation of RCL. The sponsor will monitor for gene vector-related risks in the postmarket setting through routine PV activities and, if a secondary malignancy develops, the USPI includes information for reporting and obtaining instructions for sample collection. The IR response further clarified that the “long term follow up scheme” listed in the PVP refers to the LTFU postmarketing study AUTO1-LT2.

Furthermore, the IR response indicated that GvHD is included as an important potential risk rather than an important identified risk “because although it met criteria of an ADR, the pathology of GvHD, including severe events post infusion is not clearly understood in patients who receive previous SCT.” For the important potential risk of antigenicity and immunogenicity, the IR response indicated that the CAT binding domain of obe-cel is derived from a murine sequence and could result in the development of antibodies, which could cause safety issues such as CRS or autoimmune reactions. The sponsor will closely monitor for AE reports of autoimmune reactions, CRS, and ICANS in the postmarket setting to “assess and further characterize the risks of antigenicity and immunogenicity.”

Finally, the IR response clarified that pediatric patients who complete study AUTO-PY1 will be asked for consent to enroll into a separate LTFU study, AUTO-LT1 (up to 15-year follow-up). The sponsor also submitted a revised PVP (dated January 2024) reflecting the information above.

DPV IR #4

We are reviewing the protocol synopsis for your proposed long-term follow-up postmarket study AUTO1-LT2, submitted to BLA 125813/0.12 (received January 25, 2024), and have the following comments and requests:

1. The protocol synopsis indicates “the study will use secondary data available in established registries.” Please specify which registries you are considering for use in study AUTO1-LT2.
2. We note the study will include individuals who receive out-of-specification product. Please perform separate analyses and reporting for the population who receives out-of-specification product.
3. Analysis of reports of secondary malignancies have raised concerns regarding an association between CAR-T cell products and insertional oncogenesis, particularly with respect to T cell malignancies. There appear to be significant challenges in obtaining appropriate samples and variability in approaches to performing molecular analyses to assess the risk of insertional oncogenesis following administration of CAR T cell products. Please provide a copy of the testing algorithm that will be used to assess any reports of secondary malignancy following administration of Aucatzyl in the postmarket setting, if the BLA is approved.

4. We note that you plan to include a minimum 5-year recruitment period for study AUTO1-LT2 and anticipate the end of data collection in 2046/47. Please consider if earlier study milestone dates are possible.
5. Please provide the following study milestones in mm/dd/yyyy format for study AUTO1-LT2:
 - Final protocol submission: Month, day, 20XX
 - Study completion date: Month, day, 20XX
 - Final study report (FSR) submission: Month, day, 20XX

Reviewer comment: The sponsor's IR response (STN 125813/0.20, sequence 0021) indicated that they have started collaborations with the Center for International Blood and Marrow Transplant (CIBMTR) and the European Society for Blood and Marrow Transplantation (EBMT) registries to collect secondary data. The sponsor acknowledged the request that analysis and reporting for the population that receives out-of-specification product be performed separately and confirmed that analysis and reporting for the out-of-specification population will be reflected in the protocol and statistical analysis plan. The sponsor also provided a draft algorithm to assess and report secondary malignancies, which was shared with OTP CMC and clinical for their review and comments. OBPV defers to OTP on the acceptability of the sponsor's proposed draft algorithm for testing of secondary malignancies. Finally, the sponsor shortened the postmarket study recruitment period from 5-years to 4-years and provided the following revised tentative study milestone dates:

- *Final protocol submission: December 16, 2024*
- *Study completion date: June 30, 2044*
- *Final study report: June 30, 2045*

DPV IR #5

We are reviewing the pharmacovigilance plan (PVP), postmarketing long-term follow-up (LTFU) registry study protocol synopsis, and draft secondary malignancy testing algorithm for obe-cel (BLA 125813/0) and have the following questions and comments/recommendations:

Pharmacovigilance Plan (PVP)

1. Please revise the important identified risk of immune effector cell-associated neurotoxicity syndrome (ICANS) to the broader category of neurologic toxicities, which includes ICANS and other neurologic toxicities. This terminology aligns with class risks for this product class.
2. Should obe-cel be approved, you are required to perform enhanced pharmacovigilance as follows:
 - a. Secondary malignancies: (i) Submit expedited (15-day) reports to FAERS for events of secondary malignancy, regardless of seriousness or labeled status. (ii) In your periodic safety reports, provide aggregate safety assessments (based on interval and cumulative postmarketing safety

data) for the risk of all secondary malignancies, and specifically for T cell malignancies. In your assessments, specify the data sources for reports of secondary T cell malignancy, i.e., clinical trial data, or data from postmarketing safety study(ies), or data from postmarketing spontaneous reports.

- b. Overdose/medication dosing errors: For 3 years post-licensure, in your quarterly periodic safety reports, provide aggregate safety assessments (based on interval and cumulative postmarketing safety data) for the risk of overdose/dosing errors.

Postmarketing Long-Term Follow-up (LTFU) Registry Study

1. Please comment if the postmarketing LTFU registry study (AUTO1-LT2) will include assessment of tumor lysis syndrome (TLS) and hypersensitivity reactions.
2. Please include assessment of neurologic toxicities, including ICANS and other neurologic toxicities (e.g., parkinsonism, Guillain-Barré syndrome, immune mediated myelitis, peripheral neuropathies, cranial nerve palsies), rather than only ICANS, in the postmarketing LTFU registry study.
3. The PVP indicates that antigenicity and immunogenicity, gene vector related risks, pregnancy and lactation, and the new occurrence or exacerbation of an autoimmune disorder will be included in the postmarketing LTFU registry study. Please specify these safety outcomes in the full study protocol (anticipated to be submitted December 16, 2024).
4. Please specify in the full study protocol that healthcare providers and sites participating in the postmarketing LTFU registry study will be required to notify the sponsor of any new malignancies within 72-hours of awareness in order to facilitate sample collection and testing.
5. In periodic safety update reports, please include interim summaries on the status of the postmarketing LTFU registry study, including total number of individuals enrolled in the study, a summary of cases of any secondary malignancies (including demographic and clinical summaries, progress in sample collection, and results from sample testing), and any other potential or confirmed safety findings.
6. Please include the above revisions in the full study protocol for the postmarketing LTFU registry study, which is to be submitted following approval, if BLA 125813/0 is approved.

Secondary Malignancy Testing Algorithm

We are reviewing your response to Information Request (IR) Epidemiology #4 for obe-cel (BLA 125813/0.20, IR response dated February 22, 2024) and have the following questions and comments regarding the draft algorithm to assess and report secondary malignancies (i.e., response to IR Question #3):

1. Please confirm that the sample collected with the sample collection kit will be from representative malignant tissue. For example, if the malignancy is leukemia, the sample should be from the bone marrow.

2. Please provide additional details on what “insertional mutagenesis testing” will be performed. Will this be (b) (4) [REDACTED] or some other type of integration site analysis (ISA)?
3. For ISA, it is important to know how clonal frequencies change over time. If a case of secondary malignancy with an abnormally clonal population occurs, we recommend repeated testing.
4. To optimize the ability to obtain patient consent for sample collection of secondary malignancies, we recommend an approach where patients are consented for testing of secondary malignancies when they first receive the therapy. If a secondary malignancy occurs, then patients would be reconsented again at that time.

Reviewer comment: The sponsor’s IR response (STN 125813/0.34, sequence 0035) acknowledged CBER’s requests and revised the PVP important identified risk of ICANS to include the broader category of neurologic toxicities. The sponsor also agreed to perform enhanced PV activities for secondary malignancies and overdose/medication dosing errors.

For the postmarketing LTFU registry study, the sponsor indicated they are working with the CIBMTR and EBMT registries to ascertain that data on TLS and hypersensitivity reactions are collected from the U.S. and Europe, respectively. In addition, the study will include assessment of neurologic toxicities, including but not limited to ICANS, and the sponsor confirmed ongoing discussions with the registries to ensure that data on antigenicity and immunogenicity, gene vector related risks, pregnancy and lactation, and the new occurrence or exacerbation of autoimmune disorders will be collected. The sponsor also acknowledged CBER’s request for the full study protocol to specify that healthcare providers and sites participating in the registry study will be required to notify the sponsor of any new malignancies within 72 hours of awareness in order to facilitate sample collection and testing. Furthermore, the sponsor confirmed that interim summaries of the postmarketing registry study will be included in periodic safety update reports and that the above requested revisions will be included in the full study protocol, which is to be submitted following approval, if BLA 125813/0 is approved.

For the draft secondary malignancy testing algorithm, the sponsor confirmed that samples collected for secondary malignancy testing will be from the representative malignant tissue. Insertional mutagenesis testing will be performed by a third-party vendor; the sponsor is working to select a vendor and then will make a final determination on the testing methodology. In addition, the sponsor clarified that individuals who did not consent to sample collection and ISA testing when they first received therapy would be asked for consent again if a secondary malignancy occurs. A revised draft secondary malignancy testing algorithm was provided in the sponsor’s IR response that included the additional consent process. Finally, in a follow-up IR response (STN 125813/0.36, sequence 0037) the sponsor indicated their plans to select a third-party vendor by the end of August 2024; they will then make a final determination

on ISA testing methodology and submit an updated secondary malignancy testing algorithm to FDA.

The sponsor submitted an updated secondary malignancy testing algorithm (STN 125813/0.53) that indicated they will contract with (b) (4) using (b) (4) for ISA testing. OBPV defers to OTP clinical and CMC for acceptability of the sponsor's ISA testing plans.

DPV IR #6

We acknowledge your proposal to revise the Pharmacovigilance Plan (PVP) for obe-cel, submitted under BLA 125813/0, to modify the important potential risk of "GvHD" to "Aggravation of GvHD." Please submit details on your assessment of the new findings for GvHD and the data that support your conclusions. In addition, include your proposed labeling changes to the Highlights and Sections 5 and 6 of the USPI.

Reviewer comment: The sponsor's IR response (STN 125813/0.45) provided their assessment and rationale for modifying the important potential risk of "GvHD" to "Aggravation of GvHD"; the sponsor provided a revised PVP and proposed labeling changes. OBPV/DPV defers to OTP for review of the sponsor's proposed labeling changes and clinical assessment of GvHD versus aggravation of GvHD.

DPV IR #7

As communicated during the late-cycle meeting for obe-cel BLA 125813/0, we have determined that a Risk Evaluation and Mitigation Strategy (REMS) will not be required. Please submit a revised Pharmacovigilance Plan (track change and clean versions) that removes references to the REMS.

Reviewer comment: The sponsor submitted a revised PVP that removed references to the REMS, as requested (STN 125813/0.50).

6.3 Risk Evaluation and Mitigation Strategy (REMS)

During 2017 – 2022, FDA approved the following BCMA- or CD19-directed autologous CAR T cell immunotherapy products (listed alphabetically by trade name):

- Abecma
- Breyanzi
- Carvykti
- Kymriah
- Tecartus
- Yescarta

In addition to class labeling for CRS and neurological toxicities which are included in the boxed warnings, the initial approvals for the above products had included REMS programs to mitigate the risks of CRS and neurological toxicities. During March – June

2024, on the basis of the cumulative aggregate postmarketing data for the product class and availability of non-REMS educational materials, FDA approved class modifications for CAR T cell product REMS programs to minimize burden on the healthcare delivery system by removing requirements for educational and training materials. Following approvals of these modifications, the goal of the current REMS is to mitigate the risks of CRS and neurological toxicities by ensuring that hospitals and their associated clinics that dispense the above products are specially certified and have on-site, immediate access to tocilizumab (please see Risk Evaluation and Mitigation Strategies (REMS) for Autologous Chimeric Antigen Receptor (CAR) T cell Immunotherapies Modified to Minimize Burden on Healthcare Delivery System). The currently approved REMS are available at REMS@FDA.

Section 505-1 of the Federal Food, Drug, and Cosmetic Act authorizes FDA to require a REMS if FDA determines that such a strategy is necessary to ensure that the benefits of the product outweigh the risks. Given the risks for CRS and neurological toxicities across the product class (see Table 3), and in keeping in alignment with the regulatory approach for this product class, OBPV/DPV recommended a REMS for Aucatzyl (obe-cel) to ensure that hospitals and their associated clinics that dispense Aucatzyl are specially certified and have on-site, immediate access to tocilizumab.

Table 3: An overview of CRS and neurological toxicities for the currently approved CAR T cell products and obe-cel[~]

	Abecma (idecabtagene vicleucel)	Breyanzi (lisocabtagene maraleucel)	Carvykti (ciltacabtagene autoleucel)	Kymriah (tisagenlecleucel)	Tecartus (brexucabtagene autoleucel)	Yescarta (axicabtagene ciloleucel)	Obe-cel (obecabtagene autoleucel)
	n=127	n=268	n=97	n=79	n=82	n=422	n=107
CRS (all grades)	85%	46%	95%	77%	91%	90%	74%
CRS (grade 3+)	9%*	4.1%*	5%*	48%	18%	9%	2.8%
Neurotoxicity (all grades)	28%	35%	26%	71%	81%	78%	65%

[~]Note: Some labels had multiple different estimates based on different patient populations studied. These are the first estimates presented in Warnings and Precautions. Labels varied on reporting of tocilizumab use and rates of ICANS.

*Includes a fatal case of CRS

The OTP clinical team's recommendation was that a REMS was not necessary to ensure the benefits of Aucatzyl outweigh its risks. DPV defers to the OTP clinical team for overall benefit/risk assessment, and the final determination of the necessity of a REMS for Aucatzyl (please see OTP clinical review memorandum). The applicant was notified during the late cycle meeting that a REMS would not be required for Aucatzyl. The applicant's proposed REMS will not be reviewed in light of OTP's determination that a REMS is not necessary for Aucatzyl. The applicant subsequently submitted a revised PVP that removed references to REMS.

7 ANALYSIS OF SPONSOR'S PHARMACOVIGILANCE PLAN

7.1 Important Identified Risks

7.1.1 Cytokine Release Syndrome

CRS is known to be associated with CAR T cell therapies and is a diagnosis of exclusion; there are no definitive diagnostic imaging or laboratory tests. CRS can cause fatal or life-threatening reactions; symptoms include fever, hypotension, tachycardia, hypoxia, and chills. CRS occurred in the majority (n=87, 68.5%) of participants in Study AUTO-AL1 (pivotal study); CRS Grade 3 occurred in three (2.4%) participants (no Grade 4 or 5 CRS events). CRS was generally manageable with tocilizumab and steroids.

The important identified risk of CRS, which can be fatal or life-threatening, will be monitored through a PMR LTFU registry study for recipients in the postmarketing setting and routine pharmacovigilance activities. This safety concern is labeled in the following sections of the USPI:

- Boxed Warning: Cytokine Release Syndrome and Neurologic Toxicities
- Section 2.4, Management of Severe Adverse Reactions: Cytokine Release Syndrome
- Section 5.1, Warnings and Precautions: Cytokine Release Syndrome
- Section 6.1, Clinical Trials Experience
- Section 17, Patient Counseling Information

Reviewer comment: The proposed PVP is appropriate to monitor the risk of CRS.

7.1.2 Neurologic Toxicities

Neurologic toxicities, including ICANS, are known to be associated with CAR T cell therapies and can be severe or life-threatening. ICANS is a diagnosis of exclusion and can occur as CRS is resolving, after CRS resolution, or in the absence of CRS. ICANS occurred in 29 (22.8%) participants in Study AUTO-AL1 (pivotal study); ICANS Grade ≥ 3 occurred in nine (7.1%) participants. One participant experienced Grade 4 ICANS following the second dose of obe-cel after having experienced Grade 1 ICANS after the first dose. Another participant experienced Grade 5 ICANS following the second dose after having experienced Grade 1 ICANS after the first dose; this individual died due to ARDS with ongoing ICANS.

The important identified risk of neurologic toxicities, including ICANS, which can be fatal or life-threatening, will be monitored through a PMR LTFU registry study for recipients in the postmarketing setting and routine pharmacovigilance activities. This safety concern is labeled in the following sections of the USPI:

- Boxed Warning: Cytokine Release Syndrome and Neurologic Toxicities
- Section 2.4, Management of Severe Adverse Reactions: Neurologic Toxicities
- Section 5.2, Warnings and Precautions: Neurologic Toxicities
- Section 5.10, Warnings and Precautions: Effect on Ability to Drive and Use Machines

- Section 6.1, Clinical Trials Experience
- Section 17, Patient Counseling Information

Reviewer comment: The proposed PVP is appropriate to monitor the risk of neurologic toxicities, including ICANS.

7.1.3 Prolonged Cytopenias

Cytopenia is expected to occur in patients with B cell ALL receiving lymphodepleting chemotherapy with fludarabine and cyclophosphamide and CAR T cell therapy. The sponsor assessed recovery of cytopenia post-obe-cel infusion among those who achieved remission in AUTO-AL1 and reported progressively lower percentages of participants with Grade 3 or 4 neutropenia or thrombocytopenia over time: 69.4% at Day 28, 32.7% at Month 2, and 20.4% at Month 3. Among participants who achieved remission, none were reported to have neutropenia $<1 \times 10^9/L$ that lasted >6 months. Seven participants had thrombocytopenia $<100 \times 10^9/L$ that lasted for >6 months; no bleeding events were reported for these seven participants.

The important identified risk of prolonged cytopenia will be monitored through a PMR LTFU registry study for recipients in the postmarketing setting, a LTFU safety study for clinical trial subjects, and routine pharmacovigilance activities. This safety concern is labeled in the following sections of the USPI:

- Section 5.3, Warnings and Precautions: Prolonged Cytopenias
- Section 6, Adverse Reactions
- Section 17, Patient Counseling Information

Reviewer comment: The proposed PVP is appropriate to monitor the risk of prolonged cytopenia.

7.1.4 Haemophagocytic Lymphohistiocytosis/Macrophage Activation Syndrome (HLH/MAS)

HLH/MAS has been observed in association with approved CAR T cell therapies and can be life-threatening. Two (1.6%) participants experienced HLH/MAS in Study AUTO-AL1; both cases of HLH/MAS were Grade ≥ 3 (one Grade 3 event that began on Day 22 with recovery prior to the individual's death from progressive disease on Day 351 and one Grade 4 event that began on Day 41 and was ongoing when the individual died due to sepsis on Day 60).

The important identified risk of HLH/MAS will be monitored through a PMR LTFU registry study for recipients in the postmarketing setting, and routine pharmacovigilance activities. This safety concern is labeled in the following sections of the USPI:

- Section 5.6, Warnings and Precautions: Hemophagocytic Lymphohistiocytosis/Macrophage Activation Syndrome
- Section 6.1, Clinical Trials Experience

Reviewer comment: The proposed PVP is appropriate to monitor the risk of HLH/MAS.

7.1.5 Hypogammaglobulinemia

Hypogammaglobulinemia is an on-target pharmacodynamic effect that is anticipated due to the obe-cel mechanism of action (i.e., obe-cel's targeting of CD19 which is expressed on cancer and normal B cells). Hypogammaglobulinemia was experienced by 10 (7.9%) of participants in AUTO-AL1; one (0.8%) individual experienced a Grade 3 event on Day 707.

The important identified risk of hypogammaglobulinemia will be monitored through a PMR LTFU registry study for recipients in the postmarketing setting, a LTFU safety study for clinical trial subjects, and routine pharmacovigilance activities. This safety concern is labeled in the following sections of the USPI:

- Section 5.5, Warnings and Precautions: Hypogammaglobulinemia
- Section 6.1, Clinical Trials Experience

Reviewer comment: The proposed PVP is appropriate to monitor the risk of hypogammaglobulinemia.

7.1.6 Severe Infections

Many subjects who received obe-cel in clinical trials had risk factors for infection, including hypogammaglobulinemia and cytopenia. Most participants in Study AUTO-AL1 experienced infections (n=92, 72.4%), including 55 (43.3%) participants with Grade ≥ 3 infections. Five (3.9%) participants died with infections, including sepsis (n=2), neutropenic sepsis (n=2), and abdominal infection (n=1).

The important identified risk of severe infections, which can be fatal or life-threatening, will be monitored through a PMR LTFU registry study for recipients in the postmarketing setting, a LTFU safety study for clinical trial subjects, and routine pharmacovigilance activities. This safety concern is labeled in the following sections of the USPI:

- Section 5.4, Warnings and Precautions: Severe Infections
- Section 6.1, Clinical Trials Experience
- Section 17, Patient Counseling Information

Reviewer comment: The proposed PVP is appropriate to monitor the risk of severe infections.

7.2 Important Potential Risks

7.2.1 Tumor Lysis Syndrome

TLS occurs when cancer cells die rapidly and release large amounts of potassium, phosphate, and uric acid into the blood, which can lead to cardiac conduction abnormalities, seizures, and acute kidney injury. One participant in Study AUTO-AL1 developed relapsed disease (observed on Day 134) and was treated with dexamethasone beginning on Day 144; this individual experienced TLS Grade 3 on Day 146 and died due to progressive disease on Day 149. The SCS indicates that the event of TLS in this individual occurred following new anti-cancer therapy and was considered

not related to obe-cel. The important identified risk of TLS will be monitored through routine pharmacovigilance activities.

Reviewer comment: The proposed PVP is appropriate to monitor the potential risk of TLS.

7.2.2 Antigenicity and Immunogenicity

The sponsor's SCS indicates that "since obe-cel is an autologous therapy, a high rate of immune reactions is not expected." The SCS also indicates that three study participants had positive immunogenicity tests at approximately 3 months post-obe-cel infusion; these three individuals all experienced CRS (<Grade 3) and one individual experienced ICANS Grade 3. The sponsor concluded that these events were "unlikely related to a cellular immunogenicity signal." The important potential risk of antigenicity and immunogenicity will be monitored through a PMR LTFU registry study for recipients in the postmarketing setting, a LTFU safety study for clinical trial subjects, and routine pharmacovigilance activities. This potential safety concern is labeled in the USPI Section 6.2, Immunogenicity.

Reviewer comment: OBPV defers to OTP for review of cellular and humoral immunogenicity data submitted by the sponsor. The proposed PVP is appropriate to monitor the potential risk of antigenicity and immunogenicity.

7.2.3 Aggravation of Graft versus Host Disease (GvHD)

GvHD was reported in seven (5.5%) clinical trial participants, including six participants who received SCT prior to obe-cel infusion and one participant who received SCT post-obe-cel treatment with subsequent GvHD. The important potential risk of aggravation of GvHD will be monitored through a PMR LTFU registry study for recipients in the postmarketing setting, a LTFU safety study for clinical trial subjects, and routine pharmacovigilance activities. This potential safety concern is labeled in the USPI Section 6.1, Clinical Trials Experience.

Reviewer comment: The proposed PVP is appropriate to monitor the potential risk of aggravation of GvHD.

7.2.4 Secondary Malignancy

Currently approved CAR T cell therapies have Boxed Warnings and Warnings and Precautions for the risk of secondary malignancies. The sponsor indicates there were no patients identified with secondary malignancies due to insertional mutagenesis and/or RCL. There was one case of AML post-obe-cel infusion in a 58-year-old female with a history of breast cancer and suspected ongoing MDS; the sponsor reported that "bone marrow findings were consistent with secondary, treatment-related AML with monocytic differentiation post breast cancer treatment in 2019." This individual died on Day 45 due to encephalopathy caused by AML; the investigator and sponsor assessed the event as not related to obe-cel. In addition, a 67-year-old female experienced basal cell carcinoma of the skin on Day 513 post-obe-cel infusion which was assessed by the investigator and sponsor as not related to obe-cel.

The important potential risk of secondary malignancy will be monitored through a PMR LTFU registry study for recipients in the postmarketing setting, a LTFU safety study for clinical trial subjects, and routine pharmacovigilance. In addition, the sponsor will perform enhanced PV for secondary malignancies, which includes expedited (15-day) reporting of secondary malignancies (regardless of seriousness or label status) following licensure. The sponsor will also provide aggregate safety assessments of secondary malignancies, and specifically T cell malignancies, in periodic safety reports, including specifying the data sources for any reports of secondary T cell malignancies (i.e., clinical trial data, data from postmarketing safety studies, or data from postmarketing spontaneous reports). OBPV defers to OTP on the acceptability of the sponsor's proposed draft algorithm for testing of secondary malignancies. This potential safety concern is labeled in Warnings and Precautions: Secondary Malignancies.

Reviewer comment: The proposed PVP is appropriate to monitor the potential risk of secondary malignancy.

7.2.5 Gene vector-related risks

Obe-cel uses a lentiviral vector for T cell transduction. The important potential risk of gene vector-related risks, which includes insertional oncogenesis and RCL, will be monitored through a PMR LTFU registry study for recipients in the postmarketing setting, a LTFU safety study for clinical trial subjects, and routine pharmacovigilance. This potential safety concern is related to secondary malignancies which is labeled in Warnings and Precautions: Secondary Malignancies.

Reviewer comment: The proposed PVP is appropriate to monitor the potential risk of gene vector-related risks.

7.2.6 Hypersensitivity Reactions

The sponsor's draft USPI indicates that "serious hypersensitivity reactions, including anaphylaxis, may occur due to dimethyl sulfoxide (DMSO), an excipient used in AUCATZYL." No hypersensitivity reactions were reported in Study AUTO-AL1.

The important potential risk of hypersensitivity reactions will be monitored through routine pharmacovigilance activities. This potential safety concern is labeled in the USPI Section 5.8, Hypersensitivity reactions and Section 6, Adverse Reactions.

Reviewer comment: The proposed PVP is appropriate to monitor the potential risk of hypersensitivity reactions.

7.2.7 Overdose/Medication Errors

The product has a split dosing administration regimen which is different than other CAR T cell products; overdose/medication errors are a potential risk. The sponsor's SCS indicates that four clinical trial participants in Study AUTO-AL1 received a "meaningful higher first dose" than planned. No patients received a higher total target dose of CAR T-positive cells (410×10^6 CAR T-positive cells $\pm 25\%$). Among the four participants, two experienced CRS or ICANS \geq Grade 3 and did not receive their second dose. One of these two participants experienced SAEs including a Grade 3 SAE of ICANS from

Days 10 to 13, Days 18 to 21, and Days 38 to 60, a Grade 2 enterococcal bacteremia and Grade 4 SAE intra-abdominal hemorrhage on Day 28, a Grade 3 SAE of disseminated intravascular coagulation (DIC) on Day 30, a Grade 4 SAE of HLH on Day 41, a Grade 4 SAE of peritonitis on Day 59, and died on Day 60 due to a Grade 5 SAE of sepsis with ongoing HLH. The Grade 4 SAE of HLH was assessed as possibly related to obe-cel and probably related to preconditioning treatment by the study investigator and as possibly related to obe-cel by the sponsor. The fatal SAE of sepsis was assessed as unlikely related to obe-cel (probably related to preconditioning treatment) by the study investigator and as unrelated to obe-cel or preconditioning treatment by the sponsor. The other three participants who received a higher first dose than intended achieved remission following obe-cel administration.

The PVP indicates that the sponsor intends to further assess and characterize the risk of overdose of obe-cel. This safety concern is labeled in Section 10 Overdosage, which includes a statement that “in the event of a suspected overdose, any adverse reactions are to be treated in accordance with the *Management of Severe Adverse Reactions* (2.4).” In addition, the sponsor will perform enhanced PV for overdose/medication dosing errors (see IR response #5 above) including expedited reporting and summaries/assessments in periodic safety update reports.

Reviewer comment: The sponsor further commented during the Applicant Orientation Meeting held on January 5, 2024 that risk minimization measures for overdose/medication errors include labeling with detailed dosing guidance based on disease burden, a Release for Infusion Certificate (specified volume to be administered and number and type of bags required for each dose), color-coded labels for split dose infusion bags, a Dose Schedule Planner that will need two signatures to verify accuracy of the infused volume, and obe-cel specific training to FACT approved centers. In addition, OTP consulted CDER, Office of Surveillance and Epidemiology, Office of Medication Error Prevention and Risk Management, Division of Medication Error Prevention and Analysis (DMEPA) to evaluate the administration section of the proposed prescribing information and comment on whether a use-related risk analysis or human factors study was needed to identify, evaluate, and minimize the potential for medication errors. The DMEPA consult identified areas for improvement and proposed additional labeling recommendations; a human factors study was not recommended. Please see the clinical review memo for additional details on overdose/medication errors and FDA clinical assessment. The proposed PVP is appropriate to monitor the potential risk of overdose/medication dosing errors.

7.3 Important Missing Information

7.3.1 Pregnancy and Lactation

There is limited data on the use of obe-cel in pregnant individuals and a lack of information on use during lactation. The sponsor's proposed USPI indicates that obe-cel is not recommended for women who are pregnant, and that pregnancy status should be verified before treatment and should be negative. One participant in the AUTO1-AL1 study became pregnant 6-months following obe-cel infusion and was subsequently hospitalized with Grade 3 AEs of urinary tract infection, febrile neutropenia, and

pyelonephritis. On Day 430, at 30 weeks and 6 days gestation, she was hospitalized with Grade SAEs of amniotic cavity infection which led to preterm rupture of membranes and premature delivery via C-section. The male infant initially showed respiratory distress and was admitted to the neonatal ICU for intubation; he was subsequently discharged.

Missing information on the impact of obe-cel on pregnancy and lactation will be monitored through a PMR LTFU registry study for recipients in the postmarketing setting, a LTFU safety study for clinical trial subjects, and routine pharmacovigilance activities. This safety concern is labeled in Section 8, Use in Specific Populations, including Section 8.1 Pregnancy, Section 8.2 Lactation, and Section 8.3 Females and Males of Reproductive Potential.

Reviewer comment: The proposed PVP is appropriate to address missing information on the impact of obe-cel during on pregnancy and lactation.

7.3.2 Long-term Safety

The long-term safety of obe-cel is not known. The missing information on the long-term safety of obe-cel will be monitored through a PMR LTFU registry study for recipients in the postmarketing setting, a LTFU safety study for clinical trial subjects, and routine pharmacovigilance activities.

Reviewer comment: The proposed PVP is appropriate to monitor for missing information on the long-term safety of obe-cel.

7.3.3 Safety in Children

The sponsor's proposed indication for obe-cel is for use in adults 18 years and older. There is limited data on the use of obe-cel in children. The sponsor's list of clinical studies indicates that pediatric patients are planned for study in clinical study AUTO1-PY1. The missing information regarding safety in children will be monitored through a LTFU safety study for clinical trial subjects and routine pharmacovigilance activities. This safety concern is labeled in Section 8, Use in Specific Populations (Section 8.4 Pediatric Use).

Reviewer comment: The proposed PVP is appropriate to monitor for missing information on the safety of obe-cel in children.

7.3.4 New occurrence or Exacerbation of an Autoimmune Disorder

Per the FDA Guidance for Industry: *Long-Term Follow-Up After Administration of Human Gene Therapy Products (January 2020)*, transgenes encoding immune recognition factors may introduce the risk for autoimmune-like reactions upon prolonged exposure. The sponsor's PVP indicates that the effect on development of new autoimmune disorders or worsening of an existing disorder is an area requiring confirmation or further investigation. Review of the sponsor's SCS, Clinical Overview, and draft USPI did not reveal safety concerns for the occurrence of autoimmune disorders. Missing information for the new occurrence or exacerbation of an autoimmune disorder will be monitored through a PMR LTFU registry study for

recipients in the postmarketing setting, a LTFU safety study for clinical trial subjects, and routine pharmacovigilance activities.

Reviewer comment: The proposed PVP is appropriate to monitor for missing information on the new occurrence or exacerbation of an autoimmune disorder following administration of obe-cel.

8 DPV ASSESSMENT

Based on review of available data, the safety concerns from the Phase I/II clinical trials warrant a FDAAA Title IX safety PMR registry study to assess the serious risk of secondary malignancy. In addition, risks of treatment with obe-cel will be mitigated through risk communication and risk minimization measures as recommended in the USPI, including a Boxed Warning for the risks of CRS and Neurologic Toxicities, and routine pharmacovigilance activities. The sponsor is also conducting a LTFU safety study for subjects treated with obe-cel in clinical trials, and if a new malignancy occurs, ISA will be performed to determine if insertional mutagenesis could have been a potential cause or contributor to the new malignancy. For the required postmarketing registry study and postmarketing use, the sponsor has proposed a testing algorithm for secondary malignancies to assess for insertional oncogenesis. Patients in the PMR registry study will be followed for 15 years post-obe-cel infusion.

9 DPV RECOMMENDATIONS

Should the product be approved for the treatment of adult patients 18 years of age or older with relapsed or refractory B cell precursor ALL, the proposed PVP (dated May 2024) is adequate to monitor the postmarketing safety for obe-cel (Aucatzyl) which will include:

1. Routine PV, which includes AE reporting in accordance with 21 CFR 600.80
2. Enhanced PV to require expedited (15-day) reporting of secondary malignancies (regardless of seriousness or label status) following licensure. The sponsor will also provide aggregate safety assessments of secondary malignancies, and specifically T cell malignancies, in periodic safety reports, including specifying the data sources for any reports of secondary T cell malignancies (i.e., clinical trial data, data from postmarketing safety studies, or data from postmarketing spontaneous reports). In addition, for 3-years post-licensure, the sponsor will provide aggregate safety assessments for the risk of overdose/medication dosing errors in their periodic safety reports. Furthermore, the sponsor will collect additional details for cases of CRS and neurologic toxicities using a Targeted Data Questionnaire.
3. Safety-related PMR study under 505 (o) of the FDCA: The review team and SWG have concurred with the following FDAAA Title IX PMR study:
 - a) A postmarketing, prospective, multi-center, 15-year LTFU observational safety study (AUTO1-LT2), to assess the long-

- term safety and serious risk of secondary malignancies following administration of obe-cel. This study will enroll 500 adult patients with relapsed or refractory B cell precursor ALL.
- b) The sponsor will provide interim summaries on the status of the postmarketing LTFU registry study (AUTO1-LT2) in periodic safety reports, including total number of individuals enrolled, a summary of cases of any secondary malignancies, and any other potential of confirmed safety signals.

Should the BLA be approved, the PMR protocol AUTO1-LT2 design and data analysis plan will be finalized with the sponsor post-licensure. The sponsor also submitted a draft testing algorithm to assess for insertional oncogenesis for cases of secondary malignancies; OBPV defers to OTP on the acceptability of the sponsor's proposed draft algorithm for testing of secondary malignancies.

In addition to the above PMR, the sponsor is also conducting an ongoing LTFU study (AUTO-LT1) to evaluate the long-term safety and efficacy of obe-cel in individuals with B cell ALL who received the investigational product in clinical trials. OBPV defers to OTP for review of Study AUTO-LT1.

At this time, there is no safety-related agreed upon postmarketing commitment (PMC) study. OTP made a determination that a REMS is not necessary for Aucatzyl. Please see the final version of the package insert submitted by the sponsor for the final agreed-upon content and language.

REFERENCES

Advani, AS and Aster JC. Clinical manifestations, pathologic features, and diagnosis of B cell acute lymphoblastic leukemia/lymphoma. Available at: [Clinical manifestations, pathologic features, and diagnosis of B cell acute lymphoblastic leukemia/lymphoma - UpToDate](#). Accessed on December 5, 2023.

APPENDIX

Materials Reviewed

Table A1: Materials reviewed in support of this assessment

Date	Source	Document Type	Document(s) Reviewed
November 17, 2023	Sponsor	STN 125813/0	Module 1.16, Pharmacovigilance Plan
November 17, 2023	Sponsor	STN 125813/0	Module 1.14 Draft Labeling Text
November 17, 2023	Sponsor	STN 125813/0	Module 2.5 Clinical Overview
November 17, 2023	Sponsor	STN 125813/0	Module 2.7.4 Summary of Clinical Safety
December 15, 2023	Sponsor	STN 125813/0.2 (sequence 0003)	Module 5.3 Safety Update Report – Day 30
December 15, 2023	Sponsor	STN 125813/0.3 (sequence 0004)	Module 1.2 and 1.16.1, Response to PV IR #1, submission of PVP under eCTD Module 1.16.1 Risk Management (Non-REMS)
January 16, 2024	Sponsor	STN 125813/0.10 (sequence 0012)	Module 1.11.3, Response to PV IR #2, request for submission of example FACT training
January 25, 2024	Sponsor	STN 125813/0.12 (sequence 0013)	Module 1.11.3, Response to PV IR #3, questions regarding plans for LTFU in postmarket setting and PVP Module 1.16.1 Revised PVP; LTFU postmarket protocol study synopsis
February 22, 2024	Sponsor	STN 125813/0.20 (sequence 0021)	Module 1.11.3 Response to PV IR #4, questions regarding protocol synopsis for proposed LTFU postmarket study AUTO-LT2
May 13, 2024	Sponsor	STN 125813/0.34 (sequence 0035)	Module 1.11.3 Response to PV IR #5, questions/comments regarding PVP, postmarket LTFU registry study, and secondary malignancy testing algorithm Module 1.16.1 Revised PVP and LTFU postmarket study protocol synopsis

Date	Source	Document Type	Document(s) Reviewed
May 17, 2024	Sponsor	STN 125813/0.36 (sequence 0037)	Module 1.11.3 Follow-up Response to PV IR #5, questions regarding secondary malignancy testing algorithm
July 30, 2024	Sponsor	STN 125813/0.45 (sequence 0046)	Module 1.11.3 Response to PV IR #6, comments regarding sponsor's proposal to modify the PVP for the potential risk of aggravation of GvHD Module 1.16.1 Revised PVP
August 9, 2024	Sponsor	STN 125813/0.50 (sequence 0050)	Module 1.11.3 Response to PV IR #7, request for revised PVP to reflect that a REMS will not be required Module 1.16.1 Revised PVP
August 14, 2024	Sponsor	STN 125813/0.53 (sequence 0053)	Module 1.11.3 Follow-up to PV IR #5, updated secondary malignancy testing algorithm