

I concur with this review memo. A. Wensky. 10/25/2024

**FOOD AND DRUG ADMINISTRATION
Center for Biologics Evaluation and Research
Office of Therapeutic Products
Office of Pharmacology/Toxicology**

BLA NUMBER: STN #125813.000

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PRODUCT: AUCATZYL™ (obecabtagene autoleucel; obe-cel; AUTO1; CAT19 CAR T cells) suspension for intravenous infusion

APPLICANT: Autolus, Inc.
PROPOSED INDICATION: AUCATZYL™ is indicated for the treatment of adults with relapsed or refractory B-cell precursor acute lymphoblastic leukemia (ALL)

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EXECUTIVE SUMMARY:

AUCATZYL™ (obecabtagene autoleucel; obe-cel; AUTO1; CAT19 CAR T cells) is a cell suspension consisting of autologous human CD4+ and CD8+ T cells transduced with a lentiviral vector encoding a chimeric antigen receptor (CAR) consisting of an anti-CD19 single-chain variable fragment (scFv), referred to as CAT19, linked to 4-1BB and CD3ζ T cell activating domains.

In vitro pharmacology studies compared the CAT19 CAR component of obecabtagene autoleucel (obe-cel) to a reference CD19 CAR (b) (4) CAR,¹ which is used in tisagenlecleucel and axicabtagene ciloleucel). 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. Binding kinetics of the scFv binding domain of CAT19 CAR demonstrated a weaker overall binding affinity to CD19, which is driven by a faster dissociation rate, than the scFv binding domain of (b) (4) CAR.

In vivo pharmacology studies demonstrated that a single intravenous administration of obe-cel at a dose level of 2.5×10^6 CAT19 CAR T cells/animal in a systemic human tumor xenograft mouse model resulted in significant reduction in tumor burden on Day 12 post administration. On Day 16, significantly increased numbers of circulating CAR T cells were present in mice administered obe-cel cells compared to (b) (4) CAR T cells.

The potential for off-target binding of the CD19-targeted CAT 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 cell binding to the CD19 CAR binding domains 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.

PHARMACOLOGY/TOXICOLOGY RECOMMENDATION:

There are no nonclinical deficiencies identified in this submission. There are no outstanding requests for additional nonclinical data for evaluation of obe-cel. The nonclinical information provided in the BLA submission supports approval of the licensure application.

Formulation and Chemistry:

AUCATZYL™ (obecabtagene autoleucel; obe-cel; AUTO1; CAT19 CAR T cells) is a cell suspension consisting of autologous human CD4+ and CD8+ T cells transduced with a lentiviral vector encoding a CAR consisting of an anti-CD19 scFv linked to 4-1BB and CD3ζ T cell activating domains.

The manufacturing process for obe-cel is performed in a closed, continually operated environment and takes approximately (b) (4). The processing begins with the collection of the patient's white blood cells using a standard leukapheresis procedure. The fresh leukapheresis starting material undergoes isolation of T cells by (b) (4). These T cells are stimulated to proliferate, transduced with the lentiviral vector (b) (4) to introduce the CAR gene into the cell genome, and ex vivo expanded until the target CAR T cell dose is achieved. The engineered T cells are then washed, formulated, cryopreserved, and shipped back to the clinical center to be administered to the subject. Obe-cel is stored in the vapor phase of liquid nitrogen at ≤ -150 °C.

The drug substance (DS) is defined as the CD19 CAR-positive T cells, and the drug product (DP) is the final formulated obe-cel suspension for intravenous (IV) infusion filled into the proposed container closure system. The finished DP is formulated and cryopreserved in a cryopreservation medium suitable for infusion containing (b) (4) phosphate buffered

saline (PBS)/ethylenediaminetetraacetic acid (EDTA) buffer, (b) (4), human serum albumin (HSA), and dimethyl sulfoxide (DMSO).

The obe-cel product contains a total target dose of 410×10^6 CD19 CAR-positive viable T cells supplied in three or more infusion bags. The treatment regimen consists of a split dose infusion to be administered on Day 1 and Day 10 (± 2 days). The dosing regimen will be determined by the tumor burden assessed by bone marrow blast percentage from a sample obtained within 7 days prior to the start of a fludarabine (FLU) and cyclophosphamide (CY) lymphodepletion chemotherapy regimen.

Abbreviations

4-1BB	Cluster of Differentiation 137 (TNF-receptor superfamily 9)
ALL	Acute lymphoblastic leukemia
B-ALL	B cell acute lymphoblastic leukemia
(b) (4)	(b) (4)
BM	Bone marrow
CAR	Chimeric antigen receptor
CD	Cluster of differentiation
CR	Complete response
CRS	Cytokine release syndrome
CY	Cyclophosphamide
DART	Developmental and reproductive toxicity
DMSO	Dimethyl sulfoxide
DP	Drug product
(b) (4)	(b) (4)
DS	Drug substance
EDTA	Ethylenediaminetetraacetic acid
Fc	Fragment crystallizable
FLU	Fludarabine
FLuc	Firefly luciferase
Gy	Gray
HSA	human serum albumin
HSCT	Hematopoietic stem cell transplantation
ICANS	Immune effector cell-associated neurotoxicity syndrome
(b) (4)	(b) (4)
IV	Intravenous
K_a	Association constant
K_d	Dissociation constant
K_D	Binding affinity
NT	Non-transduced
p/s/cm ² /sr	Photon per second per square centimeter per steradian
r/r	Relapsed or refractory
scFv	Single-chain variable fragment
scFv-Fc	Single chain variable fragment fused to the murine IgG2a Fc domain

TCR	Tissue cross reactivity
T _m	Melting temperature
V _H	Variable heavy chain
V _L	Variable light chain

Related File(s)

IND #19534: Autolus Inc; Autologous T cells Transduced with Lentiviral Vector Expressing Anti-CD19 Chimeric Antigen Receptor (AUTO1). International Nonproprietary Name/INN: Obecabtagene autoleucl (Obe-cel); For the Treatment of Adult Patients with Relapsed or Refractory B-cell Acute Lymphoblastic Leukemia (ALL); ACTIVE.

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INTRODUCTION

B cell acute lymphoblastic leukemia (B-ALL) is a hematologic malignancy that occurs in both children and adults. As an acute leukemia, it is a serious and life-threatening disease and progresses rapidly if left untreated. Patients are predominantly children; approximately 60% of cases occur at age <20 years. The incidence of B-ALL peaks between ages 2 and 5 years with another peak in patients older than 50 years of age.²

In adults, B-ALL chemotherapy enables 90% of adult patients to achieve complete response (CR), but despite this, and in contrast to pediatric B-ALL, the prognosis of adult B-ALL is still poor with long-term remission rates of approximately 40%. About 50% of all adult patients

relapse, and 5-year overall survival (OS) in adults who relapse following standard multi-agent chemotherapy is 7%.³ The only curative option for r/r (relapsed or refractory) B-ALL consists of achieving a second CR by salvage therapy followed by an allogeneic hematopoietic stem cell transplantation (HSCT). Without consolidation by allogeneic HSCT, subsequent relapse occurs in nearly all patients. However, less than half of patients achieve a second CR and thus only a subset will be eligible for this procedure. The main objective of salvage therapy is to try to attain a second CR and to offer allogeneic HSCT to potential candidates. For patients who are candidates for allogeneic HSCT, less than one third are expected to sustain long-term, disease-free survival. Furthermore, allogeneic HSCT is associated with significant morbidity and mortality.

Since CD19 is a pan B lymphocyte biomarker, obe-cel targets B cell malignancies such as B-ALL that express this antigen. Engagement of obe-cel with CD19 expressed on target cells, including cancer cells and normal B cells, leads to activation of the anti-CD19 CAR-positive T cells and downstream signaling through the CD3 ζ domain. Proliferation and persistence by the anti-CD19 (CAT19 scFv) CAR-positive T cells following activation are enhanced by the presence of the 4-1BB co-stimulatory domain. This binding to CD19 results in anti-tumor activity and killing of CD19-expressing target cells.

The CAT19 binding domain was designed to have a rapid dissociation rate with CD19-positive cells to mimic physiological T cell engagement.

NONCLINICAL STUDIES

Note: There are minor differences between the manufacturing processes for the nonclinical (CAT19 CAR T cells) and clinical (obecabtagene autoleucel [obe-cel]) products. The main difference is that the starting material for the nonclinical product was healthy donor PBMCs, while for the clinical product it was non-stimulated leukapheresate from patients. For the nonclinical product, CD3⁺ cells were selected and activated in a similar process as the clinical material in the Phase Ib study, ALLCAR19. Despite minor differences between the nonclinical and clinical products, the constructs assessed, including the binding domain, were identical and therefore the nonclinical product is considered appropriate to assess safety and activity in the nonclinical program. Therefore, obe-cel is used throughout this memo when referring the nonclinical product evaluated.

PHARMACOLOGY STUDIES

Summary List of Pharmacology Studies

The following pharmacology studies were conducted to support the rationale for the administration of obe-cel to treat the proposed clinical indication.

In Vitro Studies

Study Number	Study Title / Publication Citation	Report Number
1	Biophysical characterization of CD19 (CAT) binding domain	10289
2	CD19 (CAT) CAR In Vitro Function	MPx2383a

In Vivo Studies

In Vivo Studies in Tumor Xenograft Animal Models

Study Number	Study Title / Publication Citation	Report Number
3	CD19 (CAT) CAR In Vivo Function	MPx2383b

Overview of Pharmacology Studies

Note: The applicant refers to the CAR tested in nonclinical studies as CAT19. CAT19 CAR is based on the 41BB- ζ CAR designed by Imai et al, 2004,² but the (b) (4) scFv is replaced with a CAT19 scFv. The faster dissociation rate of CAT19 is intended to improve safety, activity, and engraftment with a more physiological CAR T cell activation. In these studies, the activity and persistence of CAT19 CAR is compared to the original CD19 (b) (4) CAR. This latter CAR is referred to as (b) (4) CAR.

Overview of In Vitro Studies

Study #1 Biophysical characterization of CD19 (CAT) binding domain (Report No. 10289)

Summary:

Binding kinetics of CAT19 and (b) (4) scFv-Fc antibodies with recombinant CD19 were determined using (b) (4). Analysis demonstrated that the CAT19 scFv-Fc has a similar on-rate (k_a) as (b) (4) scFv-Fc ($2.153 \times 10^5 \text{ M}^{-1}\text{s}^{-1}$ vs $2.076 \times 10^5 \text{ M}^{-1}\text{s}^{-1}$, respectively), but a faster dissociation rate (k_d ; $3.096 \times 10^{-3} \text{ s}^{-1}$ vs $6.810 \times 10^{-5} \text{ s}^{-1}$, respectively). (b) (4) showed that CAT19 and (b) (4) shared residues within (b) (4). CAT19 binding was also affected by residues (b) (4). Thermal stability analysis showed comparable melting temperatures (T_m) for both antibodies (CAT19: $55.1 \text{ }^\circ\text{C}$ and (b) (4): $57.7 \text{ }^\circ\text{C}$). Cell surface expression of CAT19 CAR and (b) (4) CAR was compared to an internal marker gene and measured by (b) (4). No significant difference was observed between the median fluorescent intensities of CAT19 CAR (4560 ± 916) and (b) (4) CAR (3829 ± 1117), indicating equivalent surface stabilities for both CARs.

Reviewer Comments:

- *CAT19 scFv-Fc demonstrated a binding affinity (K_D) to CD19 that was approximately 40-fold weaker than the K_D of (b) (4) (0.328 nM). Differences in affinity were primarily driven by a difference in the dissociation rate. The faster dissociation rate of the CAT19 scFv-Fc compared to (b) (4) scFv-Fc supports the purported mechanism of action of obe-cel that a shorter interaction with CD19 target cells mimics physiological T cell*

activation and may result in reduced cytokine release and immunotoxicity, while preserving CAR T expansion and persistence.

- Results from alanine scanning suggests that (b) (4) and CAT19 bind to the same epitope on CD19. When compared to (b) (4) CAR, CAT19 CAR demonstrated comparable thermal stability and cell surface expression. These in vitro experiments support the specificity and functionality of CAT19 CAR.

Study #2 CD19 (CAT) CAR In Vitro Function (Report No. MPx2383a)

Summary:

(b) (4) assay was conducted using a CD19-expressing T cell leukemia cell line (b) (4). Specificity of obe-cel was demonstrated when co-cultured for 24 hours with (b) (4) CD19+ target cells, as significant cytotoxicity was only observed using cells expressing CD19. Obe-cel demonstrated statistically significantly greater cytotoxicity than (b) (4) CAR T cells, particularly at lower effector to target ratios.

Cytokine production of obe-cel was compared to (b) (4) CAR T cells by analyzing (b) (4)

The amount of IL-2 and IFN- γ secreted by obe-cel was comparable to that secreted by (b) (4) CAR T cells; however, there was a significantly greater amount of the cytokine TNF- α secreted by obe-cel than by (b) (4) CAR T cells (mean obe-cel: 750.7 ± 103.3 pg/ml, mean (b) (4) CAR T cells: 292.1 ± 36.51 pg/ml, $p < 0.01$).

Proliferation of obe-cel was assessed by (b) (4). After 48 hours, obe-cel showed significantly greater antigen-specific proliferation than (b) (4) CAR T cells (mean cpm \pm SEM: (b) (4): obe-cel 63158 ± 7159 , (b) (4) CAR T cells 27582 ± 2776 , $p < 0.01$; (b) (4): obe-cel 49237 ± 14006 , (b) (4) CAR T cells 13097 ± 4047 , $p < 0.05$).

Reviewer Comment:

- Results indicate that co-culture of obe-cel or (b) (4) CAR T cells with tumor cell lines expressing CD19 resulted in target-specific killing, secretion of pro-inflammatory-associated cytokines, and proliferation. However, obe-cel exhibited significantly greater cytolytic and proliferative capacity compared to (b) (4) CAR T cells. These data support the CD19-directed antitumor activity of obe-cel in vitro.

In Vivo Studies

In Vivo Studies in Tumor Xenograft Animal Models

Study #3 CD19 (CAT) CAR In Vivo Function (Report No. MPx2383b)

Report Number	MPx2383b
Report Date	04-Nov-2019

Title	CD19 (CAT) CAR In Vivo Function	
GLP Status	No	
Testing Facility	(b) (4)	
Objective(s)	To assess the activity of obe-cel in the (b) (4) tumor xenograft mouse model	
Study Animals	Strain/Breed	(b) (4)
	Species	Mouse (<i>Mus musculus</i>)
	Age	6-10 weeks old
	Body Weight	The sponsor reported that body weights were not recorded in the study.
	#/sex/group	Group 1: 7 female mice Group 2: 18 female mice Group 3: 18 female mice NOTE: The sponsor stated only female mice were used in the study to avoid variation in the data caused by possible gender-specific differences
Total #	43 mice total	
Test Article(s)	Obe-cel (CAT19 CAR T cells) NOTE: The sponsor reported that lot numbers were not assigned to test articles in the study.	
Control Article(s)	1. Non-transduced T cells 2. (b) (4) CAR T cells	
Route of Administration	Intravenous (IV)	
Description of the Disease Model and Administration Procedure	Mice were sub-lethally irradiated at 2.8 Gy (gray) on Day -8 relative to CAR T administration. On Day -7, mice were inoculated IV with 1.0×10^6 (b) (4) tumor cells expressing firefly luciferase (FLuc). Tumor engraftment was assessed on Day -1 relative to CAR T administration by (b) (4)	
Study Groups and Dose Levels	Cohorts were randomized and recipients with similar FLuc+ (b) (4) tumor burdens were distributed evenly across the groups prior to the IV administration of CAR T cells or non-transduced (NT) T cells, as negative control, on Day 0. Group 1: 2.5×10^6 Non-transduced T cells/animal (n=7) Group 2: 2.5×10^6 (b) (4) CAR T cells/animal (n=18) Group 3: 2.5×10^6 CAT19 CAR T cells/animal (n=18) NOTE: The study report did not state whether randomization was performed by body weight and then tumor burden or tumor burden alone was used for randomization.	
Dosing Regimen	Single administration	
Randomization	Yes	
Description of Masking	No	
Scheduled Sacrifice Time Points	Day 16	

Reviewer Comment:

- (b) (4) is a human B-cell line established from the peripheral blood of a 19-year-old man with acute lymphoblastic leukemia (ALL) in relapse that natively expresses CD19.

Therefore, the (b) (4) xenograft mouse appears to be an appropriate animal model to assess CAT19 CAR T cells based on the target patient population.

Key Evaluations and Assessments:

- Tumor burden was monitored by (b) (4)
- Mice were monitored using a clinical scoring system every 1 to 3 days for signs of xenogeneic graft-versus-host disease and other toxicities.
- At sacrifice on Day 16, spleen and bone marrow (BM) were analyzed for residual tumor and persisting CAR T cells by (b) (4).

Key Results:

- The results of two independent experiments showed that control mice receiving non-transduced T cells exhibited rapid, disseminated tumor infiltration. On Day 12 post-T cell administration, a significantly lower tumor burden was observed in mice administered obe-cel compared to (b) (4) CAR T cells (9.3×10^7 to 1.1×10^8 and 7.7×10^8 to 3.2×10^9 , respectively (mean p/s/cm²/sr; n = 18; p < 0.001).
- On Day 16, a significantly greater number of CAT19 CAR T cells were detected in the BM (p < 0.05) and blood (p < 0.001) compared to (b) (4) CAR T cells.

Reviewer Comment:

- *These results indicate that the lower affinity obe-cel may mediate enhanced anti-tumor responses and CAR+ T cell expansion compared to higher affinity (b) (4) CAR T cells.*

SAFETY PHARMACOLOGY STUDIES

No safety pharmacology studies with obe-cel were conducted.

PHARMACOKINETIC STUDIES

No pharmacokinetic studies with obe-cel were conducted.

TOXICOLOGY STUDIES

Summary List of Toxicology Studies

Toxicology Studies:

Per the applicant, conventional nonclinical toxicology studies were not conducted because they do not yield clinically relevant information for a CAR T cell product. The vector and transduction protocol used in the manufacture of obe-cel was optimized for human cells and transduction of non-human cells would produce cells with sub-optimal functional properties. In addition, the usefulness of animal studies in predicting cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS) is restricted by the

requirement to use immunodeficient mice lacking a fully functioning immune system to avoid a xenogeneic immune response.

Developmental and Reproductive Toxicology Studies:

No reproductive and developmental toxicity studies have been conducted with obe-cel.

Genotoxicity Studies:

No nonclinical genotoxicity studies were conducted with obe-cel based on the genotoxic risks associated with the third-generation self-inactivating lentiviral vector used to produce obe-cel, acceptable (b) (4) release criterion, and inclusion of long-term clinical monitoring for insertional mutagenesis and clonality. Clinical data suggest low risk of insertional mutagenesis/clonal proliferation.

Carcinogenicity/Tumorigenicity Studies:

No carcinogenicity or tumorigenicity studies have been conducted with obe-cel.

Other Safety Studies

Study Number	Study Title / Publication Citation	Report Number
4	Production and Characterization of Anti-CD19 Reagent for Tissue Cross Reactivity Study	10288
5	Non GLP Tissue Cross Reactivity Validation Study for CAT19, a Chimeric Antigen Receptor Binding Domain, Using Positive and Negative Control Cells/Tissues	10308
6	Tissue Cross Reactivity Study in Human Tissue Using CAT19, a Chimeric Antigen Receptor Binding Domain	10309

Note: Studies No. 4-5 are not summarized in this review memo because they are optimization and characterization studies.

Study #6 Tissue Cross Reactivity Study in Human Tissue Using CAT19, a Chimeric Antigen Receptor Binding Domain (Report No. 10309)

Objective:

To characterize the potential cross-reactivity of the CAT19 CAR binding domain in frozen human tissues and blood smears, using IHC techniques.

Note: The sponsor did not provide any detailed information on the test or control articles beyond the binding domain used.

Methods and Key Results:

- A panel of 42 different frozen human tissues and blood smears (3 donors per tissue) was evaluated by (b) (4) using (b) (4) as

the detection system. Two different concentrations of the CAT19 CAR binding domain (1 and 3 µg/mL) were investigated. An anti-H5N1 (influenza) construct was used as a non-binding negative control reagent.

- The CAT19 CAR binding domain produced positive staining of cells in lymphoid organs, particularly in lymphoid follicles. More specifically, the CAT19 CAR binding domain produced minimal to moderate (intensity) and occasional to frequent membranous (with variable cytoplasmic) staining of resident lymphoid cells in follicles of the lymph nodes, tonsil, spleen (white pulp), thymus, ureter, and gut-associated-lymphoid-tissue throughout the gastrointestinal tract (stomach, duodenum, jejunum, ileum, cecum colon, rectum, and lymphoid nodules in the esophagus).
- The CAT19 CAR binding domain also elicited minimal (intensity) and rare to occasional membranous (with variable cytoplasmic) staining in lymphoid cell infiltrates in breast and parotid salivary gland tissues.
- Staining was generally seen at both concentrations (1 and 3 µg/mL) but was more evident at the higher concentration.
- No unexpected TCR was observed. The distribution of cells binding to the CD19 CAR binding domains was consistent with the expected distribution of endogenous B cells in lymphoid organs other organs associated with lymphocyte cell infiltration. The morphology of stained cells was consistent with B lymphocytes.

Reviewer Comment:

- *The data indicate that human tissue cross reactivity with the CAT19 CAR binding domain was consistent with the expected profile of CD19 expression on B lymphocytes. There was no concerning off-target staining based on the data presented.*

APPLICANT'S PROPOSED LABEL

- Section 13.1 ('Carcinogenesis, Mutagenesis, Impairment of Fertility' under '13. NONCLINICAL TOXICOLOGY') should be revised, as applicable, to accurately reflect the available nonclinical data. The following should be added: "No studies have been conducted to evaluate the effects of AUCATZYL™ on fertility."

CONCLUSION OF NONCLINICAL STUDIES

Review of the nonclinical studies did not identify any safety concerns that could not be addressed in the product label. The nonclinical data supports approval of the license application.

KEY WORDS/TERMS

AUCATZYL™, obecabtagene autoleucel, obe-cel, AUTO1, CAT19 CAR, CD19 CAR T cells, Chimeric Antigen Receptor, ALL, acute lymphoblastic leukemia, pharmacology, toxicology, lentivirus, tumor-bearing mice, (b) (4) mice

REFERENCES

1. A. K. Fielding et al., "Outcome of 609 adults after relapse of acute lymphoblastic leukemia (ALL); an MRC UKALL12/ECOG 2993 study," *Blood* 109, no. 3 (Feb 1, 2007)
2. C. Imai et al., "Chimeric receptors with 4-1BB signaling capacity provoke potent cytotoxicity against acute lymphoblastic leukemia," *Leukemia* 18, no. 4 (Apr 2004)
3. C. H. Pui, L. L. Robison, and A. T. Look, "Acute lymphoblastic leukaemia," *Lancet* 371, no. 9617 (Mar 22, 2008)