

## **Clinical Pharmacology BLA Review**

Office of Clinical Evaluation  
Office of Therapeutic Products

BLA	125813/0
Product	AUCATZYL (obecabtagene autoleucel, obe-cel) Cell Suspension (dispersion) for IV infusion
Applicant	Autolus Inc.
Indication	Treatment of adult patients (18 years and over) with relapsed or refractory (r/r) B cell precursor acute lymphoblastic leukemia (ALL)
Date Received	November 17, 2023
Reviewer	Xiaofei Wang, Ph.D.
RPM	Danielle Bauman
Through	'Lola Fashoyin-Aje, MD, MPH Director (Acting), Division of Clinical Evaluation Hematology

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## 1 EXECUTIVE SUMMARY

Autolus Inc. seeks approval of its BLA for AUCATZYL (obecabtagene autoleucel, AUTO1, obe-cel) for the treatment of adult patients (18 years and over) with relapsed or refractory (r/r) B cell precursor acute lymphoblastic leukemia (ALL). AUCATZYL is a CD19-directed genetically modified autologous T cell immunotherapy consisting of the patient's own T cell expressing an anti-CD19 (CAT) CAR. AUCATZYL is a cell suspension for intravenous infusion. The proposed target dose of AUCATZYL is  $410 \times 10^6$  chimeric antigen receptor-positive (CAR+) viable T cells with split dosing regimen. There are two split dosing regimens based on patient's bone marrow blast percentage:

- for patients with bone marrow blast percentage > 20%, AUCATZYL is to be administered  $10 \times 10^6$  CAR+ viable T cells on Day 1 and  $400 \times 10^6$  CAR+ viable T cells on Day 10 ( $10/400 \times 10^6$  CAR+ viable T cells).
- for patients with bone marrow blast percentage  $\leq$  20%, AUCATZYL is to be administered  $100 \times 10^6$  CAR+ viable T cells on Day 1 and  $310 \times 10^6$  CAR+ viable T cells on Day 10 ( $100/310 \times 10^6$  CAR+ viable T cells).

The clinical pharmacology data in the current BLA derives from one clinical study: an open-label, multi-center, multi-national, single-arm Phase 1b/2 study in adult patients with r/r B ALL (Study FELIX, AUTO-AL1). After administration, AUCATZYL exhibited a rapid expansion, followed by contraction and persistence. Patients who received a CAR T cell regimen of  $10/400 \times 10^6$  CAR+ viable T cells (> 20% bone marrow blasts) had higher AUCATZYL exposure compared to patients who received  $100/310 \times 10^6$  CAR+ viable T cells ( $\leq$  20% bone marrow blasts). For both dosing regimens, median T<sub>max</sub> was achieved at Day 14 (range: Day 2 to Day 55). Persistency of AUCATZYL was observed up to 36.5 months and 18 months in peripheral blood and bone marrow, respectively. Higher tumor burden (bone marrow blast percentage) appeared to be associated with higher AUCATZYL expansion. No association between AUCATZYL exposure and tumor responses (overall complete remission and duration of remission) was identified. Patients who experienced any grade of cytokine release syndrome (CRS) or immune effector-associated neurotoxicity syndrome (ICANS) had substantially higher expansion (AUC<sub>0-28d</sub> and C<sub>max</sub>) compared to patients without CRS or ICANS. Humoral and cellular immune responses against AUCATZAL did not show significant impact on clinical outcomes. Due to the small sample size, the definitive conclusion cannot be drawn. Based on data cutoff date of June 09, 2023, there was no identified positive result for replication-competent lentivirus testing in evaluable patients treated with AUCATZYL in the safety follow up.

The proposed dosing regimen of AUCATZYL administered by intravenous (IV) injection is acceptable. From clinical pharmacology standpoint, the original BLA is approvable.

## **2 RECOMMENDATION**

The clinical pharmacology information in this BLA supports approval.

## **3 INTRODUCTION**

AUCATZYL (obecabtagene autoleucel, AUTO-1, obe-cel) is a CD19-directed genetically modified autologous T cell immunotherapy comprised of autologous T cells that are genetically modified using a lentiviral vector to encode an anti-CD19 chimeric antigen receptor (CAR). The CAR is composed of a murine anti-CD19 single chain variable

fragment (scFv) linked to 4-1BB and CD3-zeta co-stimulatory domains. Engagement of anti-CD19 (CAT) CAR-positive T cells with CD19 expressed on target cells, such as cancer cells and normal B cells, leads to activation of the anti-CD19 (CAT) CAR-positive T cells and downstream signaling through the CD3-zeta domain. Proliferation and persistence by the anti-CD19 (CAT) 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.

## **4 SUMMARY OF IMPORTANT CLINICAL PHARMACOLOGY FINDINGS**

### Pharmacokinetics/Cellular Kinetics

- After administration, AUCATZYL exhibited a rapid expansion, followed by contraction and persistence. Patients who received  $10/400 \times 10^6$  CAR+ viable T cells (> 20% bone marrow blasts) had higher AUCATZYL exposure compared to patients who received  $100/310 \times 10^6$  CAR+ viable T cells ( $\leq$  20% bone marrow blasts). For both dosing regimens, median T<sub>max</sub> was achieved after the second AUCATZYL infusion at Day 14 (Range: Day 2 – Day 55). Persistency of AUCATZYL was observed up to 36.5 months and 18 months in peripheral blood and bone marrow, respectively.
- High inter-patient variability was observed for the AUCATZYL expansion including C<sub>max</sub> and AUC.
- Higher tumor burden (bone marrow blast percentage) appeared to be associated with higher AUCATZYL expansion.

### Exposure-Response Relationships

- No association between AUCATZYL exposure and tumor responses (overall complete remission and duration of remission) was identified.
- Compared to patients without CRS, patients who experienced any grade of CRS had 6.8-fold and 5.0-fold higher geometric mean AUC<sub>0-28d</sub> and C<sub>max</sub>, respectively.
- Compared to patients without ICANS, patients who experienced any grade of ICANS had 2.9-fold and 3.3-fold higher geometric mean AUC<sub>0-28d</sub> and C<sub>max</sub>, respectively.

### Pharmacodynamics

- B cell aplasia was observed in most patients after infusion of AUCATZYL. In Cohort IIA, 93.1% of treated patients had B cell aplasia at Month 3 and 80% patients had B cell aplasia at Month 6 post-infusion. B cell aplasia appeared to be resolved slowly over time.
- Serum levels of cytokines such as IL-2, IL-5, IL-6, IL-7, IL-8, IL-10, IL-15, TNF- $\alpha$ , IFN- $\gamma$ , and granulocyte-macrophage colony-stimulating factors were evaluated. Cytokines levels reach a peak concentration within the first month post infusion and reverted to baseline levels by the next sampling time point.

- More than 2-fold increase in median peak concentrations were observed in CRP, ferritin, IFN- $\gamma$ , IL-6, IL-8 and IL-10 in patients with any grade of CRS compared to patients without CRS.
- Around 2-fold increase in median peak concentrations were observed in CRP, ferritin, IFN- $\gamma$ , IL-6, IL-8, IL-10, and IL-2 in patients with any grade of immune effector cell-associated neurotoxicity syndrome (ICANS) compared to patients without ICANS.
- IgG levels were lower than normal clinical range at 37.3  $\mu\text{mol/L}$  (mean) at baseline and remained low until Month 12 at interim data cutoff date (June 09, 2023).

#### Immunogenicity

- In Study FELIX, 11 out of 127 (8.7%) patients tested positive for humoral immunogenicity at baseline. All but one patient test negative post-infusion. One patient with pre-existing antibodies had positive humoral immunogenicity at Dat 28 of post-infusion. However, the ADA titers in this patient were substantially lower post-infusion. After administration of AUCATZYL, 2 out of 127 patients were positive for humoral immunogenicity at Month 3 post-infusion.
- Positive cellular immunogenicity findings observed in 3 patients at the Month 3 visit.
- Humoral and cellular immune responses against AUCATZAL did not show significant impact on clinical outcomes. Due to the small sample size, the definitive conclusion cannot be drawn.

#### Replication-Competent Lentivirus (RCL) Testing

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

## **5 LABELING COMMENTS**

### **Reviewer's Comments to the Applicant:**

#### Subsection 12.1 Mechanism of Action:

1. Please delete "CAT" from "anti-CD19(CAT) CAR" because it is not informative.
2. Please delete the second paragraph because it is promotional.

#### Subsection 12.2 Pharmacodynamics

3. B cell aplasia detailed has been added.

#### Subsection 12.3 Pharmacokinetics

4. Please add a table for PK parameters of AUCATZYL, including PK information for dosing regimens 10/400, 100/310, and overall (combined two dosing regiments).
5. Please update the PK results with patients meeting following criteria:

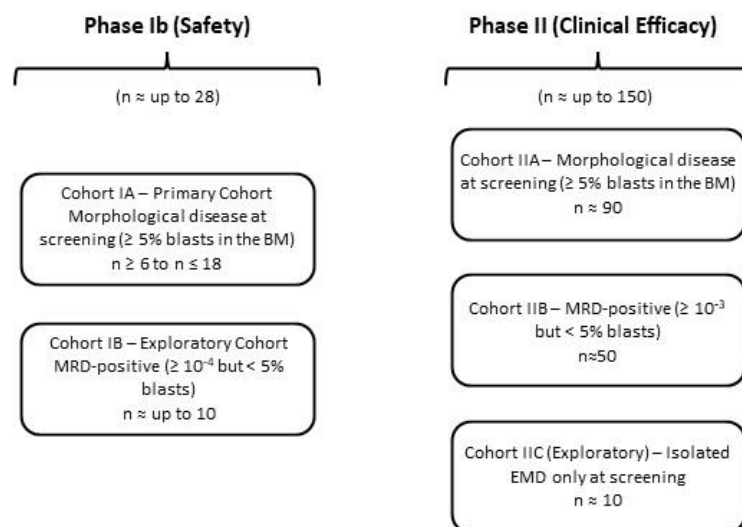
- a. FDA safety subject set population; and
- b. Patients who received two doses of AUCATZYL; and
- c. Patients who received confirming products; and
- d. Patients who received total dose of AUCATZYL within the range of  $410 \times 10^6 \pm 25\%$  CAR-positive viable T cells
6. Additional detailed information of PK in patients with CRS or ICANS has been added.
7. The statement of tocilizumab and corticosteroids was deleted.

## 6 COMPREHENSIVE CLINICAL PHARMACOLOGY REVIEW

### 6.1 Overview of Clinical Pharmacology Evaluation

The clinical pharmacology section of this BLA includes one clinical study: an open-label, multi-center, multi-national, single-arm Phase 1b/2 study in adult patients with r/r B ALL (Study FELIX, AUTO-AL1). The study consists of a Phase 1b and a Phase 2 part (Figure 1).

**Figure 1. FELIX Study Design**



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

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

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

Source: Applicant. Module 5, Study FELIX clinical study report.

### Phase 1b

**Primary Cohort 1A:** Adults aged ≥ 18 years with B ALL who had r/r disease and presence of ≥ 5% blasts in the bone marrow (BM) at screening.

*Exploratory Cohort 1B:* Adults aged  $\geq 18$  years with B ALL in morphological remission with MRD-positive disease ( $\geq 10^{-4}$  and  $< 5\%$  blasts in the BM at screening).

## **Phase II**

*Cohort IIA:* Adults aged  $\geq 18$  years with B ALL who had r/r disease and presence of  $\geq 5\%$  blasts in the BM at screening.

*Cohort IIB:* Adults aged  $\geq 18$  years with B ALL in  $\geq 2^{\text{nd}}$  CR or CRi with MRD-positive disease ( $\geq 10^{-3}$  by central (b) (4) testing and  $< 5\%$  blasts) in the BM at screening.

*Cohort IIC (exploratory):* Adults aged  $\geq 18$  years with B ALL with isolated extramedullary disease (EMD) (including isolated central nervous system [CNS] disease), with or without MRD.

Clinical pharmacology review focused on Phase II Cohort IIA and Phase 1B Cohort A for patients who received conforming AUCATZYL at the target dose of  $410 \times 10^6 \pm 25\%$  CAR+ viable T cells.

After screening, patients underwent leukapheresis. Prior to administration of AUCATZYL, patients received lymphodepleting chemotherapy (fludarabine 30 mg/m<sup>2</sup> on Days -6, -5, -4, and -3, cyclophosphamide 500 mg/m<sup>2</sup> on Day -6 and -5). All patients were to receive a target dose of  $410 \times 10^6$  CD19 CAR+ viable T cells ( $\pm 25\%$ ) as a split dose. The first AUCATZYL infusion took place on Day 1 followed by the second infusion on Day 10 ( $\pm 2$  days). Patients with  $\leq 20\%$  BM blasts received  $100/310 \times 10^6$  CD19 CAR+ viable T cells dosing regimen, patients with  $> 20\%$  BM blasts received  $10/400 \times 10^6$  CD19 CAR+ viable T cells dosing regimen.

## **6.2 General Pharmacology and Pharmacokinetics**

Pharmacokinetics/cellular kinetics (PK/CK) of AUCATZYL was evaluated by measuring the integration of the CAR transgene of AUCATZYL into genomic DNA using a validated (b) (4) assay. PK of AUCATZYL was also measured by (b) (4) to provide a supportive information.

### **6.2.1 General Pharmacokinetic Profile**

#### **6.2.1.1 Pharmacokinetics in Peripheral Blood (Transgene)**

After infusion, AUCATZYL exhibited a rapid expansion, followed by contraction and persistence.

For patients who received  $10/400 \times 10^6$  CAR+ viable T cells ( $> 20\%$  bone marrow blasts), the geometric mean (GM) of C<sub>max</sub> was 146,314 copies/ $\mu$ g DNA post-infusion, which was

numerically higher compared to patients who received  $100/310 \times 10^6$  CAR+ viable T cells ( $\leq 20\%$  bone marrow blasts) with a GM C<sub>max</sub> of 73,074 copies/ $\mu$ g DNA post-infusion. AUC<sub>0-28d</sub> was also numerically higher in patients receiving  $10/400 \times 10^6$  CAR+ viable T cells dosing regimen compared to the  $100/310 \times 10^6$  CAR+ viable T cells dosing regimen. For both dosing regimens, median T<sub>max</sub> was achieved after the second AUCATZYL infusion (median T<sub>max</sub> for all PK set patients: Day 14, Range: Day 2 – Day 55). C<sub>max</sub> were achieved at Day 20 and Day 11 for  $10/400 \times 10^6$  and  $100/310 \times 10^6$  CAR+ viable T cells dosing regimen, respectively. (Table 1, Figure 2) Persistency of AUCATZYL in peripheral blood can be observed up to 36.5 months post-dosing. High inter-patient variability was observed for the AUCATZYL expansion including C<sub>max</sub> and AUC.

**Table 1. Summary of Pharmacokinetic Parameters for AUCATZYL Transgene Levels by (b) (4) in Peripheral Blood**

Parameter	Statistics	10 × 10 <sup>6</sup> Cells then 400 × 10 <sup>6</sup> regimen (> 20% BM blasts at LD) (N=59)	100 × 10 <sup>6</sup> Cells then 310 × 10 <sup>6</sup> regimen (≤ 20% BM blasts at LD) (N=31)	Total (N=90)
C <sub>max</sub> (copies/ $\mu$ g DNA)	n	59	31	90
	Geometric Mean (Geo-CV%)	146,314 (294.4)	73,074 (186.9)	115,193 (267.0)
	Min – Max	129 – 600,000	9,290 – 589,000	129 – 600,000
T <sub>max</sub> (days)	n	59	31	90
	Median	20	11	14
	Min – Max	6 – 55	2 – 28	2 – 55
AUC <sub>0-28d</sub> (day*copies/ $\mu$ g DNA)	n	50	29	79
	Geometric Mean (Geo-CV%)	1,521,310 (191.3)	692,307 (226.8)	1,147,631 (219.5)
	Min – Max	17,900 – 6,730,000	70,400 – 7,230,000	17,900 – 7,230,000

AUC<sub>0-28d</sub>=area under the concentration-time curve (exposure) from Day 0 to Day 28; BM=bone marrow;

CAR=chimeric antigen receptor; C<sub>max</sub>=maximum serum concentration; (b) (4)

; DNA=deoxyribonucleic acid; Geo-CV%=geometric mean coefficient of variation; LD=lymphodepletion;

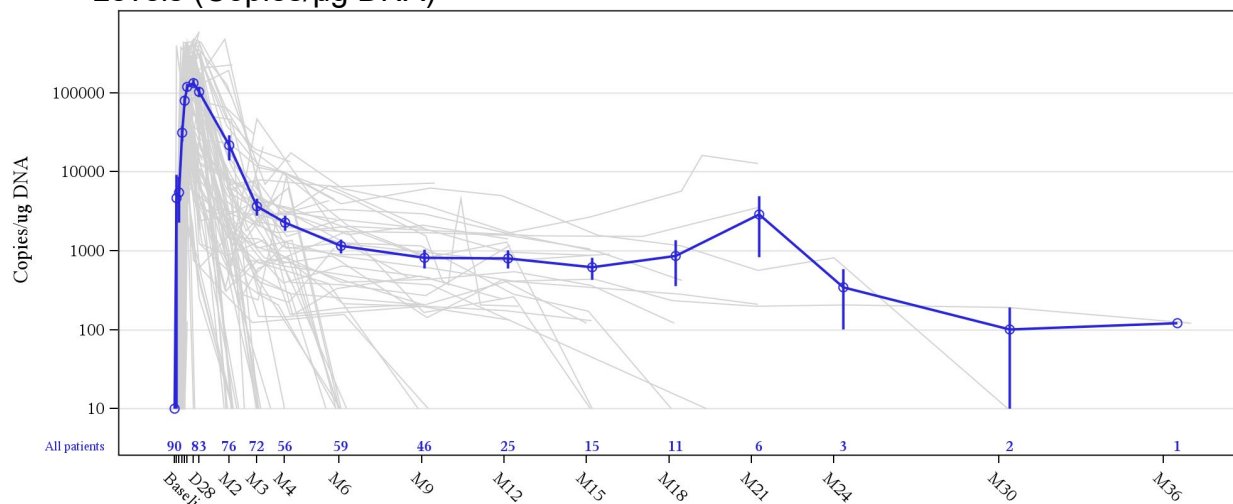
PK= pharmacokinetic; T<sub>max</sub>=time to maximum concentration.

Source: Applicant. IR response submitted on 10/08/2024.

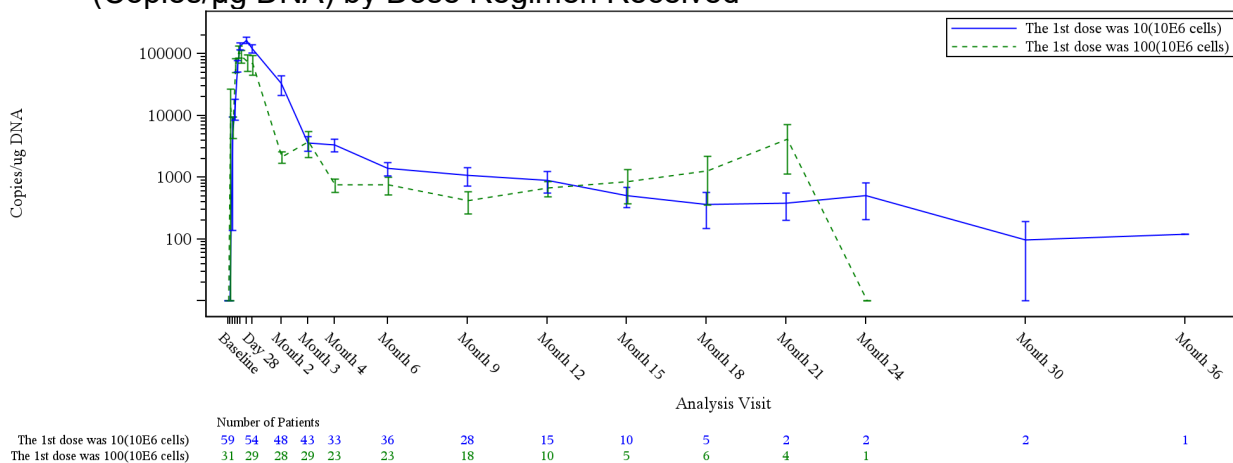


**Figure 2. Pharmacokinetic Profiles of AUCATZYL in Peripheral Blood ((b) (4) Assay)**

a. Mean (SE) and Individual Concentration-Time Profile of AUCATZYL Transgene Levels (Copies/ $\mu$ g DNA)



b. Mean (SE) Concentration-Time Profile of AUCATZYL Transgene Levels (Copies/ $\mu$ g DNA) by Dose Regimen Received



Source: Applicant. IR response submitted on 10/08/2024.

### **Delayed Second Dose**

In Cohorts 1A and IIA, with the target dose of  $410 \times 10^6 \pm 25\%$  CAR+ viable T cells, 8 patients received delayed second split dose due to adverse events (such as CRS, ICANS, etc.). Compared to patients received 2<sup>nd</sup> dose on schedule, patients received delayed 2<sup>nd</sup> split dose had higher exposure. The geomean mean (CV%) values of AUC<sub>0-28d</sub> and C<sub>max</sub> for patients received delayed 2<sup>nd</sup> dose were 3,891,921 days\*copies/ $\mu$ g DNA (44.8%) and 338,714 copies/ $\mu$ g DNA (34.0%), respectively. This observation is in line with that patients experienced CRS or ICANS had higher exposure compared to patients did not have CRS or ICANS.

### 6.2.2 Pharmacokinetics in Bone Marrow (Transgene)

The presence of AUCATZYL in bone marrow (BM) aspirate was assessed with limited sampling time points. CAR T can be identified in BM aspirate in 96.4% patients with available samples at Day 28 and 65.7% of patients with available samples at Month 6. The level of AUCATZYL transgene was highest at Day 28 post-infusion (first post-infusion sampling time point). Persistency of AUCATZYL in BM can be observed up to 18 months. This observation was consistent with the results from peripheral blood.

**Table 2. AUCATZYL Transgene (Copies/g DNA) in Bone Marrow**

Statistic	Visit				
	Day 28	Month 3	Month 6	Month 12	Month 18
n*	55	49	35	12	3
m**	53	37	23	11	1
Geometric mean (Geo-CV%)	14,302.9 (981.6)	2,234.8 (174.0)	1,491.4 (184.7)	740.7 (152.7)	1,337.3 (NA)

\*n is the number of patients with available data; \*\*m is the number of patients with non-zero values

Source: Applicant. Module 5, section 5.3.4.2. PK/PD report.

### 6.2.3 Product Characteristics and Pharmacokinetics

The relationships between AUCATZYL product characteristics, including memory phenotype (naïve phenotype, effector memory, central memory, TEMRA (effector memory cells re-expressing CD45RA T cells)) and exhaustion phenotype (PD1 positive, LAG3 positives, PD1/LAG3 double positive or TIGIT positive) and AUCATZYL PK were evaluated, and no evident association was observed.

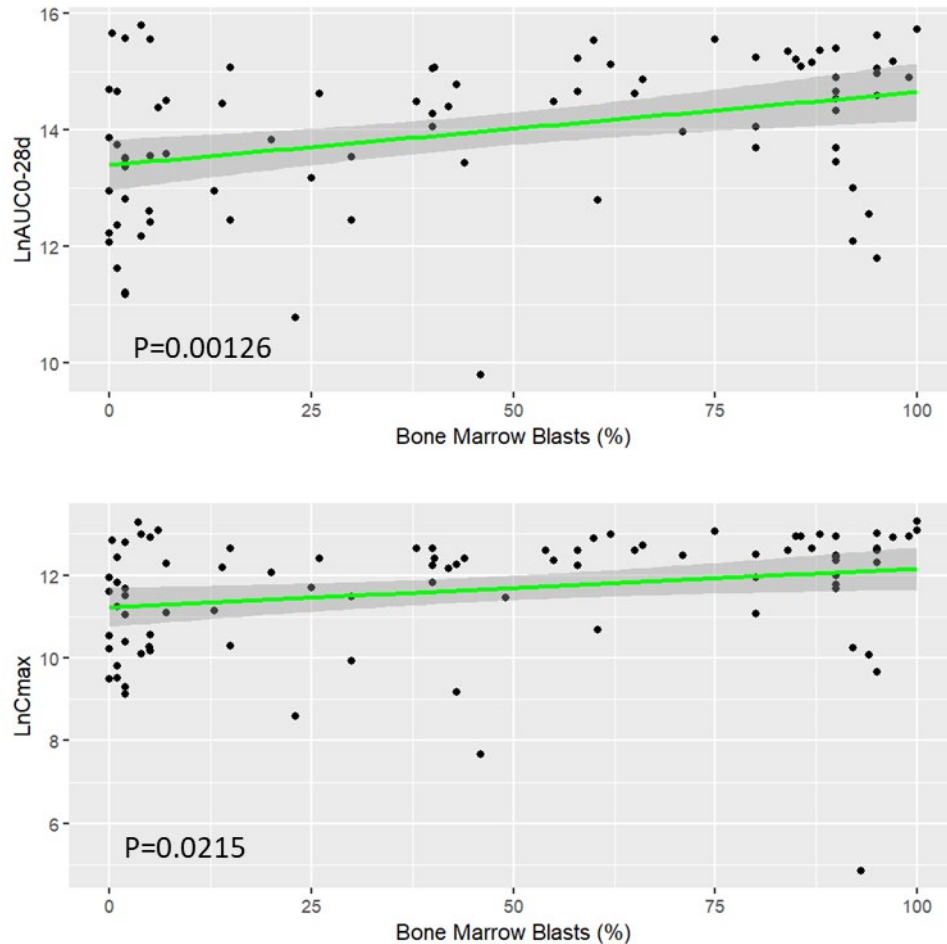
### 6.2.4 Pharmacokinetics in Specific Populations

The impacts of various intrinsic (sex, age, EMD presence at lymphodepletion, disease burden, Philadelphia chromosome/BCR-ABL status, race) and extrinsic factors (number of lines of prior therapies, and by response to previous lines of therapy [including time to relapse], previous allogeneic SCT and the use of previous targeted therapy [blinatumomab and/or inotuzumab ozogamicin]) on the PK profiles of AUCATZYL were evaluated.

#### **Tumor Burden (Bone Marrow Blasts Percentage)**

Exploratory analyses based on data from patients who received two dosing regimens showed that higher tumor burden (bone marrow blasts percentage) was associated with higher exposure of AUCATZYL (Figure 3).

**Figure 3. Tumor Burden and AUCATZYL Exposure**



Source: Reviewer's analysis.

### Reviewer's Comments:

The analysis assessing the relationship between tumor burden and AUCATZYL expansion is exploratory and based on pooled data from patients who received two different dosing regimens. Therefore, the results should be interpreted with caution.

Patients who experience any grade of CRS had 2.0-fold higher mean bone marrow blast percentage compared to patients who did not have CRS. Patients who experience any grade of ICANS had 1.8-fold higher mean bone marrow blast percentage compared to patients without ICANS.

### Race

Patients who received conforming AUCATZYL at the target dose of  $410 \times 10^6 \pm 25\%$  CAR+ viable T cells in Phase 1b Cohort A and Phase 2 Cohort A, were White (68/90, 75.6%), Asian (11/90, 12.2%), Unknown (10/90, 11.1%), and Black (1/90, 1.1%). Patients with race reported as Asian or Unknown race had higher exposure compared to patients with race reported as Black or African American or White race. There was around 2-fold increase in geometric mean Cmax in patients with race reported as Asian or Unknown race (Cmax 222,982 copies/ $\mu$ g DNA and 186,233 copies/ $\mu$ g DNA, respectively).

compared to patients with race reported as Black or African American or White race (Cmax: 96,708 copies/ $\mu$ g DNA). Similar trend was observed in geometric mean of AUC<sub>0-28d</sub>: the geometric mean AUC<sub>0-28d</sub> were 2,077,457 days\*copies/ $\mu$ g DNA and 1,702,024 days\*copies/ $\mu$ g DNA for patients with race reported as Asian or Unknown race respectively, about 1.7 to 2.1-fold higher than the geometric mean AUC<sub>0-28d</sub> in patients with race reported as Black or African American or White race (AUC<sub>0-28d</sub>: 988,059 days\*copies/ $\mu$ g DNA). Considering the small sample size of races other than White, there is no definitive conclusion whether race is a clinically significant impacting factor for AUCATZYL exposure.

### Age

For combined two dosing regimen group and  $10/410 \times 10^6$  CAR+ viable T cells dosing group, the exposure of AUCATZYL were similar between patients < 65 years and patients  $\geq 65$  years of age. However, in the  $100/300 \times 10^6$  CAR+ viable T cells dosing group, patients  $\geq 65$  years had 4-fold higher exposure (geometric means of AUC<sub>0-28d</sub> and Cmax) compared to patients <65 years of age (Table 3).

**Table 3. Summary of Pharmacokinetics Parameters for AUCATZYL Transgene Levels by (b) (4) in Peripheral Blood by Age Group by Dose Regimen Received**

Parameter	Metric	Age		Overall
		< 65 Years	≥ 65 Years	
<b>10/400 × 10<sup>6</sup> CAR+ viable T cell dosing group</b>		<b>N=45</b>	<b>N=14</b>	<b>N=59</b>
Cmax (copies/μg DNA)	n	45	14	59
	Geometric mean (Geo-CV%)	143,700 (331.9)	155,042 (212.1)	146,314 (294.4)
	Range (Min – Max)	129 – 600,000	2,120 – 478,000	129 – 600,000
Tmax (days)	n	45	14	59
	Median	21	14	20
	Range (Min – Max)	6 – 55	11 – 21	6 – 55
AUC <sub>0-28d</sub> (day*copies/μg DNA)	n	39	13	52
	Geometric mean (Geo-CV%)	1,599,733 (174.9)	1,308,361 (263.3)	1,521,310 (191.3)
	Range (Min – Max)	47,300 – 6,060,000	17,900 – 6,730,000	17,900 – 6,730,000

Parameter	Metric	Age		Overall
		< 65 Years	≥ 65 Years	
<b>100/310 × 10<sup>6</sup> CAR+ viable T cell dosing group</b>		<b>N=25</b>	<b>N=6</b>	<b>N=31</b>
Cmax (copies/μg DNA)	n	25	6	31
	Geometric mean (Geo-CV%)	55,473 (174.0)	230,377 (66.4)	73,074 (186.9)
	Range (Min – Max)	9,290 – 440,000	109,000 – 589,000	9,290 – 589,000
Tmax (days)	n	25	6	31
	Median	11	13	11

AUC <sub>0-28d</sub> (day*copies/μg DNA)	Range (Min – Max)	2 – 28	8 – 27	2 – 28
	n	24	5	29
	Geometric mean (Geo-CV%)	542,985 (223.0)	2,222,039 (68.1)	692,307 (226.8)
	Range (Min – Max)	70,400 – 7,230,000	1,050,000 – 5,780,000	70,400 – 7,230,000
<b>Combined subject group: 10/400 and 100/310 × 10<sup>6</sup> CAR+ viable T cells</b>		<b>N=70</b>	<b>N=20</b>	<b>N=90</b>
C <sub>max</sub> (copies/μg DNA)	n	70	20	90
	Geometric mean (Geo-CV%)	102,287 (296.4)	174,601 (163.0)	115,193 (267.0)
	Range (Min – Max)	129 – 600,000	2,120 – 589,000	129 – 600,000
T <sub>max</sub> (days)	n	70	20	90
	Median	14	14	14
	Range (Min – Max)	2 – 55	8 – 27	2 – 55
AUC <sub>0-28d</sub> (day*copies/μg DNA)	n	63	18	81
	Geometric mean (Geo-CV%)	1,055,942 (224.9)	1,515,734 (202.2)	1,147,631 (219.5)
	Range (Min – Max)	47,300 – 7,230,000	17,900 – 6,730,000	17,900 – 7,230,000

AUC<sub>0-28d</sub>=area under the concentration-time curve (exposure) from Day 0 to Day 28; CAR=chimeric antigen receptor; C<sub>max</sub>=maximum plasma concentration; CV%=coefficient of variation %; (b) (4); DNA=deoxyribonucleic acid; PK=pharmacokinetic; T<sub>max</sub>=time to maximum plasma concentration.

Source: Applicant. IR response submitted on 10/08/2024.

With multivariate regression analysis with tumor burden, the impact of age in the 100/300 x 10<sup>6</sup> CAR+ viable T cells dosing group was not significant. Considering the small sample size, the clinical significance of age on AUCATZYL exposure is not conclusive.

None of the other covariates was found to be significant covariates for PK of AUCATZYL.

## 6.3 Pharmacodynamics

### 6.3.1 B Cell Aplasia

B cell aplasia (absolute numbers of B cells is < 20 cells/μL) is an expected on-target effect of AUCATZYL. B cell aplasia was evaluated using a validated (b) (4) assay. B cell aplasia was observed in most patients after infusion of AUCATZYL. In Cohort IIA, 93.1% of treated patients had B cell aplasia at Month 3 and 80% patients had B cell aplasia at Month 6 post-infusion. B cell aplasia appeared to be resolved slowly over time.

### 6.3.2 Serum Biomarkers

A panel of cytokines (IL-2, IL-5, IL-6, IL-7, IL-8, IL-10, IL-15, TNF-α, IFN-γ and GM-CSF) was analyzed by (b) (4) using a validated assay. Ferritin, Immunoglobulin G (IgG) and C-reactive protein (CRP) data were captured in the electronic Case Result Form (eCRF) based on local routine assessments.

Cytokines levels reach a peak concentration within the first month post infusion and reverted to baseline levels by the next sampling time point (Day 90).

Levels of CRP (12.8 mg/L) and ferritin (1,957 µg/L) were elevated at baseline compared to normal range (CRP 8-10 mg/L and ferritin 24-336 µg/L respectively). Post-infusion, CRP and ferritin increased further with a peak concentration of CRP of 34.3 mg/L and ferritin of 4,098.5 µg/L and decreased by Day 15 for CRP (to baseline) and Day 28 for ferritin.

More than 2-fold increase in median peak concentrations were observed in CRP, ferritin, IFN-γ, IL-6, IL-8 and IL-10 in patients with any grade of CRS compared to patients without CRS.

Around 2-fold increase in median peak concentrations were observed in CRP, ferritin, IFN-γ, IL-6, IL-8, IL-10, and IL-2 in patients with any grade of immune effector cell-associated neurotoxicity syndrome (ICANS) compared to patients without ICANS.

IgG levels were lower than normal clinical range at 37.3 µmol/L (mean) at baseline and remained low until Month 12. Beyond month 12, the number of patients with results is too small to draw conclusion. The percentage of patients with value < lower limit of normal was 45.7% at baseline, 55.9% at Day 28, 55.1% at Month 3, 44.1% at Month 6 and 18.1% at Month 12.

## **6.4 Exposure / Dose-Response Relationships**

### **6.4.1 Exposure/Dose-Efficacy Response Relationships**

Exposure/dose-response relationships for efficacy were analyzed in Phase 2 Cohort IIA patients who received confirming AUCATZYL within the target dose ( $410 \times 10^6 \pm 25\%$  CAR+ viable T cells).

Two dosing regimens were evaluated based on patients' bone marrow blasts percentage. In Phase 2 Cohort IIA, all patients with the dosing regimen of  $100/310 \times 10^6$  CAR+ viable T cells (patients with bone marrow blasts percentage  $\leq 20\%$ ) (n=9) were responders (CR or CRi). For patients with  $>20\%$  bone marrow blasts ( $10/400 \times 10^6$  CAR+ viable T cells) (n=49), the responding rate (CR or CRi) was 61.2% (30/49). Bone marrow blasts percentage may be one of the cofounding factors impacting patient's response to AUCATZYL.

#### Exposure-Efficacy Response Relationships

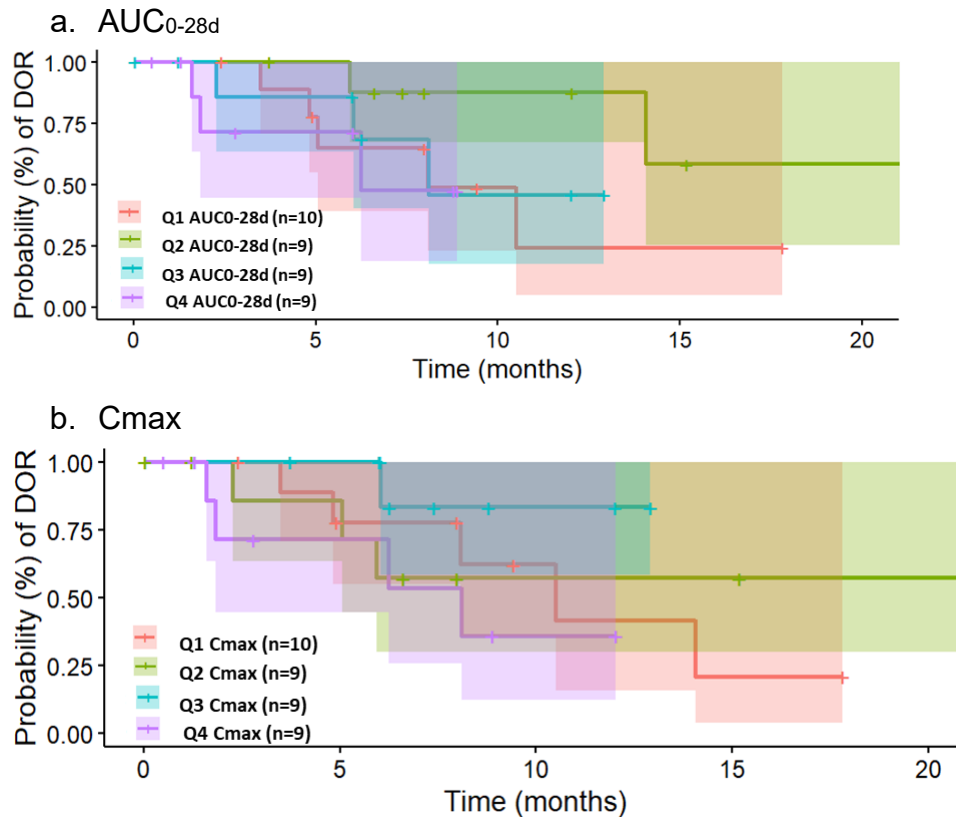
The relationships between AUCATZYL exposure (AUC0-28d and Cmax) and efficacy response (tumor responses) were evaluated. As shown in Table 3, there was no substantial difference in AUCATZYL exposure (AUC0-28d and Cmax) between responding (CR, CRi) and non-responding patients. Compared to non-responding patients, responding patients achieved peak levels earlier. Responding patients also had longer persistence (Tlast) than non-responding patients. About 75.9% (22/29) of patients who had ongoing remission had ongoing CAR T persistency at the last laboratory assessment, with a maximum observed persistency of 36.5 months. There was no evident association between AUCATZYL exposure (AUC0-28d and Cmax) and duration of remission (DOR) (Figure 3).

**Table 4. AUCATZYL Exposure and Response**

	<b>Responding Patients (n=39)</b>	<b>Non-responding Patients (n=19)</b>
<b>AUC0-28d (days*copies/μg DNA)</b>		
<b>n</b>	39	14
<b>Mean (SD)</b>	2,316,646.2 (1,695,468.1)	2,467,214.3 (2097642.6)
<b>Median (Q1, Q3)</b>	2,160,000 (779,500, 3,510,000)	1,995,000 (730,750, 3,947,500)
<b>Min, Max</b>	17,900, 6,060,000	176,000, 6,730,000
<b>GeoMean (CV%)</b>	1,444,100.1 (203.0%)	1,481,674.4 (181.0%)
<b>Cmax (copies/μg DNA)</b>		
<b>n</b>	39	19
<b>Mean (SD)</b>	234988.2 (148,647.4)	249,022.6 (168,021.8)
<b>Median (Q1, Q3)</b>	230,000 (107,000, 358,000)	293,000 (108,750, 326,000)
<b>Min, Max</b>	2,120, 478,000	129, 600,000
<b>GeoMean (CV%)</b>	154,246.1 (190.6%)	126,610.0 (674.0%)
<b>Tmax (days)</b>		
<b>n</b>	39	19
<b>Median</b>	13.9	20.9
<b>Min, Max</b>	1.8, 54.8	5.7, 27.9
<b>Tlast (days)</b>		
<b>n</b>	39	19
<b>Median</b>	174.9	30.1
<b>Min, Max</b>	26.8, 626.9	13.7, 359.2

Source: Reviewer's analysis.

**Figure 4. Duration of Response Stratified by AUCATZYL Exposures (AUC0-28d, Cmax)**



Source: Reviewer's analysis.

#### 6.4.2 Exposure / Dose-Safety Response Relationships

Exposure/dose-response relationships for safety were analyzed in Phase 1b Cohort IA and Phase 2 Cohort IIA patients who received confirming AUCATZYL within the target dose ( $410 \times 10^6 \pm 25\%$  CAR+ viable T cells).

There was no severe (Grade  $\geq 3$ ) CRS and ICANS for the dose regimen of  $100/310 \times 10^6$  CAR+ viable T cells. For the dose regimen of  $10/400 \times 10^6$  CAR+ viable T cells, the incidence of severe (Grade  $\geq 3$ ) CRS and ICANS were 3.4% (2/59) and 8.5% (5/59), respectively.

##### Exposure-Safety Response Relationships

In Phase 1b Cohort A and Phase 2 Cohort A, for patients who received AUCATZYL within the target dose range:  $410 \times 10^6 \pm 25\%$  CAR+ viable T cells, 2.2% (2/90) patients had severe CRS (Grade  $\geq 3$ ) and 5.6% (5/90) had severe ICANS ((Grade  $\geq 3$ ). Considering the low incidence rates of Grade 3 or higher CRS and ICANS, exposure-safety response relationship analysis was for patients who experiences any grade of CRS or any grade of ICANS.



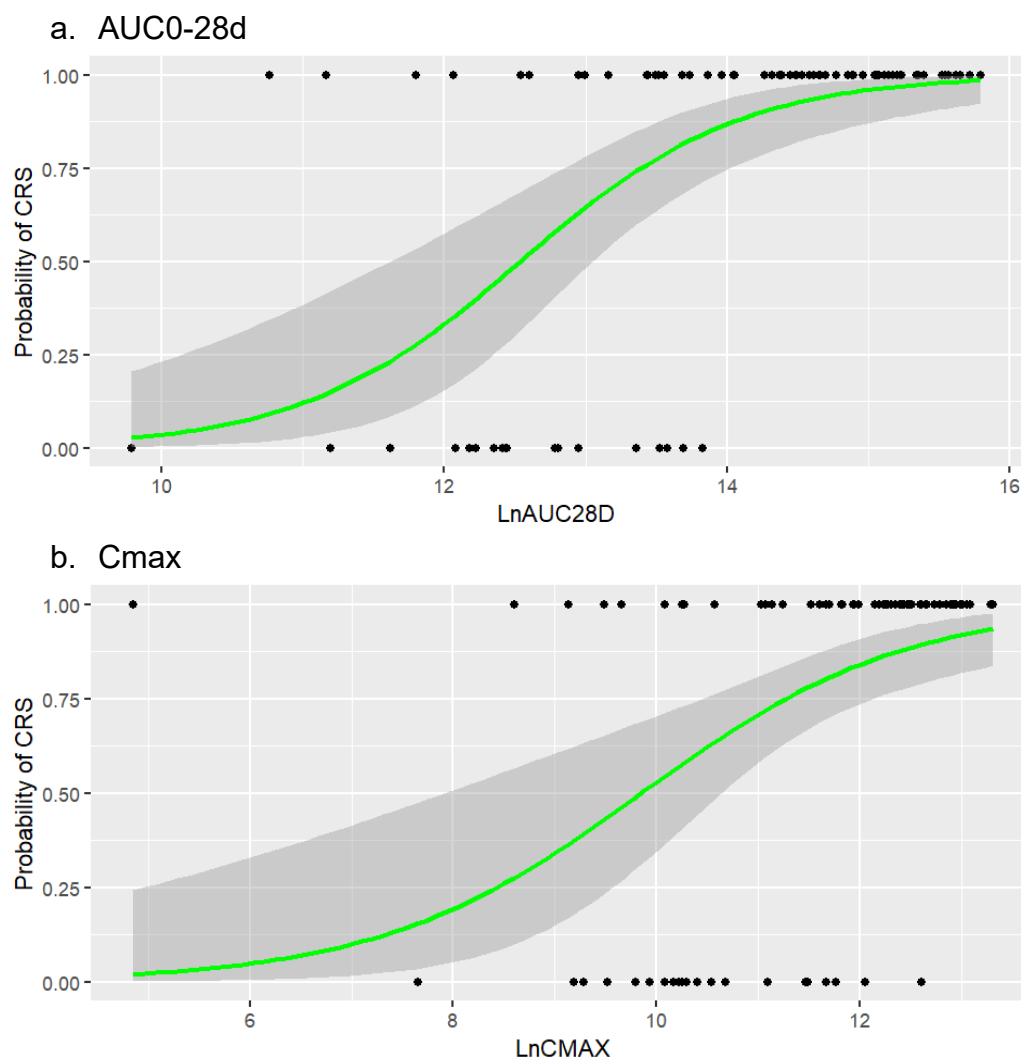
As shown in Table 4, patients who experienced any grade of CRS had substantially higher expansion ( $AUC_{0-28d}$  and  $C_{max}$ ) compared to patients without CRS. Higher exposure of AUCATZYL ( $AUC_{0-28d}$  and  $C_{max}$ ) was positively associated with higher risks of CRS (Figure 4).

**Table 5. AUCATZYL Exposure and Cytokine Release Syndrome (CRS)**

	<b>Patients with CRS (n=70)</b>	<b>Patients without CRS (n=20)</b>
<b>AUC0-28d (days*copies/<math>\mu</math>g DNA)</b>		
<b>n</b>	64	17
<b>Mean (SD)</b>	2,569,807.8 (1,863,884.7)	350,352.9 (260,569.7)
<b>Median (Q1, Q3)</b>	2,225,000 (989,000, 3,700,000)	252,000 (194,000, 422,000)
<b>Min, Max</b>	47,300, 7,230,000	17,900, 887,000
<b>GeoMean (CV%)</b>	1,716,718.1 (153.9%)	251,980.5 (123.9%)
<b>Cmax (copies/<math>\mu</math>g DNA)</b>		
<b>n</b>	70	20
<b>Mean (SD)</b>	248,383.4 (149,836.5)	56,299 (67,964.14)
<b>Median (Q1, Q3)</b>	247,500 (136,250, 352,250)	28,850 (19,950, 73,050)
<b>Min, Max</b>	129, 600,000	2,120, 298,000
<b>GeoMean (CV%)</b>	164,635.6 (222.9%)	33,005.7 (153.7%)
<b>Tmax (days)</b>		
<b>n</b>	70	20
<b>Median</b>	14.0	13.8
<b>Min, Max</b>	1.8, 54.8	7.9, 27.9

Source: Reviewer's analysis.

**Figure 5. AUCATZYL Exposure and Cytokine Release Syndrome (CRS)**



LnAUC28D: natural logarithm of AUC0-28d, LnCmax: natural logarithm of Cmax  
Source: Reviewer's analysis.

A similar trend was observed for ICANS. Patients who experienced any grade of ICANS had substantially higher expansion (AUC<sub>0-28d</sub> and Cmax) compared to patients without ICANS (Table 6). Higher exposure of AUCATZYL (AUC<sub>0-28d</sub> and Cmax) was positively associated with higher risks of ICANS. (Figure 6)

**Table 6. AUCATZYL Exposure and Immune Effector Associated Neurotoxicities (ICANS)**

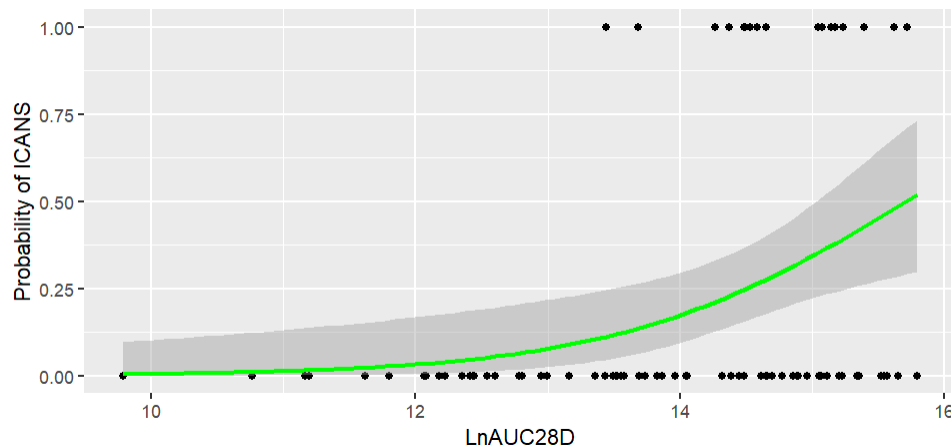
	Patients with ICANS (n=21)	Patients without ICANS (n=69)
<b>AUC0-28d</b> (days*copies/ $\mu$ g DNA)		
<b>n</b>	18	63
<b>Mean (SD)</b>	3068666.7 (1675474.0)	1,828,376.2 (1,870,223.6)

<b>Median (Q1, Q3)</b>	2,870,000 (1,955,000, 3,857,500)	1,010,000 (327,000, 2,885,000)
<b>Min, Max</b>	686,000, 6,730,000	17,900, 7,230,000
<b>GeoMean (CV%)</b>	2,617,357.7 (67.7%)	906,774.0 (240.6%)
<b>Cmax (copies/μg DNA)</b>		
<b>n</b>	21	69
<b>Mean (SD)</b>	322,833.3 (143,322.5)	170,048.1 (144,719.3)
<b>Median (Q1, Q3)</b>	295,000 (230,000, 413,000)	136,000 (28,900, 294,000)
<b>Min, Max</b>	64,500, 600,000	129, 467,000
<b>GeoMean (CV%)</b>	288,150.0 (56.9%)	87,144.2 (303.1%)
<b>Tmax (days)</b>		
<b>n</b>	21	69
<b>Median</b>	20.9	13.9
<b>Min, Max</b>	8.0, 54.8	1.8, 28.0

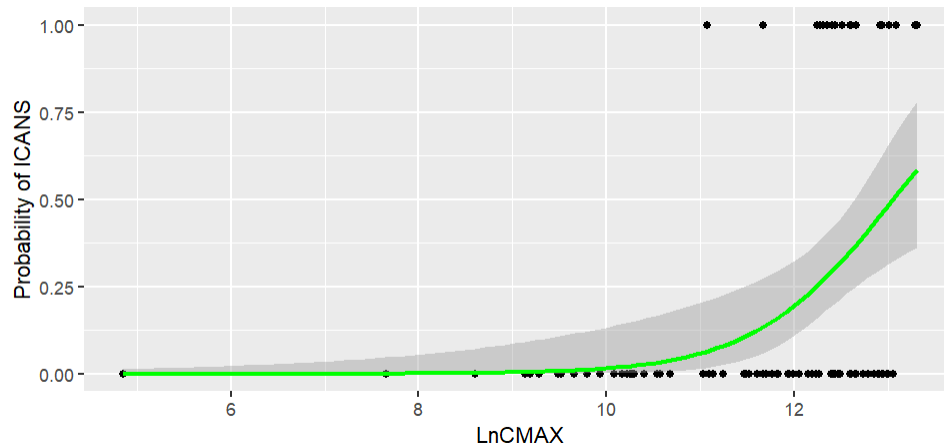
Source: Reviewer's analysis.

**Figure 6. AUCATZYL Exposure and Immune Effector Associated Neurotoxicities (ICANS)**

a. AUC0-28d



b. Cmax



LnAUC28D: natural logarithm of AUC0-28d, LnCmax: natural logarithm of Cmax  
Source: Reviewer's analysis.

### 6.4.3 Dose Evaluation

#### Dose Rationale

the Applicant proposed a bone marrow blast percentage-based 2-step fractionated dosing regimen as following:

BM Blast %	Dosing Schedule	
	Dose 1 on Day 1	Dose 2 on Day 10 (±2 days)
≤20% blasts	100 × 10 <sup>6</sup> CD19 CAR+ viable T cells	310 × 10 <sup>6</sup> CD19 CAR+ viable T cells
>20% blasts	10 × 10 <sup>6</sup> CD19 CAR+ viable T cells	400 × 10 <sup>6</sup> CD19 CAR+ viable T cells

The purpose of this 2-step fractionated dosing approach is to minimize the established immunotoxicity risk observed with CAR T cell therapy, considering a higher disease burden is linked to greater CAR T cell expansion and the inherent expansion and persistency properties of AUCATZYL.

The 2-step fractionated dosing regimen in Study FELIX is based on data from Studies CARPALL and ALLCAR19, where AUCATZYL has been administered to 21 pediatric and 20 adult patients with B-ALL. In adults, a dose ranging 10 x 10<sup>6</sup> to 410 x 10<sup>6</sup> CAT T cells has been safely administered. In Study ALLCAR19, the safety of AUCATZYL in adult patients with r/r B-ALL at the target dose of 410 x 10<sup>6</sup> CD19 CAR+ viable T cells with similar split dosing regimen. The selected total dose was based on the doses of available CAR T therapies in adult ALL.

The ALLCAR19 study also incorporated the principles of splitting the dose based on disease burden. The spacing between the dose fractions takes into consideration the duration of IL-15 surge following lymphodepletion, which is important for CAR T cell

expansion and function. The cellular immune response at the time of the second dose, on Day 10, is expected to be significantly reduced by the lymphodepleting chemotherapy administered before AUTO1 infusion. Additionally, the humoral immune response, that takes approximately 14 days to be generated, is expected to be impaired by the B cell aplasia and subsequent hypogammaglobulinaemia induced by the CD19 CAR T cells administered on Day 1. In Study ALLCAR19, AUCATZYL was well tolerated and effective.

In current application, the proposed dosing regimen of AUCATZYL administered by intravenous (IV) infusion has demonstrated clinical efficacy with a tolerable safety profile; therefore, the proposed dosing regimen is acceptable.

## **6.5 Immunogenicity**

### **6.5.1 Humoral Immunogenicity (Anti-drug Antibodies)**

The presence of anti-drug antibody against AUCATZYL was assessed in 127 patients in Study FELIX using a validated (b) (4) immunoassay. Anti-AUCATZYL CAR protein antibodies (ADA) in serum were assessed at baseline (Day -6), and post-infusion (on Day 28, Month 3, and at relapse). The results showed that 11 out of 127 (8.7%) patients tested positive for humoral immunogenicity at baseline. Among these 11 patients, 1 patient also had positive humoral immunogenicity at Day 28 of post-infusion. However, the ADA titers in this patient were substantially lower post-infusion (detectable at < 1/20 dilution) compared at baseline (1/640 dilution). This patient achieved a best overall response (BOR) of CR.

After administration of AUCATZYL, 2 out of 127 patients were positive for ADA at Month 3 post-infusion. Both patients were negative for ADA at baseline and both achieved a BOR of CR or CRi. None of the adverse events of the two patients appeared to be related to the ADA positive signal.

### **6.5.2 Cellular Immunogenicity**

Cellular immunogenicity testing was performed using an off the shelf validated (b) (4) assay in available samples (75 out of 127 patients). Each sample was tested against 3 peptide pools. Positive immunogenicity findings observed in 3 (2.4%) patients at the Month 3 visit. All 3 patients demonstrated CR and any safety events were unlikely to be related to the immunogenicity signal.

Overall, humoral and cellular immune responses against AUCATZAL did not show significant impact on clinical outcomes. Due to the small sample size, the definitive conclusion cannot be drawn.

## 6.6 Replication-competent Lentivirus (RCL) Testing

AUCATZYL comprises lentiviral vector transduced T cells. Therefore, the presence of replication-competent lentivirus (RCL) in the blood of treated patients were monitored using a validated (b) (4) method. Based on data cutoff date of June 09, 2023, there was no identified positive result for replication-competent lentivirus testing in evaluable patients treated with AUCATZYL in the safety follow up.

## 7 APPENDIX - INDIVIDUAL STUDY

### 7.1 Study #1 – Study FELIX (AUTO-AL1)

Interim Analysis Data Cutoff Date: June 09, 2023

**Title:** An open-label, multi-center, Phase Ib/II study evaluating the safety and efficacy of AUTO1 (obe-cel), a CAR T cell treatment targeting CD19, in adult patients with relapsed or refractory B-cell acute lymphoblastic leukemia (Study FELIX, AUTO-AL1).

**Objectives (ClinPharm-related, listed as Secondary Objectives):**

- To evaluate the expansion and persistency of obe-cel (AUCATZYL).
- To evaluate the duration of B-cell aplasia.

**Study Design (focusing on clinpharm-related parts)**

FELIX is a Phase Ib/II, open-label, single- arm multi-center study to evaluate the safety and efficacy of obe-cel when administered to adult patients with relapsed or refractory (r/r) B-cell acute lymphoblastic leukemia (B ALL).

Patients were enrolled into the following cohorts:

**Phase Ib**

**Primary Cohort IA:** Adults aged  $\geq 18$  years with B ALL who had r/r disease and presence of  $\geq 5\%$  blasts in the bone marrow (BM) at screening.

**Cohort IB (exploratory):** Adults aged  $\geq 18$  years with B ALL in morphological remission with minimal residual disease (MRD)-positive disease ( $\geq 10^{-4}$  and  $< 5\%$  blasts in the BM at screening).

**Phase II**

**Cohort IIA:** Adults aged  $\geq 18$  years with B ALL who had r/r disease and presence of  $\geq 5\%$  blasts in the BM at screening.

**Cohort IIB:** Adults aged  $\geq 18$  years with B ALL in  $\geq 2$ nd CR or CRi with MRD-positive disease ( $\geq 10^{-3}$  by central (b) (4) testing and  $< 5\%$  blasts) in the BM at screening.

**Cohort IIC (exploratory):** Adults aged  $\geq 18$  years with B ALL with isolated extramedullary disease (EMD) (including isolated central nervous system [CNS] disease), with or without MRD.

Both, Phase Ib and Phase II, involved consented patients going through the following 5 sequential stages: screening, leukapheresis, lymphodepletion (referred to as pre-conditioning in the study protocol and the statistical outputs), treatment, and follow-up.

Lymphodepletion regimen: intravenous (i.v.) fludarabine  $30 \text{ mg/m}^2$  on Days -6, -5, -4, and -3 (total dose  $120 \text{ mg/m}^2$ ), and i.v. cyclophosphamide  $500 \text{ mg/m}^2$  on Days -6 and -5 (total dose  $1,000 \text{ mg/m}^2$ ).

Please refer to Study Treatment section for information of obe-cel treatment.

**Number of Subjects**

Planned: ~ 215 patients were expected to be enrolled; Phase Ib: 6 to 28 patients to be treated with obe-cel, Phase II across 3 cohorts: ~ 150 patients (at least 90 patients in Cohort IIA, ~50 in Cohort IIB, and ~ 10 in Cohort IIC)

Enrolled: 153; Phase Ib: N=24 (Cohort IA: n=21, Cohort Ib: n=3)

Phase II: N=129 (Cohort IIA: n=112; Cohort IIB: n=10; Cohort IIC: n=7)

Infused Set: N=173 (patients who received at least 1 infusion of obe-cel (Phase Ib: N=16; Cohort IA: n=13; Cohort Ib: n=3. Phase II: N=111, Phase IIA: n=94; Cohort IIB: n=10; Cohort IIC: n=7).

**Diagnosis and Criteria for Inclusion:**

- Male or female adult patients (aged 18 years and older)
- Relapsed or refractory CD19-positive B ALL
- Cohort A: presence of  $\geq 5\%$  blasts in BM at screening
- Cohort B: MRD-positive defined as  $\geq 10^{-3}$  and  $< 5\%$  blast in BM at screening

**Study Treatments*****Obecabtagene autoleucl (obe-cel, AUTO-1)***

Autologous enriched T cells that are transduced with lentiviral vector to express an anti-CD19 chimeric antigen receptor (CAR).

Patients were to receive obe-cel i.v. as a split dose based on disease burden at lymphodepletion with a target dose of  $410 \times 10^6$  CD19 CAR-positive T cells.

Patients with low disease burden ( $\leq 20\%$  blasts) were to receive:

- Dose 1:  $100 \times 10^6$  CD19 CAR-positive T cells;
- Dose 2:  $310 \times 10^6$  CD19 CAR-positive T cells.

Patients with high disease burden ( $> 20\%$  blasts) were to receive:

- Dose 1:  $10 \times 10^6$  CD19 CAR-positive T cells;
- Dose 2:  $400 \times 10^6$  CD19 CAR-positive T cells.

The first split dose was given on Day 1 and the second split dose on Day 10 ( $\pm 2$  days), with no administration permitted after Day 21. A delay of the second dose beyond Day 10 ( $\pm 2$  days) was allowed if the patient developed Grade 1 or 2 CRS or Grade 1 ICANS, that had resolved by the time of infusion of the second dose. The decision to administer the second split dose was made by the Investigator, based on clinical observations following the initial dose.

**Clinical Pharmacology Assessment**

Expansion and persistency of CD19 CAR-positive T cells in BM aspirate and peripheral blood were assessed as determined by (b) (4). The PK profile of AUCATZYL was also monitored with (b) (4) assay with less frequent sampling time points to provide supportive evidence.

Depletion of circulating B-cells was assessed by (b) (4) in the peripheral blood. Time to B-cell recovery (time from AUCATZYL (obe-cel) infusion to reaching  $\geq 20$  B cells/ $\mu$ L peripheral blood) was summarized using the Kaplan-Meier method.

Biomarker data including serum cytokine levels, ferritin and C-reactive protein were summarized descriptively.

Humoral and cellular immunogenicity against obe-cel were evaluated pre- and post-obe-cel treatment.

**Clinical Pharmacology Assessment Results:**

- PK analyses demonstrated a robust expansion, as demonstrated by the C<sub>max</sub> of 114,982 copies/ $\mu$ g/DNA and AUC<sub>0-28d</sub> of 1,138,188 copies/ $\mu$ g DNA x days (geometric means) and prolonged persistency of obe-cel up to 21 months in Cohort IIA.
- 27 of 36 patients (75%) who had ongoing remission in Cohort IIA had ongoing CAR T persistency at the last laboratory assessment as of the data cut-off date.
- B-cell aplasia was observed in most patients and resolved slowly over time in a manner that may follow loss of persistency.

Source: Applicant. Module 5, section 5.3.5.2.