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BLA Clinical Review Addendum

Application Type	Original BLA
Application Number(s)	125868/0
Priority or Standard	Priority
Submit Date(s)	August 06, 2025
Received Date(s)	August 06, 2025
Original PDUFA Goal Date	April 06, 2026
Major Amendment Date	March 27, 2026
PDUFA Date	July 06, 2026
Branch/Division/Office	MHB/DCEH/OCE/OTP
Clinical Reviewer	Ailian (Emily) Xiong, MD, PhD
Clinical Pharmacology Reviewer	Yang Chang, PhD, Pharm D
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Clinical Team leader	Mona Elmacken, MD
Clinical Pharmacology Team Leader (Acting)	Xiaofei Wang, PhD
Supervisory Concurrence	Upendra Mahat, MD Bindu George, MD Asha Das, MD
Review Completion Date	June 24, 2026
Established Name	allogeneic regulatory T cell immunotherapy with HSPC and T cells-vldq
(Proposed) Trade Name	TREGZI
Pharmacologic Class	Allogeneic stem cell and T-cell immunotherapy derived from an HLA-matched donor
Applicant	Orca Biosystems Inc
Formulation(s)	Cell suspension for intravenous infusion
Dosing Regimen	A single dose consisting of 4 single-dose infusion bags comprising: the purified hematopoietic stem and progenitor cells (HSPC) with dose range of $\geq 1.0 \times 10^6$ cells/kg in 100 mL volume to be administered on day0;

	- the purified regulatory T-cells (Treg) with the dose of 1.3 to 3.0×10^6 cells/kg in 100 mL volume to be administered on day 0; - the conventional T-cells (Tcon) with the dose of 1.3 to 6.9×10^6 cells/kg in 15 mL volume to be administered after the start of HSPC infusion on day+2 to +3; - Tcon diluent in 30mL volume
Applicant Proposed Indication(s)/Population(s)	For use in adult patients with hematologic malignancies to improve survival free of Graft-Versus-Host disease (GVHD) in conjunction with an appropriate preparative regimen.
Recommendation on Regulatory Action	Traditional approval
Recommended Indication(s)/Population(s) (if applicable)	For use in matched donor hematopoietic stem cell transplantation with myeloablative preparative regimen, for hematopoietic and immunologic reconstitution and to improve survival free of chronic GVHD disease in the treatment of adults with hematological malignancies.

MHB=Malignant Hematology Branch

DCEH=Division of Clinical Evaluation Hematology

OTP=Office of Therapeutic Products

Executive Summary:

On August 06, 2025, Orca Biosystems Inc submitted original biologics license application (BLA) 125868.0 for allogeneic regulatory T cell immunotherapy with HSPC and T cells-vldq (Tregzi) for the proposed indication for use in adult patients with hematologic malignancies to improve survival free of Graft-Versus-Host disease (GVHD) in conjunction with an appropriate preparative regimen. The original PDUFA due date was April 06, 2026. A major amendment was issued due to CMC and inspection issues on March 27, 2026. The clinical team completed data review and the original review memo, dated March 27, 2026. There was no new clinical data submitted since the major amendment date. The recommendation from the clinical team remains to grant traditional approval based on the demonstration of safety and substantial evidence of effectiveness of Tregzi in Precision T Phase 3 study for the following indication:

Tregzi is an allogeneic stem cell and T-cell immunotherapy indicated for use in matched donor hematopoietic stem cell transplantation with myeloablative preparative regimen, for hematopoietic and immunologic reconstitution and to improve survival free of cGVHD in the treatment of adults with hematologic malignancies.

This document is an addendum to the original BLA Clinical Review and Evaluation Memo, dated on March 27, 2026, which includes the detailed review of clinical data and the basis for approval recommendation. This document provides additional details regarding the recommendation doses, labeling recommendations, minor revisions to original memo, pediatric development plan, and post marketing commitment.

1. Approved Doses and Clinical Pharmacology revision

Following resolution of the CMC deficiency identified in the original review, the applicant completed a reanalysis of the Phase 3 Precision-T clinical trial batch data using a revised (b) (4) approach to replicate the revised analytical method with appropriate controls to the extent possible, enabling reliable cellular dose measurements to be established. Based on the totality of clinical and CMC data, the approved dose ranges for Tregzi are: HSPCs $\geq 1.0 \times 10^6$ viable cells/kg on Day 0; Tregs 1.3×10^6 to 3.7×10^6 viable cells/kg on Day 0; and Tcons 1.3×10^6 to 6.9×10^6 viable cells/kg on Day +2 to +3, administered with 30 mL Tcon diluent. These approved ranges reflect refinement from the originally proposed ranges for Tregs and Tcons. These approved ranges reflect refinements from the originally proposed ranges for Tregs and Tcons, and are based on the recalculated actual dose ranges from the Precision-T clinical trial data

The clinical pharmacology review team concurs that the approved weight-based dosing regimen, with sequential administration of HSPCs and Tregs on Day 0 followed by Tcons on Day +2 to +3, is appropriate for the indicated adult patient population. With these deficiencies resolved, the clinical pharmacology program is now considered to provide supportive evidence of effectiveness, and no alternative dosing regimen based on intrinsic patient factor is recommended at this time.

2. Labeling Recommendations

The labeling discussion did not occur when the original clinical review memo was completed. Therefore, labeling reviews and recommendations are included in this addendum.

Significant revisions were made to the Applicant's proposed United States Prescribing Information to enhance clarity and completeness of the prescribing information. Please see [Table 1](#) below for a summary of significant changes to the United States Prescribing Information.

Table 1: FDA - Summary of Significant Labeling Changes (High level changes and not direct quotations)

Section	Proposed Labeling	Approved Labeling
Section 1 Indication and Usage	Proposed indication: TREGZI is an allogeneic stem cell and T-cell immunotherapy derived from an HLA-matched donor indicated for use in adult patients with hematologic malignancies to improve survival free of graft-versus-host disease (GVHD) in conjunction with an appropriate preparative regimen.	TREGZI is indicated for use in matched donor hematopoietic stem cell transplantation with myeloablative preparative regimen, for hematopoietic and immunologic reconstitution and to improve chronic graft-versus-host disease-free survival, in the treatment of adults with hematological malignancies.
Section 2 Dosage and Administration	Proposed doses: A single dose consisting of 3 components: - the purified hematopoietic stem and progenitor cells (HSPC) with dose range of $\geq 1.0 \times 10^6$ cells/kg in 100 mL volume to be administered on day0; - the purified regulatory T-cells (Treg) with the dose of $(b) (4)$ to 3.5×10^6 cells/kg in 100 mL volume to be administered on day 0; - the conventional T-cells (Tcon) with the dose of $(b) (4)$ to 6.9×10^6 cells/kg in 15 mL volume to be administered after the start of HSPC infusion on day+2 to +3;	Following significant edits were made to Section 2. - Generally, the section was revised and reorganized for clarity - Revised approved doses based on the clinical and CMC data - the purified hematopoietic stem and progenitor cells (HSPC) with dose range of $\geq 1.0 \times 10^6$ cells/kg in 100 mL volume to be administered on day0; - the purified regulatory T-cells (Treg) with the dose of 1.3 to 3.0×10^6 cells/kg in 100 mL volume to be administered on day 0; - the conventional T-cells (Tcon) with the dose of 1.3 to 6.9×10^6 cells/kg in 15 mL volume to be administered after the start of HSPC infusion on day+2 to +3;
Section 3 Dosage and Strength		Revised Table 2 TREGZI Cell Components and Diluent for clarity
Section 5 Warnings and Precautions	Proposed warnings and precautions including positive and negative safety data.	Following significant edits were made to Section 5 - Move safety data from clinical trial to section 6.1 - Remove negative data - Add a statement to Section 5.3, that serious hypersensitivity reactions including anaphylaxis may occur due to DMSO, human serum albumin (HSA), Dextran or murine protein present in TREGZI. - Revision to Section 5.5 to include risk of infections and guidance for monitoring and treatment
Section 6 Adverse Reactions	Proposed safety data per the Applicant's analysis.	Revised based on FDA review team adjudication of adverse events reported in the clinical study.

Section 8 Use in Specific Population		Revised to make this section clear and concise
Section 11 Description		Following significant edits were made to Section 11 - Revised for clarity and to conform with labeling requirements. - Redundant information with section 16 removed.
Section 12 Clinical pharmacology		Following significant edits were made to Section 12 - Removing specific mechanistic claims cannot be verified. - Adding non-clinical studies to support MOA of the product.
Section 14 Clinical Studies		Following significant edits were made to Section 14 - Revised the first paragraph to summarize the study design and patient eligibility criteria. - Added median time (range) from randomization to administration of TREGZI or SoC allograft. - Added clarity to describe the primary efficacy endpoint and listed secondary efficacy endpoints. - Revision based on FDA's review of the clinical study data submitted to the original BLA
Section 16 How Supplied/Storage and Handling		Revised to make this section clear

Source: Created by FDA Clinical Review Team and Associate Director of Labeling

3. Pediatric Development Plan

Tregzi has orphan drug designation for use in matched donor hematopoietic stem cell transplantation with myeloablative preparative regimen, for hematopoietic and immunologic reconstitution and to improve survival free of cGVHD in the treatment of adults with hematologic malignancies and is therefore exempt from Pediatric Research Equity Act (PREA) requirements.

The substantial evidence of effectiveness and safety of Tregzi was demonstrated in adult patients in Precision T Phase 3 study. (b) (4)

(b) (4). The review team had an informal Tcon on June 12, 2026 with the applicant to clarify their (b) (4) study plan. The Applicant clarified that they have not treated (b) (4)

(b) (4)

FDA confirmed that, with the support from the Precision-T study in adult patients, (b) (4)

(b) (4). FDA also asked the Applicant to ensure sufficient numbers of patients in each age group in order to allow for benefit risk assessment. The Applicant agreed with the recommendation, and agreed to requesting a meeting with FDA to (b) (4).

4. Revisions from Original Memo

Table 2. FDA-Adverse Reactions occurring in $\geq 10\%$ of patients treated with TREGZI or unmanipulated allograft control arm in Precision-T Study (Corrected from Table 28 in the original memo)

Adverse Reactions	TREGZI, N = 88			SoC, N=94	
	All Grades %	Grade 3 or Higher %		All Grades %	Grade 3 or Higher %
Infections and infestations ^a					
Viral infections	51	14		47	19
Infections - pathogen unspecified	45	18		56	30
Bacterial infections	40	18		38	16
Fungal infections	20	3		18	0
Gastrointestinal disorders					
Diarrhea*	69	1		79	6
Abdominal pain*	45	0		54	1
Vomiting	44	1		35	0
Nausea*	41	1		44	2
Immune system disorders					
Acute graft-versus-host disease ^b	38	6		46	15
General disorders and administration site conditions					
Mucositis*	85	28		88	37
Edema*	30	0		38	3
Respiratory, thoracic and mediastinal disorders					
Pneumonia	5	5		17	15
Skin and Subcutaneous Tissue Disorders					
Rash*	65	0		55	0
Vascular Disorders					
Hemorrhage*	39	6		33	1

Adverse Reactions	TREGZI, N = 88		SoC, N=94	
	All Grades %	Grade 3 or Higher %	All Grades %	Grade 3 or Higher %
Abbreviations: GVHD, Graft-Versus-Host disease. * includes multiple related terms a infections and infestations were calculated for the first 2 years after transplantation. b aGVHD graded by MAGIC standardization criteria (Harris 2016) as determined by an independent review committee; calculated for the first year after transplantation. Other clinically important adverse reactions that occurred in less than 10% of patients treated with TREGZI include the following: <i>Hepatobiliary disorders:</i> veno-occlusive liver disease 3% in TREGZI group and 2% in control group. <i>Immune system disorders:</i> moderate to severe chronic graft-versus-host disease (GVHD) 13% in TREGZI group and 41% in control group as per International NIH Chronic GVHD Diagnosis and Staging. <i>Injury, poisoning, and procedural complications:</i> Secondary graft failure 1% in TREGZI group and 0% in control group.				

Table 3. FDA-Efficacy Results from Precision-T Study (corrected from Table 7 in the original memo)

Endpoint		TREGZI (N = 93) ³	SoC Control (N = 94)	Comparison
cGFS ^a				
	Number (%) of patients with events	14 (15.1%)	44 (46.8%)	
	Median, months [95% CI]	NE [NE, NE]	7.3 [6.3, 15.5]	
	P value (log-rank)			<.00001
	Hazard Ratio ¹ [95% CI]			0.26 [0.14, 0.47]
Time to moderate or severe cGVHD ^b				
	Number (%) of patients with events	7 (7.5%)	30 (31.9%)	
	Cumulative Incidence % at 12 months [95% CI]	12.6 [5.3, 23.1]	44.0 [31.3, 56.1]	
	P value (Gray's test)			.00002
	Hazard Ratio ² [95% CI]			0.19 [0.08, 0.43]

Abbreviations: cGFS, cGVHD-free survival; cGVHD, chronic graft-versus-host disease; CI, confidence interval; DRI, Disease Risk Index; EAC, endpoint adjudication committee; HLA, human leukocyte antigen; MSD, matched sibling donor; MUD, matched unrelated donor; NE, not estimable. NIH, National Institutes of Health; SoC, standard of care.

^a Stratified log-rank test was used to compare cGFS per EAC between the TREGZI group and the control group

^b Stratified Gray's test was used to compare time to moderate or severe cGVHD per EAC between the TREGZI group and the control group, treating death as a competing risk. An event for this time-to-event endpoint was defined as the first occurrence of moderate to severe cGVHD per NIH consensus criteria. Patients were followed for cGVHD for 2 years post transplant.

¹ Based on a stratified Cox proportional hazards model

² Based on a stratified subdistribution proportional hazards model

^{a,b,1,2} Stratified by randomization stratification factors: donor type (8/8 HLA-MSD versus 8/8 HLA-MUD) and DRI risk category (intermediate risk versus high risk)

³ Four subjects randomized to the TREGZI group did not receive treatment and were censored at Day 1. One subject randomized to the TREGZI group received cryopreserved SoC alloHCT and was analyzed according to the randomized treatment assignment.

Table 4. FDA – Grade ≥3 Laboratory Abnormalities worsening from Baseline in at least 10% of Patients (corrected from Table 31 in the original memo)

Laboratory Test	TREGZI N=88 n (%)	SoC N=94 n (%)
Lymphocyte count decreased	84 (98)	85 (94)
Platelet count decreased	81 (93)	89 (96)
Leukocytes decreased	77 (89)	82 (89)
Neutrophils decreased	66 (77)	75 (83)
Hemoglobin decreased	61 (70)	75 (81)
Alanine aminotransferase increased	10 (11)	7 (7.5)
Aspartate aminotransferase increased	8 (9.2)	6 (6.5)
Creatinine increased	4(5)	3(3)
Total bilirubin increased	4(5)	7(8)

Source: FDA analysis of ADLB dataset. Data cutoff July 15, 2024.

Lab tests are graded according to National Cancer Institute (NCI) common terminology criteria for adverse events (CTCAE) version 5.0.

5. Post Marketing Commitments (PMC)

Given the data for secondary endpoints of overall survival (OS) and graft relapse free survival (GRFS) were not mature at the interim analysis at the original BLA approval (data cutoff date of July 15, 2024), the clinical review team recommends that the complete and submit the final report and datasets for the Phase 3 component of Precision-T study with final analysis and formal hypothesis testing of the secondary endpoints including overall survival and GVHD- and relapse free survival (GRFS) as outlined in the statistical analysis plan. The Applicant agreed with this PMC, and agreed with following timelines for submission of study report:

Database lock for 40th death: May/2026

Primary analysis report submission: May/2027

Final study (5 year follow up)

Study completion: 09/2029

Final report submission: 09/2030