Summary Basis for Regulatory Action

Date:	June 30, 2026
From:	Elizabeth Lessey-Morillon, PhD, CBER/OTP/OCTHT/DCT1
BLA STN:	125868/0
Applicant:	Orca Biosystems Inc
Submission Receipt Date:	August 6, 2025
Major Amendment:	March 27, 2026
PDUFA Action Due Date:	July 6, 2026 (Internal OTP Goal Date: June 30, 2026)
Proper Name:	Allogeneic regulatory T cell immunotherapy with HSPC and T cells-vldq
Proprietary Name:	TREGZI
Indication:	For use in matched donor hematopoietic stem cell transplantation with myeloablative preparative regimen, for hematopoietic and immunologic reconstitution and to improve chronic graft vs host disease (cGVHD)-free survival, in the treatment of adults with hematological malignancies

*PDUFA=Prescription Drug User Fee Act

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

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Discipline Reviews	Reviewer / Consultant - Office/Division
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CMC • CMC Product (Product Office and OCBQ/DBSQC) • Facilities review (OCBQ/DMPQ) • Establishment Inspection Report (OCBQ/DMPQ and Product Office) • QC, Test Methods, Product Quality (OCBQ/DBSQC)	• Elizabeth Lessey-Morillon, PhD, CBER/OTP/OCTHT • Karin Knudson, PhD, CBER/OTP/OCTHT • Saravanan Karumbayaram, M Pharm, PhD, CBER/OTP/OCTHT • Ruipeng Wang, PhD, CBER/OTP/OCTHT • Jana Highsmith, CBER/OCBQ/DMPQ • Hector Carrero, CBER/OCBQ/DMPQ • Salil Ghosh, MS, PhD, CBER/OCBQ/DBSQC • Claire Wernly, PhD, CBER/OCBQ/DBSQC • Marie Anderson, PhD, CBER/OCBQ/DBSQC
Clinical • Clinical (Product Office) • Postmarketing safety Pharmacovigilance review (OBPV/DE) • BIMO	• Ailian (Emily) Xiong, MD, PhD, CBER/OTP/OCE/DCEH/MHB • Joseph Wynne, MD, PhD CDER/OND/OOD/DHMI • Jaspal (JP) Ahluwalia, MD, MPH, CBER/OBPV/DPV • Jennifer Chan, PharmD, CBER/OCBQ/DIS
Statistical • Clinical data (OBPV/DB) • Non-clinical data	• Remy MacDonald, PhD, CBER/OBPV/DB • Fang Chen, PhD, CBER/OBPV
Non-clinical/Pharmacology/Toxicology • Toxicology (Product Office) • Developmental toxicology (Product Office) • Animal pharmacology	• Yongjie Zhou, MD, MS, PhD, CBER/OTP/OPT • Eric Qiao, PhD, CBER/OTP/OPT
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Labeling • Promotional (OCBQ/APLB) • PNR Review	• CAPT Teresa Vu, PharmD, MBA, CBER/OCBQ/DCM/APLB • Oluchi Elekwachi, PharmD, MPH, CBER/OCBQ/DCM/APLB
Other Reviews not captured above in categories: • CDER Consults	• Mona Mansouri, PhD, CBER/OTP/OCTHT

• Devices • CMC/OPPT • Division of Human Tissues	• Andrey Sarafanov, PhD CBER/OTP/OPPT • Haarin Chun, PhD, CBER/OTP/OPPT • Safa Karandish, BS, MT, CBER/OTP/OCTHT • Simone Porter, MD, CBER/OTP/OCTHT • Joseph Wynne, MD, PhD CDER/OND/OOD • Jennifer Reed, PhD, CBER/OTP/OPPT • Sukhanya Jayachandra, PhD, CBER/OTP/OCTHT • Qibing Zhou, PhD, CDER/OPQ/OPQA III/DPQA XV • Xu Di, PhD, CDER/OPQ/OPQA III/DPQA XV • Frances Namuswe, PhD, CDER/OPQ/OPQA III/DPQA XV

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1. Introduction

Orca Biosystems Inc (hereafter referred as 'the Applicant') submitted Biologics License Application (BLA), STN BL 125868/0, for licensure of allogeneic regulatory T cell immunotherapy with HSPC and T cells-vldq, with the proprietary name, TREGZI. 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 vs host disease (cGVHD)-free survival, in the treatment of adults with hematological malignancies. This document summarizes the regulatory basis for approval of TREGZI.

TREGZI is an allogeneic regulatory T cell-based immunotherapy isolated from the mobilized peripheral blood of a donor HLA-matched to the recipient and administered intravenously after appropriate myeloablative conditioning. TREGZI contains hematopoietic stem and progenitor cells (HSPCs), regulatory T cells (Tregs), conventional T cells (Tcons), and Tcon diluent provided in four (4) separate infusion bags labeled for the specific patient. HSPCs (target dose: ≥1.0 x10^6 viable cells per Kg) and Tregs (target dose: 1.3 × 10^6 to 3.5 × 10^6 viable cells per Kg) are administered on day 0 followed by administration of Tcons (target dose: 1.3 × 10^6 to 6.9 × 10^6 viable cells per Kg) on day + 2 to day +3. Tcons are diluted with the Tcon diluent prior to infusion. HSPCs are expected to reconstitute the immunologic and hematopoietic system, Tregs are expected to help preserve immune function and decrease severity of GVHD, and Tcons are expected to accelerate immune reconstitution.

The Applicant has provided safety and substantial evidence of effectiveness of TREGZI from the Precision-T study. The early Phase 1b portion of the Precision-T study enrolled 155 patients with various types of hematological malignancies and treated 154 patients with TREGZI. The initial preliminary efficacy and safety data from Phase 1b study supported phase 3 Precision-T study.

The phase 3 portion of Precision-T is an open label, multicenter, randomized, study (NCT05316701) that compared TREGZI to the standard-of-care (SoC) allograft in adult patients aged 18 to 65 years with acute leukemias (acute lymphoblastic leukemia [ALL] or acute myelogenous leukemia [AML]) in complete remission (CR) or CR with incomplete recovery (CRi) and in patients with myelodysplastic syndrome (MDS) who were eligible for allogeneic transplant per 2017 International Expert Panel recommendations (de Witte et al, 2017) or therapy-related/secondary MDS. Precision-T Study enrolled 187 patients who were randomized (1:1) to receive either TREGZI followed by single-agent tacrolimus or SoC unmanipulated allograft followed by GVHD prophylaxis with tacrolimus and methotrexate. Both TREGZI and the SoC allograft were derived from G-CSF-mobilized peripheral blood apheresis product from 8/8 HLA-

matched (at alleles A, B, C, and DRB1) sibling donors (MSD) or unrelated donors (MUD) and were administered after a myeloablative conditioning regimen such as total body irradiation (TBI)-based or chemotherapy-based options. The primary endpoint of the Phase 3 portion of Precision-T was moderate or severe chronic GVHD-free survival (cGFS), defined as the time from allogeneic hematopoietic stem cell transplantation (alloHSCT) (i.e. day 0) to either death from any cause or the first onset of moderate or severe chronic GVHD graded per 2014 National Institutes of Health (NIH) consensus criteria (Jagasia et al. 2014) within 2 years after day 0 as determined by a blinded independent endpoint adjudication committee (EAC). The median cGFS was not estimable (NE) (95% CI: NE, NE) in TREGZI arm vs 7.3 (95% CI: 6.3, 15.5) months in SoC arm (HR = 0.26 [95% CI: 0.14, 0.47]; $P < .00001$) after a median follow up times of 8.48 (range: 0 to 22) months and 9.03 (range: 0 to 20) months, respectively. The cumulative incidence rate estimate at 12 months was 12.6% (95% CI: 5.3%, 23.1%) for TREGZI arm and 44% (95% CI: 31.1%, 56.1%) for SoC arm (HR = 0.19 [95% CI: 0.08, 0.43]; $P = .00002$). The most common (≥ 10%) Grade 3 or higher adverse reactions in TREGZI arm were: mucositis (28%), bacterial infections (18%), infections – pathogen unspecified (18%) and viral infections (14%). The rate of Grade 3 to 4 hematological toxicity was similar between TREGZI arm and SoC arm.

In summary, Phase 3 Precision-T study is an adequate and well controlled trial with an active concurrent comparator. The treatment with TREGZI demonstrated highly persuasive, clinically meaningful and statistically significant improvement in cGVHD-free survival (cGFS) in patients with hematological malignancies who are eligible for allogeneic hematopoietic transplantation following a myeloablative conditioning regimen compared to patients who received standard alloHSCT followed by tacrolimus and methotrexate. Further, the results demonstrate a statistically significant improvement in time to moderate or severe cGVHD, and key efficacy results were consistent across relevant subgroups. At the time of the primary analysis of cGFS, OS was immature; results from the interim OS analysis did not demonstrate a statistically significant difference between two arms. GVHD relapse free survival (GRFS) was not tested since OS did not reach the statistical significance at the interim analysis per the prespecified hierarchical testing plan. The adverse events observed in subjects treated with TREGZI are typical and known adverse events seen in patients undergoing alloHSCT. These results demonstrate a favorable benefit risk of TREGZI, and denotes clinical benefit in adult patients with hematological malignancies undergoing matched related donor allogeneic HSCT following a myeloablative conditioning regimen, and therefore supports traditional approval. In the context of one well designed adequate and well controlled trial with highly persuasive results, the results from Phase 1b Precision-T study provide confirmatory evidence to substantiate the results of Phase 3 Precision-T study.

During review, FDA designated an amendment as a major amendment on March 27, 2026, to review a substantive amount of new data submitted late in the review cycle to address outstanding major Chemistry, Manufacturing and Controls (CMC) issues regarding assay methodology, method validation, manufacturing consistency concerns, and proposed used of ineligible donors. The applicant made revisions to the donor eligibility process to only use eligible donors per 21 CFR 1271 Subpart C in the manufacture of the commercial lots. The remaining issues were not fully resolved and require CMC PMCs to address, as detailed in Section 3.

Application Specific Contextually Appropriate Regulatory Considerations:

Chemistry Manufacturing and Controls (CMC)

FDA took multiple regulatory considerations into account during the development and review of the BLA for TREGZI, which posed regulatory challenges as a fresh, donor-matched, single lot product for each patient. The approval of this BLA balances pre- and post-approval CMC expectations, enabling timely access to a product addressing significant unmet medical need with clear clinical benefits, while also balancing patient access with generation of evidence to be gathered in the post-marketing setting.

Key regulatory considerations for CMC in the review of TREGZI include:

- Given the favorable clinical benefit of TREGZI, the Agency agreed to accept and review significant CMC information after the designation of a major amendment late in the review cycle. This allowed the applicant to address major CMC deficiencies and use the PMC pathway as a structured approach to finalize the requested studies (see Section 3.a. Product Quality for PMC summary). This adjustment reflected the clinical significance of the program and required extraordinary CMC team effort to complete review within the mandated timelines.

- The specifications for all three drug products were based on the Phase 3 efficacy study (Precision-T study) but also leveraged prior knowledge of HSPCs and related stem cell transplant experience, as applicable. The CMC review team also considered the logistical constraints of infusing the fresh product to the patient within 72 hours from end of first apheresis collection in assessing the product lot release tests. All three cellular products are released based on rapid microbial detection for an interim sterility assurance before obtaining the final 14-day (b) (4) sterility test results and based on demonstrated manufacturing controls. The Treg Potency assay was accepted for lot release despite known limitations compared to direct biological function assessment (e.g., (b) (4) assay). The canonical (b) (4) used to identify Tregs was not required for release given logistical constraints (e.g., sample volume, assay timing) and supplemental supportive data.

- The Agency exercised regulatory judgement to allow a shortened product sample retain duration based on feasibility and stability concerns of a fresh product, and not requiring the applicant to retain product samples for the standard six-month period after expiration per 21 CFR 600.13.

2. Background

In the United States, the 5-year age-adjusted incidence rates (2019 to 2023) for acute lymphocytic leukemia (ALL), acute myeloid leukemia (AML), and myelodysplastic syndrome (MDS) were 1.9, 4.4, and 4.3, respectively, per 100,000 people per year

(National Cancer Institute 2026)[1]. In 2024, over 9,000 patients underwent alloHSCT, the most common indication for alloHSCT in adults is AML[2].

Myeloablative conditioning (MAC) alloHSCT is a standard treatment option with a potential for cure for patients high risk hematological malignancies undergoing HSCT. However, its use remains limited due to risk of various serious complications such as GVHD and opportunistic infections.

GVHD is a serious complication following alloHSCT, and arises when the immunocompetent T cells from the donor graft recognize the recipient's tissues as foreign and initiate an immune response against them. Acute GVHD typically occurs within 100 days post alloHSCT, and mainly affects skin, liver and gastrointestinal tract. Chronic GVHD typically occurs after day 100, can affect multiple organs, and is a leading cause of morbidity, non-relapse mortality and impaired quality of life.

There are no FDA approved therapies for the prevention of cGVHD in alloHSCT setting. Current standard prevention strategies rely on off-label use of calcineurin inhibitor-based regimens, most commonly tacrolimus combined with methotrexate or mycophenolate mofetil. Emerging approaches such as post-transplant cyclophosphamide and abatacept show promise in reducing cGVHD rates, particularly in haploidentical and unrelated donor transplants, but none of these agents are FDA approved specifically for chronic GVHD prevention. There remains a high need for development of therapies that help decrease the risk of cGVHD and improve survival following alloHSCT.

TREGZI is an allogeneic regulatory T cell-based immunotherapy isolated from the mobilized peripheral blood of a donor HLA-matched to the recipient, and administered intravenously after appropriate myeloablative conditioning. It is indicated for use in matched donor HSCT with myeloablative preparative regimen, for hematopoietic and immunologic reconstitution and to improve cGVHD-free survival, in the treatment of adults with hematological malignancies.

Key regulatory history of TREGZI is summarized in Table 1.

Table 1. Regulatory History of TREGZI

Regulatory Events / Milestones	Date
1. IND submission	May 16, 2019
2. Orphan Drug designation granted	January 30, 2024
3. Regenerative Medicine Advanced Therapy Designation granted	July 30, 2020
4. Pre-BLA meeting	March 27, 2025
5. BLA 125868/0 submission	August 6, 2025
6. BLA filed	October 1, 2025
7. Mid-Cycle communication	Meeting Cancelled
8. Late-Cycle meeting	January 23, 2026

[1] Surveillance, Epidemiology, and End Results (SEER) Program (www.seer.cancer.gov)
[2] Broglie L, Xu K, Oloyede T, Chen M, Allbee-Johnson M. Current Uses and Outcomes of Cellular Therapy in the US, Summary Slides 2025 (Center for International Blood and Marrow Transplant Research (CIBMTR)

9. Major Amendment	March 27, 2026
10. Action Due Date	July 6, 2026

3. Chemistry Manufacturing and Controls (CMC)

The review team concludes that the TREGZI manufacturing process and controls can produce a product with consistent quality attributes, and the review team recommends approval with Post-Marketing Commitments (PMCs).

a. Product Quality

TREGZI consists of three separate cell products made from donor apheresis material collected after Granulocyte-Colony Stimulating Factor (G-CSF) mobilization: 1) Hematopoietic stem and progenitor cells (HSPCs), 2) Regulatory T cells (Tregs), and 3) Conventional T cells (Tcons).

Manufacturing Summary

All three cellular drug products (DPs) are derived from a single matched donor through (b) (4) steps. The donor apheresis material is shipped to the manufacturing site where, upon arrival, it is (b) (4) After final formulation and fill of all three cellular DP components and a Tcon dilution buffer, the products are shipped to a treatment center for administration.

The final DPs are tested for sterility, endotoxin, appearance, identity, purity, viable cell dose (i.e., Tregs, HSPCs, or T cells), , and potency. Because the Treg and HSPC DPs are administered within 72 hours post-apheresis collection or seven days post-apheresis collection for the Tcon DP, they are released based on a negative (b) (4) test result, while final sterility results are pending until after product administration.

Manufacturing Controls

The manufacturing control strategy consists of: 1) raw material and reagent qualification programs, 2) in-process monitoring, 3) in-process control testing, 4) lot release and stability testing, 5) manufacturing process validation and continuous process verification, and 6) traceability through chain of identity and chain of custody (COI/COC).The source material is a patient-matched apheresis material and the manufacturer maintains control and traceability from receipt of the apheresis material through shipment of the product to the treatment center. The manufacturer maintains a raw material and reagent qualification program consisting of vendor qualification, confirmation of certificates of

analysis, and material testing. Critical process parameters are established for unit operations based on process knowledge and risk assessment. In-process monitoring and controls are implemented in the process. Process validation studies demonstrated control of the manufacturing process, while supportive extended characterization studies will be completed as a PMC. Product testing on the formulated drug product includes sterility, endotoxin, purity, identity, appearance, dose, purity, and potency. TREGZI is available for infusion based on rapid microbial testing as an interim sterility assurance, while final sterility results remain pending until after administration. Although all assays have been validated, supplemental validation studies will be performed as PMCs to provide a more robust assessment of assay control. Implementation and qualification of reference materials for the methods will be completed as PMCs to improve the assays.

Drug Product Stability and Shelf Life

Treg and HSPC DPs are stable when stored at 5 ± 3°C, with a 72-hour shelf life post-apheresis collection, and (b) (4) in-use stability at (b) (4) . Tcon DP is stable when cryopreserved at < -125°C, with a 7-day post-apheresis collection shelf life and 4-hour in-use stability at 5 ± 3°C post-thaw. Tcon Diluent is stable when stored at °C, with a shelf life.

Comparability

The commercial SAC-02 manufacturing facility and investigational manufacturing facility were deemed equivalent.

CMC Commitments (PMCs):

The CMC issues below were identified but could not be resolved during the review cycle. However, the Agency considered the risk of delaying effective therapy for an unmet medical need. Therefore, these CMC issues will be resolved through the following PMCs:

- The analytical method validation studies for (b) (4) Assays are sufficient to support control over the analytical methods for approval, based on ranges derived from historical experience, manufacturing process knowledge, and risk assessment. Supplemental validation studies can address remaining concerns post-approval, which include 1) the number of replicates in the validation studies used to demonstrate accuracy, linearity, and precision was limited due to replicate failures and specific analytes not meeting pre-determined acceptance criteria across batches; and 2) the previously agreed upon intermediate precision assessments across remain outstanding. In addition, implementation of reference material for the assays is pending. Regulatory judgment considered the limitations of the product manufacturing and testing process and risk of delaying patient access. Supplemental validation studies with adequate sample sizes, broader ranges, and intermediate precision assessments across will establish a more robust analytical foundation post-approval. Addition of reference material will provide additional

assurance of assay and product consistency post-approval. Additional revisions to the method validation reports and adjustments to report generation, not able to be adequately addressed under the review timeline, will also be addressed by PMC.

- To further assure manufacturing consistency at the SAC-02 facility, post-approval extended characterization studies, including evaluation of , are needed. Prior to completion of these studies, the assay needs to be qualified. A PMC for assay qualification and completion of characterization studies to evaluate consistency during the commercial manufacturing process at SAC-02 facility is needed.

- Due to limited manufacturing data from the SAC-02 facility, quarterly reporting of batch production records, extended characterization testing, and submission of trending analyses for the first two years post-approval to monitor manufacturing consistency.

- Updates to qualification criteria for critical manufacturing and testing reagents to improve manufacturing and testing method consistency.

- Submission of the final study report evaluating real-time cumulative leachables using validated analytical methods.

- Updates to Module 3 to reflect changes made during the BLA review.

Manufacturing Risks, Potential Safety Concerns, and Management

Transmission of infectious diseases is controlled through reagent qualification and control of the manufacturing process. Transmission of infectious diseases by the starting allogeneic donor material is controlled by donor screening and testing to allow only eligible donors, qualification of apheresis collection facilities, and starting material acceptance requirements. The manufacturing process is of limited duration and includes (b) (4) manufacturing processes, including (b) (4) system, which is FDA approved. The risk mitigation measures include segregation activities during the manufacturing process, use of closed manufacturing processes where possible, aseptic operations performed in a (b) (4) , operator training and use of personal protective equipment, use of sterile single use materials, where possible, validated cleaning procedures including for product contacting components, and environmental monitoring. All manufacturing unit operations are performed aseptically by trained operators.

b. Testing Specifications

The analytical methods and their validations and/or qualifications reviewed for TREGZI were found to be adequate for their intended purpose with the associated PMCs. The lot release specifications for the Treg, HSPC, and Tcon DPs, are shown in Table 2, Table 3, and Table 4, respectively.

Table 2. Treg DP Lot Release Specifications

Attribute	Acceptance criteria
(b) (4)	(b) (4)
Treg Phenotype	Treg detected
Viability	(b) (4)
% Viable Treg Cells	(b) (4)
Viable Treg Cell Dose	1.3×10^6 - 3.5×10^6 cells cells/kg
(b) (4) Potency	(b) (4)
Appearance	Clear to opaque liquid Color is off-white, white, yellow, orange, to red No visible foreign particles No defects
Interim Sterility Assurance[1]	No organisms detected
Endotoxin	(b) (4)

[1] *Final* *sterility results available after release*

Table 3. HSPC DP Lot Release Specifications

Attribute	Acceptance criteria
(b) (4)	(b) (4)
HSPC Phenotype Identity	HSPC detected
Viability	(b) (4)
% Viable HSPC	(b) (4)
(b) (4)	(b) (4)
Viable HSPC Cell Dose	≥ 1.0×10^6 cells/kg
Appearance	Clear to opaque liquid Color is off-white, white, yellow, orange, to red No visible foreign particles No defects
Interim Sterility Assurance[1]	No organism detected
Endotoxin	(b) (4)

[1] *Final* *sterility results available after release*

Table 4. Tcon DP Lot Release Specifications

Attribute	Acceptance criteria
Tcon Phenotype	T Cell detected
Viability	(b) (4)
Viable T Cell Dose	1.3×10^6 to 6.9×10^6 cells/kg
Appearance	Clear to opaque liquid Color is off-white, white, yellow, orange, to red No visible foreign particles No defects
Endotoxin	(b) (4)
Interim Sterility Assurance [1]	No organisms detected

[1] *Final* (b) (4) *sterility results available after release*

The lot release specifications for Tcon Diluent, used to dilute the Tcon product component prior to administration, are provided in Table 5.

Table 5. Tcon DP Diluent Lot Release Specifications

Test Attribute	Acceptance Criterion
Visual Inspection	Liquid Clarity: Clear Color: Colorless to yellow No visible foreign particles Minimal headspace Container Integrity No defect
HSA Concentration	(b) (4)
(b) (4)	(b) (4)
(b) (4)	(b) (4)
Sterility	No growth detected
(b) (4) Bacterial Endotoxins Test (b) (4) Assay	(b) (4)
(b) (4) Microbial Enumeration Test	(b) (4)
(b) (4) Test	Pass (b) (4)

Division of Biological Standards and Quality Control (DBSQC)

The analytical methods and their validations and/or qualifications reviewed for the TREGZI (Allogeneic regulatory T cell immunotherapy with HSPC and T cells-vldq) drug substance(s) and drug product were found to be adequate for their intended use.

c. CBER Lot Release

CBER Lot Release, including the submission of product samples and lot release protocols to CBER, is not required because each lot is intended to treat a single patient. Consequently, the failure of a single lot would have minimal potential impact on public health.

d. Facilities Review / Inspection

Facility information and data provided in the BLA were reviewed by CBER and found to be sufficient and acceptable. The facility involved in the manufacture of TREGZI is listed in the table below. The activities performed and inspectional history are noted in the table.

Name/Address	FEI number	DUNS number	Inspection/ Waiver	Results/Justification
Orca Biosystems Inc. 7910 Metro Air Parkway, Sacramento, CA 95837 Drug substance manufacturing, drug product manufacturing and release testing	3035546696	119463419	Pre-license inspection	CBER/DMPQ January 2026 VAI

Acronym keys: CBER- Center for Biologics Evaluation and Research; DMPQ- Division of Manufacturing and Product Quality; VAI- Voluntary Action Indicated

CBER/DMPQ conducted a pre-license inspection (PLI) of the Orca Biosystems Inc. facility from January 8 - 15, 2026. A Form FDA 483 was issued at the end of the inspection. All inspectional issues were resolved, and the inspection was classified as VAI.

e. Container/Closure System

The Treg, and HSPC DP are stored in separate 150 mL bags at a target fill volume of 100 mL. Tcon DP is stored in Freezing Bag at a target fill volume of 15mL. The Tcon Diluent is stored in 50 mL -based bag at a target fill volume of 38 mL.

The *drug products* are filled into the plastic/polymer bags as the final container:

DP	Material	Bag Size	Supplier
HSPC	(b) (4)	150 mL	(b) (4)
Treg	(b) (4)	150 mL	(b) (4)
Tcon	(b) (4)	50 mL	(b) (4)
Tcon Diluent	(b) (4)	50 mL	(b) (4)

Orca conducted the container closure integrity testing, employing the method and (b) (4) test method (the test was performed at (b) (4) in , and the (b) (4) test was performed at (b) (4) in); all acceptance criteria were met.

f. Environmental Assessment

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

4. Nonclinical Pharmacology/Toxicology

While no formal nonclinical pharmacology, distribution, or toxicology studies were conducted with TREGZI, the applicant provided the scientific rationale for this application with published data from nonclinical studies evaluating the mechanisms of action of hematopoietic stem cells (HSCs), Tregs, Tcons, and their combinations regarding hematopoietic and immunologic reconstitution and GVHD. Data from these published studies demonstrated key mechanistic findings that contributed to understanding T cell biology and functions in GVHD development and suppression. Additionally, the applicant provided a study report summarizing multiple proof-of-concept (POC) studies evaluating the ability of human Tcons to induce xenogeneic GVHD and the ability of Tregs co-administered with Tcons to mitigate Tcon-induced xenogeneic GVHD in sub-lethally irradiated immunodeficient mice.

Published data show that HSCs could be successfully isolated from murine and human bone marrow (BM) using specific cell surface markers: Thy-1lo Lin- Sca-1+ cells in mice (0.05% of BM cells) and Thy-1+ Lin- CD34+ cells in humans (0.05-0.1% of fetal BM cells). These purified HSCs were shown to be essential for hematopoietic engraftment and immune reconstitution, with as few as 30 murine HSCs sufficient to proliferate, differentiate into most blood lineages (myelomonocytic, B, and T cells), and rescue lethally irradiated mice upon transplantation.

Published nonclinical studies also show that Tregs suppressed Tcon activation and proliferation through direct cell contact, inhibiting interleukin-2 (IL-2) production, and promoting recipient dendritic cell death. Foxp3 expression was essential for Treg development and function, and highly purified, functionally suppressive Tregs could be successfully isolated using specific cell surface markers: CD4+CD25+CD127low/-.

Studies using murine GVHD models demonstrate that mature donor T cells mediated GVHD following allogeneic BM transplantation, while T cell-depleted BM (TCD-BM) prevented GVHD and preserved engraftment and immune reconstitution. A 1:1 donor Treg:Tcon ratio prevented GVHD when administered on the same day as TCD-BM. Early Treg administration, two days prior to Tcon administration, maximized GVHD suppression at lower Treg doses (1:10 Treg:Tcon ratio) while preserving graft-versus-leukemia effects. Data from this study provided the scientific rationale for administering Tregs two days earlier than Tcons clinically.

In the applicant's POC studies using xenogeneic models, co-administration of human donor Tregs with Tcons demonstrated dose-dependent GVHD inhibition in sub-lethally irradiated immunodeficient mice. Coadministration of a 2:1 Treg:Tcon ratio provided significantly longer median survival (78.8 days) compared to 1:1 (60.6 days) or Tcons alone (22.5 days).

No genotoxicity, carcinogenicity, and developmental and reproductive toxicity studies were conducted for TREGZI. These studies are not warranted based on the product characteristics, biological activity, and safety profile.

5. Clinical Pharmacology

Traditional pharmacokinetic and pharmacodynamic studies were not conducted for TREGZI, as standard PK/PD analyses are not applicable for this allogeneic cell therapy. The actual dosing issues were resolved during the review.

6. Clinical/Statistical

a. Clinical Program

The phase 3 portion of Precision-T study provides the safety and substantial evidence of effectiveness of TREGZI. Phase 3 Precision-T is an open label, multicenter, randomized, study (NCT05316701) that compared TREGZI to the standard-of-care (SoC) allograft in adult patients aged 18 to 65 years with acute leukemias (acute lymphoblastic leukemia [ALL] or acute myelogenous leukemia [AML]) in complete remission (CR) or CR with incomplete recovery (CRi) and in patients with myelodysplastic syndrome (MDS) who were eligible for allogeneic transplant per 2017 International Expert Panel recommendations (de Witte et al, 2017) or therapy-related/secondary MDS. The primary endpoint of the phase 3 component of Precision-T was evaluated in the ITT population (n=93 TREGZI arm and n=94 in the SoC arm). moderate or severe chronic GVHD-free survival (cGFS), defined as the time from alloHSCT (i.e. day 0) to either death from any cause or the first onset of moderate or severe chronic GVHD graded per 2014 National Institutes of Health (NIH) consensus criteria (Jagasia et al. 2014) within 2 years after day 0 as determined by a blinded independent endpoint adjudication committee (EAC). Key secondary efficacy endpoints in hierarchical testing order included: time to moderate-to-severe cGVHD, overall survival (OS), and GVHD-free, GRFS through 2 years. Patient-reported outcomes were evaluated as exploratory endpoint.

b. Efficacy Evaluation

Precision T Study met the primary efficacy endpoint of chronic graft-versus-host-disease free survival (cGFS) and the first secondary endpoint of time to moderate or severe chronic graft versus host disease (cGVHD) with statistically significant improvement in TREGZI arm compared to standard of care (SoC) arm.
Key efficacy outcomes are summarized as below:

- The median cGFS was not estimable (NE) (95% CI: NE, NE) in TREGZI arm vs 7.3 (95% CI: 6.3, 15.5) months in SoC arm (HR = 0.26 [95% CI: 0.14, 0.47]; *P* < .00001) after a median follow up times of 8.48 (range: 0 to 22) months and 9.03 (range: 0 to 20) months, respectively.
- The endpoint adjudication committee (EAC) assessed secondary endpoint analysis of time to moderate-to-severe cGVHD: the cumulative incidence rate estimate at 12 months was 12.6% (95% CI: 5.3%, 23.1%) for TREGZI arm and 44% (95% CI: 31.1%, 56.1%) for SoC arm (HR = 0.19 [95% CI: 0.08, 0.43]; *P* = .00002).

- At the time of the primary analysis of cGFS, overall survival (OS) was immature. Results from the interim analysis of OS did not demonstrate a statistically significant difference (HR = 0.49 [95% CI: 0.20, 1.22]; *P* = .11823) between both arms. However, there was a trend for improvement in OS in TREGZI arm.
- GVHD relapse free survival (GRFS) was not tested since the OS did not reach statistical significance at interim analysis per the prespecified hierarchical testing plan.
- While cGFS is a clinical benefit in itself, additional data that includes secondary endpoints related to overall survival and GVHD- and relapse free survival (GRFS) would provide a comprehensive understanding of the benefits of the product. As noted below the timelines for this data submission is May 2027.

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

Bioresearch Monitoring (BIMO) inspection assignments were issued for the sponsor and two domestic clinical investigators that participated in the conduct of Protocol Precision-T. The inspections did not reveal significant issues that impacted the data submitted in this original Biologics License Application (BLA).

d. Pediatrics

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

(b) (4)

e. Other Special Populations

The efficacy of TREGZI has not been studied in any other special populations.

7. Safety and Pharmacovigilance

The primary evidence of the safety of TREGZI for the proposed indication derives from the phase 3 component of Precision-T Study. Phase 1b component of Precision-T study provides supportive evidence of safety. The primary safety analysis was conducted in 88 patients treated on TREGZI arm and 94 patients treated on the SoC alloHSCT arm. Key summary of safety is provided below:

- All patients on TREGZI arm and 99% of patients on SoC arm experienced at least one treatment-emergent adverse event (TEAE). The most common (≥5%) Grade 3 to 4 TEAEs in TREGZI arm were: febrile neutropenia (35%), bacterial

infection (30%), mucositis (28%), viral infection (6.8%), hemorrhage (5.7%), and renal disorders (5.7%).

- At the data cutoff, the rate of death from AEs was higher in patients randomized to the SoC arm (11%) compared to TREGZI arm (3.4%). A higher rate of death due to AE on SoC arm compared to TREGZI arm was also observed on Days 42 and 100 post transplantation: 1) TREGZI arm: 0%; SoC arm: 5.7% on Day 42; 2) TREGZI arm: 3.4%; SoC arm:7.3% on Day 100.
- The most common (≥ 10%) Grade 3 or higher adverse reactions in TREGZI arm were: mucositis (28%), bacterial infections (18%), infections – pathogen unspecified (18%) and viral infections (14%).
- The rate of serious adverse events (SAEs) was higher in the SoC arm (TREGZI arm: 36%; SOC arm: 56%).
- The rate of Grade 3 to 4 hematological toxicity was similar between TREGZI arm and SoC arm.
- There was a slightly higher rate of bacterial infection on TREGZI arm (TREGZI arm 40%; SoC arm: 36%) within the first 100 days after infusion. However, the rates of bacterial infection were similar between TREGZI arm and SoC arm within 2 years after the infusion.

The safety data from the Phase 1b study was consistent with the Phase 3 study. However, for labelling purposes the safety data from the Phase 3 study was considered adequate to inform the safety of the product.

In summary, adverse events observed in subjects treated with TREGZI are typical and known adverse events seen in patients undergoing alloHSCT. Overall, with the exception of early bacterial infections, the safety profile of TREGZI was favorable compared to that of SoC alloHSCT.

Based on a review of the results from the Precision-T study (both Phase 1b and Phase 3), the review team concludes that the safety risks of TREGZI can be adequately mitigated through the methods outlined in the applicant's pharmacovigilance plan (PVP). The review team concurs with the applicant's proposed pharmacovigilance activities as described in the PVP.

The proposed PVP is adequate to monitor postmarketing safety for TREGZI through routine pharmacovigilance in accordance with 21 CFR 600.80. The available safety data do not substantiate the need for a Risk Evaluation and Mitigation Strategy (REMS) or a safety-related postmarketing requirement or commitment (PMR/PMC) study.

8. Labeling

The proposed proprietary name, TREGZI, was received by the Advertising and Promotional Labeling Branch (APLB) on September 18, 2025, and was found acceptable. CBER communicated the acceptability of the proprietary name to the applicant on December 3, 2025. Proposed name suffixes were submitted on December 11, 2025, and the proposed suffix – vldq was found acceptable on June 26, 2026.

The APLB reviewed the proposed Prescribing Information, and Package and Container Labels. We provided our Labeling Review memo on March 16, 2026, from a promotional and comprehension perspective.

The Office of Review Management and Regulatory Review (ORMRR) and the Office of Cellular Therapy and Human Tissue reviewed the package and container labels on June 29, 2026 and June 30, 2026, and with the agreed revisions determined they meet regulatory/statutory requirements.

The Office of Therapeutic Products labeling review team, together with the relevant discipline review teams, reviewed and revised the proposed prescribing information to ensure that it meets regulatory/statutory requirements, is consistent with current labeling practice, conveys clinically meaningful and scientifically accurate information needed for the safe and effective use of the product, and provides clear and concise information for the healthcare providers. With the agreed revisions, the prescribing information is acceptable.

Several significant changes were made to the proposed prescribing information to enhance clarity and completeness of the prescribing information. The indication statement was revised to include myeloablative preparative regimen, add for hematopoietic and immunologic reconstitution, and to improve chronic graft-versus-host disease-free (cGVHD) -free survival. The Adverse Reactions Section (United States Prescribing Information (USPI), Section 6) was revised to comprehensively capture the adverse events occurring following TREGZI and present data comparing to SoC allograft arm side by side. Similarly, the Clinical Studies Section (USPI, Section 14) was restructured to provide comprehensive description of the pivotal trial, population characteristics, and efficacy endpoints that served as the substantial evidence for TREGZI's approval.

9. Advisory Committee Meeting

The submitted information, including clinical study design and trial results, did not raise unresolved scientific or regulatory questions that would benefit from advisory committee discussion. Therefore, this BLA was not referred to the Cellular, Tissue, and Gene Therapies Advisory Committee.

10. Other Relevant Regulatory Issues

The submission was granted priority review.

11. Recommendations and Benefit/Risk Assessment

a. Recommended Regulatory Action

The Applicant has provided evidence of safety and substantial evidence of effectiveness to support traditional approval of TREGZI 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. The review team recommends granting a traditional approval for TREGZI for above indication.

b. Benefit/Risk Assessment

The benefit-risk assessment for TREGZI for the indicated population is based on the results of the Phase 3 component of the Precision-T study, a Phase 3, randomized (1:1), open-label, multicenter study. A total of 187 patients with ALL or AML in CR or CRi or patients with MDS who were eligible for allogeneic transplant per 2017 International Expert Panel recommendations (de Witte et al, 2017) or therapy-related/secondary MDS were enrolled. The study compared TREGZI followed by a single agent tacrolimus for patients with hematological malignancies who are eligible for alloHSCT following a myeloablative conditioning regimen to a standard of care (SoC) allografts followed by tacrolimus and methotrexate.

The primary efficacy endpoint was cGFS determined by a blinded EAC using NIH 2014 chronic GVHD consensus criteria. Key secondary efficacy outcome measures in hierarchical testing order are time to moderate-to-severe cGVHD, OS, and GVHD and relapse free survival.

The totality of the data from Precision-T study demonstrated a favorable benefit-risk profile for TREGZI as a treatment for adult patients with hematologic malignancies who are eligible for allogenic hematopoietic transplantation to improve survival free of cGVHD in conjunction with a myeloablative preparative regimen.

Efficacy: Precision T study demonstrated clinically meaningful statistically significant improvement in cGFS of TREGZI compared to SoC ((HR = 0.26 [95% CI: 0.14, 0.47]; P < .00001) per EAC assessment. Results from the interim analysis of OS did not demonstrate a statistically significant difference (HR = 0.49 [95% CI: 0.20, 1.22]; P = .11823) between two arms. OS was immature at the time of primary analysis of cGFS but considered from a safety perspective. However, there was a trend for improvement in OS in TREGZI arm.

Safety: The rate of adverse reactions including acute GVHD (aGVHD), cGVHD, grade 3 and higher infections, death due to AEs was lower on TREGZI arm compared with SoC arm. The rate of infections, graft failure, veno-occlusive disease/sinusoidal obstruction syndrome (VOD/SOS) are similar in two arms.

Overall benefit-risk assessment:

Overall, the benefit of TREGZI outweighs its risks in the indicated population 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.

c. Recommendation for Postmarketing Activities

Postmarketing commitments (PMCs) subject to reporting requirements under section 506B

The Applicant agreed to the following Clinical PMC:

1. Orca Biosystems Inc. commits to 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.

   Primary analysis report submission: May 31, 2027

   Final Report Submission: September 30, 2030

Postmarketing commitments (PMCs) not subject to the reporting requirements under section 506B

The Applicant agreed to the following CMC PMCs:

2. Orca Biosystems, Inc. commits to revise and update all method validation reports (b) (4) based on the revisions requested in information requests sent April 24, 2026 to June 18, 2026. Orca Biosystems, Inc. will submit the final study report(s) as a Prior Approval Supplement by August 31, 2026.

   Final Report Submission: August 31, 2026

3. Orca Biosystems, Inc. commits to establish a system to improve the quality and integrity of data handling for future study data. Orca Biosystems, Inc. will submit the proposal as a Product Correspondence by August 31, 2026. Orca Biosystems, Inc. will submit the implementation report as a Product Correspondence by July 31, 2027.

   Proposal Submission: August 31, 2026

   Final Implementation Report: July 31, 2027

4. Orca Biosystems, Inc. commits to perform a full risk assessment of the (b) (4) Assay procedures and controls to evaluate the root cause of the repeatability validation parameter failures during the method validation studies performed under VAL-0178 and reported in VAL-0212. After completion of the risk and root cause assessments, as necessary, corrective actions will be proposed, justified, and implemented. Orca Biosystems, Inc. will submit the risk assessment and, if necessary, proposed corrective actions as Prior Approval Supplement by September 30, 2026. Orca Biosystems, Inc. will submit a final study report

summarizing the implemented corrective actions and, as needed, updated assay Standard Operating Procedures and/or Work Instructions as a Prior Approval Supplement by July 31, 2027.
Risk Assessment Submission: September 30, 2026

Final Report Submission: July 31, 2027

5. Orca Biosystems, Inc. commits to perform supplemental validation of the (b) (4) Assay assessing all validation parameters using a statistically justified number of new batches. The validation study will incorporate any method procedure and control changes deemed necessary by the risk assessment in PMC #3. Orca Biosystems, Inc. will submit the study protocol as Product Correspondence by December 31, 2026. Orca Biosystems, Inc. will submit the final study report(s) as a Prior Approval Supplement by July 31, 2027.

   Study Protocol Submission: December 31, 2026

   Final Report Submission: July 31, 2027

6. Orca Biosystems, Inc. commits to perform supplemental validation of the (b) (4) Assays using (b) (4) to evaluate intermediate precision of the assay when (b) (4) . Orca Biosystems, Inc. will submit the study protocol(s) as Product Correspondence by September 30, 2026. Orca Biosystems, Inc. will submit the final study report(s) as a Prior Approval Supplement by July 31, 2027.

   Study Protocol Submission: September 30, 2026

   Final Report Submission: July 31, 2027

7. Orca Biosystems, Inc. commits to perform supplemental validation of the following (b) (4) for the (b) (4) Assay:

   (b) (4)

Orca Biosystems, Inc. will submit study protocol(s) as Product Correspondence by September 30, 2026. Orca Biosystems, Inc. will submit the final study report(s) as a Prior Approval Supplement by July 31, 2027.

Study Protocol Submission: September 30, 2026

Final Report Submission: July 31, 2027

8. Orca Biosystems, Inc. commits to perform supplemental validation to assess all validation parameters for the (b) (4) across the range of (b) (4) unless otherwise indicated, using a (b) (4) . Orca Biosystems, Inc. will establish a LOD. Orca Biosystems, Inc. will submit study protocol(s) as Product Correspondence by September 30, 2026. Orca Biosystems, Inc. will submit the final study report(s) as a Prior Approval Supplement by July 31, 2027.

   Study Protocol Submission: September 30, 2026

   Final Report Submission: July 31, 2027

9. Orca Biosystems, Inc. commits to perform supplemental validation of the following (b) (4) for the Assay:

   (b) (4)

   Orca Biosystems, Inc. will submit study protocol(s) as Product Correspondence by September 30, 2026. Orca Biosystems, Inc. will submit the final study report(s) as a Prior Approval Supplement by July 31, 2027.

   Study Protocol Submission: September 30, 2026

   Final Report Submission: July 31, 2027

10. Orca Biosystems, Inc. commits to perform supplemental validation of the (b) (4) to evaluate

intermediate precision of the assay when (b) (4) . Orca Biosystems, Inc. will submit the study protocol(s) as Product Correspondence by September 30, 2026. Orca Biosystems, Inc. will submit the final study report(s) as a Prior Approval Supplement by July 31, 2027.

Study Protocol Submission: September 30, 2026

Final Report Submission: July 31, 2027

11. Orca Biosystems, Inc. commits to perform supplemental validation of the (b) (4) to evaluate intermediate precision of the assay when . Orca Biosystems, Inc. will submit the study protocol(s) as Product Correspondence by September 30, 2026. Orca Biosystems, Inc. will submit the final study report(s) as a Prior Approval Supplement by July 31, 2027.

    Study Protocol Submission: September 30, 2026

    Final Report Submission: July 31, 2027

12. Orca Biosystems, Inc commits to the following for the first two years of commercial manufacturing:

    a. Submit batch production records, including in-process test results, lot release data, and characterization data quarterly.

    b. Conduct extended characterization testing for (b) (4) commercial-scale lots.

    Orca Biosystems, Inc. will provide interim reports as Product Correspondence quarterly for 2 years after the start of commercial manufacturing. Orca Biosystems, Inc. will submit the final study report(s) as a Prior Approval Supplement by November 30, 2028.

    Interim Report Submission: Quarterly for 2 years after start of commercial manufacturing

    Final Report Submission: November 30, 2028

13. Orca Biosystems, Inc commits to conduct the following concerning the characterization assay:

    (b) (4)

(b) (4)

Orca Biosystems, Inc. will submit the revised SOPs and/or WIs as Prior Approval Supplement by September 30, 2026. Orca Biosystems, Inc. will submit the study protocol(s) as Product Correspondence by October 31, 2026. Orca Biosystems, Inc. will submit the final study report(s) as a Prior Approval Supplement by September 30, 2027.

Revised SOPs/Wis Submission: September 30, 2026

Study Protocol Submission: October 31, 2026

Final Report Submission: September 30, 2027

14. Orca Biosystems, Inc. commits to perform the following concerning the use of reference materials in their release assays:

    a. Qualification of reference materials for the to establish defined operating ranges, release criteria, and acceptance limits.

    b. Revise the release method standard operating procedures (SOPs) and/or Work Instructions (WIs) to include use of the reference material for the (b) (4)

(b) (4)

Orca Biosystems, Inc. will submit the revised SOPs and/or WIs, and the final study report(s) as a Prior Approval Supplement by December 31, 2026.
Final Report Submission: December 31, 2026

15. Orca Biosystems, Inc. commits to performing a study evaluating to revise the (b) (4) assay acceptance criteria of critical manufacturing (b) (4) and release testing (b) (4) Orca Biosystems, Inc. will submit the study protocol(s) as Product Correspondence by October 31, 2026. Orca Biosystems, Inc. will submit the final study report(s) as a Prior Approval Supplement by August 31, 2027.

    Study Protocol Submission: October 31, 2026

    Final Report Submission: August 31, 2027

16. Orca Biosystems, Inc. commits to providing full leachables study results using validated analytical methods for compounds identified as extractables with high-risk levels. Orca Biosystems, Inc. will submit the final study report(s) as a Prior Approval Supplement by November 30, 2026.

    Final Report Submission: November 30, 2026

17. Orca Biosystems, Inc. commits to update all eCTD Module 3 sections in BLA 125868, as applicable, to incorporate changes to your submission resulting from the interactive review process from the original BLA submission review period. The Module 3 update will include a detailed summary table of all changes with hyperlinks. Orca Biosystems, Inc. will submit the revised Module 3 as a PMC-

    Final Study Report by August 31, 2026.

    Full Module 3 Update: August 31, 2026