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**FOOD AND DRUG ADMINISTRATION
Center for Biologics Evaluation and Research
Office of Therapeutic Products
Office of Pharmacology and Toxicology
Division of Pharmacology/Toxicology 2
Pharmacology/Toxicology Branch 2**

BLA NUMBER: 125868.024/.050

DATE RECEIVED BY CBER: 12/11/2025

DATE REVIEW COMPLETED: 06/08/2026

PRODUCT: (b) (4) (TREGZI)

APPLICANT: Orca Biosystems Inc

PROPOSED INDICATION: Use in adult patients with hematologic malignancies to improve survival free of Graft-Versus-Host disease (GVHD) in conjunction with an appropriate preparative regimen

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EXECUTIVE SUMMARY:

TREGZI ((b) (4)) is an allogeneic hematopoietic stem cell and T cell immunotherapy indicated for hematopoietic and immunologic reconstitution and to improve survival free of chronic graft vs host disease (cGVHD) in adult patients with hematologic malignancies undergoing a myeloablative preparative regimen. TREGZI is derived from human leukocyte antigen (HLA)-matched donor peripheral blood and consists of purified hematopoietic stem and progenitor cells (HSPCs), regulatory T cells (Tregs), conventional T cells (Tcons), and Tcon diluent.

This supplement includes the applicant's preliminary leachables study conducted to support the safety of manufacturing process flows and post-manufacturing storage of each of the components of TREGZI for a representative storage duration (48 hours for Tregs and HSPCs, (b) (4) for Tcons, and (b) (4) for Tcon diluent). This review memo summarizes the pharmacology/toxicology review of the toxicological risk assessment conducted for the leachable compounds identified by this study. Based on the review of this risk assessment, there are no outstanding P/T issues.

PHARMACOLOGY/TOXICOLOGY RECOMMENDATION:

Based on review of the leachables toxicological risk assessment, the data provide sufficient support for approval of STN #125868.24.

Formulation and Chemistry:

A single dose of TREGZI contains four drug products (DPs) stored in separate infusion bags:

- HSPC DP (HSPCs in multiple electrolytes injection Type 1 [MEI] with 2% human serum albumin [HSA]) stored in a (b) (4) bag
- Treg DP (Tregs in MEI with 2% HSA) stored in a (b) (4) bag
- Tcon DP (Tcons in MEI with 3-4% HSA, 7.5% dimethyl sulfoxide [DMSO], and 1.8% hydroxyethyl starch [hetastarch]) stored in a (b) (4) bag
- Tcon diluent DP (MEI with 2% HSA) stored in a (b) (4) bag

Abbreviations

Abbreviation	Full Term
AET	Analytical Evaluation Threshold
Admin	Administration
BW	Body Weight
cGVHD	Chronic Graft-Versus-Host Disease
CMC	Chemistry, Manufacturing, and Controls
DMSO	Dimethyl Sulfoxide
DP(s)	Drug Product(s)
(b) (4)	
(b) (4)	
GVHD	Graft-Versus-Host Disease

HLA	Human Leukocyte Antigen
HSPC(s)	Hematopoietic Stem and Progenitor Cell(s)
HSA	Human Serum Albumin
IV	Intravenous
(b) (4)	(b) (4)
LOAEL	Lowest Observed Adverse Effect Level
MAC	Myeloablative Conditioning
MEI	Multiple Electrolytes Injection Type 1
MF	Modifying Factor
MOS	Margin of Safety
NOAEL	No Observed Adverse Effect Level
PDE	Permitted Daily Exposure
POD	Point of Departure
PVC	Polyvinyl Chloride
SCT	Safety Concern Threshold
Tcon(s)	Conventional T Cell(s)
Treg(s)	Regulatory T Cell(s)

INTRODUCTION

TREGZI ((b) (4)) is an allogeneic hematopoietic stem cell and T cell immunotherapy derived from human leukocyte antigen (HLA)-matched donor peripheral blood. TREGZI is indicated to improve survival free of chronic graft-versus-host disease (cGVHD) in adult patients with hematologic malignancies and consists of purified hematopoietic stem and progenitor cells (HSPCs), regulatory T cells (Tregs), and conventional T cells (Tcons), which are intended to reduce GVHD while preserving graft-versus-infection and graft-versus-tumor effects. TREGZI is administered intravenously (IV) after myeloablative conditioning (MAC), with the HSPC ($>1.0 \times 10^6$ cells/kg) and Treg ((b) (4)) - 3.5×10^6 cells/kg) DPs being administered on Day 0, followed by Tcon DP ((b) (4)) - 6.9×10^6 cells/kg) diluted 1:2 with Tcon diluent DP on Day 2 to Day 3.

In response to CMC Information Request #7 (received 12/12/2025), the applicant included preliminary reports for screening and toxicological risk assessment of leachables potentially arising from TREGZI DP administration. These reports summarize the results of leachables screens performed using ((b) (4))

methods. The applicant also includes a toxicological risk assessment including permitted daily exposure (PDE) calculations for all identified leachables.

NONCLINICAL STUDIES

Study Number	Study Title	Report Number
1	TREGZI Drug Product Leachables Screening Study	RPT-0456

Study #1

Methods:

Manufacturing and storage of HSPC, Treg, Tcon, and Tcon diluent DPs were simulated by passing the process solutions and excipients through all manufacturing and storage single-use materials under historically observed process durations and temperatures to produce mock DP samples. HSPC, Treg, Tcon, and Tcon diluent mock DP samples were then (b) (4) before analysis. Additionally, mock administration solutions were generated by transferring simulated excipient solutions through single-use administration materials (e.g., syringes, IV sets, saline bags, etc.) to produce administration (admin) samples. Mock DP and admin samples were produced in (b) (4) and analyzed for leachables by (b) (4). The levels of detected leachables in both sample types were summed to produce a total exposure per dose of TREGZI administered. An analytical evaluation threshold (AET) for organic leachables was calculated from a safety concern threshold (SCT) of 120 µg/day for products administered for less than one month¹, a total administration volume of (b) (4) mL, and an uncertainty factor of (b) (4) to account for analytical variability and multiple sources of leachables (i.e., DP containers and admin materials):

(b) (4)

Reviewer's note: Although TREGZI is administered over the course of two to three days, the sponsor has assumed a worst-case scenario in which all components are administered on the same day.

Toxicological Risk Assessment

(b) (4) total leachable compounds were detected, with (b) (4) detected at levels above the AET. For each compound, the applicant performed a literature review to identify existing data on the compound's safety parameters. Where data did not exist for a compound of interest, toxicological data was sought for structurally similar compounds (a toxicological analogue). This information was used to select a point of departure (POD), such as a no observed adverse effect level (NOAEL) or a lowest observed adverse effect level (LOAEL), in order to calculate the permitted daily exposure (PDE) for each leachable (Table 1):

(b) (4)

where BW is patient body weight (assumed to be 50 kg) and modifying factor (MF) is the product of various factors accounting for species extrapolation, route of exposure, individual

¹ Food and Drug Administration, M7(R2) Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk, (2023).

variability, exposure duration extrapolation, likelihood of severe toxicity, and differences between POD types.²

Table 1. Identities and PDEs of leachables detected above AET

Compound	CAS RN	Sum per Dose (µg)	Parenteral PDE (µg/day)	Margin of Safety
(b)	(4)			

Source: BLA 125788/50, Report RPT-0456v2, Table 5 (page 21)

Reviewer's comment: Due to a lack of published compound-specific data, the PDE for both (b) (4) and the additional unidentified (b) (4) related leachable were determined based on a toxicological analogue ((b) (4)). This reviewer finds this approach reasonable.

Results:

- The PDE values calculated for each of the (b) (4) leachables are summarized in Table 1.

Reviewer's note: The sponsor provided revised per dose leachables levels and revised RPT-0456 and EPR-038 response to CMC IR#25 (received 05/15/2026). The revised values were the result of correcting a unit conversion error in which the per dose leachable level was erroneously calculated as the volume of the sample divided by the detected leachable concentration rather than the volume of the sample multiplied by the detected leachable concentration.

- (b) (4) leachable compounds ((b) (4)) had margins of safety (MOS; defined as the parenteral PDE divided by the total exposure per dose) above one but substantially below ten.

² "Impurities: Guideline For Residual Solvents Q3C(R8)," ed. International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (2021).

Reviewer's comment: In general, a worst-case scenario MOS^{(b) (4)} indicates that a compound poses low toxicological risk. Additionally, the per dose exposures to each these (b) (4) compounds were comparable or below established regulatory tolerable daily intake values for each compound (or toxicological analogue) as provided by the applicant in Study Report# EPR-0038. Thus, the risk posed by these compounds is likely minimal.

- (b) (4) was detected in a (b) (4) out of (b) (4) at a per dose level of (b) (4).

Reviewer's comment: The applicant provided a toxicological risk assessment of the (b) (4), noting that (b) (4) are generally not considered to pose mutagenic or systemic toxicity risks due to limited in vivo persistence^{3,4}. Additionally, the applicant stated that the (b) (4) reduces the likelihood of immunogenicity. This reviewer agrees that the safety risk posed by the (b) (4) is low.

COMMUNICATIONS WITH THE APPLICANT

P/T IR #4 was sent to the applicant on 06/03/2026 and the response was received on 06/04/2026. The applicant clarified in their response that the original leachables levels were erroneously calculated by dividing the sample volume (mL) by the detected leachable concentration (µg/mL) rather than by multiplying these values. The applicant also provided the raw values for leachable concentrations as well as the individual calculations used to convert them to per administration exposure levels. This reviewer finds this response adequate, and as the corrected leachable exposure levels were all found to be below their respective PDEs, no post-marketing commitment (PMC) is recommended at this time.

CONCLUSION OF RISK ASSESSMENT

This leachables screen and toxicological risk assessment did not identify any leachables present above their respective PDEs. While several leachables were found to have a MOS < 10, given the single administration of TREGZI, lack of reported acute toxicities related to leachables in clinical studies with TREGZI, and the worst-case scenario assumptions made by the applicant in these studies regarding interval between HSPCs/Treg and Tcon DP administration, the risks posed by these leachables are acceptable at the time of approval.

Reviewer's note: Per the consulting CMC reviewer, Orca Biosystems Inc. commits to providing additional leachables study results by October 2026. These results will be obtained using validated analytical methods for compounds identified as extractables with high-risk levels

³ "Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals S6(R1)," ed. International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (2011).

⁴ Y. Tasdemiroglu, R. G. Gourdie, and J. Q. He, "In vivo degradation forms, anti-degradation strategies, and clinical applications of therapeutic peptides in non-infectious chronic diseases," no. 1879-0712 (Electronic).

(Section 3.2.S.2.3.2, pages 59–74, and Report RPT-0327, pages 19–20). Additional P/T review will be required for these data.