



**Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research (CBER)
Office of Biostatistics and Pharmacovigilance (OBPV)
Division of Pharmacovigilance (DPV)**

PHARMACOVIGILANCE ORIGINAL BLA MEMORANDUM

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To: Elizabeth Lessey-Morillon, PhD.
Chair of the Review Committee
Office of Therapeutic Products

Through: Craig Zinderman, MD, MPH
Acting Director DPV
OBPV, CBER, FDA

Subject: Review of Pharmacovigilance Plan

Sponsor: Orca Biosystems Inc.

Product: (b) (4)

Application Type / Number BLA / STN 125868/0

Proposed Indication For use in adult patients with hematologic malignancies to improve survival free of graft-versus-host disease

Submission Date: August 6, 2025

Action Due Date: April 6, 2026

1 OBJECTIVE

The purpose of this review is to assess the adequacy of the sponsor's pharmacovigilance plan (PVP) submitted under the original BLA 125868/0 based on the

safety profile of [REDACTED] Our review will determine whether any safety-related studies such as Post-Marketing Requirements (PMRs) and/or Post-Marketing Commitments (PMCs) are warranted, or if Risk Evaluation and Mitigation Strategies (REMS) are required for (b) (4) [REDACTED] should the indication for this product be approved. Please refer to Appendix A for the complete list of materials reviewed for this memorandum.

2 BACKGROUND

Allogeneic hematopoietic stem cell transplantation (allo-HSCT) is a potentially curative treatment for hematologic malignancies, including acute leukemias, myelodysplastic syndromes, and lymphomas. Graft-versus-host disease (GVHD) is a major complication of allo-HSCT and occurs when donor T cells recognize recipient tissues as foreign, leading to immune-mediated injury most commonly involving the skin, gastrointestinal tract, and liver. Acute GVHD develops in approximately 30–50% of patients receiving human leukocyte antigen (HLA)-matched transplants, and chronic GVHD occurs in approximately 30–50%, contributing substantially to post-transplant morbidity and mortality. Prevention of GVHD must be balanced with preservation of the beneficial graft-versus-leukemia (GVL) effect.

This type of allogeneic cell therapy consists of purified regulatory T cells (Tregs), conventional T cells (Tcons), and hematopoietic stem and progenitor cells (HSPCs) derived from an HLA-matched donor. HSPCs engraft and restore hematopoiesis, Tcons support immune reconstitution and GVL activity, and Tregs suppress alloreactive immune responses that drive GVHD. By delivering defined populations of these cells, the product is designed to promote durable engraftment and immune recovery while reducing the incidence and severity of GVHD.

3 PRODUCT INFORMATION

3.1 Product Description

(b) (4) [REDACTED] is an allogeneic stem cell and T-cell immunotherapy isolated from the mobilized peripheral blood of an HLA-matched donor comprising of purified Regulatory T-cells, Conventional T-cells and purified hematopoietic stem and progenitor cells.

3.2 Proposed Indication

The sponsor's proposed indication statement as submitted to the original BLA 125868/0 is:

(b) (4) [REDACTED] 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.

OBPV defers to product office on the final language for the indication statement. Please see the final version of the package insert submitted by the sponsor for the final agreed-upon indication after FDA review.

4 PERTINENT REGULATORY HISTORY

This is a new BLA for a product that does not have market authorization elsewhere in the world. FDA granted (b) (4) Orphan Drug Designation (ODD) in 2024.

5 DESCRIPTION OF (b) (4) CLINICAL TRIAL SAFETY DATABASE

The clinical safety data submitted in support of this application are derived from the following clinical studies:

- Precision-T Phase 1b is a single-arm, multicenter study conducted in participants aged 18 to 75 years with advanced hematologic malignancies undergoing myeloablative conditioning (MAC) allogeneic hematopoietic cell transplantation (alloHCT) across multiple centers in the United States. The study enrolled 154 participants (with 110 meeting phase 3 eligibility criteria included in the primary integrated safety analysis) and aimed to characterize the safety and efficacy of (b) (4) followed by tacrolimus in participants undergoing alloHCT from HLA-matched donors (related or unrelated) who were not otherwise eligible for the Phase 3 component of Precision-T. The study included participants with active leukemia, aged 66-75 years, with mild renal/hepatic impairment, and low-risk disease features. First patient enrolled on December 06, 2019, with enrollment completed in Q2 2025. Data cut-off occurred on April 30, 2025.
- Precision-T Phase 3 is a randomized, open-label, multicenter study conducted in participants aged 18 to 65 years with acute leukemia (myeloid, lymphoid, or mixed phenotype) in complete remission (CR) or myelodysplastic syndrome (MDS) eligible for transplant across 19 centers in the United States. The study enrolled 187 participants and aimed to compare rates of chronic graft-versus-host disease (cGVHD)-free survival between participants undergoing alloHCT with either (b) (4) followed by single-agent tacrolimus or standard of care (SoC) unmanipulated allograft followed by tacrolimus plus methotrexate. Participants were randomized 1:1 to receive either (b) (4) (N=93)¹ or SoC (N=94), with stratification by donor type (matched sibling donor vs. matched unrelated donor) and Disease Risk Index category (intermediate vs. high risk). First patient randomized on

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- ¹ 93 participants were randomized to (b) (4) but only 88 were treated and included in the safety analysis
 - 1 participant had COVID-19 on scheduled treatment day and received cryopreserved SoC instead (counted in SoC safety group)
 - 4 participants did not receive (b) (4) as of data cutoff (2 withdrew consent, 1 relapsed, 1 received (b) (4) after data cutoff)

June 21, 2022, with enrollment completed in Q2 2025. Data cut-off occurred on July 15, 2024.

Reviewer comment: OBPV reviews clinical trial safety data to inform our understanding of the adequacy of the pharmacovigilance plan. However, we defer to the product office clinical reviewer, in collaboration with the biostatistics reviewer, for detailed analysis and assessment of safety issues identified in the clinical trials. Please refer to the clinical reviewer's assessment and the final approved package insert for comprehensive evaluation of the clinical safety database.

6 SPONSOR'S PHARMACOVIGILANCE PLAN

Table 1. Sponsor's Pharmacovigilance Plan*

Type of Concern	Safety Concern	Proposed Action
Identified	Graft-Versus-Host Disease (GVHD)	Routine pharmacovigilance practices to monitor, identify, and evaluate reports of GVHD reactions in patients treated with [REDACTED] in post-marketing and clinical study environments (Precision-T). Further characterize incidence, severity, risk factors, and outcomes.
Identified	Graft Failure	Routine pharmacovigilance practices to monitor, identify, and evaluate reports of graft failure in patients treated with (b) (4) [REDACTED] in post-marketing and clinical study environments (Precision-T). Further characterize incidence, severity, risk factors, and outcomes.
Potential	Batch Manufacturing Failure	Routine pharmacovigilance practices to monitor and evaluate the clinical course and engraftment of patients who received [REDACTED] infusions from a batch considered a manufacturing failure. Ongoing monitoring through Precision-T study.
Potential	Infusion-Related Reactions	Routine pharmacovigilance practices to monitor, identify, and evaluate reports of infusion-related reactions in post-marketing and clinical study environments (Precision-T). Further characterize incidence, severity, risk factors, and outcomes.
Potential	Hypersensitivity	Routine pharmacovigilance practices to monitor, identify, and evaluate reports of hypersensitivity in post-marketing and clinical study environments (Precision-T). Further characterize incidence, severity, risk factors, and outcomes.
Potential	Secondary Malignancy, including Post-transplant	Routine pharmacovigilance practices to monitor, identify, and evaluate reports of secondary malignancy and PTLD in post-marketing and clinical study

	Lymphoproliferative Disorder (PTLD)	environments (Precision-T). Further characterize incidence, severity, risk factors, and outcomes.
Potential	Grade ≥3 Infection	Routine pharmacovigilance practices to monitor, identify, and evaluate reports of Grade ≥3 infections in post-marketing and clinical study environments (Precision-T). Further characterize incidence, severity, risk factors, and outcomes.
Potential	Thrombotic Microangiopathy (TMA)	Routine pharmacovigilance practices to monitor, identify, and evaluate reports of TMA in post-marketing and clinical study environments (Precision-T). Further characterize incidence, severity, risk factors, and outcomes.
Potential	Hepatic Veno-Occlusive Disease (VOD) or Sinusoidal Obstruction Syndrome (SOS)	Routine pharmacovigilance practices to monitor, identify, and evaluate reports of VOD/SOS in post-marketing and clinical study environments (Precision-T). Further characterize incidence, severity, risk factors, and outcomes.
Potential	Transmission of Serious Infection	Routine pharmacovigilance practices to monitor, identify, and evaluate reports of donor-derived infections in post-marketing and clinical study environments (Precision-T). Further characterize incidence, severity, risk factors, and outcomes.
Potential	Sepsis	Routine pharmacovigilance practices to monitor, identify, and evaluate reports of sepsis in post-marketing and clinical study environments (Precision-T). Further characterize incidence, severity, risk factors, and outcomes.
Missing	Use in Pediatric Population	Routine pharmacovigilance to monitor reported occurrence of pediatric exposure to (b) (4) in post-marketing setting. (b) (4) is not indicated for use in pediatric patients. (b) (4) PREA waiver granted.
Missing	Use in Elderly Population	Routine pharmacovigilance to monitor, identify, and evaluate safety and outcomes of patients over age 65 treated with (b) (4) through Precision-T study and post-marketing surveillance in real-world setting.

*Adapted from Tables 5.1-5.15 Pharmacovigilance Plan, 125868/0

7 ANALYSIS OF SPONSOR'S PHARMACOVIGILANCE PLAN

7.1 Important Identified Risks

7.1.1 Graft-Versus-Host Disease (GVHD)

Acute and chronic GVHD are multisystem disorders common in patients undergoing myeloablative allogeneic hematopoietic stem cell transplantation (MAC-alloHCT). Acute

GVHD generally occurs within 100 days of transplant with maculopapular rash, gastrointestinal symptoms, and elevated bilirubin. Chronic GVHD is usually diagnosed after 100 days, with manifestations including scleroderma-like or lichen planus-like skin involvement, gastrointestinal ulcerations and sclerosis, and increased bilirubin.

In the Phase 3 study (N=187), acute GVHD was reported in 34.1% of (b) (4) patients and 46.8% in the standard of care (SoC) group. Grade ≥ 3 acute GVHD occurred in 6.8% of (b) (4) patients compared to 12.8% in the SoC group. The median time to onset was similar between groups (26.0 days for (b) (4) vs. 25.5 days for SoC), and 70% of acute GVHD cases in the (b) (4) group resolved.

Chronic GVHD of all grades occurred in 15.9% of (b) (4) patients and 47.9% in the SoC group. Moderate or severe chronic GVHD occurred in 12.5% of (b) (4) patients compared to 34.0% in the SoC group. The median time to onset was 184.5 days in the (b) (4) group versus 160.0 days in the SoC group.

Transplantation with (b) (4) was associated with lower rates and severity of both acute and chronic GVHD compared to SoC. The favorable safety profile was maintained across age groups. Patients received standardized GVHD prophylaxis according to institutional protocols. Mitigation strategy is routine pharmacovigilance.

7.1.2 Graft Failure Graft failure is a serious complication of allogeneic HSCT classified as primary (failure to achieve initial engraftment) or secondary (loss of graft function after initial engraftment). In the Primary Integrated Safety Analysis Set (N=198)², overall graft failure occurred in 1.5% of (b) (4) patients compared to 0% in the SoC group. Primary graft failure occurred in 2 participants (1.0%), both grade 4 events. Secondary graft failure occurred in 1 participant (0.5%). None of the 3 participants with graft failure died.

In the Phase 3 study, neutrophil engraftment was achieved in 100% of (b) (4) patients with a median time of 13 days, and platelet engraftment was achieved in 98.9% with a median time of 17 days. Notably, 2.5% of patients received (b) (4) product that did not meet the target HSPC dose, yet all 5 participants achieved neutrophil engraftment by day +18 and platelet engraftment by day +35. The incidence of graft failure with (b) (4) was low, all cases were non-fatal, and most participants achieved eventual engraftment. Mitigation strategy is routine pharmacovigilance.

7.2 Important Potential Risks

7.2.1 Batch Manufacturing Failure Batch manufacturing failure refers to production of (b) (4) product that does not meet the target hematopoietic stem and progenitor cell (HSPC) dose specification of 1.6×10^6 viable HSPCs/kg body weight. In

² 198 Orca-T patients = 88 (Phase 3 treated) + 110 (Phase 1b who were also phase 3-eligible)

the Primary Integrated Safety Analysis Set (N=198), an [REDACTED] product was successfully manufactured for all 198 participants. However, 2.5% of patients received product that did not meet the target HSPC dose.

Despite receiving below-target HSPC doses, all 5 participants achieved neutrophil engraftment by day +18 and platelet engraftment by day +35. None experienced secondary graft failure. While batch manufacturing failure represents a potential risk, clinical data demonstrate that even when manufacturing does not meet target specifications, clinical outcomes including engraftment remain favorable. Mitigation strategy is routine pharmacovigilance.

7.2.2 Infusion-Related Reactions Infusion-related reactions (IRR) are acute adverse events occurring during or shortly after product infusion. In the Phase 3 study (N=182), the overall incidence of IRR was 22.7% in the [REDACTED] group compared to 13.8% in the SoC group. All IRR events in the [REDACTED] group were grade 1 (11.4%) or grade 2 (11.4%), with no grade ≥3 events reported, compared to 2.1% grade 3 events in the SoC group.

In the Primary Integrated Safety Analysis Set (N=198), the overall IRR incidence was 31.8% in the [REDACTED] group versus 13.8% in the SoC group. All events were grade 1 or 2. Cytokine release syndrome (CRS) was rare, occurring in only 1 participant (0.5%) in the [REDACTED] group as a grade 1 event that resolved within one day.

While IRR incidence was higher with [REDACTED] likely due to three separate infusions versus one, events were notably milder with no severe reactions. IRR was managed with standard premedication and monitoring protocols. Mitigation strategy is routine pharmacovigilance.

7.2.3 Hypersensitivity Hypersensitivity reactions are immune-mediated responses that can occur following infusion of biological products. Using a broad search strategy, the overall incidence of hypersensitivity in the Phase 3 study (N=182) was 25.0% in the (b) (4) [REDACTED] group compared to 8.5% in the SoC group. Notably, all grade ≥3 events identified by the broad search were cases of stomatitis, a complication commonly associated with myeloablative conditioning rather than true hypersensitivity reactions.

Using a narrow, clinically specific search strategy, the incidence of hypersensitivity in the Phase 3 study was 2.3% in the [REDACTED] group compared to 0% in the SoC group. In the Primary Integrated Safety Analysis Set (N=198), the narrow search identified hypersensitivity in 2.0% of [REDACTED] patients versus 0% in the SoC group.

While broad search criteria suggested elevated hypersensitivity with [REDACTED] clinically specific criteria demonstrated very low incidence of true hypersensitivity reactions. The risk appears manageable with standard premedication protocols. Mitigation strategy is routine pharmacovigilance.

7.2.4 Secondary Malignancy, Including Post-transplant Lymphoproliferative Disorder (PTLD) Secondary malignancies are a known long-term complication following allogeneic HSCT due to prolonged immunosuppression and prior exposure to

chemotherapy and radiation. In the Phase 3 study (N=182), secondary malignancy occurred in 1.1% of [REDACTED] patients compared to 2.1% in the SoC group. No cases of post-transplant lymphoproliferative disorder (PTLD) were reported in either group.

In the Primary Integrated Safety Analysis Set (N=198), secondary malignancy occurred in 1.0% of [REDACTED] patients versus 3.2% in the SoC group. No cases of PTLD were observed in either group.

The observed incidence with [REDACTED] was low and lower than SoC. The absence of any PTLD cases is reassuring, though longer follow-up is needed as these malignancies may develop years after transplantation. The follow-up period in the Phase 3 study was approximately two years. Mitigation strategy is routine pharmacovigilance.

7.2.5 Grade ≥ 3 Infection Grade ≥ 3 infections are expected complications following myeloablative conditioning and allogeneic HSCT due to prolonged immunosuppression. In the Primary Integrated Safety Analysis Set (N=198), the overall incidence of grade ≥ 3 infections was 45.5% in the [REDACTED] group compared to 51.1% in the SoC group.

Bacterial infections occurred in 37.4% of [REDACTED] patients versus 38.3% in the SoC group. The most common bacterial infections ($\geq 3\%$) included sepsis (11.6%), bacterial sepsis (6.1%), and streptococcal sepsis (2.5%). The median time to onset was 8 days in the [REDACTED] group compared to 16 days in the SoC group, and 91.9% of bacterial infections resolved.

Viral infections occurred in 19.7% of [REDACTED] patients compared to 29.8% in the SoC group. The most common viral infections ($\geq 2\%$) included COVID-19 (6.6%), herpes simplex (2.0%), and viral pneumonia (2.0%).

Fungal infections occurred in 4.0% of [REDACTED] patients versus 2.1% in the SoC group. All events were grade 3 except for one grade 5 aspergillus infection in the (b) (4) [REDACTED] group.

Transplantation with [REDACTED] was not associated with an overall increase in grade ≥ 3 infections compared to SoC. Patients received standardized antimicrobial prophylaxis according to institutional protocols. Mitigation strategy is routine pharmacovigilance.

7.2.6 Thrombotic Microangiopathy (TMA) Thrombotic microangiopathy is a known complication of allogeneic HSCT characterized by microangiopathic hemolytic anemia, thrombocytopenia, and organ dysfunction. In the Phase 3 study (N=182), TMA occurred in 0% of [REDACTED] patients compared to 1.1% in the SoC group.

In the Primary Integrated Safety Analysis Set (N=198), TMA occurred in 0.5% of (b) (4) [REDACTED] patients versus 1.1% in the SoC group. In the 90-day safety update, TMA occurred in 1.0% of [REDACTED] patients compared to 2.1% in the SoC group.

The observed incidence with [REDACTED] was very low and comparable to or lower than SoC. All cases were grade 1-2 and resolved. Mitigation strategy is routine pharmacovigilance.

7.2.7 Hepatic Veno-Occlusive Disease (VOD) or Sinusoidal Obstruction Syndrome (SOS) Hepatic veno-occlusive disease (VOD), also known as sinusoidal obstruction syndrome (SOS), is a potentially life-threatening complication of allogeneic HSCT characterized by hepatomegaly, hyperbilirubinemia, and fluid retention. In the Phase 3 study (N=182), VOD/SOS occurred in 3.4% of [REDACTED] patients compared to 2.1% in the SoC group.

In the Primary Integrated Safety Analysis Set (N=198), VOD/SOS occurred in 3.0% of (b) (4) [REDACTED] patients versus 2.1% in the SoC group. The [REDACTED] cases included 4 grade 3 events, all of which resolved, and 2 grade 4 events, both ongoing at data cutoff. No fatal cases occurred in either group.

The incidence with [REDACTED] was low and comparable to SoC. Patients received standard VOD/SOS prophylaxis according to institutional protocols. Mitigation strategy is routine pharmacovigilance.

7.2.8 Transmission of Serious Infection

Transmission of serious infection from donor to recipient is a potential risk associated with allogeneic cellular therapies derived from human blood. To mitigate this risk, all donors were screened for HIV, HTLV, HBV, HCV, T. pallidum, T. cruzi, West Nile virus, transmissible spongiform encephalopathy (TSE) agents, vaccinia, and Zika virus. In the Primary Integrated Safety Analysis Set (N=198), there were zero cases of donor-derived transmission of serious infection in either group. While transmission is a theoretical risk, the comprehensive donor screening program appears highly effective. Mitigation strategy is routine pharmacovigilance.

7.2.9 Sepsis

Sepsis is a life-threatening complication that can occur following allogeneic HSCT, particularly in the early post-transplant period due to neutropenia and immunosuppression. In the Primary Integrated Safety Analysis Set (N=198), sepsis within 14 days of infusion occurred in 19.2% of [REDACTED] patients compared to 7.4% in the SoC group. Notably, there were no fatal cases of early sepsis (0%) in the (b) (4) [REDACTED] group compared to 2.1% in the SoC group, and all early sepsis cases in the [REDACTED] group resolved.

Sepsis occurring on or after day +14 was reported in 7.1% of (b) (4) [REDACTED] patients compared to 11.7% in the SoC group. There was one fatal case (0.5%) in the (b) (4) [REDACTED] group compared to 0% in the SoC group.

While there was higher incidence of early sepsis in the [REDACTED] group, the favorable outcomes with complete resolution and no early mortality, combined with lower rates of late sepsis, suggest that sepsis remains a manageable complication. Mitigation strategy is routine pharmacovigilance.

7.3 Important Missing Information

7.3.1 Use in Pediatric Population

(b) (4) is not indicated for use in pediatric patients.

7.3.2 Use in Elderly Population

The Precision-T Phase 1b allowed patients up to age 75, and three patients over the age of 65 were treated. The Precision-T Phase 3 excluded patients over age 65. There is no biological mechanism on which to expect a different safety profile for those patients over the age of 65 compared to those who are 65 or younger. Mitigation strategy for this missing information is routine pharmacovigilance.

8 DPV ASSESSMENT

Based on a review of the results of the study Precision-T, (both Phase 1b and Phase 3), we conclude that (b) (4) safety risks can be adequately mitigated with the methods outlined in the sponsor's PVP. DPV concurs with the sponsor's proposed pharmacovigilance activities in the proposed PVP.

9 DPV RECOMMENDATIONS

Should the product be approved for the new indication of use in adult patients with hematologic malignancies to improve survival free of graft-versus-host disease (GVHD), the proposed PVP dated July 2, 2025, is adequate to monitor postmarketing safety for (b) (4) with routine pharmacovigilance in accordance with 21 CFR 600.80. The available safety data do not substantiate a need for a Risk Evaluation and Mitigation Strategy (REMS) or a safety-related postmarketing requirement or commitment (PMR/PMC) study. Please see the final version of the package insert submitted by the sponsor for the final agreed-upon language for the label.

APPENDIX A
Materials Reviewed

Table A1: Materials reviewed in support of this assessment

Date	Source	Document Type	Document(s) Reviewed
August 6, 2025	Orca Biosystems, Inc.	125868/0.1	Module 1.14.1.2, Label Draft (Annotated) Module 1.16.1, Pharmacovigilance Plan (PVP), v1.0 Module 2.7.4, Summary of Clinical Safety Module 5.3.5.1, Clinical Study Report (CSRs) Module 5.3.5.3, Integrated Summary of Safety (ISS)