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NDA/BLA Multi-disciplinary Review and Evaluation

Disclaimer: In this document, the sections labeled as “Data” and “The Applicant’s Position” are completed by the Applicant, which do not necessarily reflect the positions of the FDA.

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
PDUFA Goal Date	April 06, 2026
Division/Office	OCE/DCEH /MHB
Review Completion Date	March 27, 2026
Established Name	(b) (4)
(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 (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; - 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)	(b) (4) 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 chronic GVHD disease in the treatment of adults with hematological malignancies.

Table of Contents

Reviewers of Multi-Disciplinary Review and Evaluation	10
Additional Reviewers of Application	10
Glossary.....	11
1 Executive Summary.....	14
1.1. Product Introduction	14
1.2. Conclusions on the Substantial Evidence of Effectiveness	14
1.3. Benefit-Risk Assessment (BRA).....	18
1.4. Patient Experience Data	21
2 Therapeutic Context	23
2.1. Analysis of Condition	23
2.2. Analysis of Current Treatment Options	24
3 Regulatory Background	27
3.1. U.S. Regulatory Actions and Marketing History.....	27
3.2. Summary of Presubmission/Submission Regulatory Activity	27
4 Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety	34
4.1. Office of Scientific Investigations (OSI).....	34
4.2. Product Quality	34
4.3. Clinical Microbiology.....	36
4.4. Devices and Companion Diagnostic Issues	36
5 Nonclinical Pharmacology/Toxicology	37
5.1. Executive Summary	37
5.2. Referenced NDAs, BLAs, DMFs	38
5.3. Pharmacology.....	38
5.4. ADME/PK	40
5.5. Toxicology	40
5.5.1. Genetic Toxicology.....	40
5.5.2. Carcinogenicity	41

5.5.3.	Reproductive and Developmental Toxicology	41
5.5.4.	Other Toxicology Studies	41
6	Clinical Pharmacology.....	42
6.1.	Executive Summary.....	42
6.2.	Summary of Clinical Pharmacology Assessment.....	42
6.2.1.	Pharmacology and Clinical Pharmacokinetics.....	42
6.2.2.	General Dosing and Therapeutic Individualization	46
6.2.2.1.	General Dosing.....	46
6.2.2.2.	Therapeutic Individualization	49
6.2.2.3.	Outstanding Issues	50
6.3.	Comprehensive Clinical Pharmacology Review	50
6.3.1.	General Pharmacology and Pharmacokinetic Characteristics.....	50
6.3.2.	Clinical Pharmacology Questions	51
7	Sources of Clinical Data	54
7.1.	Table of Clinical Studies	54
7.2.	Review Strategy	57
8	Statistical and Clinical Evaluation	59
8.1.	Review of Relevant Individual Trials Used to Support Efficacy.....	59
8.1.1.	Precision-T	59
8.1.2.	Study Results	67
8.1.3.	Integrated Review of Effectiveness	94
8.1.4.	Assessment of Efficacy Across Trials	95
8.1.5.	Integrated Assessment of Effectiveness	96
8.2.	Review of Safety	97
8.2.1.	Safety Review Approach.....	98
8.2.2.	Review of the Safety Database.....	99
8.2.3.	Adequacy of Applicant's Clinical Safety Assessments.....	105
8.2.4.	Safety Results.....	108
8.2.5.	Analysis of Submission-Specific Safety Issues	132
8.2.5.1.	Secondary Malignancy, Including PTLD.....	133
8.2.5.2.	Grade ≥ 3 Infection.....	134

8.2.5.3.	Graft Failure (Primary or Secondary)	136
8.2.5.4.	TMA	137
8.2.5.5.	VOD/SOS	138
8.2.6.	Clinical Outcome Assessment (COA) Analyses Informing Safety/Tolerability	138
8.2.7.	Safety Analyses by Demographic Subgroups	138
8.2.8.	Specific Safety Studies/Clinical Trials	139
8.2.9.	Additional Safety Explorations	139
8.2.10.	Safety in the Postmarket Setting	141
8.2.11.	Integrated Assessment of Safety	142
8.3.	Statistical Issues	147
8.4.	Conclusions and Recommendations	147
8.4.1.	Approach to Substantial Evidence of Effectiveness	149
9	Advisory Committee Meeting and Other External Consultations	151
10	Pediatrics	152
11	Labeling Recommendations	153
12	Risk Evaluation and Mitigation Strategies (REMS)	154
13	Postmarketing Requirements and Commitment	155
14	Associate Director of Labeling (OTP/OCE)	156
15	Branch Chief (Malignant Hematology Branch)	157
16	Oncology Center of Excellence (OCE) Signatory	158
17	Division Director (Division of Clinical Evaluation Hematology)	159
18	Director (Office of Clinical Evaluation)	160
19	Appendices	161
19.1.	References	161
19.1.1.	The Applicant's List of References:	161
19.1.2.	The FDA's References:	164
19.2.	Financial Disclosure	166
19.3.	Nonclinical Pharmacology/Toxicology	167

19.4.	OCP Appendices (Technical documents supporting OCP recommendations)	167
19.4.1.	Population PK Analysis	167
19.4.1.1.	Executive Summary	167
19.4.1.2.	PPK Assessment Summary.....	167
19.4.1.3.	PPK Review Issues.....	168
19.4.1.4.	Reviewer’s Independent Analysis.....	168
19.4.2.	Exposure-Response Analysis	168
19.4.2.1.	ER (efficacy) Executive Summary	168
19.4.2.2.	ER (efficacy) Assessment Summary.....	168
19.4.2.3.	ER (safety) Executive Summary	170
19.4.2.4.	ER (safety) Assessment Summary.....	170
19.4.2.5.	ER Review Issues	171
19.4.2.6.	Reviewer’s Independent Analysis.....	171
19.4.2.7.	Overall benefit-risk evaluation based on E-R analyses.....	171
19.5.	Additional Safety Analyses Conducted by FDA.....	171
19.6.	FDA Grouped Terms	171

Table of Tables

Table 1. Applicant – FDA Interactions	27
Table 2. FDA-Regulatory History.....	29
Table 3. Applicant – Exposure-Response Analyses.....	43
Table 7. Applicant - Listing of Relevant Clinical Trials	55
Table 11. Applicant - Baseline Disease Characteristics (Precision-T Phase 3 ITT Analysis Set)	74
Table 12. Applicant - Efficacy of Orca-T Versus SoC (Precision-T Phase 3 ITT Analysis Set)	77
Table 13. FDA-Efficacy results of Precision-T in ITT Analysis Population	82
Table 14. Applicant – Safety Population, Size, and Denominators.....	100
Table 15. FDA-Baseline Demographic Characteristics-Safety Population	102
Table 16. FDA-Baseline Disease Characteristics-Safety Population	102
Table 17. Applicant - Treatment-Emergent Period	104
Table 18. Applicant - Summary of On-Study Deaths by Primary Cause (Precision-T Phase 3 Safety Analysis Set).....	108
Table 19. Applicant - Grade 5 Treatment-Emergent Adverse Events (Precision-T Phase 3 Safety Analysis Set)	109
Table 20. FDA-Deaths in the safety population (July 15,2024)	110
Table 21. FDA-Causes of Death from AEs (July 15,2024).....	111
Table 22. FDA-Deaths in the safety population (April 30, 2025).....	111
Table 23. FDA-Causes of Death from Adverse events (April30,2025).....	112
Table 24. Applicant – Treatment-Emergent SAEs Occurring in >1 Participant Overall (Precision-T Phase 3 Safety Analysis Set)	113
Table 25. FDA-Nonfatal SAEs in ≥ 2% patients.....	115
Table 26. FDA-Summary of aGVHD in Safety Population	118
Table 27. FDA-Summary of cGVHD in Safety Population	119
Table 28. FDA-Summary of Infusion Related Reaction in Safety Population	120
Table 29. Applicant - Summary of Adverse Events – (Precision-T Phase 3 Safety Analysis Set)	121

Table 30. Applicant - Treatment-Emergent Adverse Events Reported in $\geq 10\%$ of Participants (Precision-T Phase 3 Safety Analysis Set)	121
Table 31. FDA-Any Grade TEAEs Occurring in Patients	124
Table 32. FDA- Any-Grade TEAEs Occurring in $\geq 10\%$ of Primary Safety Population By Preferred Term	124
Table 33. FDA-Summary of TEAEs in $\geq 10\%$ of Primary Safety Population by System Organ Class	126
Table 34. FDA-Adverse Reactions occurring in $>10\%$ and with higher frequency in (b) (4) group compared to Control group	127
Table 35. Applicant - Laboratory Abnormalities Worsening From Baseline to Grade 3 or 4 (Precision-T Phase 3 Safety Analysis Set).....	129
Table 36. FDA – Laboratory Abnormalities worsening from Baseline in at least 10% of Patients	130
Table 37. FDA – Grade ≥ 3 Laboratory Abnormalities worsening from Baseline in at least 10% of Patients.....	130
Table 38. FDA-AESIs analysis in Safety Population	133
Table 39. FDA- Grade 3 and higher Infections in the Safety Population	135
Table 40. FDA-Neutrophil Recovery	137
Table 41. FDA-Platelet Recovery	137
Table 42. FDA-Deaths occurring in ISS Population	143
Table 43. FDA-Most Common TEAEs Precision-T study Occurring in $\geq 20\%$ of Integrated Safety Population	144
Table 44. FDA-Grade 3 and Higher TEAEs Occurring in $\geq 5\%$ of Integrated Safety Population.....	145
Table 45. FDA-AESI Analysis in ISS Population.....	145
Table 46. FDA – Grade ≥ 3 Key Laboratory Abnormalities worsening from Baseline in at least 5% of Patients in ISS Population	146

Table of Figures

Figure 1. FDA-KM Plot of cGFS per EAC Assessment of OOS Products	35
Figure 2. Applicant – Precision-T Phase 3 Participant Disposition	70
Figure 3. Applicant - KM Plot of cGFS per EAC Assessment by Treatment Group (Precision-T Phase 3 ITT Analysis Set).....	78
Figure 4. Applicant – Forest Plot of cGFS by Subgroups (Precision-T Phase 3 ITT Analysis Set)	79
Figure 5. FDA-KM Plot of cGFS per EAC assessment (ITT Analysis set).....	81
Figure 6. FDA-KM Plot of cGFS per EAC assessment (Primary Safety Analysis set) ...	83
Figure 8. Applicant-KM Plot of OS by Treatment Group (Precision-T Phase 3 ITT Analysis Set)	86
Figure 9. Applicant-KM Plot of GRFS by Treatment Group (Precision-T Phase 3 ITT Analysis Set)	86
Figure 10. FDA-Plot of Cumulative Incidence of Moderate or Severe cGVHD in ITT Analysis Set.....	88
Figure 11. FDA-KM plot of OS in ITT Analysis Set.....	90
Figure 12.FDA-KM Plot of GRFS in ITT Analysis Set.....	90

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DCEH=Division of Clinical Evaluation Hematology

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Glossary

β-hCG	beta-human chorionic gonadotropin
ADME	absorption, distribution, metabolism, excretion
AE	adverse event
AESI	adverse event of special interest
aGVHD	acute graft-versus-host disease
alloHCT	allogeneic hematopoietic cell transplantation
ALL	acute lymphoid leukemia
AML	acute myeloid leukemia
BFT	busulfan/fludarabine/thiotepa
BLA	biologics license application
CBER	Center for Biologics Evaluation and Research
CFR	Code of Federal Regulations
cGFS	chronic graft-versus-host disease-free survival
cGVHD	chronic graft-versus-host disease
CMC	chemistry, manufacturing, and controls
CR	complete response
CRi	complete response with incomplete hematologic recovery
CRO	contract research organization
CSR	clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
DLCO	diffusing capacity of the lung for carbon monoxide
DMC	data monitoring committee
DRI	Disease Risk Index
EAC	endpoint adjudication committee
ECG	electrocardiogram
eGFR	estimated glomerular filtration rate
FDA	Food and Drug Administration
G-CSF	granulocyte colony-stimulating factor

GRFS	graft-versus-host disease-free and relapse-free survival
GVHD	graft-versus-host disease
GVI	graft versus infection
GVL	graft versus leukemia
GVT	graft versus tumor
HCT	hematopoietic cell transplantation
HCT-CI	Hematopoietic Cell Transplantation-Specific Comorbidity Index
HLA	human leukocyte antigen
HSPC	hematopoietic stem and progenitor cell
ICH	International Conference on Harmonization
IL	interleukin
IND	Investigational New Drug
ITT	intent to treat
IV	intravenous(ly)
LTFU	long-term follow-up
MAC	myeloablative conditioning
MAGIC	Mount Sinai Acute GVHD International Consortium
MDS	myelodysplastic syndrome
MedDRA	Medical Dictionary for Regulatory Activities
MPAL	mixed phenotype acute leukemia
MSD	matched sibling donor
MUD	matched unrelated donor
NDA	new drug application
NMDP	National Marrow Donor Program
NME	new molecular entity
NRM	nonrelapse mortality
OPQ	Office of Pharmaceutical Quality
OS	overall survival
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation

PBSC	peripheral blood stem cell
PD	pharmacodynamics
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PT	preferred term
PTLD	posttransplantation lymphoproliferative disorder
QoL	quality of life
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
SoC	standard of care
SOC	system organ class
TBI	total body irradiation
TCD	T-cell depletion
Tcon	conventional T cell
TEAE	treatment emergent adverse event
Treg	regulatory T cell
ULN	upper limit of normal
VOD	veno-occlusive disease

1 Executive Summary

1.1. Product Introduction

(b) (4) (TREGZI) is an allogeneic stem cell and T-cell immunotherapy derived from the mobilized peripheral blood of an 8/8 HLA-matched donor.

(b) (4) is composed of 4 single-dose infusion bags comprising the following cell components and a diluent:

- The purified hematopoietic stem and progenitor cells (HSPCs), with proposed dose of $\geq 1.0 \times 10^6$ cells, and purified regulatory T-cells (Tregs), with proposed dose of $(b) (4) \times 10^6$ to 3.5×10^6 cells, administered on day 0, and
- The conventional T-cells (Tcons), with proposed dose of $(b) (4) \times 10^6$ to 6.9×10^6 cells, administered day +2 to +3 (after the start of HSPC infusion on day 0).

(b) (4) is preceded by myeloablative preparative regimen, to promote graft engraftment. The administered HSPCs are purified (b) (4) to reduce the risk of Graft-versus-host-disease (GVHD) while providing for hematopoietic and immunologic reconstitution. Purified Tregs are administered on the same day after the HSPCs prior to the administration of Tcons, because they are thought to be immunosuppressive and will help to control the development of GVHD and will promote immune reconstitution. Tcons drug substance is prepared (b) (4)

Tcons are expected to help reconstitute the immune system by restoring peripheral T cell counts, reduce the incidence of relapse and infection but increase the risk of graft versus host disease. Tcons are administered approximately two to three days later to accelerate immune reconstitution and mitigate the high infection risks that are associated with T-cell depleted HSPCs grafts. Acceleration of immune cell reconstitution is characterized by the complete or partial restoration of peripheral blood T-cell counts. Tregs are known to expand rapidly in vivo in patients who are lymphodepleted and infusing these cells prior to Tcons has been reported to improve immune reconstitution (Nguyen et al. 2007). In summary, the sequential administration of HSPCs and Tregs on day 0 and Tcons on day +2 is intended to provide both immune reconstitution and GVHD control.

1.2. Conclusions on the Substantial Evidence of Effectiveness

Substantial evidence of effectiveness of (b) (4) in adult patients with advanced hematologic malignancies undergoing myeloablative conditioning (MAC)-

based condition regimen followed by allogeneic hematopoietic stem cell transplantation (AlloHSCT) was demonstrated in an adequate and well controlled study, Phase 3 component of Precision-T Study.

Phase 3 portion of Precision-T is an open label, multicenter, randomized, study (NCT05316701) that compared (b) (4) 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 (b) (4) followed by single-agent tacrolimus or SoC unmanipulated allograft followed by GVHD prophylaxis with tacrolimus and methotrexate. Both (b) (4) and the unmanipulated 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.

Efficacy:

The primary endpoint of the phase 3 component of Precision-T was 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, relapse-free survival (GRFS) through 2 years. Patient-reported outcomes were evaluated as exploratory endpoint. The Primary efficacy analysis was conducted in the intend-to-treat (ITT) population (93 patients randomized to (b) (4) arm and 94 patients randomized to SoC arm). Key efficacy outcomes are summarized below:

- The median cGFS was NE (95% CI: NE, NE) in (b) (4) 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 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 (b) (4) 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, 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 two arms. However, there was a trend for improvement in OS in the (b) (4) arm.

- GRFS was not tested since the OS did not reach statistical significance at interim analysis per the prespecified hierarchical testing plan.

In summary, Phase 3 Precision-T study met its primary endpoint with statistically significant improvement in (b) (4) arm compared to SoC allograft arm. The magnitude of treatment effect was robust and consistent across key subgroups. The magnitude of treatment effect was similarly robust on secondary endpoints, and consistent across subgroups.

Safety:

The primary evidence of the safety of (b) (4) for the proposed indication derives from Precision-T phase 3 study. Precision-T phase 1b component of the study provides supportive evidence of safety. The primary safety analysis was conducted in 88 patients treated on (b) (4) arm and 94 patients treated on the SoC alloHSCT arm.

- All patients on (b) (4) arm and 99% of patients on SoC arm experienced at least one treatment-emergent adverse event (TEAE). The most common ($\geq 5\%$) Grade 3 to 4 TEAEs in the (b) (4) arm were: febrile neutropenia (35%), bacterial infection (30%), mucositis (28%), viral infection (6.8%), hemorrhage (5.7%), and renal disorders (5.7%).
- The rate of death from AEs was higher in patients randomized to the SoC arm (11%) compared to the (b) (4) arm (3.4%). A higher rate of death due to AE on SoC arm was observed compared to (b) (4) arm on Days 42 and 100 post transplantation: 1) (b) (4) arm: 0%; SoC arm: 5.7% on Day 42 ; 2) (b) (4) arm: 3.4%; SoC arm: 7.3% on Day 100. The rate of serious adverse events (SAEs) was higher in the SoC arm ((b) (4) arm: 36%; SOC arm: 56%).
- The rate of Grade 3 to 4 hematological toxicity was similar between (b) (4) arm and SoC arm.
- There was a slightly higher rate of bacterial infection on (b) (4) arm ((b) (4) arm 44%; SoC arm: 35%) within the 100 days after infusion. However, the rates of bacterial infection were similar between the (b) (4) arm and SoC arm within 2 years after the infusion. The early higher rate of bacterial infection may be due to the T cells depletion in HPSCs of (b) (4). Notably, this higher rate of early bacterial infection did not attribute to a higher rate of SAEs due to infections and did not attribute to a higher rate of early deaths on (b) (4) arm.

In summary, adverse events observed in subjects treated with (b) (4) are typical and known adverse events seen in patients undergoing alloHSCT. Overall, with the exception of early bacterial infections, the safety profile of (b) (4) was favorable compared to that of SoC alloHSCT.

Conclusion:

The clinical review team recommends granting a traditional approval of (b) (4) for the following indication:

(b) (4) 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 recommendation is based on demonstration of safety and substantial evidence of effectiveness of (b) (4) in Precision T Phase 3 study, an adequate and well controlled investigation. The treatment with (b) (4) demonstrated 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 unmanipulated alloH SCT 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. GRFS was not tested since OS did not reach the statistical significance at the interim analysis per the prespecified hierarchical testing plan. The clinical review team recommends including a post marketing commitment (PMC) from the Applicant to submit the final analysis of OS and GRFS when the data mature.

Precision-T Study also demonstrates a comparable or better safety profile in (b) (4) arm compared to SoC allograft arm.

Taken together, these efficacy and safety data denote clinical benefit in the indicated population, and therefore supports a traditional approval of (b) (4)

1.3. Benefit-Risk Assessment (BRA)

Benefit-Risk Summary and Assessment

The benefit-risk assessment for (b) (4) for the indicated population is primarily 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 (b) (4) followed by a single agent tacrolimus for patients with hematological malignancies who are eligible for allogeneic hematopoietic transplantation following a myeloablative conditioning regimen to unmanipulated grafts 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 (b) (4) as a treatment for adult patients with hematologic malignancies who are eligible for allogeneic 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 (b) (4) compared to SoC ((HR = 0.26 [95% CI: 0.14, 0.47]; $P < .00001$) per EAC assessment after median duration of follow up of 8.48 (range: 0 to 22) months and 9.03 (range: 0 to 20) months, respectively. The EAC-assessed secondary endpoint of time to moderate-to-severe cGVHD also demonstrated the significant improvement in (b) (4) arm compared with SoC arm (HR = 0.19 [95% CI: 0.08, 0.43]; $P = .00002$). OS was immature at the time of primary analysis of cGFS. The FDA considered (b) (4) effect on OS as part of the safety 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. However, there was a trend for improvement in OS in the (b) (4) arm.

Safety: The rate of adverse reactions including acute GVHD (aGVHD), cGVHD, grade 3 and higher infections, death due to AEs was lower on the (b) (4) 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 (b) (4) 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 survival free of cGVHD in the treatment of adults with hematologic malignancies.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
<u>Analysis of Condition</u>	- AlloHSCT is the only curative treatment option for a variety of high-risk hematological malignancies including AML, ALL, MPAL, and MDS. - Severe cGVHD occurs in about 40% of patients after alloHSCT. - Without treatment, cGVHD can cause severe multisystem tissue damage due to chronic inflammation and fibrosis. cGVHD can be fatal.	cGVHD is a serious and life threatening disease.
<u>Current Treatment Options</u>	- There are no FDA approved therapies for the prevention of cGVHD Some current off label used options include: - Tacrolimus or cyclosporine: calcineurin inhibitors (CNI) are more effective at prevention of aGVHD than cGVHD. CNI+Methotrexate (MTX): Multiple trials demonstrated consistently 45-65% rate of cGVHD (Flowers et al. 2011, Cutler et al. 2014). - CNI+mycophenolate mofetil (MMF): preferred in reduced intensity conditioning (RIC)/non-myeloablative transplants. CNI+MMF demonstrated with about 32.5% of cGVHD (Schemid C et al. 2006). - CNI+sirolimus: CNI+sirolimus demonstrated a 2-year cGVHD rate of 53% in a phase3 randomized trial but with increased toxicities (BMT CTN#0402) (Cutler et al. 2014) - Post-transplant cyclophosphamide (PTCy)- based regimens are associated with higher chronic GVHD-free survival (GFS). However, it is cardiotoxic.	There is unmet medical need for an effective and tolerable cGVHD prevention therapy.
<u>Benefit</u>	- Precision-T, is an open-label, multicenter, randomized, controlled phase 3 trial that compared (b) (4) to SoC alloHSCT in patients with high-risk hematologic malignancies undergoing myeloablative allo-HSCT. - The primary efficacy endpoint was cGFS determined by a blinded EAC using NIH 2014 chronic GVHD consensus criteria. Precision-T study demonstrated clinically meaningful statistically significant improvement in cGFS of (b) (4) compared to SoC (HR = 0.26 [95% CI: 0.14, 0.47]; $P < .00001$) per EAC assessment. The IRC-assessed secondary	This study demonstrated statistically significant improvement in cGFS and time to moderate or severe cGVHD with (b) (4) compared to the SoC arm in the proposed patient population. The statistically significant improvement in cGFS compared to the control arm represents clinical benefit in the

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	endpoint of time to moderate-to-severe cGVHD also demonstrated the significant improvement in (b) (4) arm compared with SoC arm (HR = 0.19 [95% CI: 0.08, 0.43]; $P = .00002$) after median follow up times of 8.48 (range: 0 to 22) months and 9.03 (range: 0 to 20) months, respectively.	proposed patient population.
Risk and Risk Management	- The safety profile of (b) (4) represent the typical toxicities of myeloablative conditioning regimen and the risks associated with alloHSCT in general. - The rate of aGVHD, cGVHD, grade 3 and higher infections, death due to AEs were lower on (b) (4) arm compared with SoC. Adverse reactions including all grade infections, graft failure, veno-occlusive disease/sinusoidal obstruction syndrome (VOD/SOS) are comparable with SoC and other products in this class.	The safety profile of (b) (4) is acceptable in the proposed patient population, and can be addressed through product labeling.

1.4. Patient Experience Data

Patient Experience Data Relevant to this Application (check all that apply)

☐	The patient experience data that was submitted as part of the application, include:			Section where discussed, if applicable
	x	Clinical outcome assessment (COA) data, such as		[Section 8.1 Study endpoints]
		x	Patient reported outcome (PRO)	[Section 8.1 Study endpoints]
		☐	Observer reported outcome (ObsRO)	
		☐	Clinician reported outcome (ClinRO)	
		☐	Performance outcome (PerfO)	

☐	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)	
☐	Patient-focused drug development or other stakeholder meeting summary reports	[e.g., Section 2.1 Analysis of Condition]
☐	Observational survey studies designed to capture patient experience data	
☐	Natural history studies	
☐	Patient preference studies (e.g., submitted studies or scientific publications)	
☐	Other: (Please specify)	
☐	Patient experience data that was not submitted in the application, but was considered in this review.	

X

Cross-Disciplinary Team Leader

2 Therapeutic Context

2.1. Analysis of Condition

The Applicant's Position:

In the United States, the 5-year age-adjusted incidence rates (2018 to 2022) for acute lymphoid leukemia (ALL), acute myeloid leukemia (AML), and myelodysplastic syndrome (MDS) were 1.9, 4.3, and 3.9, respectively, per 100,000 people ([National Cancer Institute 2025](#)). The 5-year relative survival rates of ALL, AML, and MDS are 72.6%, 32.9%, and 38.9%, respectively.

Myeloablative conditioning (MAC)-allogeneic hematopoietic cell transplantation (alloHCT) is a standard treatment option for a variety of high-risk hematological malignancies including AML, ALL, MPAL, and MDS, but its therapeutic utility remains limited by many potentially lethal complications, including graft-versus-host disease (GVHD) and opportunistic infections ([Sureda et al. 2015](#)). Following a high-dose chemotherapy regimen to debulk the tumor, mobilized peripheral blood containing hematopoietic stem cells are delivered to the patient, which leads to engraftment of the donor immune system and a graft-versus-tumor effect ([Gupta et al. 2003](#); [Weiden et al. 1979](#)). The tumor debulking regimens cause irreversible cytopenia in patients, and the subsequent alloHCT is required to re-establish hematopoiesis ([Atilla et al. 2017](#)).

AlloHCT is the only curative treatment option available to many patients with high-risk hematologic disease, but the procedure itself carries substantial risk of morbidity and mortality. While disease relapse is the leading cause of death following alloHCT, approximately 10% to 20% of patients undergoing alloHCT will die due to the toxicity of this therapy rather than due to their underlying malignancy ([Giebel et al. 2016](#); [Tanaka et al. 2016](#); [Kurosawa et al. 2013](#)). A leading cause of this treatment-related mortality is acute and/or chronic graft-versus-host disease (GVHD), accounting for approximately 4% to 9% of deaths after transplantation ([Spellman et al. 2025](#)).

Acute GVHD (aGVHD) is a multisystem disorder characterized by an immune response against host tissues (most commonly the liver, skin, and gastrointestinal tract) and is historically defined as GVHD occurring within 100 days of transplantation. aGVHD is associated with significant morbidity and mortality and has also been associated with decreased quality of life, increased hospitalization times, and increased corticosteroid use ([Lee et al. 2006](#)). aGVHD manifests as maculopapular rash, gastrointestinal symptoms, and elevated bilirubin.

cGVHD has historically been defined to occur after 100 days but has been recognized as a distinct clinical entity that can occur at any time after alloHCT ([Jagasia et al. 2015](#)). A patient's risk of nonrelapse mortality (NRM) more than doubles with cGVHD, and there is a corresponding decrease in OS in these patients (approximately 50% relative

increase in death) ([Boyiadzis et al. 2015](#)). Beyond increased mortality risk, cGVHD is associated with significant morbidity and economic consequences. Affected organs include the skin (eg, sclerotic changes), eye (eg, dry eyes and cataracts), gastrointestinal tract (eg, dry mouth and dysphagia), liver, genitalia, and lung (eg, restrictive lung disease). In addition, patients with moderate or severe cGVHD experience significantly poorer QoL with chronic lung disease, hypertension, diabetes, or arthritis ([Pidala et al. 2011](#)).

The FDA's Assessment:

The FDA agrees with the Applicant's assessment that cGVHD is a serious and life-threatening condition.

2.2. Analysis of Current Treatment Options

MAC-alloHCT is a standard treatment option for patients with a variety of high-risk hematologic malignancies, including AML, ALL, mixed phenotype acute leukemia (MPAL), and MDS, but its therapeutic utility remains limited by many potentially lethal complications, including graft-versus-host disease (GVHD) and opportunistic infections ([Suredda et al. 2015](#)). Indeed, MAC-alloHCT is curative in only some patients, with 3-year survival ranging from 27% to 72% in adults with advanced hematologic malignancies, depending on donor type, disease type, and disease stage ([Spellman et al. 2025](#)). Even after HLA-matched alloHCT, the leading causes of death remain disease relapse (19% to 47% of patients), organ failure (16% to 48% of patients), infection (14% to 26% of patients), and GVHD (4% to 9% of patients). Better strategies for alloHCT therefore remain critically needed to improve patient outcomes.

T-cell depletion (TCD) of donor grafts is an accepted method to prevent aGVHD and cGVHD. There is extensive experience with TCD of marrow grafts, and such techniques have involved physical adsorption of T cells to protein ligands such as lectins, elutriation, and immunoadsorption or immunodepletion with T-cell or lymphocyte-specific monoclonal antibodies. These methods have yielded results in marrow grafts with a broad range of TCD (approximately 1-log to 3-log depletion of T cells) ([Ho and Soiffer 2001](#)). However, the risk of aGVHD and/or cGVHD may be greater with peripheral blood stem cell (PBSC) grafts, and strategies for TCD of PBSC allografts are of considerable interest.

Investigators have performed TCD of granulocyte colony-stimulating factor (G-CSF)-mobilized PBSC grafts and observed incidences of aGVHD and cGVHD of <10% despite the use of haploidentical grafts and the lack of any posttransplantation GVHD prophylaxis ([Aversa et al. 2005; 2001; Handgretinger et al. 2001](#)). Consequences of TCD include impaired immune recovery and increased incidence of relapse. Persistent immune dysregulation is a known complication of alloHCT and can manifest as opportunistic infections ([Luznik et al. 2022; Pasquini et al. 2021](#)), especially in the setting of cGVHD. Peripheral blood T lymphocyte counts do not return to normal levels

until approximately 3 to 12 months after hematopoietic cell transplantation (HCT), and functional T cell recovery may be even more protracted, especially after TCD HCT ([Dekker et al. 2020](#); [Witherspoon et al. 1981](#)). Additionally, when marrow grafts are depleted of T cells, the risk of leukemia relapse may be higher due to reduced GVL effects normally mediated by T cells ([Wagner et al. 2005](#); [Gale et al. 1994](#)).

Regulatory T cells (Tregs) are a specialized T-cell subset that can suppress the immune effector response of other “conventional” T cells (Tcons) through various contact-dependent and independent mechanisms (eg, reducing the activity of antigen-presenting cells; secreting anti-inflammatory cytokines like interleukin [IL]-10, transforming growth factor [TGF]β, and IL 35) . For example, Tregs suppress the activation and proliferation of nonregulatory CD4+ or CD8+ T cells in vitro in response to polyclonal stimuli ([Thornton and Shevach 1998](#)). The role of Tregs in MAC-alloHCT has been explored in retrospective and prospective studies.

In murine models of MAC-alloHCT, CD4+CD25+ Tregs can provide protection against lethal GVHD while preserving the GVL effect of graft T cells following allogeneic bone marrow transplantation in mice . Retrospective studies in humans have shown a positive correlation between the dose of Tregs in alloHCT and reductions in both GVHD and NRM . More recently, prospective clinical studies of Tregs in alloHCT have provided further support for this approach.

In a study of haploidentical alloHCT, 43 participants with acute leukemia received an infusion of donor Tregs prior to infusion of CD34+ hematopoietic stem and progenitor cells (HSPCs) and Tcons with no posttransplantation immunosuppression . Compared with a historical cohort of patients treated with HSPCs alone in previous trials at the same center, the incidence of relapse was lower, there was a trend toward better survival, and grade ≥2 GVHD was not significantly different from the historical control patients. In another clinical trial of nonmyeloablative alloHCT utilizing cord blood transplantation and sirolimus and mycophenolate mofetil as GVHD prophylaxis, the use of Tregs was shown to be safe and may have been effective in reducing GVHD rates . Tregs have also been used in the posttransplantation setting (after MAC-alloHCT) to treat GVHD with no concerning safety events and some evidence of efficacy .

Apart from GVHD, the most frequent causes of treatment-related mortality with alloHCT include infection and organ failure, which may result from immunosuppressive therapies that must accompany alloHCT to allow for donor stem cell engraftment and prevention of both aGVHD and cGVHD .

The Applicant’s Position:

Orca-T, a T-cell-depleted peripheral blood stem cell graft with addback of Tregs and Tcons, is designed to address the limitations of standard MAC-alloHCT by reducing GVHD incidence while preserving immune reconstitution and GVL effects, thereby aiming to improve transplantation outcomes in patients with high-risk hematologic

malignancies. Furthermore, Orca-T reduces the need for immunosuppressive GVHD prophylaxis and the accompanying risks of those treatments.

The FDA's Assessment:

There are no FDA approved therapies for the prevention of cGVHD in alloHSCT setting. Current standard prevention strategies rely on off-label use of CNI-based regimens, most commonly tacrolimus combined with methotrexate or mycophenolate mofetil. These regimens were primarily designed to prevent aGVHD and provide only modest protection against cGVHD ([Nash et al. 2000](#)). The combination of tacrolimus plus sirolimus represents the most significant advance to date, demonstrating a 35% reduction in chronic GVHD incidence (35% vs. 53% at 2 years) compared to tacrolimus plus methotrexate in the landmark BMT CTN 0402 trial, though this benefit comes with increased risk of thrombotic microangiopathy (13% vs. 3%) ([Cutler et al. 2014](#)). 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 ([Luznik et al. 2010](#); [Watkins et al. 2021](#)). The persistent high incidence of cGVHD across all current prophylaxis regimens underscores the critical unmet need for novel prevention strategies in prevention of cGVHD and improve the cGVHD free survival rates.

3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

The Applicant's Position:

The sponsor received a designation of Orca-T as Regenerative Medicine Advanced Therapy (RMAT) on 30 July 2020 under Section 506(g)(3) of the Food and Drug Cosmetic Act (FDCA).

Orca-T is not currently approved or marketed in the US or any other country globally. The clinical development program is being conducted under Investigational New Drug (IND) 18876, and the relevant regulatory history is included in Section 3.2.

The FDA's Assessment:

The FDA agrees with the Applicant's statement that (b) (4) is not currently registered or approved in the United States or in any other countries.

3.2. Summary of Presubmission/Submission Regulatory Activity

The Applicant's Position:

A summary of relevant regulatory correspondence with the Agency under IND 18876 is provided in **Error! Reference source not found..**

Table 1. Applicant – FDA Interactions

Date	FDA Interactions
14 Jun 2019	Initial IND 18873 clearance
14 Jun 2019	"Study May Proceed" letter received
10 Apr 2020	ODD (DRU-2020-7460) is granted for the <i>treatment to enhance cell engraftment in patients receiving hematopoietic stem cell transplant</i>
30 Jul 2020	RMAT Designation granted
03 Mar 2021	Type B RMAT Quality/Clinical Teleconference Meeting (CRMTS #1308) to discuss phase 3 development plans (Briefing Package, SN0016)
14 Jul 2021	Type B End-of-Phase 2 Teleconference Meeting (CRMTS #13372) to discuss and agree on the clinical and CMC plans to commence the registrational, phase 3 clinical study (Briefing Package, SN0021; amended SN0022)
19 May 2022	Type B CMC Teleconference Meeting (CRMTS #14000) to discuss and agree on proposed technology transfer plan for the manufacture of Orca-T drug products from the current clinical manufacturing facility to the commercial manufacturing facility and to discuss (b) (4) (Briefing Package, SN0040)
16 Feb 2023	Type B Clinical WRO Meeting (CRMTS #14525) regarding acceptability of using relapse-free survival data from phase 1b component of Precision-T study with the

Date	FDA Interactions
	support of real-world data from CIBMTR registry as primary evidence of effectiveness to support a marketing application (Briefing Package, SN0045)
18 Aug 2023	Type B CMC WRO Meeting (CRMTS #15135) regarding the sponsor's material control strategies and other miscellaneous CMC topics (e.g, contamination control, sample retains, regulatory product designation, drug product stability, and analytical methods for sterility testing) (Briefing Package, SN0053; amended SN0056)
29 Aug 2023	Submission of sponsor responses to FDA comments and clarifying questions from FDA written feedback received for Type B meeting 18 Aug 2023 (SN0057)
13 Sept 2023	Submission of the revised iPSP seeking formal pediatric waiver under waiver to conduct pediatric studies under PREA (21 UC 335c) based on Orca-T's ODD (DRU-2020-7460) for the (b) (4) (SN0059)
26 Sept 2023	OOPD communication that PREA waiver based on existing orphan designation (DRU-2020-7460) for the (b) (4) falls outside the scope of the indication the sponsor is seeking under CBER
06 Nov 2023	Submission of revised ODD request to OOPD for the intended indication of <i>prevention of moderate to severe chronic graft-vs.-host disease and/or death in patients with advanced hematologic malignancies undergoing related or unrelated allogeneic hematopoietic stem cell transplant (alloHCT)</i>
30 Jan 2024	ODD (DRU-2023-9854) granted for the <i>prevention of graft-versus-host disease and/or death in patients undergoing hematopoietic stem cell transplantation</i>
01 Feb 2024	Sponsor withdrawal of ODD DRU-2020-7460
14 Feb 2024	Submission of the revised iPSP seeking formal pediatric waiver under waiver to conduct pediatric studies under PREA (21 UC 335c) based on newly granted ODD (DRU-2023-9854) for the <i>prevention of graft-versus-host disease and/or death in patients undergoing hematopoietic stem cell transplantation</i> (SN0073)
15 Feb 2024	Type B Clinical/Statistical Teleconference Meeting (CRMTS #15418): FDA provided feedback regarding the updated Precision-T phase 3 SAP ahead of the planned interim analysis for the Precision-T Phase 3 study (Briefing Package, SN0070)
06 Mar 2024	FDA communication regarding iPSP waiver submitted on 14 Feb 2024. FDA confirmed an iPSP is not needed and is exempt from PREA
22 Mar 2024	Submission of updated Precision-T Phase 3 SAP v3.0 following Type B meeting with FDA on 15 Feb 2024 (SN0075)
09 Apr 2024	Type B CMC Meeting Request for PPQ strategy and facility topics (SN0076); The meeting was denied by FDA on 26 Apr 2024
16 May 2024	Submission of CMC request for comments and advice related to Orca Bio's commercial facility ((b) (4)), the APS, PPQ, and Orca-T DP stability strategies to support the planned Orca-T BLA and subsequent commercial manufacturing (SN0079)
13 Jun 2024	Submission of responses to clinical IR received on 12 Jun 2024 regarding Type B meeting package submitted 24 May 2024 for meeting ID #20285 (SN0082)
11 Jul 2024	Type B Clinical/Statistical Virtual Face to Face Meeting (ID #20285) to align with FDA regarding ISS SAP for planned BLA. (Briefing Package, SN0080)
16 Aug 2024	Submission of responses to statistics IR received on 07 Aug 2024 regarding the Precision-T Phase 3 SAP v3.0 submitted on 22 Mar 2024 (SN0091)
21 Aug 2024	Submission of response/clarification request regarding FDA's CMC comments and advice received on 05 Aug 2024 regarding APS process (SN0092)

Date	FDA Interactions
23 Sep 2024	Submission of updated Precision-T Phase 3 SAP v4.0 (SN0094) in response to FDA comments received on 23 Aug 2024
18 Dec 2024	Submission of updated Precision-T Phase 3 SAP v4.0 Memo dated 13 Dec 2024 and response to statistical information request received on 27 Nov 2024, regarding the Precision-T Phase 3 SAP v4.0 Memo dated 21 Oct 2024. In alignment with FDA's comments, the originally pre-specified 2-sided alpha of .0464, as outlined in SAP version 4.0, will be used for the primary analysis for cGFS (SN0098)
29 Jan 2025	Receipt of FDA preliminary comments for Type B CMC Virtual Face to Face Meeting (ID #20952) to seek agency feedback regarding the suitability of the sponsor's potency assay strategy and other miscellaneous CMC topics (eg, microbial control testing, contamination control strategy, PPQ, comparability and Tcon diluent manufacturing). The meeting was scheduled for 31 Jan 2025 and formally cancelled by the sponsor. (Briefing Package, SN0099)
12 Feb 2025	Submission of responses and clarifying questions regarding FDA preliminary comments for Type B CMC Meeting (ID #20952) received on 29 Jan 2025 (SN0101; amended SN0102)
04 Mar 2025	Receipt of FDA response to request for clarification for Type B CMC Meeting (ID #20952)
12 Mar 2025	Sponsor withdrawal of proposed proprietary name (b) (4) and request for proprietary name TREGZI (SN0104)
27 Mar 2025	Type B pre-BLA Face to Face Meeting (ID #21154) to seek agency feedback regarding the suitability of the sponsor's plans for BLA filing (Briefing Package, SN0103)
28 Apr 2025	Receipt of FDA proprietary name withdrawal letter for (b) (4)
03 Jun 2025	Type C Facilities Meeting (ID #21325) to seek agency feedback and agreement related to Orca Bio's commercial facility ((b) (4)) control strategy, scale out plans, and validation needs for equipment (Briefing Package, SN0108)
06 Aug 2025	Submission of BLA 125868
Abbreviations: BLA, biologics license application; CBER, Center for Biologics Evaluation and Research; CMC, chemistry, manufacturing, and controls; DP, drug product; GMP, Good Manufacturing Practice; IND, Investigational New Drug; iPSP, initial pediatric study plan; IR, information request; ISS, integrated safety summary; MLR, mixed lymphocyte release; ODD, orphan drug designation; OOPD, office of orphan products development; PPQ, process performance qualification; PREA, Pediatric Research Equity Act; RMAT, Regenerative Medicine Advanced Therapy; SAP, statistical analysis plan; SN, sequence number (sequence and serial number aligned in sequence 0046); WRO, written response only	

The FDA's Assessment:

In addition to the Applicant's summary of regulatory activities, the following key pre- and post-submission interactions are listed in [Table 2](#).

Table 2. FDA-Regulatory History

Date	FDA Interactions	Key Comments Provided by FDA
03 Mar 2021	Type B RMAT Meeting to discuss phase 3 development plans	FDA advised: • A randomized controlled Phase 3 trial will be required to support a BLA for the indication of prevention of cGVHD. • The proposed single arm phase 2 trial can be used to inform the design of phase 3 trial, but not sufficient to support the marketing approval. • Specify a hierarchical order to test secondary endpoints. • cGVHD free survival follow up through 18 months as the primary endpoint
14 Jul 2021	Type B EOP2 Meeting to discuss and agree on the clinical/CMC plans to commence the registrational, phase 3 clinical study	FDA advised: • Statistical analysis plan (SAP) addresses the efficacy in separate indications for patients with matched related donor and matched unrelated donors. • Sponsor decided to use the follow-up for primary endpoint of cGFS at 24 month. • Use the ITT population as primary efficacy population
29 Nov 2021	Clinical IR re the phase 3 pivotal study design	FDA advised: • Critical information to be included in the pathology report including: 1) slides be reviewed by a central pathology lab; 2) findings for disease characteristics; 3) raw data for organ staging of aGVHD and cGVHD for our review • Adding additional stopping rules: maximum allowable rate for 1) product failure rates; 2) Grade 5 toxicity at least probably or directly related to the product; 3) day 100 Grade 4-5 opportunistic infections.

Date	FDA Interactions	Key Comments Provided by FDA
16 Feb 2023	Type B Clinical WRO Meeting regarding acceptability of using relapse-free survival data from phase 1b component of Precision-T study with the support of real-world data from CIBMTR registry as primary evidence of effectiveness to support a marketing application	FDA advised: - Phase 1b single arm trial with RWD was not enough to support a marketing application, FDA recommended a RCT for the initial BLA - Same preparative regimen in both arms.
19 Dec 2023	SAP v2.0 submission	NRM and OS were added as secondary endpoints as hierarchical test procedure

Date	FDA Interactions	Key Comments Provided by FDA
15 Feb 2024	Type B Clinical/Statistical Meeting: FDA provided feedback regarding the updated Precision-T phase 3 SAP ahead of the planned interim analysis for the Precision-T Phase 3 study	FDA advised: - Revise the definition of primary endpoint of cGFS from 'the time of randomization' to 'from the time of HSCT' due to the relevance. - FDA advised to use the composite strategy for handling endpoint events. - Recommend OS as the first in the hierarchical testing of secondary endpoints
20 Mar 2024	SAP version 3.0 submitted	- NRM and RFS were removed from secondary endpoints to exploratory endpoints - Modified sequence of hierarchical tests: time to moderate or severe cGVHD, GRFS, and OS - Proposed the primary analysis for OS performed when 40 deaths are observed or 2 years after the end of enrollment, whichever is earlier
11 Jul 2024	Type B Clinical/Statistical Meeting to align with FDA regarding ISS SAP for planned BLA.	Sponsor informed FDA: - the enrollment to the phase 3 study has been completed with 187 patients and an interim analysis is planned to perform - Plan to submit pre-BLA in Q4 2024 FDA advised: - FDA does not agree with the pooling of safety data from phase1b and phase 3 as the primary safety analysis set. - The pooling safety data can be used as integrated safety analysis set to support the BLA

Date	FDA Interactions	Key Comments Provided by FDA
19 Sept 2024	SAP version 4.0	- Revised sequence of hierarchical tests: time to moderate or severe cGVHD, OS, and GRFS - Revised the primary analysis for GRFS from up to 1 year to up to 2 years - Revised the calculation of cGFS from HSCT instead of randomization per FDA's advice
13 Nov 2025	Expanded access protocol submission	Allowed to proceed
22 Dec 2025	Clinical IR	FDA requested clarification on the discrepancies in incidences of cGVHD and aGVHD between the primary efficacy set and primary safety set. The Applicant clarified the efficacy endpoint analysis in the primary efficacy analysis set was based on the EAC's assessment, while the safety analysis of GVHD was based on investigators' assessments. FDA clarified that GVHD analysis per EAC assessment will be used for both efficacy and primary safety analyses.
18 Feb 2026	Clinical IR	FDA requested source bilirubin lab data for a total of 22 randomly selected patients (11 for each arm) for further adjudication of GVHD assessments.

Abbreviation: BLA, Biologics License Application; cGFS, Chronic GVHD Free Survival; GVHD, Graft-Versus-Host-Disease; HCT, Hematopoietic Cell Transplantation; ISS, Integrated Safety Set; NRM, Non-Relapse Mortality; OS, Overall Survival; RCT, Randomized Controlled Trial; RFS, Relapse-Free Survival; RWD, Real World Data; SAP: Statistical Analysis Plan.

4 Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

OSI office conducted inspections for study Precision-T at clinical site 001 (city of hope national medical center in Durate CA), site 003 (Stanford health care in Stanford CA), and Orca Biosystems, Inc (the Applicant). These study sites were selected due to the consideration of factors including the highest accrual, highest death rates, numbers of protocol deviations, and inspection history.

Site 001: 51 patients were treated. A form 483 was issued with the final classification of voluntary action indicated (VAI). Major findings are:

- Underreporting of AEs, late SAE reporting
- Did not document late SAE/AESI reporting as protocol deviations in OnCore.
- Some protocol deviation issues including timing for the tacrolimus administration.

The preventive measures were proposed to be implemented including: quarterly trainings, establishment of daily communication workflow to discuss patient status and any changes, creation of an off-hours SAE reporting policy, weekly review AE logs and monthly QC reviews for tacrolimus dosing to reflect proper timing of administration per protocol.

Site 003: 19 patients were treated. A form 483 was issued with the final classification of voluntary action indicated (VAI). The major issue revealed was that SAEs were not reported to the Sponsor within 24 hours as required by protocol.

The corrective and preventive actions taken included: the updated SOP and new detailed work instruction was created to address late reporting.

The Applicant (Orca Bio): No major issues were identified, and the final classification was Voluntary Action Indicated.

These underreporting or late reporting of AE/SAEs were included in the ADAE dataset which were included in the safety characterization of (b) (4). The stat reviewer has conducted sensitivity analysis in the per-protocol population which excludes patients with major protocol violations (e.g., missing methotrexate doses, improper timing for tacrolimus etc.). The analysis demonstrated similar results as in ITT population. Therefore, these issues do not impact the interpretation of the efficacy and safety data of (b) (4).

4.2. Product Quality

Some patients received non-conforming products in the (b) (4) arm of the phase 3 Precision-T study.

- Patients received doses of Treg cells out of the specification (Viable Treg acceptance: (b) (4) $\times 10^6$ cells /kg)

(b) (6) received viable Treg dose at 1.3×10^6 cells /kg
 (b) (6) received viable Treg dose at 1.2×10^6 cells /kg
 (b) (6) received viable Treg dose at 1.5×10^6 cells/kg
 (b) (6) received viable Treg dose at 1.5×10^6 cells/kg
 (b) (6) received viable Treg dose at 1.4×10^6 cells/kg

- Patients received doses of HSPCs out of specification (Viable HSPC $\geq$ (b) (4) $\times 10^6$ cells/kg):

(b) (6) received viable HSPC dose at 1.3×10^6 cells/kg
 (b) (6) received viable HSPC dose at 1×10^6 cells/kg
 (b) (6) received viable HSPC dose at 1.4×10^6 cells/kg
 (b) (6) received viable HSPC dose at 1.4×10^6 cells/kg
 (b) (6) received viable HSPC dose at 2.3×10^6 cells/kg, but with 49% of HSPC (a.c. $\geq 53\%$) and 1840 residual viable T cell dose (a.c. $\leq 50 \times 10^3$ /kg)

(b) (6) received viable HSPC dose at 5.4×10^6 cells/kg, but with 86 residual viable T cell dose (a.c. $\leq 50 \times 10^3$ /kg)

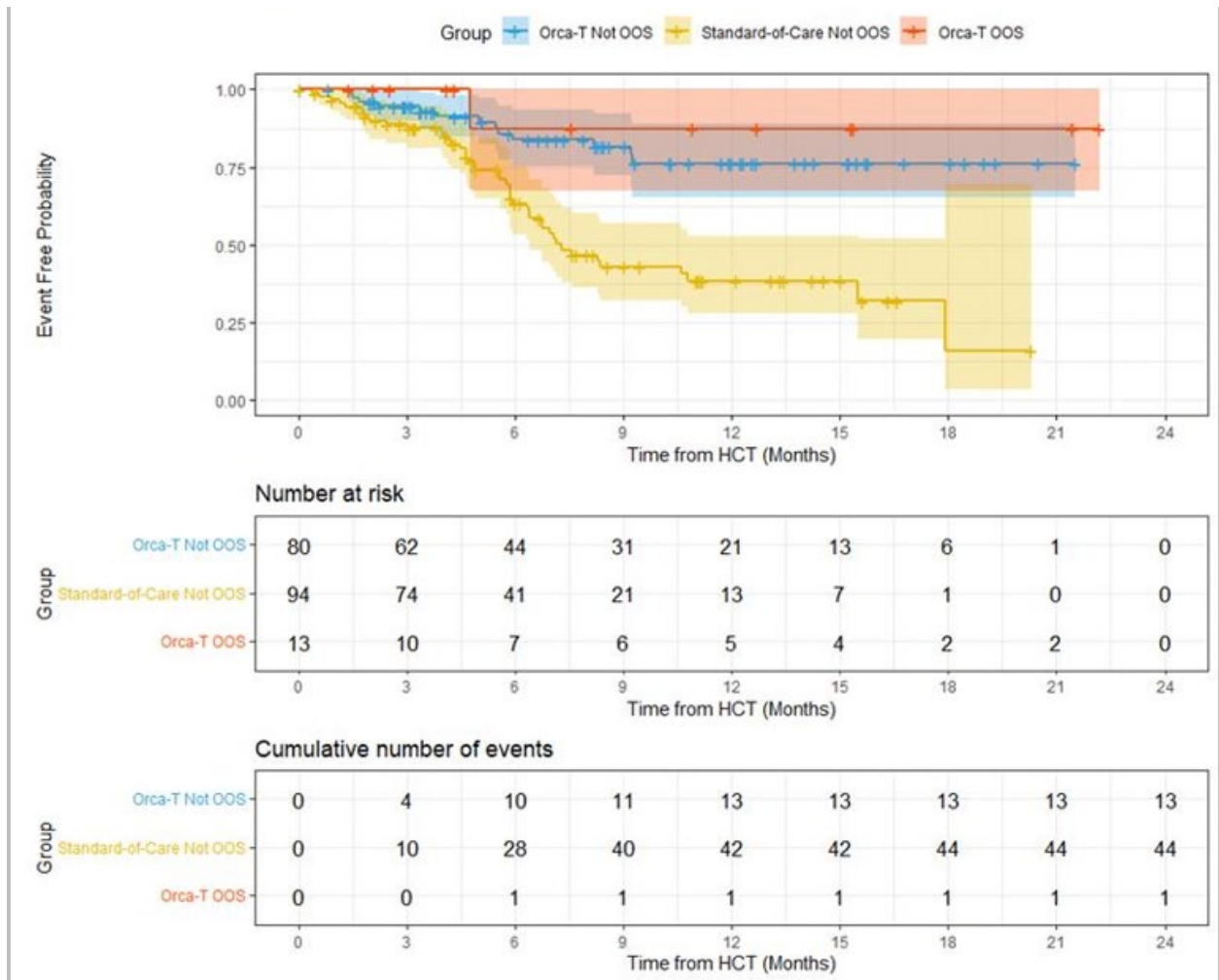
- Patients received doses of Tcon cells out of specification (Viable Tcon (b) (4) $\times 10^6$ cells/kg):

(b) (6) received viable Tcon dose at 6.9×10^6 cells /kg
 (b) (6) received viable Tcon dose at 1.3×10^6 cells /kg

Given the ITT nature of the efficacy and safety analysis, these patients with OOS products were included in the primary analysis sets for the evaluation of the totality of the data for this BLA. Meanwhile, subgroup efficacy analysis for these OOS products have been conducted to rule out the impact of these OOS products on the efficacy results.

- Considering the sample size for each individual OOS product to Treg, Tcon, or HSPC components was very limited (2-6), a subgroup analysis between patients received in-spec products on (b) (4) arm (n=80) and patients on SOC(n=94) arm was conducted. The analysis demonstrated the consistent efficacy results as the ITT population ([Figure 1](#)).
- The analysis of all OOS products (n=13), all in-spec product (n=80), and SOC was conducted. The subgroup analysis for the impact of OOS products on the efficacy outcomes did not raise clinical concerns related to efficacy ([Figure 1](#)).

Figure 1. FDA-KM Plot of cGFS per EAC Assessment of OOS Products



Abbreviation: OOS, out of specification; HCT, hematopoietic stem cell transplant.

Refer to CMC review memo for details on product quality.

4.3. Clinical Microbiology

Refer to CMC review memo.

4.4. Devices and Companion Diagnostic Issues

Refer to CMC review memo.

5 Nonclinical Pharmacology/Toxicology

5.1. Executive Summary

(b) (4) is an HSPC and T-cell immunotherapy designed to improve survival free of cGVHD in adult patients with hematologic malignancies undergoing a myeloablative preparative regimen. (b) (4) consists of four drug products (DPs): three cellular DPs and one Tcon Diluent DP. The three cellular DPs contain distinct cell types derived from human leukocyte antigen (HLA)-matched donor peripheral blood apheresis: HSPCs, Tregs, and Tcons. Following an appropriate myeloablative conditioning (MAC) regimen, HSPC DP (dose level: $\geq 1.0 \times 10^6$ viable HSPCs/kg per patient) followed by Treg DP (dose level range: $(b) (4) \times 10^6$ to 3.5×10^6 viable Tregs/kg per patient) are intravenously (IV) administered on day 0, while Tcon DP (dose level range: $(b) (4) \times 10^6$ to 6.9×10^6 viable Tcons/kg per patient) admixed with Tcon Diluent DP is IV administered on day +2.

While no formal nonclinical pharmacology, distribution, or toxicology studies were conducted with (b) (4) the applicant provided the scientific rationale for this application with published data from nonclinical studies evaluating the mechanisms of action (MOAs) of HSPCs, Treg, Tcons, and their combinations regarding hematopoietic and immunologic reconstitution and GVHD. Data from these published studies demonstrate 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 HSPCs could be successfully isolated from murine and human bone marrow (BM) using specific cell surface markers: Thy-1^{lo}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 HSPCs were shown to be essential for hematopoietic engraftment and immune reconstitution, with as few as 30 murine HSPCs 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 IL-2 production and promoting recipient dendritic cell death. Foxp3 expression was essential for Treg development and function, and CD4⁺CD25⁺CD127^{low/-} markers enabled isolation of highly purified, functionally suppressive Tregs.

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 (Day 0, two days before Tcons) maximized GVHD suppression at lower Treg doses (1:10 Treg:Tcon ratio) while preserving graft-versus-leukemia (GVL) effects.

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, with a 2:1 Treg:Tcon ratio providing 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 (DART) studies were conducted for (b) (4). These studies are not warranted based on the product characteristics, biological activity, and safety profile.

5.2. Referenced NDAs, BLAs, DMFs

The Applicant's Position:

Not Applicable

5.3. Pharmacology

Primary Pharmacology

Orca-T is an allogeneic stem cell and T-cell immunotherapy isolated from a donor's mobilized peripheral blood. It is composed of purified HSPCs, Tregs, and Tcons. Orca-T is designed such that cell populations that are known and/or thought to promote engraftment and reduce GVHD (HSPCs and Tregs, respectively) are administered to patients first, followed by Tcons, which are thought to mediate GVL and GVI. Production of Orca-T involves the fresh isolation and purification of cells via (b) (4).

No direct modifications of the cells, (b) (4) are involved.

As the product comprises endogenous human cells, no representative nonclinical in vitro assays or in vivo models currently exist that accurately address the characteristics of the product in humans. Furthermore, the individual cellular components of Orca-T have been studied extensively in the clinical context of alloHCT. As such, traditional nonclinical pharmacokinetic, pharmacologic, and toxicologic studies are neither appropriate nor necessary to assess the biological plausibility, safe and active dose levels, or potential toxicity of treatment with Orca-T, as described in the Food and Drug Administration Guidance for Industry: Preclinical Assessment of Investigational Cellular

and Gene Therapy Products . Therefore, formal nonclinical pharmacology, pharmacokinetic, and toxicology studies were not conducted.

The FDA's Assessment:

Information is included in the P/T BLA review memo.

Secondary Pharmacology

The Applicant's Position:

See section 5.3.

The FDA's Assessment:

Information is included in the P/T BLA review memo.

Safety Pharmacology

The Applicant's Position:

See section 5.3.

The FDA's Assessment:

Information is included in the P/T BLA review memo.

5.4. ADME/PK

The Applicant's Position:

See section 5.3.

The FDA's Assessment:

Information is included in the P/T BLA review memo.

5.5. Toxicology

The Applicant's Position:

See section 5.3.

The FDA's Assessment:

Information is included in the P/T BLA review memo.

5.5.1. Genetic Toxicology

The Applicant's Position:

See section 5.3.

The FDA's Assessment:

Information is included in the P/T BLA review memo.

5.5.2. **Carcinogenicity**

The Applicant's Position:

See section 5.3.

The FDA's Assessment: Information is included in the P/T BLA review memo.

5.5.3. **Reproductive and Developmental Toxicology**

The Applicant's Position:

See section 5.3.

The FDA's Assessment:

Information is included in the P/T BLA review memo.

5.5.4. **Other Toxicology Studies**

The Applicant's Position:

See section 5.3.

The FDA's Assessment:

Information is included in the P/T BLA review memo.

6 Clinical Pharmacology

6.1. Executive Summary

The FDA's Assessment:

(b) (4) is an allogeneic cell therapy comprising three cellular components (HSPCs, Tregs, and Tcons) administered sequentially with weight-based dosing, for which traditional pharmacokinetic and pharmacodynamic studies are not applicable. Of the 93 participants randomized to receive (b) (4) 88 participants received all three components. The applicant conducted exploratory exposure-response analyses in 88 participants from the phase 3 Precision-T study to evaluate relationships between cellular doses and clinical endpoints: neutrophil engraftment by day +28 (HSPCs), moderate or severe chronic GVHD at one year (Tregs), and CD3 count over time (Tcons). No statistically significant exposure-response relationships were identified for any cellular component.

Per CMC review, the applicant failed to use critical controls in critical release assays, including dose determining assays used to quantify HSPCs, Tregs, and Tcons. The applicant has not provided a complete reanalysis of the data with appropriate controls. At this time, the cell dose data reported for Precision-T cannot be considered reliable.

From a clinical pharmacology perspective, the actual cellular doses administered and confirmation of the Treg:Tcon ratio, and all exposure-response analyses need to be re-assessed based on the Applicant's satisfied reanalysis results in future.

6.2. Summary of Clinical Pharmacology Assessment

6.2.1. Pharmacology and Clinical Pharmacokinetics

Data:

Cell therapies, unlike traditional small molecule drugs, present unique challenges for clinical pharmacokinetic (PK) and pharmacodynamic (PD) reporting due to the inherent complexity of living cells as therapeutic agents, their dynamic behavior in vivo, and the lack of a well-defined dose analogous to drug concentrations. As such, standard PK and PD analyses do not apply, and specific studies evaluating the PK and PD of Orca-T were not conducted. The dynamic nature of cell therapies necessitates a shift from traditional drug-centric PK/PD approaches to a focus on characterizing the relationship between cell exposure and therapeutic response, ie, exposure-response relationship.

Exploratory exposure-response analyses were performed for 88 participants in the phase 3 safety analysis set who received all 3 drug product infusions to evaluate the exposure-response relationship for each of Orca-T's components.

The exposure-related variables (independent variables) and output endpoints (dependent variables) for the analyses are listed in [Table 3](#). Selection of these endpoints was based on the biological plausibility of an effect produced by each component of Orca-T, and only those participants whose drug product met release specifications were included in the respective analyses.

Table 3. Applicant – Exposure-Response Analyses

Dose Specification	Endpoint(s)
HSPCs	
Total number of viable CD34+ cells	neutrophil engraftment ^a by day +28 (yes or no)
Dose of viable CD34+ cells/kg	neutrophil engraftment ^a by day +28 (yes or no)
Tregs	
Total number of viable Treg cells	moderate or severe cGVHD (yes or no) at 1 year
Dose of viable Treg cells/kg	moderate or severe cGVHD (yes or no) at 1 year
Tcons	
Total number of viable Tcon cells	CD3 count over time
Dose of viable Tcon cells/kg	CD3 count over time

Abbreviations: ANC, absolute neutrophil count; cGVHD, chronic graft-versus-host disease; HSPCs, hematopoietic stem and progenitor cells; Tcon(s), conventional T cells; Treg(s), regulatory T cells.

^a Neutrophil engraftment was defined as achieving an ANC $\geq 500/\text{mm}^3$ for 3 consecutive days by day +28. The first of the 3 days was designated the day of engraftment. If ANC never dropped below $500/\text{mm}^3$, day +1 was designated as the day of engraftment.

A stratified logistic model was used for the binary endpoints. The stratification was the conditioning regimen (total body irradiation [TBI] vs non-TBI). For CD3 count over time, longitudinal analysis models were applied with appropriate covariates.

Neutrophil Engraftment by Day +28

All 88 participants had neutrophil engraftment within 28 days of infusion, and therefore, no exposure-response relationship was identified between neutrophil engraftment and the CD34+ dose.

Moderate or Severe cGVHD at 1 Year

The relationship between the probability of developing moderate or severe cGVHD (yes or no) at 1 year and the total number of viable Tregs or number of viable Tregs/kg was modeled through a stratified logistic model stratified by the conditioning regimen (TBI vs non-TBI).

The estimated odds ratio (95% CI) of developing moderate or severe cGVHD corresponding to an increase of 10^6 cells or 10^6 cells/kg was 1.00 ([0.99, 1.02], $P = 0.568$) and 1.23 ([0.20, 7.49], $P = 0.819$), respectively ([Table 4](#), Applicant – Summary of

Exposure-Response Analysis – Moderate to Severe cGVHD (Precision-T Phase 3 Safety Analysis Set)). No exposure-response relationship was identified between cGVHD and the Treg dose.

Table 4. Applicant – Summary of Exposure-Response Analysis – Moderate to Severe cGVHD (Precision-T Phase 3 Safety Analysis Set)

Dose Specification	Number of Participants Included in the Analysis	Odds Ratio Estimate (95% CI)	P Value (2-sided)
Total number of viable Tregs (10^6 cells) ^a	88	1.005 (0.987, 1.024)	0.5681
Dose of viable Tregs/kg (10^6 cells/kg) ^b	88	1.234 (0.203, 7.489)	0.8190

Abbreviations: cGVHD, chronic graft-versus-host disease; CI, confidence interval; TBI, total body irradiation; Treg, regulatory T cell.

^a Logistic model stratified by TBI (Yes vs No) with total number of viable Treg cells as the independent variable was used.

^b Logistic model stratified by TBI (Yes vs No) with dose of viable Treg cells/kg as the independent variable was used.

Source: Precision-T Phase 3 CSR, Table 14.3.3.2

CD3 Count Over Time

The relationship between the CD3 count (per μ L) over time and the total number of viable Tcons or number of viable Tcons/kg was modeled through a longitudinal linear model with an unstructured covariance structure for the residuals. Other variables included in the model were TBI (yes vs no) and visit of the CD3 count measurement.

The estimated increase of CD3 per μ L (95% CI) corresponding to an increase of 10^6 Tcons or 10^6 Tcons/kg was 0.316 ([-0.421, 1.054], $P = 0.395$) and 12.630 ([-54.542, 82.803], $P = 0.721$), respectively (Table 5. Applicant – Summary of Exposure-Response Analysis – CD3 Count (per μ L)

(Precision-T Phase 3 Safety Analysis Set)). No exposure-response relationship was identified between CD3 count and the Tcon dose.

Table 5. Applicant – Summary of Exposure-Response Analysis – CD3 Count (per μ L) (Precision-T Phase 3 Safety Analysis Set)

Dose Specification	Number of Participants Included in the Analysis ^c	Coefficient of Fixed Effect Estimate (95% CI)	P value (2-sided)
Total number of viable Tcons (10^6 cells) ^a	75	0.3163 (-0.4210, 1.0537)	0.3949
Dose of viable Tcons/kg (10^6 cells/kg) ^b	75	12.6304 (-57.5424, 82.8033)	0.7205

Abbreviations: CI, confidence interval; TBI, total body irradiation; Tcon, conventional T cell.

^a Longitudinal linear model with an unstructured covariance structure for the residuals was used. Other variables included in the model: total number of viable Tcon cells, TBI (Yes vs No), and visit of the CD3 count measurement.

^b Longitudinal linear model with an unstructured covariance structure for the residuals was used. Other variables included in the model: dose of viable Tcon cells/kg, TBI (Yes vs No), and visit of the CD3 count measurement.

^c Of the 88 participants who received Orca-T in the safety analysis set, 13 participants with missing CD3 count measurements were excluded from the modeling.

Dose Specification	Number of Participants Included in the Analysis ^c	Coefficient of Fixed Effect Estimate (95% CI)	P value (2-sided)
Total number of viable Tcons (10 ⁶ cells) ^a	75	0.3163 (-0.4210, 1.0537)	0.3949
Dose of viable Tcons/kg (10 ⁶ cells/kg) ^b	75	12.6304 (-57.5424, 82.8033)	0.7205

Source: Precision-T Phase 3 CSR, Table 14.3.3.3

The Applicant's Position:

Orca-T is an allogeneic cell therapy for which standard PK and PD analyses do not apply. For this reason, nonclinical and clinical studies analyzing the PK and PD of Orca-T were not conducted. Limited exposure-response analyses were performed as exploratory endpoints in the phase 3 component of Precision-T to evaluate the exposure-response relationship for each of Orca-T's components. Neutrophil engraftment by day +28, moderate or severe cGVHD at 1 year, and CD3 count over time were evaluated based on the biological plausibility of an effect produced by each component of Orca-T (HSPC, Treg, and Tcon, respectively).

The exploratory analyses demonstrated that no exposure-response relationship was identified between cGVHD and the Treg dose and between CD3 count and the Tcon dose. Additionally, all participants had neutrophil engraftment by day +28, regardless of HSPC dose, demonstrating that no exposure-response relationship was identified between neutrophil engraftment and the CD34+ dose. These findings indicate that the Orca-T doses administered in Precision-T were adequate and sufficient to elicit the intended therapeutic response.

In conclusion, results of the exploratory exposure-response analyses support the appropriateness of the selected study doses, ratio, and dosing schedule of the cellular components of Orca-T. These findings indicate that the administered doses were sufficient to achieve the desired pharmacologic and clinical effects in participants with advanced hematologic malignancies undergoing MAC-alloHCT.

The FDA's Assessment:

FDA agrees that traditional pharmacokinetic and pharmacodynamic studies are not applicable to (b) (4) given its nature as an allogeneic cell therapy comprising unmodified human cellular components. The applicant conducted exploratory exposure-response analyses to evaluate whether the doses administered in Precision-T were adequate to achieve the intended therapeutic effects for each cellular component.

Per CMC review, the applicant failed to use critical controls in critical release assays for the phase 3 clinical trial batches, including dose determining assays used to quantify

HSPCs, Tregs, and Tcons. The applicant has not provided a complete reanalysis of the data with appropriate controls. At this time, the cell dose data reported for Precision-T cannot be considered reliable. Please refer to the CMC review for details.

From a clinical pharmacology perspective, the CMC issues with the phase 3 clinical trial batches prevent verification of the actual cellular doses administered and confirmation of the Treg:Tcon ratio, and undermine all exposure-response analyses.

6.2.2. General Dosing and Therapeutic Individualization

6.2.2.1. General Dosing

Data:

Target cellular dosages for Precision-T were identified based on preclinical studies of alloHCT, early clinical experience with a product similar to Orca-T (summarized below), and manufacturing feasibility. [Table 6](#) . Applicant – Precision-T Dosing Regimen and Target Dose Range summarizes the dosing regimen and target dose range for Orca-T.

Table 6 . Applicant – Precision-T Dosing Regimen and Target Dose Range

Orca-T Drug Product	Dose Regimen	Target Dose Range (Cells per Patient kg)
HSPC	IV, once, on day 0	$\geq 1^{(b)} \times 10^6$
Treg	IV, once, on day 0	(b) (4)
Tcon	IV, once, 48 to 72 hours after the start of HSPC infusion (typically day +2)	(b) (4)
Tcon diluent	Administered with Tcon drug product	N/A

Abbreviations: HSPC, hematopoietic stem and progenitor cell; IV, intravenous(ly); Tcon, conventional T cell; Treg, regulatory T cell.

In a single-institution, phase 1/2 trial performed at Stanford University School of Medicine, participants with advanced hematologic malignancies undergo MAC-alloHCT using mobilized peripheral blood from either an HLA-matched sibling donor (MSD) or matched unrelated donor (MUD). In the completed dose-escalating portion of the study evaluating 12 participants, the Treg dose escalation was established as the ratio of Tregs to Tcons, with an initial target dose of 1×10^6 Tregs/kg and 3×10^6 CD3+ Tcons/kg (1:3 ratio). After GVHD was observed in 1 patient, the Treg:Tcon ratio was

increased to 1:1 with doses of 1×10^6 Tregs/kg and 1×10^6 Tcons/kg. Since no dose-limiting toxicity was observed, the target dose was escalated to 3×10^6 Tregs/kg and 3×10^6 CD3+ Tcons/kg. The maximally tolerated target dose was not reached, as this was the maximal quantity of Tregs that could be obtained from 2 apheresis collections. The study results suggested that administration of highly purified Tregs and CD34-selected HSPCs, followed by infusion of an equal ratio (1:1) of Tregs to Tcons in participants undergoing MAC-alloHCT was both safe and feasible.

The Stanford phase 1/2 trial served as a clinical proof-of-concept study that provided the rationale for the Precision-T study of Orca-T. Participants enrolled in Precision-T were treated on the same schedule and with similar cellular products (ie, HSPCs, Tregs, and Tcons) as the phase 1/2 trial using Good Manufacturing Process standards of quality for clinical manufacturing. In Precision-T, participants underwent MAC regimens followed by the infusion of purified HSPCs and Tregs (defined as CD4+CD25+CD127– T cells) on day 0 of transplantation. Participants then received cryopreserved Tcons on day +2 (between 48 and 72 hours after the start of HSPC infusion on day 0) followed by single-agent GVHD prophylaxis initiated on day +3. This dosing schedule of Orca-T was designed such that cell populations that are known and/or thought to promote engraftment and reduce GVHD (HSPCs and Tregs, respectively) are administered to patients first, followed by Tcons, which are thought to mediate GVL and GVI. Tregs are known to expand rapidly in vivo in patients who are lymphodepleted.

Target doses in Precision-T are $\geq 1^{(b) (4)} \times 10^6$ viable cells/kg of body weight for HSPCs, (b) (4) viable cells/kg of body weight for Tregs, and (b) (4) viable cells/kg of body weight for Tcons, with no dose modifications allowed. As each donor apheresis product contained variable amounts of HSPCs, Tregs, and Tcons, the actual cell dosage formulated in each drug product varied for each patient and could have been higher or lower than target doses, but each dose was controlled to dose ranges that were based on the accumulated data from prior and ongoing studies.

The doses of Orca-T used in the phase 1b and phase 3 components of Precision-T do not exceed the doses that would be present in a standard HCT allograft.

The Applicant's Position:

The upper limit for each component of Orca-T (HSPCs, Tregs, Tcons) is determined by the cellular abundance and G-CSF mobilization of the donor, as well as apheresis volume and other technical limitations of collecting cells from the donor. As such, the doses of Orca-T do not exceed those that would be present in a standard HCT allograft. No increases in toxicity or decreases in efficacy have been observed at the highest doses of Orca-T that are technically possible. Furthermore, standard HCT allografts are not associated with dose-dependent toxicities. Therefore, the doses collected during apheresis in Precision-T are within the appropriate range, and there does not appear to be any safety or efficacy reason to impose an upper limit.

The Precision-T study was not designed to prospectively evaluate lower doses than those that would be representative of a standard HCT allograft. However, 4 participants in Precision-T received Orca-T product that did not meet the target HSPC dose ($1^{(b)(4)} \times 10^6$ viable HSPCs/kg). Despite the lower HSPC dose, all participants in the Orca-T group achieved neutrophil engraftment within 28 days of infusion. Therefore, administration of cellular doses that are below the current specifications or lower than those tested may provide similar clinical benefit to patients, but the data are insufficient to draw any meaningful conclusions.

The 1:1 ratio of Tregs:Tcons and the administration schedule of the cellular components of OrcaT (ie, Tregs on day 0 with HSPCs, followed by Tcons on day +2) are critical for the prevention of GVHD. While Tcons enhance GVL effects, Tcons are also a contributing factor for GVHD risk; therefore, the Tcon dose is a critical factor in balancing immune reconstitution and GVHD risk. Administering a sufficient dose of Tregs 2 days prior to Tcons allows sufficient time for Treg expansion in vivo to mitigate the GVHD risk associated with Tcon administration. This dosing strategy is supported by positive results from the phase 3 component of Precision-T as well as by preclinical studies, a phase 1/2b clinical study that served as the proof of concept for Precision-T, and preliminary results from the phase 1b component of Precision-T.

The FDA's Assessment:

The applicant's rationale for the dosing strategy is based on the 1:1 Treg:Tcon ratio and sequential administration schedule (Tregs on day 0, Tcons on day +2) to allow time for Treg expansion in vivo to mitigate GVHD risk while maintaining graft-versus-leukemia effects. The proposed target dose ranges in the protocol are $\geq 1^{(b)(4)} \times 10^6$ HSPCs/kg, $^{(b)(4)}$ Tregs/kg, and $^{(b)(4)}$ Tcons/kg.

Of the 93 participants randomized to receive $^{(b)(4)}$ 88 participants received all three infusions. The actual dose ranges administered in the phase 3 Precision-T study were $1.0-11.3 \times 10^6$ HSPCs/kg (median 4.10×10^6), $1.2-3.5 \times 10^6$ Tregs/kg (median 2.35×10^6), and $1.8-6.9 \times 10^6$ Tcons/kg (median 3.60×10^6). The Treg:Tcon ratio ranged from 0.26 to 1.48 (median 0.64, mean 0.68; 25th and 75th quantiles: 0.51 and 0.81, respectively). Four participants received product that did not meet the protocol target HSPC dose ($1^{(b)(4)} \times 10^6$ viable HSPCs/kg). All 88 participants received the Tcon infusion within 72 hours after the HSPC infusion.

Based on the efficacy and safety data from Precision-T, the dose ranges for each component used in Precision-T appear acceptable. However, per CMC review, the applicant failed to use critical controls in critical release assays for the phase 3 clinical trial batches, including dose determining assays used to quantify HSPCs, Tregs, and Tcons. The applicant must provide complete reanalysis of the phase 3 clinical trial data with appropriate controls to establish reliable cellular dose measurements. Due to

above mentioned deficiency regarding dose determining assay, the actual recommended dose ranges for each component need to be re-defined.

6.2.2.2. Therapeutic Individualization

Data:

Orca-T is an allogeneic stem cell and T cell immunotherapy isolated from a donor's mobilized peripheral blood and is uniquely donor- and recipient-specific. Production of Orca-T involves the fresh isolation of cells via (b) (4)

No direct modifications of the cells, (b) (4), are involved.

Orca-T has been administered based on subject body weight as described in section 6.2.2.1. The target cellular dosages for Orca-T were identified based on preclinical studies of alloHCT, early clinical experience with a product similar to Orca-T, and manufacturing feasibility.

The Applicant's Position:

Orca-T is uniquely donor- and recipient-specific, with therapeutic individualization achieved through administration based on patient body weight and targeted cell doses identified from preclinical studies and early clinical experience. The product's manufacturing and dosing approach are designed to ensure consistent delivery of purified HSPCs, Tregs, and Tcons without direct modification, supporting individualized therapy while maintaining feasibility and reproducibility across patients undergoing MAC-alloHCT.

The FDA's Assessment:

The applicant's approach to therapeutic individualization through weight-based dosing is consistent with standard practice for allogeneic HCT and is appropriate for a cellular therapy product. However, the CMC issues with the phase 3 clinical trial batches prevent verification of the actual cellular doses administered to individual patients in Precision-T, and the degree of inter-patient variability in cellular composition cannot be reliably assessed. Please refer to the CMC review for details.

Furthermore, the applicant has not provided data on therapeutic individualization for special populations, including pediatric patients, geriatric patients, or patients with renal or hepatic impairment. The Precision-T study enrolled only adults (age ≥ 18 years), and no information has been provided regarding the appropriateness of the proposed weight-based dosing approach across different patient populations or body weight ranges.

6.2.2.3. Outstanding Issues

Data:

Not Applicable

The Applicant's Position:

Not Applicable

The FDA's Assessment:

Not Applicable

6.3. Comprehensive Clinical Pharmacology Review

6.3.1. General Pharmacology and Pharmacokinetic Characteristics

Data:

Cell therapies, unlike traditional small molecule drugs, present unique challenges for clinical PK and PD reporting due to the inherent complexity of living cells as therapeutic agents, their dynamic behavior in vivo, and the lack of a well-defined dose analogous to drug concentrations. As such, standard PK and PD analyses do not apply, and specific studies evaluating the PK and PD of Orca-T were not conducted. The dynamic nature of cell therapies necessitates a shift from traditional drug-centric PK/PD approaches to a focus on characterizing the relationship between cell exposure and therapeutic response, ie, exposure-response relationship.

The Applicant's Position:

Standard PK and PD analyses are not applicable to Orca-T due to its nature as a living cell therapy product. Instead, the focus has been on characterizing the relationship between cell exposure and therapeutic response, consistent with the dynamic properties of cell therapies.

The FDA's Assessment:

FDA agrees that standard PK and PD analyses are not applicable to (b) (4) given its nature as an allogeneic cell therapy comprising unmodified human cellular components. The applicant's approach to focus on exposure-response relationships rather than traditional PK/PD parameters is appropriate for this type of product. However, the CMC issues with the phase 3 clinical trial batches prevent reliable characterization of the relationship between cell exposure and therapeutic response. Please refer to the CMC review for details and section 6.1 for discussion of exposure-response analyses.

6.3.2. Clinical Pharmacology Questions

6.3.2.1 Does the clinical pharmacology program provide supportive evidence of effectiveness?

Data:

Precision-T was a multicenter phase 1b/3 study evaluating the safety and efficacy of Orca-T in adults with advanced hematologic malignancies undergoing MAC-alloHCT. Limited exposure-response analyses were conducted as exploratory endpoints in the phase 3 component (see section 6.2.1). Neutrophil engraftment by day +28, moderate or severe cGVHD at 1 year, and CD3 count over time were evaluated.

The exploratory analyses demonstrated that no exposure-response relationship was identified between cGVHD and the Treg dose and between CD3 count and the Tcon dose. Additionally, all participants had neutrophil engraftment by day +28, regardless of HSPC dose, demonstrating that no exposure-response relationship was identified between neutrophil engraftment and the CD34+ dose. These findings indicate that the Orca-T doses administered in Precision-T were adequate and sufficient to elicit the intended therapeutic response.

The Applicant's Position:

Results of the exploratory exposure-response analyses support the appropriateness of the selected study doses, ratio, and dosing schedule of the cellular components of Orca-T. Doses outside of those studied may be similarly safe and effective, but no exposure-response relationship has been observed to date. These findings indicate that the administered doses were sufficient to achieve the desired pharmacologic and clinical effects in participants with advanced hematologic malignancies undergoing MAC-alloHCT.

The FDA's Assessment:

No. The clinical pharmacology program does not provide supportive evidence of effectiveness due to CMC issues with the phase 3 clinical trial batches. While the clinical outcomes observed in Precision-T suggest therapeutic activity, the CMC issues prevent reliable characterization of exposure-response relationships. The applicant's conclusion that "doses administered were adequate and sufficient" cannot be substantiated without reliable dose measurements. Please refer to the CMC review for details and [Section 6.1](#) for discussion of exposure-response analyses.

6.3.2.2 Is the proposed dosing regimen appropriate for the general patient population for which the indication is being sought?

Data:

Exploratory exposure-responses analyses (section [6.2.1](#)) indicated no dose-response relationship between Orca-T doses and endpoints selected based on the biological plausibility of an effect produced by each component of Orca-T. Furthermore, weight-based dosing helps to ensure an appropriate dose for each patient.

The Applicant's Position:

The doses of Orca-T used in Precision-T do not exceed the doses that would be present in a standard HCT allograft and were sufficient to achieve the desired pharmacologic and clinical effects in participants with advanced hematologic malignancies undergoing MAC-alloHCT. No dose-response relationship has been observed, and weight-based dosing helps to ensure an appropriate dose for each patient.

The FDA's Assessment:

Cannot be determined. While the dosing regimen used in Precision-T (weight-based dosing with sequential administration of HSPCs and Tregs on day 0, Tcons on day +2) is associated with clinical outcomes observed in the trial, the CMC issues with the

phase 3 clinical trial batches prevent verification of the actual doses administered. FDA cannot confirm that the proposed dosing regimen is appropriate for the general patient population without reliable dose measurements. Please refer to the CMC review for details and [Section 6.2.2.1](#) for discussion of general dosing.

6.3.2.3 Is an alternative dosing regimen or management strategy required for subpopulations based on intrinsic patient factors (e.g. race, ethnicity, age, performance status, genetic subpopulations, etc.)?

Data:

Standard PK and PD analyses do not apply for a cell therapy. As such, specific studies evaluating the PK and PD of Orca-T were not conducted, and neither were PK or PD examined based on intrinsic patient factors.

The Applicant's Position:

No data suggest differences in dosing would be warranted based on intrinsic patient factors. Therefore, no dose adjustment is recommended based on any of these patient factors.

The FDA's Assessment:

Cannot be determined. The available data are insufficient to assess whether alternative dosing regimens are required for subpopulations based on intrinsic patient factors.

The Precision-T phase 3 study enrolled only adults (age ≥ 18 years), and no subgroup analyses evaluating exposure-response relationships or clinical outcomes across different patient populations (age, sex, race, ethnicity, body weight extremes) have been provided. (b) (4) has not been studied in pediatric patients, and the appropriateness of the proposed weight-based dosing for this population is unknown.

Additionally, the CMC issues with the phase 3 clinical trial batches prevent reliable assessment of whether different patient subpopulations received different actual cellular doses or whether dose-response relationships vary across subgroups. Please refer to the CMC review for details.

6.3.2.4 Are there clinically relevant food-drug or drug-drug interactions, and what is the appropriate management strategy?

Data:

Not applicable

The Applicant's Position:

Food-drug studies are not applicable, as Orca-T is a cell therapy administered by intravenous infusion.

The FDA's Assessment:

FDA agrees that food-drug interaction studies are not applicable for (b) (4) given its route of administration (intravenous infusion of cellular components)

X

X

Primary Reviewer

Team Leader

7 Sources of Clinical Data

7.1. Table of Clinical Studies

Data:

An overview of the clinical studies supporting the efficacy and safety is presented in [Table 4](#). Applicant - Listing of Relevant Clinical Trials

Table 4. Applicant - Listing of Relevant Clinical Trials

Trial Identity	Trial Design	Regimen/Schedule/ Route	Study Endpoints	Treatment Duration/ Follow-Up	No. of Patients Enrolled	Study Population	No. of Centers and Countries
<i>Primary Study to Support Efficacy and Safety</i>							
Precision-T phase 3 component (NCT05316701)	Phase 1b/3 randomized, open-label, multicenter study designed to compare the safety and efficacy of Orca-T to that of a control consisting of SoC MAC-alloHCT	<u>Day 0:</u> HSPCs IV ($\geq 1.0 \times 10^6$ cells/kg) Tregs IV (0.9×10^6 to 3.5×10^6 cells/kg) <u>48-72 hours after HSPC start:</u> Tcons IV (0.9×10^6 to 6.9×10^6 cells/kg)	<u>Primary:</u> • cGFS <u>Secondary:</u> • Time to GVHD • OS • GRFS	Single dose/Randomization through 730 days after transplantation	174	Adults with acute leukemia (myeloid, lymphoid, or mixed phenotype) in CR/CRi or MDS	19 centers in the United States
<i>Additional Studies to Support Safety</i>							
Precision-T phase 1b component (NCT04013685)	Phase 1b single-arm study to characterize safety and efficacy	The HSPC and Treg DPs were administered IV on study day 0. The Tcon drug product was to be infused between 48 and 72 hours after the start of HSPC infusion	<u>Primary:</u> • Primary graft failure • Incidence of grade 3 or 4 aGVHD • TEAEs <u>Secondary:</u> • cGFS • GRFS • OS • NRM • RFS • Time to disease relapse	Single dose/Randomization through 365 days after transplantation	154	Adults with acute leukemia (myeloid, lymphoid, or mixed phenotype) in CR/CRi, MDS, BPDCN or CML	21 centers in the United States

-
- Time to moderate or severe cGVHD
 - Neutrophil engraftment
 - Platelet engraftment
 - Secondary graft failure
-

Abbreviations: aGVHD, acute GVHD; BPDCN, blastic plasmacytoid dendritic cell neoplasm; cGFS, chronic GVHD-free survival; CML, chronic myeloid leukemia; CR, complete remission; CRi, CR with incomplete hematologic recovery; DP, drug product; GRFS, GVHD-free and relapse-free survival; GVHD, graft-versus-host disease; HSPC, hematopoietic stem and progenitor cell; MAC-alloHCT, myeloablative conditioning-allogeneic hematopoietic cell transplantation; MDS, myelodysplastic syndrome; NRM, nonrelapse mortality; OS, overall survival; RFS, relapse-free survival; SoC, standard of care; Tcon, conventional T cell; TEAE, treatment-emergent adverse events; Treg, regulatory T cell.

The Applicant's Position:

The primary evidence to support the efficacy and safety of (b) (4) in the proposed indicated population is provided by the randomized phase 3 component of the Precision-T study (Orca-T N = 88; SoC N = 94). Supportive safety evidence is provided by the primary integrated safety analysis set, which includes all participants from phase 3 and a subset of participants from the phase 1b component of Precision-T who met key eligibility criteria for phase 3 (Orca-T N = 110).

The FDA's Assessment:

FDA agrees with the Applicant's assessment.

7.2. Review Strategy

The FDA's assessment:

The main documents used in the review of efficacy and safety include:

- Documents included with BLA125868 including but not limited to clinical study report (CSR), patient narratives, exposure response report, endpoint adjudication committee charter, pathology reports, clinical overview, summary of clinical efficacy, summary of clinical safety etc.
- Relevant published references

Data used for evaluation of BLA 125868 included:

- Efficacy: Data from the RCT, phase 3 component of the Precision-T study were used for efficacy analysis.
- Safety:
 - Data from RCT, phase 3 component of the Precision-T study were used for the primary safety analysis (Section 8.2.4).
 - Data from single-arm, phase 1b component of the Precision-T study were used for supportive safety analysis (Section 8.2.11).
 - The integrated safety analysis set include phase 1b and phase 3 of Precision-T study (Section 8.2.11).

Data cutoff date:

- Primary efficacy analysis: used data cutoff date of July 15, 2024.
- Primary safety analysis: used data cutoff date of July 15, 2024.

The safety update dataset as data cutoff date of April 30, 2025 submitted by the Sponsor included additional 9 months of follow up and were evaluated in integrated analysis set.

8 Statistical and Clinical Evaluation

8.1. Review of Relevant Individual Trials Used to Support Efficacy

8.1.1. Precision-T

Trial Design

The Applicant's Description:

Precision-T is a multicenter phase 1b/3 study evaluating the safety and efficacy of Orca-T in adults with advanced hematologic malignancies undergoing MAC-alloHCT.

The phase 3 component of Precision-T is a randomized, open-label study in participants aged 18 to 65 years who have 1 of the following disease types: acute leukemia (myeloid, lymphoid, or mixed phenotype) in complete remission (CR) or CR with incomplete hematologic recovery (CRi), high-risk MDS with $\leq 10\%$ blasts in the bone marrow and eligible for alloHCT per International Expert Panel recommendations, or treatment-related MDS.

Participants enrolled in the phase 3 component were randomized in a 1:1 ratio to receive either Orca-T followed by single-agent tacrolimus or standard-of-care (SoC) control allograft derived from mobilized peripheral blood followed by GVHD prophylaxis with tacrolimus and methotrexate. Randomization was stratified by donor type (matched sibling donor versus matched unrelated donor) and DRI category (intermediate risk or high risk). Approximately 174 participants were to be enrolled onto the phase 3 component.

While the phase 3 component of the study is open label, Orca Bio and contract research organizations (CROs) were partially blinded such that participant treatment assignment and participant-level treatment-revealing data were available only to the investigator, participants, and specific Orca Bio and CRO study team members.

Donors and recipients were randomized only after evaluation by the investigators at the respective sites and approval by the Orca Bio medical monitor. Randomization occurred prior to the transfer of apheresis products to Orca Bio's manufacturing facility.

All donors received mobilization therapy per institutional guidelines with daily G-CSF. The mobilization phase started on the first day of administration of G-CSF and continued until the final day of leukapheresis. For donors matched with recipients assigned to receive Orca-T, a large-volume apheresis was performed, which typically started on the fifth day of G-CSF administration (typically day -2). For donors matched with recipients assigned to the SoC group, G-CSF

mobilization was performed according to local institutional or donor center practices. PBSCs were collected by apheresis according to local institutional guidelines. Plasma and red cell depletion were allowed for volume reduction or ABO incompatibility, but any other form of graft manipulation (including ex vivo TCD) was not permitted. For both Orca-T and SoC groups, single-day donor collections were strongly preferred over 2-day collections, but up to 2 leukapheresis procedures may have been performed to obtain the minimum CD34+ cell target.

Prior to Orca-T or SoC infusion, all participants received the investigator's choice of MAC regimen from those allowed per protocol. Investigators were permitted to choose different MAC regimen for each of the possible treatment assignments (ie, different regimens that were contingent upon assignment to receive either Orca-T or SoC); this choice was declared prior to randomization and could not be altered after randomization.

For recipients assigned to the Orca-T group, the investigator's choice from the MAC regimens was administered per local institutional standards prior to Orca-T administration. Target cellular dosages were identified based on preclinical studies, early clinical experience, and manufacturing feasibility. The Orca T HSPC and Treg drug products were administered intravenously (IV) through a central venous catheter on study day 0. Orca-T Tcon drug product was to be infused between 48 and 72 hours after the start of HSPC infusion unless a participant had a Karnofsky performance score <30% or an uncontrolled infection, in which case the Tcon infusion could be delayed up to day +5 to allow for control of infection and/or improvement in performance score. Single-agent GVHD prophylaxis with tacrolimus began on the day following Tcon infusion (typically day +3), starting no fewer than 12 hours after the start of the Tcon infusion. No dose modifications of Orca-T were permitted during the study.

For recipients assigned to the SoC control group, the investigator's choice from the MAC regimens above was administered per local institutional standards prior to IV administration of an unmanipulated allograft derived from G-CSF-mobilized donor PBSCs through a central venous catheter on day 0. Dual-agent GVHD prophylaxis was administered with tacrolimus beginning on day -3 and methotrexate beginning at least 24 hours after the PBSC infusion (day +1).

During active participation in the study, participants were followed for efficacy and safety up to day +730 (with day 0 defined as the day the participant received the Orca-T HSPC infusion or SoC allograft infusion). After day +730 or after withdrawing from active participation, participants entered long-term follow-up (LTFU) and were followed every 6 months for long term survival and disease status until death, loss to follow-up, withdrawal of consent, or study termination.

An independent data monitoring committee (DMC) regularly reviewed safety data. The DMC was composed of 4 members (including the DMC Chair) who did

not have any conflict of interests with Orca Bio. A quorum for DMC meetings required 3 members, including 2 clinicians and a biostatistician.

An independent endpoint adjudication committee (EAC) performed a blinded determination as to whether the criteria for aGVHD and/or cGVHD were met for each participant. The EAC then graded aGVHD according to Mount Sinai Acute GVHD International Consortium (MAGIC) criteria and graded cGVHD according to 2014 International National Institutes of Health (NIH) Chronic GVHD Diagnosis and Staging Consensus Working Group criteria. The EAC was composed of a minimum of 3 experts in GVHD assessment.

The design of the phase 3 component of the Precision-T trial incorporated feedback from the Food and Drug Administration (FDA) via an end-of-phase 2 meeting in July 2021 and following submission of a Precision-T Protocol amendment in November 2021 to include the phase 3 component of the study. FDA provided feedback on aspects of the study design that included the intended study population, the use of conventional alloHCT as SoC for the comparator arm, the choice of MAC regimens, the choice of GVHD prophylaxis regimen for both the Orca-T and SoC arms, the adequacy of the primary and supportive secondary endpoints, the statistical analysis plan, and the length of follow-up.

The phase 1b component of Precision-T is a single-arm study to characterize the safety and efficacy of Orca-T in participants who meet the following criteria:

- Aged 18 to 75 years
- Have 1 of the following disease types:
 - Active (ie, not in CR) and/or disease risk index very high AML, ALL, or MPAL (Armand et al. 2012)
 - MDS with >10% to <20% bone marrow blast burden
 - Blastic plasmacytoid dendritic cell neoplasm
 - Chronic myeloid leukemia (CML) in chronic phase with a history of blast crisis or accelerated phase and/or resistant to or intolerant of >1 tyrosine kinase inhibitor
 - AML with inv(16) and without complex cytogenetics with high-risk disease features (eg, molecular markers, relapsed disease in second CR or beyond, clonal evolution)
- Would be eligible for the phase 3 component of the study but have mild impairments in renal and/or hepatic function as defined by an estimated glomerular filtration rate of 50 to <60 mL/min and/or a total bilirubin of >upper limit of normal (ULN) to $\leq 2 \times$ ULN

Although protocol version 5.0 and earlier included participants in the phase 1b component who would have subsequently met eligibility requirements for the phase 3 component of the study, participants enrolled onto the Precision-T Study prior to institution of version 6.0 of the protocol were not subject to randomization and will, therefore, be analyzed as part of the phase 1b population. Up to

approximately 227 participants were to be enrolled on the phase 1b component of the study across all disease types under study.

Data from the phase 1b component of Precision-T are considered supportive for safety and are included in Module 2.7.4 but are not presented in this document.

The FDA's Assessment:

Overall, FDA agrees with the Applicant's overview of the study design of phase 1 and phase 3 components of the study, eligibility criteria of the phase 1 component of the study, and the study treatments that were received on the Precision-T study.

Eligibility Criteria

The Applicant's Description:

Key eligibility criteria for the phase 3 component of Precision-T are described below for both donors and recipients. Full eligibility criteria are provided in the Precision-T Protocol and Phase 3 CSR.

Donor Eligibility

Inclusion:

- Age ≥ 16 to ≤ 75 years
- 8/8 HLA-matched sibling or unrelated donor (typed using DNA-based high-resolution methods)
- Willing to undergo up to 2 consecutive days of peripheral blood stem cell (PBSC) collection within North America or Hawaii and capable of undergoing leukapheresis
- Met all federal and National Marrow Donor Program (NMDP) (or institutional) standards for donation of viable leukocyte-rich cells as defined by 21 Code of Federal Regulations [CFR] § 1271.2018 and all relevant FDA Guidance for Industry. Donors who did not meet every federal criterion may still have qualified if they were a first- or second-degree relative or if urgent medical need was documented.
- Female donors of child-bearing potential must have had a negative serum/urine β -hCG test at screening and again within 1 to 5 days before mobilization.

Exclusion:

- Evidence of active infection
- Positive for HIV-1/2, HTLV-1/2, HBV, or HCV;
- Potential for Zika virus infection
- Pregnant or breastfeeding

Recipient Eligibility:

Inclusion:

- Planned MAC-alloHCT using a protocol-specified MAC regimen
- 8/8 HLA-matched sibling or unrelated donor
- Cardiac ejection fraction $\geq 45\%$ (or shortening fraction $\geq 27\%$)
- DLCO $\geq 50\%$ (Hb-adjusted)
- ALT/AST $< 3 \times$ ULN
- Negative serum/urine β -hCG in women of child-bearing potential
- Age ≥ 18 to ≤ 65 years
- Diagnosed with 1 of the following histopathologically confirmed disease:
- AML, ALL, MPAL in CR/CRi
- MDS eligible for transplant per 2017 International Expert Panel recommendations or therapy-related/secondary MDS; MDS enrollment limited to participants with $\leq 10\%$ marrow blasts
- DRI overall risk categorization of intermediate or high
- Total bilirubin $\leq$ ULN
- eGFR ≥ 60 mL/min.

Exclusion:

- Prior alloHCT
- Currently receiving corticosteroids or other immunosuppressive therapy; corticosteroids ≤ 10 mg/day were allowed
- Planned donor-lymphocyte infusion or TCD (eg, posttransplantation cyclophosphamide, peritransplantation ATG, alemtuzumab)
- Positive antidonor HLA antibodies
- Karnofsky score $< 70\%$
- HCT-CI > 4
- Uncontrolled infection
- Seropositivity for HIV-1/2, HTLV-1/2, HBsAg, or HCV antibody
- Known allergy or hypersensitivity to, or intolerance of tacrolimus
- Documented allergy or hypersensitivity to iron dextran or bovine, murine, algal, or *Streptomyces avidinii* proteins
- Concurrent malignancies within 1 year, except nonmelanoma skin cancers that had been curatively resected
- Psychosocial circumstances that precluded transplantation or participating responsibly in follow-up care
- Pregnant or breastfeeding
- Unwilling to use effective forms of birth control or abstinence for 1 year after transplantation
- Any serious medical condition that, in the investigator's or medical monitor's judgment, would preclude safe participation in or completion of the study or could affect compliance with the protocol or interpretation of results

The FDA's Assessment:

FDA agrees with the Applicant's description of the donor eligibility criteria and phase 3 study recipient eligibility criteria.

Study Endpoints

The Applicant's Description:

The primary endpoint for the pivotal efficacy analysis was cGFS, defined as the time from the date of alloHCT (day 0) to the date of death from any cause or the first onset of moderate or severe cGVHD (graded per NIH consensus criteria and assessed by a blinded external EAC), whichever is earliest, within 2 years after day 0. For subjects who were randomized but did not receive the product, were censored at Day 0,

Secondary endpoints were as follows:

- Time to moderate or severe cGVHD, defined as the time from alloHCT to the first onset of moderate or severe cGVHD (graded per NIH consensus criteria and assessed by a blinded external EAC) within 2 years after day 0. Death within 2 years after day 0 without prior moderate or severe cGVHD was considered a competing event.
- OS, defined as the time from randomization to death from any cause
- GRFS, defined as the time from alloHCT to death from any cause, relapse, the first onset of grade 3 or 4 aGVHD (graded per MAGIC criteria), or the first onset of moderate or severe cGVHD (graded per NIH consensus criteria), whichever is earliest, within 2 years from day 0

The FDA's Assessment:

FDA agrees with the Applicant's description of the endpoints of Precision-T study in general.

Statistical Analysis Plan and Amendments

The Applicant's Description:

The original statistical analysis plan (SAP) for Precision-T Phase 3 was finalized on 19 December 2023 (Version 2.0). Amendment 1 to the SAP (Version 3.0) was completed on 20 March 2024, with a memo dated 8 May 2024. Amendment 2 (Version 4.0) was finalized on 19 September 2024, with memos dated 21 October 2024 and 13 December 2024, prior to the database lock for the primary analysis.

The analysis of efficacy endpoints was based on the ITT analysis set, which included all randomized participants, regardless of whether they received Orca-T/SoC or not. Participants were analyzed according to their randomized treatment group. An independent, blinded EAC assessed GVHD for the primary endpoint (cGFS) and the secondary endpoints of time to moderate or severe cGVHD and GRFS.

The primary endpoint of cGFS per EAC was used to evaluate the effect of the experimental regimen for alloHCT against an SoC. To achieve 90% power with a true HR = 0.40 and 1-sided alpha of .025, the required number of events needed was 56 events (see [Fleming and Harrington 2005](#), p. 395 and [Al-Khalidi et al. 2011](#), Equation 5). This true HR of 0.40 corresponds approximately to 12-month event-free cGFS rates of 79% versus 55% for Orca-T and SoC, respectively (event rates at 12 months equal to 21% of participants for Orca-T versus 45% of participants for SoC). The number of participants required to achieve 56 events based on the above assumptions is 165 participants. In order to account for 5% loss to follow-up in both treatment groups, 174 participants were to be randomized.

A single interim analysis was planned to assess both primary and secondary endpoints when 37 primary endpoint (cGFS) events per EAC were observed. Events contributing to the primary endpoint (ie, moderate or severe cGVHD and death) occurred at a more rapid rate than expected. As a result, Orca Bio decided to forego the interim analysis and proceed directly to the primary analysis. To minimize the potential introduction of bias into the conduct of the study, the study biostatistics/programming team was kept blinded to the treatment information of individual participants until the primary analysis was triggered.

Interim analyses were planned to assess the secondary endpoints of OS and GRFS per EAC when 56 primary endpoint (cGFS) events per EAC were observed. The primary analyses for OS and GRFS will be performed when 40 deaths are observed or 2 years after the end of enrollment, whichever is earlier.

Subgroup analyses were performed on the primary and secondary endpoints using the primary estimand for the subgroups defined below. Additionally, subgroup analyses were conducted on the primary and secondary endpoints derived based on investigators' assessment of aGVHD and/or cGVHD. Key safety tables were also be repeated for the same subgroups. The subgroups analyzed included the following:

- Gender (male or female)
- Gender match between donor and recipient (gender matched or gender mismatched)
- Race (Caucasian or non-Caucasian)
- Ethnicity (Hispanic/Latino or non-Hispanic/Latino)

- DRI score (intermediate or high)
- Donor status (MSD or MUD)
- Underlying disease (AML, ALL, MPAL, or MDS)
- HCT Comorbidity Index (HCT-CI) score (score ≤ 2 or score ≥ 3)
- Conditioning regimen (total body irradiation [TBI]-based or BFT)
- Receipt of DLI (yes or no)
- FLT3, BCR-ABL, or IDH1/2 inhibitors for prevention of relapse (yes or no)
- Use of rituximab after HCT (yes or no)
- Sites (Stanford or non-Stanford)
- Relationship of CMV status at baseline between donor and recipient (positive/positive, positive/negative, negative/positive, or negative/negative)
- Relationship of ABO types between donor and recipient (A/A, A/AB, etc.)
- Recipient age in years (≥ 55 or < 55)
- Donor age in years (above or below median)
- MRD at baseline (participants with ALL or AML) (positive or negative)
- Steroid responsive aGVHD treatment or steroid refractory aGVHD treatment or steroid dependent aGVHD treatment (participants who develop aGVHD with grade ≥ 2 only)

If the number of participants in either arm for a given subgroup was less than 5, efficacy tables were not repeated for that subgroup.

The FDA's Assessment:

FDA agrees with the Applicant's description. In addition, statistical testing of the primary and secondary endpoints followed a hierarchical testing method. The primary endpoint of cGFS per EAC was to be tested first. The secondary endpoints were to be tested sequentially if the primary endpoint was statistically significant:

- If (b) (4) demonstrated superiority to SoC with respect to cGFS per EAC, the secondary endpoint of time to moderate or severe cGVHD per EAC was to be tested.
- If (b) (4) demonstrated superiority to SoC with respect to time to moderate or severe cGVHD per EAC, the secondary endpoint of OS was to be tested.
- If (b) (4) demonstrated superiority to SoC with respect to OS, GRFS per EAC up to 2 years was to be tested.

Protocol Amendments

The Applicant's Description:

There were 9 global protocol amendments and 6 protocol clarification memoranda to the original Precision-T protocol dated 13 May 2019 (Table 8. Applicant - Precision-T Phase 3 Protocol Amendments). The protocol amendments did not have a significant impact on trial integrity or interpretation of study results.

Table 8. Applicant - Precision-T Phase 3 Protocol Amendments

Protocol Version and Date^a	Summary of Key Changes
Version 1.0 (13 May 2019)	Original protocol issued; outlined phase 1b objectives, endpoints, and design for Orca-T in MAC-alloHCT.
Version 6.0 (17 Jan 2022)	Initiated Phase 3 component; added phase 3-specific objectives, endpoints, eligibility criteria; incorporated Data Monitoring Committee and Endpoint Review Committee; refined conditioning regimen options; updated statistical considerations; extended follow-up to 2 years post-transplant.
Version 7.0 (06 October 2022)	Inclusion criteria were updated for phase 3 and 1b components.
Version 8.0 ^b (16 March 2023)	Eligibility for the phase 1b component was expanded. Myelofibrosis was removed as an allowed diagnosis. Objectives and endpoints were modified to align with each other.
Version 9.0 (09 May 2023)	Updated stopping criteria to align with FDA information requests; clarified reporting requirements for adverse events and death details; updated safety monitoring and endpoint adjudication procedures.

a Protocol versions 1-5 are for the Precision-T phase 1b component only

b Protocol version 8 was submitted to the FDA but was not released as a standalone version to clinical sites due to additional edits that were needed following finalization.

The FDA's Assessment:

FDA agrees with the Applicant's description of the protocol amendment. FDA agrees with the Applicant that the protocol amendments did not have a significant impact on trial integrity or interpretation of study results.

8.1.2. Study Results**Compliance with Good Clinical Practices****Data:**

The Precision-T Phase 3 study was conducted in compliance with the protocol, International Council for Harmonisation Good Clinical Practice guidelines, the

Declaration of Helsinki, and applicable regulatory requirements. Institutional review board or independent ethics committee approval was obtained for the protocol, amendments, and informed consent forms prior to the initiation of the study, and written informed consent was obtained from all participants before the study procedures commenced.

The study was monitored for adherence to the protocol and regulatory requirements. An independent DMC oversaw participant safety and data integrity, and an EAC performed blinded adjudication of aGVHD and cGVHD.

The Applicant's Position:

The Applicant confirms that the Precision-T Phase 3 study was conducted in compliance with Good Clinical Practice and applicable regulatory requirements, with appropriate oversight to ensure the reliability and integrity of the submitted data.

The FDA's Assessment:

FDA agrees with the Applicant's description.

Financial Disclosure

Data:

The Applicant has submitted financial disclosure information for all clinical investigators who participated in the Precision-T Phase 3 study, in accordance with 21 CFR Part 54. No investigator disclosed any significant financial interests that would raise questions about the integrity of the study data.

The Applicant's Position:

The Applicant has submitted financial disclosure information for all clinical investigators who participated in the Precision-T Phase 3 study, in accordance with 21 CFR Part 54. No investigator disclosed any significant financial interests that would raise questions about the integrity of the study data.

The FDA's Assessment:

Financial disclosure information was provided for 28 principal investigators, 1 interim principal investigator, and 554 sub-investigators, 1 of whom was noted to have disclosable financial interests. The reason for the disclosable financial interest was that has stock options in Orca Bio with unknown value. The Applicant provided a description

of proactive steps that have been taken to minimize potential bias from this reported financial interest. These steps included: 1) the PI was designated as a non-consenting investigator; 2) the disclosure statement of the financial interest to potential impacted parties; 3) recused the PI from impacted activities including situations where he is the sole individual providing approval or sign-off on research, clinical, and/or business matters, committee activities etc. related to Orca Bio.

The review of the financial disclosures did not identify issues that could impact the integrity of the clinical data provided in this submission.

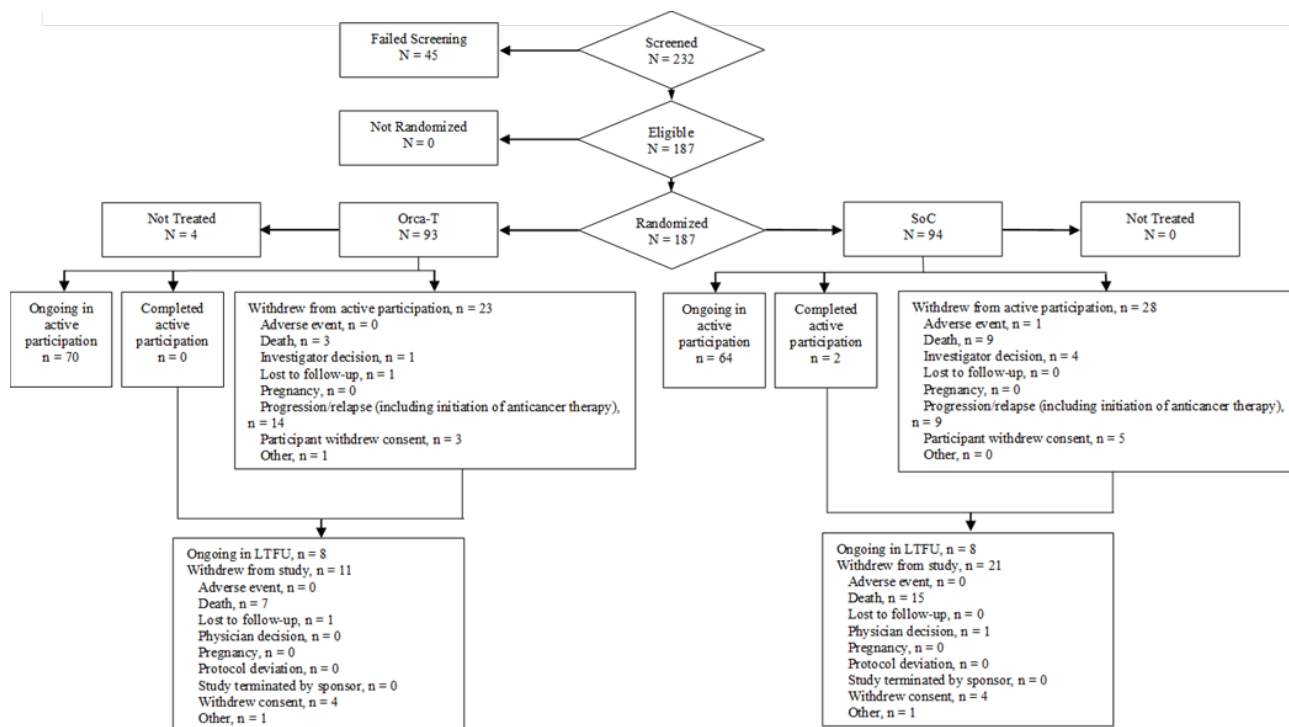
Patient Disposition

Data:

As of the data cutoff date of 15 July 2024, a total of 187 participants were randomized in the phase 3 component of Precision-T to receive either Orca-T (N = 93) or SoC (N = 94). Of those randomized to receive Orca-T, 89 participants were treated, 1 of whom had COVID-19 on the scheduled treatment day and subsequently received a cryopreserved SoC alloHCT instead of Orca-T. Four additional participants who were randomized to Orca-T did not receive an Orca-T infusion as of the data cutoff date: 2 withdrew consent prior to receiving Orca-T, 1 relapsed after randomization and did not enter remission, and 1 received Orca-T after the data cutoff date. Of those randomized to receive SoC, 94 participants were treated, 1 of whom received an allograft derived from a haploidentical donor and was not included in the safety analysis set.

Among those in the Orca-T group, 70 participants (75%) were ongoing in active participation as of the data cutoff date, and no participant had completed active participation. Twenty-three participants (25%) randomized to receive Orca-T withdrew from active participation prior to completion: 14 (15%) due to disease progression/relapse (including initiation of anticancer therapy), 3 (3%) due to death, 3 (3%) due to withdrawal of consent, 1 (1%) for other reasons (disease relapse prior to day 0 and did not enter remission), 1 (1%) who was lost to follow-up, and 1 (1%) due to investigator decision.

Among those in the SoC group, 64 participants (68%) were ongoing in active participation as of the data cutoff date, and 2 participants (2%) completed active participation. Twenty-eight participants (30%) withdrew from active participation prior to completion: 9 (10%) due to disease progression/relapse, 9 (10%) due to death, 5 (5%) due to withdrawal of consent, 4 (4%) due to investigator decision, and 1 (1%) due to an adverse event (AE) (upper gastrointestinal [GI] hemorrhage). Participant disposition is summarized in [Figure 2](#).

Figure 2. Applicant – Precision-T Phase 3 Participant Disposition

Abbreviations: LTFU, long-term follow-up; SoC, standard of care.

a (b) (6) ended active participation, had not ended of study as of the data cutoff date, and did not continue to survival follow up.

b (b) (6) ended active participation but had not ended of study as of the data cutoff date. Information on LTFU and survival follow-up were missing.

Source: Precision-T Phase 3 CSR, Table 14.1.1.2

The Applicant's Position:

The analysis populations for Precision-T were presented to the Agency during the Type B End-of-Phase 2 Meeting. A majority of participants in the ITT analysis set remained in active participation as of the clinical cutoff, and the most common reason for withdrawal from active participation (disease progression or relapse) was consistent with the disease under study.

The FDA's Assessment:

The FDA agrees with the Applicant's description of patient disposition. Among 45 patients with screen failure, 35 did not meet the inclusion/exclusion criteria, 4 withdrew the consent prior to enrollment, 4 had donor issues (i.e. donor withdrew the consent, donor ineligible due to medical conditions, unable to be cleared by NMDP in time etc.), 2 had the schedule conflict.

Protocol Violations/Deviations

Data:

A total of 37 participants (20%) had at least 1 important protocol deviation: 10 (11%) in the Orca-T group and 27 (29%) in the SoC group. In the Orca-T group, important protocol deviations were related to study treatment compliance (5 participants; 5%), study treatment administration/dispensation (5 participants; 5%), study procedures/assessments (1 participant; 1%), concomitant medication (1 participant; 1%), and study treatment randomization (1 participant; 1%). In the SoC group, important protocol deviations were related to study treatment compliance (15 participants; 16%), study treatment administration/dispensation (1 participant; 1%), study procedures/assessments (4 participants; 4%), concomitant medication (3 participants; 3%), missing endpoint assessments (3 participants; 3%), study treatment randomization (2 participants; 2%), and exclusion criteria (1 participant; 1%).

The incidence of important protocol deviations was somewhat higher in the SoC group, primarily due to deviations in the timing (but not dosing) of tacrolimus administration and methotrexate doses withheld. Both groups had therapeutic levels of tacrolimus administered, and methotrexate dose modifications were expected in this population due to potential toxicity. Differences in the incidence of important protocol deviations did not substantially affect the interpretation of the results of the study. Sensitivity analyses conducted using the per-protocol analysis set, which excluded participants with important protocol deviations that may have affected efficacy, demonstrated similar results to the intention-to-treat (ITT) analysis set. Important protocol deviations are summarized in Table 9.

Applicant – Important Protocol Deviation (Precision-T Phase 3 ITT Analysis Set)

Table 9. Applicant – Important Protocol Deviation (Precision-T Phase 3 ITT Analysis Set)

Deviation Category Deviation Subtype	Orca-T (N = 93) n (%)	SoC (N = 94) n (%)	Total (N = 187) n (%)
At least 1 important protocol deviation	10 (10.8)	27 (28.7)	37 (19.8)
Protocol deviation			
Study treatment compliance	5 (5.4)	15 (16.0)	20 (10.7)
Study treatment admin/dispense	5 (5.4)	1 (1.1)	6 (3.2)
Study procedures/assessments	1 (1.1)	4 (4.3)	5 (2.7)
Concomitant medication	1 (1.1)	3 (3.2)	4 (2.1)
Missing endpoint assessments	0	3 (3.2)	3 (1.6)

Study treatment randomization	1 (1.1)	2 (2.1)	3 (1.6)
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Source: Precision-T Phase 3 CSR, Table 14.1.2

The Applicant's Position:

The important protocol deviations identified during the phase 3 component of Precision-T did not substantially affect the integrity or interpretability of the study results.

The FDA's Assessment:

FDA agrees with the Applicant's description and assessment. The incidence of important protocol deviations was higher in the SoC group. These differences were mainly due to deviations in the timing of tacrolimus administration and methotrexate doses modification and withholding doses due to toxicities. The methotrexate was used for GVHD prophylaxis on SoC arm not on Orca-T arm. The toxicities from methotrexate reflected the real-world practice. In addition, sensitivity analyses conducted using the per-protocol analysis set, which excluded participants with important protocol deviations demonstrated similar results to the intention-to-treat (ITT) analysis set. Based on the categories within which the major deviations occurred on both arms, the FDA agrees that it is unlikely that the protocol deviations and differences between two arms had a meaningful impact on safety or efficacy outcomes from the study.

Demographic Characteristics

Data:

Participant demographics in the ITT analysis set are summarized in [Table 10](#). Applicant - Participant Demographics (Precision-T Phase 3 ITT Analysis Set)

Table 10. Applicant - Participant Demographics (Precision-T Phase 3 ITT Analysis Set)

	Orca-T (N = 93)	SoC (N = 94)	Total (N = 187)
Age (years)			
n	93	94	187
Mean (SD)	43.4 (12.63)	43.8 (12.91)	43.6 (12.74)
Median (Q1, Q3)	44.0 (33.0, 54.0)	43.0 (33.0, 55.0)	44.0 (33.0, 55.0)
Min, Max	19, 65	20, 63	19, 65
Age category, n (%)			
≥18 to <55	70 (75.3)	67 (71.3)	137 (73.3)

≥55 to ≤65	23 (24.7)	27 (28.7)	50 (26.7)
Sex, n (%)			
Female	40 (43.0)	44 (46.8)	84 (44.9)
Male	53 (57.0)	50 (53.2)	103 (55.1)
Sex match between donor and recipient, n (%)			
Matched	54 (58.1)	50 (53.2)	104 (55.6)
Mismatched	39 (41.9)	44 (46.8)	83 (44.4)
Female - Male	20 (21.5)	21 (22.3)	41 (21.9)
Male - Female	19 (20.4)	23 (24.5)	42 (22.5)
Race, n (%)			
American Indian or Alaska Native	1 (1.1)	2 (2.1)	3 (1.6)
Asian	10 (10.8)	8 (8.5)	18 (9.6)
Black or African American	1 (1.1)	2 (2.1)	3 (1.6)
Native Hawaiian or other Pacific Islander	1 (1.1)	1 (1.1)	2 (1.1)
White/Caucasian	76 (81.7)	63 (67.0)	139 (74.3)
Not reported	4 (4.3)	18 (19.1)	22 (11.8)
Ethnicity, n (%)			
Hispanic or Latino	26 (28.0)	24 (25.5)	50 (26.7)
Not Hispanic or Latino	62 (66.7)	59 (62.8)	121 (64.7)
Not reported	5 (5.4)	11 (11.7)	16 (8.6)

Abbreviations: Max, maximum; Min, minimum; Q1, first quartile; Q3, third quartile; SD, standard deviation; SoC, standard of care.

Source: Precision-T Phase 3 CSR, Table 14.1.3.2

The Applicant's Position:

Demographics were similar between the Orca-T and SoC groups and were representative of the intended patient population.

The FDA's Assessment:

FDA agrees with the Applicant's assessment. Demographics characteristics were balanced between (b) (4) arm and SoC arm and were representative of the indicated patient population. None of the analyses revealed any impact of demographics on outcome measures.

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

Data:

Baseline disease characteristics in the ITT analysis set are summarized in [Table 5](#).

Table 5. Applicant - Baseline Disease Characteristics (Precision-T Phase 3 ITT Analysis Set)

	Orca-T (N = 93) n (%)	SoC (N = 94) n (%)	Total (N = 187) n (%)
Primary disease			
ALL	30 (32.3)	27 (28.7)	57 (30.5)
AML	49 (52.7)	51 (54.3)	100 (53.5)
High-risk MDS	12 (12.9)	11 (11.7)	23 (12.3)
MPAL	2 (2.2)	5 (5.3)	7 (3.7)
ALL			
Remission status			
CR1	23 (24.7)	20 (21.3)	43 (23.0)
CR2	6 (6.5)	6 (6.4)	12 (6.4)
CR3	1 (1.1)	1 (1.1)	2 (1.1)
NA	0	0	0
AML			
Remission status			
CR1	45 (48.4)	42 (44.7)	87 (46.5)
CR2	4 (4.3)	8 (8.5)	12 (6.4)
CR3	0	1 (1.1)	1 (0.5)
NA	0	0	0
MDS			
IPSS-R score			
<4.5	5 (5.4)	5 (5.3)	10 (5.3)
≥4.5 to <6	4 (4.3)	2 (2.1)	6 (3.2)

≥6	3 (3.2)	4 (4.3)	7 (3.7)
MPAL			
Remission status			
CR1	1 (1.1)	5 (5.3)	6 (3.2)
CR2	1 (1.1)	0	1 (0.5)
CR3	0	0	0
NA	0	0	0
Donor type, n (%)			
Matched sibling donor	46 (49.5)	49 (52.1)	95 (50.8)
Matched unrelated donor	47 (50.5)	45 (47.9)	92 (49.2)
DRI score, n (%)			
High	19 (20.4)	16 (17.0)	35 (18.7)
Intermediate	74 (79.6)	78 (83.0)	152 (81.3)
Baseline HCT-CI score			
0	18 (19.4)	27 (28.7)	45 (24.1)
1	30 (32.3)	18 (19.1)	48 (25.7)
2	22 (23.7)	20 (21.3)	42 (22.5)
3	11 (11.8)	21 (22.3)	32 (17.1)
4	12 (12.9)	7 (7.4)	19 (10.2)
5	0	1 (1.1)	1 (0.5)

Abbreviations: ALL, acute lymphoid leukemia; AML, acute myeloid leukemia; CR, complete remission; DRI, Disease Risk Index; HCT-CI, hematopoietic cell transplantation-specific comorbidity index; IPSS-R, revised international prognostic scoring system; Max, maximum; MDS, myelodysplastic syndrome; Min, minimum; MPAL, mixed phenotype acute leukemia; NA, not available; Q1, first quartile; Q3, third quartile; SD, standard deviation; SoC, standard of care.

Ideal body weight: For height over or equal to 5 feet: Men = 50kg + 2.3kg × (height in inch - 60); Women = 45.5kg + 2.3kg × (height in inch - 60). For height less than 5 feet: Men = 50kg - 2.3kg × (60 - height in inch); Women = 45.5kg - 2.3kg × (60 - height in inch).

Adjusted ideal body weight = ideal body weight + 0.5 × (actual body weight - ideal body weight)

Body surface area = square root of (height in cm × weight in kg/3600)

Source: Precision-T Phase 3 CSR, Table 14.1.4

The Applicant's Position:

Baseline disease characteristics were similar between the Orca-T and SoC groups and were representative of the intended patient population.

The FDA's Assessment:

Version date: February 10, 2025 (ALL NDA/ BLA reviews)

Disclaimer: In this document, the sections labeled as "Data" and "The Applicant's Position" are completed by the Applicant and do not necessarily reflect the positions of the FDA.

FDA agrees with the Applicant's assessment on baseline disease characteristics analysis in ITT population. The study population was representative of the general population with hematologic malignancies eligible for allogeneic transplant with a myeloablative conditioning regimen. Disease characteristics were balanced within the two arms. None of the analyses revealed any impact of disease characteristics on outcome measures.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Data:

Study treatments were administered by qualified personnel at study sites and recorded on the appropriate CRF. Of the 93 participants randomized to receive Orca-T, 88 participants (95%) received all 3 Orca-T infusions. All 88 participants received the Tcon infusion within 72 hours after the HSPC infusion. Of the 94 participants randomized to receive SoC, 93 participants (98.9%) received the intended unmanipulated allograft. Reasons for not receiving Orca-T or SoC are described above under participant disposition. .

In the Orca-T group, all 88 participants received single-agent tacrolimus. In the SoC group 93 participants (99%) tacrolimus, and 92 participants (98%) received methotrexate.

The Applicant's Position:

All but a few participants received the treatment to which they were randomized. Concomitant medication usage was as expected for this patient population.

The FDA's Assessment:

FDA agrees with the Applicant's assessment.

Efficacy Results – Primary Endpoint (Including Sensitivity Analyses)

Data:

The KM estimate of median cGFS was not reached for the Orca-T group and was 7.3 (95% CI: 6.3, 15.5) months for the SoC group after median follow up times of 8.48 (range: 0 to 22.2) months and 9.03 (range: 0 to 20.3) months, respectively.

The 2-sided *P* value from the stratified log-rank test stratified by the randomization stratification factors was <.00001, which is statistically significant per the prespecified critical value of .0464. The estimated HR was 0.26 (95% CI: 0.14, 0.47) using a stratified Cox model also stratified by the randomization stratification factors. The KM

cGFS estimates for Orca-T and SoC were 78.0% (95% CI: 65.0%, 86.6%) and 38.4% (95% CI: 26.2%, 50.5%), respectively, at 12 months.

The magnitude of the treatment effect of Orca-T on cGFS was robust and consistent across subgroups, including donor status and DRI score.

Using investigator assessment of cGVHD as a sensitivity analysis, the KM estimate of median cGFS was 21.6 (95% CI: not estimable, not estimable) months for the Orca-T group and was 6.4 (95% CI: 5.6, 9.3) months for the SoC group. The KM cGFS estimates for Orca-T and SoC were 73.8% (95% CI: 60.0%, 83.5%) and 31.2% (95% CI: 19.5%, 43.6%), respectively, at 12 months. The overall kappa coefficient for concordance between EAC and investigator assessment of moderate or severe cGVHD was 0.8038, indicating a high degree of concordance between EAC and investigator assessments.

Other sensitivity analyses, including assessments using the per-protocol analysis set and alternative missing data handling approaches were consistent with the primary analysis and supported the robustness of the primary endpoint results.

Subgroup analyses demonstrated consistent treatment benefit across subgroups including age, sex, race, disease type, donor type, and DRI risk category.

The efficacy data are summarized in [Table 6.](#) , [Figure 3.](#) , and [Figure 4.](#) .

Table 6. Applicant - Efficacy of Orca-T Versus SoC (Precision-T Phase 3 ITT Analysis Set)

Efficacy Endpoint	Orca-T (N = 93) n (%)	SoC (N = 94) n (%)
cGFS		
Participants with events, n (%)	14 (15.1)	44 (46.8)
Median Kaplan-Meier estimate, months (95% CI)	NE (NE, NE)	7.3 (6.3, 15.5)
Kaplan-Meier estimate at 12 months (95% CI)	78.0% (65.0%, 86.6%)	38.4% (26.2%, 50.5%)
Median follow-up time, months (95% CI)	8.48 (6.90, 11.70)	9.03 (7.62, 11.20)
P value	<.00001	
Hazard ratio (95% CI)	0.26 (0.14, 0.47)	
Moderate or severe cGVHD		
Participants with events, n (%)	7 (7.5)	30 (31.9)
Cumulative incidence rate estimate at 12 months (95% CI)	12.6 (5.3, 23.1)	44.0 (31.3, 56.1)
P value	.00002	
Hazard ratio (95% CI)	0.19 (0.08, 0.43)	
OS		

Participants who died, n (%)	7 (7.5)	15 (16.0)
Median Kaplan Meier estimate, months (95% CI)	NE (NE, NE)	NE (20.9, NE)
Event-free rate estimate, 12 months (95% CI)	93.9 (85.8, 97.4)	83.1 (72.9, 89.8)
Hazard ratio (95% CI)	0.49 (0.20, 1.22)	

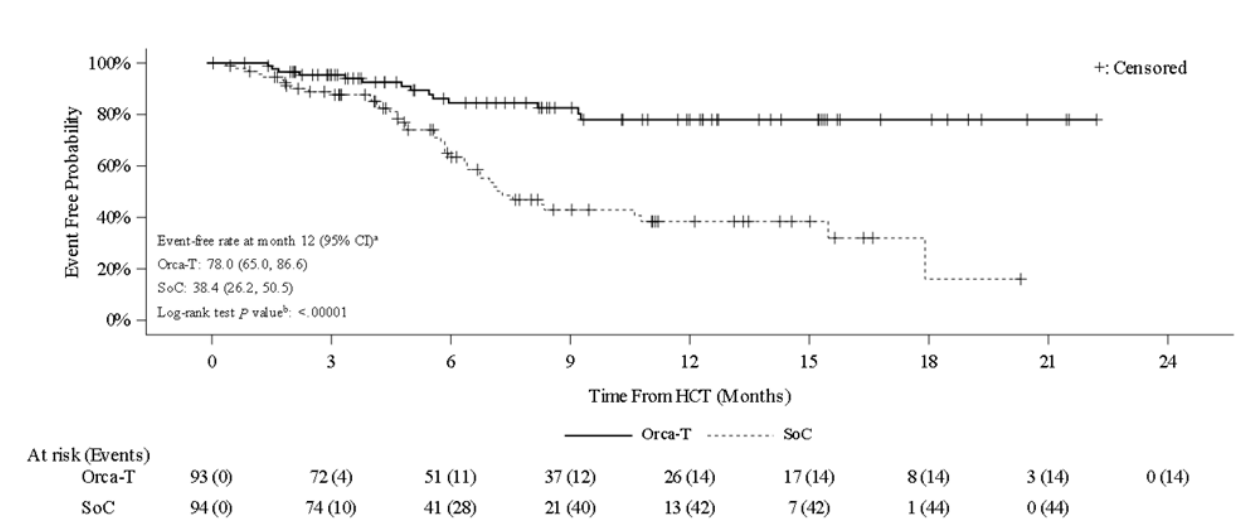
GRFS

Participants with events, n (%)	26 (28.0)	54 (57.4)
Median Kaplan Meier estimate, months (95% CI)	NE (NE, NE)	5.8 (4.9, 8.3)
Event-free rate estimate, 12 months (95% CI)	63.1 (50.0, 73.6)	30.9 (20.0, 42.4)
Hazard ratio (95% CI)	0.37 (0.23, 0.60)	

Abbreviations: cGFS, cGVHD-free survival; cGVHD, chronic graft-versus-host disease; CI, confidence interval; GRFS, graft-versus-host disease-free and relapse-free survival; OS, overall survival; SoC, standard of care.

Source: Precision-T Phase 3 CSR, Table 14.2.1.1.1.1, Table 14.2.2.1.1.1, Table 14.2.6.1.1, and Table 14.2.3.1.1.1

Figure 3. Applicant - KM Plot of cGFS per EAC Assessment by Treatment Group (Precision-T Phase 3 ITT Analysis Set)



Abbreviations: cGFS, cGVHD-free survival; cGVHD, chronic graft-versus-host disease; CI, confidence interval; DRI, Disease Risk Index; EAC, endpoint adjudication committee; HCT, hematopoietic cell transplantation; HLA, human leukocyte antigen; MSD, matched sibling donor; MUD, matched unrelated donor; NIH, National Institutes of Health; SoC, standard of care.

cGFS is defined as the time from the date of HCT to the date of death from any cause or the first onset of moderate or severe cGVHD (graded per NIH consensus criteria), whichever is earlier, within 2 years after day 0.

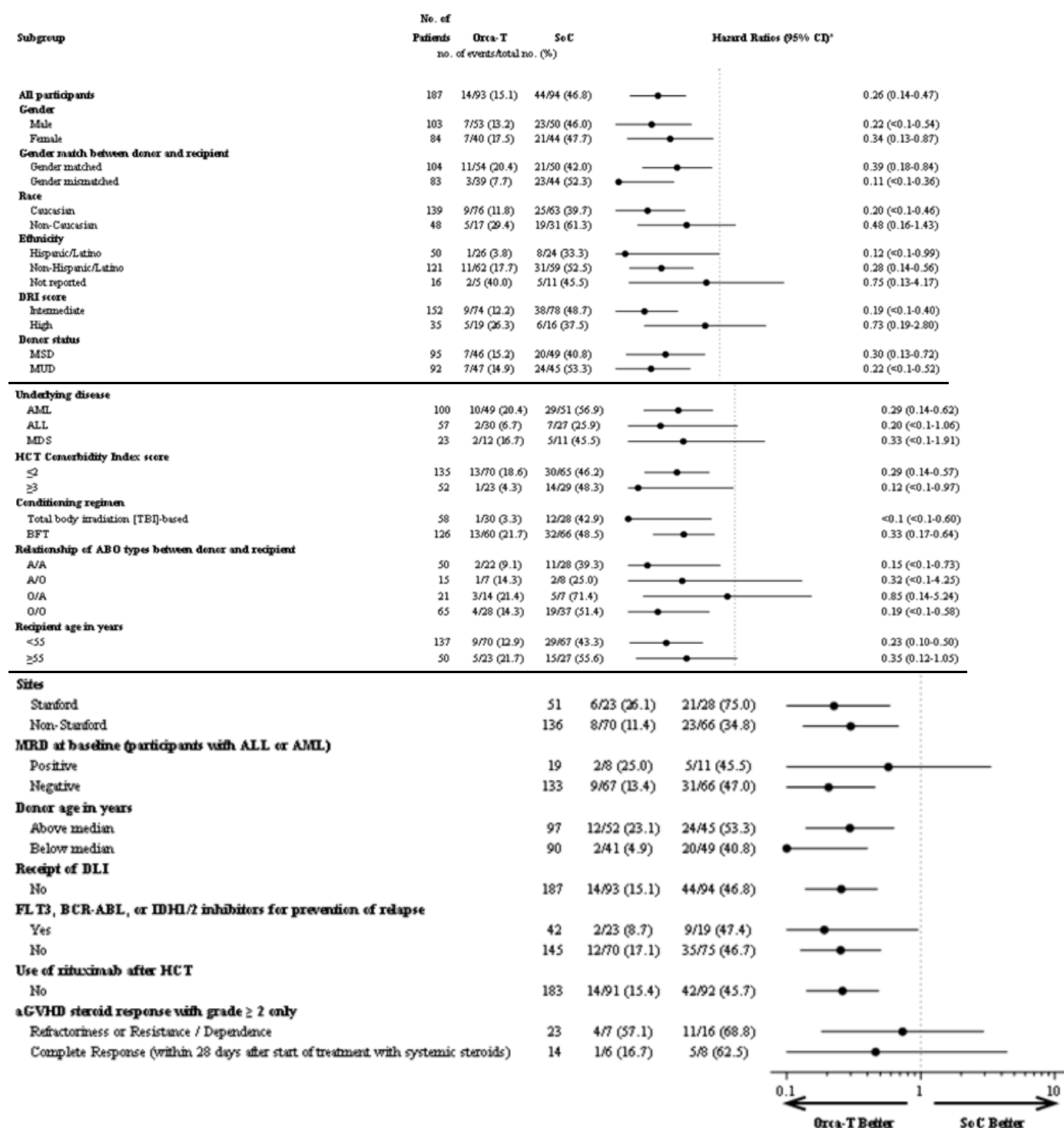
a Point estimates for the event-free probability at specific months were based on the Kaplan-Meier method. The 95% CIs were calculated using Greenwood's formula.

b The log-rank test was stratified by randomization stratification factors: donor type (8/8 HLA-MSD versus 8/8 HLA-MUD) and DRI risk category (intermediate risk or high risk).

SoC is the reference group.

Source: Precision-T Phase 3 CSR, Figure 14.2.1.1.1

Figure 4. Applicant – Forest Plot of cGFS by Subgroups (Precision-T Phase 3 ITT Analysis Set)



Abbreviations: cGFS, cGVHD-free survival; cGVHD, chronic graft-versus-host disease; CI, confidence interval; DRI, Disease Risk Index; EAC, endpoint adjudication committee; EDC, electronic data capture; HCT, hematopoietic cell transplantation; HLA, human leukocyte antigen; MSD, matched sibling donor; MUD, matched unrelated donor; NE, not estimable; NIH, National Institutes of

Health; SoC, standard of care.

cGFS is defined as the time from the date of HCT to the date of death from any cause or the first onset of moderate or severe cGVHD (graded per NIH consensus criteria), whichever is earlier, within 2 years after day 0.

a All the subgroups are defined based on the data form EDC. Stratified hazard ratio by randomization stratification factors at randomization is provided. For the DRI score or Donor status, the stratified hazard ratio is based on a single stratification factor (ie, Donor status or DRI score).

Hazard ratio is presented as Orca-T versus SoC and calculated with SoC as reference group.

Source: Precision-T Phase 3 CSR, Figure 14.3.1.1.1

The Applicant's Position:

Orca-T administered following MAC led to a compelling efficacy profile in adults undergoing allogeneic hematopoietic cell transplantation, with a significantly prolonged moderate or severe cGFS compared with SoC (HR = 0.26 [95% CI: 0.14, 0.47]; $P < .00001$), consistent across multiple prespecified sensitivity analyses and subgroups. With a substantial follow-up period (median: 8.5 months for Orca-T), the majority of participants who received Orca-T remained event-free at 12 months (78.0%), supporting a robust and durable treatment effect. The magnitude of the treatment effect of Orca-T on cGFS was robust and consistent across subgroups, including donor status and DRI score.

The FDA's Assessment:

FDA adjudicated response assessment (aGVHD and cGVHD) in about 15% patients from each arm to verify the data integrity. Patient narratives, eCRF, GVHD pathology reports, and EAC assessment reports were used for adjudication. None of the subjects received DLI.

- The discrepancy in endpoint assessments between investigators and EAC were compared. FDA agreed with EAC's assessment, and it is used in both efficacy and primary safety analysis throughout the BLA review.
- Furthermore, considering that the bilirubin lab result is the most objective measure among all evaluation elements per MAGIC and NIH consensus criteria, the source lab reports for bilirubin were requested for 11 patients in each arm randomly and intended to represent approximately 10% of patient population in each arm. After the adjudication and review all documents including bilirubin source lab data, eCRF, patient narratives, and available pathology reports, FDA agreed with all EAC's GVHD assessments.
- FDA reviewed the concomitant medication that might impact the outcome of allogeneic hematopoietic transplantation and found no evidence of this type of bias. For example, (i) FDA reviewed and confirmed that none of the study participants in either arm received donor lymphocyte infusion (DLI) since it might have an impact on GVHD, engraftment, and relapse rates. (ii) Since the receipt of Rituximab might impact GVHD, the FDA confirmed that post-transplantation 3 and 2 patients on the (b) (4) arm and on the SOC arm received Rituximab, respectively. The reasons included elevated EBV-PCR (1 subject per

arm), hemolytic anemia (1 patient on the (b) (4) arm and 2 for unknown reasons (1 patient per arm).

The original study was designed to perform an interim efficacy analysis at 37 cGFS events and a final analysis at 56 cGFS events. However, the Sponsor reported that cGFS events were occurring at a faster rate than anticipated, with more than 56 cGFS events identified by investigators by July 15, 2024. Due to this accelerated event rate, the Sponsor proposed to forego the interim analysis and test the primary efficacy as data cutoff of July 15, 2024.

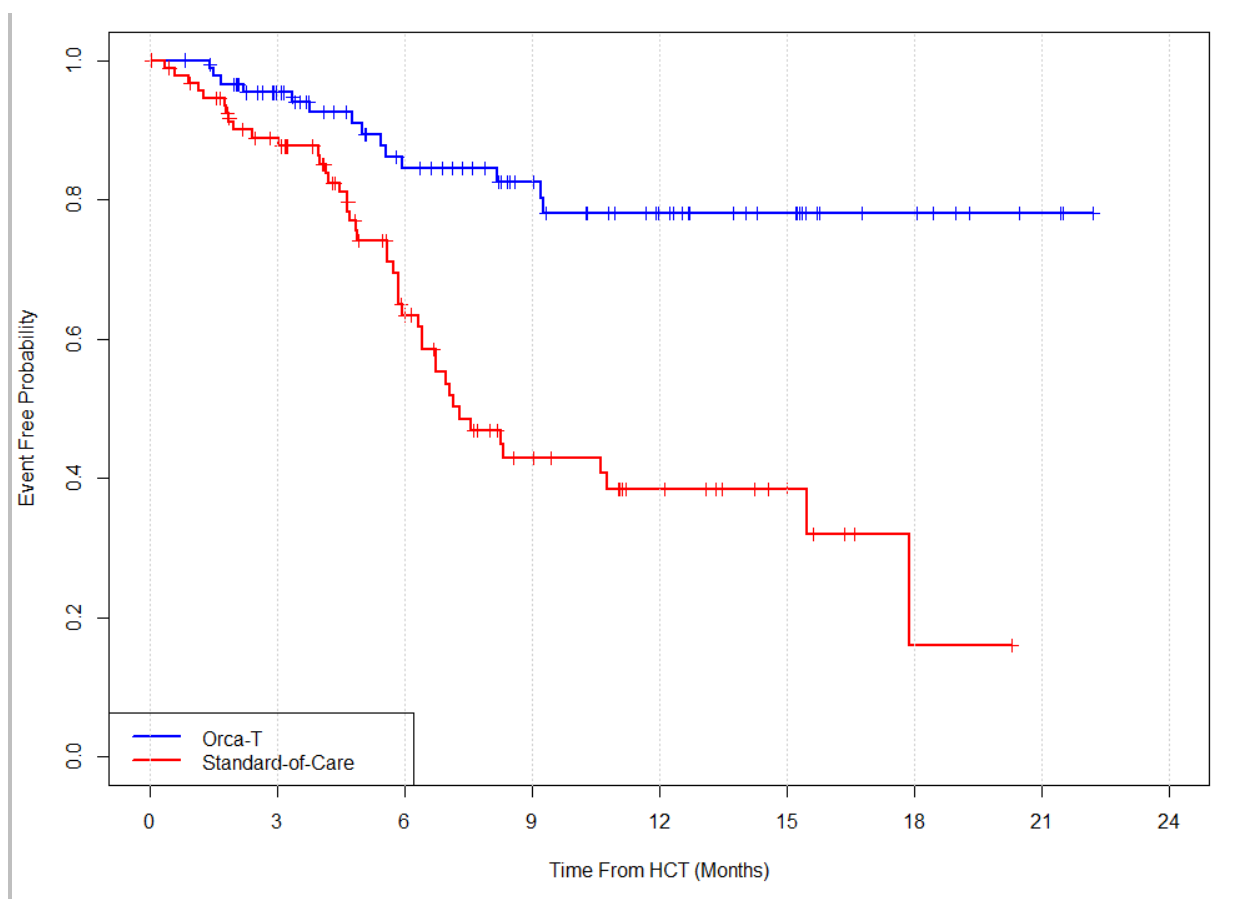
Overall, the clinical review team agrees that the Precision-T phase 3 study met its primary endpoint, demonstrating a statistically significant improvement in cGFS. The clinical review team also agrees that the magnitude of the treatment effect of (b) (4) on cGFS was consistent across key subgroups, including donor status and DRI score.

The primary analysis of cGFS demonstrated a statistically significant improvement for the (b) (4) group compared with SoC group. Based on the pre-specified stratified Cox proportional hazards model, the estimated HR was 0.26 (95% CI: 0.14, 0.47), corresponding to a 74% reduction in the risk of a cGFS event for participants treated with (b) (4) relative to SoC. This result was supported by the pre-specified stratified log-rank test, which yielded a two-sided p-value <0.00001, meeting the prespecified critical value of 0.0464 for statistical significance ([Figure 5](#)). The median cGFS was not reached in the (b) (4) group, whereas it was 7.3 months (95% CI: 6.3, 15.5) in the SoC group. At 12 months, the Kaplan-Meier estimate of cGFS was 78.0% (95% CI: 65.0%, 86.6%) for (b) (4) compared with 38.4% (95% CI: 26.2%, 50.5%) for SoC.

FDA conducted a sensitivity analysis on the primary endpoint of cGFS to confirm the treatment effect in patients who have received the actual treatment (Safety population). The efficacy was consistent with the results in ITT population: HR was 0.26 (95% CI: 0.14, 0.47), P<0.00001 ([Figure 6](#)).

For the primary endpoint cGFS, FDA notes the early separation of the curves for the first 100 days. Our analysis shows that this separation was mainly caused by the higher rate of early death during the first 100 days on the SOC arm compared to the (b) (4) arm. On Day 42, there were zero (0%) deaths on the (b) (4) arm versus 3 (3%) on the SOC arm, and by Day 100, there were 3 (3%) deaths on the (b) (4) arm versus 8 (8.3%) on the SOC arm.

Figure 5. FDA-KM Plot of cGFS per EAC assessment (ITT Analysis set)



Source: FDA Statistical reviewer. Abbreviations: EAC, endpoint adjudication committee.

Table 7. FDA-Efficacy results of Precision-T in ITT Analysis Population

Endpoint	TREGZI (N = 93)	SoC (N = 94)
cGFS ^a		
Median, months [95% CI]	NE [NE, NE]	7.3 [6.3, 15.5]
% at 12 months [95% CI]	78.0 [65.0, 86.6]	38.4 [26.2, 50.5]
Stratified HR [95% CI]	0.26 [0.14, 0.47]	
Log-rank <i>P</i> value	<.00001	
KM estimate cumulative incidence rate of moderate or severe cGVHD		
% at 12 months [95% CI]	12.6 [5.3, 23.1]	44.0 [31.3, 56.1]
Stratified HR [95% CI]	0.19 [0.08, 0.43]	
Stratified Gray's test <i>P</i> value	.00002	

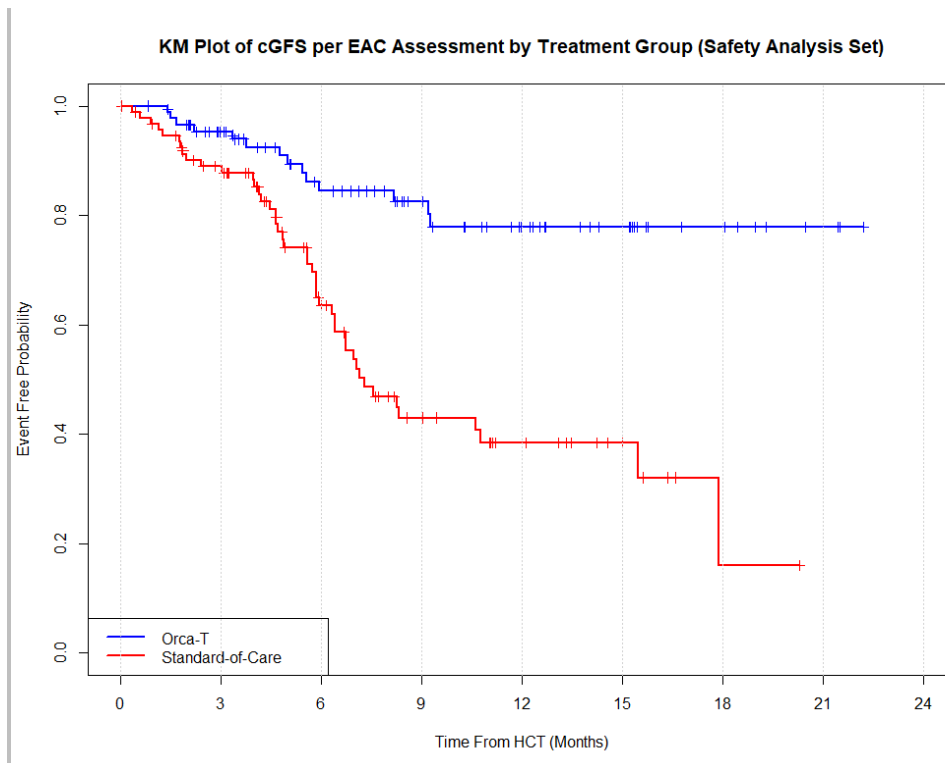
Median follow-up, months (range)	8.5 months (range: 0-22)	9.0 months (range: 0-20)
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Source: FDA statistical reviewer's analysis.

Abbreviations: cGFS, cGVHD-free survival; cGVHD, chronic graft-versus-host disease; CI, confidence interval; HR, hazard ratio; NE, not estimable; NIH, National Institutes of Health; SoC, standard of care.

a cGFS is defined as death by any cause or moderate-to-severe cGVHD as defined by NIH consensus criteria.

Figure 6. FDA-KM Plot of cGFS per EAC assessment (Primary Safety Analysis set)



Source: FDA statistical reviewer's analysis

Data Quality and Integrity

Data:

Orca Bio implemented a risk-based monitoring program that combined remote data reviews with targeted on-site visits, and a subset of case-report-form entries underwent source-data verification in line with the Site Monitoring Plan. Investigators entered the verified data into the 21 CFR Part 11-compliant (b) (4) electronic data-capture system, which features role-based access, audit trails, and electronic signatures to ensure traceability through database lock. Data-management quality control included programmed edit checks, manual review, and systematic investigation of outliers, while

the Statistical Analysis Plan prespecified hierarchical rules for imputing partially missing dates for AEs, concomitant medications, and related datasets to protect the integrity of time-to-event analyses. All tables, listings, and figures were generated with validated SAS® version 9.4 (or later) programs that underwent independent quality control under the sponsor's standard operating procedures. Routine monitoring findings, data-management reconciliation, and database-lock checks did not identify any unresolved critical or systemic issues that could compromise the integrity of the efficacy or safety data.

The Applicant's Position:

No issues related to data quality and integrity were identified by the applicant.

The FDA's Assessment:

FDA agrees with the Applicant's assessment. Please refer to Section 8.2.3 for reviewer's comment on the data quality and integrity.

Efficacy Results – Secondary and other relevant endpoints

Data:

In the ITT analysis set, secondary efficacy endpoints included time to moderate or severe cGVHD, OS, and GRFS. Efficacy data are summarized in [Table 6](#).

The cumulative incidence of moderate or severe cGVHD at 12 months was 12.6% (95% CI: 5.3%, 23.1%) in the Orca-T group compared with 44.0% (95% CI: 31.3%, 56.1%) in the SoC group. Because the primary endpoint of cGFS per EAC was statistically significant, formal hypothesis testing of time to moderate or severe cGVHD was conducted using a prespecified critical value of .05 per the hierarchical testing procedure outlined in the Precision-T Phase 3 SAP. The 2-sided *P* value from the stratified Gray's test stratified by the randomization stratification factors was .00002, which is statistically significant. The estimated HR was 0.19 (95% CI: 0.08, 0.43) using a stratified subdistribution proportional hazards model also stratified by the randomization stratification factors.

In an interim analysis of OS, the Kaplan-Meier estimate of OS at 12 months was 93.9% (95% CI: 85.8%, 97.4%) in the Orca-T group compared with 83.1% (95% CI: 72.9%, 89.8%) in the SoC group. The KM estimate of median OS was not reached for either group after median follow-up times for survival of 11.04 (range: 0.2 to 23.9) months for Orca-T and 11.47 (range: 0.7 to 24.3) months for SoC. The primary analysis for OS will be conducted using a prespecified critical value of .05 when 40 participants have died or 2 years after the end of enrollment, whichever is earlier.

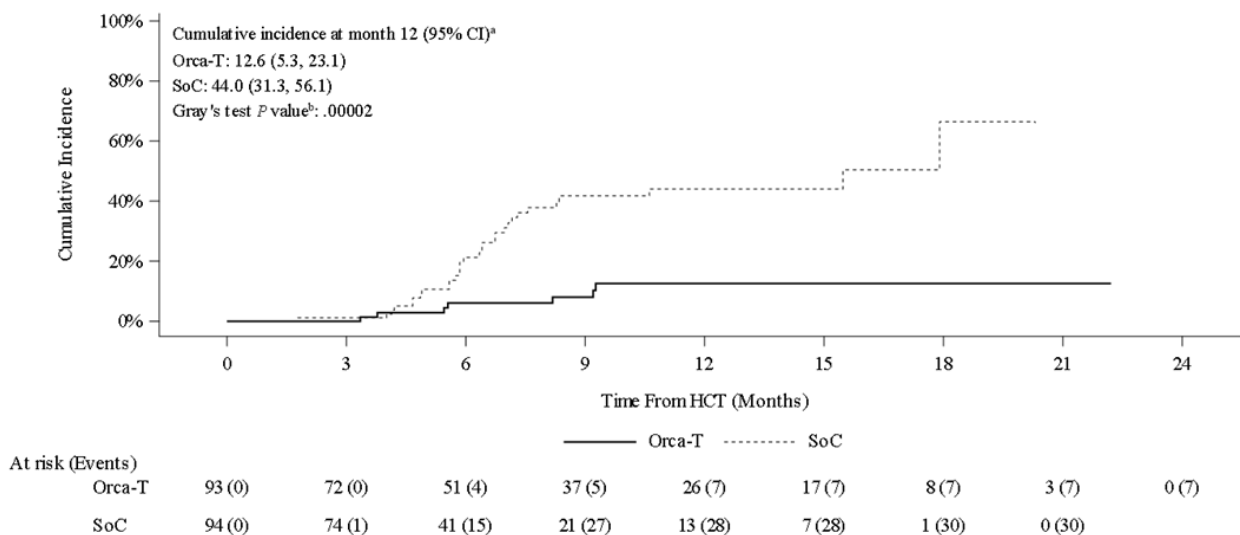
In an interim analysis of GRFS, the KM estimate of median GRFS was not reached for the Orca-T group and was 5.8 (95% CI: 4.9, 8.3) months for the SoC group after median follow-up times of 11.70 (95% CI: 8.41, 12.55) months and 9.46 (95% CI: 7.72, 13.11) months, respectively. The 12-month event-free estimate was 63.1% (95% CI: 50.0%, 73.6%) in the Orca-T group versus 30.9% (95% CI: 20.0%, 42.4%) in the SoC group. The primary analysis for GRFS will be conducted using a prespecified critical value of .05 when 40 participants have died or 2 years after the end of enrollment, whichever is earlier.

Subgroup analyses for moderate or severe cGVHD, OS, and GRFS demonstrated consistent treatment effects across age, sex, disease type, donor type, and DRI risk categories.

NRM was examined as an exploratory endpoint. Overall, 3 participants (3.6%) in the Orca-T group and 9 participants (10.6%) in the SoC group died without prior disease relapse. The cumulative incidence rate estimate at 12 months was 3.6% (95% CI: 1.0%, 9.4%) for Orca-T and 11.8% (95% CI: 5.2%, 21.4%) for SoC. The estimated HR was 0.35 (95% CI: 0.09, 1.32) using a stratified subdistribution proportional hazards model stratified by the randomization factors.

Plots of the cumulative incidence of moderate or severe cGVHD, KM curves for OS, and KM curves for GRFS are presented in **Error! Reference source not found.**, , and , respectively.

Figure . Plot of Cumulative Incidence of Moderate or Severe cGVHD (Precision-T Phase 3 ITT Analysis Set)



Abbreviations: cGVHD, chronic graft-versus-host disease; CI, confidence interval; DRI, Disease Risk Index; EAC, endpoint adjudication committee; HCT, hematopoietic cell transplantation; HLA, human leukocyte antigen; MSD, matched sibling donor;

MUD, matched unrelated donor; SoC, standard of care.

Time to moderate or severe cGVHD is defined as the time from HCT to the first onset of moderate or severe cGVHD within 2 years after day 0. Death within 2 years after day 0 without prior moderate or severe cGVHD is considered a competing event.

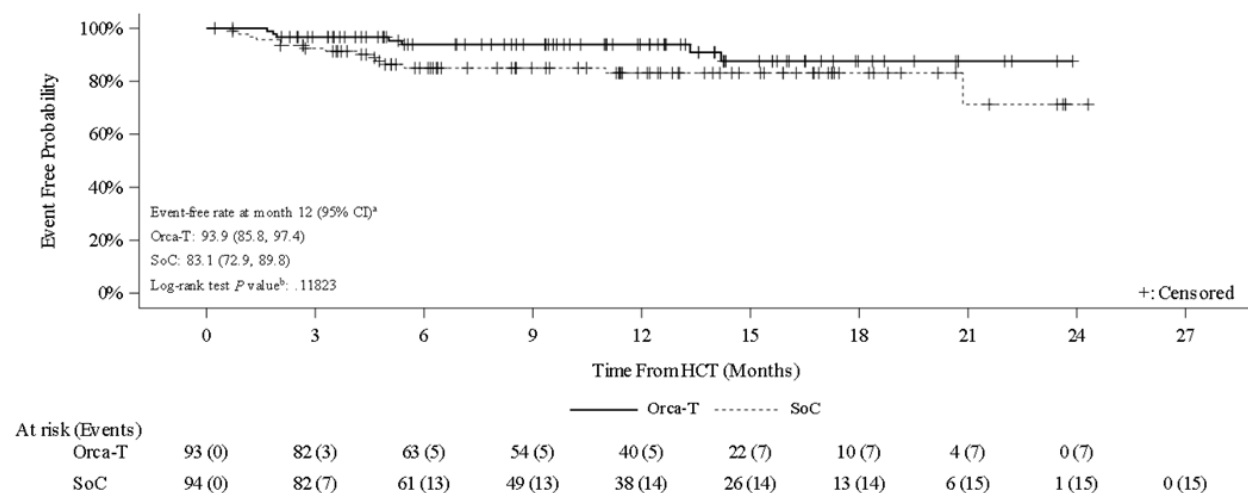
a Cumulative incidence rates were estimated based on the non-parametric method described in Gray (1988), treating death as a competing risk.

b Gray's test was stratified by randomization stratification factors: donor type (8/8 HLA-MSD versus 8/8 HLA-MUD) and DRI risk category (intermediate risk or high risk).

SoC is the reference group.

Source: Precision-T Phase 3 CSR, Figure 14.2.2.1.1

Figure 7. Applicant-KM Plot of OS by Treatment Group (Precision-T Phase 3 ITT Analysis Set)



Abbreviations: CI, confidence interval; DRI, Disease Risk Index; HCT, hematopoietic cell transplantation; HLA, human leukocyte antigen; ITT, intention to treat; MSD, matched sibling donor; MUD, matched unrelated donor; OS, overall survival; SoC, standard of care.

OS is defined as the time from randomization to death from any cause.

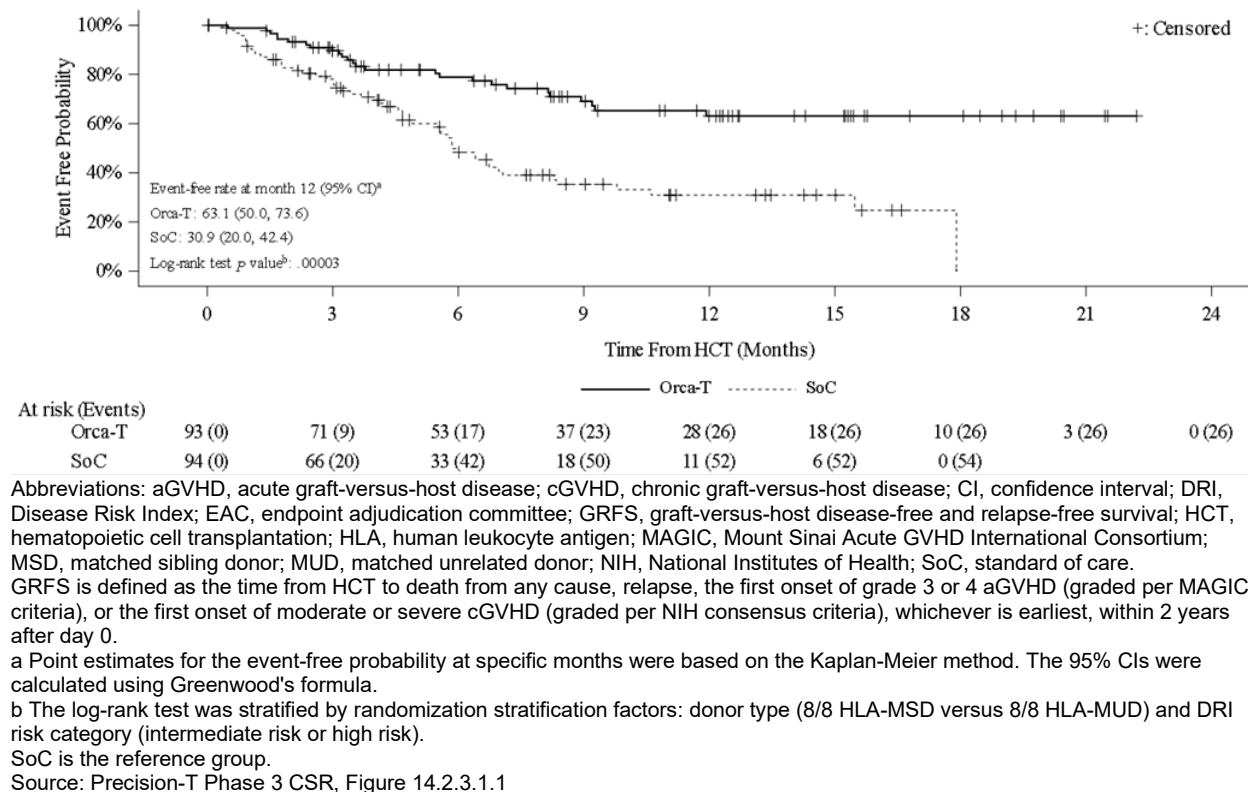
a Point estimates for the event-free probability at specific months were based on the Kaplan-Meier method. The 95% CIs were calculated using Greenwood's formula.

b The log-rank test and Cox model were stratified by randomization stratification factors: donor type (8/8 HLA-MSD versus 8/8 HLA - MUD) and DRI risk category (intermediate risk or high risk).

SoC is the reference group.

Source: Precision-T Phase 3 CSR, Figure 14.2.6.1

Figure 8. Applicant-KM Plot of GRFS by Treatment Group (Precision-T Phase 3 ITT Analysis Set)



The Applicant's Position:

The secondary endpoint of time to moderate or severe cGVHD per EAC was significantly improved following treatment with Orca-T versus SoC. The primary analysis for the secondary endpoints of OS and GRFS will be conducted when 40 participants have died or 2 years after the end of enrollment, whichever is earlier. Interim analyses for OS and GRFS per EAC showed trends toward improvement with Orca-T relative to SoC. The rate of NRM was also lower in the Orca-T group than in the SoC group.

The FDA's Assessment:

The analysis of the first secondary endpoint, time to moderate or severe cGVHD, was formally tested because the primary endpoint (cGFS) was statistically significant, following the pre-specified hierarchical testing procedure. A plot of the cumulative incidence of time to moderate or severe cGVHD for each arm is displayed in [Figure 9](#) below. This analysis demonstrated a significant reduction in the incidence of moderate or severe cGVHD in the (b) (4) group compared to the SoC group. The pre-specified analysis using the stratified Gray's test yielded a two-sided P value of 0.00002, which is statistically significant against the prespecified critical value of 0.05. The estimated treatment effect was a HR of 0.19 (95% CI: 0.08,0.43), calculated using a

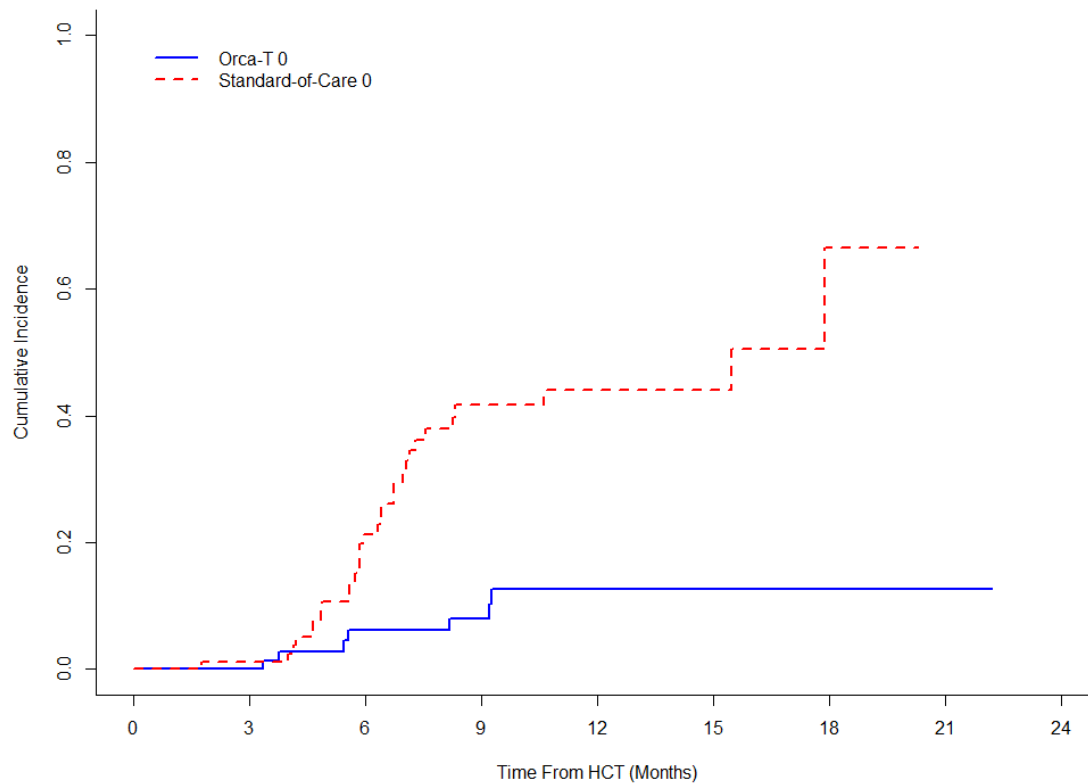
stratified sub distribution proportional hazards model, indicating an 81% reduction in the cumulative incidence of the event. Supportively, the overall number of participants experiencing this event was markedly lower in the (b) (4) group (7 participants, 7.5%) compared to the SoC group (30 participants, 31.9%). Furthermore, the cumulative incidence rate estimate at 12 months was substantially lower for (b) (4) (12.6%) than for SoC (44.0%) ([Figure 10](#)).

The original study was designed to perform an interim efficacy analysis at 37 cGFS events and a final analysis at 56 cGFS events. However, the Sponsor reported that cGFS events were occurring at a faster rate than anticipated, with more than 56 cGFS events identified by investigators by July 15, 2024. Due to this accelerated event rate, the Sponsor proposed to forego the interim analysis and test the primary efficacy as data cutoff of July 15, 2024. Therefore, the median time for follow up for cGFS was about 8.5 months in (b) (4) arm and 9 months on SoC arm. It is possible that cGVHD or death events could continue to occur in the first 2 years, however the low numbers of moderate to severe cGVHD events in the (b) (4) arm in the secondary endpoint analysis and the hazard ratio (HR=0.26 [95% CI: 0.14, 0.47]; $p<.00001$) of cGFS suggest that treatment effect of this product on moderate to severe cGVHD provide reasonable assurance that is unlikely that cGVHD events will exceed the control arm ([Figure 6](#)).

The interim analysis of the secondary endpoint, OS, was conducted as a formal hypothesis test because the preceding endpoint in the hierarchy (time to moderate or severe cGVHD) was statistically significant. A plot of the KM curves for each arm is displayed in [Figure 10](#) below. The pre-specified analysis using the stratified log-rank test yielded a two-sided P value of 0.11823, which was not statistically significant against the prespecified critical value of 0.0001 dictated by the hierarchical testing procedure. The estimated treatment effect from the stratified Cox model was a Hazard Ratio (HR) of 0.49 (95% CI: 0.20, 1.22). The KM rate estimates for OS at 12 months were 93.9% (95% CI: 85.8%, 97.4%) for (b) (4) and 83.1% (95% CI: 72.9%, 89.8%) for SoC. The primary analysis for OS is planned to be conducted later, when 40 participants have died or 2 years after the end of enrollment (whichever is earlier) and will use a 0.05 critical value.

The formal hypothesis testing was not conducted for GRFS at this time because the preceding endpoint in the hierarchical testing procedure, OS, was not statistically significant at interim analysis. The interim analysis of GRFS demonstrated a descriptive but significant advantage for the (b) (4) arm over the SoC arm ([Figure 10](#)). Despite the lack of formal testing, a descriptive analysis using the stratified log-rank test yielded a nominal P value of 0.00003. The estimated HR was 0.37 (95% CI: 0.23, 0.60). The KM rate estimates for GRFS at 12 months were 63.1% (95% CI: 50.1%, 73.6%) for (b) (4) and 30.9% (95% CI: 20.0%, 42.4%) for SoC.

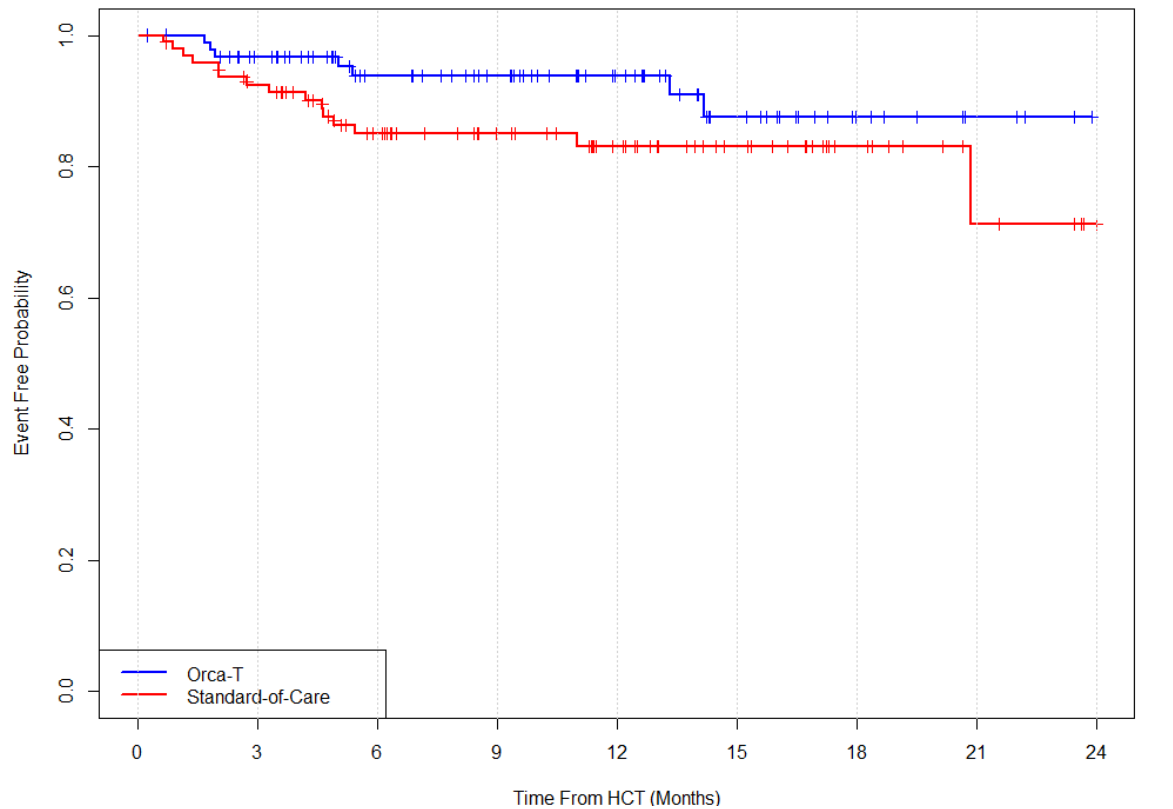
Figure 9. FDA-Plot of Cumulative Incidence of Moderate or Severe cGVHD in ITT Analysis Set



Source: FDA statistical reviewer's analysis.

Abbreviations: HCT, hematopoietic cell transplantation.

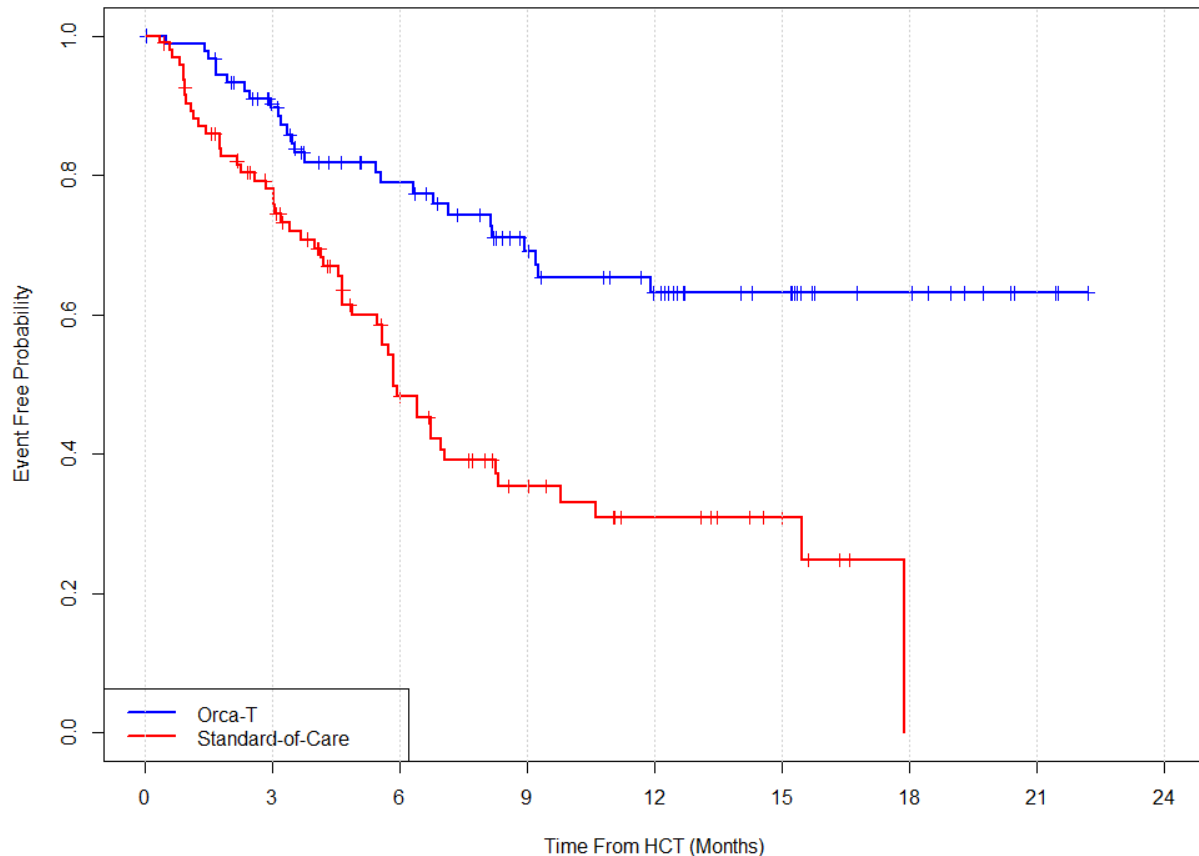
Figure 10. FDA-KM plot of OS in ITT Analysis Set



Source: FDA statistical reviewer's analysis.

Abbreviations: HCT, hematopoietic cell transplantation.

Figure 11. FDA-KM Plot of GRFS in ITT Analysis Set



Source: FDA statistical reviewer's analysis.

Dose/Dose Response

Data:

Limited exposure-response analyses are provided in section [6.2](#).

The Applicant's Position:

Exposure-response analyses indicated that the Orca-T doses administered in Precision-T were adequate and sufficient to elicit the intended therapeutic response.

The FDA's Assessment:

Please refer to FDA assessment in Section 6.2.

Durability of Response

Data:

With median follow-up times of 8.48 (range: 0 to 22.2) months and 9.03 (range: 0 to 20.3) months, the KM estimate of median cGFS was not reached for the Orca-T group and was 7.3 (95% CI: 6.3, 15.5) months for the SoC group, respectively. Furthermore, the difference between treatment groups in cGFS was maintained across subgroups as determined by demographic and disease characteristics, disease type, and type of MAC regimen employed prior to alloHCT.

The Applicant's Position:

Responses to Orca-T were durable, with a median follow-up time of 8.48 months.

The FDA's Assessment:

Please refer to FDA assessment in [Table 13](#).

Persistence of Effect

Data:

Not applicable

The Applicant's Position:

Orca-T is a cell therapy intended to be administered as a single treatment. Persistence of effect is not relevant to this type of treatment.

The FDA's Assessment:

FDA agrees with the Applicant's assessment.

Efficacy Results – Secondary or exploratory COA (PRO) endpoints

Data:

Patient-reported outcome (PRO) measures used included EQ-5D-5L, FACT-BMT, and Lee Modified 7-day cGVHD Symptom Scale. The planned exploratory analyses of these PRO measures included (a) patient compliance rates throughout the study collection period, (b) changes in health-related QoL over time, and (c) achievement of minimal clinical importance difference (MCID). To further inform on MCID, additional ad hoc analyses were conducted to determine relative differences in time to MCID and probability of achieving MCID. Due to

data limitations associated with the administration of the Lee Modified 7-day cGVHD Symptom Scale, only analyses for the EQ-5D-5L and FACT-BMT were performed. There were no prespecified hypotheses for any of the PROM analyses; however, hypothesis tests comparing performance between Orca-T and SoC were conducted to inform on significant differences ($P < 0.05$) in the general trends and patterns.

Orca-T demonstrated favorable QoL profiles across all major scores and subscores from both FACT-BMT and EQ-5D-5L in the descriptive results. Mixed models for repeated measures (MMRM) correcting for baseline score value, treatment, visit, and treatment-by-visit interaction as independent fixed effects and patients as random effects were used to predict the change in scores from baseline in the EQ-5D Index, EQ-VAS, and FACT-BMT Total and subscales across the Orca-T and SoC arms. When comparing the change in EQ-5D Index from baseline over time, the numerical differences in change from baseline were favorable for Orca-T arm at all time points. The Orca-T scores returned to prebaseline values or above unlike the SoC arm, which never returned to the baseline score, suggesting a faster and more complete recovery of QoL for participants who received Orca-T. Overall, the change from baseline in the Orca-T arm decreased by a smaller decrement and returned or exceeded baseline overtime whereas the SoC arm had a larger decrease from baseline and never exceeded baseline. Likewise, the FACT-BMT demonstrated a smaller decrement from baseline in the Orca-T arm with a faster return to baseline scores occurring on day +100 for the Orca-T arm and day +365 for the SoC arm. Overall, the Orca-T arm had smaller declines in all subscales of the FACT-TOT: FACT-PWB, FACT-FWB, and FACT-BMTS, compared with the SoC arm at all time points until approximately day 100, when the Orca-T arm exceeded the baseline score.

The health-related QoL of the Orca-T arm compared to the SoC arm was consistently higher in terms of a clinically noticeable improvement to participants as measured through EQ-5D Index scores. Throughout the study period, the number of patients who achieved MCID was significantly higher than the number of patients in the SoC arm at all time points ($P < 0.05$). the time to achieve MCID for those patients who achieved MCID was 2 months earlier in the Orca -T arm compared to the SoC arm (Orca-T: mean 2.59 months, standard deviation [SD] 3.24 versus SoC: mean 4.52 months, SD 4.03). Likewise, the number of participants who achieved MCID of FACT-BMT Total score was numerically higher throughout the entire study period in the Orca-T arm compared with the SoC arm. Beginning at day +100 through the remainder of the study period, the number of patients who achieved MCID in the Orca-T arm was significantly higher (all $P < 0.05$). The average time to achieve MCID in those participants who achieved MCID was 3 months shorter in the Orca-T arm compared with the SoC arm (Orca-T: mean 3.18 months, SD 3.421 versus SoC: mean 3.62, SD 3.72).

The Applicant's Position:

Treatment with Orca-T results in clinically meaningful improvement in health-related QoL over SoC at day +100 as measured by multiple validated PRO instruments. These findings support the idea that sustained clinical benefit confers higher health-related QoL and that patients can reach these goals with greater likelihood and faster recovery to baseline health-related QoL with Orca-T compared with SoC. The superior clinical outcomes and favorable patient experience with Orca-T over SoC should help inform treatment choices for advanced hematologic malignancies.

The FDA's Assessment:

The data from QoL (PRO) were not analyzed based on a formal testing plan. The Applicant did not seek a labeling claim based on QoL (PRO) data. The FDA approached this data as purely exploratory and descriptive only and therefore has not confirmed the Applicant's analyses or conclusions.

Additional Analyses Conducted on the Individual Trial

Data:

No additional analyses were conducted.

The Applicant's Position:

No additional analyses were conducted.

The FDA's Assessment:

FDA agrees with the Applicant's description.

8.1.3. Integrated Review of Effectiveness

The FDA's Assessment:

Not applicable.

8.1.4. **Assessment of Efficacy Across Trials**

Primary Endpoints

Data:

Not Applicable

The Applicant's Position:

Efficacy assessment was performed on only the phase 3 component of Precision-T.

The FDA's Assessment:

The primary efficacy analysis was only conducted on the phase 3 component of Precision-T study.

Secondary and Other Endpoints

Data:

Not Applicable

The Applicant's Position:

Efficacy assessment was performed on only the phase 3 part of the Precision-T trial.

The FDA's Assessment:

The efficacy analysis was only conducted on the phase 3 component of Precision-T study.

Subpopulations

Data:

Not Applicable

The Applicant's Position:

Efficacy assessment was performed on only the phase 3 part of the Precision-T trial.

The FDA's Assessment:

Not applicable.

Additional Efficacy Considerations

The FDA's Assessment:

No additional efficacy considerations.

8.1.5. Integrated Assessment of Effectiveness

Data:

The primary endpoint of moderate or severe cGFS demonstrated a statistically significant and clinically meaningful improvement with Orca-T compared with SoC in adults undergoing MAC-alloHCT. The estimated hazard ratio was 0.26 (95% CI: 0.14, 0.47; $P < .00001$), and the 12-month cGFS estimates were 78.0% for Orca-T and 38.4% for SoC. Secondary endpoints, including time to moderate or severe cGVHD, OS, and GRFS also favored Orca-T. The estimated hazard ratio for time to moderate or severe cGVHD was 0.19 (95% CI: 0.08, 0.43); $P = .00002$. The primary analysis for the secondary endpoints of OS and GRFS will be conducted when 40 participants have died or 2 years after the end of enrollment, whichever is earlier. Interim analyses for OS and GRFS showed trends toward improvement with Orca-T relative to SoC. The KM estimate of median OS was not reached for either group. The KM rate estimates for OS at 12 months were 93.9% (95% CI: 85.8%, 97.4%) for Orca-T and 83.1% (95% CI: 72.9%, 89.8%) for SoC. The KM estimate of median GRFS was not reached for the Orca-T group and was 5.9 (95% CI: 4.9, 8.3) months for the SoC group. The KM rate estimates for GRFS at 12 months were 63.8% (95% CI: 51.0%, 74.1%) for Orca-T and 32.9% (95% CI: 22.0%, 44.3%) for SoC.

The Applicant's Position:

The primary endpoint was cGFS, with moderate or severe cGVHD assessed and graded per NIH consensus criteria by an external EAC that was blinded to treatment assignment. The primary endpoint of cGFS was significantly prolonged following Orca-T treatment versus SoC (HR = 0.26 [95% CI: 0.14, 0.47]; $P < .00001$). The secondary endpoint of time to moderate or severe cGVHD was similarly improved for Orca-T (HR = 0.19 [95% CI: 0.08, 0.43]; $P = .00002$), and interim analyses of OS and GRFS also showed trends towards improvement with Orca-T over SoC. These efficacy results indicate a clinically significant

improvement in the intended patient population and were consistent across evaluated subgroups, including age, sex, race, disease type, donor type, and conditioning regimen.

The FDA's Assessment:

The primary efficacy assessment was supported by the phase 3 component of the Precision-T study. No integrated efficacy analysis was conducted. FDA agrees with the Applicant's description of the efficacy data.

8.2. Review of Safety

Data:

The primary safety data presented in this Biologic License Application (BLA) are derived from a single phase 3 study of Orca-T (Precision-T) in adults undergoing MAC-alloHCT for high-risk hematologic malignancies. The safety analysis included all participants who received either Orca-T or SoC, analyzed according to treatment received. Safety assessments included evaluation of TEAEs, SAEs, adverse events of special interest (AESIs), and laboratory abnormalities. AEs were coded using the Medical Dictionary for Regulatory Activities (MedDRA) terminology and graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE), except cGVHD and aGVHD, which were graded using NIH consensus criteria and MAGIC criteria, respectively. Where numerical grades are provided for cGVHD, NIH grades of mild, moderate, and severe appear as 1, 2, and 3, respectively.

The Applicant's Position:

The primary evidence to support the safety of Orca-T in the proposed indicated population is provided by participants with hematological malignancies who received either Orca-T (N = 88) or SoC (N = 94) in the phase 3 component of Precision-T. Supportive safety information is provided from the phase 1b component of Precision-T, including integrated safety analyses of all participants who were randomized and received either Orca-T or SoC in the phase 3 component and those participants from the phase 1b component who received Orca-T and met key eligibility requirements for the phase 3 study (N = 110). Only phase 3 data are presented here.

The FDA's Assessment:

FDA agrees with the Applicant's description.

8.2.1. Safety Review Approach

Data:

Safety data for Orca-T were collected and analyzed from the phase 3 component of Precision-T in adults undergoing MAC-alloHCT for high-risk hematologic malignancies. The safety analysis set included all participants who received either Orca-T or SoC, analyzed according to treatment received. Safety assessments included evaluation of TEAEs, SAEs, AESIs, and laboratory abnormalities. AEs were coded using MedDRA terminology and graded according to CTCAE criteria, except cGVHD and aGVHD, which were graded using NIH consensus criteria and MAGIC criteria, respectively. Where numerical grades are provided for cGVHD, NIH grades of mild, moderate, and severe appear as 1, 2, and 3, respectively.

The Applicant's Position:

The primary evidence to support the safety of Orca-T in the proposed indicated population is provided by participants with hematological malignancies who received either Orca-T (N = 88) or SoC (N = 94) in the phase 3 component of Precision-T. Standard safety assessments were used, and AESIs specific to Orca-T were assessed along with identified and potential risks.

The FDA's Assessment:

The FDA safety review was focused in 2 cohorts of patients:

1) Primary safety population:

- For (b) (4) arm, safety analysis was performed on all patients who received (b) (4) (n=88).
- For SoC arm, safety analysis included all patients who received an unmanipulated allogeneic graft (n=94).

2) Integrated safety population: includes a total of 198 patients treated with (b) (4)

- 88 patients treated with (b) (4) in phase 3 part of Precision-T study
- 110 patients treated with (b) (4) phase 1b part of Precision-T study and met the key eligibility criteria of phase 3 study
- The integrated safety dataset was considered as the supportive only.

The clinical review of the safety for this BLA is based on:

- ADSL datasets
- ADAM datasets
- Case report forms and safety narratives
- Applicant submissions in response to the review team's information requests
- Prior regulatory history
- Proposed labeling for (b) (4)
- Protocol and statistical analysis plan
- Clinical study report of safety for Precision-T

AEs were coded using the Medical Dictionary for Regulatory Activities version 28, and AE severity was graded using the National Cancer Institute's (NCI's) Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. aGVHD severity was graded per MAGIC criteria ([Harris et al. 2016](#)) and cGVHD was grade per NIH consensus criteria ([Jagasia et al. 2014](#)). Some AEs are presented throughout this review as FDA- grouped preferred terms as defined by the review team. AEs that involve more than one body system were consolidated and reported under the most commonly involved or most appropriate body system. Unless noted, all presented analyses use the FDA-grouped preferred terms. The complete list of FDA's grouped preferred terms is presented in [Appendix 19.6](#). All analyses were performed using JMP16 (SAS Institute, Inc.).

SAEs were defined as any AEs that met at least one of the following criteria: fatal, life threatening, required inpatient hospitalization or prolongation of existing hospitalization, disability/incapacity, congenital anomaly/birth defect, or medically important.

TEAEs were defined as all AEs occurring or worsening within 100 days after the infusion of Orca-T or SoC. AEs were analyzed with a focus on TEAEs in [Section 8.2.4](#).

8.2.2. Review of the Safety Database

Overall Exposure

Data:

In the phase 3 component of Precision-T that comprises the primary safety data, 88 participants received Orca-T, and 93 participants received SoC.

Additionally, a total of 154 participants received Orca-T in the phase 1b component of Precision-T, including 110 participants who met key eligibility requirements for the phase 3 component and were included in the primary integrated safety analysis set in Module 2.7.4 and Module 5.3.5.3.

Table 8. Applicant – Safety Population, Size, and Denominators

Safety Database for the Study Drug ¹			
Individuals exposed to the study drug in this development program for the indication under review			
N= 242			
(N is the sum of all available numbers from the columns below)			
Clinical Trial Groups	Orca-T (n= 242)	Active Control (n= 94)	Placebo (n= 0)
Controlled trials conducted for this indication ²	88	94	0
All other than controlled trials conducted for this indication ³	154	N/A	0
Controlled trials conducted for other indications ⁴	0	0	0

¹ *study drug* means the drug being considered for approval.

² to be used in product's labeling

³ if placebo arm patients switch to study drug in open label extension, the n should include their number; do not count twice patients who go into extension from randomized study drug arm

⁴ include n in this column only if patients exposed to the study drug for indication(s) other than that in the marketing application have been included in the safety database under review. Consider n=0 in this column if no patients treated for other indication(s) were included in this safety database.

The Applicant's Position:

A total of 88 participants received Orca-T and 94 participants received SoC in the phase 3 component of Precision-T, which serves as the primary safety data in support of the proposed indication. The phase 1b component of Precision-T included 154 participants who received Orca-T, 110 of whom met key eligibility criteria for the phase 3 component and are included in the primary integrated safety analysis set as supportive safety information.

The FDA's Assessment:

FDA agrees with the Applicant's description. The FDA safety review was focused in 2 cohorts of patients:

Primary safety population:

- For Orca-T arm, safety analysis was performed on all patients who received Orca-T (n=88).
- For SoC arm, safety analysis included all patients who received an unmanipulated allogeneic graft (n=94).
- The primary safety data are included in Section 6 of the USPI.

Integrated safety population includes a total of 198 patients treated with (b) (4)

- 88 patients treated with (b) (4) in phase 3 part of Precision-T study
- 110 patients treated with (b) (4) in phase 1b part of Precision-T study and met the key eligibility criteria of phase 3 study
- The integrated safety dataset was considered as the supportive only.

Relevant characteristics of the safety population:

Data:

The phase 3 safety population comprised 88 participants treated with Orca-T and 94 participants treated with SoC. Participant demographics and baseline disease characteristics (presented in section 8.1.2) were comparable between groups and representative of the intended patient population.

The Applicant's Position:

Demographics and baseline disease characteristics were generally as expected for the population with hematological malignancies.

The FDA's Assessment:

Overall, the population represents patient population with high-risk hematological malignancies receiving allogeneic transplantation with a MAC regimen ([Table 15](#) and [Table 16](#)).

- The median age of the safety population was 46 years (19, 65) for (b) (4) arm and 43 years (20, 63) for SoC arm.
- A higher proportion of White patients were on the (b) (4) arm compared to the SoC arm (81% vs 67%). The difference may be due to the factor that race was not reported in a large portion of patients on SoC arm (19%).
- Otherwise, the demographic characteristics were balanced between the two arms.

The overall demographic and disease characteristics are consistent with data published by CIBMTR for patients who received allogeneic transplantation with a MAC regimen: patients were younger, male, fewer comorbidities and more fit ([Alison et al. 2024](#)).

Table 9. FDA-Baseline Demographic Characteristics-Safety Population

Characteristics	(b) (4) N=88 n (%)	SoC N=94 n (%)
Age (years)		
Median (min, max)	46 (19, 65)	43 (20, 63)
Age category, n(%)		
≥18 to <55	65 (74)	68 (72)
≥55 to ≤65	23 (26)	26 (28)
Gender		
Female	37 (42)	44 (47)
Male	51 (58)	50 (53)
Race, n (%)		
White	71 (81)	63 (67)
Asian	10 (11)	8 (9)
American Indian or Alaska Native	1 (1)	2 (2)
Black or African American	1 (1)	2 (2)
Native Hawaiian or Other Pacific Islander	1 (1)	1 (1)
Unknown	4 (6)	18 (19)
Ethnicity, n (%)		
Hispanic or Latino	21 (24)	25 (27)
Not Hispanic or Latino	62 (70)	58 (62)
Unknown	5 (6)	11 (12)

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

[Table 16](#) shows the baseline characteristics of safety population for both arms in 88 patients treated with Orca-T and 94 patients treated with SoC.

Table 10. FDA-Baseline Disease Characteristics-Safety Population

	(b) (4) N=88 n (%)	SoC N=94 n (%)
Primary disease		

	(b) (4) N=88 n (%)	SoC N=94 n (%)
ALL	27 (31)	28 (30)
AML	47 (53)	50 (53)
High/Very high-risk MDS	12 (14)	11 (12)
MPAL	2 (2)	5 (5)
ALL, Remission status		
CR1	20 (23)	21 (22)
CR2	6 (7)	6 (6)
CR3	1 (1)	1 (1)
All	27 (31)	28 (30)
AML, Remission status		
CR1	43 (49)	42 (45)
CR2	4 (4)	7 (7)
CR3	0 (0)	1 (1)
All	47 (53)	50 (54)
MPAL, Remission status		
CR1	1 (1)	5 (5)
CR2	1 (1)	0 (0)
All	2 (2)	5 (5)
Donor type		
8/8 Matched related	43 (49)	48 (51)
8/8 Matched unrelated	45 (51)	46 (49)
DRI Score		
High	18 (20)	18 (19)
Intermediate	70 (80)	76 (81)
Baseline HCT-CI score		
0	18 (20)	26 (28)
1-2	51 (58)	39 (41)
3-5	19 (22)	29 (31)

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

Abbreviations: ALL, acute lymphoid leukemia; AML, acute myeloid leukemia; CR, complete remission; DRI, disease risk index; HCT-CI, hematopoietic cell transplantation-specific comorbidity index; MDS, myelodysplastic syndrome; MPAL mixed phenotype acute leukemia; SoC, standard of care; n (%), number of patients with the specified characteristic; N, number of patients in the specified group, or the total sample

Overall, the study population was representative of the general population eligible for allogeneic transplant. Disease characteristics were balanced within the two arms. None of the analyses revealed any impact of disease characteristics on outcome measures.

Adequacy of the safety database:

Data:

In the phase 3 component of Precision-T, 88 participants received Orca-T, and 94 participants received SoC. The median time on active participation was 10.02 (range: 0.1 to 23.9) months for participants in the Orca-T group and 9.17 (range: 0.7 to 24.3) months for participants in the SoC group. Including both active participation and LTFU, the median follow-up times for OS were 11.04 (range: 0.2 to 23.9) months for participants in the Orca-T groups and 11.47 (range: 0.7 to 24.3) months for participants in the SoC group. TEAEs as defined in Table 11. A were included in the safety analyses.

Table 11. Applicant - Treatment-Emergent Period

TEAE Period	Safety Data Category
Day 0 to day +100	all AEs, laboratory data, vital signs
Day 0 to 1 year	aGVHD events
Day 0 to 2 years	SAEs, AESIs, and cGVHD events, limited laboratory data: ANC, Hb, PLT, AST, ALT, Tbili, creatinine, and concomitant medications

Abbreviations: AE, adverse event; AESI, adverse event of special interest; aGVHD, acute graft-versus-host disease; ANC, absolute neutrophil count; AST, aspartate transaminase; ALT, alanine transaminase; cGVHD, chronic graft-versus-host disease; eCRF, electronic case report form; Hb, hemoglobin; HCT, hematopoietic cell transplantation; PLT, platelets; SAE, serious adverse event, Tbili, total bilirubin.

a For physical exams, the eCRF was designed to confirm whether a physical examination took place and the date of the exam. Clinical data from the physical examination was not formally collected, but clinically significant abnormal findings (ie, AEs) were recorded.

Supplementary safety information is provided by the primary integrated safety analysis set, which includes all of the participants in the phase 3 component as well as 110 additional participants who received Orca-T in the phase 1b component of Precision-T who met key eligibility criteria for the phase 3 component. The primary integrated safety analysis set represents a median overall time on active participation of 20.75 (range: 1.7 to 61.4) months for participants who received Orca-T, or approximately 11 months of additional time on active participation, and a median follow-up time for OS of 42 (range: 2.1 to 61.4) months, or approximately 31 months of additional survival follow-up time.

The Applicant's Position:

The hematological malignancies selected for Precision-T are rare diseases by definition. The size of the database reflects the rarity of this selected population while providing adequate numbers of participants and a sufficient length of follow-up to assess the safety of Orca-T in this population. Demographics and baseline disease characteristics of participants with hematological cancers in the Precision-T study were as expected in the indication population.

The safety database adequately supports benefit-risk assessment in the context of this rare disease.

The FDA's Assessment:

The applicant defined TEAE in [Table 17](#). Including: 1) AEs occurring, worsening on or after within 100 days from start of (b) (4) or SOC arm treatment; 2) preexisting AEs that lasting on or after the start of Orca-T or SOC arm treatment; 3) aGVHD within a year; 4) cGVHD. AESI, selected lab AEs, and SAEs within 2 years.

To provide a more accurate safety information to prescribers and consistent with our previous BLA reviews, the Applicant defined TEAE flag was not used for the safety analyses. Instead, FDA defined the TEAE as any AEs occurring, worsening within 100 days from start of (b) (4) or SOC arm treatment.

FDA's safety review focus is:

- TEAE period was defined as 100 days from the start of (b) (4) or SoC treatment
- aGVHD and cGVHD were analyzed separately with the aGVHD occurring within 1 year and cGVHD occurring within 2 years.
- All AESIs were analyzed separately with the occurrence within 2 years.

FDA's TEAE definition is different from the Applicant's: 1) FDA did not consider the preexisting AEs as TEAEs if AEs did not become worse; 2) FDA consider the TEAE period as within 100 days post transplantation because it is the most critical and informative period for the class of transplant products.

8.2.3. Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

Data:

Not Applicable

The Applicant's Position:

No issues were identified regarding data integrity or submission quality that could preclude a comprehensive clinical safety review.

The FDA's Assessment:

- The GVHD evaluation in the safety population by the Applicant was based on the investigators' assessment and in the efficacy population was based on the EAC's assessment. The Applicant was asked to provide additional information about the EAC assessment of aGVHD and cGVHD in the ADCM dataset. To be consistent and accurate throughout the review, FDA evaluated the GVHD in both the

efficacy population and the safety population basing the EAC's assessment along with the Sponsor's IR response. The investigators' assessment was considered as supportive.

- FDA adjudicated response assessment (aGVHD and cGVHD) in about 15% patients from each arm to verify the data integrity. Patient narratives, eCRF, GVHD pathology reports, and EAC assessment reports were used for adjudication.
 - The discrepancy in endpoint assessments between investigators and EAC were compared. FDA agreed with EAC's assessment, and it is used in both efficacy and primary safety analysis throughout the BLA review.
 - Furthermore, considering that the bilirubin lab result is the most objective measure among all evaluation elements per MAGIC and NIH consensus criteria, the source lab reports for bilirubin were requested for 11 patients in each arm. FDA agreed with all EAC's assessments. No inconsistencies were identified.

Overall, the quality and size of the safety data submitted was adequate for substantive review. No data integrity issue was identified.

Categorization of AEs

Data:

AEs were collected from the time of informed-consent signing through day +730; severity was graded per CTCAE v5.0, except for aGVHD and cGVHD which were graded by MAGIC and NIH consensus criteria, respectively. Investigators assessed causality for Orca-T; causality was not collected for participants who received SoC. Seriousness was defined using standard criteria. Events were coded with MedDRA v27.1 and summarized by system organ class (SOC) and preferred term (PT). AESIs of secondary malignancy, including posttransplantation lymphoproliferative disorder (PTLD); graft failure; veno-occlusive disease (VOD)/sinusoidal obstruction syndrome (SOS); thrombotic microangiopathy (TMA); and grade ≥ 3 infection were prospectively defined. Additional identified risks of aGVHD and cGVHD and potential risks of batch manufacturing failure, IRR, hypersensitivity, and transmission of serious infection were prospectively defined.

The Applicant's Position:

The recording, coding and categorization of AEs is appropriate and consistent with accepted standards as defined in regulations and guidance and according to clinical practice for development of oncology products and T-cell immunotherapies.

The FDA's Assessment:

FDA agrees with the Applicant's assessment.

Routine Clinical Tests

Data:

Disease assessments were performed at screening and at days +100, +365, and +730 (long-term follow-up every 6 months thereafter) per the schedule of assessments. For participants with leukemia or MDS, each assessment required a bone-marrow aspirate/biopsy with a sample sent for central minimal residual disease (MRD) testing. Other studies-including cytogenetics and imaging-were obtained as clinically indicated. All scheduled and unscheduled disease-evaluation data (local MRD, images, reports) were captured in the electronic case report form and made available to the sponsor for possible independent adjudication.

All AEs (regardless of relationship to Orca-T) were to be recorded from the date of informed consent through day +730. Clinical laboratory assessments included complete blood count with differential and clinical chemistry. Per protocol, complete blood count with differential was performed at least daily from day +3 until neutrophil engraftment; then twice weekly until day +56; then every 2 weeks until day +100; then at days +180, +270, +365, +545, and +730. Protocol-specified clinical chemistry assessments occurred at least weekly from day +3 until day +56; then every 2 weeks until day +100; then at days +180, +270, +365, +545, and +730. Additional tests may have been performed at any time during the study as determined necessary by the investigator or Orca Bio or as required by local regulations. Investigators documented their review of each laboratory report.

The Applicant's Position:

The routine safety evaluations and timepoints for collection and analysis of safety measures were appropriate for the indications investigated in the Precision-T study and were sufficient to monitor disease status, detect relapse, and evaluate the AE and laboratory profiles of Orca-T.

The FDA's Assessment:

Overall, the schedule of testing is considered adequate for the assessment of safety in the Precision-T study in the targeted patient population.

8.2.4. Safety Results

Deaths

Data:

A summary of deaths and their attributed causes is presented in [Table 12](#). Applicant - Summary of On-Study Deaths by Primary Cause (Precision-T Phase 3 Safety Analysis Set)

Grade 5 TEAEs are summarized by SOC and PT in Table 13. Applicant - Grade 5 Treatment-Emergent Adverse Events (Precision-T Phase 3 Safety Analysis Set).

Table 12. Applicant - Summary of On-Study Deaths by Primary Cause (Precision-T Phase 3 Safety Analysis Set)

	Orca-T (N = 88) n (%)	SoC (N = 94) n (%)	Total (N = 182) n (%)
Number of participants who died	7 (8.0)	15 (16.0)	22 (12.1)
Primary cause of death	7 (8.0)	15 (16.0)	22 (12.1)
Primary disease recurrence	4 (4.5)	3 (3.2)	7 (3.8)
GVHD	1 (1.1)	5 (5.3)	6 (3.3)
Acute GVHD	1 (1.1)	4 (4.3)	5 (2.7)
Chronic GVHD	0	1 (1.1)	1 (0.5)
Infection	2 (2.3)	3 (3.2)	5 (2.7)
Bacterial	0	3 (3.2)	3 (1.6)
Viral	2 (2.3)	0	2 (1.1)
Organ failure	0	3 (3.2)	3 (1.6)
Pulmonary	0	2 (2.1)	2 (1.1)
Other	0	1 (1.1)	1 (0.5)
Other	0	1 (1.1)	1 (0.5)
Within day +100	3 (3.4)	8 (8.5)	11 (6.0)
Within day +180	5 (5.7)	13 (13.8)	18 (9.9)

Source: Precision-T Phase 3 CSR, Table 14.3.5.6

Table 13. Applicant - Grade 5 Treatment-Emergent Adverse Events (Precision-T Phase 3 Safety Analysis Set)

System Organ Class Preferred Term	Orca-T (N = 88) n (%)	SoC (N = 94) n (%)	Total (N = 182) n (%)
Participants with any TEAE leading to death	5 (5.7)	10 (10.6)	15 (8.2)
Immune system disorders	2 (2.3)	3 (3.2)	5 (2.7)
Acute graft-versus-host disease	1 (1.1)	3 (3.2)	4 (2.2)
Chronic graft-versus-host disease	1 (1.1)	0	1 (0.5)
Respiratory, thoracic and mediastinal disorders	2 (2.3)	2 (2.1)	4 (2.2)
Respiratory failure	2 (2.3)	1 (1.1)	3 (1.6)
Hypoxia	0	1 (1.1)	1 (0.5)
Vascular disorders	1 (1.1)	3 (3.2)	4 (2.2)
Distributive shock	1 (1.1)	1 (1.1)	2 (1.1)
Hypovolaemic shock	0	1 (1.1)	1 (0.5)
Shock haemorrhagic	0	1 (1.1)	1 (0.5)
General disorders and administration site conditions	1 (1.1)	2 (2.1)	3 (1.6)
Multiple organ dysfunction syndrome	1 (1.1)	2 (2.1)	3 (1.6)
Infections and infestations	0	1 (1.1)	1 (0.5)
Septic shock	0	1 (1.1)	1 (0.5)
Injury, poisoning and procedural complications	0	1 (1.1)	1 (0.5)
Aortic injury	0	1 (1.1)	1 (0.5)

Source: Precision-T Phase 3 CSR, Table 14.3.2.1.

The Applicant's Position:

In the phase 3 component of Precision-T, 8% of participants who received Orca-T and 16% of participants who received SoC had died as of the primary analysis cutoff date. The incidence of death due to disease progression was similar between groups, but the incidence of deaths due to AEs was higher among participants who received SoC,

including deaths due to GVHD and organ failure. As described in section 8.1.2, the rate of NRM was also lower in the Orca-T group than in the SoC group.

The FDA's Assessment:

The reviewer reviewed all death narratives to confirm the cause of death. Relevant datasets and eCRFs were reviewed as needed to reach a conclusion on cause of death. Disease progression was considered as cause of death when supported by imaging, biopsy, autopsy, or clinical narratives.

The primary safety analysis was conducted using the data cutoff date of July 15, 2024. There were no deaths occurred prior to the treatment start. The review team analyzed all deaths in the safety population of both arms using both the July 15, 2024, data cutoff date (original submission) (Table 20 and Table 21) and April 30, 2025, data cutoff date (90-day safety update) (Table 22 and Table 23).

Deaths during the main study follow-up as of Data cutoff date (July 15, 2024)

At the time of Data cutoff of July 15, 2024, the most common cause of death in (b) (4) arm was disease progression and adverse events (Table 20) in SOC arm. The overall death rate from AEs was 3.4% in the (b) (4) arm compared to 11 % in the SOC arm. The AE death rate within the first 42 days of the treatment start was 0% in the (b) (4) arm compared to 5.3% in the SOC arm. The AE death rate after 100 days of the treatment start was 0% in the (b) (4) arm compared to 3% in the SOC arm. Out of the 3 deaths from AE that occurred in the (b) (4) arm, all of 3 occurred between day 42 and day 100.

Table 14. FDA-Deaths in the safety population (July 15, 2024)

Primary cause	Orca-T N=88 n (%)	SOC N=94 n (%)
Total Death	7 (8)	15 (16)
Disease progression	4 (4.5)	3 (3)
Adverse events	3 (3.4)	10 (11)
Other	0 (0)	2 (2)
Deaths occurring ≤42 days	0 (0)	5 (5.3)
Disease progression	0 (0)	0 (0)
Adverse events	0 (0)	5 (5.3)
Other	0 (0)	0(0)
Deaths occurring >42 days and ≤100 days	3 (3.4)	3 (3)
Disease progression	0 (0)	0 (0)
Adverse events	3 (3.4)	3 (3)
Other	0 (0)	0 (0)
Deaths occurring >100 days	4 (4.5)	7 (7.4)

Disease progression	4 (4.5)	3 (3)
Adverse events	0 (0)	3 (3)
Other(respiratory failure)	0 (0)	1(1)

Source: FDA analysis of ADSL, ADDTH. Data cutoff date: July 15, 2024.

In the safety population, the primary cause of death due to an AE was driven by aGVHD in SOC arm as shown in [Table 21](#) below and there was no aGVHD attributed death in (b) (4) arm.

Table 15. FDA-Causes of Death from AEs (July 15,2024)

	(b) (4) N=88 n (%)	SoC N=94 n (%)
Total Death	7 (8)	15 (16)
Adverse events	3 (3.4)	10 (10.6)
aGVHD	0 (0)	3(3)
Aortic injury	0 (0)	1(1)
Distributive shock	1(1)	1(1)
Hypoxia	0 (0)	1(1)
Multiple organ dysfunction syndrome	1(1)	2(2)
Respiratory failure	1(1)	0 (0)
Septic shock	0 (0)	1(1)

Source: FDA analysis of ADSL, ADDTH datasets.

Deaths after the main study follow-up as of Data cutoff (April 30, 2025)

Table 16. FDA-Deaths in the safety population (April 30, 2025)

Primary cause	(b) (4) N=89* n (%)	SoC N=94 n (%)
Total Death	14(16)	23(24)
Disease progression	9(10)	8(8.5)
Adverse events	5(5.6)	13(14)
Other	0(0)	1(1.1)
Deaths occurring ≤42 days	0(0)	5(5.3)
Disease progression	0(0)	0(0)
Adverse events	0(0)	5(5.2)
Other	0(0)	0(0)
Deaths occurring >42 days and ≤100 days	3(3.4)	3(3.1)
Disease progression	0(0)	0(0)
Adverse events	3(3.4)	3(3.1)
Other	0(0)	0(0)
Deaths occurring >100 days	11(12)	15(16)
Disease progression	9(10)	8(8.5)

Adverse events	2(2)	6((6.4)
Other(respiratory failure)	0(0)	1(1.1)

Source: FDA analysis of ADSL, ADDTH datasets.

* One patient on (b) (4) arm was treated after the primary cutoff of July 15, 2024. Data for this patient were included in 90 day safety follow up data analysis as data cutoff of April 30, 2025

Table 17. FDA-Causes of Death from Adverse events (April30,2025)

	(b) (4) N=89* n (%)	SoC N=94 n (%)
Total Death	14	23
Adverse events	5	13
aGVHD	2	3
cGVHD	1	1
Aortic injury	0	1
Cardiac arrest	0	1
Distributive shock	0	1
Hypoxia	0	1
Infection	2	0
Major GI bleeding	0	1
Multiple organ dysfunction syndrome	0	2
Respiratory failure	0	1
Septic shock	0	1

Source: FDA analysis of ADSL, ADDTH datasets. Data cutoff date: April30, 2025.

* One patient on (b) (4) arm was treated after the primary cutoff of July 15, 2024. Data for this patient were included in 90 day safety follow up data analysis as data cutoff of April 30, 2025

- The most common death cause was disease progression on (b) (4) arm and AEs on SoC arm.
- Death due to AEs within 42 days was 5.2% on SoC arm and no death due to AE occurred on (b) (4) arm.
- Death due to AEs within 100 days was higher on SoC arm compared to (b) (4) arm: 8.4% versus 3.4%.
- Overall, the most common cause of death from AE in (b) (4) arm was infection and aGVHD and in SoC arm was aGVHD and multiple organ dysfunction syndrome.

Serious Adverse Events

Data:

A summary of the most common SAEs (>1 participant overall by PT) by SOC and PT is provided in [Table 18. 24](#).

The most common SAEs by SOC were as follows:

- **Orca-T group:** infections and infestations (22 participants, 25%), immune system disorders (8 participants, 9%), and general disorders and administration site conditions (6 participants, 7%)
- **SoC group:** infections and infestations (29 participants, 31%); immune system disorders (18 participants, 19%); and respiratory, thoracic, and mediastinal disorders (14 participants, 15%)

The participant incidence of SAEs favored Orca-T for most SOC, with the largest imbalances in respiratory, thoracic, and mediastinal disorders (Orca-T: 3%, SoC: 15%); immune system disorders (Orca-T: 9%, SoC: 19%); vascular disorders (Orca-T: 1%, SoC: 9%); infections and infestations (Orca-T: 25%, SoC: 31%); and gastrointestinal disorders (Orca-T: 6%, SoC: 12%). The only SOC for which the incidence of SAEs was notably higher in the Orca-T group was hepatobiliary disorders (Orca-T: 6%, SoC: 3%).

The most common SAEs by PT were as follows:

- **Orca-T group:** sepsis (7 participants, 8%), aGVHD (6 participants, 7%), and pyrexia (5 participants, 6%)
- **SoC group:** aGVHD (12 participants, 13%) and sepsis, pneumonia, and cGVHD (6 participants, 6% each)

Imbalances in SAEs of $\geq 3\%$ of participants by PT were aGVHD (Orca-T: 7%, SoC: 13%), cGVHD (Orca-T: 1%, SoC: 6%), pneumonia (Orca-T: 1%, SoC: 6%), pyrexia (Orca-T: 6%, SoC: 1%), acute respiratory failure (Orca-T: 0%, SoC: 3%), and hypotension (Orca-T: 0%, SoC: 3%).

Table 18. Applicant – Treatment-Emergent SAEs Occurring in >1 Participant Overall (Precision-T Phase 3 Safety Analysis Set)

System Organ Class Preferred Term	Orca-T (N = 88) n (%)	SoC (N = 94) n (%)	Total (N = 182) n (%)
Participants with any treatment-emergent SAE	34 (38.6)	53 (56.4)	87 (47.8)
Infections and infestations			
Sepsis	7 (8.0)	6 (6.4)	13 (7.1)
Bacterial sepsis	4 (4.5)	4 (4.3)	8 (4.4)
Appendicitis	1 (1.1)	1 (1.1)	2 (1.1)
COVID-19 pneumonia	1 (1.1)	1 (1.1)	2 (1.1)
Influenza	1 (1.1)	1 (1.1)	2 (1.1)
Pneumonia	1 (1.1)	6 (6.4)	7 (3.8)
Rhinovirus infection	1 (1.1)	1 (1.1)	2 (1.1)
Septic shock	1 (1.1)	3 (3.2)	4 (2.2)
Staphylococcal sepsis	1 (1.1)	3 (3.2)	4 (2.2)
Immune system disorders			

System Organ Class Preferred Term	Orca-T (N = 88) n (%)	SoC (N = 94) n (%)	Total (N = 182) n (%)
Acute graft-versus-host disease	6 (6.8)	12 (12.8)	18 (9.9)
Chronic graft-versus-host disease	1 (1.1)	6 (6.4)	7 (3.8)
General disorders and administration site conditions			
Pyrexia	5 (5.7)	1 (1.1)	6 (3.3)
Multiple organ dysfunction syndrome	1 (1.1)	3 (3.2)	4 (2.2)
Hepatobiliary disorders			
Venoocclusive liver disease	3 (3.4)	1 (1.1)	4 (2.2)
Cholecystitis acute	1 (1.1)	1 (1.1)	2 (1.1)
Renal and urinary disorders			
Acute kidney injury	2 (2.3)	4 (4.3)	6 (3.3)
Respiratory, thoracic and mediastinal disorders			
Respiratory failure	2 (2.3)	2 (2.1)	4 (2.2)
Pleural effusion	1 (1.1)	1 (1.1)	2 (1.1)
Pulmonary embolism	1 (1.1)	2 (2.1)	3 (1.6)
Blood and lymphatic system disorders			
Anaemia	1 (1.1)	1 (1.1)	2 (1.1)
Thrombocytopenia	1 (1.1)	2 (2.1)	3 (1.6)
Gastrointestinal disorders			
Diarrhoea	1 (1.1)	1 (1.1)	2 (1.1)
Stomatitis	1 (1.1)	2 (2.1)	3 (1.6)
Vascular disorders			
Distributive shock	1 (1.1)	1 (1.1)	2 (1.1)

Source: Precision-T Phase 3 CSR, Table 14.3.2.2.1.1

The Applicant's Position:

The overall incidence of SAEs was lower in participants who received Orca-T (39%) than in participants who received SoC (56%). The participant incidence of SAEs favored Orca-T for most SOC, with the largest imbalances in respiratory, thoracic, and mediastinal disorders (12% lower for Orca-T); immune system disorders (10% lower for Orca-T); vascular disorders (8% lower for Orca-T); infections and infestations (6% lower for Orca-T); and gastrointestinal disorders (6% lower for Orca-T). The only SOC for which the incidence of SAEs was notably higher in the Orca-T group was hepatobiliary disorders (3% higher for Orca-T). Similarly, most imbalances by PT favored SAEs, with the greatest differences observed for aGVHD (6% lower for Orca-T), cGVHD (5% lower for Orca-T), pneumonia (5% lower for Orca-T), pyrexia (5% higher for Orca-T), acute respiratory failure (3% lower for Orca-T), and hypotension (3% lower for Orca-T).

The FDA's Assessment:

The FDA's review of safety is focused on SAEs that occurred up to 2 years after infusion. The total incidence of SAEs was lower on (b) (4) arm compared to SoC arm (36% versus 56%). The incidence of Grade 3-4 SAEs was also lower on (b) (4) arm compared to SoC arm (26% versus 47%).

Nonfatal SAEs occurred in at least 2% of patients are presented in [Table 25](#).

Table 19. FDA-Nonfatal SAEs in ≥ 2% patients

PT or FDA Grouped PT	(b) (4) N=88 n (%)		SOC, N=94 n (%)	
	All Grades	Grade 3-4	All Grades	Grade 3-4
Patients with any SAE	32(36)	23(26)	53(56)	44(47)
Bacterial infectious disorders*	16 (18)	16 (18)	15 (16)	13 (14)
Viral infectious disorders*	6 (6.8)	6 (6.8)	9 (9.6)	11 (12)
Pyrexia	5 (5.7)	2 (2.3)	1 (1.1)	0 (0)
Venoocclusive liver disease	3 (3.4)	3 (3.4)	1 (1.1)	1 (1.1)
Encephalopathy*	2 (2.3)	2 (2.3)	1 (1.1)	1 (1.1)
Hemorrhage*	2 (2.3)	2 (2.3)	2 (2.1)	2 (2.1)
Infections - pathogen unspecified*	2 (2.3)	1 (1.1)	11 (12)	11 (12)
Renal disorder*	2 (2.3)	2 (2.3)	4 (4.3)	4 (4.3)
Cytomegalovirus infection*	1 (1.1)	1 (1.1)	2 (2.1)	2 (2.1)
Fungal infectious disorders*	1 (1.1)	1 (1.1)	1 (1.1)	1 (1.1)

Source: FDA analysis of ADAE dataset * FDA grouped terms, See Appendix 19.6.

GVHD were excluded from [Table 25](#) above because the ADAE dataset did not adequately capture these events. GVHD data were reported in the ADCE2 dataset and the sponsor's response to IR request. See [Section 8.1.2](#) for review of GVHD in the safety population.

Dropouts and/or Discontinuations Due to Adverse Effects**Data:**

In the Orca-T group, no participant had an AE that led to withdrawal from active participation or withdrawal from study. In the SoC group, 1 participant had a fatal AE of hypovolemic shock that led to withdrawal from study.

The Applicant's Position:

In the Orca-T group, no participant had an AE that led to treatment interruption, withdrawal from active participation, or withdrawal from study.

The FDA's Assessment:

FDA agrees with the Applicant's position.

Dose Interruptions, Delays, and/or Reductions Due to Adverse Effects

Data:

No participant who received Orca-T had an AE that led to treatment interruption, delay, or dose reduction. In the SoC arm, 1 participant had an AE of anemia that led to treatment interruption.

The Applicant's Position:

Orca-T is administered as a single dose consisting of 3 infusions. Dose reductions would not apply for a product administered as a single dose.

The FDA's Assessment:

FDA agrees with the Applicant's position.

Significant Adverse Events

Data:

AESIs are described in section [8.2.5](#).

Other identified risks of Orca-T include aGVHD and cGVHD. Thirty-four percent of participants in the Orca-T group and 47% of participants in the SoC group had aGVHD. Six percent of participants in the Orca-T group and 10% of participants in the SoC group had aGVHD with a worst grade of 3 or 4. The median duration of aGVHD was 45.0 (range: 6 to 616) days in the Orca-T group and 69.5 (range: 1 to 433) days in the SoC group. As of the data cutoff date (15 July 2024), aGVHD had resolved in 21 of 30 participants (70%) in the Orca-T group and 34 of 44 participants (77%) in the SoC group. Among those whose aGVHD had resolved, the median time to resolution was 36.0 (range: 6 to 109) days in the Orca-T group and 53.0 (range: 7 to 388) days in the SoC group.

Sixteen percent of participants in the Orca-T group and 48% of participants in the SoC group had cGVHD. Thirteen percent of participants in the Orca-T group and 34% of

participants in the SoC group had moderate or severe cGVHD. The median duration of cGVHD was 152.0 (range: 47 to 322) days in the Orca-T group and 294.0 (range: 1 to 550) days in the SoC group. As of the data cutoff date (15 July 2024), cGVHD had resolved in 4 of 14 participants (29%) in the Orca-T group and 8 of 45 participants (18%) in the SoC group. Among those whose cGVHD had resolved, the median time to resolution was 157.5 (range: 57 to 226) days in the Orca-T group and 191.5 (range: 86 to 480) days in the SoC group.

Other potential risks associated with Orca-T include IRR and hypersensitivity. Overall, 4 participants (5%) in the Orca-T group and 2 participants (2%) in the SoC group had an AE with the PT IRR. Using a broader search strategy that included terms identified by medical review as common symptoms of IRR occurring within 24 hours of an infusion, 10% of participants had an IRR following the HSPC and Treg infusions on day 0, and 15% of participants had an IRR following the Tcon infusion on day +2. In the SoC group, 14% of participants had an IRR after the infusion on day 0. No participant in the Orca-T group and 2 participants in the SoC group had a grade 3 IRR; no participant had a grade 4 or grade 5 IRR.

No participant in the Orca-T group had an AE with the PT of hypersensitivity or drug hypersensitivity, and 1 participant (1%) in the SoC group had an AE with the PT of drug hypersensitivity. Using a search strategy of the PTs identified by medical review as specifically associated with hypersensitivity, no participant in the Orca-T group had a potential hypersensitivity event after the HSPC and Treg infusions on day 0, and 2% of participants had a potential hypersensitivity event after the Tcon infusion on day +2: 1 participant with grade 1 cytokine release syndrome, and 1 participant with grade 2 IRR. No participant in the SoC group had a potential hypersensitivity event.

Twenty-four participants (27.3%) who received Orca-T and 43 participants (45.7%) who received SoC were rehospitalized after alloHCT due to an AE. Among those who were rehospitalized for AEs, 3 participants (3.4%) who received Orca-T and 5 participants (5.3%) who received SoC were admitted to the intensive care unit.

The Applicant's Position:

Not only did fewer participants in the Orca-T group than in the SoC group have any grade aGVHD, grade 3 or 4 aGVHD, any grade cGVHD, and moderate or severe cGVHD, but the median durations and the median times to resolutions of aGVHD and cGVHD were also shorter in the Orca-T group than in the SoC group. IRR and hypersensitivity were infrequent; events in the Orca-T group were nonserious and mild. The incidence of IRR was low in both groups, with no grade ≥ 3 events of potential IRR in the Orca-T group versus 2% of participants with grade 3 potential IRR in the SoC group. The incidence of rehospitalization due to AEs was also lower among participants who received Orca-T (27%) than those who received SoC (46%).

The FDA's Assessment:

There is a discrepancy in aGVHD/cGVHD analysis between for efficacy endpoint analysis and for safety analysis. The Applicant clarified that the primary analysis for efficacy is based on aGVHD/cGVHD evaluation provided by the external endpoint adjudication committee (EAC) that was blinded to treatment assignment, while the safety analysis is based on the assessments provided by investigators. To be consistent and more accurate throughout the BLA evaluation, FDA used the EAC adjudicated aGVHD/cGVHD assessment as the basis for both efficacy and safety evaluation of GVHD.

[Table 26](#) and [Table 27](#) summaries aGVHD/cGVHD per EAC assessments. Fewer incidences of Grade 3 and higher aGVHD occurred on (b) (4) arm compared with SoC arm (6% versus 15%). Similarly, fewer incidences of moderate to severe cGVHDs occurred on (b) (4) arm compared with SoC arm (8% versus 32%).

The EAC data serve the purpose of blinded, independent review for the specific primary and secondary efficacy endpoints of the study and, therefore, do not include all parameters around GVHD that might be relevant for the analysis of safety. Given the limited information provided from EAC adjudication form, the duration and resolution time assessment of EAC adjudicated GVHD were evaluated per investigators assessment as below as of the data cutoff date (15 July 2024):

- aGVHD resolved in 70% (19/27) of patients for (b) (4) arm and 76% (32/42) for SoC arm. Among cases of acute GVHD that resolved, the median time to resolution was 36.0 days (range: 6 to 109 days) for (b) (4) arm and 64 days (range 7 to 388 days) for SoC arm.
- cGVHD had resolved in 40% (4/10) of patients in (b) (4) group and 29% (11/38) of patients in SoC group. Among those whose cGVHD had resolved, the median time to resolution was 157.5 (range: 57 to 226) days for (b) (4) arm and 287 (range: 100 to 480) days for SoC arm.

Table 20. FDA-Summary of aGVHD in Safety Population

	(b) (4) N=88 n (%)		SOC, N=94 n (%)	
Parameter	All Grades	Grade 3 and higher	All Grades	Grade 3 and higher
aGVHD*	33 (38)	5 (6)	44 (47)	14 (15)

Source: FDA analysis of ADAECE dataset and Sponsor's response. Data cutoff July 15, 2024.

*aGVHD was graded per MAGIC standardization criteria and was determined by an independent review committee.

Table 21. FDA-Summary of cGVHD in Safety Population

	(b) (4) N=88 n (%)		SOC, N=94 n (%)	
Parameter	All Grades	Moderate or severe	All Grades	Moderate or severe
cGVHD*	11 (13)	7 (8)	39 (41)	30 (32)

Source: FDA analysis of ADAECE dataset and Sponsor's response. Data cutoff July 15, 2024.

*cGVHD was graded per NIH consensus criteria and was determined by an independent review committee.

IRR were defined as any AE occurring within 24 hours of an (b) (4) or SoC infusion regardless of whether the transplant product was determined to cause the AE. This conservative approach and broad definition were intended to ensure that potential safety signals immediately following the infusion were not missed.

IRR occurred in 20 (23%) patients in the (b) (4) arm and in 13 (14%) patients in the control arm. No Grade 3 to 4 infusion reaction occurred in patients in the (b) (4) arm and in 2 (2.1%) patients in the SoC arm and both of them are grade 3. See [Table 28](#) below.

The most common infusion reactions included rash, sinus tachycardia, pruritus, hypotension, chills, cytokine release syndrome, arthralgia, tachycardia, dizziness, drug eruption, erythema, peripheral edema, pyrexia, dyspnea, and flushing.

Hypersensitivity included broad SMQ of hypersensitivity within 24 hours after an (b) (4) or SoC infusion and narrow PTs of allergic transfusion reaction,

cytokine release syndrome, drug hypersensitivity, hypersensitivity , infusion-related reaction within 24 hours after an (b) (4) or SoC infusion.

Table 22. FDA-Summary of Infusion Related Reaction in Safety Population

Preferred Terms or FDA grouped Term	(b) (4) N=88 n (%)		SOC N=94 n (%)	
	All Grades	Grade 3 or Higher	All Grades	Grade 3 or Higher
Rash	4 (4.5)	0(0)	1(1.1)	0(0)
Sinus tachycardia	4 (4.5)	0(0)	5(5.3)	1(1.1)
Pruritus	3 (3.4)	0(0)	1(1.1)	0(0)
Hypotension	2 (2.3)	0(0)	1(1.1)	0(0)
Arthralgia	1 (1.1)	0(0)	0(0)	0(0)
Chills	1 (1.1)	0(0)	0(0)	0(0)
Cough	1 (1.1)	0(0)	0(0)	0(0)
Cytokine release syndrome	1 (1.1)	0(0)	0(0)	0(0)
Dizziness	1 (1.1)	0(0)	3 (3.2)	1(1.1)
Drug eruption	1 (1.1)	0(0)	0(0)	0(0)
Erythema	1 (1.1)	0(0)	0(0)	0(0)
Infusion related reaction	1 (1.1)	0(0)	0(0)	0(0)
Peripheral edema	2(2.3)	0(0)	1(1.1)	0(0)
Pyrexia	1 (1.1)	0(0)	0(0)	0(0)
Tachycardia	1 (1.1)	0(0)	0(0)	0(0)
Dyspnoea	0(0)	0(0)	1(1.1)	0(0)
Flushing	0(0)	0(0)	1(1.1)	0(0)

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

Treatment Emergent Adverse Events and Adverse Reactions

Data:

An overall summary of TEAEs is provided in Table 23. 29. The most common AEs by PT (>10% of participants overall) are summarized in Table 24. A

In both the Orca-T and SoC groups, 100% of participants had at least 1 AE, and these AEs were grade ≥3 in 80 participants (91%) and 92 participants (98%), respectively. AEs were deemed by the investigator to be related to Orca-T in 48 participants (55%); relatedness of AEs was not collected for SoC.

Thirty-four participants (39%) in the Orca-T group and 53 participants (56%) in the SoC group had an SAE. No participant in either group had an AE that led to the end of active participation. No participant in the Orca T group had an AE that led to treatment interruption or study discontinuation. One participant in the SoC group had an AE that led to treatment interruption, and 1 participant in the SoC group had an AE that led to

treatment discontinuation. Five participants (6%) in the Orca-T group and 10 participants (8%) in the SoC group had AEs that led to the participant's death.

Table 23. Applicant - Summary of Adverse Events – (Precision-T Phase 3 Safety Analysis Set)

	Orca-T (N = 88) n (%)	SoC (N = 94) n (%)	Total (N = 182) n (%)
Participants with any TEAE	88 (100)	94 (100)	182 (100)
Participants with any grade ≥3 TEAE	80 (90.9)	92 (97.9)	172 (94.5)
Participants with any grade ≥3 TEAE (excluding GVHD)	80 (90.9)	91 (96.8)	171 (94.0)
Participants with any Orca-T-related TEAE ^a	47 (53.4)	NA	47 (25.8)
Participants with any serious TEAE	34 (38.6)	53 (56.4)	87 (47.8)
Participants with any TEAE leading to treatment interruption	0	1 (1.1)	1 (0.5)
Participants with any TEAE leading to end of active participation	0	0	0
Participants with any TEAE leading to study discontinuation	0	1 (1.1)	1 (0.5)
Participants with any TEAE leading to death	5 (5.7)	10 (10.6)	15 (8.2)

Source: Precision-T Phase 3 CSR, Table 14.3.1.1.1.

Table 24. Applicant - Treatment-Emergent Adverse Events Reported in ≥10% of Participants (Precision-T Phase 3 Safety Analysis Set)

Preferred Term	Orca-T (N = 88) n (%)	SoC (N = 94) n (%)	Total (N = 182) n (%)
Participants with any TEAE	88 (100)	94 (100)	182 (100)
Nausea	79 (89.8)	79 (84.0)	158 (86.8)
Diarrhoea	72 (81.8)	83 (88.3)	155 (85.2)
Hypomagnesaemia	49 (55.7)	53 (56.4)	102 (56.0)
Fatigue	50 (56.8)	48 (51.1)	98 (53.8)
Thrombocytopenia	47 (53.4)	46 (48.9)	93 (51.1)
Decreased appetite	40 (45.5)	47 (50.0)	87 (47.8)
Vomiting	44 (50.0)	43 (45.7)	87 (47.8)
Stomatitis	33 (37.5)	52 (55.3)	85 (46.7)
Febrile neutropenia	32 (36.4)	43 (45.7)	75 (41.2)

Acute graft-versus-host disease	30 (34.1)	44 (46.8)	74 (40.7)
Headache	33 (37.5)	39 (41.5)	72 (39.6)
Anaemia	37 (42.0)	34 (36.2)	71 (39.0)
Constipation	26 (29.5)	35 (37.2)	61 (33.5)
Abdominal pain	27 (30.7)	32 (34.0)	59 (32.4)
Chronic graft-versus-host disease	14 (15.9)	45 (47.9)	59 (32.4)
Mucosal inflammation	29 (33.0)	29 (30.9)	58 (31.9)
Insomnia	25 (28.4)	32 (34.0)	57 (31.3)
Dyspepsia	21 (23.9)	31 (33.0)	52 (28.6)
Neutropenia	26 (29.5)	25 (26.6)	51 (28.0)
Oedema peripheral	21 (23.9)	26 (27.7)	47 (25.8)
Pyrexia	23 (26.1)	23 (24.5)	46 (25.3)
Blood creatinine increased	23 (26.1)	22 (23.4)	45 (24.7)
Hypokalaemia	18 (20.5)	24 (25.5)	42 (23.1)
Pruritus	22 (25.0)	18 (19.1)	40 (22.0)
Epistaxis	23 (26.1)	16 (17.0)	39 (21.4)
Hyperglycaemia	15 (17.0)	24 (25.5)	39 (21.4)
Hypertension	20 (22.7)	19 (20.2)	39 (21.4)
Cough	15 (17.0)	23 (24.5)	38 (20.9)
Leukopenia	22 (25.0)	16 (17.0)	38 (20.9)
Oropharyngeal pain	22 (25.0)	14 (14.9)	36 (19.8)
Sinus tachycardia	15 (17.0)	21 (22.3)	36 (19.8)
Dry mouth	19 (21.6)	15 (16.0)	34 (18.7)
Rash	14 (15.9)	18 (19.1)	32 (17.6)
Tremor	12 (13.6)	19 (20.2)	31 (17.0)
Dizziness	15 (17.0)	15 (16.0)	30 (16.5)
Alanine aminotransferase increased	13 (14.8)	15 (16.0)	28 (15.4)
Hyponatraemia	15 (17.0)	13 (13.8)	28 (15.4)
Arthralgia	15 (17.0)	11 (11.7)	26 (14.3)
Pain in extremity	14 (15.9)	12 (12.8)	26 (14.3)
Vitamin D deficiency	9 (10.2)	17 (18.1)	26 (14.3)
Dysgeusia	14 (15.9)	11 (11.7)	25 (13.7)
Hypotension	13 (14.8)	12 (12.8)	25 (13.7)
Dry skin	15 (17.0)	9 (9.6)	24 (13.2)
Dyspnoea	12 (13.6)	12 (12.8)	24 (13.2)
Hypertransaminasaemia	14 (15.9)	10 (10.6)	24 (13.2)
Oesophagitis	11 (12.5)	13 (13.8)	24 (13.2)
Skin hyperpigmentation	11 (12.5)	13 (13.8)	24 (13.2)
Aspartate aminotransferase increased	10 (11.4)	13 (13.8)	23 (12.6)

Haemorrhoids	12 (13.6)	10 (10.6)	22 (12.1)
Anxiety	8 (9.1)	13 (13.8)	21 (11.5)
Sepsis	12 (13.6)	9 (9.6)	21 (11.5)
Back pain	12 (13.6)	8 (8.5)	20 (11.0)
Erythema	10 (11.4)	10 (10.6)	20 (11.0)
Hypocalcaemia	6 (6.8)	13 (13.8)	19 (10.4)

Source: Precision-T Phase 3 CSR, Table 14.3.2.2.2.

The Applicant's Position:

Participants who received Orca-T had a lower incidence of SAEs, fatal AEs, grade ≥ 3 infections, any grade aGVHD, grade 3 or 4 aGVHD, any grade cGVHD, and moderate or severe cGVHD. The incidence of IRRs was low, and events in the Orca-T group were mild. Other events of interest were infrequent in both groups (hypersensitivity, secondary malignancy, TMA, and VOD/SOS). Thus, the overall safety profile of Orca-T is favorable compared with SoC.

The FDA's Assessment:

FDA's analysis of nonlaboratory Adverse Events per FDA grouped term in the primary safety set (n=88 on (b) (4) arm and n=94 on SoC arm) is displayed in [Table 31](#), [Table 32](#) and per SOC in [Table 33](#). All AE of special interest (AESI) including IRR, hypersensitivity, secondary malignancy, TMA and VOD/SOS were focused in [Section 8.2.5](#)

- FDA's TEAE analysis in this section focused on any AEs occurring or worsening 100 days on or after the infusion of (b) (4) or SoC infusions regardless of relatedness to products.
- GVHD were excluded from TEAE analysis because the ADAE dataset did not adequately capture these events. GVHD data were reported in the ADAECE dataset. See [Section 8.2.5](#) for review of GVHD in the safety population.
- Infections included in TEAE analysis are classified by the pathogen type based on the high-level group term. Some infections such as upper respiratory tract infection, EBV infection, and CMV infection are also presented to be more informative for this class of product. Infections were also analyzed for the period up to 2 years as one of AE of special interest in [Section 8.2.5](#).
- TEAEs occurred in almost 100% of patients on both arms. Grade ≥ 3 TEAEs occurred in 76% patients on (b) (4) arm and 80% patients on SoC arm. Deaths due to AEs were 4.5% on (b) (4) arm and 10% on SoC arm.
- The most common nonlaboratory TEAEs ($\geq 20\%$) per FDA grouped or PT on (b) (4) arm were mucositis, diarrhea, rash, pain, bacterial infection,

abdominal pain, vomiting, decreased appetite, nausea, xerosis, hemorrhage, febrile neutropenia, edema, fatigue, headache, viral infections, constipation, pyrexia, upper respiratory tract infection, hypertension, eye disorders, sleep disorders, tachycardia, and dizziness ([Table 32](#)).

- Overall, within the first 100 days after the infusion, compared to patients who received SoC graft, patients who received (b) (4) had a lower incidence of Grade 4-5 TEAEs (9.1% versus 15%) and deaths due to AE (4.5 versus 10%).

Table 25. FDA-Any Grade TEAEs Occurring in Patients

TEAE by PT or FDA Grouped PT	(b) (4) N=88 n (%)	SOC, N=94 n (%)
All Grade TEAE	88 (100)	93 (99)
Grade 3-5 TEAE	67 (76)	75 (80)
Grade 3 TEAE	59 (67)	61 (65)
Grade 4-5 TEAE	8 (9.1)	14 (15)
Grade 5	4 (4.5)	9 (10)

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

Table 26. FDA- Any-Grade TEAEs Occurring in ≥10% of Primary Safety Population By Preferred Term

TEAE by PT or FDA Grouped PT	(b) (4) N=88 n (%)		SOC, N=94 n (%)	
	All Grades	Grade 3 and Higher	All Grades	Grade 3 and Higher
Patients with any TEAE	88(100)	67 (76)	93(99)	75(80)
Mucositis*	75 (85)	25 (28)	83 (88)	35 (37)
Diarrhea*	61 (69)	1 (1.1)	74 (79)	6 (6.4)
Rash*	57 (65)	0 (0)	52 (55)	0 (0)
Pain*	46 (52)	0 (0)	43 (46)	3 (3.2)
Abdominal pain*	40 (45)	0 (0)	51 (54)	1 (1.1)
Bacterial infection*	39 (44)	26 (30)	33 (35)	20 (21)
Vomiting	39 (44)	1 (1.1)	33 (35)	0 (0)
Decreased appetite*	37 (42)	4 (4.5)	38 (40)	6 (6.4)
Nausea*	36 (41)	1 (1.1)	41 (44)	2 (2.1)
Hemorrhage*	34 (39)	5 (5.7)	31 (33)	1 (1.1)
Xerosis*	34 (39)	0 (0)	25 (27)	0 (0)
Febrile neutropenia	31 (35)	31 (35)	43 (46)	41 (44)

TEAE by PT or FDA Grouped PT	(b) (4) N=88 n (%)		SOC, N=94 n (%)	
	All Grades	Grade 3 and Higher	All Grades	Grade 3 and Higher
Edema*	26 (30)	0 (0)	36 (38)	3 (3.2)
Headache*	26 (30)	0 (0)	34 (36)	0 (0)
Fatigue*	25 (28)	0 (0)	33 (35)	2 (2.1)
Viral infection*	24 (27)	6 (6.8)	29 (31)	6 (6.4)
Constipation	21 (24)	0 (0)	22 (23)	1 (1.1)
Upper respiratory tract infection*	21 (24)	0 (0)	33 (35)	2 (2.1)
Hypertension	20 (23)	4 (4.5)	14 (15)	6 (6.4)
Pyrexia	20 (23)	2 (2.3)	23 (24)	0 (0)
Eye disorders*	19 (22)	1 (1.1)	17 (18)	0 (0)
Dizziness*	18 (20)	1 (1.1)	17 (18)	2 (2.1)
Sleep disorders*	18 (20)	0 (0)	19 (20)	0 (0)
Tachycardia*	16 (18)	0 (0)	28 (30)	2 (2.1)
Peripheral neuropathy*	15 (17)	1 (1.1)	14 (15)	0 (0)
Fungal infection*	14 (16)	2 (2.3)	15 (16)	2 (2.1)
Hypotension*	13 (15)	3 (3.4)	12 (13)	3 (3.2)
Skin disorder*	13 (15)	0 (0)	20 (21)	0 (0)
Taste disorder*	13 (15)	0 (0)	12 (13)	0 (0)
Dyspnea*	12 (14)	0 (0)	15 (16)	2 (2.1)
Tremor*	12 (14)	0 (0)	18 (19)	0 (0)
Cytomegalovirus infection*	11 (13)	2 (2.3)	8 (8.5)	2 (2.1)
Hemorrhoids	11 (13)	0 (0)	9 (9.6)	0 (0)

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

* FDA grouped terms, See Appendix 19.6

Table 27. FDA-Summary of TEAEs in ≥10% of Primary Safety Population by System Organ Class

System Organ Class	(b) (4) ██████████ N=88 n (%)		SOC, N=94 n (%)	
	All Grades	Grade 3 and Higher	All Grades	Grade 3 and Higher
Cardiac Disorders				
Tachycardia*	16 (18)	0 (0)	28 (30)	2 (2.1)
Eye Disorders				
Eye disorders*	19 (22)	1 (1.1)	17 (18)	0 (0)
Gastrointestinal Disorders				
Mucositis*	75 (85)	25 (28)	83 (88)	35 (37)
Diarrhea*	61 (69)	1 (1.1)	74 (79)	6 (6.4)
Abdominal pain*	40 (45)	0 (0)	51 (54)	1 (1.1)
Vomiting	39 (44)	1 (1.1)	33 (35)	0 (0)
Nausea*	36 (41)	1 (1.1)	41 (44)	2 (2.1)
Constipation	21 (24)	0 (0)	22 (23)	1 (1.1)
Hemorrhoids	11 (13)	0 (0)	9 (9.6)	0 (0)
General Disorders and Administration Site Conditions				
Edema*	26 (30)	0 (0)	36 (38)	3 (3.2)
Fatigue*	25 (28)	0 (0)	33 (35)	2 (2.1)
Pyrexia	20 (23)	2 (2.3)	23 (24)	0 (0)
Pain*	46 (52)	0 (0)	43 (46)	3 (3.2)
Infections and Infestations				
Bacterial infection*	39 (44)	26 (30)	33 (35)	20 (21)
Febrile neutropenia	31 (35)	31 (35)	43 (46)	41 (44)
Viral infection*	24 (27)	6 (6.8)	29 (31)	6 (6.4)
Upper respiratory tract infection*	21 (24)	0 (0)	33 (35)	2 (2.1)
Fungal infection*	14 (16)	2 (2.3)	15 (16)	2 (2.1)
Cytomegalovirus infection*	11 (13)	2 (2.3)	8 (8.5)	2 (2.1)
Metabolism and Nutrition Disorders				
Decreased appetite*	37 (42)	4 (4.5)	38 (40)	6 (6.4)
Nervous System Disorders				

	(b) (4) N=88 n (%)		SOC, N=94 n (%)	
System Organ Class	All Grades	Grade 3 and Higher	All Grades	Grade 3 and Higher
Headache*	26 (30)	0 (0)	34 (36)	0 (0)
Dizziness*	18 (20)	1 (1.1)	17 (18)	2 (2.1)
Peripheral neuropathy*	15 (17)	1 (1.1)	14 (15)	0 (0)
Taste disorder*	13 (15)	0 (0)	12 (13)	0 (0)
Tremor*	12 (14)	0 (0)	18 (19)	0 (0)
Psychiatric Disorders				
Sleep disorders*	18 (20)	0 (0)	19 (20)	0 (0)
Skin and Subcutaneous Tissue Disorders				
Rash*	57 (65)	0 (0)	52 (55)	0 (0)
Xerosis*	34 (39)	0 (0)	25 (27)	0 (0)
Skin disorder*	13 (15)	0 (0)	20 (21)	0 (0)
Vascular Disorders				
Hemorrhage*	34 (39)	5 (5.7)	31 (33)	1 (1.1)
Hypertension	20 (23)	4 (4.5)	14 (15)	6 (6.4)
Hypotension*	13 (15)	3 (3.4)	12 (13)	3 (3.2)

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

* FDA grouped terms, See Appendix 19.6

Other clinically important adverse reactions in < 10% of patients (n=89) included the following:

- Hepatobiliary disorders: veno-occlusive liver disease (3%) for (b) (4) arm versus (0%) for SoC arm.

The review team considers certain adverse events, e.g. hemorrhoids, unlikely to be related to either (b) (4) or the SoC allograft and therefore does not recommend inclusion in the USPI. Following adverse reactions will be included in the USPI:

Table 28. FDA-Adverse Reactions occurring in ≥10% and with higher frequency in (b) (4) group compared to Control group

Adverse Reactions	(b) (4) N = 88		SoC, N=94	
	All Grades %	Grade 3 or Higher %	All Grades %	Grade 3 or Higher %
Infections and infestations^a				

	(b) (4) N = 88		SoC, N=94	
	All Grades %	Grade 3 or Higher %	All Grades %	Grade 3 or Higher %
Adverse Reactions				
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	51	1
Vomiting	44	1	35	0
Nausea*	41	1	44	2
Immune system disorders				
Acute graft-versus-host disease ^b	38	6	47	15
General disorders and administration site conditions				
Mucositis*	85	28	88	37
Edema*	30	0	38	3
Respiratory, thoracic and mediastinal disorders				
Pneumonia	1	1	18	15
Skin and Subcutaneous Tissue Disorders				
Rash*	65	0	55	0
Vascular Disorders				
Hemorrhage*	39	6	33	1
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.				

Laboratory Findings

Data:

A summary of laboratory abnormalities that worsened from baseline is provided in [Table 29](#).

Hematology laboratory abnormalities that worsened from baseline to grade 3 or 4 were platelet count decreased (Orca-T group: 82 participants, 93.2%; SoC group: 90 participants, 96.8%), neutrophil count decreased (Orca-T group: 67 participants, 77.0%; SoC group: 76 participants, 84.4%), and anemia (Orca-T group: 62 participants, 70.5%; SoC group: 76 participants, 81.7%) anemia.

Chemistry laboratory abnormalities that worsened from baseline to grade 3 or 4 were ALT increased (Orca-T group: 17 participants, 19.5%; SoC group: 21 participants, 22.6%), AST increased (Orca-T group: 11 participants, 12.6%; SoC group: 12 participants, 12.9%), blood bilirubin increased (Orca-T group: 4 participants, 4.6%; SoC group: 11 participants, 11.8%), and creatinine increased (Orca-T group: 4 participants, 4.6%; SoC group: 3 participants, 3.2%).

Table 29. Applicant - Laboratory Abnormalities Worsening From Baseline to Grade 3 or 4 (Precision-T Phase 3 Safety Analysis Set)

Laboratory Parameter	Orca-T (N = 88) n/m (%)	SoC (N = 94) n/m (%)	Total (N = 182) n/m (%)
Hematology			
Anemia	62/88 (70.5)	76/93 (81.7)	138/181 (76.2)
Neutrophil count decreased	67/87 (77.0)	76/90 (84.4)	143/177 (80.8)
Platelet count decreased	82/88 (93.2)	90/93 (96.8)	172/181 (95.0)
Chemistry			
ALT increased	17/87 (19.5)	21/93 (22.6)	38/180 (21.1)
AST increased	11/87 (12.6)	12/93 (12.9)	23/180 (12.8)
Blood bilirubin increased	4/87 (4.6)	11/93 (11.8)	15/180 (8.3)
Creatinine increased	4/87 (4.6)	3/93 (3.2)	7/180 (3.9)

Source: Precision-T Phase 3 CSR, Table 14.3.4.1.4.

The Applicant's Position:

Overall, no clinical meaningful hematology, chemistry or liver chemistry trends were observed during the first 30 days of Orca-T infusion and during the interventional phase of the study.

The FDA's Assessment:

FDA's assessment of laboratory abnormalities includes the safety population in the (b) (4) and SoC arms.

Table 30. FDA – Laboratory Abnormalities worsening from Baseline in at least 10% of Patients

Laboratory Test	(b) (4) N=88 n (%)		SOC, N=94 n (%)	
	All Grades	Grade 3 and Higher	All Grades	Grade 3 and Higher
Lymphocyte decreased	84 (98)	84 (98)	85 (94)	85 (94)
Platelet decreased	81 (93)	81 (93)	89 (96)	89 (96)
White blood cell decreased	77 (89)	77 (89)	82 (89)	82 (89)
Hemoglobin decreased	74 (85)	61 (70)	84 (90)	75 (81)
Neutrophil count decreased	68 (79)	66 (77)	76 (84)	75 (83)
Albumin decreased	64 (74)	4 (4.6)	70 (75)	5 (5.4)
Creatinine increased	43 (49)	4 (4.6)	54 (58)	3 (3.2)
Sodium decreased	35 (40)	3 (3.4)	50 (54)	2 (2.2)
AST increased	34 (39)	8 (9.2)	48 (52)	6 (6.5)
Potassium decreased	34 (39)	3 (3.4)	34 (37)	10 (11)
ALT increased	33 (38)	10 (11)	44 (47)	7 (7.5)
ALP increased	25 (29)	0 (0)	20 (22)	0 (0)
GFRE decreased	22 (26)	6 (7)	28 (30)	5 (5.4)
Total bilirubin increased	19 (22)	4 (4.6)	23 (25)	7 (7.5)
Eosinophils increased	12 (15)	0 (0)	31 (38)	0 (0)

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.

Abbreviations: AST: Aspartate Aminotransferase, ALT: Alanine Aminotransferase, ALP:Alkaline Phosphatase, GFRE, Glomerular Filtration Rate, Estimated.

Table 31. FDA – Grade ≥3 Laboratory Abnormalities worsening from Baseline in at least 10% of Patients

Laboratory Test	(b) (4) N=88 n (%)	SoC, N=94 n (%)
Lymphocyte count decreased	85 (98)	86 (95)
Platelet count decreased	82 (93)	90 (96)
Leukocytes decreased	78 (89)	83 (89)
Neutrophil count decreased	67 (77)	76 (84)
Hemoglobin decreased	62 (70)	75 (80)
ALT increased	10 (11)	7 (7.4)

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.

Abbreviations: ALT: Alanine Aminotransferase

- Baseline value is defined as the last non-missing value prior to the day of conditioning regimen for both (b) (4) Arm and SoC arm (Day -40 to Day-4). Worsening is defined as a postbaseline abnormality that is at least 1 grade higher than baseline.
- Denominators are numbers of participants with non-missing baseline and at least 1 postbaseline assessment.
- [Table 36](#) and [Table 37](#) above represent the treatment emergent hematologic, chemistry, and coagulopathy laboratory tests abnormalities (day0-100).
- Cytopenia of all grades were the most common laboratory abnormalities as expected and reflect toxicity of the entire investigational protocol including conditioning regimen and the transplant graft.
- ALT increased was the most common Grade 3-4 chemistry laboratory abnormality.

Vital Signs

Data:

Vital-sign parameters collected 30 minutes and 1 hour after each infusion were temperature, pulse, supine blood pressure (systolic/diastolic), respiratory rate, and pulse oximetry. Vital signs were similar across infusions.

The Applicant's Position:

Overall, no clinically meaningful changes in vital signs were observed, and no differences were apparent between Orca-T and SoC.

The FDA's Assessment:

FDA agrees with the Applicant's assessment.

Electrocardiograms (ECGs)

Data:

Not Applicable

The Applicant's Position:

ECG parameters were not collected as part of the Precision-T study.

The FDA's Assessment:

Not applicable

QT

Data:

Not Applicable

The Applicant's Position:

QT parameters were not collected as part of the Precision-T study.

The FDA's Assessment:

Not applicable

Immunogenicity

Data:

Not Applicable

The Applicant's Position:

As Orca-T is intended for a single infusion, there is no risk of antidrug antibody-mediated sensitization and anaphylactic reactions with subsequent doses. Given the low immunogenicity risk, the immunogenicity of Orca-T has not been evaluated in clinical studies.

The FDA's Assessment:

Not Applicable.

8.2.5. Analysis of Submission-Specific Safety Issues

AESIs for Orca-T are secondary malignancy, including PTLT; grade ≥ 3 infection; graft failure (primary or secondary); TMA; and VOD/SOS.

The FDA's Assessment:

FDA's analysis of AESI in the safety population is summarized in [Table 38](#) and is described in details in more details in the individual sections as below ([Section 8.2.5.1](#), [Section 8.2.5.2](#), [Section 8.5.2.3](#), [Section 8.5.2.4](#), and [Section 8.2.5.5](#)). The analysis

included all AESI events occurred from study day 0 up to 2 years after the infusion of (b) (4) or SoC.

Table 32. FDA-AESIs analysis in Safety Population

AESI	(b) (4) N=88 n (%)		SOC, N=94 n (%)	
	All Grades	Grade 3 and Higher	All Grades	Grade 3 and Higher
Secondary malignancy, including PTLD	1((1.1))	1(1.1)	2(2.1)	1(1)
Graft failure (primary or secondary)	1((1.1))	1((1.1))	0	0
Infections ^a	83(94)	36(41)	75(80)	48(51)
Viral infection	45(51)	12(14)	44(47)	18(19)
Infections - pathogen unspecified	40(45)	16(18)	53(56)	28(30)
Bacterial infection	35(40)	16(18)	36(38)	15(16)
Fungal infection	18(20)	3(3.4)	17(18)	0(0)
Ectoparasitic disorders	6(6.8)	0(0)	4(4.3)	0(0)
Helminthic disorders	0(0)	0(0)	1(1)	0(0)
TMA	0(0)	0(0)	1(1)	0(0)
VOD/SOS	3(3.4)	3(3.4)	2(2.1)	1(1)

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

Abbreviation: AESI, adverse events of special interest; PTLD, posttransplantation lymphoproliferative disorder; SOS, sinusoidal obstruction syndrome; TMA, thrombotic microangiopathy; VOD, veno-occlusive disease.

a, Infections were analyzed per high level grouped term (AEHLGT) in ADAE dataset.

- Overall, the AESI profile for (b) (4) arm seemed favorable to SoC arm. Refer to individual sections below for details.

8.2.5.1. Secondary Malignancy, Including PTLD

Data:

One participant (1.1%) in the Orca-T group had a secondary malignancy of grade 3 testis cancer. Two participants (2.1%) in the SoC group had a secondary malignancy: 1 participant with grade 1 neuroendocrine tumor and 1 participant with grade 3 testis cancer. A third participant had an AE of grade 1 cancer pain, but the participant had relapsed without evidence of a secondary malignancy. No participant in either group had PTLD.

The Applicant's Position:

Although only a very limited number of patients (1/88) developed secondary malignancies in the Precision-T trial, the potential long-term risk remains a concern. Patient monitoring for secondary malignancies should be performed.

The FDA's Assessment:

FDA agrees with the Applicant's analysis. In the primary safety population, no participant in either arm developed PTLD.

Secondary malignancy was reported in 1/88 (1%) patients on phase 3 study on (b) (4) arm: the patient developed grade 3 testis cancer on day 288. The patient received BFT as the conditioning regimen and received multiple lines of previous treatments.

Secondary malignancy was reported in 2/94 (2%) patients on phase 3 study on the SoC arm: a patient with grade 1 pancreatic neuroendocrine tumor developed on day 196 and 1 patient developed testicular cancer on day 341. Both patients received BFT conditioning regimens and received multiple prior lines of therapies.

Although none of these secondary malignancies were clearly related to the (b) (4) risk of secondary malignancy and post-transplant lymphoproliferative disorders including PTLD remains, and therefore will be included in Section 5 Warnings and Precautions of the USPI. Further, a standard long term monitoring similar to that for patients undergoing allogeneic HSCT should be performed for patients receiving (b) (4)

8.2.5.2. Grade $\geq$ 3 Infection

Data:

Overall, 39 participants (44.3%) in the Orca-T group and 48 participants (51.1%) in the SoC group had a grade $\geq$ 3 infection. Overall, 32 participants (36.4%) in the Orca-T group and 36 participants (38.3%) in the SoC group had a grade $\geq$ 3 bacterial infection. Overall, 17 participants (19.3%) in the Orca-T group and 28 participants (29.8%) in the SoC group had a grade $\geq$ 3 viral infection. Overall, 3 participants (3.4%) in the Orca-T group and 2 participants (2.1%) in the SoC group had a grade $\geq$ 3 fungal infection.

The Applicant's Position:

Overall, infection occurs commonly in patients who receive transplants. The rate of infection was lower for participants in the Orca-T group (44%) compared with the SoC group (51%).

The FDA's Assessment:

FDA's analysis for Grade 3 and 4 infections is shown in [Table 39](#).

Table 33. FDA- Grade 3 and higher Infections in the Safety Population

	(b) (4) N=88 n (%)		SOC N=94 n (%)	
	Grade 3	Grade4	Grade 3	Grade4 ^c
Infections^a				
Bacterial infection	14(16)	2(2)	9(9.5)	6(6.4)
Bacterial sepsis	7(8)	0(0)	1(1)	3(3.2)
Streptococcal infection	4(4.5)	0(0)	0(0)	0(0)
Escherichia infection	2(2.3)	1(1.1)	2(2.1)	0(0)
Clostridium difficile infection	2(2.3)	0(0)	1(1)	0(0)
Staphylococcal infection	1(1.1)	0(0)	3(3.4)	1(1)
Viral infection^b	12(14)	0(0)	18(19)	0(0)
COVID-19	5(5.7)	0(0)	10(11)	0(0)
Cytomegalovirus infection	2(2.3)	0(0)	4(4.3)	0(0)
Epstein-Barr virus infection	1(1.1)	0(0)	1(1)	0(0)
Adenovirus infection	0(0)	0(0)	2(2.1)	0(0)
Infections - pathogen unspecified	13(15)	3(3.4)	22(23)	5(5.3)
Sepsis	10(11)	3(3.4)	8(8.5)	3(3.2)
Enterocolitis infectious	1(1.1)	0(0)	0(0)	0(0)
Pneumonia	1(1.1)	0(0)	9(9.6)	2(2.1)
Urinary tract infection	1(1.1)	0(0)	2(2.1)	0(0)
Fungal infection	3(3.4)	0(0)	0(0)	0(0)
Candida infection	1(1.1)	0(0)	0(0)	0(0)
Laryngitis fungal	1(1.1)	0(0)	0(0)	0(0)
Pneumocystis jirovecii pneumonia	1(1.1)	0(0)	0(0)	0(0)

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

a, Analyzed per high level grouped term; b, 1 case of grade 1 JC virus occurred on (b) (4) arm, onset on day 12, outcome is recovered. c, 1 case of grade 5 sepsis on SOC arm not included

- Patients on (b) (4) arm had a higher incidence of any grade of infections compared with the Soc arm (94% versus 80%), however, the grade 3 and higher infections were much lower in (b) (4) arm compared with SoC arm (41% versus 51%) ([Table 39](#)).
- Bacterial infection: The total incidences of Grade 3 and higher bacterial infections were similar between (b) (4) arm and SoC arm. However, Grade 4 bacteria was lower on (b) (4) arm compared with SoC arm (2% versus 6.4%)
- Viral infection: The severity and incidences of viral infections were lower on (b) (4) arm compared with SoC arm.
- Infections-pathogen unspecified: The severity and incidences of infections-

pathogen unspecified were lower on (b) (4) arm compared with SoC arm.

- Fungal infections: A total of 3 (3.4%) patients developed any fungal infection and all of them are grade 1.
- Overall, (b) (4) arm showed at least comparable or less severe infections compared with SoC arm.

8.2.5.3. Graft Failure (Primary or Secondary)

Data:

One participant (1.1%) in the Orca-T group and no participant in the SoC group had graft failure. The participant in the Orca-T group had a grade 4 event of transplant failure on day +33. The participant ended study on day +76 and was alive as of the data cutoff date. All participants (100%) in the Orca-T group and 89 participants (94.7%) in the SoC group achieved neutrophil engraftment within 28 days of infusion. The median time to neutrophil engraftment was 13 (range: 9 to 19) days in the Orca-T group and 14 (range: 9 to 22) days in the SoC group. Eighty-seven participants (98.9%) in the Orca-T group and 86 participants (91.5%) in the SoC group achieved platelet engraftment within 50 days of infusion. The median time to platelet engraftment was 17 (range: 11 to 33) days in the Orca-T group and 18 (range: 1 to 123) days in the SoC group.

The Applicant's Position:

In patients who received Orca-T, graft failure was rare; however, patients should be monitored closely for laboratory evidence of hematopoietic recovery.

The FDA's Assessment:

Patient (b) (6) developed a Grade 4 secondary graft failure on day 33. The patient was alive and discontinued the study on Day 103 due to disease progression. This patient received 3e6/kg HSPC cells, 1.4e6/kg Treg cells, and 3.4e6/kg Tcon cells. The 3e6 HSPC cells/kg are within the product specification. At the time of completion of the clinical review memo, the substantive manufacturing issues identified by the CMC review team were not identified as specifically applicable to the product administered to this subject. Therefore, the attribution of the secondary graft failure to the issues identified as substantive manufacturing issues is not considered a contributing cause for the graft failure.

[Table 40](#) and [Table 41](#) showed the Neutrophil and platelet recovery in the safety population.

Table 34. FDA-Neutrophil Recovery

Neutrophil recovery	(b) (4) N=88 n (%)	SOC, N=94 n (%)
≤Day 28	88(100)	89(95)
≤Day 100	88(100)	89(95)
Days to engraftment		
Median (Q1,Q3)	13(12,15)	14(12,16)
Min, Max	9,19	9,22

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

Table 35. FDA-Platelet Recovery

Platelet recovery	(b) (4) N=88 n (%)	SOC, N=94 n (%)
≤Day 50	87(99)	87(93)
≤Day 100	87(99)	86(92)
Days to engraftment		
Median(Q1,Q3)	17(15,18)	18(15,20)
Min, Max	11,33	1, 123

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

8.2.5.4. TMA

Data:

No participant in the Orca-T group and 1 participant in the SoC group had TMA. The participant in the SoC group had a grade 2 TMA that began on day +26 and resolved by day +42.

The Applicant's Position:

No evidence of TMA in patients receiving Orca-T has occurred to date.

The FDA's Assessment:

FDA agrees with the Applicant's assessment. In general, TMA is a known complication in patients undergoing alloHSCT. There is no biologic/mechanistic rationale to suggest that risk of TMA will be different in patients undergoing (b) (4) compared to SoC alloHSCT.

8.2.5.5. VOD/SOS

Data:

Overall, 3 participants (3.4%) in the Orca-T group and 2 participants (2.1%) in the SoC group had VOD/SOS (all with the PT veno-occlusive liver disease). One participant who received Orca-T had a grade 3 event that began on day +32 and resolved by day +49, and 2 participants had grade 4 events: 1 that began on day +11 and was ongoing at the time of the data cutoff date, and 1 that began on day +19 and was ongoing at the time of the data cutoff date. One participant who received SoC had a grade 2 event that began on day +5 and was ongoing at the time of the data cutoff date, and 1 participant had a grade 4 event that began on day +34 and was ongoing at the time of the data cutoff date.

The Applicant's Position:

The incidence of VOD/SOS was infrequent.

The FDA's Assessment:

FDA agrees with the Applicant's assessment.

8.2.6. Clinical Outcome Assessment (COA) Analyses Informing Safety/Tolerability

Data:

PRO measures are described in section 8.1.2.

The Applicant's Position:

See section 8.1.2

The FDA's Assessment:

The data from COA (PRO) were not analyzed based on a formal testing plan. The Applicant did not seek a labeling claim based on COA (PRO) data. The FDA approached this data as purely exploratory and descriptive only.

8.2.7. Safety Analyses by Demographic Subgroups

Data:

Across prespecified subgroups based on age, sex, race, disease type, donor type, and conditioning regimen, the overall safety profile was generally similar for Orca-T across subgroups, and no subgroup-specific safety signals emerged. The safety profile of Orca-T remained favorable to SoC across subgroups.

The Applicant's Position:

The safety of Orca-T was similar across subgroups based on age, sex, race, primary disease, donor type, and conditioning regimen. Furthermore the safety profile of Orca-T remained favorable to SoC across all subgroups examined.

The FDA's Assessment:

FDA agrees with the description.

8.2.8. Specific Safety Studies/Clinical Trials

Data:

Not Applicable

The Applicant's Position:

Not Applicable

The FDA's Assessment:

Not Applicable.

8.2.9. Additional Safety Explorations

Human Carcinogenicity or Tumor Development

Data:

Secondary malignancies, including PTLD are an AESI for Orca-T and are described in section [8.2.5](#).

The Applicant's Position:

One participant (1.1%) who received Orca-T in the phase 3 component of Precision-T developed testis cancer. Secondary malignancies and malignancies of donor origins is a warning in the proposed Orca-T prescribing information.

The FDA's Assessment:

FDA agrees with the Applicant's position.

Human Reproduction and Pregnancy

Data:

There are no available data on Orca-T use in pregnant women. No animal reproductive and developmental toxicity studies have been conducted with Orca-T to assess whether it can cause fetal harm when administered to a pregnant woman. It is not known if Orca-T has the potential to be transferred to the fetus.

The Applicant's Position:

The safety of Orca-T in pregnant patients has not been established.

The FDA's Assessment:

No studies have been conducted to evaluate the safety of Orca-T in pregnant patients.

Pediatrics and Assessment of Effects on Growth

Data:

Orca-T has not been administered to pediatric patients.

The Applicant's Position:

The safety of Orca-T in pediatric patients has not been established.

The FDA's Assessment:

FDA agrees with the Applicant's position. No studies have been conducted in pediatric patients.

Overdose, Drug Abuse Potential, Withdrawal, and Rebound

Data:

There are no data on the effects of Orca-T overdose. The Orca-T drug product is intended to be infused in its entirety at the time of allogeneic transplantation, and overdose is not applicable in the context of a cellular therapy.

The Applicant's Position:

Not applicable

The FDA's Assessment:

Not Applicable

8.2.10. Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

Data:

Not Applicable

The Applicant's Position:

Not applicable. Orca-T has not been marketed in any country to date.

The FDA's Assessment:

FDA agrees with the Applicant's assessments.

Expectations on Safety in the Postmarket Setting

Data:

Not Applicable

The Applicant's Position:

Potential safety concerns beyond the risks observed in clinical trials are not expected. It is the Applicant's position that the safe use of Orca-T can be appropriately managed in a postmarketing setting with product labeling, as well as routine pharmacovigilance to monitor for unexpected AEs.

The FDA's Assessment:

FDA agrees with the Applicant's position.

8.2.11. Integrated Assessment of Safety

Data:

In the primary integrated safety analysis set (Module 2.7.4 and Module 5.3.5.3), participants who received Orca-T had a lower incidence of SAEs (Orca-T: 40%, SoC: 56%), deaths due to AEs (Orca-T: 4%; SoC: 11%), grade ≥ 3 infections (Orca-T: 46%, SoC: 51%), aGVHD (Orca-T: 37%, SoC: 47%), and moderate or severe cGVHD (Orca-T: 16%, SoC: 34%). The safety profile of Orca-T in the primary integrated safety analysis set was similar to that in the phase 3 component of Precision-T; no new safety signals were observed.

The Applicant's Position:

Overall, treatment with Orca-T was well tolerated in clinical studies and toxicities were managed with appropriate monitoring and intervention. The AESIs for Orca-T are secondary malignancy, including PTLN; grade ≥ 3 infection; graft failure (primary or secondary); TMA; and VOD/SOS.

The risks of Orca-T are toxicities that treating physicians and cell therapy experts are well trained to manage and are acceptable for a population with a serious and life-threatening condition.

The FDA's Assessment:

FDA agrees with the Applicant's assessment that in general the safety profile from 88 patients in Phase 3 component of Precision-T study is manageable and consistent with that observed in Phase 1b component (n=110), and generally representative of adverse events seen post allogeneic HSCT.

The integrated safety analysis (ISS) included:

- 88 patients in the primary safety population in phase 3 component of Precision-T study;
- 110 patients in phase 1b component of Precision-T study.

There are inherent limitations with any pooling of data across studies due to potential differences in patient, disease, and treatment characteristics, differences in sample size and thus the precision of the estimates, and other factors. Therefore, the integrated safety data analysis is considered supportive only.

The same FDA grouped terms were used to recode the AEs that were coded in dictionary code AEs columns in AE data sets. AEs were analyzed with a focus on TEAEs defined as all AEs occurring or worsening within 100 days after the infusion of Orca-T or SoC with all causes in the integrated safety analysis in this section. AESIs included secondary malignancy, including PTLTD; grade ≥ 3 infection; graft failure (primary or secondary); TMA; and VOD/SOS. AESI was defined as any AESI occurring or worsening within 2 years after the infusion of (b) (4)

Deaths:

Table 36. FDA-Deaths occurring in ISS Population

Parameter	Phase 1b, N=110 n (%)	Phase 3, N=88 n (%)	ISS, N=198 n (%)
All deaths	23 (21)	7 (8)	30 (15)
Disease progression	14 (13)	4 (4.5)	18 (9)
Adverse events	2 (1.8)	3 (3.4)	5 (2.5)
Other causes	7 (6.4)	0(0)	7 (3.5)
Fatal AEs ≤ 100 days after (b) (4)	0 (0)	3 (3.4)	3 (1.5)
Fatal AEs > 100 days after (b) (4)	24 (22)	3 (3.4)	27 (14)

Source: FDA ISS analysis of ADSL, ADDTH datasets. Data cutoff date: July 15, 2024.

TEAE:

[Table 43](#) shows the most common TEAEs in $\geq 20\%$ by FDA grouped PTs in 198 patients who received (b) (4) in phase 1b and phase 3 component of Precision-T study (phase1b n=110, and Phase 3, n=88).

Table 37. FDA-Most Common TEAEs Precision-T study Occurring in $\geq 20\%$ of Integrated Safety Population

TEAE by PT or FDA Grouped PT	Phase 1b, N=110 n (%)		Phase 3, N=88 n (%)		ISS, N=198 n (%)	
	All Grades	Grade 3 and Higher	All Grades	Grade 3 and Higher	All Grades	Grade 3 and Higher
Patients with any TEAE	110 (100)	100 (90)	88 (100)	79(90)	198(100)	179(90)
Mucositis*	91 (83)	29 (26)	75 (85)	25 (28)	166(84)	54 (27)
Diarrhea*	81 (74)	3 (2.7)	61 (69)	1 (1.1)	142(72)	4 (2)
Rash*	73 (66)	3 (2.7)	57 (65)	0 (0)	130 (66)	3 (1.5)
Pain*	54 (49)	0 (0)	46 (52)	0 (0)	100 (51)	0 (0)
Abdominal pain*	46 (42)	0 (0)	40 (45)	0 (0)	86 (43)	0 (0)
Bacterial infection*	41 (37)	30(27)	39 (44)	26 (30)	80 (40)	52 (26)
Nausea*	39 (35)	2 (1.8)	36 (41)	1 (1.1)	75 (38)	3 (1.5)
Vomiting	33 (30)	2 (1.8)	39 (44)	1 (1.1)	72 (36)	3 (1.5)
Febrile neutropenia	38 (35)	34 (31)	31 (35)	31 (35)	69 (35)	65 (33)
Fatigue*	43 (39)	0 (0)	25 (28)	0 (0)	68 (34)	0 (0)
Decreased appetite*	30 (27)	3 (2.7)	37 (42)	4 (4.5)	67 (34)	7 (3.5)
Hemorrhage*	33 (30)	3 (2.7)	34 (39)	5 (5.7)	67 (34)	8 (4)
Edema*	39 (35)	2 (1.8)	26 (30)	0 (0)	65 (33)	2 (1)
Headache*	39 (35)	0 (0)	26 (30)	0 (0)	65 (33)	0 (0)
Xerosis*	24 (22)	0 (0)	34 (39)	0 (0)	58 (29)	0 (0)
Viral infection*	23 (21)	6 (5.4)	29 (31)	6 (6.4)	52 (26)	12 (6.1)
Pyrexia	30 (27)	1 (0.9)	20 (23)	2 (2.3)	50 (25)	3 (1.5)
Dizziness*	29 (26)	5 (4.5)	18 (20)	1 (1.1)	47 (24)	6 (3)
Upper respiratory tract infection*	24 (22)	0 (0)	21 (24)	0 (0)	45 (23)	0 (0)
Constipation	23 (21)	0 (0)	21 (24)	0 (0)	44 (22)	0 (0)
Sleep disorders*	22 (20)	0 (0)	18 (20)	0(0)	40 (20)	0 (0)
Hypertension*	19 (17)	5 (4.5)	20 (23)	4 (4.5)	39 (20)	9 (4.5)

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

* FDA grouped terms, See Appendix 19.6

Table 44 shows Grade3 and higher TEAEs in $\geq 5\%$ by FDA grouped PTs in 198 patients who received (b) (4) in phase 1b and phase 3 component of Precision-T study (phase1b n=110, and Phase 3, n=88).

Table 38. FDA-Grade 3 and Higher TEAEs Occurring in ≥ 5% of Integrated Safety Population

TEAE by PT or FDA Grouped PT	Phase 1b, N=110 n (%)	Phase 3 N=88 n (%)	ISS N=198 n (%)
Febrile neutropenia	34 (31)	31(35)	65 (33)
Mucositis*	29 (26)	25(28)	54 (27)
Bacterial infection*	26 (24)	26(30)	52 (26)
Renal disorder*	9 (8)	5(6)	14 (7)
Viral infection*	6 (5.4)	6(7)	12 (6)

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

* FDA grouped terms, See Appendix 19.6

AESI**Table 39. FDA-AESI Analysis in ISS Population**

Preferred Term	Phase 1b, N=110 n (%)		Orca-T, N=88 n (%)		ISS, N=198 n (%)	
	All Grades	Grade 3 and Higher	All Grades	Grade 3 and Higher	All Grades	Grade 3 and Higher
Secondary malignancy, including PTLD	1 (0.9)	0 (0)	1 (1.1)	1 (1.1)	2 (1)	1 (0.5)
Graft failure (primary or secondary)	2 (1.8)	2 (1.8)	1(1.1)	1((1.1)	3 (1.5)	3 (1.5)
Infections ^a	89 (81)	50 (45)	83(94)	36(41)	172 (87)	86 (43)
Viral infection	63 (57)	19 (17)	45(51)	12(14)	108 (55)	31 (16)
Infections - pathogen unspecified	43 (39)	24 (22)	40(45)	16(18)	83 (42)	40 (20)
Bacterial infection	43 (39)	22 (20)	35(40)	16(18)	78 (39)	38 (19)
Fungal infection	27 (25)	5 (45)	18(20)	3(3.4)	45 (23)	8 (4)
Ectoparasitic disorders	4 (3.6)	0(0)	6(6.8)	0(0)	10 (5)	0(0)
TMA	1(0.9)	0(0)	0(0)	0(0)	1(0.5)	1(0.5)
VOD/SOS	3 (2.7)	3 (2.7)	3(3.4)	3(3.4)	6 (3)	6 (3)

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

Abbreviation: AESI, adverse events of special interest; PTLD, posttransplantation lymphoproliferative disorder; SOS, sinusoidal obstruction syndrome; TMA, thrombotic microangiopathy; VOD, veno-occlusive disease.

a, Infections were analyzed per high level grouped term (AEHLGT) in ADAE dataset.

Lab AEs

Table 40. FDA – Grade ≥3 Key Laboratory Abnormalities worsening from Baseline in at least 5% of Patients in ISS Population

Laboratory Test	Phase 1b, N=110 n (%)	Phase3 N=88 n (%)	ISS N=198 n (%)
Platelet count decreased	82 (75)	82 (93)	186 (94)
Neutrophils decreased	95 (86)	67 (77)	162 (84)
Hemoglobin decreased	85 (77)	62 (70)	147 (75)
ALT increased	5(4.5)	10 (11)	15 (7.6)
AST increased	4 (3.6)	8 (9.2)	12 (6.2)

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

Abbreviations: ALT, Alanine Aminotransferase; AST, aspartate aminotransferase.

The key hematologic and chemical laboratories abnormalities remain consistent in ISS safety population with the primary safety population. No additional safety concerns were identified from ISS safety set.

SUMMARY AND CONCLUSIONS

8.3. Statistical Issues

The FDA's Assessment:

Stat review team does not have major statistical issues. Minor issues included that FDA did not agree with the proposed handling of missing assessments for the last secondary endpoint of GRFS, as communicated previously. The applicant did not incorporate FDA's suggestion for this endpoint but stat team note that this endpoint would not be used for regulatory decision-making.

8.4. Conclusions and Recommendations

The FDA's Assessment:

Substantial evidence of effectiveness of (b) (4) in adult patients with advanced hematologic malignancies undergoing myeloablative conditioning (MAC)-AlloHSCT is based on one adequate and well controlled phase 3 portion of Precision-T study. Precision-T is an open label, multicenter, randomized, phase 3 study (NCT05316701) that compares (b) (4) to the SoC MAC-alloHCT 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) or 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 enrolled 187 patients who were randomized (1:1) to receive either (b) (4) followed by single-agent tacrolimus or SoC control allograft derived from mobilized peripheral blood followed by GVHD prophylaxis with tacrolimus and methotrexate. Patients on both arms received a myeloablative conditioning regimen prior to receiving the alloHSCT. Donor Lymphocyte infusion (DLI) was prohibited in the protocol and none of the patients in the study received DLI.

Efficacy: The primary efficacy outcome measure was cGFS as determined by a blinded independent EAC. cGFS is defined as the time from transplantation to either death from any cause or the first onset of moderate-to-severe cGVHD based on NIH consensus criteria ([Jagasia 2015](#)). Key secondary efficacy endpoints included: time to moderate-to-severe cGVHD, OS, and GVHD-free, GRFS through 2 years. The Primary efficacy analysis was conducted in the intend-to-treat population, which included 93 patients randomized to (b) (4) arm and 94 patients randomized to SoC allograft arm:

- The primary analysis for the cGFS demonstrated a statistically significant difference between (b) (4) arm versus SoC arm (HR = 0.26 [95% CI:

0.14, 0.47]; $P < .00001$) after median follow up times of 8.48 (range: 0 to 22) months and 9.03 (range: 0 to 20) months, respectively.

- The secondary endpoint analysis of cumulative incidence of time to moderate or severe cGVHD at month 12 demonstrated a significant difference between (b) (4) arm versus SoC arm (HR = 0.19 [95% CI: 0.08, 0.43]; $P = .00002$).
- At the time of interim analysis, OS was immature. The interim analysis of OS failed to demonstrate a statistically significant difference (HR = 0.49 [95% CI: 0.20, 1.22]; $P = .11823$). However, a trend towards OS improvement was observed in (b) (4) arm compared to SoC allograft arm.
- GRFS was not tested since the OS was not significant at interim per the hierarchical testing.

Safety: The primary evidence of the safety of (b) (4) for the proposed indication derives from Precision-T phase 3 study. Precision-T phase 1b part provides supportive evidence of safety. The primary safety analysis was conducted in 88 patients on (b) (4) arm and 94 patients on the SoC arm who have received the actual treatment.

- All patients on Orca-T arm and 99% of patients on SOC arm experienced at least one TEAE. The most common ($\geq 5\%$) Grade 3 to 4 TEAEs in the (b) (4) were: febrile neutropenia (35%), bacterial infection (30%), mucositis (28%), viral infection (6.8%), hemorrhage (5.7%), and renal disorders (5.7%).
- The rate of death from AEs was higher on SoC arm (Orca-T arm: 3.4%; SOC arm: 11%). In addition, a proportion of early deaths occurred on SoC arm (5.7%) compared with (b) (4) arm with no deaths occurred within 42 days after the infusion.
- The rate of serious adverse events (SAEs) was higher in the SoC arm ((b) (4) arm: 36%; SOC arm: 56%).
- The rate of Grade 3 to 4 hematological toxicity was similar between (b) (4) arm and SoC arm.
- There was a slightly higher rate in bacterial infection on (b) (4) arm ((b) (4) arm 44%; SoC arm: 35%) within the 100 days after the infusion. However, the rates of bacterial infection were similar between the (b) (4) arm and SoC arm within 2 years after the infusion. The early higher rate of bacterial infection may be due to the T cell depletion in HPSCs of (b) (4). Notably, this higher rate of early bacterial infection did not attribute to a higher rate of SAEs due to infections and did not attribute to a higher rate of early deaths on (b) (4) arm.

In conclusion, Phase 3 of Precision-T study demonstrates a clinically meaningful and statistically significant improvement in cGFS; a statistically significant improvement in

time to moderate or severe cGVHD; trends in improvement of OS and GRFS at the interim analysis. Precision-T also demonstrated a comparable or better safety profile in this patient population with limited available therapies. Overall, these data denote clinical benefit in adult patients with hematologic malignancies undergoing allogeneic hematopoietic transplantation with a myeloablative conditioning regimen. Therefore, the clinical review team recommends granting a traditional approval to (b) (4) 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.

8.4.1. Approach to Substantial Evidence of Effectiveness

Select from the options below to indicate how substantial evidence of effectiveness (SEE) was established (if applicable). If there are multiple indications, repeat items 1–3 for each indication.

1. Verbatim indication:

Clinical Team's recommended indication, when the product is approved, is (b) (4) (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 chronic graft vs host disease (cGVHD) in the treatment of adults with hematologic malignancies".

2. SEE was established with (check **one** of the options for traditional or accelerated approval pathways and complete response not due to lack of demonstrating SEE)

a. Adequate and well-controlled clinical investigation(s):

- i. ☐ Two or more adequate and well-controlled clinical investigations, **OR**
- ii. ☒ One adequate and well-controlled clinical investigation with highly persuasive results that is considered to be the scientific equivalent of two clinical investigations

OR

b. ☐ One adequate and well-controlled clinical investigation and confirmatory evidence^{1,2,3}

OR

c. ☐ Evidence that supported SEE from a prior approval (e.g., 505(b)(2) application relying only on a previous determination of effectiveness; extrapolation; over-the-counter switch)²

3. Complete response, if applicable

- a. SEE was established
b. ☐ SEE was not established (if checked, omit item 2)

¹ FDA draft guidance for industry *Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products* (2019)

² FDA guidance for industry *Providing Clinical Evidence of Effectiveness for Human Drugs and Biological Products* (1998)

³ Demonstrating Substantial Evidence of Effectiveness Based on One Adequate and Well-Controlled Clinical Investigation and Confirmatory Evidence (2023)]

X

X

Primary Clinical Reviewer

Clinical Team Leader

X

OCE MORE Team Leader

X

X

Clinical Pharmacology Reviewer

Clinical Pharmacology Team Leader

9 Advisory Committee Meeting and Other External Consultations

The FDA's Assessment:

Advisory committee meeting was not convened for this submission. No external consultations were required.

10 Pediatrics

The Applicant's Position:

Safety and efficacy of Orca-T in pediatric patients have not been established. Orca-T received orphan designation (DRU-2023-9854) in January 2024 for the *prevention of graft-versus-host disease and/or death in patients undergoing hematopoietic stem cell transplant* and as such is exempt from the Pediatric Research Equity Act (PREA) requirement to conduct pediatric studies.

The FDA's Assessment:

FDA agrees with the Applicant's assessments.

11 Labeling Recommendations

Data:

This is an original application.

The Applicant's Position:

Not applicable – initial application

The FDA's Assessment:

The labelling discussions have not occurred yet but labelling comments will be included as a separate addendum when labelling discussions are complete and a near final draft is available.

12 Risk Evaluation and Mitigation Strategies (REMS)

The FDA's Assessment:

Based on a review of the results of the study Precision-T, (both Phase 1b and Phase 3), OBPV review team conclude that (b) (4) safety risks can be adequately mitigated with the methods outlined in the sponsor's proposed PVP dated July 2, 2025. The proposed PVP is adequate to monitor postmarketing safety for (b) (4) with routine pharmacovigilance in accordance with 21 CFR 600.80.

Based on the available safety data, a REMS or a safety-related postmarketing requirement or commitment (PMR/PMC) study is not required.

13 Postmarketing Requirements and Commitment

The FDA's Assessment:

FDA PMC/PMR Checklist for U.S. Population Representativeness

The following were evaluated and considered as part of FDA's review:	Is a PMC/PMR needed?
☐ The patients enrolled in the clinical trial are representative of the racial, ethnic, and age group of the U.S. population for the proposed indication.	___ Yes _x_ No
☐ Does the FDA review indicate uncertainties in the safety and/or efficacy findings by demographic factors (e.g. race, ethnicity, sex, age, etc.) to warrant further investigation as part of a PMR/PMC?	___ Yes _x_ No
☐ Other considerations (e.g.: PK/PD), if applicable: A PMC is requested for the completion and submission of final study report and datasets for the final analysis of OS, GRFS, and primary endpoint (cGFS) update with longer follow up.	x___ Yes ___ No

14 Associate Director of Labeling (OTP/OCE)

15 Branch Chief (Malignant Hematology Branch)

The Malignant Hematology Branch (MHB) concurs with the primary clinical review team and the Oncology Center of Excellence's recommendation to grant a traditional approval to (b) (4) (TREGZI) 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 graft vs host disease (cGVHD) in the treatment of adults with hematologic malignancies.

X

16 Oncology Center of Excellence (OCE) Signatory

This application was reviewed by the Oncology Center of Excellence (OCE) per the OCE Intercenter Agreement. My signature below represents an approval recommendation for the clinical portion of this application under the OCE.

X

17 Division Director (Division of Clinical Evaluation Hematology)

X

18 Director (Office of Clinical Evaluation)

19 Appendices

19.1. References

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19.1.2. The FDA's References:

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19.2.Financial Disclosure**The Applicant's Position:**

Orca Bio checked all 22 clinical sites that enrolled at least 1 subject in the Precision-T study. One subinvestigator was identified to have equity interest as defined in 21 CFR 54.2(b).

Covered Clinical Study (Name and/or Number):* Precision-T

Was a list of clinical investigators provided:	Yes ☒ X	No ☐ (Request list from Applicant)
Total number of investigators identified: <u>28 Principal Investigators</u>		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): <u>None</u>		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): <u>1</u>		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: <u>0</u> Significant payments of other sorts: <u>0</u> Proprietary interest in the product tested held by investigator: <u>0</u> Significant equity interest held by investigator in study: <u>1</u> Sponsor of covered study: <u>0</u>		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒ X	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) <u>0</u>		
Is an attachment provided with the	Yes ☐	No ☐ (Request explanation

reason:		from Applicant)
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*The table above should be filled by the applicant, and confirmed/edited by the FDA.

The FDA's Assessment:

The Applicant employed appropriate conflict of interest management plan to minimize bias of study results. This plan included proactive measures to limit participation in potentially biasing activities and clear disclosures in any resulting data or materials. The equity interest held by one investigator is not likely to have negatively impacted the integrity of Precision-T's conduct or findings.

19.3. Nonclinical Pharmacology/Toxicology

Data:

Not Applicable

The Applicant's Position:

All nonclinical/toxicology data are included in section 5.

The FDA's Assessment:

[FDA will complete this section.]

19.4. OCP Appendices (Technical documents supporting OCP recommendations)

19.4.1. Population PK Analysis

19.4.1.1. Executive Summary

The FDA's Assessment:

Not applicable.

19.4.1.2. PPK Assessment Summary

The Applicant's Position:

Not applicable

The FDA's Assessment:

Not applicable.

19.4.1.3. PPK Review Issues

Not applicable

19.4.1.4. Reviewer's Independent Analysis

Not applicable

19.4.2. Exposure-Response Analysis

19.4.2.1. ER (efficacy) Executive Summary

The FDA's Assessment:

Please refer to Section 6.1.

19.4.2.2. ER (efficacy) Assessment Summary

The Applicant's Position:

General Information	
Goal of ER analysis	Limited exposure response analyses were conducted as exploratory endpoints in the phase 3 component. Neutrophil engraftment by day +28, moderate or severe cGVHD at 1 year, and CD3 count over time were evaluated.
Study Included	<i>Exploratory exposure-response analyses were performed for 88 participants in the safety analysis set who received all 3 Orca-T infusions to evaluate the exposure-response relationship for each of Orca-T's components.</i>
Endpoint	<i>Exploratory:</i> <i><u>HSPC dose and neutrophil engraftment by day +28</u></i> <i><u>Treg dose and moderate or severe cGVHD at 1 year</u></i> <i><u>Tcon dose and CD3 count over time</u></i>
No. of Patients (total, and with individual PK)	<i>88 total, 88 with moderate or severe cGVHD response, 75 with CD3 count</i>

Population Characteristics (Table XX)	General	<i>Age median (range) 44.0 (19 to 65) years</i> <i>53 (57%) male</i> <i>40 (43%) female</i> <i>76 (82%) white/Caucasian</i> <i>10 (11%) Asian</i> <i>4 (4%) race not reported</i> <i>1 (1%) American Indian or Alaska native</i> <i>1 (1%) black or African American</i> <i>1 (1%) native Hawaiian or other Pacific islander</i>	
	Pediatrics (if any)	None	
Doses Included		<i>HSPC: median 4.10×10^6 viable cells/kg</i> <i>Treg: median 2.35×10^6 viable cells/kg</i> <i>Tcon: median 3.60×10^6 viable cells/kg</i>	
Exposure Metrics Explored (range)		<i>HSPC: 1.0×10^6 to 11.3×10^6 viable cells/kg</i> <i>Treg: 1.2×10^6 to 3.5×10^6 viable cells/kg</i> <i>Tcon: 1.8×10^6 to 6.9×10^6 viable cells/kg</i>	
Covariates Evaluated		<i>A stratified logistic model was used for the binary endpoints. The stratification was the conditioning regimen (TBI vs non-TBI). For CD3 count over time, longitudinal analysis models were applied with appropriate covariates.</i>	
Final Model Parameters		Summary	Acceptability [FDA's comments]
Model Structure		<i>For primary and major secondary endpoints</i>	
Model Parameter Estimates		<i>Table XXs (for primary and major secondary endpoints)</i>	
Model Evaluation			
Covariates and Clinical Relevance			
Simulation for Specific Population			

Visualization of E-R relationships	<i>Figure XX (if quantile analysis is included, provide Table XX of baseline demographics stratified by quantiles)</i>	
Overall Clinical Relevance for ER	The exploratory analyses demonstrated that no exposure-response relationship was identified between cGVHD and the Treg dose and between CD3 count and the Tcon dose. Additionally, all participants had neutrophil engraftment by day +28, regardless of HSPC dose, demonstrating that no exposure-response relationship was identified between neutrophil engraftment and the CD34+ dose. These findings indicate that the Orca-T doses administered in Precision-T were adequate and sufficient to elicit the intended therapeutic response.	
Labeling Language	Description	Acceptability [FDA's comments]
12.2 Pharmacodynamics	Not applicable	

19.4.2.3. ER (safety) Executive SummaryThe FDA's Assessment:

Not applicable

19.4.2.4. ER (safety) Assessment SummaryThe Applicant's Position:

Not applicable

The FDA's Assessment:

Not applicable

19.4.2.5. ER Review Issues

Please refer to Section 6.2.1

19.4.2.6. Reviewer's Independent Analysis

Please refer to Section 6.2.1

19.4.2.7. Overall benefit-risk evaluation based on E-R analyses

The Applicant's Position:

The exploratory analyses demonstrated that no exposure-response relationship was identified between cGVHD and the Treg dose and between CD3 count and the Tcon dose. Additionally, all participants had neutrophil engraftment by day +28, regardless of HSPC dose, demonstrating that no exposure-response relationship was identified between neutrophil engraftment and the CD34+ dose. These findings indicate that the Orca-T doses administered in Precision-T were adequate and sufficient to elicit the intended therapeutic response.

The FDA's Assessment:

Please refer to Section 6.2.1.

19.5.Additional Safety Analyses Conducted by FDA

The FDA's Assessment:

Not applicable

19.6.FDA Grouped Terms

FDA grouped PT term	AEDECOD/PT
Abdominal pain	Abdominal discomfort Abdominal pain Abdominal pain lower Abdominal pain upper Abdominal tenderness Dyspepsia Epigastric discomfort

Anorectal disorders	Anal fistula Anogenital warts Anorectal discomfort Perirectal abscess Proctitis Rectal fissure
Arrhythmia	Atrial fibrillation Atrial flutter Palpitations Supraventricular tachycardia
Arthropod infestation	Arthropod infestation Lice infestation Strongyloidiasis
Ataxia	Balance disorder Extrapyramidal disorder Gait disturbance
Bacterial infectious disorders	High level group term
Hypotension	Hypotension Orthostatic hypotension
Hypertension	Blood pressure increased Hypertension Diastolic hypertension Pulmonary hypertension
Bone fracture	Compression fracture Femur fracture Hip fracture Lumbar vertebral fracture Rib fracture Spinal compression fracture
Cardiac failure	Ejection fraction decreased Heart failure with reduced ejection fraction
Coagulopathy	Coagulopathy Disseminated intravascular coagulation

Cytomegalovirus infection	High level group term Cytomegalovirus colitis Cytomegalovirus enterocolitis Cytomegalovirus infection Cytomegalovirus infection reactivation Cytomegalovirus test positive Cytomegalovirus viraemia
Decreased appetite	Decreased appetite Hypophagia
Delirium	Delirium Hallucination Hallucinations, mixed Hallucination, visual
Diabetes	Diabetes mellitus Steroid diabetes
Diarrhea	Anal incontinence Diarrhoea Enteritis
Colitis	Colitis Neutropenic colitis
Dizziness	Dizziness Dizziness postural Presyncope Syncope Vertigo
Dyspnea	Dyspnoea Dyspnoea exertional Nocturnal dyspnoea Obstructive airways disorder Wheezing
Ear disorders	Cerumen impaction Deafness neurosensory Dysphonia Ear congestion Ear discomfort Ear infection Ear swelling Excessive cerumen production Foreign body in ear Hypoacusis Otitis media Tinnitus Tympanic membrane perforation
Ecchymosis	Contusion Ecchymosis

Edema	Ascites Face oedema Generalised oedema Hypervolaemia Joint swelling Localised oedema Lymphoedema Oedema Oedema peripheral Periorbital oedema Periorbital swelling Peripheral swelling Pleural effusion Pulmonary oedema Swelling Swelling face
Encephalopathy	Brain fog Cognitive disorder Confusional state Depressed level of consciousness Disturbance in attention Hepatic encephalopathy Memory impairment Mental status changes Metabolic encephalopathy Posterior reversible encephalopathy syndrome Somnolence Toxic encephalopathy Uraemic encephalopathy
Epstein-Barr virus infection	HLGT Epstein-Barr virus infection reactivation Epstein-Barr virus infection Epstein-Barr viraemia

Eye disorders	Anisocoria Cataract Cataract nuclear Chalazion Chorioretinal scar Choroidal detachment Conjunctival haemorrhage Conjunctival hyperaemia Conjunctivitis Conjunctivitis allergic Deafness unilateral Diplopia Ectropion Eye irritation Eye pruritus Glaucoma Intraocular pressure increased Iritis Lacrimation increased Meibomian gland dysfunction Myopia Noninfective conjunctivitis Ocular hyperaemia Ocular surface disease Photophobia Photopsia Photosensitivity reaction Punctate keratitis Retinal tear Scleritis Vision blurred Visual field defect Visual impairment Vitreous floaters
Fatigue	Asthenia Fatigue Lethargy Malaise
Fungal infectious disorders	HLGT
Gallbladder disorders	Acute cholecystitis necrotic Biliary dilatation Cholecystitis Cholecystitis acute Cholelithiasis Gallbladder polyp

Gastrointestinal disorders	Gastritis Gastroenteritis Gastrointestinal disorder Gastrointestinal inflammation Gastrointestinal stoma complication Gastroesophageal reflux disease Ileus Ileus paralytic Gastrointestinal wall thickening Impaired gastric emptying Small intestinal obstruction Large intestine polyp Peptic ulcer Diverticulitis Inflammatory bowel disease
Headache	Headache Migraine
Bradycardia	Bradycardia Heart rate decreased Sinus bradycardia
Tachycardia	Heart rate increased Sinus tachycardia Tachycardia
Hemorrhage	Anal haemorrhage Cystitis haemorrhagic Epistaxis Gastrointestinal haemorrhage Haematochezia Haematoma Haematuria Haematemesis Haemoptysis Haemorrhoidal haemorrhage Heavy menstrual bleeding Intermenstrual bleeding Intra-abdominal haemorrhage Large intestinal haemorrhage Lower gastrointestinal haemorrhage Melaena Mouth haemorrhage Rectal haemorrhage Retinal haemorrhage Ulcer haemorrhage Upper gastrointestinal haemorrhage Uterine haemorrhage Vaginal haemorrhage
Hypersensitivity	Angioedema Drug hypersensitivity Hypersensitivity
Infections - pathogen unspecified	HLGT

Transfusion reaction	Allergic transfusion reaction Transfusion reaction
Local Infusion site reaction	Catheter site erythema Catheter site irritation Catheter site vesicles Infusion site extravasation Infusion site reaction Injection site reaction Vascular access complication Vascular access site inflammation Vascular access site oedema
Liver disorder	Drug-induced liver injury Hepatic fibrosis Hepatosplenomegaly Hepatic steatosis Hepatomegaly Hepatojugular reflux Liver injury Hepatorenal syndrome
Malignancy	Basal cell carcinoma Pancreatic neuroendocrine tumour Testis cancer Neoplasm malignant Squamous cell carcinoma of skin
Menstrual disorders	Amenorrhoea Dysmenorrhoea Menstruation irregular Premature menopause
Affective disorders	Anxiety Depression Mood altered Mania
Mucositis	Gingivitis Gingival pain Glossodynia Lip ulceration Mouth ulceration Mucosal inflammation Oesophageal pain Oesophagitis Oral pain Oropharyngeal pain Proctalgia Stomatitis Tongue ulceration
Motor dysfunction	Dystonia Muscle spasms Muscular weakness Musculoskeletal stiffness Myopathy

Musculoskeletal disorders	Carpal tunnel syndrome Ligament sprain Limb injury Orthopnoea Osteoarthritis Osteopenia Osteoporosis Periarthritis Perichondritis Plantar fasciitis Rotator cuff syndrome Tendonitis Tenosynovitis
Nail disorders	Ingrowing nail Nail discolouration Nail hypertrophy Nail pigmentation Onychoclasia Paronychia
Nausea	Nausea Retching
Non-cardiac chest pain	Chest discomfort Musculoskeletal chest pain Non-cardiac chest pain
Nutrition disorders	Angular cheilitis Folate deficiency Iron deficiency Macroglossia Malnutrition Vitamin B1 decreased Vitamin B12 deficiency Vitamin C deficiency Vitamin D decreased Vitamin D deficiency
Oral disorders	Cheilitis Dental caries Gingival discolouration Leukoplakia oral Lip injury Oropharyngeal discolouration Tongue disorder Tongue discolouration Tooth infection Oral dysaesthesia Paraesthesia oral

Pain	Arthralgia Back pain Bone pain Breast tenderness Cancer pain Catheter site pain Coccydynia Ear pain Eye pain Facial pain Flank pain Gastrointestinal pain Groin pain Incision site pain Musculoskeletal pain Myalgia Neck pain Odynophagia Pain Pain in extremity Pain in jaw Pain of skin Pelvic pain Pleuritic pain Procedural pain Rhinalgia Sacral pain Salivary gland pain Sciatica Scrotal pain Suprapubic pain Tenderness Tendon pain Testicular pain Toothache Vascular access site pain Vulvovaginal pain
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Peripheral neuropathy	Hypoaesthesia Nerve compression Neuralgia Neuropathic pruritus Neuropathy peripheral Paraesthesia Peripheral motor neuropathy Peripheral sensorimotor neuropathy Peripheral sensory neuropathy Sensation of foreign body
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Rash	Acne Acute generalised exanthematous pustulosis Blister Blood blister Dermal cyst Dermatitis Dermatitis acneiform Dermatitis bullous Drug eruption Eczema Eczema nummular Erythema Erythema multiforme Folliculitis Impetigo Intertrigo Macule Palmar erythema Palmar-plantar erythrodysesthesia syndrome Papule Petechiae Plantar erythema Pruritus Purpura Rash Rash erythematous Rash macular Rash maculo-papular Rash morbilliform Rash papular Rash pruritic Rash pustular Rosacea Seborrheic dermatitis Seborrheic keratosis Skin hyperpigmentation Skin irritation Urticaria
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Renal disorder	Acute kidney injury Azotaemia Chronic kidney disease Hydronephrosis Nephrolithiasis Proteinuria Renal colic Renal disorder
Respiratory failure	Acute respiratory distress syndrome Acute respiratory failure Respiratory depression Respiratory failure
Shock	Distributive shock Hypovolaemic shock Septic shock Shock haemorrhagic
Skin disorder	Decubitus ulcer Dermatosis Sensitive skin Skin abrasion Skin discolouration Skin discomfort Skin disorder Skin exfoliation Skin fissures Skin hypopigmentation Skin laceration Skin lesion Skin odour abnormal Skin reaction Skin tightness Skin ulcer Skin wound Sticky skin Skin wrinkling
Sleep disorders	Abnormal dreams Insomnia Restless legs syndrome Sleep apnoea syndrome
Taste disorder	Dysgeusia Hypogeusia Taste disorder

Thrombosis	Deep vein thrombosis Device related thrombosis Embolism Pulmonary embolism Superficial vein thrombosis Thrombosis
Tremor	Essential tremor Tremor
URI	Acute sinusitis Chronic sinusitis Cough Laryngeal inflammation Paranasal sinus hypersecretion Paranasal sinus inflammation Pharyngeal inflammation Rales Respiratory tract infection Rhinitis Rhinorrhoea Sinus congestion Sinusitis Upper respiratory tract infection Upper-airway cough syndrome
Vaginal disorder	Atrophic vulvovaginitis Vaginal discharge Vaginal infection Vulvovaginal burning sensation Vulvovaginal dryness Vulvovaginal erythema Vulvovaginal mycotic infection Vulvovaginal pruritus
Viral infectious disorders	HLGT

Xerosis	Nasal dryness Dry eye Dry mouth Dry skin Dry throat Xerosis
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