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Review Completion Date / Stamped Date	
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Applicant	Orca Biosystems Inc
Established Name	(b) (4)
(Proposed) Trade Name	TREGZI (PNR)
Pharmacologic Class	
Formulation(s), including Adjuvants, etc	An allogeneic hematopoietic graft isolated from a donor's mobilized peripheral blood of an 8/8 HLA-matched donor and is uniquely donor- and recipient- specific.
Dosage Form(s) and Route(s) of Administration	TREGZI is for intravenous use only and is available as 4 single-dose infusion bags (HSPCs, Tregs, Tcons, and Tcon diluent).

	Administer an appropriate preparative regimen before infusion.
Dosing Regimen	TREGZI is a suspension for intravenous infusion. TREGZI is provided in separate infusion bags labeled for the specific patient. A single dose of TREGZI consists of: • A minimum dose of HSPCs of 1.0×10^6 cells per patient kilograms. • A dose of Tregs of $(b) (4) \times 10^6$ to 3.5×10^6 cells per patient kilograms. • A dose of Tcons of $(b) (4) \times 10^6$ to 6.9×10^6 cells per patient kilograms.
Indication(s) and Intended Population(s)	Adult patients with hematologic malignancies to improve survival free of chronic Graft-Versus-Host disease (cGVHD) in conjunction with an appropriate preparative regimen.

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GLOSSARY

AE	adverse event
aGVHD	acute graft-versus-host disease
ALL	acute lymphoid leukemia
alloHCT	allogeneic hematopoietic cell transplantation
ALT	alanine transaminase
AML	acute myeloid leukemia
AST	aspartate transaminase

ASTCT	American Society for Transplantation and Cellular Therapy
ATG	antithymocyte globulin
BFT	busulfan/fludarabine/thiotepa
BLA	Biologics Licensing Application
cGFS	moderate or severe chronic graft-versus-host disease-free survival
cGVHD	chronic graft-versus-host disease
CI	confidence interval
CML	chronic myeloid leukemia
CMV	cytomegalovirus
CR	complete remission
CRi	complete remission with incomplete hematologic recovery
CRO	contract research organization
CSR	clinical study report
Cy	cyclophosphamide
DLCO	diffusing capacity of the lung for carbon monoxide
DLI	donor lymphocyte infusion
DMC	data monitoring committee
DRI	Disease Risk Index
EAC	endpoint adjudication committee
eGFR	Estimated glomerular filtration rate
EU	European Union
FDA	Food and Drug Administration
G-CSF	granulocyte colony-stimulating factor
GI	gastrointestinal
GRFS	graft-versus-host disease-free and relapse-free survival
GVHD	graft-versus-host disease
GVL	graft-versus-leukemia
HBsAg	hepatitis B surface antigen
HCT	hematopoietic cell transplantation
HCT-CI	Hematopoietic Cell Transplantation-Specific Comorbidity Index
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HLA	human leukocyte antigen
HR	hazard ratio
HSPC	hematopoietic stem and progenitor cell
HTLV	human T lymphotropic virus
ITT	intention-to-treat
IV	intravenous(ly)
KM	Kaplan-Meier

MAC	myeloablative conditioning
MAGIC	Mount Sinai Acute GVHD International Consortium
MDS	myelodysplastic syndrome
MFI	mean fluorescence intensity
MPAL	mixed phenotype acute leukemia
MRD	minimal residual disease
MSD	matched sibling donor
MUD	matched unrelated donor
MUGA	multigated acquisition
NIH	National Institutes of Health
NRM	nonrelapse mortality
OS	overall survival
PBSC	peripheral blood stem cell
PT	preferred term
PTLD	posttransplantation lymphoproliferative disorder
RFS	relapse-free survival
SAE	serious adverse event
SAP	statistical analysis plan
SoC	standard-of-care
SOC	system organ class
SOS	sinusoidal obstruction syndrome
TBI	total body irradiation
TCD	T-cell depletion
Tcon	conventional T cell
TMA	thrombotic microangiopathy
Treg	regulatory T cell
ULN	upper limit of normal
VOD	veno-occlusive disease
WHO	World Health Organization
WOCBP	women of childbearing potential

1. Executive Summary

Orca-T, under the trade name of TREGZI, is an allogeneic stem cell and T-cell immunotherapy derived from a human leukocyte antigen (HLA)-matched donor. The proposed indication is treatment of adult patients with hematologic malignancies to improve survival free of chronic graft-versus-host disease (cGVHD) in conjunction with a myeloablative preparative regimen. In this original Biologics Licensing Application (BLA), Orca Biosystems Inc. submitted efficacy and safety results from one study, Precision-T, to support the proposed indication.

Precision-T was a multicenter, Phase 1b/3 study evaluating Orca-T in participants with advanced hematologic malignancies undergoing myeloablative conditioning-allogeneic

hematopoietic cell transplantation (MAC-alloHCT). The phase 3 component of the study serves as the primary evidence of efficacy and safety and the focus of this review memo.

The Phase 3 component was a randomized, open-label, multicenter study designed to compare the outcomes between participants who received Orca-T followed by single-agent tacrolimus or standard of care (SoC) allograft followed by GVHD prophylaxis with tacrolimus and methotrexate. Participants were randomized in a 1:1 ratio to receive Orca-T or SoC. Randomization was stratified by donor type and Disease Risk Index (DRI) risk category. A total of 187 patients were randomized (93 Orca-T; 94 SoC).

The primary endpoint was chronic GVHD-free survival (cGFS), defined as the time from hematopoietic cell transplantation (HCT) to the earliest occurrence of either death from any cause or the first onset of moderate or severe cGVHD, within 2 years after Day 0. The stratified Cox proportional hazards model yielded a hazard ratio (HR) of 0.26 (95% CI: 0.14, 0.47), and the stratified log-rank test was statistically significant ($P < 0.00001$; prespecified $\alpha=0.0464$), demonstrating a statistically significant improvement in cGFS for Orca-T compared with SoC. The median cGFS was not reached in the Orca-T group, whereas it was 7.3 months (95% CI: 6.3, 15.5) in the SoC group.

Three key secondary endpoints were included in the hierarchical testing: time to moderate/severe chronic GVHD (cGVHD), overall survival (OS), and GVHD-free/relapse-free survival (GRFS). Orca-T showed a statistically significant reduction in the incidence of moderate or severe cGVHD, compared to SoC group (HR=0.19; 95% CI: 0.08, 0.43; $P=0.00002$). The interim analysis of OS did not demonstrate statistical significance; therefore, in accordance with the pre-specified hierarchical testing procedure, GRFS was not formally tested at the interim analysis.

Safety outcomes were generally favorable. Mortality during the study period was lower with Orca-T compared with SoC (8% vs. 16%). Serious adverse events (SAEs) occurred less frequently in the Orca-T arm than in the SoC arm (39% vs. 56%). All participants in both arms experienced at least one adverse event (AE); of these, grade ≥ 3 AEs occurred in 80 participants (91%) in the Orca-T arm and 92 participants (98%) in the SoC arm.

Secondary malignancies occurred in 1.1% of participants in the Orca-T arm (one grade 3 testicular cancer) versus 2.1% in the SoC arm (one grade 1 neuroendocrine tumor and one grade 3 testicular cancer). Grade ≥ 3 infections were reported in 44.3% of the Orca-T arm versus 51.1% of the SoC arm. Graft failure occurred in 1.1% of the Orca-T arm versus 0% of the SoC arm, while thrombotic microangiopathy (TMA) occurred in 0% of the Orca-T arm versus 1.1% of the SoC arm. Veno-occlusive disease (VOD)/sinusoidal obstruction syndrome (SOS) rates were 3.4% in the Orca-T arm versus 2.1% in the SoC arm.

I have verified the primary efficacy and key secondary efficacy analyses results for the phase 3 portion of Precision-T. The statistical evidence supports the approval of Orca-T for treatment of adult patients with hematologic malignancies to improve survival free of GVHD in conjunction with a myeloablative preparative regimen.

2. Clinical and Regulatory Background

2.1 Disease or Health-Related Condition(s) Studied

The disease conditions studied involve high-risk hematological malignancies that require MAC-alloHCT as a standard treatment approach. While MAC-alloHCT represents a potentially curative therapy, its clinical utility is significantly limited by several life-threatening complications, most notably GVHD and opportunistic infections. The current therapeutic landscape demonstrates substantial room for improvement, with 5-year survival rates ranging from 20% to 60% depending on donor type and disease characteristics. The leading causes of mortality following allogeneic transplantation from HLA-matched donors include disease relapse occurring in 29% to 57% of cases, infections in 11% to 19%, GVHD in 8% to 10%, and organ failure in 8% to 19% of patients.

2.2 Currently Available, Pharmacologically Unrelated Treatment(s)/Intervention(s) for the Proposed Indication(s)

Allogeneic hematopoietic cell transplantation (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.

2.4 Previous Human Experience with the Product (Including Foreign Experience)

The preliminary safety and efficacy of TREGZI has been explored in Study (b) (4) (IND (b) (4)), a Phase I/II trial examining the safety and efficacy of using TREGZI in place of a standard alloHCT. Preliminary clinical data on 21 subjects treated with TREGZI suggested that TREGZI might have the potential to meaningfully reduce the toxicity and mortality associated with alloHCT while preserving its therapeutic effect.

Up to approximately 227 participants were enrolled across all disease types in the phase 1b portion of Precision-T, a multicenter, single-arm study designed to characterize the safety and efficacy of Orca-T in adults aged 18 to 75 years with advanced hematologic malignancies undergoing MAC-alloHCT. Participants who were not eligible for the phase 3 portion of the study or enrolled before protocol version 6.0 were included in the phase 1b.

2.5 Summary of Pre- and Post-submission Regulatory Activity Related to the Submission

Major regulatory history with key statistical related issues is summarized as follows:

- On February 15, 2024, a Type B meeting was held to gain alignment with the agency on key aspects of the phase 3 Statistical Analysis Plan (SAP). The primary endpoint was originally specified as the time from randomization to the earliest occurrence of death from any cause or the first onset of chronic GVHD within 2 years after randomization. FDA noted that events occurring in participants who never undergo transplantation are less important and may

confound interpretation of the primary endpoint. Accordingly, FDA recommended revising the definition to include events only from the time of HCT. The Sponsor revised the endpoint to cGFS, defined as the time from HCT to death from any cause or the first onset of moderate or severe chronic GVHD, whichever occurs first, within 2 years after randomization. FDA confirmed this revised definition as acceptable.

Additionally, the hierarchical testing strategy for the secondary endpoints was specified in the following order: GRFS, time to moderate to severe chronic GVHD, non-relapse mortality (NRM), OS, and relapse-free survival (RFS). FDA noted that endpoints such as GRFS, RFS, and NRM are currently not used as endpoints to support approval for a GVHD indication and therefore recommended that these endpoints be evaluated as exploratory endpoints. RFS and NRM were moved to exploratory endpoints, while GRFS was repositioned after time to moderate to severe chronic GVHD in the hierarchy. The revised testing hierarchy was therefore time to moderate to severe chronic GVHD, GRFS, and OS.

- On August 7, 2024, FDA sent an information request regarding the SAP version 3.0, dated March 22, 2024. FDA reiterated their February 2024 recommendation that the primary endpoint definition of chronic GVHD-free survival should start from the time of HCT rather than randomization to avoid confounding from events in patients who never undergo transplantation, and the Sponsor agreed to update the cGFS definition to measure time from HCT to death or moderate/severe chronic GVHD while censoring non-transplanted patients at randomization.

Regarding missing chronic GVHD assessments, FDA disagreed with the Sponsor's proposed approach of disregarding single missing assessments and censoring only after 2 or more consecutive missing assessments, arguing this could inflate event-free time since chronic GVHD could occur during missed assessment periods, and instead recommended using the last non-missing assessment plus 1 day as the event time for patients who later develop chronic GVHD, which the Sponsor accepted and agreed to implement for any pattern of missing assessments.

For general censoring rules, the Sponsor had proposed "Participants who received HSCT (either SoC or Orca-T) but have no cGVHD assessment after randomization will be censored at randomization except that a death within 100 + 7a days after day 0 will be counted as an event if the participant has not ended active participation prior to the death. That is, deaths after 2 consecutive missing cGVHD assessments will not be counted as events, while deaths prior to the first scheduled cGVHD assessment and deaths after only 1 missing scheduled cGVHD assessment will be counted as events if the participant has not ended active participation prior to the death." The FDA did not agree with the Sponsor's proposal to include survival components for some patients while censoring others based on consecutive missing assessments, recommending instead that such

patients be censored at HCT or last known assessment. This prompted the Sponsor to propose two alternative approaches for handling death events after a missing assessment. The FDA recommended the latter of these two approaches (consider the death event to have occurred 1 day after the last cGVHD assessment prior to the first missing cGVHD assessment). The Sponsor revised the SAP accordingly and indicated that deaths within 56 + 3 days after day 0 will be counted as an event since no cGVHD assessment is scheduled prior to the visit of day +56, which the FDA found acceptable.

Finally, FDA recommended repositioning overall survival above GVHD-free relapse-free survival in the hierarchical testing strategy since OS is more clinically relevant and used in regulatory decision-making for GVHD indications compared to GRFS, and the Sponsor agreed to this reordering while retaining GRFS as a secondary endpoint after OS for potential inclusion in future EU marketing authorization applications.

- On November 27, 2024, FDA sent an information request regarding the Precision-T Phase 3 SAP v4.0 Memo dated October 21, 2024, addressing concerns about proposed changes to the statistical testing approach for the primary efficacy endpoint. The original study design included a planned interim efficacy analysis at 37 cGFS events per the Event Adjudication Committee (EAC) and a final analysis at 56 cGFS events per the EAC, with pre-specified alpha allocation of 0.0116 for the interim analysis and 0.0464 for the final primary efficacy analysis. 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, while data cleaning for the interim analysis was still ongoing. Due to this accelerated event rate, the Sponsor proposed to forego the interim analysis and test the primary efficacy endpoint at a two-sided alpha level of 0.05. However, FDA did not agree with the Sponsor's proposal to allocate a two-sided alpha level of 0.05 for the primary efficacy analysis at the time of the final analysis and instead requested that the Sponsor conduct the final analysis using the originally pre-specified two-sided alpha level of 0.0464 from SAP version 4.0. The Sponsor agreed to FDA's request and committed to conducting the primary analysis for cGFS at the originally pre-specified two-sided alpha level of 0.0464.

3. SUBMISSION QUALITY AND GOOD CLINICAL PRACTICES

3.1 Submission Quality and Completeness

The submission was adequately organized for conducting a complete statistical review without unreasonable difficulty.

3.2 Compliance With Good Clinical Practices And Data Integrity

There were no issues with data integrity identified when conducting data analyses.

5.1 Review Strategy

For this review, the phase 3 component of the Precision-T study constitutes the primary source of evidence for safety and efficacy of Orca-T.

5.2 BLA/IND Documents That Serve as the Basis for the Statistical Review

The documents considered for statistical review include:

- Submission in BLA 125868/0 (original submission)
 - Module 1.2 Cover Letters
 - Module 1.6 Meetings
 - Module 1.14 Labeling
 - Module 2.5 Clinical Overview
 - Module 2.7 Clinical Summary
 - Module 5 Clinical Study Reports
 - Module 5.3.5.1 Datasets
- Submission in BLA 125868/9
 - Module 5.3.5.1 Precision-T Phase 3 – Swimmer Plot Figures Related to the Censoring of cGFS
- Submission in BLA 125868/11
 - Module 1.11.3 Clinical Information Amendment-Response to Statistical IR#1
- Submission in BLA 125868/29
 - Module 1.11.3 Clinical Information Amendment-Response to Statistical IR#2

5.3 Table of Studies/Clinical Trials

Table 1 provides an overview of the phase 3 component of the Precision-T study.

Table 1: Overview of the phase 3 component of the Precision-T study

Study Name	Trial Design	Number of Subjects	Study Population	Study Objective(s)

Precision-T (phase 3 component)	Randomized, open-label, multicenter study	Orca-T: 93 SoC: 94	Participants aged 18 to 65 years with acute leukemia (myeloid, lymphoid, or mixed phenotype) in complete remission (CR) or complete remission with incomplete hematologic recovery (CRi), or with myelodysplastic syndrome (MDS) eligible for transplantation according to the 2017 International Expert Panel recommendations, including therapy-related or secondary MDS.	<u>Primary:</u> • To compare rates of cGFS between participants eligible for alloHCT who received either Orca-T followed by single-agent tacrolimus or a control consisting of SoC unmanipulated allograft followed by tacrolimus plus methotrexate <u>Secondary:</u> • To compare time to moderate or severe cGVHD between participants undergoing alloHCT with either Orca-T or SoC • To compare OS between participants undergoing alloHCT with either Orca-T or SoC • To compare GRFS up to 2 years between participants undergoing alloHCT with either Orca-T or SoC
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Source: Adapted from BLA 125868/0; Module 5.2 Tabular Listing of All Clinical Studies.

6. DISCUSSION OF INDIVIDUAL STUDIES/CLINICAL TRIALS

6.1 Precision-T

The protocol for Precision-T was titled “A Phase Ib/Randomized Phase III Trial of Patients with Advanced Hematologic Malignancies Undergoing Allogeneic Hematopoietic Cell Transplantation with Either Orca-T, a T-cell-Depleted Graft with

Additional Infusion of Conventional T cells and Regulatory T cells or Standard-of-Care Allogeneic Graft.”

There were nine versions of the protocol and four versions of the statistical analysis plan (SAP). Please see Table A1 in the Appendix for the SAP version history. In this section, I highlight the important changes between the different versions.

6.1.1 Objectives

Primary Efficacy Objective:

1. To compare survival free of moderate-to-severe cGVHD between participants eligible for alloHCT who received either Orca-T followed by single-agent tacrolimus or a control consisting of SoC unmanipulated allograft followed by tacrolimus plus methotrexate.

Secondary Efficacy Objectives:

1. To compare time to moderate or severe cGVHD between participants undergoing alloHCT with either Orca-T or SoC.
2. To compare overall survival (OS) between participants undergoing alloHCT with either Orca-T or SoC.
3. To compare graft-versus-host disease (GVHD)-free and relapse-free survival (GRFS) up to 2 years between participants undergoing alloHCT with either Orca-T or SoC.

6.1.2 Design Overview

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. The phase 1b component was a single-arm study to characterize the safety and efficacy of Orca-T. The phase 3 component was a randomized, open-label study. Participants enrolled onto the phase 3 component were randomized in a 1:1 ratio to receive either Orca-T or SoC allogeneic graft. The planned enrollment was approximately 174 patients. Randomization was stratified by donor type (human leukocyte antigen [HLA] matched sibling donor [MSD] vs. matched unrelated donor [MUD]) and DRI category (intermediate vs. high risk). The phase 3 component, summarized below, serves as the primary evidence of efficacy and safety.

6.1.3 Population

Key eligibility criteria are described below.

Selected inclusion criteria (recipient):

- Planned to undergo MAC-alloHCT with a MAC regimen: total body irradiation (TBI), TBI/etoposide, or busulfan/fludarabine/thiotepa (BFT)
- Matched to a donor by either of the following:
 - MSD who was an 8/8 match for HLA-A, -B, -C, and -DRB1, all typed using DNA-based high-resolution methods

- MUD who was an 8/8 match at HLA-A, -B, -C, and -DRB1, all typed using DNA-based high-resolution methods
 - Aged ≥ 18 and ≤ 65 years (i.e., from age 18 to <66 years old) at the time of enrollment
 - Diagnosed with 1 of the following histopathologically confirmed diseases:
 - Acute myeloid, lymphoid or mixed phenotype/undifferentiated leukemia in CR or CRi, with or without the presence of known minimal residual disease.
 - MDS that was either of the following:
 - Indicated for alloHCT per the 2017 International Expert Panel recommendations
 - Diagnosed with therapy-related/secondary MDS as defined by the World Health Organization (WHO) classification of myeloid malignancies.
- For MDS, enrollment was limited to participants with $\leq 10\%$ blast burden in the bone marrow based on a bone marrow biopsy performed during screening.
- DRI overall risk categorization of intermediate or high

Selected exclusion criteria (recipient):

- Prior alloHCT
- Positive antidonor HLA antibodies against a mismatched allele in the selected donor determined by either of the following:
 - Positive crossmatch test of any titer (by complement-dependent cytotoxicity or flow cytometric testing) to any of the following HLA loci (if mismatched): HLA-A, -B, -C, -DRB1, -DQB1, -DQA1, -DPB1, or -DPA1
 - Presence of antidonor HLA antibody to any of the following HLA loci (if mismatched): HLA-A, -B, -C, -DRB1, -DQB1, -DQA1, -DPB1, or -DPA1 with mean fluorescence intensity (MFI) >1000 by solid phase immunoassay
- Karnofsky performance score $<70\%$
- HCT-Specific Comorbidity Index (HCT-CI) >4
- 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
- Women who were pregnant or breastfeeding

6.1.4 Study Treatments or Agents Mandated by the Protocol

Treatment

Orca-T: includes hematopoietic stem and progenitor cells (HSPC), regulatory T cells (Treg), and conventional T cells (Tcon). The Orca-T HSPCs and Tregs were administered

intravenous (IV) through a central venous catheter on day 0. Orca-T Tcons were to be infused between 48 and 72 hours after the start of HSPC infusion.

Table 2: Orca-T treatment description

Orca-T Component:	Dose Regimen	Intended Use
HSPC	IV, entire bag, once, on day 0	hematopoietic reconstitution
T _{reg}	IV, entire bag, once, on day 0	GVHD control
T _{con}	IV, entire bag, once, 48 to 72 hours after the start of HSPC infusion (typically day +2)	immune reconstitution

Source: BLA 125868/0; Precision-T Protocol Version 9.0, Page 15.

SoC: includes unmanipulated allograft derived from granulocyte colony-stimulating factor (G-CSF) mobilized donor peripheral blood stem cell (PBSCs), administered IV through a central venous catheter on day 0.

GVHD Prophylaxis

Orca-T: single-agent tacrolimus starting on the day after Tcon infusion (typically day +3)

SoC: dual-agent prophylaxis consisting of tacrolimus plus methotrexate starting on day -3

6.1.6 Sites and Centers

This study was conducted at 19 study centers in the continental United States.

6.1.7 Surveillance/Monitoring

An independent data monitoring committee (DMC) regularly reviewed safety data. The DMC was composed of four members (including the DMC Chair) who did not have any conflict of interests with Orca Bio.

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.

6.1.8 Endpoints and Criteria for Study Success

Primary Efficacy Endpoint:

1. cGFS, defined as the time from HCT to the earliest occurrence of either death from any cause or the first onset of moderate or severe cGVHD, within 2 years after Day 0.

Secondary Efficacy Endpoints:

1. Time to moderate or severe cGVHD: 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 will be treated as a competing event.
2. OS: defined as the time from randomization to death from any cause.
3. GRFS up to 2 years: defined as the time from HCT to the earliest occurrence of death from any cause, relapse, first onset of grade 3 or 4 acute GVHD (aGVHD), or first onset of moderate or severe cGVHD, within 2 years after Day 0.

Reviewer's Comment:

The primary endpoint was originally specified as the time from randomization to the earliest occurrence of death from any cause or the first onset of cGVHD within 2 years after randomization. FDA noted that events (e.g., death) occurring in participants who never undergo transplantation are less scientifically relevant and may confound interpretation of the primary endpoint. Accordingly, FDA recommended revising the definition to include events only from the time of HCT. The applicant revised the endpoint to chronic GVHD-free survival (cGFS), defined as the time from HCT to death from any cause or the first onset of moderate or severe cGVHD, whichever occurs first, within 2 years after randomization. FDA confirmed this revised definition as acceptable.

6.1.9 Statistical Considerations & Statistical Analysis Plan

Treatment Assignment:

Subjects were randomized in a 1:1 ratio to either the Orca-T or SoC arm. Randomization was stratified by donor type (HLA-MSD versus HLA-MUD) and DRI risk category (intermediate risk or high risk).

Statistical Hypotheses:

Primary Endpoint (cGFS per EAC Assessment)

The null and alternative statistical hypotheses for the primary efficacy endpoint are as follows:

$$H_0: \text{HRCGFS} = \Delta\text{CGFS}(\text{ORCA-T})(t) / \Delta\text{CGFS}(\text{SOC})(t) = 1$$

$$H_A: \text{HRCGFS} = \Delta\text{CGFS}(\text{ORCA-T})(t) / \Delta\text{CGFS}(\text{SOC})(t) \neq 1,$$

where HRCGFS= Hazard ratio for cGFS, $\Delta\text{CGFS}(\text{ORCA-T})(t)$ = Hazard rate of cGFS for Orca-T, and $\Delta\text{CGFS}(\text{SOC})(t)$ = Hazard rate of cGFS for SOC.

Secondary Endpoints:

Secondary Endpoint 1 (Time to Moderate or Severe cGVHD per EAC)

$$H_0: \text{HRCSFS} = \Delta\text{CSFS}(\text{ORCA-T})(t) / \Delta\text{CSFS}(\text{SOC})(t) = 1$$

$$H_A: \text{HRCSFS} = \Delta\text{CSFS}(\text{ORCA-T})(t) / \Delta\text{CSFS}(\text{SOC})(t) \neq 1,$$

where HRCFSFS= Cause-specific hazard ratio for moderate to severe cGVHD,
 $\Delta\text{CSFS}(\text{ORCA-T})(t)$ = Cause-specific hazard rate of moderate or severe cGVHD for Orca-T, and $\Delta\text{CSFS}(\text{SOC})(t)$ = Cause-specific hazard rate of moderate or severe cGVHD for SOC.

Secondary Endpoint 2 (Overall Survival)

H_0 : $\text{HROS} = \Delta\text{OS}(\text{ORCA-T})(t) / \Delta\text{OS}(\text{SOC})(t) = 1$
 H_A : $\text{HROS} = \Delta\text{OS}(\text{ORCA-T})(t) / \Delta\text{OS}(\text{SOC})(t) \neq 1$,

where HROS= Hazard ratio for OS, $\Delta\text{OS}(\text{ORCA-T})(t)$ = Hazard rate of OS for Orca-T, and $\Delta\text{OS}(\text{SOC})(t)$ = Hazard rate of OS for SOC.

Secondary Endpoint 3 (GRFS per EAC)

H_0 : $\text{HRGRFS} = \Delta\text{GRFS}(\text{ORCA-T})(t) / \Delta\text{GRFS}(\text{SOC})(t) = 1$
 H_A : $\text{HRGRFS} = \Delta\text{GRFS}(\text{ORCA-T})(t) / \Delta\text{GRFS}(\text{SOC})(t) \neq 1$,

where HRGRFS= Hazard ratio for GRFS, $\Delta\text{GRFS}(\text{ORCA-T})(t)$ = Hazard rate of GRFS for Orca-T, and $\Delta\text{GRFS}(\text{SOC})(t)$ = Hazard rate of GRFS for SOC.

Statistical Methods

Primary Endpoint (cGFS per EAC)

A 2-sided stratified log-rank test stratified by the randomization factors was used to compare cGFS per EAC between the Orca-T group the SoC group. The HR with a 95% CI was estimated from a stratified Cox regression model stratified by the randomization factors.

Secondary Endpoint 1 (Time to Moderate or Severe cGVHD per EAC)

A 2-sided stratified Gray's test stratified by the randomization factors was used to compare time to moderate or severe cGVHD per EAC between the Orca-T group the SoC group. The HR with a 95% CI was estimated from the stratified subdistribution proportional hazards model stratified by randomization stratification factors.

Secondary Endpoint 2 (Overall Survival)

A 2-sided stratified log-rank test stratified by the randomization factors was used to compare OS between the Orca-T group the SoC group. The HR with a 95% CI was estimated from a stratified Cox regression model stratified by the randomization factors.

Secondary Endpoint 3 (GRFS per EAC)

A 2-sided stratified log-rank test stratified by the randomization factors was used to compare GRFS per EAC between the Orca-T group the SoC group. The HR with a 95% CI was estimated from a stratified Cox regression model stratified by the randomization factors.

Sample Size Estimation:

To achieve 90% power with a true HR = 0.40 and 1-sided alpha of 0.025, the required number of events needed was 56 events. The 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 was 165 participants. To account for 5% loss to follow-up in both treatment groups, 174 participants were to be randomized.

Interim analyses planned

The interim and primary analyses for each secondary endpoint, if tested, were planned as described in Figure 1 below.

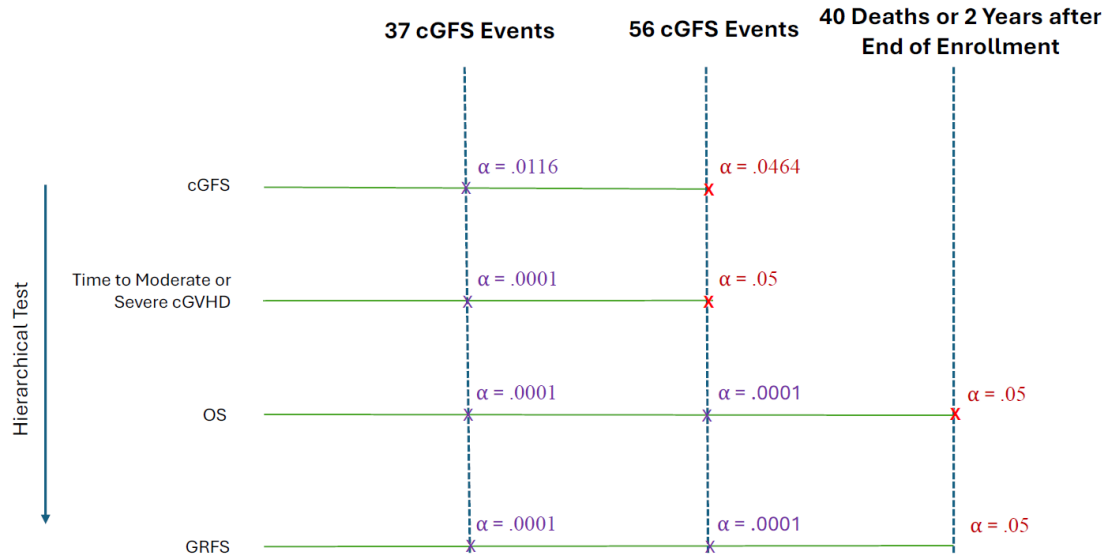
A single interim analysis was planned to assess the primary endpoint, cGFS, when 37 primary endpoint (cGFS) events per EAC had been observed. This represented two-thirds of the expected 56 primary efficacy events at the time of the primary analysis. The efficacy boundary for cGFS was based on the Lan–DeMets spending function to approximate an O’Brien–Fleming boundary to control the overall 2-sided alpha of .05. The critical 2-sided P value corresponding to this spending function was .0116 for the interim analysis and .0464 for the primary analysis. Due to the EAC review process, more than 37 or 56 events could have been included for the respective analysis. If more than 37 or 56 events were used for the analysis, the efficacy boundaries were to be adjusted correspondingly using the alpha spending function.

A single interim analysis was planned to assess the first secondary endpoint, time to moderate or severe cGVHD per EAC, when 37 primary endpoint (cGFS) events per EAC had been observed. The primary analysis of time to moderate or severe cGVHD per EAC was planned when 56 primary endpoint (cGFS) events per EAC had been observed.

Two interim analyses were planned to assess the other secondary endpoints, OS and GRFS: when 37 primary endpoint (cGFS) events per EAC had been observed and when 56 primary endpoint (cGFS) events per EAC had been observed. The primary analysis for OS and GRFS was to be performed when 40 deaths had been observed or 2 years after the end of enrollment, whichever was earlier.

For all secondary endpoints, a generalized Haybittle–Peto boundary was to be used between the interim and primary analyses. That is, the critical value for the P value at each of the interim analyses was 2-sided .0001, while the critical value at the primary analysis remained a 2-sided .05.

Figure 1: Planned Interim and Primary Analyses of Primary and Secondary Endpoints



Source: BLA 125868/0; Module 5.3.5.1, Precision-T Phase 3 Clinical Study Report, Figure 1

Reviewer's Comment:

cGFS events accrued more rapidly than the applicant had initially anticipated. By 15 July 2024, more than 56 cGFS events (approximately 60) had been identified by investigators while data cleaning for the interim analysis was ongoing. The applicant therefore proposed to forgo the interim analysis and proceed directly to the primary analysis, applying a two-sided alpha level of 0.05 for the primary efficacy analysis in place of the adjusted alpha that would have been used had the interim analysis been conducted. The FDA did not agree with the applicant's proposal to use a two-sided alpha of 0.05 and asked that the final analysis be conducted at the pre-specified two-sided alpha level of 0.0464, as outlined in SAP Version 4.0. The applicant agreed to conduct the primary analysis for cGFS at this originally pre-specified alpha level.

Multiplicity Adjustment:

Statistical testing of the primary and secondary endpoints followed a hierarchical testing structure. First the primary endpoint of cGFS per EAC was to be tested. If the primary endpoint was significant, secondary endpoints were to be tested sequentially in the order as described in Section 6.1.8.

Analysis Populations:

Intent-to-treat population (ITT): All enrolled participants who are randomized to either Orca-T or SoC, regardless of whether they receive Orca-T/SoC or not. Participants will

be analyzed according to their randomized treatment assignment. Analyses of the primary and secondary efficacy endpoints were based on the ITT population.

Per-protocol population: All participants in the ITT analysis set who meet all inclusion/exclusion criteria, receive their randomized treatment, and do not experience any important protocol deviations that may affect evaluation of the efficacy of the treatment.

Safety population: Participants in the ITT analysis set who have received either Orca-T or SoC from donors who are 8/8 match for HLA-A, -B, -C, and -DRB1, analyzed according to the treatment received.

Sensitivity Analyses:

Several sensitivity and supplementary analyses were performed. These analyses differ from the primary estimand in one or more of the following aspects:

- The per-protocol analysis set was used instead of the ITT analysis set.
- For GVHD related endpoints, assessments per investigator were used instead of assessments per EAC.
- Unstratified analyses were performed instead of stratified analyses.
- Hypothetical policy was used instead of treatment policy to handle intercurrent events.
- Different approaches were used when there were events of interest or a competing event following consecutive missing assessments.

Subgroup Analyses:

Several prespecified subgroup analyses were performed as per the SAP. These include:

- 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)

General Censoring Rules:

Primary Endpoint (cGFS):

- Participants who received HCT and are alive and free from moderate or severe cGVHD will be censored at the last documented absence of moderate or severe cGVHD.
- Participants who received HCT but have no cGVHD assessment after day 0 will be censored at day 0 except that a death within 56 + 3 days after day 0 will be counted as an event since no cGVHD assessment is scheduled prior to the visit of day +56.
- Participants who do not receive HCT will be censored at randomization with a hypothetical day 0 added at randomization.

Secondary Endpoint 1 (Time to Moderate or Severe cGVHD):

- Participants who received HCT, and are still alive, and have not experienced moderate or severe cGVHD will be censored at the last documented absence of moderate or severe cGVHD.
- Participants who received HCT but have no cGVHD assessment after day 0 will be censored at day 0 except that a death within 56 + 3 days after day 0 will be counted as a competing event since no cGVHD survey is scheduled prior to the visit of day +56.
- Participants who do not receive HCT will be censored at randomization with a hypothetical day 0 added at randomization.

Secondary Endpoint 2 (OS):

- Participants who are alive will be censored at the date last known to be alive.

Secondary Endpoint 3 (GRFS up to 2 Year):

- Participants who receive HCT and are alive and free from disease relapse, grade 3 or 4 aGVHD, and moderate or severe cGVHD will be censored at the latest one of the following: the last documented absence of grade 3 or 4 aGVHD, or moderate or severe cGVHD, or the last disease assessment.
- Participants who do not receive HCT will be censored at randomization with a hypothetical day 0 added at randomization.

Handling of Missing Assessments:

Primary Endpoint (cGFS):

- A participant will be censored at the last cGVHD assessment prior to the first missing cGVHD assessment if no cGFS event (moderate or severe cGVHD, or death) has occurred up to the data cutoff date.
- A participant will be considered to have an event at one day after the last cGVHD assessment prior to the first cGVHD missing assessment if the first onset of cGFS event (moderate or severe cGVHD, or death) is after the first cGVHD missing assessment.

Secondary Endpoint 1 (Time to Moderate or Severe cGVHD):

- A participant will be censored at the last cGVHD assessment prior to the first missing cGVHD assessment if neither event (moderate or severe cGVHD) or competing event (death) occurs up to the data cutoff date.
- A participant will be considered to have an event at one day after the last cGVHD assessment prior to the first cGVHD missing assessment if the first onset of moderate or severe cGVHD is after the first cGVHD missing assessment.
- A participant will be considered to have a competing event at one day after the last cGVHD assessment prior to the first cGVHD missing assessment if no moderate or severe cGVHD occurs prior to the death and the death is after the first cGVHD missing assessment.

Secondary Endpoint 2 (OS):

Missing assessments will be disregarded, and all available data will be used for the derivation of OS.

Secondary Endpoint 3 (GRFS up to 2 Year):

Missing assessments will be disregarded, and all available data (including all assessments and/or events after the missing assessments) will be included for the derivation of GRFS.

Reviewer's comment:

FDA did not agree with the proposed handling of missing assessments, as communicated previously. However, the applicant did not incorporate FDA's suggestion for this endpoint. We note that this endpoint would not be used for regulatory decision-making.

6.1.10 Study Population and Disposition

6.1.10.1 Populations Enrolled/Analyzed

Table 3 summarizes the analysis populations. A total of 187 subjects were randomized to receive either Orca-T (n=93) or SoC (n=94). Of the 93 participants randomized to Orca-T, 89 participants were treated. One participant developed COVID-19 on the scheduled treatment day and subsequently received a cryopreserved SoC alloHCT instead of Orca-T. Thus, 88 participants (94.6%) received all three Orca-T infusions. Four additional participants randomized to Orca-T did not receive an Orca-T infusion as of the data cutoff date: two withdrew consent prior to receiving Orca-T, one relapsed after randomization and did not enter remission, and one received Orca-T after the data cutoff date (15 July 2024).

Of the 94 participants randomized to SoC, 93 participants (98.9%) received the intended unmanipulated allograft and one received an allograft derived from a haploidentical donor. One participant originally randomized to Orca-T developed COVID-19 on the scheduled treatment day and subsequently received a cryopreserved SoC alloHCT instead; this participant was included in the SoC group for the safety analysis set.

The per-protocol analysis set included 83 participants in the Orca-T group and 85 participants in the SoC group who met all eligibility criteria, received their randomized treatment, and did not experience any important protocol deviations. In the Orca-T group, four participants did not receive treatment, and six participants who received Orca-T had an important protocol deviation that may have affected efficacy evaluation. In the SoC group, all randomized participants received treatment; however, nine participants had an important protocol deviation that may have affected efficacy evaluation.

Table 3. Analysis populations

	Orca-T N = 93	SoC N=94
ITT analysis set, n (%)	93 (100.0)	94 (100.0)
Safety analysis set, n (%)	88 (94.6)	94 (100.0)
Per-protocol analysis set, n (%)	83 (89.2)	85 (91.4)

Source: Adapted from BLA 125868/0; Module 5.3.5.1, Precision-T Phase 3 Demographic Data Tables, Table 14.1.1.1

Abbreviations: N, number of subjects in the specified group; n (%), number of subjects with the specified characteristics

6.1.10.1.1 Demographics

Table 4 summarizes the demographic and baseline characteristics of the ITT population. Overall, baseline characteristics were generally balanced between the Orca-T and SoC treatment groups. A higher proportion of participants in the Orca-T group were White/Caucasian compared with the SoC group (81.7% vs 67.0%), while a larger

proportion of participants in the SoC group had race not reported (19.1% vs 4.3%). Other demographic characteristics, including age, sex, ethnicity, and donor–recipient sex match, were similar between treatment groups.

Table 4. Subject baseline characteristics (ITT population)

	Orca-T N = 93	SoC N=94
Age (Years)	-	-
N	93	94
Mean (SD)	43.4 (12.63)	43.8 (12.91)
Median	44.0	43.0
Q1, Q3	33.0, 54.0	33.0, 55.0
Min, Max	19, 65	20, 63
Age Group, n (%)	-	-
≥18 to <55	70 (75.3)	67 (71.3)
≥55 to ≤65	23 (24.7)	27 (28.7)
Sex, n (%)	-	-
Female	40 (43.0)	44 (46.8)
Male	53 (57.0)	50 (53.2)
Race, n (%)	-	-
American Indian or Alaska Native	1 (1.1)	2 (2.1)
Asian	10 (10.8)	8 (8.5)
Black or African American	1 (1.1)	2 (2.1)
Native Hawaiian or other Pacific Islander	1 (1.1)	1 (1.1)
White/Caucasian	76 (81.7)	63 (67.0)
Not reported	4 (4.3)	18 (19.1)
Ethnicity, n (%)	-	-
Hispanic or Latino	26 (28.0)	24 (25.5)
Not Hispanic or Latino	62 (66.7)	59 (62.8)
Not reported	5 (5.4)	11 (11.7)
Sex match between donor and recipient, n (%)	-	-
Matched	54 (58.1)	50 (53.2)
Mismatched	39 (41.9)	44 (46.8)
Female – Male	20 (21.5)	21 (22.3)
Male – Female	19 (20.4)	23 (24.5)

Source: Adapted from BLA 125868/0; Module 5.3.5.1, Precision-T Phase 3 Demographic Data Tables, Table 14.1.3.2

Abbreviations: N, number of subjects in the specified group; n (%), number of subjects with the specified characteristics; SD, standard deviation; Q1, first quartile; Q3, third quartile; Min, minimum; Max, maximum

6.1.10.1.2 Medical/Behavioral Characterization of the Enrolled Population

Baseline medical characteristics are summarized in Table 5. The distribution of primary disease was similar between treatment groups. In the Orca-T group, the primary disease was acute myeloid leukemia (AML) in 49 participants (52.7%), acute lymphoblastic leukemia (ALL) in 30 (32.3%), high-risk myelodysplastic syndrome (MDS) in 12 (12.9%), and mixed phenotype acute leukemia (MPAL) in 2 (2.2%). Corresponding proportions in the SoC group were 51 (54.3%) with AML, 27 (28.7%) with ALL, 11 (11.7%) with high-risk MDS, and 5 (5.3%) with MPAL.

Donor type was balanced across groups. In the Orca-T group, 46 participants (49.5%) received a matched sibling donor and 47 (50.5%) received a matched unrelated donor, compared with 49 (52.1%) and 45 (47.9%), respectively, in the SoC group.

Disease Risk Index (DRI) scores were also comparable between groups. In the Orca-T group, 19 participants (20.4%) were classified as high risk and 74 (79.6%) as intermediate risk, while in the SoC group, 16 (17.0%) were high risk and 78 (83.0%) were intermediate risk.

Overall, baseline disease and transplant characteristics were well balanced between the Orca-T and SoC groups.

Table 5. Medical Characteristics at Baseline

	Orca-T N = 93	SoC N=94
Primary disease, n (%)		
ALL	30 (32.3)	27 (28.7)
AML	49 (52.7)	51 (54.3)
High-risk MDS	12 (12.9)	11 (11.7)
MPAL	2 (2.2)	5 (5.3)
Donor type, n (%)		
Matched sibling donor	46 (49.5)	49 (52.1)
Matched unrelated donor	47 (50.5)	45 (47.9)
DRI score, n (%)		
High	19 (20.4)	16 (17.0)
Intermediate	74 (79.6)	78 (83.0)

Source: Adapted from BLA 125868/0; Module 5.3.5.1, Precision-T Phase 3 Clinical Study Report, Table 9

Abbreviations: ALL, acute lymphoid leukemia; AML, acute myeloid leukemia; MDS, myelodysplastic syndrome; MPAL, mixed phenotype acute leukemia; DRI, Disease Risk Index; N, number of subjects in the specified group; n (%), number of subjects with the specified characteristics

6.1.10.1.3 Subject Disposition

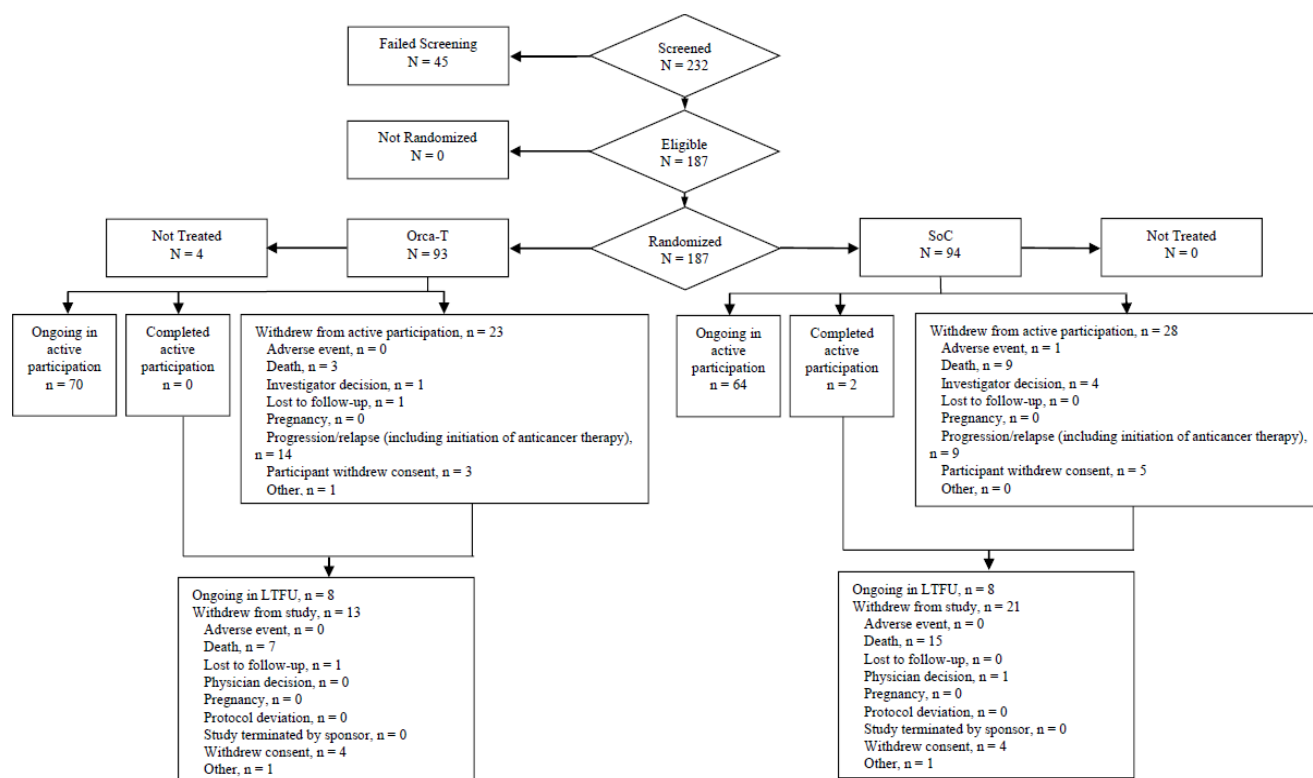
Participant disposition is summarized in Figure 2 below. A total of 187 subjects were randomized to receive either Orca-T (n=93) or SoC (n=94). Of those randomized to

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 (15 July 2024): two withdrew consent prior to receiving Orca-T, one relapsed after randomization and did not enter remission, and one received Orca-T after the data cutoff date. Of those randomized to receive SoC, 94 participants were treated, one of whom received an allograft derived from a haploidentical donor.

Among those in the Orca-T group, 70 participants (75%) were ongoing in active participation as of the data cutoff date (15 July 2024), 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), three (3%) due to death, three (3%) due to withdrawal of consent, one (1%) for other reasons (disease relapse prior to day 0 and did not enter remission), one (1%) who was lost to follow-up, and one (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 (15 July 2024), and two participants (2%) completed active participation. Twenty-eight participants (30%) withdrew from active participation prior to completion: nine (10%) due to disease progression/relapse, nine (10%) due to death, five (5%) due to withdrawal of consent, four (4%) due to investigator decision, and one (1%) due to an adverse event (AE) (upper gastrointestinal [GI] hemorrhage).

Figure 2: Participant Disposition



Source: BLA 125868/0; Module 5.3.5.1, Precision-T Phase 3 Clinical Study Report, Figure 2

6.1.11 Efficacy Analyses

6.1.11.1 Analyses of Primary Endpoint(s)

A 2-sided stratified log-rank test stratified by the randomization factors was used to compare cGFS per EAC between the Orca-T group the SoC group, and the HR with a 95% CI was estimated from a stratified Cox regression model. The analysis results showed that the estimated HR was 0.26 (95% CI: 0.14, 0.47) and the 2-sided P value was < 0.00001 , which is statistically significant per the prespecified critical value of 0.0464. The primary analysis of cGFS demonstrated a statistically significant improvement in cGFS for the Orca-T group compared with SoC.

Kaplan-Meier (KM) curves representing cGFS with cGVHD assessed by the independent EAC for the Orca-T and SoC groups are presented in Figure 3 below. The median cGFS was not reached in the Orca-T group, whereas it was 7.3 months (95% CI: 6.3, 15.5) in the SoC group. At 12 months, the KM estimate of cGFS was 78.0% (95% CI: 65.0%, 86.6%) for Orca-T compared with 38.4% (95% CI: 26.2%, 50.5%) for SoC.

Sensitivity analyses based on investigator-assessed chronic GVHD were consistent with the primary analysis. Using investigator assessment of cGVHD, the KM estimate of

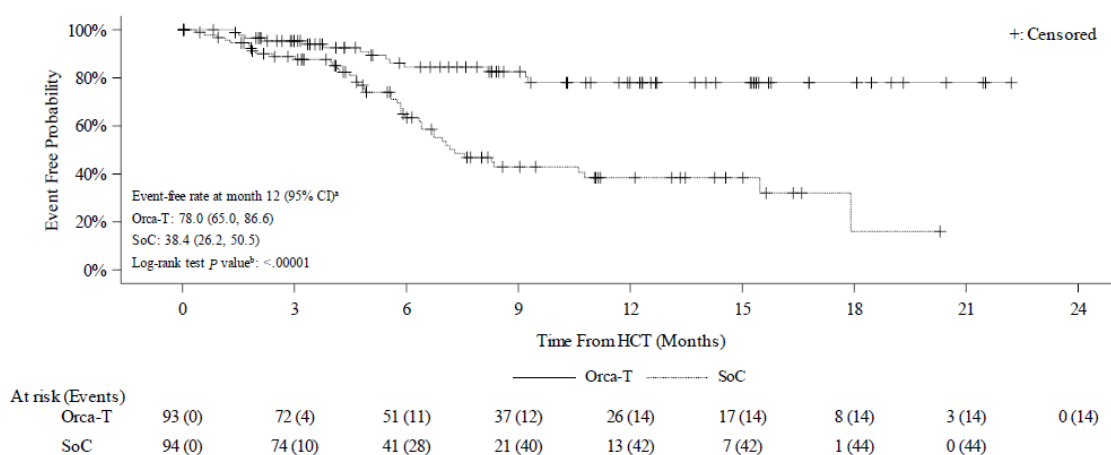
median cGFS was 21.6 (95% CI: not estimable, not estimable) months for the Orca-T group and was 6.4 (95% CI: 5.6, 9.3) months for the SoC group after median follow-up times of 8.48 (range: 0 to 21.6) months and 8.97 (range: 0 to 17.9) months, respectively. The KM cGFS estimates for Orca-T and SoC were 73.8% (95% CI: 60.0%, 83.5%) and 31.2% (95% CI: 19.5%, 43.6%), respectively, at 12 months.

Reviewer's comment:

We note that the KM estimate of median cGFS for Orca-T was estimable based on investigator-assessed cGVHD but not for cGVHD assessed by the independent EAC. This occurred because an investigator-assessed event occurred near the end of the study period, causing the survival curve to fall below 50%. By contrast, this event had not been confirmed by the EAC by the end of the study period.

Additional sensitivity and supplemental analyses as described in Section 6.1.9, including the per-protocol analysis set and unstratified analyses, supported the primary analysis results.

Figure 3: KM Plot of cGFS per EAC Assessment by Treatment Group (ITT Analysis Set)



Source: BLA 125868/0; Module 5.3.5.1, Precision-T Phase 3 Clinical Study Report, Figure 3

6.1.11.2 Analyses of Secondary Endpoints

Secondary Endpoint (Time to Moderate or Severe cGVHD):

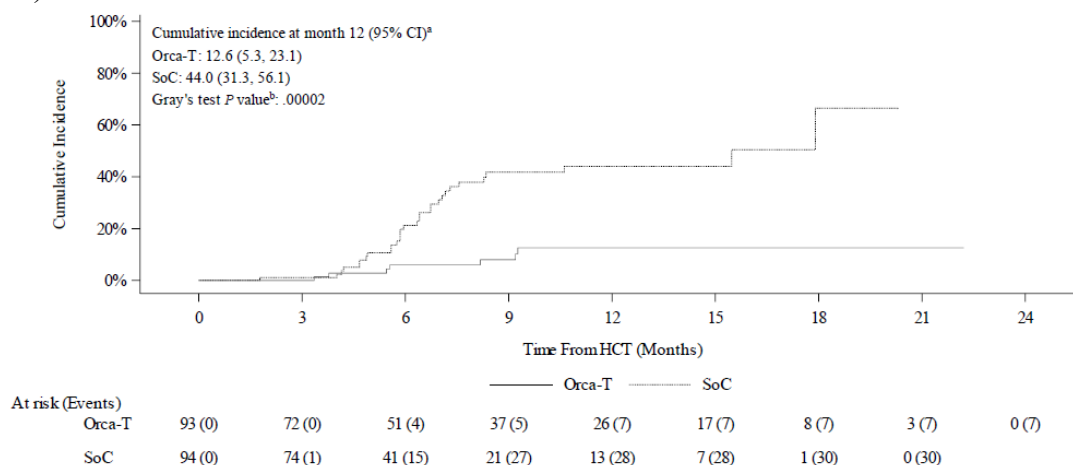
A 2-sided stratified Gray's test stratified by the randomization factors was used to compare time to moderate or severe cGVHD per EAC between the Orca-T group the SoC group, and the HR with a 95% CI was estimated from a stratified Cox regression model stratified by the randomization factors. The estimated HR was 0.19 (95% CI: 0.08,0.43) and the stratified Gray's test yielded a two-sided P value of 0.00002, which is statistically

significant. This analysis demonstrated a statistically significant reduction in the incidence of moderate or severe cGVHD in the Orca-T group compared to the SoC group.

A plot of the cumulative incidence of time to moderate or severe cGVHD for each arm is displayed in Figure 4 below. Overall, 7 participants (7.5%) in the Orca-T group and 30 participants (31.9%) in the SoC group had moderate or severe cGVHD. The cumulative incidence rate estimate at 12 months was 12.6% (95% CI: 5.3%, 23.1%) for Orca-T and 44.0% (95% CI: 31.3%, 56.1%) for SoC.

Results of the sensitivity and supplemental analyses as described in Section 6.1.9 support the primary analysis results.

Figure 4: Plot of Cumulative Incidence of Moderate or Severe cGVHD (ITT Analysis Set)



Source: BLA 125868/0; Module 5.3.5.1, Precision-T Phase 3 Clinical Study Report, Figure 5

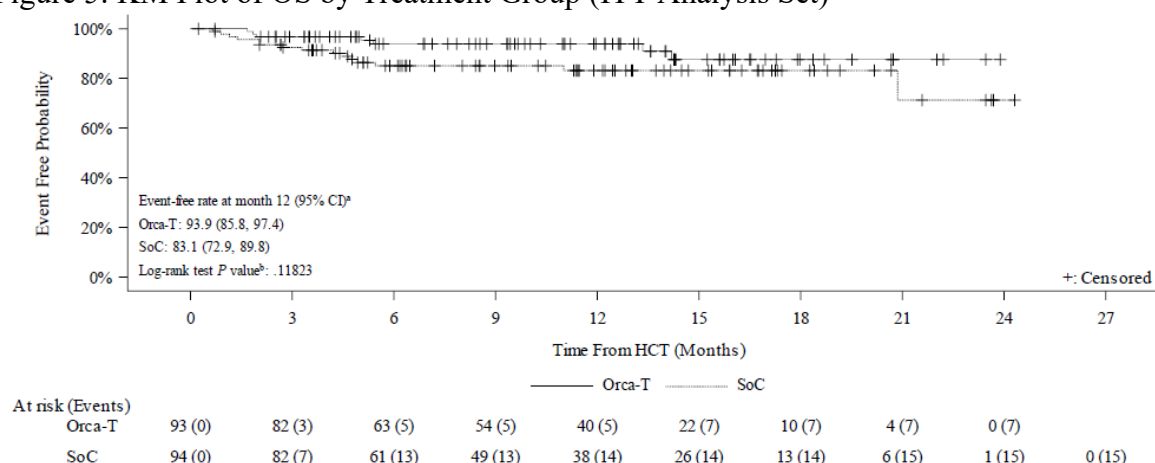
Secondary Endpoint (OS):

A 2-sided stratified log-rank test stratified by the randomization factors was used to compare OS between the Orca-T group the SoC group, and the HR with a 95% CI was estimated from a stratified Cox regression model stratified by the randomization factors.

The stratified log-rank test yielded a two-sided P value of 0.11823, which was not statistically significant. The estimated HR was 0.49 (95% CI: 0.20, 1.22). The current OS analysis is an interim analysis, and the primary analysis for OS is planned to be conducted later, when 40 participants have died or 2 years after the end of enrollment.

A plot of the KM curves for each arm is displayed in Figure 5 below. 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.

Figure 5: KM Plot of OS by Treatment Group (ITT Analysis Set)



Source: BLA 125868/0; Module 5.3.5.1, Precision-T Phase 3 Clinical Study Report, Figure 6

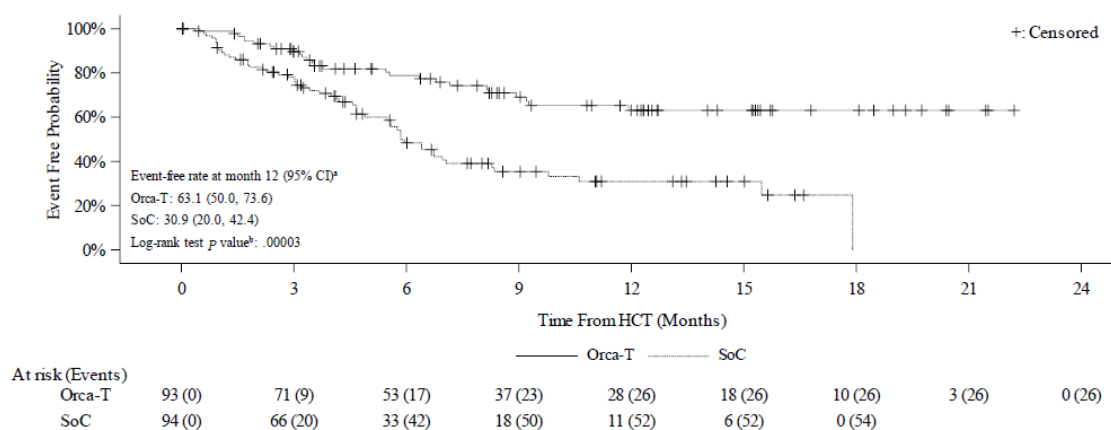
Secondary Endpoint (GRFS up to 2 Year):

A 2-sided stratified log-rank test stratified by the randomization factors was used to compare GRFS per EAC between the Orca-T group the SoC group, and the HR with a 95% CI was estimated from a stratified Cox regression model stratified by the randomization factors.

Because OS was not statistically significant, formal hypothesis testing of GRFS was not conducted per the hierarchical testing procedure as outlined in Section 6.1.9. The estimated HR was 0.37 (95% CI: 0.23, 0.60). Per the SAP, if the OS endpoint is met at the primary analysis, the primary analysis for GRFS will be conducted when 40 participants have died or 2 years after the end of enrollment, whichever is earlier.

A plot of the KM curves for each arm is displayed in Figure 6 below. The KM rate estimates for GRFS at 12 months were 63.1% (95% CI: 50.1%, 73.6%) for Orca-T and 30.9% (95% CI: 20.0%, 42.4%) for SoC.

Figure 6: KM Plot of GRFS by Treatment Group (ITT Analysis Set)



Source: BLA 125868/0; Module 5.3.5.1, Precision-T Phase 3 Clinical Study Report, Figure 7

6.1.11.3 Subpopulation Analyses

The magnitude of the treatment effect of Orca-T on the primary endpoint of cGFS was relatively consistent across all analyzed subgroups, including demographic factors of gender, race, and ethnicity, as well as DRI score, donor status (MSD vs. MUD), disease type (AML, ALL, and MDS), Hematopoietic Cell Transplantation-Comorbidity Index (HCT-CI) score, and conditioning regimens. For example, the HR for the DRI high risk subgroup was 0.73 (95% CI: 0.19, 2.80) and for the intermediate risk subgroup was 0.19 (95% CI: 0.09, 0.40). The HR for the MUD subgroup was 0.22 (95% CI: 0.09, 0.52) and for the MSD subgroup was 0.30 (95% CI: 0.13, 0.72). The HRs for the AML, ALL, and MDS subgroups were 0.29 (95% CI: 0.14, 0.62), 0.20 (95% CI: 0.04, 1.06), and 0.33 (95% CI: 0.06, 1.91), respectively. The HR for HCT-CI score group 1 (≤ 2) was 0.29 (95% CI: 0.14, 0.57) and for score group 2 (≥ 3) was 0.12 (95% CI: 0.02, 0.97). The HR for the total body irradiation (TBI)-based conditioning subgroup was 0.07 (95% CI: 0.01, 0.60) and for the busulfan, fludarabine, and thiotepea (BFT) subgroup was 0.33 (95% CI: 0.17, 0.64).

6.1.11.4 Dropouts and/or Discontinuations

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), three (3%) due to death, three (3%) due to withdrawal of consent, one (1%) for other reasons (disease relapse prior to day 0 and did not enter remission), one (1%) who was lost to follow-up, and one (1%) due to investigator decision.

Twenty-eight participants (30%) randomized to the SoC group withdrew from active participation prior to completion: nine (10%) due to disease progression/relapse, nine (10%) due to death, five (5%) due to withdrawal of consent, four (4%) due to investigator decision, and one (1%) due to an AE (upper GI hemorrhage).

6.1.12 Safety Analyses

6.1.12.3 Deaths

Seven participants (8.0%) in the Orca-T group and 15 participants (16.0%) in the SoC group died on study.

6.1.12.4 Nonfatal Serious Adverse Events

Serious adverse events (SAEs) were summarized by system organ class (SOC) and preferred term (PT). The most common SAEs by SOC in the Orca-T group were infections and infestations (twenty-two participants, 25%), immune system disorders (eight participants, 9%), and general disorders and administration site conditions (six participants, 7%). In the SoC group, the most common SAEs by SOC were infections and infestations (twenty-nine participants, 31%), immune system disorders (eighteen participants, 19%), and respiratory, thoracic, and mediastinal disorders (fourteen participants, 15%).

By PT, the most common SAEs in the Orca-T group were sepsis (seven participants, 8%), acute graft-versus-host disease (aGVHD) (six participants, 7%), and pyrexia (five participants, 6%), while in the SoC group they were aGVHD (twelve participants, 13%) and sepsis, pneumonia, and chronic graft-versus-host disease (cGVHD) (six participants, 6% each).

6.1.12.5 Adverse Events of Special Interest (AESI)

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

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: one with grade 1 neuroendocrine tumor and one 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 PTLT.

Overall, 39 participants (44.3%) in the Orca-T group and 48 participants (51.1%) in the SoC group had a grade ≥ 3 infection. 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, ended study on day +76 and was alive as of the data cutoff date (15 July 2024). No participant in the Orca-T group and one 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. Overall, three participants (3.4%) in the Orca-T group and two (2.1%) in the SoC group had VOD/SOS (all with the PT veno-occlusive liver disease).

10. CONCLUSIONS

10.1 Statistical Issues and Collective Evidence

The applicant has submitted the results of one clinical study, Precision-T, on an allogeneic stem cell and T-cell immunotherapy derived from an HLA-matched donor indicated for use in adult patients with hematologic malignancies to improve survival free of GVHD in conjunction with an appropriate preparative regimen.

Precision-T was a multicenter, phase 1b/3 study evaluating the safety and efficacy of Orca-T in participants with advanced hematologic malignancies undergoing MAC-alloHCT. Ninety-three participants were randomized to the Orca-T arm and 94 were randomized to the SoC arm. The primary endpoint was cGFS, defined as the time from transplantation (Day 0) to either death from any cause or the first onset of moderate-to-severe chronic GVHD (per NIH consensus criteria), whichever occurs first, within 2 years post-transplant. The secondary endpoints were time to moderate-to-severe chronic GVHD, OS, and GRFS through 2 years.

The primary analysis for the primary endpoint of cGFS with cGVHD assessed by the independent EAC demonstrated a statistically significant difference between the Orca-T treatment versus SoC (HR = 0.26 [95% CI: 0.14, 0.47]; $P < .00001$). 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. Similarly, the analysis for the secondary endpoint of time to moderate or severe cGVHD per EAC demonstrated a statistically significant difference between the Orca-T treatment versus SoC (HR = 0.19 [95% CI: 0.08, 0.43]; $P = .00002$). Overall, 7 participants (7.5%) in the Orca-T group and 30 participants (31.9%) in the SoC group had moderate or severe cGVHD. The interim analysis for OS failed to demonstrate a statistically significant difference (HR = 0.49 [95% CI: 0.20, 1.22]; $P = .11823$). Because OS was not statistically significant, formal hypothesis testing of GRFS was not conducted at interim per the hierarchical testing procedure. 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.

Safety outcomes were generally favorable. Mortality during the study period was lower with Orca-T compared with SoC (8% vs. 16%). Serious adverse events (SAEs) occurred less frequently in the Orca-T arm than in the SoC arm (39% vs. 56%). All participants (100%) in both arms experienced at least one adverse event (AE); of these, grade ≥ 3 AEs occurred in 80 participants (91%) in the Orca-T arm and 92 participants (98%) in the SoC arm.

Secondary malignancies occurred in 1.1% of participants in the Orca-T arm (one grade 3 testicular cancer) versus 2.1% in the SoC arm (one grade 1 neuroendocrine tumor and one grade 3 testicular cancer). Grade ≥ 3 infections were reported in 44.3% of the Orca-T arm versus 51.1% of the SoC arm. Graft failure occurred in 1.1% of the Orca-T arm versus 0% of the SoC arm, while thrombotic microangiopathy (TMA) occurred in 0% of the Orca-T arm versus 1.1% of the SoC arm. Veno-occlusive disease (VOD)/sinusoidal

obstruction syndrome (SOS) rates were 3.4% in the Orca-T arm versus 2.1% in the SoC arm.

10.2 Conclusions and Recommendations

The efficacy evaluation of Orca-T was based on the data from the Precision-T study. This study met the primary efficacy endpoint of cGFS and the first secondary endpoint of time to moderate or severe cGVHD. Based on the available data from Precision-T, there is substantial evidence to support approval of Orca-T for patients with advanced hematologic malignancies undergoing MAC-alloHCT.

Appendix:

Table A1. SAP Versions, Precision-T

Precision-T SAP	Document Date	Key SAP Changes
SAP Version 1.0	20 January 2022	-
SAP Version 2.0	19 December 2023	- Version 2.0 adds NRM and OS as secondary endpoints, and were added to the hierarchical test procedure. - Version 2.0 corrected the critical <i>P</i> value at the interim analysis for the primary endpoint cGFS. Instead of O'Brien-Fleming boundary, version 2.0 specifies a Haybittle-Peto boundary to be used for each of the secondary endpoints at the interim and final analysis.
SAP Version 3.0	20 March 2024	- NRM and RFS were removed from secondary endpoints and are included as exploratory endpoints - Modified the sequence of tests within the hierarchical test scheme for the remaining secondary endpoints. Now the first one is time to moderate or severe cGVHD, followed by GRFS, with OS being the last one - The primary analysis for OS is changed to be event-driven and will be performed when 40 deaths are observed or 2 years after the end of the enrollment, whichever is earlier.

		• To accommodate the extended primary analysis for GRFS per EAC up to 1 year and OS, extra interim analyses have been incorporated.
SAP Version 4.0	19 September 2024	• For the hierarchical testing order, GRFS is now moved to be after OS. • The primary analysis for GRFS up to 1 year was removed; the primary analysis of GRFS up to 2 years is now planned at the same time of the OS primary analysis. • cGFS will be calculated from HCT (day 0) instead of randomization date.