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Official Title of Study	Precision-T (Phase III component)
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PRECISION-T CLINICAL STUDY PROTOCOL

Date and Version	Version 9.0, 09 May 2023
Study Name	Precision-T™
Protocol Title	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
Investigational Product	Orca-T
Development Phase	1b/3
Investigational New Drug No.	18873
Sponsor	Orca Bio, Inc.
Sponsor Contact	Anna Pavlova, MD, PhD 3475 Edison Way, Suite B Menlo Park, CA 94025 anna@orcabio.com M: (530) 414-9743
Supersedes	Version 8.0, 16 March 2023 Version 7.0, 06 October 2022 Version 6.0, 17 January 2022

The study will be conducted in accordance with standards of Good Clinical Practice, as defined by the International Conference on Harmonization and all applicable federal and local regulations.

PROTOCOL SIGNATURE PAGE

Study Name: Precision-T (TRGFT-201)

Protocol Title: 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

Sponsor: Orca Bio, Inc.

Version/Date: Version 9.0, 09 May 2023

Investigator Statement
I have received and read the above-mentioned protocol and its attachments. I agree to conduct the described study in compliance with all stipulations of the protocol, regulations, and ICH E6 Guideline for Good Clinical Practice (GCP). I accept the responsibilities included herein in my role as Principal Investigator for the study and will ensure that all subinvestigators and study personnel comply with the provisions of this protocol.

Principal Investigator
Name:_____

Principal Investigator
Signature:_____

Date:_____

PROTOCOL AMENDMENT, VERSION 9.0: RATIONALE

The following is an amendment to the Precision-T Protocol that has been modified to update the following:

- **Section 3.3.2:** Stopping criteria were amended to align with stopping criteria provided to the Food and Drug Administration as part of an information request in January 2022.
- **Section 6.3.2:** Language was added to clarify that FLT3, BCR-ABL, or IDH1/2 inhibitors used for maintenance and declared by the investigator prior to randomization are acceptable. This does not represent a procedural change from previous protocol versions; rather, this simply clarifies the guidance in the protocol.

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AE	adverse event
AESI	adverse event of special interest
alloHCT	allogeneic hematopoietic cell transplantation
ALT	alanine transaminase
AML	acute myeloid leukemia
ANC	absolute neutrophil count
AST	aspartate transaminase
ASTCT	American Society for Transplantation and Cellular Therapy
ATG	antithymocyte globulin
BF	busulfan/fludarabine
BFT	busulfan/fludarabine/thiotepa
BM	bone marrow
BPDCN	blastic plasmacytoid dendritic cell neoplasm
BSA	body surface area
BUN	blood urea nitrogen
CBC	complete blood count
CIBMTR	Center for International Blood and Marrow Transplant Research
CGFS	chronic graft-versus-host-free survival
CML	chronic myeloid leukemia
CMV	cytomegalovirus
CR	complete remission
CRF	case report form
CRi	complete remission with incomplete hematologic recovery
CRO	contract research organization
CRS	cytokine release syndrome
CT	computed tomography
CTL	cytotoxic T lymphocyte
CTCAE	Common Terminology Criteria for Adverse Events
Cy	cyclophosphamide
DIPSS	Dynamic International Prognostic Scoring System
DLCO	diffusing capacity of the lung for carbon monoxide
DLI	donor lymphocyte infusion
EBMT	European Society for Blood and Marrow Transplantation
EBV	Epstein-Barr virus
EC	ethics committee
ECG	electrocardiogram
eCRF	electronic case report form
EF	ejection fraction
eGFR	estimated glomerular filtration rate
FEV1	forced expiratory volume in the first second
FSH	follicle-stimulating hormone
G-CSF	granulocyte colony-stimulating factor

GCP	Good Clinical Practice
GI	gastrointestinal
GRFS	GVHD-free and relapse-free survival
GVHD	graft-versus-host disease
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCG	human chorionic gonadotropin
HCT	hematopoietic cell transplantation
HCT-CI	Hematopoietic Cell Transplantation-Specific Comorbidity Index
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HLA	human leukocyte antigen
HRT	hormone replacement therapy
HSPC	hematopoietic stem and progenitor cell
HSV	herpes simplex virus
HTLV	human T-lymphotropic virus
ICF	informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IEC	independent ethics committee
IPSS	International Prognostic Scoring System
IPSS-R	Revised International Prognostic Scoring System
IRB	institutional review board
IRR	infusion-related reaction
ITT	intention to treat
IV	intravenous(ly)
LTFU	long-term follow-up
LVEF	left ventricular ejection fraction
MAC	myeloablative conditioning
MAGIC	Mount Sinai Acute GVHD International Consortium
MDS	myelodysplastic syndrome
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intention to treat
MRD	minimal residual disease
MSD	matched sibling donor
MUD	matched unrelated donor
MUGA	multigated acquisition
NAT	nucleic acid test(ing)
NIH	National Institutes of Health
NK	natural killer (cell)
NMDP	National Marrow Donor Program
NR	no response
NRM	nonrelapse mortality
OMRS	Oral Mucosa Rating Scale

OS	overall survival
PBSC	peripheral blood stem cell
PET	positron emission tomography
PFT	pulmonary function test
PO	oral(ly)
PR	partial response
PRO	patient-reported outcome
P-ROM	photographic range of motion
PT	prothrombin time
PTLD	posttransplant(ation) lymphoproliferative disorder
PTT	partial thromboplastin time
RBC	red blood cell
SAE	serious adverse event
SoA	schedule of activities
SoC	standard of care
SUSAR	suspected unexpected serious adverse reaction
TBI	total body irradiation
TCD	T-cell depletion
TEAE	treatment-emergent adverse event
T_{con}	conventional T cell
T_{reg}	regulatory T cell
ULN	upper limit of normal
VGPR	very good partial response
VZV	Varicella zoster virus
WBC	white blood cell
WHO	World Health Organization
WNV	West Nile virus
WOCBP	woman or women of childbearing potential

SYNOPSIS

Orca Bio, Inc.	**Study Name:** Precision-T (formerly TRGFT-201)
Investigational Product: Orca-T	**Phase of Development:** 1b/3

Protocol Title:

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

Study Design:

This study includes Phase 3 and Phase 1b components. All participants in both components will undergo myeloablative conditioning (MAC) prior to allogeneic hematopoietic stem cell transplantation (alloHCT). Allografts are derived from granulocyte colony-stimulating factor (G-CSF)-mobilized peripheral blood, and donors are human leukocyte antigen (HLA)-matched (8/8) related or unrelated donors.

Phase 3: The Phase 3 is a randomized, open-label, multicenter study component of the Precision-T Study that will compare the outcomes between participants aged 18 to 65 years receiving Orca-T followed by single-agent tacrolimus or standard-of-care (SoC) control allograft derived from mobilized peripheral blood followed by graft-versus-host disease (GVHD) prophylaxis with tacrolimus and methotrexate. Participants with acute leukemia (myeloid, lymphoid, or mixed phenotype) in complete remission or high-risk myelodysplastic syndrome are eligible for the Phase 3 study. Participants enrolled onto the Phase 3 component will be randomized in a 1:1 ratio to either the Orca-T or SoC arm.

Phase 1b: The Phase 1b is a single-arm, multicenter study component of the Precision-T Study that aims to further characterize the safety and efficacy of Orca-T in participants aged 18 to 75 years with active (ie, not in complete response) leukemia and/or are disease risk index very high (Armand 2014), blastic plasmacytoid dendritic cell neoplasm (BPDCN), chronic myeloid leukemia (CML) with a history of blast crisis or accelerated phase, or participants who would be eligible for the Phase 3 component of Precision-T but have mild impairments of either renal and/or hepatic function as defined by an estimated glomerular filtration rate (eGFR) of 50 to <60 mL/min and/or a total bilirubin of >upper limit of normal (ULN) to ≤2x ULN. All participants enrolled onto the Precision-T Study prior to institution of Version 6 of the protocol were not subject to randomization and will therefore be analyzed as part of the Phase 1b population, regardless of whether they would have subsequently been eligible for the Phase 3 component.

Phase 3 Objectives:

Primary:

The primary objective of the Phase 3 component of Precision-T is to compare rates of survival free of moderate to severe chronic GVHD (cGVHD) (CGFS) between participants undergoing alloHCT with either Orca-T followed by single-agent tacrolimus or a control consisting of SoC unmanipulated allograft followed by tacrolimus plus methotrexate.

Secondary:

- To compare the rates of GVHD-free and relapse-free survival (GRFS) between participants undergoing alloHCT with either Orca-T or SoC
- To compare the rates of moderate-to-severe cGVHD between participants undergoing alloHCT with either Orca-T or SoC
- To compare the rates of relapse-free survival between participants undergoing alloHCT with either Orca-T or SoC

Phase 1b Objectives:

Primary:

The primary objective of the Phase 1b component of Precision-T is to characterize the safety of administration of Orca-T followed by tacrolimus in participants undergoing alloHCT from HLA-matched donors (related or unrelated) who are not otherwise eligible for the Phase 3 component of Precision-T.

Secondary:

- To determine the 1-year overall survival, nonrelapse mortality, and GRFS in participants undergoing alloHCT with Orca-T
- To measure the incidence and severity of acute GVHD (aGVHD) and cGVHD in participants undergoing alloHCT with Orca-T
- To measure the incidence of serious infections in participants undergoing alloHCT with Orca-T
- To measure the incidence and timing of engraftment in participants undergoing alloHCT with Orca-T

The Phase 1b objectives also apply to all participants enrolled onto Precision-T prior to institution of Version 6 of the protocol who were not subject to randomization and will therefore be analyzed as part of the Phase 1b population.

Study Sites: Multicenter in the continental United States

Study Populations:

Phase 3 Study Population (Recipients)

Adults aged 18 to 65 years who are eligible for alloHCT with 1 of the following diagnoses:

- Acute myeloid, lymphoid, or mixed phenotype/undifferentiated leukemia in complete remission (CR) or in complete remission with incomplete hematologic recovery (CRi)
- Myelodysplastic syndrome (MDS) with ≤10% blasts in the bone marrow who are eligible for transplant per 2017 International Expert Panel recommendations (de Witte 2017)

and who meet all of the following criteria:

- Are Disease Risk Index (DRI) risk category intermediate or high
- Have an HLA-identical related or unrelated donor
- Are planned to undergo a MAC-alloHCT with 1 of the conditioning regimens described in section 6.3.1.1

Phase 1b Study Population (Recipients)

Adults who are eligible for alloHCT with 1 of the following diagnoses:

- Acute myeloid, lymphoid, or mixed phenotype/undifferentiated leukemia who are not in CR or CRi (active disease) and/or MDS with >10% to <20% bone marrow blast burden (ages 18 to 75 years)
- Acute leukemia in CR/CRi or MDS that is DRI intermediate to high risk (ages 66 to 75 years)
- BPDCN (ages 18 to 65 years)
- Participants aged 18 to 65 who would be eligible for the Phase 3 component of Precision-T except for mild impairments of renal and/or hepatic function as defined by an eGFR of 50 to <60 mL/min and/or a total bilirubin of >ULN to ≤2 x ULN and diagnosed with either of the following:
  - Acute myeloid, lymphoid, or mixed phenotype/undifferentiated leukemia that is in CR/CRi and DRI intermediate to high risk
  - MDS that is DRI intermediate to high risk

- Acute or chronic leukemia in remission that is DRI low risk (ages 18 to 65 years), including the following:
  - CML in chronic phase but with a history of accelerated phase or blast crisis or who are resistant to or intolerant of more than 1 first- and second-generation tyrosine kinase inhibitors
  - Acute myeloid leukemia (AML) with inv(16) without accompanying complex cytogenetics

and who meet all of the following criteria:

- Have an HLA-identical related or unrelated donor
- Are planned to undergo MAC-alloHCT

Participants eligible for the Phase 3 component of Precision-T must be randomized and enrolled onto the Phase 3 rather than enrolling onto the Phase 1b. Please note that all participants enrolled onto Precision-T prior to institution of Version 6 of the protocol were not subject to randomization and will therefore be analyzed as part of the Phase 1b population, regardless of whether they would have subsequently been eligible for the Phase 3 component.

Number of Participants:

Phase 3: up to approximately 174 participants

Phase 1b: approximately 105 participants have been enrolled on Versions 1 through 5; with implementation of Version 6 of the Precision-T protocol, up to an additional approximately 122 participants may be enrolled, for a total of up to approximately 227 participants across all populations

Treatment Description:

Recipients eligible for the Phase 3 component of Precision-T will be randomized to receive either Orca-T or SoC. Participants eligible for the Phase 1b component of this study will receive Orca-T.

Orca-T includes hematopoietic stem and progenitor cells (HSPC), regulatory T cells (T_{reg}), and conventional T cells (T_{con}):

Orca-T Component:	Dose Regimen	[redacted]
HSPC	IV, entire bag, [redacted]	[redacted]
T_{reg}	IV, entire bag, [redacted]	[redacted]
T_{con}	IV, entire bag, [redacted]	[redacted]

SoC consists of an unmanipulated allograft derived from the peripheral blood of a G-CSF-mobilized, matched donor.

GVHD Prophylaxis

Based on treatment arm assignment, recipients will receive GVHD prophylaxis as follows:

Orca-T: single-agent tacrolimus starting on the day after T_{con} infusion (typically day +3)

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

Study Duration:

Approximately 40 months for the main study (per individual subject: 1 month, screening and MAC; 3 days, Orca-T administration [redacted] or SoC allograft administration [day 0]; 2 years follow-up), followed by long-term survival and disease status follow-up

Primary Endpoints:

Phase 3: CGFS. An event for this time-to-event outcome is defined as death by any cause or moderate-to-severe cGVHD as defined by National Institutes of Health consensus criteria.

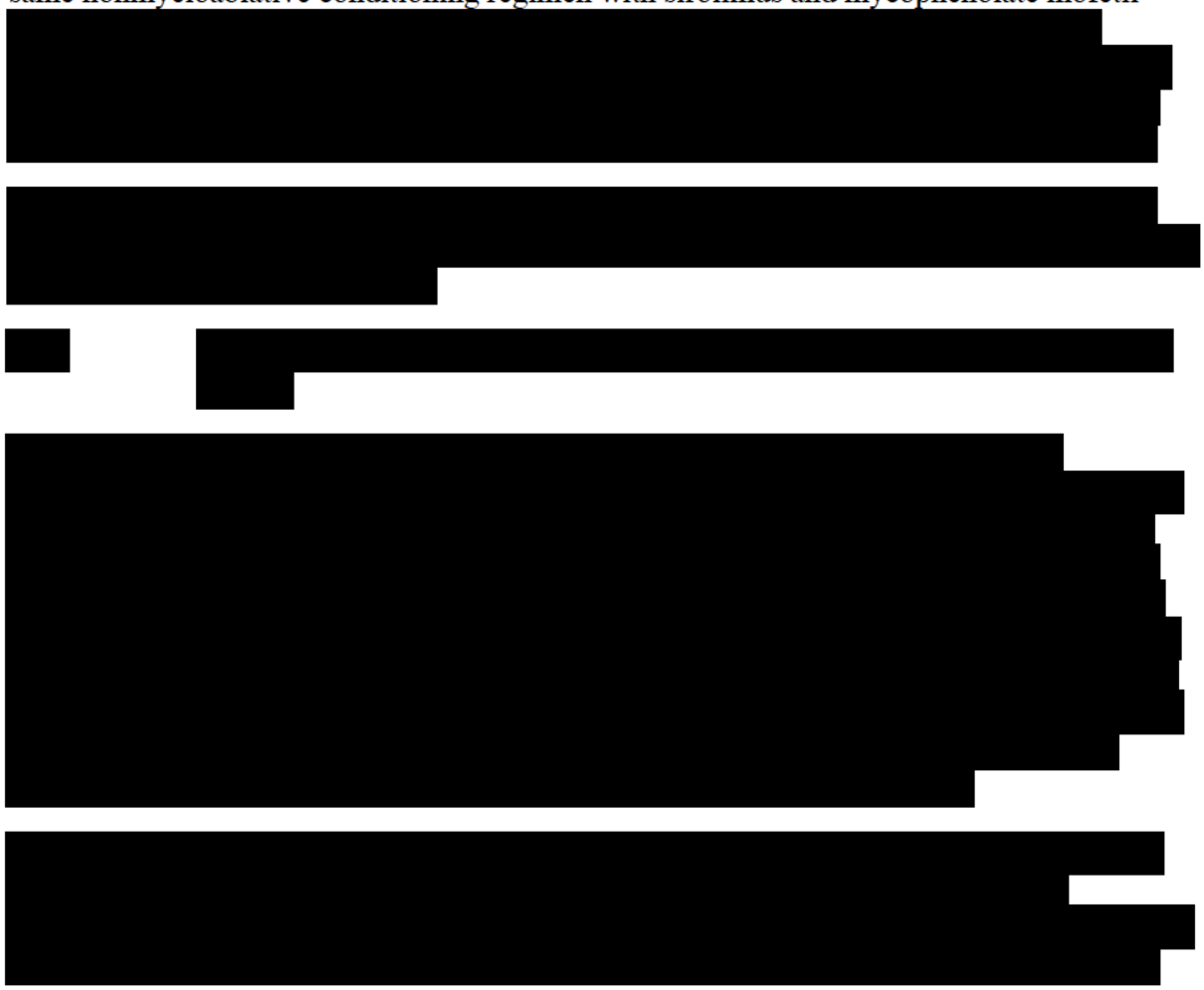
Phase 1b:

- Incidence of primary graft failure
- Incidence, severity, and timing of grade 3 or 4 aGVHD

[redacted]

[redacted]

same nonmyeloablative conditioning regimen with sirolimus and mycophenolate mofetil



1.3 Precision-T Study Overview

Precision-T is a multicenter, open-label, Phase 1b/3 study in adults undergoing MAC-alloHCT with HLA-identical related or unrelated donor for acute leukemia; high- or very high-risk myelodysplastic syndrome (MDS), and blastic plasmacytoid dendritic cell neoplasm (BPDCN). The study consists of 2 components: a Phase 1b component and a Phase 3 component.

The Phase 3 component of Precision-T is a randomized, open-label, multicenter study designed to compare the safety and efficacy of Orca-T followed by single-agent tacrolimus to that of a control consisting of standard-of-care (SoC) MAC-alloHCT followed by GVHD prophylaxis with tacrolimus and methotrexate in participants with acute leukemia in complete remission with DRI risk category of intermediate to high (Armand 2014) and in participants with myelodysplastic syndrome.

Participants enrolled onto the Phase 3 component of Precision-T will be randomized 1:1 to receive either Orca-T or SoC. Randomization will be stratified by the following:

- Donor type (HLA-matched related versus HLA-matched unrelated)
- DRI risk category (intermediate risk or high risk)

The Phase 1b component of Precision-T is designed to further characterize the safety and tolerability of Orca-T and to perform an initial assessment of the efficacy of Orca-T in participants ineligible for the randomized Phase 3 component of Precision-T. These include participants with 1 of the following characteristics:

- Active acute leukemia (ie, participants with acute leukemia who are not in either a complete remission [CR] or a CR with incomplete hematologic recovery [CRi]) (Armand 2014)
- Diagnosed with BPDCN
- Participants who have mildly impaired renal and/or hepatic function (defined as estimate glomerular filtration rate [eGFR] of 50 to 59 mL/min or total bilirubin >upper limit of normal [ULN]) but would otherwise be eligible for the Phase 3 component of Precision-T
- Diagnosed with acute leukemia in remission (CR/CRi) that is DRI intermediate-to-high risk or MDS and aged 66 to 75 years
- Diagnosed with DRI low-risk acute myeloid leukemia (AML) or chronic myeloid leukemia (CML), specifically:
    - CML in chronic phase with a prior history of accelerated phase or blast crisis, or resistant to or intolerant of more than 1 first and/or second-generation tyrosine kinase inhibitors
    - AML with inv(16) without accompanying complex cytogenetics. Such participants are considered DRI low risk and are therefore not eligible for the Phase 3 component of Precision-T. However, these participants may be candidates for alloHCT if they have certain high-risk features such as a history of relapse.
- Phase 1b legacy component: All participants consented onto Precision-T prior to institution of Version 6 of the protocol at a given participating center were not subject to randomization and will therefore be enrolled onto the Phase 1b and analyzed as part of the Phase 1b population, regardless of whether they would have subsequently been eligible for the Phase 3 component.

[redacted]

1.3.2 Patient Populations

AlloHCT bears high risks of NRM, GVHD, opportunistic infection, and disease relapse (D'Souza 2017). However, alloHCT is often the best and only curative treatment option for patients with acute leukemia, BPDCN, or MDS eligible for alloHCT per International Expert Panel recommendations. These populations are therefore considered appropriate for a Phase 1b/3 study with Orca-T, which seeks to improve such outcomes in these populations.

1.3.2.1 Phase 3 Participant Population

[redacted] Most data from these studies have been derived from participants aged 18 to 65 years with acute leukemia (AML, ALL, MPAL) in CR or with MDS. As such, eligibility for the Phase 3 component of Precision-T is limited to participants with these conditions and with HLA–matched related or unrelated donors. To further reduce the heterogeneity of the Phase 3 population, enrollment is limited to participants with DRI risk categories of intermediate or high (Armand 2014). At randomization, participants with be stratified based on donor type (unrelated versus related) and DRI risk category (intermediate versus high).

1.3.2.2 Phase 1b Participant Population

In order to obtain additional safety and preliminary efficacy data for Orca-T in the context of patient populations not well represented on the Precision-T Study to date, participants with the following underlying malignancies will be assigned to the Phase 1b component of Precision-T:

a) Acute myeloid, lymphoid, or mixed phenotype/undifferentiated leukemia (AML, ALL, or MPAL) that is not in CR/CRi or MDS with >10% to <20% bone marrow blast burden (active leukemia cohort, participants aged 18 to 75 years); these patients would be classified as DRI very high risk

b) Acute leukemia in CR/CRi or MDS that is DRI intermediate to high risk (ages 66 to 75 years)

c) BPDCN (ages 18 to 65 years)

d) Participants aged 18 to 65 years who would be eligible for the Phase 3 component of Precision-T except for mild impairments of renal and/or hepatic function as defined by an eGFR of 50 to <60 mL/min and/or a total bilirubin of >ULN to ≤2x ULN and diagnosed with either of the following:

   - Acute myeloid, lymphoid, or mixed phenotype/undifferentiated leukemia that is in CR/CRi and DRI intermediate to high risk
   - MDS that is DRI intermediate to high risk

e) Participants diagnosed with AML or CML that is DRI low risk:

   - CML in chronic phase with a prior history of accelerated phase or blast crisis, or resistant to or intolerant of more than one first and/or second-generation tyrosine kinase inhibitors.
   - AML with inv(16) without accompanying complex cytogenetics. Such participants are considered DRI low risk and are therefore not eligible for the Phase 3 component of Precision-T. However, these participants may be candidates for alloHCT if they have certain high-risk features such as a history of relapse.

These cohorts (a through f) will be analyzed separately for safety, and stopping criteria have been defined for these cohorts (section 3.3).

In addition to the aforementioned participants who will continue to be assigned to Phase 1b, all participants treated on Precision-T prior to the implementation of randomization (Version 6 of the Precision-T Protocol) will be analyzed as part of the Phase 1b population.

[redacted]

product may not conform to all specifications. The sponsor medical monitor, sponsor, or

1.3.4 Conditioning Regimen Options

Versions 1 through 5 of the Precision-T protocol allowed investigators to choose any myeloablative conditioning (preparative) regimen for administration prior to Orca-T. To reduce the heterogeneity introduced by the use of disparate conditioning regimens prior to Orca-T, in Version 6 of the Precision-T protocol, the choice of condition regimen has been limited to the regimens listed in section 7.3.1.1. The allowed regimens include both total body irradiation (TBI)-based options (TBI/cyclophosphamide [Cy] and TBI/etoposide) and a non-TBI-based option (busulfan/fludarabine/thiotepa [BFT]).

BFT was chosen as the sole allowed non-TBI regimen based on evidence that this regimen may lead to reduced relapse risk in the context of Orca-T (Hoeg 2021). This is consistent with evidence that BFT may reduce relapse risk in the context of an unmanipulated allograft followed by GVHD prophylaxis with a calcineurin inhibitor plus methotrexate

(Saraceni 2017, Sora 2020, Sora 2017). Indeed, studies comparing myeloablative BFT to myeloablative busulfan/fludarabine (BF) alone followed by calcineurin inhibitor/methotrexate prophylaxis have indicated that overall survival is the either same (Saraceni 2018) or improved (Sora 2020) using the BFT regimen in the context of advanced hematologic malignancies. Of note, neither study found a difference in aGVHD or cGVHD incidence between BF and BFT-treated participants. Thus, the BFT regimen represents an acceptable conditioning regimen choice for participants enrolled on Precision-T and receiving a non-TBI-based regimen, regardless of whether they are assigned to the Orca-T arm or the SoC arm.

An additional conditioning regimen option has been added to the Phase 1b component of Precision-T. Participants enrolled onto the Phase 1b component of the Precision-T Study must receive 1 of the MAC regimens described above (see also Table 6-1) or a total marrow and lymphoid irradiation (TMLI)-based regimen (Table 6-2). Preliminary evidence suggests that a combination of TMLI, fludarabine, and melphalan may provide better relapse prevention with reduced toxicity (Jensen 2018).

2 TRIAL OBJECTIVES AND ENDPOINTS

2.1 Phase 3 Objectives

2.1.1 Phase 3 Primary Objective

The primary objective of the Phase 3 component of Precision-T is to compare rates of survival free of moderate-to-severe cGVHD (CGFS) between participants undergoing alloHCT with either Orca-T followed by single-agent tacrolimus or a control consisting of SoC unmanipulated allograft followed by tacrolimus plus methotrexate.

2.1.2 Phase 3 Secondary Objectives

- To compare the rates of GVHD-free and relapse-free survival (GRFS) between participants undergoing alloHCT with either Orca-T or SoC
- To compare the rates of moderate-to-severe cGVHD between participants undergoing alloHCT with either Orca-T or SoC
- To compare the rates of relapse-free survival between participants undergoing alloHCT with either Orca-T or SoC

[redacted]

[redacted]

2.2 Phase 1b Objectives

2.2.1 Phase 1b Primary Objectives

The primary objective of the Phase 1b component of Precision-T is to characterize the safety of administration of Orca-T followed by tacrolimus in participants undergoing alloHCT from HLA-matched donors (related or unrelated) who are not otherwise eligible for the Phase 3 component of Precision-T.

2.2.2 Phase 1b Secondary Objectives

- To determine OS, NRM, RFS, and GRFS in participants undergoing alloHCT with Orca-T
- To measure the incidence and severity of aGVHD and cGVHD in participants undergoing alloHCT with Orca-T
- To measure the incidence of steroid-refractory aGVHD in participants undergoing alloHCT with Orca-T
- To measure the incidence of serious infections in participants undergoing alloHCT with Orca-T
- To measure the incidence and timing of engraftment in participants undergoing alloHCT with Orca-T

[redacted]

2.3 Study Endpoints

For brevity, detailed definitions of the following endpoints are deferred to section 9.2; brief descriptions are listed here.

2.3.1 Phase 3 Primary Endpoint

- CGFS. An event for this time-to-event outcome is defined as death by any cause or moderate-to-severe cGVHD as defined by National Institutes of Health (NIH) consensus criteria (Jagasia, 2015) (appendix 11.5.1.3) from the date of randomization until 2 years after transplant. cGVHD will be assessed and graded by an external EAC that is blinded to treatment assignment (section 3.2.2).

2.3.2 Phase 3 Secondary Endpoints

- GRFS (Holtan 2015) from day 0 through day +365. An event for this time-to-event outcome is defined as death from any cause, relapse, grade 3 or 4 aGVHD (graded per Mount Sinai aGVHD International Consortium [MAGIC]), or moderate-to-severe cGVHD (graded per NIH consensus criteria). aGVHD and cGVHD will be assessed and graded by an external EAC (section 3.2.2).
- Moderate-to-severe cGVHD. An event for this time-to-event outcome is defined as moderate-to-severe cGVHD as defined by NIH consensus criteria (Jagasia 2015, appendix 11.5.1.3). cGVHD will be assessed and graded by an external EAC (section 3.2.2).
- Relapse-free survival from day 0 through day +730.

For relapse-based endpoints, relapse is defined as follows:

- For acute leukemias, relapse is defined as any of the following (minimal residual disease [MRD] positivity alone is insufficient).
    - ≥5% blasts in the bone marrow or peripheral blood
    - Reappearance of pretransplant cytogenetic abnormality
    - New evidence or redevelopment of extramedullary disease
- For MDS, relapse is defined as any of the following:
    - Satisfying criteria for evolution into acute leukemia

  - Reappearance of pretransplant morphologic abnormalities detected in bone marrow specimens
  - Reappearance of pretransplant cytogenetic abnormality in at least 1 metaphase on each of 2 separate consecutive examinations at least 1 month apart, regardless of the number of metaphases analyzed

- For CML, post-alloHCT relapse is defined in section 11.15.

Institution of any anticancer therapy to treat MRD such as withdrawal of immunosuppression or donor lymphocyte infusion (DLI) will be considered evidence of relapse regardless of whether the criteria described above are met. MRD positivity must be demonstrated using an MRD assay appropriate for the disease in question (eg, multiparameter flow cytometry, polymerase chain reaction, or next-generation sequencing). MRD positivity alone is insufficient to establish the presence of relapse.

DLI given for reasons other than relapse (eg, for mixed chimerism) does not constitute evidence of relapse unless other findings are consistent with relapse. Planned therapies to prevent relapse (eg, FLT3 inhibitors in the setting of CR or CRi) are allowed and do not constitute evidence of relapse.

2.3.4 Phase 1b Primary Endpoints

- The incidence and timing of primary graft failure
- The incidence and severity of grade 3 or 4 aGVHD
- Treatment-emergent adverse events (TEAEs)

2.3.5 Phase 1b Secondary Endpoints

The secondary endpoints for the Phase 1b are below. These endpoints are described in greater detail in sections 2.3.2 and 2.3.3.

- OS through day +730
- NRM through day +365
- RFS through day +730
- GRFS (Holtan 2015) from day 0 through day +365
- Incidence and severity (all grades) of aGVHD at day +180
- Incidence and severity (all grades) of cGVHD at day +365
- Incidence of steroid-refractory aGVHD at day +180

- Incidence of serious infections through day +365
- Incidence and timing of neutrophil engraftment
- Incidence and timing of platelet engraftment
- Secondary graft failure

[redacted]

3 TRIAL STUDY DESIGN

This is a multicenter, open-label Phase 1b/3 study in adults undergoing alloHCT with an HLA-identical related or unrelated donor. Up to approximately 227 participants will be enrolled on the Phase 1b component of the study across all disease types under study, and approximately 174 participants will be enrolled onto the Phase 3 component.

For participants assigned to the Orca-T arm, Orca-T will be administered after the investigator's choice from the myeloablative conditioning regimens allowed in section 6.3.1.1. Single-agent GVHD prophylaxis with tacrolimus will be administered as outlined in section 6.3.1.2.1.

For participants assigned to the SoC control arm, an unmanipulated allograft derived from G-CSF-mobilized donor PBSCs will be administered after the investigator's choice from the myeloablative conditioning regimens allowed in section 6.3.1.1. Dual-agent GVHD prophylaxis will be administered as outlined in section 6.3.1.2.2.

Under Protocol Versions 1 through 5, a safety monitoring committee met at regular intervals to review safety data and make recommendations regarding the conduct of the trial. Starting with Version 6 of the Precision-T Protocol, an independent data monitoring committee (DMC) assumed safety monitoring duties. The DMC is described in further detail in the Precision-T DMC Charter.

3.1 Study Arms

Participants who undergo alloHCT for high-risk hematologic malignancies have markedly different outcomes based on the presence or absence of detectable disease, with patients with active disease having much poorer outcomes (Wong 2005, Michallet 2000, Ogawa 2018). This poor prognosis extends to patients who are in a morphologic CR but are positive for MRD (Buckley 2013). Similarly, patients with MDS may have distinct outcomes and adverse events (Aes) following alloHCT compared with patients with acute leukemias (Kindwall-Keller 2009, McLornan 2019).

Participants assigned to the Phase 3 component will be randomized to receive either Orca-T or SoC alloHCT. All participants eligible for the Phase 3 must be enrolled onto that study component and be randomized.

3.2 Review Committees

3.2.1 Data Monitoring Committee

An independent DMC will be established to regularly review safety data. The DMC will be composed of a minimum of 3 members who do not have any conflict of interests with the trial sponsor, including 2 clinicians and a biostatistician. The full membership, mandate, and processes of the DMC will be detailed in a separate DMC charter. The DMC will also be responsible for performing an interim analysis of efficacy data as described in section 9.4.7.

3.2.2 Endpoint Adjudication Committee

An independent endpoint adjudication committee (EAC) will perform a blinded determination as to whether the criteria for aGVHD and/or cGVHD have been met for each participant, and the EAC will then grade aGVHD and cGVHD according to MAGIC grading criteria and 2014 International NIH Chronic GVHD Diagnosis and Staging Consensus Working Group criteria, respectively (see sections 11.5.1 and 11.5.2). The EAC will be composed of a minimum of 3 experts in GVHD assessment. The full membership, mandate, and processes of the EAC will be detailed in the EAC Charter.

3.3 Study Stopping Rules

This section defines stopping rules following the observation of specified safety events potentially associated with Orca-T.

For the Phase 1b component of Precision-T, analyses for safety will be performed on a continuous rolling basis by the sponsor.

For the Phase 3 component of Precision-T, the DMC will meet at least quarterly to review accumulated safety data obtained from both the Phase 3 and Phase 1b components. DMC oversight of trial safety data is described in further detail in the Precision-T DMC Charter. The DMC may recommend stopping a component of the study based on their assessment of safety data.

Upon any activation of a stopping rule, enrollment onto that cohort (eg, the Phase 1b cohort for participants age 66 to 75 years) within the study will be paused, the DMC will convene to review all available data to date, and the DMC may recommend to the sponsor 1 of the following:

- Termination of a component of the study
- Amendment of the study protocol to modify the diagnoses allowed for enrollment, dose regimen(s) of Orca-T, GVHD prophylaxis, conditioning regimen(s), and/or other provision(s) to be determined by the DMC, such as modification to the Orca-T manufacturing procedure. No participants would be accrued into the study component in question until the study protocol is amended accordingly.

Section 9.1.3 describes the statistical justification for these stopping criteria.

[redacted]

The stopping criteria reflect a maximum acceptable rate of 4% for manufacturing failure

[redacted]

3.4 Medical Monitoring

There will be 2 medical monitors for this study:

- A sponsor medical monitor will continue to provide primary oversight for participant enrollment on the Phase 1b component.
- A medical monitor not affiliated with the sponsor, but rather employed by a contract research organization (CRO), will provide primary oversight for participants randomized on the Phase 3 component.

For questions or concerns regarding Precision-T, queries should initially be directed to the CRO medical monitor. The CRO medical monitor may further direct questions to the sponsor medical monitor in limited circumstances due to participant safety concerns.

4 STUDY POPULATIONS

4.1 Enrollment Procedure

Potential donors and recipients will be approached for the study after the decision to proceed with transplantation is made and a suitable HLA-matched donor is identified.

Donors and recipients may be enrolled (Phase 1b component) or randomized (Phase 3 component) only after evaluation by the investigators at the respective sites and approval by the medical monitor (sponsor medical monitor for Phase 1b and CRO medical monitor for Phase 3). For both recipients and donors, the results of all relevant screening tests and procedures must be submitted to the sponsor or designee, including results of the most recent bone marrow biopsy/aspirate, safety laboratories, and infectious disease markers. All personal identifiable information should be redacted from these documents before submission.

Donor study procedures, including informed consent, may be overseen at the investigator's site (eg, related donors who reside near the investigator's site) or via the National Marrow Donor Program (NMDP) (eg, unrelated donors and related donors who do not reside near the investigator's site).

Enrollment (Phase 1b component) or randomization (Phase 3 component) must occur prior to the transfer of apheresis products to Orca Bio's manufacturing facility.

For the Phase 3 component, investigators must declare the planned conditioning regimen for each participant prior to randomization. Investigators may choose different regimens that are contingent upon eventual treatment-arm assignment (eg, BFT if assigned to the Orca-T arm and TBI/Cy if assigned to SoC), but this choice should be stated prior to randomization and must not be altered after randomization.

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as a protocol waiver or exemption, is not permitted.

4.1.1 Randomization

Once the participant is deemed eligible and has given written informed consent, participants eligible for the Phase 3 component of Precision-T will be randomized to a treatment arm (Orca-T or SoC). All eligibility criteria must be confirmed prior to randomization.

Randomization will be stratified by the following:

- Donor type (sibling vs. unrelated)
- DRI category (intermediate risk or high risk)

4.2 Donor Inclusion/Exclusion Criteria

4.2.1 Donor Inclusion Criteria

For both the Phase 1b and Phase 3 components of Precision-T, donors must meet all of the following criteria:

1. Age ≥16 and ≤75 years at time of enrollment
2. Matched to the participant as follows:

   Either of the following:

   a. Matched related donor who is an 8/8 match for HLA-A, -B, -C, and -DRB1, all typed using DNA-based high-resolution methods

   b. Matched unrelated donor who is an 8/8 match for HLA-A, -B, -C, and -DRB1, all typed using DNA-based high-resolution methods
3. Willing to donate PBSC for up to 2 consecutive days
4. Able to donate within North America or Hawaii
5. Meets federal eligibility criteria for donors of viable, leukocyte-rich cells or tissues as defined by 21 CFR § 1271 2018 and all relevant FDA Guidance for Industry (Eligibility Determination for Donors of Human Cells, Tissues, and Cellular and Tissue-Based Products, 2007; Use of Donor Screening Tests to Test Donors of Human Cells, Tissues and Cellular and Tissue-Based Products for Infection with Treponema pallidum [Syphilis], 2015; Use of Nucleic Acid Tests to Reduce the Risk of Transmission of Hepatitis B Virus from Donors of Human Cells, Tissues, and Cellular and Tissue-Based Products, 2016; Use of Nucleic Acid Tests to Reduce the Risk of Transmission of West Nile Virus from Living Donors of Human Cells, Tissues, and Cellular and Tissue-Based Products [HCT/Ps], 2016; Donor Screening Recommendations to Reduce the Risk of Transmission of Zika Virus by Human Cells, Tissues, and Cellular and Tissue-Based Products, 2018).
6. Donors not meeting federal eligibility as described in criterion #5, may nonetheless be included if either of the following apply per 21 CFR § 1271.65 2018:

   a. The donor is a first-degree or second-degree blood relative of the recipient

   b. Urgent medical need, meaning no comparable human cell product is available and the recipient is likely to suffer death or serious morbidity without the human cell product, as attested by the investigator.
7. Meets all other criteria for donation as specified by standard NMDP guidelines (NMDP donors) or institutional standards (non-NMDP donors).
8. Female donors of child-bearing potential must have a negative serum or urine beta human chorionic gonadotropin (HCG) test at screening and within 1 to 5 days prior to mobilization

9. Capable of undergoing leukapheresis, have adequate venous access, and are willing to undergo insertion of a central catheter should leukapheresis via peripheral vein be inadequate
10. Be agreeable to an additional donation of peripheral blood mononuclear cells (or bone marrow harvest) in the event of graft failure or mobilization failure

4.2.2 Donor Exclusion Criteria (Phases 1b and 3)

For both the Phase 1b and Phase 3 components of Precision-T, donors meeting any of the following exclusion criteria will not be eligible:

1. Evidence of active infection
2. Seropositive for human immunodeficiency virus (HIV)-1 or -2 or human T-lymphotropic virus (HTLV)-1 or -2
3. Positive for anti-hepatitis C (HCV) antibody or HCV nucleic acid testing (NAT)
4. Positive serologic or PCR test results indicating acute or chronic hepatitis B virus (HBV) infection
    a. Donors whose HBV infection status cannot be determined conclusively by serologic test results (www.cdc.gov/hepatitis/hbv/pdfs/serologicchartv8.pdf) must be negative for HBV by PCR to be eligible for study participation
5. Potential for Zika virus infection as defined as any of the following:
    a. Medical diagnosis of Zika virus infection in the past 6 months
    b. Residence in, or travel to, an area with active Zika virus transmission within the past 6 months.
    c. Unprotected sex within the past 6 months with a person who is known to have either of the risk factors listed above (donor exclusion criterion 5.a or 5.b)

    Donors determined to be ineligible based on the results of Zika virus screening may be determined to be eligible if:

    d. The donor has no signs or symptoms consistent with active Zika virus infection

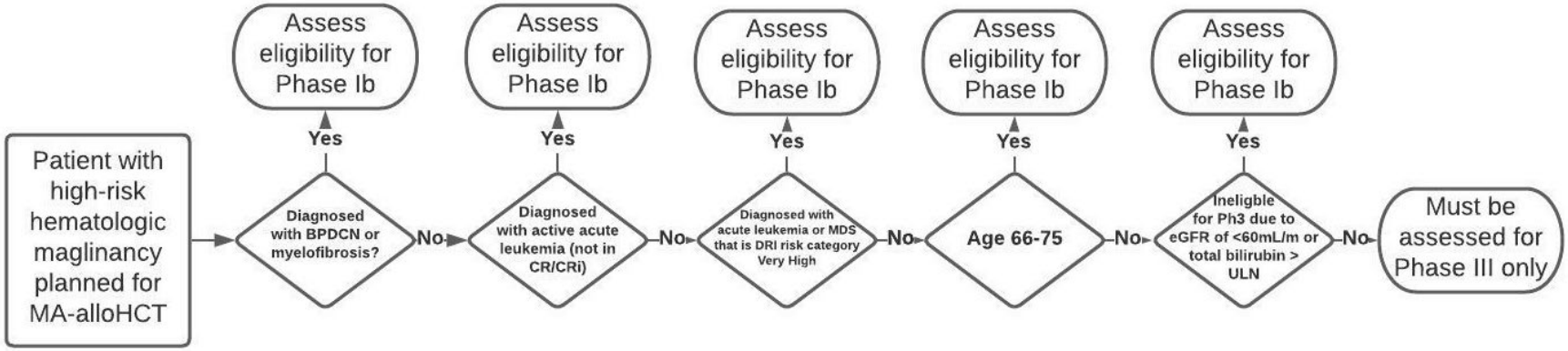
    and

    e. Either of the following is true:
        i) The donor is a first-degree or second-degree blood relative of the recipient
        ii) Urgent medical need, meaning no comparable human cell product is available and the recipient is likely to suffer death or serious morbidity without the human cell product, as attested by the investigator.
6. Women who are pregnant or breastfeeding

4.3 Recipient Inclusion/Exclusion Criteria

Recipients are eligible for either the Phase 1b or Phase 3 component depending on age and disease characteristics (Figure 4-1). Participants eligible for the Phase 3 may not be enrolled on the Phase 1b.

Figure 4-1 Recipient Eligibility Flowchart



Abbreviations: BPDCN, blastic plasmacytoid dentritic cell neoplasm; CR, complete remission; CRi, complete remission with incomplete hematologic recovery; DRI, Disease Risk Index; eGFR, estimated glomerular filtration rate; MA-alloHCT, myeloablative allogeneic hematopoietic cell transplant; MDS, myelodysplastic syndrome; ULN, upper limit of normal.

4.3.1 Global Recipient Inclusion Criteria (Applicable to both the Phase 1b and Phase 3 Components of Precision-T)

Recipients in either the Phase 3 or Phase 1b components of this study must meet all of the following criteria:

1. Planned to undergo MAC-alloHCT including 1 of the MAC regimens listed in section 6.3.1.1
2. Matched to a related or unrelated donor as follows:

   Either 1 of the following:

   a. Matched sibling donor who is an 8/8 match for HLA-A, -B, -C, and DRB1, all typed using DNA-based high-resolution methods, or

   b. Matched unrelated donor who is a 8/8 match at HLA-A, -B, -C, and DRB1, all typed using DNA-based high resolution methods
3. Cardiac ejection fraction at rest ≥45% or shortening fraction of ≥27% by echocardiogram or radionuclide scan (multigated acquisition [MUGA])
4. Diffusing capacity of the lung for carbon monoxide (DLCO) (adjusted for hemoglobin) ≥50%
5. Negative serum or urine beta-HCG test in females of childbearing potential (WOCBP) (see appendix 11.11)
6. Alanine transaminase (ALT)/aspartate transaminase (AST) <3 times ULN

4.3.2 Phase 3-Specific Recipient Inclusion Criteria

Recipients randomized to the Phase 3 component of this study must meet all of the following Phase 3-specific criteria:

1. Aged ≥18 and ≤65 years (ie, from age 18 to <66 years old) at the time of enrollment
2. Diagnosed with 1 of the following histopathologically confirmed diseases:
   a. Acute myeloid, lymphoid or mixed phenotype/undifferentiated leukemia in CR or CRi, with or without the presence of known minimal residual disease. CR/CRi is defined in appendix 11.13.1.1, and this assessment should be based on pathologic analysis of the screening bone marrow biopsy.
   b. MDS that is either of the following:
      - Indicated for alloHCT per the 2017 International Expert Panel recommendations (de Witte 2017) (see section 11.4)
      - Diagnosed with therapy-related/secondary MDS as defined by the World Health Organization (WHO) classification of myeloid malignancies (WHO 2017) (section 11.6.1)

For MDS, enrollment is limited to participants with ≤10% blast burden in the bone marrow based on a bone marrow biopsy performed during screening. Participants with >10% to <20% bone marrow blast burden may be considered for the Phase 1b active disease/DRI very high risk.

3. DRI overall risk categorization of intermediate or high per Armand et al. (2014)
4. Total bilirubin ≤ULN (participants with Gilbert's syndrome may be included where hemolysis has been excluded and with approval of the medical monitor)
5. eGFR ≥60 mL/minute

Note: Upon activation of Version 6 of the Precision-T protocol at each participating transplant center, participants who are eligible for the Phase 3 may not be enrolled onto the Phase 1b component of Precision-T. Participants consented to earlier versions of the protocol (ie, prior to implementation of Version 6) may continue on the study component for which they were initially consented.

4.3.3 Phase 1b-Specific Recipient Inclusion Criteria

1. Participants must be diagnosed with the following histopathologically confirmed diseases to be eligible for the Phase 1b component of the study. Allowable age ranges are listed within the specific disease categories below. Eligible cohorts include the following diagnoses:
   a. Acute myeloid, lymphoid, or mixed phenotype/undifferentiated leukemia (AML, ALL, or MPAL) that is not in morphologic CR/CRi and participants with MDS with >10% to <20% bone marrow blast burden (active leukemia cohort, participants aged 18 to 75 years)
   b. AML, ALL, MPAL, or MDS that is in morphologic CR/CRi and intermediate to high risk per the DRI in participants aged 66 to 75 years at the time of enrollment. Participants with MDS must be indicated for alloHCT per 2017 International Expert Panel recommendations (de Witte 2017) and/or have therapy-related/secondary MDS as defined by the WHO classification of myeloid malignancies (WHO 2017) (section 11.6.1)
   c. BPDCN (participants aged 18 to 65 years) (see the 2016 revision to the World Health Organization classification of myeloid neoplasms and acute leukemia [Daniel 2016])
   d. Participants aged 18 to 65 years who have mild impairments of renal and/or hepatic function as defined by an eGFR of 50 to <60 mL/min and/or a total bilirubin of >ULN to ≤2x ULN and diagnosed with either of the following:
      - Acute myeloid, lymphoid, or mixed phenotype/undifferentiated leukemia that is in CR/CRi and DRI intermediate to high risk
      - MDS that is DRI intermediate to high risk

e. DRI low risk leukemia, including the following:

- CML in chronic phase with a history of blast crisis or accelerated phase (with chronic phase, blast crisis, and accelerated phase as defined by WHO 2017) and/or participants with chronic-phase CML that is resistant to or intolerant of more than 1 first and/or second-generation tyrosine kinase inhibitors (participants aged 18 to 65 years).

  Participants with CML in blast crisis or accelerated phase that has not been controlled to the point of reverting to chronic phase may be considered for enrollment into the active leukemia cohort (cohort "A" above), and

- AML with inv(16) and without complex cytogenetics with high-risk disease features (eg, molecular markers, relapsed disease currently in CR2 and beyond, clonal evolution, etc.) (participants aged 18 to 65 years).

2. eGFR ≥50 mL/minute
3. Total bilirubin ≤2x ULN (participants with Gilbert's syndrome may be included where hemolysis has been excluded and with approval of the medical monitor)

4.3.4 Global Recipient Exclusion Criteria (Applicable to both the Phase 1b and Phase 3 components of this study)

Recipients meeting any of the following exclusion criteria will not be eligible:

1. Prior alloHCT
2. Currently receiving corticosteroids or other immunosuppressive therapy. Topical corticosteroids or oral systemic corticosteroid doses less than or equal to 10 mg/day are allowed.
3. Planned DLI
4. Planned pharmaceutical in vivo or ex vivo TCD, eg, posttransplant Cy, peritransplant antithymocyte globulin (ATG), or alemtuzumab. For participants who have previously been exposed to a TCD agent, a 5 half-life washout of the agent must occur prior to planned day 0 (day 0 is defined as the day of infusion of the T_{reg} and HSPC drug products of Orca-T for participants assigned to an Orca-T arm or day of allograft infusion for participants assigned to the SoC arm).
5. Recipient 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

6. Karnofsky performance score <70% (appendix 11.8)
7. HCT-Specific Comorbidity Index (HCT-CI) >4 (appendix 11.9)
8. Uncontrolled bacterial, viral or fungal infections (currently taking antimicrobial therapy and with progression or no clinical improvement) at time of enrollment. Per American Society for Transplantation and Cellular Therapy (ASTCT) guidelines, a negative SARS-CoV-2 test is not required prior to alloHCT given prolonged viral shedding. However, alloHCT should be deferred in participants with signs or symptoms consistent with active COVID-19 infection (Dioverti 2022).
9. Seropositive for HIV-1 or -2, HTLV-1 or -2, hepatitis B surface antigen (HBsAg), or hepatitis C antibody
10. Known allergy or hypersensitivity to, or intolerance of, tacrolimus; section 6.3.1.1.1)
11. Documented allergy or hypersensitivity to iron dextran or bovine, murine, algal, or *Streptomyces avidinii* proteins
12. Any uncontrolled autoimmune disease requiring active immunosuppressive treatment
13. Concurrent malignancies within 1 year, except nonmelanoma skin cancers that have been curatively resected
14. Psychosocial circumstances that preclude the participant being able to go through transplant or participate responsibly in follow-up care
15. Women who are pregnant or breastfeeding
16. WOCBP or men who have sexual contact with WOCBP who are unwilling to use effective forms of birth control or abstinence for 1 year after transplantation. A WOCBP is defined in section 11.11.
17. Any serious medical condition or abnormality in clinical laboratory tests that, in the investigator's or medical monitor's judgment, precludes the recipient's safe participation in and completion of the study, or which could affect compliance with the protocol or interpretation of results.

5 DONOR PROCEDURES AND GENERATION OF ORCA-T

Scheduled activities for donors donating for participants assigned to either an Orca-T arm or the SoC arm are shown in appendices 11.1.1 and 11.1.2, respectively.

5.1 Mobilization Therapy

All donors will receive mobilization therapy per institutional guideline treatment with daily G-CSF. [redacted]. The Mobilization Phase starts on the first day of administration of G-CSF and continues until the final day of leukapheresis.

While not required per protocol, monitoring donor peripheral blood $CD34^+$ cell counts prior to donation is recommended to identify donors who are mobilizing poorly.

5.2 Cell Collection

5.2.1 Donor Apheresis for Participants Assigned to Orca-T Arms

For participants assigned to receive Orca-T, a large volume apheresis must be performed in accordance with the Study and Administration Manual. [redacted]

Single-day donor collections are strongly preferred over 2-day collections. If a 2-day collection is required, to the degree possible, the first day's apheresis (day -3) collection will be scheduled for afternoon hours, and the second day's (day -2) will be scheduled for early morning, thereby limiting the time from the end of the first collection to the infusion of the cellular products. In addition, for 2-day collections, donor sites/apheresis centers should perform a $CD34^+$ count on the day 1 apheresis product itself (ie, not based on the donor peripheral blood $CD34^+$ count alone) and report this result to the sponsor.

5.2.2 Donor Apheresis for Participants Assigned to the SoC Arm

For participants assigned to the SoC arm, donors will undergo G-CSF mobilization according to local institutional and donor center practices; biosimilar products are acceptable. PBSCs will be collected by apheresis according to local institutional guidelines. Plasma and red cell depletion are allowed for volume reduction or ABO incompatibility, but any other form of graft manipulation (including ex vivo TCD) is not permitted.

The target stem cell dose Is a minimum of 2 x 10^6/kg and a maximum 10 x 10^6/kg $CD34^+$ cells based on the participant's body weight (section 6.1.2).

Single-day donor collections are strongly preferred over 2-day collections. However, up to 2 leukapheresis procedures may be performed to obtain the minimum $CD34^+$ cell target. If, after 2 leukapheresis procedures, fewer than 2 x 10^6/kg $CD34^+$ cells have been collected, transplant centers will have the discretion to continue PBSC harvesting or to proceed to bone marrow harvesting to obtain sufficient cells. A third leukapheresis procedure is discouraged. If bone marrow harvesting is needed to meet the desired cell dose, the transplant center must notify the CRO medical monitor.

[redacted]

5.3 Outcomes Following Processing (Orca-T Participants Only)

Specifications and dosages for the components of Orca-T are described in the Orca-T IND CMC section.

After manufacturing of Orca-T, 1 of the following outcomes will occur:

- Successful production of Orca-T at the intended dose level. This product(s) will be available for administration to the recipient per protocol (section 6.1). All Orca-T components should be administered to the recipient in their entirety.
- Failure to produce an Orca-T drug product that conforms to all specifications. [redacted] The sponsor quality assurance unit will review the product and take 1 of the following actions:
    - Release the product for use AS-IS or for use with modification
    - Reject the product and return all available cell fractions to the recipient at the discretion of the investigator

  The investigator may also consider salvage donor bone marrow harvest and/or additional apheresis collection(s). Recipients in these cases will continue to be followed and to be analyzed as part of the intent-to-treat population. However, they should also pursue further care per local institutional standard care.

The Study and Administration Manual describes details of the apheresis procedure, including minimum cell yields and transportation requirements.

6 RECIPIENT TREATMENTS

6.1 Investigational Product

Orca-T, the investigational product under study in this protocol, is a cellular therapy product. Detailed information describing the preparation, administration, and storage of Orca-T is located in the Orca-T Study and Administration Manual.

6.1.1 Description, Packaging, and Labeling: Orca-T

Orca-T components are provided as single-dose transfer bags, with an approximate fill volume of 100 mL each for both the T_{reg} and the HSPC drug products. The T_{con} drug product will be provided frozen and stored in the vapor phase of liquid nitrogen in an approximate volume of 15 mL. [redacted] The T_{con} drug product is cryopreserved and additionally contains dimethylsulfoxide and Hetastarch. The bags and/or primary bag container will have labels bearing the appropriate label text as required by regulatory authorities.

6.1.2 Dosing of Orca-T Drug Products

If the participant's actual weight is ≤120% of the IBW, dosing of Orca-T cellular drug products is based on recipient actual body weight rounded to the nearest kg, as assessed during screening. Dosing should be adjusted to a dose based on ABW if the participant's actual weight is >120% of the IBW. IBW will be determined using the method of Devine (1974). ABW [in kg] is equal to [(actual weight–- IBW) x 0.40] + IBW.

All recipients must have appropriate long-term central venous access placed per institutional standard practice prior to initiation of the conditioning regimen. Premedication with acetaminophen or paracetamol (eg, 500 to 1000 mg) and diphenhydramine (eg, 25 to 50 mg) should be administered prior to administration of each component of Orca-T unless contraindicated. Acetaminophen/paracetamol may be omitted as required by institutional guidelines.

[redacted]

Detailed information describing the preparation, administration, and storage of Orca-T is located in the Orca-T Study and Administration Manual.

Subjects must meet all of the following criteria on day 0 and day +2 before receiving Orca-T:

- Karnofsky performance score ≥30%
- No evidence of uncontrolled bacterial, viral, or fungal infection (includes currently taking antimicrobial therapy with progression or no clinical improvement)

[redacted]
Initiation of GVHD prophylaxis should be delayed until the day following T_{con} infusion in these situations. [redacted] These participants will continue to be followed on the study for the protocol-prespecified efficacy outcome and be considered "on study" but "off treatment." Refer to section 9.3 for description of the analysis populations.

6.1.3 Dose Modifications

Dose modifications of Orca-T are not allowed. The HSPC and T_{reg} drug products of Orca-T should each be administered to the recipient in their entirety. The T_{con} drug product should be prepared and administered as instructed in the Study and Administration Manual.

6.2 SoC Graft

Participants assigned to the SoC arm will receive a peripheral-blood-derived graft from their donor, with donor apheresis performed as described in section 5.2.2. Prior to infusion, grafts should be stored per local institutional guidelines for the storage of peripheral-blood-derived grafts. Grafts should be administered through an indwelling central venous catheter.

6.3 Concomitant Therapy

All concomitant medications, blood products, procedures, radiotherapy or other treatments with therapeutic intent administered to recipients will be recorded from the beginning of the conditioning regimen (section 6.3.1.1) through the safety reporting period (section 8.2.5.1). Any concomitant therapy given for a study protocol-related AE must be recorded from the time of informed consent. Any treatment for AEs of special interest (AESI) and GVHD of any type will be recorded all times. Initial treatment for disease recurrence/relapse must also be recorded.

6.3.1 Required Therapies

6.3.1.1 MAC Regimens

All recipients assigned to the Orca-T or SoC arms will receive a MAC regimen per investigator's choice amongst the regimens listed below. For the Phase 3 component, investigators must declare the planned conditioning regimen for each participant prior to randomization. Investigators may choose different regimens contingent upon eventual treatment-arm assignment (eg, BFT if assigned to Orca-T arm and TBI/Cy if assigned to SoC), but this choice must be stated prior to randomization and must not be altered after randomization.

Allowed condition regimens are shown in Table 6-1.

Table 6-1 Myeloablative Conditioning Regimens

TBI/Cy ▪ TBI (1200–1420 cGy) ▪ Cy (100-120 mg/kg)
TBI/Etoposide ▪ TBI (1200–1320 cGy) ▪ etoposide (60 mg/kg)
BFT ▪ busulfan[1] (9.6 mg/kg IV) ▪ fludarabine (160 mg/m^2) ▪ thiotepa (10 mg/kg)

Abbreviations: BFT, busulfan/fludarabine/thiotepa; Cy, cyclophosphamide; IV, intravenous(ly); TBI, total body irradiation.

[1] Alternatively, busulfan may be dosed to maintain an average daily AUC of 4,800–6,000 µM-min (19.7–24.6 mg*H/L) per institutional practice. (Note: total doses are listed)

Doses of conditioning agents and schedule of administration may vary slightly based on institutional practices. Modifications to the conditioning regimen doses must be approved by the medical monitor prior to initiating the treatment. Nonmyeloablative doses and/or regimens are not permitted.

For the Phase 3 component, investigators must declare the planned conditioning regimen for each participant prior to randomization. Investigators may choose different regimens dependent on eventual treatment-arm assignment, but this choice must be stated prior to randomization and not altered after randomization.

6.3.1.1.1 Phase 1b-Specific Myeloablative Conditioning Regimens

Participants enrolled onto the Phase 1b component of the Precision-T Study must receive 1 of the myeloablative regimens listed in Table 6-1 or the following total marrow and lymphoid irradiation (TMLI)-based regimen (Jensen 2018) (Table 6-2):

Table 6-2 Phase 1b-Specific, TMLI-Based Conditioning Regimen

TMLI/Fludarabine/Melphalan ▪ TMLI (1200–2000 cGy) ▪ Fludarabine (125 mg/m^2) ▪ Melphalan (140mg/m^2)

Abbreviations: TMLI, total marrow and lymphoid irradiation.

Doses of conditioning agents and schedule of administration may vary slightly based on institutional practices. Nonmyeloablative doses and/or regimens are not permitted. The TMLI/fludarabine/melphalan regimen is allowed only for participants in Phase 1b; participants enrolled onto the Phase 3 component of Precision-T must receive 1 of the conditioning regimens listed in Table 6-1.

6.3.1.2 GVHD Prophylaxis

6.3.1.2.1 GVHD Prophylaxis: Orca-T Arms

All Orca-T recipients will receive GVHD prophylaxis consisting of single-agent tacrolimus. GVHD prophylaxis should begin on the day following T_{con} infusion (typically day +3), starting no fewer than 12 hours after the start of the T_{con} infusion.

Tacrolimus should be initiated at 0.03 mg/kg/day IV, with a target trough blood level of 5 to 10 ng/mL. If a trough level of <5 ng/mL is noted prior to the start of tapering of GVHD prophylaxis (see section 6.3.1.2.3), tacrolimus dosing must be increased to target the recommended trough level unless clinically contraindicated due to toxicity. Oral (PO) administration is permissible when the participant is able to tolerate food; tacrolimus dosing may be initiated via PO route if tolerated.

6.3.1.2.2 GVHD Prophylaxis: SoC Arm

GVHD prophylaxis for the SoC arm will consist of tacrolimus plus methotrexate.

Tacrolimus plus methotrexate:

- Tacrolimus: Tacrolimus should be initiated at 0.03 mg/kg/day IV on day -3, with a target trough blood level of 5 to 10 ng/mL. If a trough level of <5 ng/mL is noted prior to the start of tapering of GVHD prophylaxis (see section 6.3.1.2.3), tacrolimus dosing should be increased to target the recommended trough level unless clinically contraindicated due to toxicity. PO administration is permissible when the participant is able to tolerate food; tacrolimus dosing may be initiated via PO route if tolerated.
- Methotrexate: Methotrexate should be administered at the doses of 15 mg/m^2 IV bolus on day +1, and 10 mg/m^2 IV bolus on days +3, +6, and +11 after hematopoietic stem cell infusion. The day +1 dose of methotrexate should be given at least 24 hours after the hematopoietic stem cell infusion ends. Dose reduction of MTX due to worsening creatinine clearance after initiation of the conditioning regimen, high serum levels, or development of oral mucositis is allowed according to institutional practices. Leucovorin rescue is allowed according to institutional practices.

6.3.1.2.3 Tapering of GVHD Prophylaxis

Tacrolimus taper can be initiated at a minimum of 90 days after HCT if there is no evidence of active GVHD, with a suggested taper to the prophylaxis regimen of approximately 20% of the dose per month. Initiating a GVHD prophylaxis taper prior to day +90 may only occur with medical monitor approval and in the setting of intolerance/toxicity of tacrolimus (ie, early taper is not allowed for lack of GVHD alone).

For recipients who develop grade ≥2 aGVHD or cGVHD prior to day +90, treatment of GVHD should take precedence. For instance, completion of a corticosteroid taper should be considered before tapering of tacrolimus.

6.3.1.2.4 Modifications to GVHD Prophylaxis Regimen

With the exception of dose modifications, all modifications to the GVHD prophylaxis regimens must be discussed with the medical monitor, sponsor and/or designee, including in cases of intolerance. The reason(s) for modification will be recorded in the case report form (CRF).

6.3.1.2.5 Initial Treatment of aGVHD

If a participant enrolled on the Phase 1b or either arm of the Phase 3 component of Precision-T develops aGVHD, the following treatment approach should be followed for first-line treatment of aGVHD (adapted from ASTCT guidelines for treatment of aGVHD) (Martin 2012):

a. **Skin disease only** (grade 1) – The recommended treatment is topical steroids.
b. **Skin disease only** (grade 2 or 3) – The recommended treatment is 1 mg/kg/day methylprednisolone or equivalently dosed prednisone.
c. **Grade 2 upper gastrointestinal (GI) only–-** The recommended treatment is 1 mg/kg/day methylprednisolone or equivalently dosed prednisone.
d. Any grade lower GI aGVHD, hepatic aGVHD, or stage 3 skin aGVHD–- The recommended treatment is methylprednisolone 2 mg/kg/day or equivalently dosed prednisone.

Participants who are refractory or resistant to, dependent upon, or intolerant of corticosteroids, per BMT−NIH−CIBMTR Task Force definition (appendices 11.5.1.3 and 11.5.2.2) (Schoemans 2018), may be considered for second-line therapy according to local institutional standards.

6.3.1.2.6 Antimicrobial Prophylaxis

All cytomegalovirus (CMV)-seropositive recipients should receive letermovir prophylaxis beginning between day 0 and day +28; therapy should continue through day +100. Letermovir may be omitted for CMV-seropositive recipients only if contraindicated (eg, known hypersensitivity to letermovir) with medical monitor approval. Otherwise, all participants will receive prophylaxis against bacterial, fungal, and viral infections during the peritransplant period according to institutional practices, and any treatment should be recorded in the CRF.

6.3.2 Allowed Therapies

Standard supportive care for HCT-related toxicity is permitted, including growth factors, IV immunoglobulin and blood product transfusions per local institutional standards. Cellular blood products (except for the HCT graft products themselves) should be irradiated in accordance with standard institutional guidelines. Other standard supportive care for symptom control or procedure-related toxicities is allowed, such as analgesics, antiemetics,

electrolyte replacement, and hydration. Other prescribed medications for nonneoplastic conditions are allowed, as well as vitamins and nutritional supplements.

FLT3 inhibitors, BCR-ABL inhibitors, and IDH1/2 inhibitors may be used after transplant to prevent relapse per institutional practice. Intention to use these relapse-prevention therapies should be declared by the investigator prior to randomization for participants enrolled on the Precision-T Phase 3 component.

Concomitant prednisone (or equivalent) may be used at a dose of ≤10 mg/day. The use of high-dose corticosteroid treatment to manage GVHD (section 8.4.1), hypersensitivity reactions, or other noncancer-related symptoms including use as premedication for known hypersensitivity reactions (eg, hypersensitivity to contrast for scans) and use as an antiemetic is allowed. Physiologic doses of corticosteroids for management of adrenal insufficiency are also allowed.

Active infections may be treated in accordance with standard institutional guidelines. Viral-specific cytotoxic T lymphocyte (CTL) (donor- or third party-derived) may be administered for infections not responding to standard therapy, upon discussion with the medical monitor, sponsor, and/or designee.

For participants enrolled onto the Phase 3 component of Precision-T, the use of other investigational agents is not allowed for either the donor or recipient. As noted above, FLT3, BCR-ABL, or IDH1/2 inhibitors used for the prevention of relapse are not prohibited, provided that their intended use is declared by the investigator prior to randomization.

For participants enrolled onto the Phase 1b component of Precision-T, investigational agents may be considered upon approval of the medical monitor, sponsor, and/or designee after review of the research protocol and other supporting documents (eg, currently approved Investigator's Brochure). Coenrollment on other studies that do not involve other investigational agents (eg, observational studies) may be allowed with medical monitor approval.

Treatment of posttransplantation lymphoproliferative disorder (PTLD) (section 8.3.1) should be discussed with the medical monitor, sponsor, and/or designee.

6.3.3 Prohibited Therapies

Subjects may not receive other investigational therapies (except for participants enrolled onto the Phase 1b component of Precision-T, as allowed by the medical monitor per section 6.3.2), immunosuppressive medications, radiotherapy, chimeric antigen receptor-T (CAR-T) cells, or other systemic antineoplastic therapy during the study except as explicitly allowed per protocol (see section 6.3.2).

ATG is not allowed for GVHD prophylaxis on either Orca-T or SoC arms.

6.3.3.1 DLI

Preplanned DLIs are not permitted. Unplanned DLIs may not be administered without prior consultation with the medical monitor. Viral-specific CTL (donor derived or third party) may be given for treatment of infections not responding to standard therapy (eg, CMV, Epstein-Barr virus [EBV], adenovirus) with medical monitor approval.

7 DISCONTINUATION/WITHDRAWAL CRITERIA

7.1 Withdrawal from the Study

A subject may be discontinued and/or withdrawn from the study at any time for any of the following reasons:

- AE(s) that, in the judgment of the participant, may be intolerable to continue therapy or, by judgment of the investigator, may cause severe or permanent harm or that rule out continuation in the study protocol.
- Withdrawal of consent
- Investigator decision: The investigator has the right to terminate the participation of any participant at any time if she or he deems it in the participants best interest. Reasons for study discontinuation might be 1 of the following:
    - Pregnancy
    - Unrelated medical illness or complication
    - Relevant noncompliance with the protocol, including nonreceipt of an HCT
    - Administrative reasons
- Lost to follow-up (see details below, section 7.2)
- Death
- Initiation of a new anticancer therapy including chemotherapy, radiotherapy, or other cellular therapy for relapse. DLI for indications other than relapse is not allowed. However, if a participant does receive a DLI for a nonrelapse indication (a deviation), they should nonetheless continue to be followed per protocol.
- Participants who are otherwise withdrawn from study may be followed as described in section 8, unless the subject withdraws their consent for long-term follow-up (LTFU).

The sponsor or designee must be notified of all subject withdrawals. The reason(s) for withdrawal must be documented in the subject's medical records and CRF. All data otherwise required at the end of the study must be obtained.

7.2 Lost to Follow-Up

A participant will be considered lost to follow-up if he or she repeatedly does not return for scheduled visits and cannot be contacted by the study site.

The following actions must be taken if a participant does not return to the clinic for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible, counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow up, the investigator or designee must make every effort to regain contact with the participant (where possible, by 3 telephone calls and, if necessary, a certified letter sent to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.
- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

8 RECIPIENT STUDY ASSESSMENTS AND PROCEDURES

Scheduled activities for recipients are shown in section 11.1.3.

Only subjects who meet all inclusion and exclusion criteria will be enrolled in this study.

Demographics include age, gender, and race.

Medical history includes a thorough review of significant past medical history, current conditions, any treatment for prior malignancies and response to prior treatment, and any concomitant therapies.

Disease history should include tumor type, stage, grade and grading system, sites of metastases, and mutational status/cytogenetics.

Prior therapies includes all prior treatments for the primary disease, including dates, responses, and durations of responses.

Participants withdrawn from the study due to initiation of new therapy for relapsed disease will be followed for GVHD, survival, and serious AEs (SAEs) considered related to the study product.

During LTFU, participants will be followed for survival and disease status, which may be collected via telephone calls, participant medical records, and/or clinic visits. This includes survival for participants who have progressive disease or relapse while on study. Where available, dates of disease recurrence or progression, the next anticancer therapy administered, dates, and responses will be recorded. If the recipient withdraws from the study, the site's staff may use a public information source (eg, county records) to obtain information about survival status only.

8.1 Disease Evaluation

Disease evaluations (ie, evaluation of the recipient's underlying malignancy) should be performed at the timepoints described in the Precision-T Recipient Schedule of Assessments (appendix 11.1.3). For participants with a history of leukemia or MDS, assessments should include at least a bone marrow aspirate/biopsy, including a sample for central assessment of MRD. The aspirate and biopsy should be evaluated locally for relapse. Other tests may be obtained as clinically indicated, such as cytogenetics or imaging. All data, including images and results of local MRD testing, scheduled or unscheduled, will be made available to the sponsor for possible independent adjudication.

8.2 AEs

8.2.1 Definitions

8.2.1.1 AE

An AE is any untoward medical occurrence associated with the use of Orca—T (Orca-T arm) or the unmanipulated allograft infusion (SoC arm), whether or not considered related to Orca-T or the SoC infusion. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), a symptom, or disease temporally associated with the use of Orca-T or SoC, whether or not considered related to Orca-T or SoC.

All protocol-related AEs must be collected as outlined in section 8.2.5.

The following information should be considered when determining whether or not to record a test result, medical condition, or other incident on the AE CRF:

- From the time of signing the informed consent form (ICF), all Aes should be recorded.
- All medical conditions present or ongoing prior to signing the ICF should be recorded.
- All Aes (regardless of relationship to study drug) should be recorded from the date of informed consent through the end of the safety reporting period (section 8.2.5.1). Complications that occur in association with any procedure (eg, biopsy) should be recorded as Aes with assessed severity whether or not the procedure was protocol mandated.
- Changes in medical conditions and Aes, including changes in severity, frequency, or character, during the safety reporting period should be recorded.

8.2.1.1.1 Examples of Events Meeting the AE Definition

1. Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, electrocardiogram [ECG], radiological scans, vital signs measurements), including those that worsen from baseline or are considered clinically significant in the medical and scientific judgment of the investigator (ie, not related to progression of underlying disease).
2. Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.
3. New conditions detected or diagnosed after study treatment administration even though it may have been present before the start of the study.
4. Signs, symptoms, or the clinical sequelae of a medication error of the study product.
5. Signs, symptoms, or the clinical sequelae of a suspected abuse or misuse of the study product.
6. Pregnancy in a female participant or female partner of a male participant.

7. Transmission of an infectious agent through the study product.
8. Lack of efficacy or failure of expected pharmacological action per se should not be reported as an AE or SAE. Such instances will otherwise be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy may be reported as an AE or SAE if they fulfill the definition of an AE or SAE.

8.2.1.2 SAE

An SAE or serious adverse reaction is any untoward medical occurrence that, at any dose, constitutes 1 of the following:

- Results in death
- Is life threatening

  NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe. CTCAE grade 4 events are not automatically defined as life threatening for SAE determination. For example, a grade 4 increase in ALT may or may not be deemed as life threatening by the investigator and/or sponsor.

- Requires inpatient hospitalization or prolongation of existing hospitalization

  NOTE: Per International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) SAE definition, hospitalization itself is not an AE but is an outcome of the event. Thus, hospitalization in the absence of an AE is not regarded as an AE and is not subject to expedited reporting. The following are examples of hospitalization that are not considered to be AEs:

  - Protocol-specified admission (eg, for procedure required by study protocol)
  - Admission for treatment of target disease of the study, or for a pre-existing condition (unless it is a worsening or increase in frequency of hospital admissions as judged by the clinical investigator)
  - Diagnostic admission (eg, for a work-up of an existing condition such as persistent pretreatment laboratory abnormality)
  - Administrative admission (eg, for annual physical)
  - Social admission (eg, placement for lack of place to sleep)
  - Elective admission (eg, for elective surgery)

- Results in persistent or significant disability/incapacity

  NOTE: This definition is not intended to include experiences of relatively minor medical significance, such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, or

accidental trauma (ie, sprained ankle) that may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

- Is a congenital anomaly/birth defect
- Did not meet any of the above criteria, but, based upon appropriate medical judgment, could have jeopardized the subject and might have required medical or surgical intervention to prevent 1 of the outcomes listed above.

8.2.2 Potential AEs

The investigator and any designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following up AEs that are serious and those considered related to the study treatment or study procedures.

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and nonleading verbal questioning of the participant is the preferred method to inquire about AE occurrences.

8.2.3 AE Severity

aGVHD and cGVHD should be rated according to MAGIC and NIH consensus criteria as described in section 11.5. Otherwise, the investigator will rate severity of each AE according to the CTCAE Version 5.0. The highest grade throughout the course of an event should be reported. A new event should not be entered if the grade of an existing event changes. For all reported SAEs that increase in severity, the supplemental electronic CRFs (eCRFs) also need to be updated to reflect change in severity.

When CTCAE Version 5.0 criteria cannot be used, the AE should be graded as defined below:

- **Grade 1**: The AE is transient and easily tolerated by the subject (mild).
- **Grade 2**: The AE causes the subject discomfort and interrupts the subject's usual activities (moderate).
- **Grade 3 or 4**: The AE causes considerable interference with the subject's usual activities and may be incapacitating or life threatening (severe).
- **Grade 5**: The AE resulted in death of the subject (severe).

An event is defined as serious when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

8.2.4 Assessment of Causality

The investigator will use the following definitions to assess the relationship of the AE to the use of study drug:

- **Not Related:** A clinical event, including laboratory test abnormality, with a temporal relationship to study product in which a causal relationship is improbable and/or in which other drugs, chemicals, underlying disease or other causes provide plausible explanations.
- **Related:** A clinical event, including laboratory test abnormality, where the relationship to study product is definite, probable, possible and/or cannot be ruled out when considering other drugs, chemicals, underlying diseases, or other possible causes.

The investigator should consider the following in assessing causality:

- Alternative causes, such as underlying disease, concomitant therapy, and other risk factors as well as the temporal relationship of the event to study treatment administration will be considered and investigated.
- The investigator will also consult the Investigator's Brochure (IB) in his/her assessment.
- For each AE/SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred, and the investigator has minimal information to include in the initial report to the sponsor. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the electronic data capture system for the study.
- The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is 1 of the criteria used when determining regulatory reporting requirements.

8.2.5 Reporting and Recording of AEs

8.2.5.1 Safety Reporting Period

The safety reporting period for all AEs and SAEs is from the time of signing of the ICF through day +730 (with day 0 defined as the day the recipient receives the Orca-T HSPC drug product [if assigned to Orca-T] or allograft infusion [if assigned to SoC]). Each SAE must be followed until the SAE returns to baseline (resolves or recovers to baseline), the SAE stabilizes (resolves or recovers with sequelae), the SAE is considered not recovered or not resolved by the investigator, or the subject dies (the SAE may be ongoing at the time of death). SAE outcome may not be possible to collect when a subject withdraws consent.

All nonserious AEs will be followed through the safety reporting period.

8.2.5.2 AE Reporting: Phase 1b

In the event of an SAE, whether associated with study drug or not, the investigator will notify the Precision-T sponsor within 24 hours of the site being made aware of the SAE. All SAEs must be reported using the SAE report form. Detailed instructions on how to complete this form are described in the Precision-T SAE/AESI Report Form Completion Guidelines.

Suspected unexpected serious adverse reactions (SUSAR) for the study drug will be reported in accordance with 21 Code of Federal Regulations (CFR) 312.32.

8.2.5.3 AE Reporting: Phase 3

For the Phase 3 component of Precision-T, all SAEs should be reported to the sponsor within 24 hours of the site being made aware of the SAE. All SAEs must be reported using the SAE report form. Detailed instructions on how to complete this form are described in the Precision-T SAE/AESI Report Form Completion Guidelines. SUSARs for the study drug will be reported in accordance with 21 CFR 312.32.

8.2.5.4 AE and SAE Recording

1. When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
2. All AEs will be recorded in source documents based on the reporting guidelines outlined herein, with sufficient detail to allow for grading per CTCAE Version 5, and reported with all relevant information on the appropriate eCRF page.
3. It is **not** acceptable for the investigator to send photocopies of the participant's medical records to the sponsor and/or designated CRO in lieu of completion of the appropriate CRF page.
4. There may be instances when copies of medical records for certain cases are requested by the sponsor and/or CRO, designee, or regulatory authority. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to the sponsor or designee.
5. The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

8.2.6 Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs, and any nonserious AEs of special interest (section 8.3), will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in section 7.2).

8.3 AESIs

AESIs for both the Phase 1b and Phase 3 components of Precision-T are as follows:

- PTLD
- Any primary or secondary graft failure event
- Any grade veno-occulsive disorder/sinusoidal obstruction syndrome
- Any grade thrombotic microangiopathy (TMA)
- Any grade ≥2 infection

For all AESIs, the overall specific diagnosis (eg, PTLD), not an individual sign and/or symptom, should be reported as described in the Precision-T SAE/AESI Report Form Completion Guidelines. If the AESI in question meets criteria for seriousness per section 8.2.1.2., the event is an SAE and should be reported as described in section 8.2.5. AESIs should be reported within 5 business days of the site being made aware of the AESI.

All data relevant to diagnosis, staging, grading, treatment, and outcomes of AESIs must be made available to the sponsor for later independent review or adjudication. This includes all source documents such as medical notes, laboratory and imaging studies, biopsies, pathology, and consultant reports.

8.3.1 Posttransplant Lymphoproliferative Disorder

PTLD is defined as a lymphoma that occurs after HCT or solid organ transplantation. It is a known complication of HCT and may be generally diagnosed and treated according to local institutional standards. Suggested approaches to the diagnosis of PTLD are as follows:

- Participants suspected of PTLD (eg, fever of unknown origin >39°C with lymphadenopathy and/or hepatosplenomegaly) should undergo appropriate imaging studies (eg, computed tomography [CT] and/or positron emission tomography [PET] scanning of at least the chest and abdomen) and testing for EBV viremia. Biopsies should be sought and include studies of routine morphology, immunophenotyping, and EBV (eg, EBER in situ hybridization) testing.
- The diagnosis of PTLD requires a biopsy consistent with the 2017 WHO classification of PTLD (nondestructive [plasmacytic hyperplasia, infectious-mononucleosis–like and florid follicular hyperplasia], polymorphic, monomorphic, or Hodgkin-lymphoma-like), along with lymphoma-type-appropriate staging procedures such as CT with or without ^{18}F-fluorodeoxyglucose PET (Swerdlow 2016, Swerdlow 2017, Dierickx 2018).

Treatment of PTLD, such as reduction of immunosuppression, rituximab, chemotherapy radiation, cellular therapy and/or antivirals, should be discussed with the medical monitor, sponsor, or designee.

8.4 GVHD

aGVHD and cGVHD are components of the primary and key secondary endpoints of the Phase 3 component of Precision-T. The following instructions for assessment, staging, and grading of GVHD will apply to participants enrolled on the Precision-T Phase 3 and Phase 1b components.

8.4.1 Assessment, Staging, and Grading of aGVHD

aGVHD will be staged and graded per MAGIC standardization criteria (Harris 2016). Please see the guidelines for the assessment of aGVHD and for documentation of signs, symptoms, and testing associated with aGVHD assessment in section 11.15.

The time of onset of acute grades 2 to 4 and 3 or 4 aGVHD will be recorded, as well as the maximum grade achieved. Responsiveness to treatment should also be assessed according to section 11.5.1.2. The aGVHD endpoint will be evaluated through day +365.

An assessment for aGVHD should be performed at all visits indicated by the Recipient SoA (appendix 11.1.2) and at any unscheduled visit through day +365. These assessments should be recorded in the dedicated aGVHD eCRF.

Treatment of aGVHD should be implemented per section 6.3.1.2.5.

8.4.1.1 Documentation of aGVHD

As noted in section 3.2.2, an EAC will independently grade and assess aGVHD. To facilitate review, if a participant develops grade ≥2 aGVHD, sites should perform the following tasks at a) initial diagnosis of aGVHD and b) any future study visit in which signs or symptoms of aGVHD worsen:

- A careful history and physical should be performed, taking care to record all signs and symptoms that are possibly or probably related to aGVHD.
- Visible manifestations of aGVHD (eg, rash) should be described in detail. This should include descriptions of skin findings, body areas involved, and a percentage of body surface area involved.
- Daily diarrhea volumes should be measured and reported.
- Symptoms such as abdominal pain or nausea should be described in detail, and longevity of symptoms should be reported.
- Pathology reports from any biopsies performed to assess for aGVHD (eg, colonoscopy with biopsy) should be provided to the sponsor.

Guidelines for the assessment of aGVHD and for documentation of signs, symptoms, and testing associated with aGVHD assessment are listed in section 11.4.

8.4.2 Assessment, Staging, and Grading of cGVHD

cGVHD will be diagnosed, staged, and graded per the International NIH Chronic GVHD Diagnosis and Staging Consensus Working Group criteria (Jagasia 2015) appendix 11.5.1.3). Nine organs will be scored on a 0 to 3 scale to reflect degree of cGVHD involvement. Liver and pulmonary function test results and use of systemic therapy for treatment of cGVHD will also be recorded. These data will allow calculation of the NIH global severity scores of mild, moderate, and severe cGVHD. Assessment of development of cGVHD will occur up to 2 years after HCT. For participants who develop cGVHD, responsiveness to treatment should be assessed according to appendix 11.5.2.2.

An assessment for cGVHD should be performed at all visits indicated by the Recipient SoA (appendix 11.1.3) and at any unscheduled visit through day +730. These assessments should be recorded in the dedicated cGVHD eCRF.

Guidelines for the assessment of cGVHD and for documentation of signs, symptoms, and testing associated with cGVHD assessment are listed in appendix 11.16.

8.4.2.1 Documentation of cGVHD

cGVHD should be assessed and graded as described in Jagasia 2015 (see also appendix 11.5.2). Nine organ systems will be scored as part of this assessment. As noted in section 3.2.2, an EAC will independently grade and assess cGVHD. To facilitate review, if a participant develops any grade cGVHD, sites should perform the following tasks at a) initial diagnosis of cGVHD and b) at any future study visit in which signs or symptoms of cGVHD worsen (ie, organ scoring and/or grade of cGVHD is increased):

- A careful history and physical should be performed, taking care to record all signs and symptoms that are possibly or probably related to cGVHD.
- Visible manifestations of cGVHD (eg, lichen planus-like features, sclerotic features) should be described in detail. This should include descriptions of findings, body areas involved, and a percentage of body surface area involved. Examination should include skin, mouth, eyes, genitalia, etc.
- Limitations in the range of motion of joints should be documented according to the scoring system in section 11.17.
- Pathology reports from any biopsies performed to assess for cGVHD should be provided to the sponsor.
- Consultation notes from specialists assessing for the presence of cGVHD (eg, ophthalmology assessments) should be provided to the sponsor.

Guidelines for the assessment of cGVHD and for documentation of signs, symptoms, and testing associated with cGVHD assessment are listed in section 11.17.

8.4.3 Responses to GVHD Treatment

Responses to all therapies will be recorded according to appendix 11.5.1.2 for cGVHD and by the International NIH Chronic GVHD Diagnosis and Staging Consensus Working Group criteria for chronic GVHD (appendix 11.5.2.2) (Lee 2015).

8.5 Study Modifications in Response to the COVID-19 Pandemic

8.5.1 General Guidelines

Sites participating in Precision-T should review current ASTCT guidelines for prevention, diagnosis, and management of COVID-19 in donors and recipients (Waghmare 2020). Sites should additionally make any site-specific COVID-19 guidelines and procedures available to the sponsor for review upon request.

8.5.2 Prevention of COVID-19 After Transplant and Monitoring for COVID-19

Recipients of alloHCT have compromised immune systems and may be at particularly high risk for poor outcomes related to COVID-19 (Dholaria 2020).

- Sites should review current ASTCT guidelines and local institutional procedures to minimize the study participants' (both donors and recipients) risk of exposure to SARS-CoV-2 (Waghmare 2020).
- When deemed clinically appropriate by the investigator, protocol-specified follow-up clinic visits should be modified to minimize the participant's risk of exposure to SARS-CoV-2. This may include conversion of in-person visits to alternative visits (eg, phone contacts or video visits).

8.6 QOL Assessments

The value of patient-reported outcomes (PROs) is increasingly recognized in HCT, as studies regarding the relationship between PROs and HCT complications are emerging. Baseline PROs are associated with healthcare utilization after HCT and risk of aGVHD in alloHCT recipients (Johnson 2021). These findings underscore the potential utility of pretransplantation PROs as important prognostic factors for HCT.

QOL is individualized, highly subjective, and may change over time. For patients diagnosed with hematological malignancies, QOL domains are initially impaired at diagnosis, yet improve within 6 months (Alibhai 2009). With HCT being a potentially curative therapy for hematologic malignancies, early studies have focused on HCT outcomes. As a result of advances in symptom management and cellular therapies, patients are living longer. This is exemplified by the longitudinal evaluations and identifying not only the impact of posttransplant complications but also the impact such treatment modalities have on QOL.

8.6.1 Instruments

At timepoints specified in the Recipient SoA (appendix 11.1.3), questionnaires will be administered to all participants enrolled on Precision-T.

To gain an understanding of global QOL, longitudinal assessments will be conducted utilizing the EQ-5D. To identify changes in overall health status in the context of HCT, QOL will be measured by the Functional Assessment of Cancer Therapy - Bone Marrow Transplant (FACT-BMT).

8.6.1.1 EQ-5D-5L

The EQ-5D is a well-known, reliable, and valid standardized measure of health status developed by the EuroQol Group in 1990 to provide a simple, generic measure of health for clinical and economic appraisal. The EQ-5D is a descriptive measure that consists of 2 sections: a short questionnaire and a visual analog scale (VAS). The questionnaire covers five dimensions (5D): mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension requires a response to a health state, which requires a response to 1 of 5 levels (5L): no problems, slight problems, moderate problems, severe problems, and extreme problems. Respondents also self-rate their perceived health status on vertical VAS, ranging from 0 (the worst possible health status) to 100 (the best possible health status) (Herdman 2011).

8.6.1.2 FACT-BMT

The FACT-BMT provides a comprehensive overview regarding the multidimensional construct of QOL (Cella 1993; Kopp 2000). It is a reliable and valid instrument that measures 5 dimensions of QOL in HCT recipients. FACT-BMT is comprised of the FACT-General (FACT-G) instrument which includes 27 items (Cella 1993) and the Bone Marrow Transplantation Subscale (BMTS), which is a 23- item instrument (McQuellon 1997). The FACT-G assesses QOL domains: physical (7 items), social (7 items, including sexual satisfaction), emotional (6 items), and functional (7 items, including work, sleep, and leisure activities) (Cella 1993). The transplant-specific segment assesses physical well-being, social/ family well-being, emotional well-being, functional well-being, and additional concerns (McQuellon 1997).

The FACT-BMT takes approximately 10 to 15 minutes to complete. Participants respond to questions using a 5-point Likert-type response scale ranging from 0 to 4 (0 = not at all; 1 = a little bit; 2 = somewhat; 3 = quite a bit; and 4 = very much). Higher scores indicate a better QOL.

9 STATISTICAL CONSIDERATIONS

9.1 Sample Size and Power Calculation

9.1.1 Phase 3: Sample Size

Assume the effect of the experimental regimen for bone marrow transplant (BMT), against a standard of care, is assessed using a time-to-event Cox regression analysis, where the primary endpoint is CGFS. To achieve 90% power with a true HR = 0.40 and 1-sided alpha of 0.025, the required number of events needed is 56 events (see Fleming and Harrington [Fleming 1991] p. 395 and Al-Khalidi et al, [Al-Khalidi 2011] Equation 5.) This true HR of 0.40 corresponds approximately to 12-month event-free CGFS rates of 55% versus 79% (equal to event rates at 12 months equal to 45% of participants for SoC vs 21% of participants for Orca-T).

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 arms, 174 participants will be randomized.

9.1.2 Phase 1b Sample Size: Protocol Versions 1 Through 5

Prior to Version 6 of the Precision-T Protocol, the sample size of the study as a whole was based on the presence of 3 arms; Arms I, II, and III (28 participants in each arm) were set primarily to ensure adequate power to rule out excessive primary graft failure in any of the arms (analyzed separately). For reference purposes, the justification for the sample size in Versions 1 through 5 of the protocol is retained below in italics:

> *The same stopping rules and sample size calculations were used for all three arms. Historical control data (Olsson 2015) indicate primary graft failure occurred in approximately 2.5% of PBSC-based transplants with matched related or unrelated donors. They further report odds ratios for PGF for patients with AML/ALL with active disease vs. AML/ALL in CR (Arm II vs Arm I, OR = 1.54) and MDS vs. AML/ALL (Arm III vs Arm I, OR=1.38), which would correspond to only slightly increased PGF incidence of 3.9% and 3.5%. Therefore, we set a maximum acceptable PGF rate of 5% for each of the three arms, and propose the same stopping rule in each arm where enrollment will cease if 4 or more graft failures are observed among n=28 evaluable patients. If the true graft failure rate is as expected (≤ 5%), there is a ≤ 4.9% chance of observing 4 or more graft failures in n = 28 patients (type I error). If the true graft failure rate is 15% higher than expected, then there is an 84% chance of observing 4 or more graft failures in n = 28 patients (power).*
>
> *All calculations were based on exact binomial distributions.*

Starting with Protocol Version 6, the sample size of the remaining Phase 1b component of Precision-T will be based on the methodology described in section 9.1.3.

9.1.3 Phase 1b Sample Size: Protocol Version 6 and Subsequent Versions

In Version 6 and subsequent versions of the Precision-T Protocol, Arms I, II, and III are eliminated from the Phase 1b component of the study, as noted in section 3.1. Participants

eligible for the Phase 1b component, starting with Version 6 of the protocol, include the following categories/diagnoses:

A. AML, ALL, or MPAL that is not in morphologic CR (or CRi); note that these patients would be categorized as very high overall risk per the DRI (Armand 2014)
B. MF that is eligible for transplant per National Comprehensive Cancer Network Guidelines
C. BPDCN (see the 2016 revision to the World Health Organization classification of myeloid neoplasms and acute leukemia (Daniel 2016))
D. Participants aged 66 to 75 years with AML, ALL, or MPAL that is in morphologic CR and DRI intermediate-to-high risk; or MDS that is DRI intermediate-to-high risk. (Armand 2014)
E. Participants with AML, ALL, MPAL, or MDS that would qualify for the Precision-T Phase 3 component except for having mildly impaired renal and/or hepatic function, defined as eGFR of 50 to 59 mL/min or a total bilirubin ≥ULN up to 2x ULN.
F. Participants with DRI low-risk AML or CML, including the following:
    a. CML in chronic phase with a previous history of accelerated phase or blast crisis, and/or participants with chronic-phase CML that is resistant, or the participant is intolerant to, more than 1 first- and/or second-generation tyrosine kinase inhibitors
    b. Participants with AML with inv(16) without accompanying complex cytogenetics

[redacted]

9.1.4 Phase 1b: Justification for Additional Stopping Rules as Described in Section 4.3

The stopping criteria (section 3.3.1, Table 3-1) also reflect a maximum acceptable rate of 5% for primary or secondary graft failure by day +100. This stopping rule has over an 8% chance of being triggered if the infection rate is 5%, and an 86% chance of being triggered if the true

infection rate is 20%. If the true failure rate is 20%, the stopping rule will be triggered on average after approximately 17 participants are evaluable for this endpoint.

In addition, the stopping criteria for grade ≥3 aGVHD (section 3.3.1, Table 3-2) reflect a maximum acceptable rate of 15% for these events occurring by day +100. This stopping rule has an 11% chance of being triggered if the true toxicity rate is 15%, and an 85% chance of being triggered if the true toxicity rate is 35%. If the true toxicity rate is 35%, the stopping rule will be triggered on average after approximately 14 participants are evaluable for the safety endpoint.

The stopping criteria for manufacturing failure (section 3.3.2, Table 3-3) reflect a maximum acceptable rate of 4% of these events occurring. This stopping rule has a 9.5% chance of being triggered if the failure rate is 4%, and an 80% chance of being triggered if the true failure rate is 16%. If the true failure rate is 16%, the stopping rule will be triggered on average after approximately 16 participants are evaluable for this endpoint.

The stopping criteria for grade 5 toxicity that is at least probably related to Orca-T by day +100 (section 3.3.2, Table 3-4) reflect a maximum acceptable rate of 8% of these events occurring. This stopping rule has a 9.2% chance of being triggered if the failure rate is 8%, and an 81% chance of being triggered if the true failure rate is 24%. If the true failure rate is 24%, the stopping rule will be triggered on average after approximately 16 participants are evaluable for this endpoint.

The stopping criteria for grade 4 or 5 infections occurring through day +100 (section 3.3.2, Table 3-5) reflect a maximum acceptable rate of 30% of these events occurring. This stopping rule has a 10% chance of being triggered if the infection rate is 30%, and an 87% chance of being triggered if the true infection rate is 55%. If the true failure rate is 55%, the stopping rule will be triggered on average after approximately 17 participants are evaluable for this endpoint.

9.2 Endpoints

Endpoints are described in section 2.3 above. Primary and secondary endpoints are defined in this study for recipients only.

9.3 Analysis Populations

9.3.1 Donor Populations

- Donor set: all donor subjects who complete at least 1 screening procedure
- Donor intention-to-treat (ITT) analysis set: all donor subjects who complete mobilization and initiate apheresis

9.3.2 Phase 3: Recipient Populations

Analysis Set	Description
Enrolled Population	All participants who sign informed consent are deemed to be eligible for the study by the medical monitor upon reviewing and signing the eligibility packet.
ITT Population	All enrolled participants who are randomized to either Orca-T or SoC. Participants will be analyzed according to their randomized treatment assignment. For participants assigned to the Orca-T arm, participants for whom a manufacturing failure occurs or donor mobilization fails will be included in the ITT population.
mITT Population	All participants in the ITT population who are treated with their randomized treatment assignment. Participants who do not undergo HCT due to relapse prior to Orca-T or SoC treatment will not be included in the mITT population. In addition, participants randomized to Orca-T for whom a manufacturing failure occurs or donor mobilization fails will be included in the mITT.
Per-Protocol Population	All participants in the mITT analysis set who meet all inclusion/exclusion criteria, receive their randomized treatment, do not experience any major protocol deviations, undergo HCT and have at least 1 post-baseline assessment of cGVHD or survival status. Participants randomized to Orca-T for whom a manufacturing failure occurs or donor mobilization fails will not be included in the per-protocol population.
Safety Analysis Population	Participants in the ITT analysis set analyzed according to the treatment received.

Abbreviations: cGVHD, chronic graft-versus-host disease; HCT, hematopoietic cell transplantation; ITT, intent to treat; mITT, modified intent to treat; SoC, standard of care.

The main efficacy analysis set for Phase 3 component will be the ITT population. The ITT population includes any participants assigned to the Orca-T arm for whom a manufacturing failure occurs or in cases where the donor mobilization fails (ie, when the apheresis product contains too few $CD34^+$ hematopoietic stem cells to produce an Orca-T product).

The modified ITT (mITT) population is defined as all participants undergoing randomization with the exception of participants who are unable to undergo transplant due to clinical decline (eg, relapse) prior to day of transplant (day 0).

Safety for the Phase 3 component of Precision-T will be based on the safety analysis population.

9.3.3 Phase 1b: Recipient Populations

Analysis Set	Description
Enrolled Population	All participants who sign informed consent are deemed to be eligible for the study by the medical monitor upon reviewing and signing the eligibility packet.
Full Analysis Population	All enrolled participants who receive any amount of Orca-T
Safety Analysis Population	Full analysis participants who have at least 1 postbaseline safety evaluation.

For the sake of clarity, participants who are unable to receive Orca-T due to a failure to produce Orca-T (section 5) are excluded from these populations for the Phase 1b component of Precision-T only.

9.4 Statistical Analyses

The statistical analysis plan (SAP) will be developed and finalized before database lock and will describe the participant populations to be included in the analyses and procedures for accounting for missing, unused, and spurious data. Additional details regarding the statistical analyses, including subgroup analyses and analyses of intercurrent events, are also described in the SAP.

As a general strategy, continuous efficacy and safety endpoints will be summarized using the 5-number summary (mean, standard deviation, median, minimum, and maximum). Frequency distributions (counts and percentages) will be used to summarize categorical endpoints.

9.4.1 Disposition of the Study Subjects

The disposition of subjects will be described with summaries by arm and dose, where applicable, of the number of subjects enrolled, the number of subjects treated, and the number of subjects who discontinued early from the study. These analyses will be performed for donor and recipient populations.

9.4.2 Demographic and Baseline Characteristics

Demographic and baseline characteristics will be summarized and compared by arm and dose, where applicable. These analyses will be performed for donor and recipient populations.

9.4.3 Exposure to Study Treatment

For donors, frequency distributions of the number of mobilization doses, mobilization agents, and apheresis procedures, as well as frequency distributions of production of Orca-T will be presented.

For recipients, frequency distributions of the received doses of the components of Orca-T will be presented by arm, using the recipient full analysis set.

9.4.4 Analysis of Safety and Efficacy

For Phase 3, efficacy will be analyzed using the ITT analysis set (a sensitivity analysis will utilize the mITT analysis set). For Phase 1b, efficacy will be analyzed using the full analysis set. For both phases, safety will be analyzed using the safety analysis set.

9.4.4.1 Analysis of Primary Endpoint

For Phase 3, the final analysis will occur when 56 CGFS events are observed. Nearly all of the experimental 1-sided 0.025 false positive error rate will be spent at the time of the final analysis of the primary endpoint, as the O'Brien-Fleming boundary used for the interim analyses preserved the (1-sided) 0.005 false positive error rate (see SAP). To be specific, at least 0.0250 – 0.0006 = 0.0244 of the (1-sided) false positive error remains for the final analysis. Hence, the 2-sided p-value that will be used at the final analysis is 0.049. Statistical significance will be achieved at the final analysis with an estimated HR = 0.573, corresponding to estimated 12-month event-free rates of 55% versus 71%.

The primary efficacy hypothesis will be tested using a Cox's Proportional Hazard model stratified by the randomization strata to calculate the hazard ratio and the associated 90% CI.

Kaplan-Meier survival estimates (product-limit estimates) will be presented by treatment group together with a summary of associated statistics for survival time with associated 2-sided 90% CIs.

In particular, the survival rate at 6, 12, 18, and 24 months will be estimated with corresponding 2-sided 90% CIs. The CIs for the median will be calculated according to Brookmeyer and Crowley (1982), and the CIs for the survival function estimates at the time points defined above will be derived using the log-log transformation according to Kalbfleisch and Prentice (2002). The estimate of the standard error will be computed using Greenwood's formula.

The primary Phase 3 efficacy analysis will be based on the ITT population, with participants who are lost to follow-up or do not experience CGFS censored at their last on-study visit date. Participants who relapse after randomization and prior to receiving study treatment will be censored at their date of relapse.

Sensitivity analyses of the primary Phase 3 endpoint will be performed as described in the SAP.

The Phase 1b primary endpoint of incidence and timing of primary graft failure will be analyzed by presenting the percentage of participants with primary graft failure through day +28 along with the associated 90% Clopper-Pearson exact binomial confidence interval. Timing will be analyzed by computing median time to primary graft failure along with 25th and 75th percentiles based on a Kaplan-Meier analysis.

The primary Phase 1b endpoint of incidence and severity of grade ≥3 aGVHD by day +100 will be analyzed by presenting a frequency analysis of this endpoint along with the associated 90% Clopper-Pearson exact binomial confidence interval. Frequencies by severity may also be presented.

9.4.4.2 Analysis of Secondary Endpoints

For Phase 1b: Neutrophil engraftment through day +28, platelet engraftment through day +50, secondary graft failure through day +100, aGVHD through day +180, steroid-refractory aGVHD though day +180, cGVHD through day +730, PTLD through day +730, disease relapse through day +730, and NRM will be summarized using the cumulative incidence method, treating death (or, for NRM, disease relapse/progression) as a competing risk. Maximum stages, grades and/or severity scores for aGVHD and cGVHD will also be summarized as frequencies and percentages. GVHD progression-free survival will be analyzed using Kaplan-Meier method, with quartiles and associated 90% confidence intervals presented.

Overall survival will be estimated using the Kaplan-Meier method, with quartile estimates and associated 90% confidence intervals presented.

For Phase 3: Analysis of moderate-to-severe cGVHD through day +730 will utilize the cumulative incidence method, with death included as a competing event. Medians and quartiles will be generated along with associated 90% confidence intervals.

Analysis of GRFS through day +365 will be based on a Cox Proportional model as described above for the primary efficacy endpoint.

Analysis of relapse-free survival through day +730 will be based on a Cox Proportional model as described above for the Phase 3 primary efficacy endpoint.

Analysis of the Phase 3 secondary endpoints at the interim and final analyses will proceed using a hierarchial testing procedure as described in the SAP. If the trial is not stopped at the time of the interim analysis, the p-values used in the final analysis of the secondary endpoint(s) will be the p-value used for the final analysis of the primary endpoint, specifically a 1-sided 0.0244 p-value if the endpoint was not tested at the time of the interim analysis using the gatekeeping procedure. If the secondary endpoint was tested at the time of the interim analysis, the p-value used for the final analysis will be adjusted as described in the SAP.

Safety analyses for both phases will involve examination of the incidence, severity, and type of TEAEs reported, changes in vital signs and laboratory test results from baseline (the assessment prior to first dose) to specified time points throughout the study, and concomitant therapy use. Safety analyses are described in further detail below.

9.4.4.3 TEAEs

TEAEs reported during the study will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). The incidence of TEAEs will be summarized by arm, dose, and the following:

- System organ class (SOC) and preferred term
- SOC, preferred term, and severity

These summaries will be presented for the following subsets:

- All AEs
- SAEs
- AESIs
- AEs leading to treatment discontinuation

For tables reporting AEs by severity, if a subject has multiple occurrences of an AE with the same SOC and preferred term, the most severe event will be presented.

9.4.4.4 Clinical Laboratory Evaluation

Laboratory parameters will be summarized by arm and dose at each visit. Each summary will include the values of the laboratory parameters and their change from baseline. Shift tables from baseline will be presented for laboratory values in the chemistry and hematology panels. Parameters will be classified according to the laboratory reference normal ranges. A listing will be provided for values out of the normal range as well as clinically significant abnormal laboratory values.

9.4.4.5 Vital Signs

Vital signs, including pulse, blood pressure, temperature, height, and body weight will be summarized by time point. For each assessment of vital signs, change and percent change in vital signs from baseline will be summarized by disease and cohort.

9.4.4.6 Karnofsky Performance Status

Karnofsky performance status will be summarized for each visit by arm and dose. Shifts from baseline to the best and worst post-baseline score may be tabulated.

9.4.5 QOL

With the implementation of Version 6 of the Precision-T protocol, QOL will be assessed for all participants enrolled on Precision-T.

EQ-5D-5L

EQ-5D-5L evaluation of the 5 different dimensions of health states is divided into 5 levels of perceived health problems. A unique health state is defined by combining 1 level from each of the dimensions. A health profile will be generated by visit and by treatment. Summary statistics will be derived, including numbers of participants and proportions of categorical responses for the 5 EQ-5D dimensions. Using the ANCOVA model, changes in health dimension and severity from baseline will be assessed over time. Mean, standard deviation (SD), minimum, median, and maximum scores will be provided for by visit and by treatment. The significance of change within each treatment group and significance of the difference between the treatment groups will be reported. Additionally, the EQ VAS score will be summarized using mean, SD, minimum, median, and maximum scores by visit and by treatment. For the health state index and EQ VAS scores, mean, SD, minimum, median, and maximum will be provided.

FACT-BMT

FACT-BMT subscores (physical, functional, social/family, emotional and BMT-specific items) and overall FACT-BMT score will be summarized utilizing descriptive statistics. The relationship between QOL scores and types and severity of cGVHD will be assessed after controlling for background covariates including age, gender, disease, time from alloHCT, donor MAC regimen, GVHD prophylaxis, performance status at HCT, and number of HCTs. A series of repeated measures analyses of variance (ANOVA) will occur on the FACT-BMT subscales to assess change over time in response to BMT.

Modified 7-Day Lee cGVHD Symptom Scale

The Lee cGVHD Symptom Scale (LSS), published in 2002, was developed to measure symptom burden in adults diagnosed with cGVHD (Lee 2002). The scale has been modified since the original publication, and the modified cGVHD Symptom Scale (mLSS) is frequently used to measure cGVHD symptom burden in clinical trials (Teh 2020). In the Precision-T Study, participants diagnosed with cGVHD will be assessed using the mLSS per the recipient SoA (appendix 11.1.3).

9.4.6 Analysis of Pharmacodynamics

Absolute values of pharmacodynamic measures may be described by 5-number summaries and value versus time graphs. Where applicable, absolute and percent changes from baseline will also be described. [redacted] Regressions may be performed as appropriate. Exploratory analyses may be performed to evaluate a possible correlation between each of these endpoints and primary and/or secondary endpoints including toxicities. Additional analyses may also be performed. Details will be provided in the SAP.

9.4.7 Interim Analyses

An interim analysis will be performed for the primary and secondary efficacy endpoints in Phase 3 only. The O'Brien-Fleming boundary for definitive evidence of benefit will be used, protecting an experimental 1-sided 0.025 false-positive error rate.

A single interim analysis is planned for when 37 primary endpoint events are observed. This represents 2/3 of the expected 56 primary efficacy events at the time of the final analysis. Based on 2/3 of the expected total number of events, a 1-sided alpha = 0.0006 will be utilized for the interim analysis of the primary efficacy endpoint.

At the time of the interim analysis, testing of the primary and secondary endpoints will utilize a gate-keeping algorithm with the endpoints tested in the following order:

(1) CGFS (primary efficacy endpoint)

(2) GVHD and relapse-free survival through day +365

(3) Moderate-to-severe cGVHD

(4) Relapse-free survival through day +730

The 1-sided nominal p-value that will be used for the interim analysis of the primary endpoint will be 0.0006. At $L = 36$ events, this boundary would be crossed with an estimated HR = 0.326, corresponding approximately to estimated 12-month event-free CGFS rates of 55% (SoC) versus 82% (Orca-T).

A hierarchal testing strategy will be used for the interim analysis with the above 4 endpoints tested in order. Specifically, if the interim analysis of the primary endpoint of CGFS rejects the null hypothesis of no treatment effect, the secondary efficacy endpoints will be tested first for GRFS, then for moderate-to-severe cGVHD, and finally for RFS. Testing of GRFS will be performed only if the null hypothesis for the primary endpoint is rejected. Testing of moderate-to-severe cGVHD will be performed only if the null hypotheses for the primary endpoint and for GRFS are rejected. Testing of RFS will be performed only if the null hypotheses for the primary endpoint, GRFS, and moderate-to-severe cGVHD are rejected. The p-values used in the testing of each of the secondary endpoints will be computed based on the observed information fraction for that endpoint at the time of the interim analysis.

If the treatment effect for the primary efficacy endpoint is significant, no further testing of this endpoint (at the time of the final analysis) will occur, although descriptive statistics may be presented at that time. Similarly, if (after using the hierarchal testing strategy) the estimated treatment difference for any of the secondary efficacy endpoints is significant at the time of the interim analysis, no further testing of that endpoint will occur at the time of the final analysis, although descriptive statistics may be generated at that time. Only endpoints that are not significant at the time of the interim analysis will be tested at the time of the final analysis.

In addition to the above interim analysis, a sample size re-estimation procedure will be used when 2/3 of the 174 participants (115 participants) have been enrolled and followed for at least 3 months. Details on this analysis are found in the SAP.

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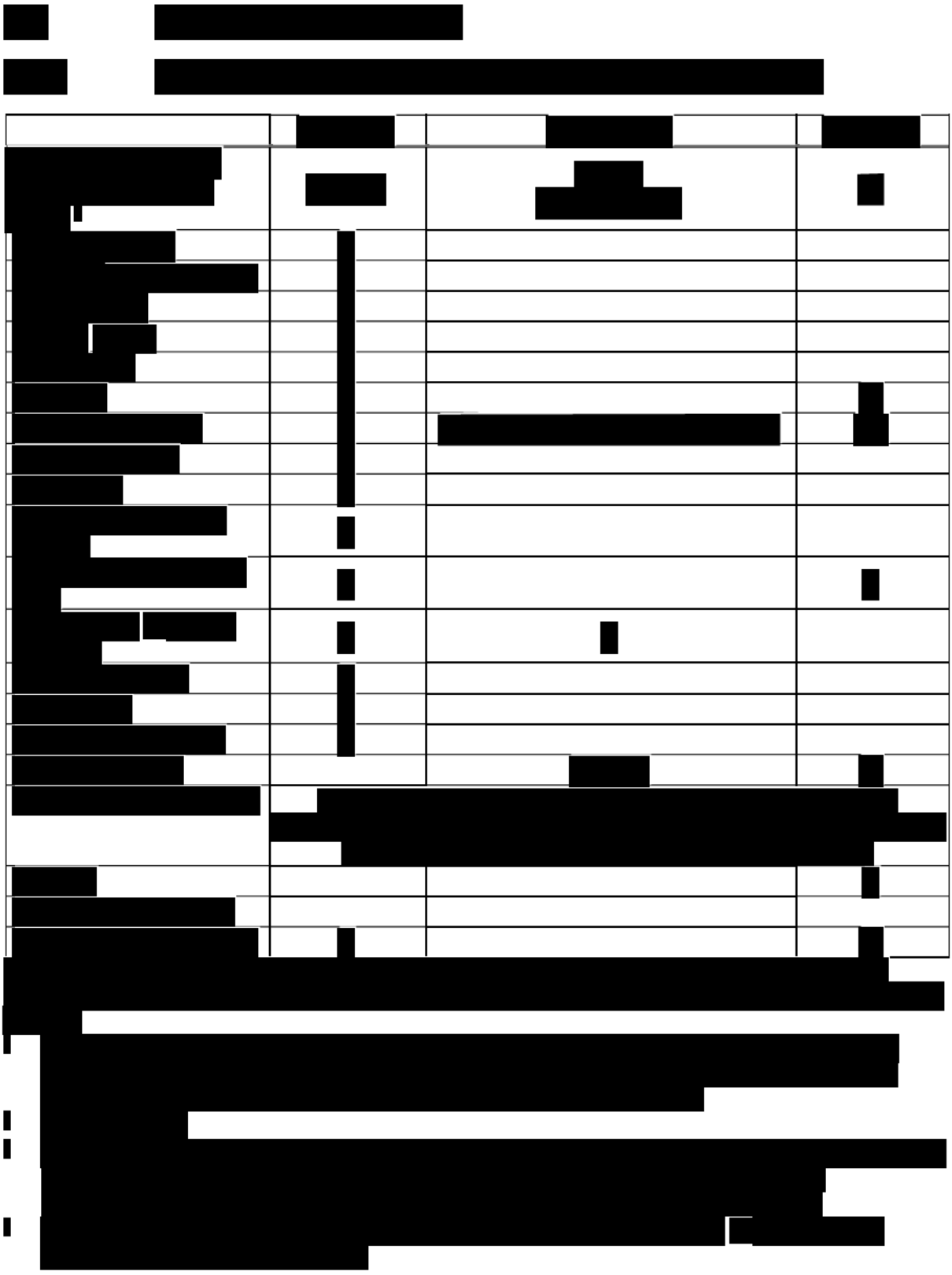
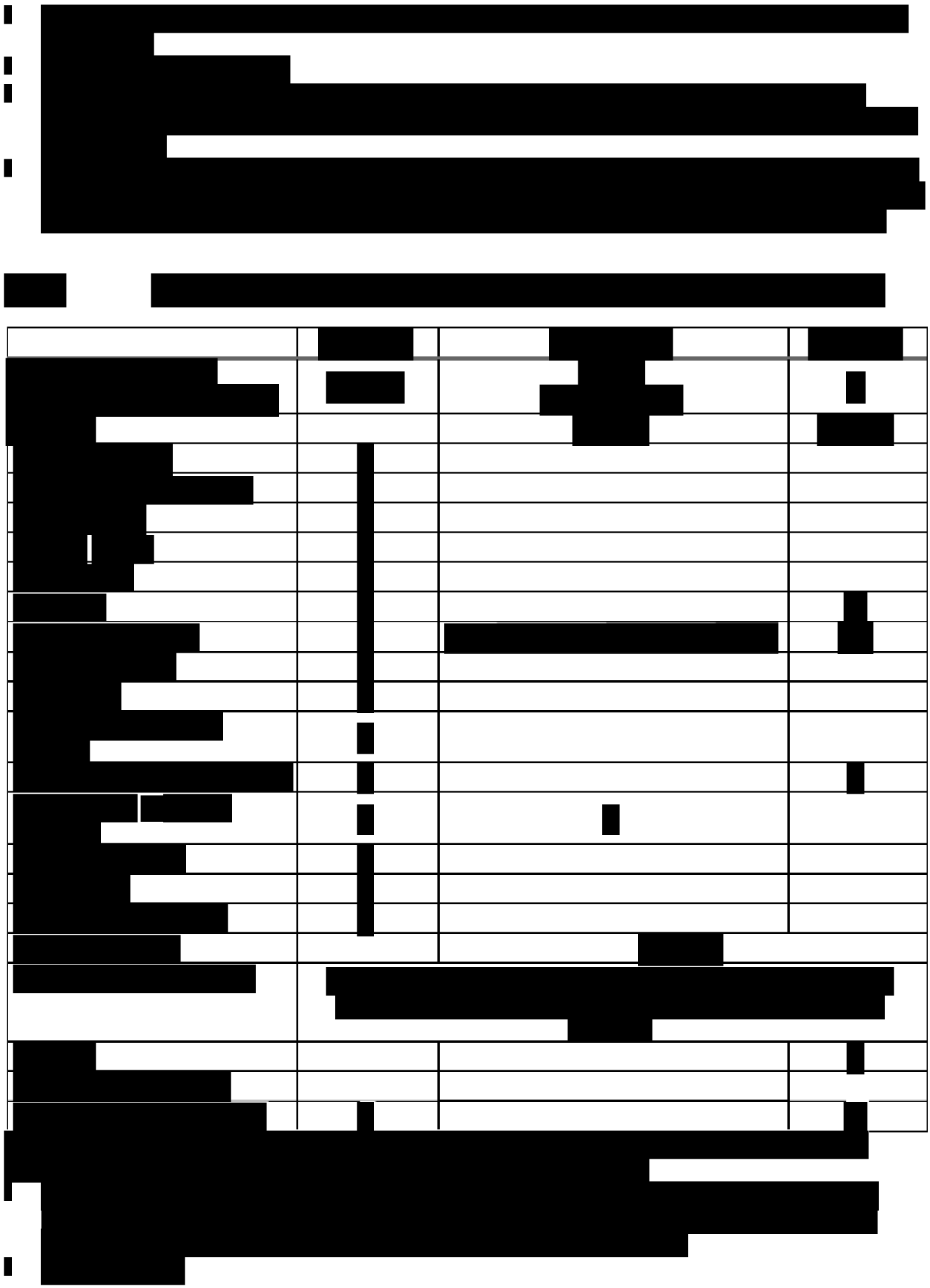
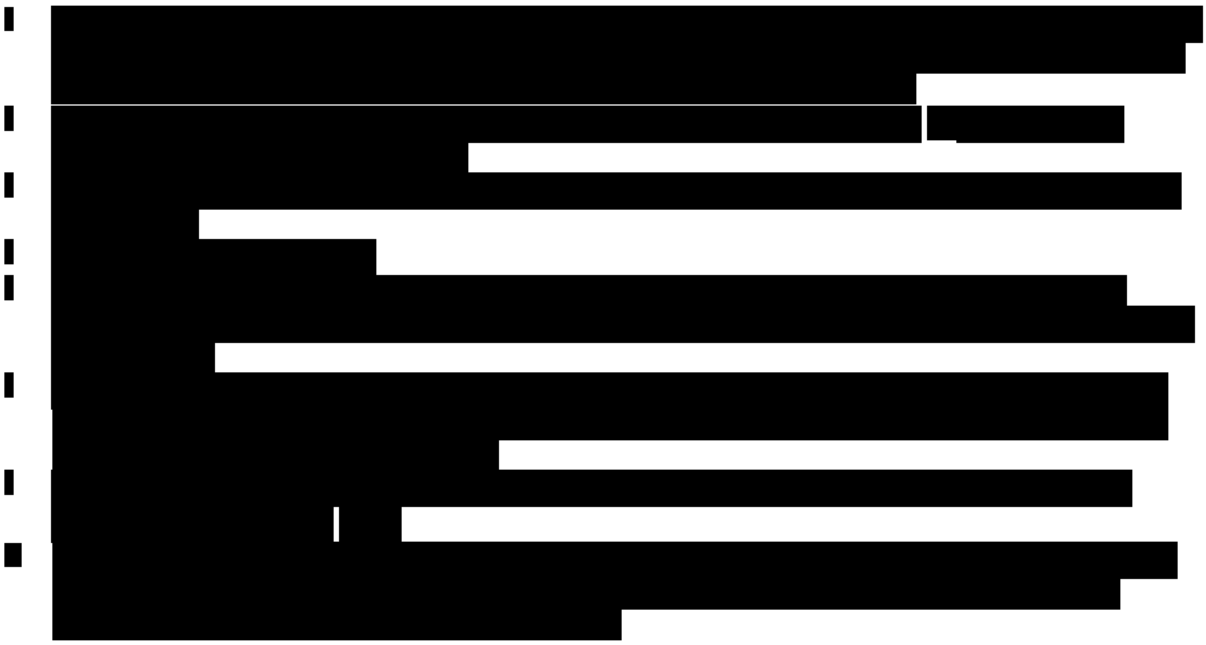
11 APPENDICES







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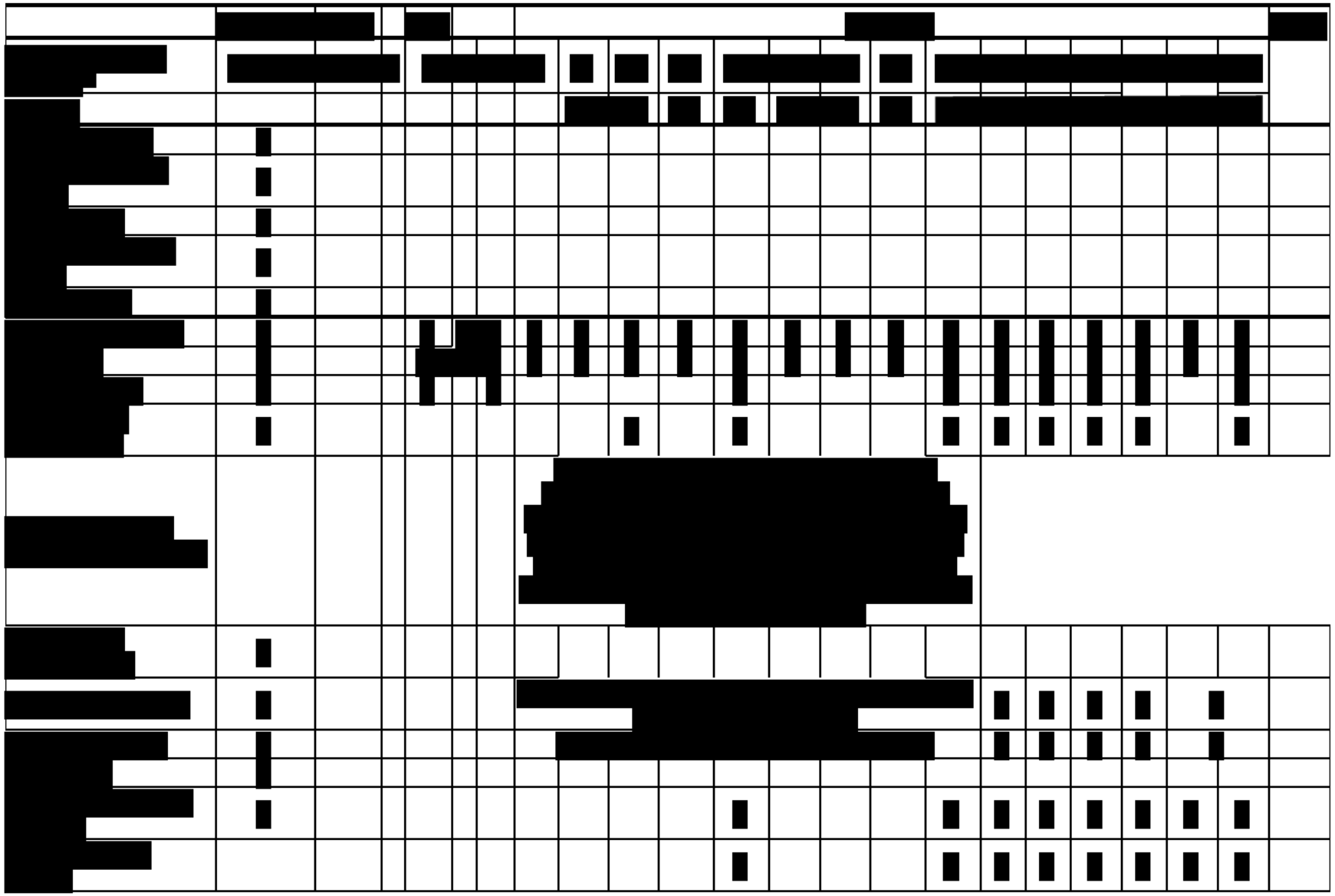
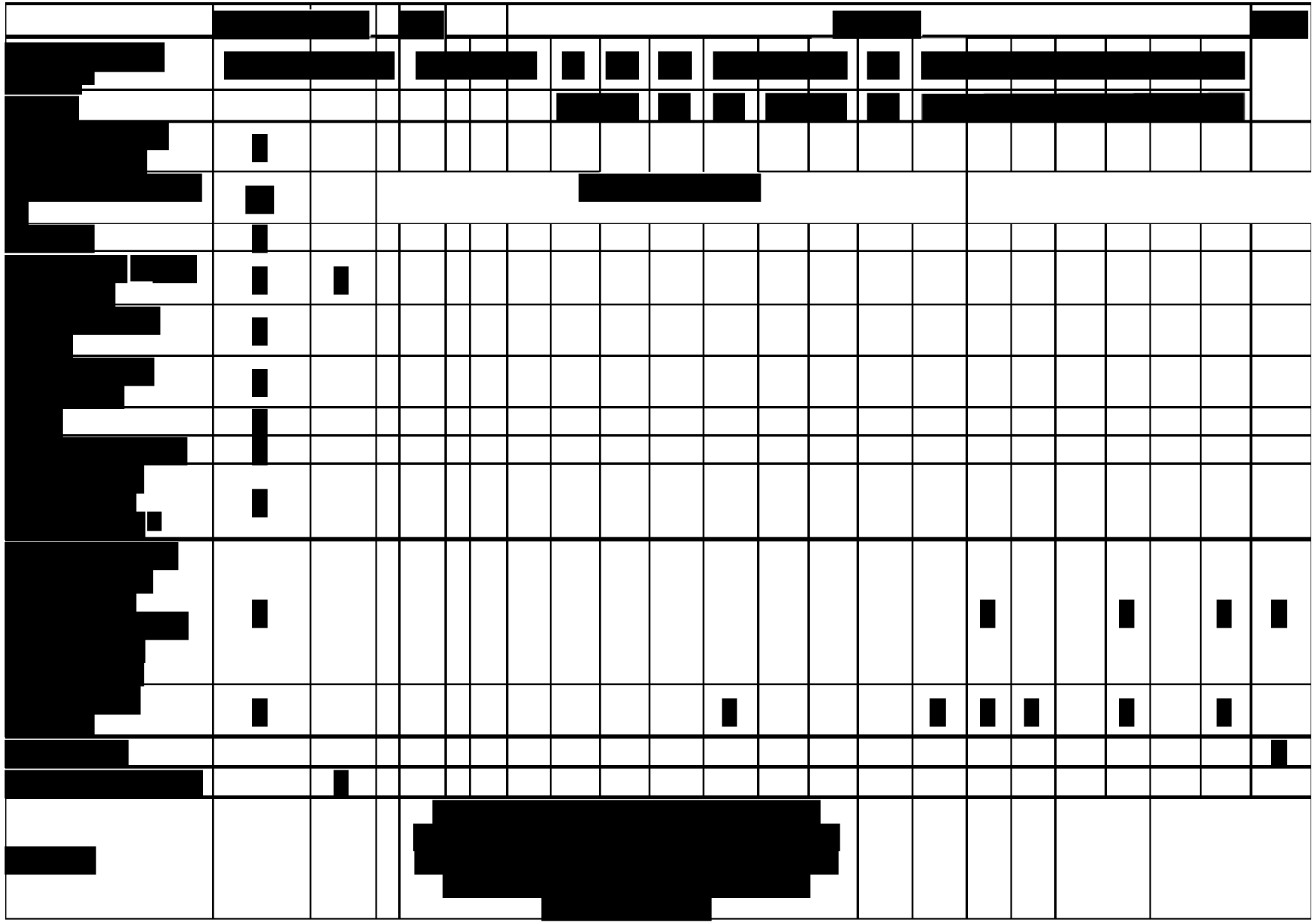
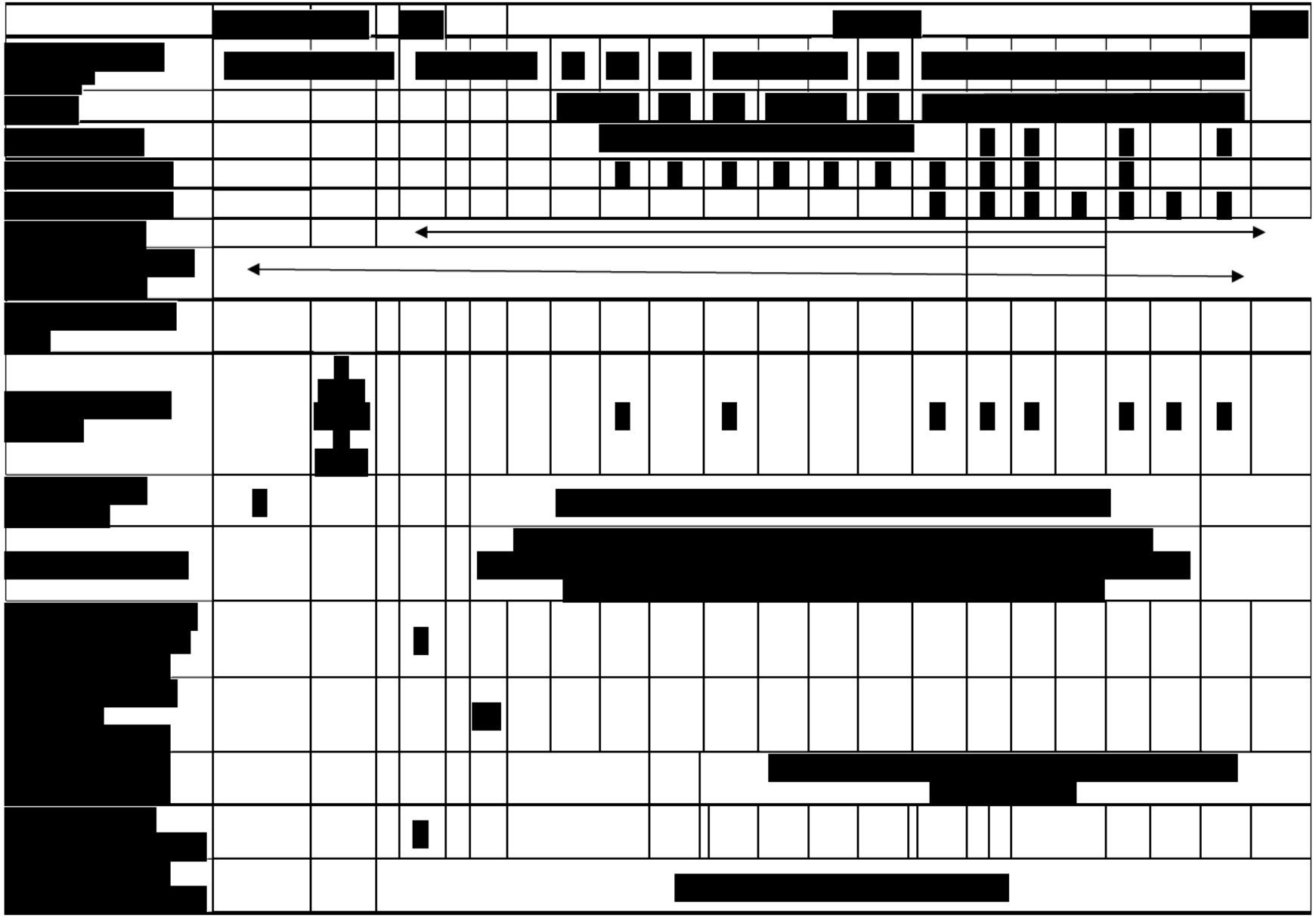






11.2 Quality Control and Assurance

Quality assurance and quality control systems will be implemented and maintained with Standard Operating Procedures by the sponsor or designee, as appropriate, to ensure that this clinical study is conducted and data are generated, documented (recorded) and reported in compliance with the protocol, ICH E6 Good Clinical Practice (GCP): Consolidated Guidance, the Declaration of Helsinki, and the applicable regulatory requirements.

This study will be monitored by the sponsor in accordance with GCP and may be audited or reviewed by independent Quality Assurance personnel, Independent Ethics Committee (IEC), and/or regulatory authorities. This implies that monitors and auditors/inspectors will have the right to inspect the study sites at any time during and/or after completion of the study and will have direct access to data/source documents, including the subject's file, study specific correspondence, and ICF. By participating in this study, investigators agree to this requirement.

Measures will be undertaken to protect the confidentiality of records that could identify subjects, respecting the privacy and confidentiality rules in accordance with applicable regulatory requirements.

11.3 Study Governance Considerations

11.3.1 Ethics Committee Approval

At a minimum, the following documents must be reviewed and approved by Ethics Committees (ECs) (including institutional review boards [IRBs] and IECs), as required by local laws and EC requirements, before subjects are screened for entry into the study:

- Study protocol and amendment(s)
- Written ICF(s) and consent form updates
- Subject recruitment procedures (eg, advertisements)
- Written information to be provided to subjects
- IB and available safety information. Note: ECs do not generally approve IBs.
- Information about payments and compensation available to subjects, if applicable

The EC approval must be in writing, clearly identifying the study (by protocol date and/or version) and the documents reviewed, including informed consent and date of the review. The investigator has the responsibility to provide the sponsor with the written EC approval prior to initiating any study-related procedures. The investigator also has the responsibility to inform the EC of serious and unexpected AEs and protocol deviations and provide the EC with a synopsis of the study report upon study completion according to the EC's policy.

The NMDP IRB will be responsible for the review and continuing oversight of protocol procedures that relate only to NMDP unrelated donors. The IRB used by the Principal

Investigator's institution will be responsible for the review and continuing oversight of protocol procedures that relate to any study subjects other than NMDP unrelated donors.

11.3.2 Ethical Conduct of the Study

This study is to be conducted in accordance with the protocol, sponsor's standard operating procedures, ICH E6 GCP, the Declaration of Helsinki and all other applicable regulatory requirements. Investigators must immediately notify the sponsor or designee (if applicable) of serious breaches in GCP that have occurred at their study site, which are likely to effect to a significant degree (a) the safety or physical or mental integrity of the subjects of the study or (b) the scientific value of the study.

11.3.3 Financial Disclosure

Information on financial disclosure will be collected for all studies.

11.3.4 Subject Information and Consent

Note: all references to "subject" in this section refer to the study subject (recipient or donor as applicable) or his/her legally acceptable representative.

A conference will be held with the participant, and family if available, to discuss this study and alternative treatments available for the treatment of the underlying disease. The conference will be conducted by the Principal Investigator or other designated physician. Potential risks associated with the study treatments should be discussed as objectively as possible.

Prior to participation in any study-specific procedures, each subject must sign and date an EC -approved written ICF in a language the subject can understand.

The sponsor will provide a template of the consent form to each center. Each center will customize the template according to their local requirements and submit it for review by their local EC.

The language in the written information about the study should be as non-technical as practical and should be understandable to the subject. Before informed consent is obtained, the investigator should provide the subject ample time and opportunity to inquire about the study and to decide whether or not to participate.

All questions about the study should be answered to the satisfaction of the subject. The written ICF should be signed and personally dated by the subject and by the person who conducted the informed consent discussion, with any additional signatures obtained as required by applicable local regulations and EC requirements. Each subject will be informed that participation is voluntary and that he/she can withdraw from the study at any time. All subjects will receive a copy of their signed and dated ICF.

11.3.5 Subject Confidentiality

In order to permit easy identification of the individual subject during and after the study, the investigator is responsible for keeping an updated log that contains subject (donor and recipient) identification information. This document will be reviewed by the site monitor for completeness. However, in order to ensure the subject's confidentiality, the document will be maintained at the site and no copy will be made.

The processing of personal data in pursuit of this study will be limited to those data that are reasonably necessary to investigate the utility of the study medications used in this study. These data will be processed with adequate precautions to ensure confidentiality according to local laws.

The sponsor ensures that the personal data are as follows:

- Collected for a specified and legitimate purpose.
- Processed fairly and lawfully.
- Accurate and up to date.

Explicit consent for the processing of personal data will be obtained prospectively from the participating subject.

The sponsor, whose responsibilities require access to personal data, agrees to keep the identity of study subjects confidential. This confidentiality will be maintained in accordance with national and local requirements. Confidentiality will be maintained by masking individual names and other personal identifiers. With the exception of date of birth and other treatment related dates, which are necessary to confirm eligibility, monitor safety, and measure outcomes, no personal identifiers will be collected by the sponsor.

11.3.6 Study Monitoring

The sponsor or designee will monitor this clinical study through monitoring visits and remote data checks to check the adequacy of site staff and facilities, and to ensure adherence to the protocol, study procedures, and applicable regulations. The site monitor will also assess proper CRF completion and source document retention. The investigator and study site staff are expected to provide adequate space for monitoring visits and to allocate sufficient time to permit adequate review of the study's progress. The investigator will permit study-related monitoring, audits, EC review and regulatory inspection(s), providing direct access to source data/documents and study-related facilities (eg, pharmacy, diagnostic laboratories).

As noted in section 3.3.2, primary medical monitoring duties for the Phase 3 trial will be performed by a non-sponsor medical monitor.

11.3.7 Study Records and Case Report Forms

11.3.7.1 Study Records

The investigator and affiliated institution shall maintain the study documents and records as specified in "Essential Documents for the Conduct of a Clinical Trial" (ICH E6 section 8), and as required by the applicable regulatory requirement(s). This includes, but is not limited to the protocol, CRFs, AE reports, subject source data (original records or certified copies), correspondence with health authorities and EC, consent forms, investigator's curriculum vitae, delegation log, monitor visit logs, laboratory reference ranges and laboratory certification or quality control procedures and laboratory director curriculum vitae. Subject source data must be maintained as original records or a certified copy (ie, copy of original information that has been verified, as indicated by a dated signature, as an exact copy having all of the same attributes and information as the original). The investigator and affiliated institution should take measures to prevent accidental or premature destruction of documents.

Study sites may utilize site-owned electronic medical record systems and/or other computer systems to generate, collect and store subject source data, provided that those systems are adherent to 21CFR part 11 requirements and other regulations pertaining to electronic systems. When such systems will be used for the study, their use and supporting infrastructure (eg, access/security, written procedures, technical support, and training as applicable) will be identified and documented in site assessment or site visit reports by the sponsor or designee. If electronic medical records are maintained (eSource data), the method of verification must be agreed upon between the investigational staff and the sponsor.

11.3.7.2 CRF

Where referenced in this protocol, CRFs refer to electronic CRFs, as defined for the study. A CRF must be completed for each subject who has given informed consent. In the case of a screen failure, at a minimum the following data will be entered into the CRF: consent date, demography, and reason for screen failure. All entries into the CRF are ultimately the responsibility of the investigator.

The CRF must be completed at the time of, or shortly after the subject's visit, with the exception of results of tests performed outside the investigator's office, so that they always reflect the latest observations of the subjects participating in the study. If certain information is Not Done, Not Available or Not Applicable, the investigator must record this according to the CRF completion instructions.

Source documents must be made available to the site monitor. Remote monitoring will evaluate CRFs for completeness and consistency. The CRF entries will be compared with the source documents to ensure that there are no discrepancies. A subset of all study data will require onsite source data verification as specified in the Site Monitoring Plan. All CRF entries, corrections and alterations are to be made by the responsible investigator or his/her designee. The site monitor may query the data but cannot edit CRF entries recorded by the site designee.

A copy of each subject's CRF will be maintained by the investigator. A copy of the subject's CRFs can be provided to the investigator at the end of the trial or at other times as requested. The investigator must sign that the CRFs provided are accurate prior to final data lock for that subject and prior to site closure.

In addition to the clinical data management systems/databases, other systems may be used to collect and analyze study data. For example:

- Laboratory Information Systems or proprietary systems will be used by the processing laboratory for storing and/or analyzing manufacturing data collected throughout the study.
- Statistical software will be used for the statistical analysis of the study data, as outlined in the Statistical Analysis Plan.

11.3.8 Source Data and Source Documents

The nature and location of all source documents will be identified to ensure that all sources of original data required to complete the CRF are known to the company and investigational staff. These source documents are to be accessible for verification by the site monitor.

Source documents are required for all data entered into the CRF, including but not limited to:

- Subject identification (name, date of birth, sex). As noted previously, subjects will be identified by a study ID and the link between the participant's name and study ID will be kept confidential.
- Documentation that a subject meets eligibility criteria, ie, medical history, physical examination, and confirmation of diagnosis (to support inclusion and exclusion criteria).
- Documentation that protocol-specific procedures were performed, including handling and administration of the study drug.
- Record of all AEs (including those not required to be recorded in the CRF per the safety reporting section of this protocol) and associated AE characteristics (including start and stop dates, investigator assessment of severity and relationship to the study medication). Prior and concomitant therapy (including start and stop dates and indication for use).
- Date of study completion and reason for early discontinuation, if applicable.

The author of an entry in the source documents should be identifiable as well as the date of the entry. Direct access to source documentation (medical records) must be allowed for the purpose of verifying that the data recorded in the CRF are consistent with the original source data. The investigator will provide certified copies of the subject's medical records in the event that site's policy does not permit direct access to the electronic medical records.

11.3.9 Use of Computerized Systems

An Electronic Data Capture system to capture protocol-required subject data will be used. Sites will enter data from source documents onto electronic CRFs for each study visit using a web-based interface. Study monitors and data management personnel will use this system to review data and generate queries and reports as needed.

Information on the above system will be provided to the investigator, site personnel, and other personnel as appropriate. Measures will be taken to ensure data security and accuracy, including but not limited to user training, granting of user accounts and privileges to trained and authorized personnel in a role-based manner, username/password/electronic signature requirements enforcement, programmed and manual edit checks as outlined in data validation specifications, computer generated audit trails, centralized data management, and routine study monitoring. The systems used will be compliant with United States 21 Code of Federal Regulations Part 11 and Annex 11 on Computerized Systems (annex to the Guide to Good Manufacturing Practice for Medicinal Products) in the European Union and Canada, and the data collected will be archived (at minimum) for the period specified by applicable regulatory requirements.

11.3.10 Retention of Data

The sponsor will inform the investigator in writing when it is acceptable to dispose of any study records. To enable evaluation and/or audits from regulatory authorities or the sponsor, the investigator agrees to keep records, including the identity of all study subjects (eg, subject identification code list and all source documents), all original signed ICFs, copies of all CRFs, original laboratory reports, detailed records of study medication disposition and all essential documents for the conduct of a clinical study. To comply with international regulations, the records should be retained by the investigator for at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region, or until at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. However, the investigator may need to retain these documents for a longer period if required by the local regulatory requirements or by an agreement with the sponsor.

11.3.11 Monitoring Committees

Monitoring committees for this study are described in section 3.2. Further details regarding the DMC and the EAC can be found in their respective charters.

11.3.12 Protocol Violations/Deviations

Unless there is a safety concern, there should be no deviations or violations of the study protocol. In the event of a safety concern, the investigator or designee must document and explain the reason for any deviation from the approved protocol. The investigator may implement a deviation from, or a change to, the protocol to eliminate an immediate hazard to study subjects without prior EC approval. Immediately after the implemented deviation or change, the investigator must submit a report explaining the reasons for the protocol violation or deviation to the EC and the sponsor. The sponsor is responsible for notifying the regulatory authorities, if required.

11.3.13 Study Termination

The sponsor reserves the right to close any investigational site(s) or terminate the study at any time for any reason. Reasons for the closure of a study site or termination of a study by the sponsor may include (but are not limited to) the following:

- Successful completion of the study at the investigational site.
- The required number of subjects for the study has been recruited.
- Failure of the investigator to comply with the protocol, GCP guidelines or local requirements.
- Safety concerns.
- Inadequate recruitment of subjects by the investigator.

11.3.14 Publication and Disclosure Policy

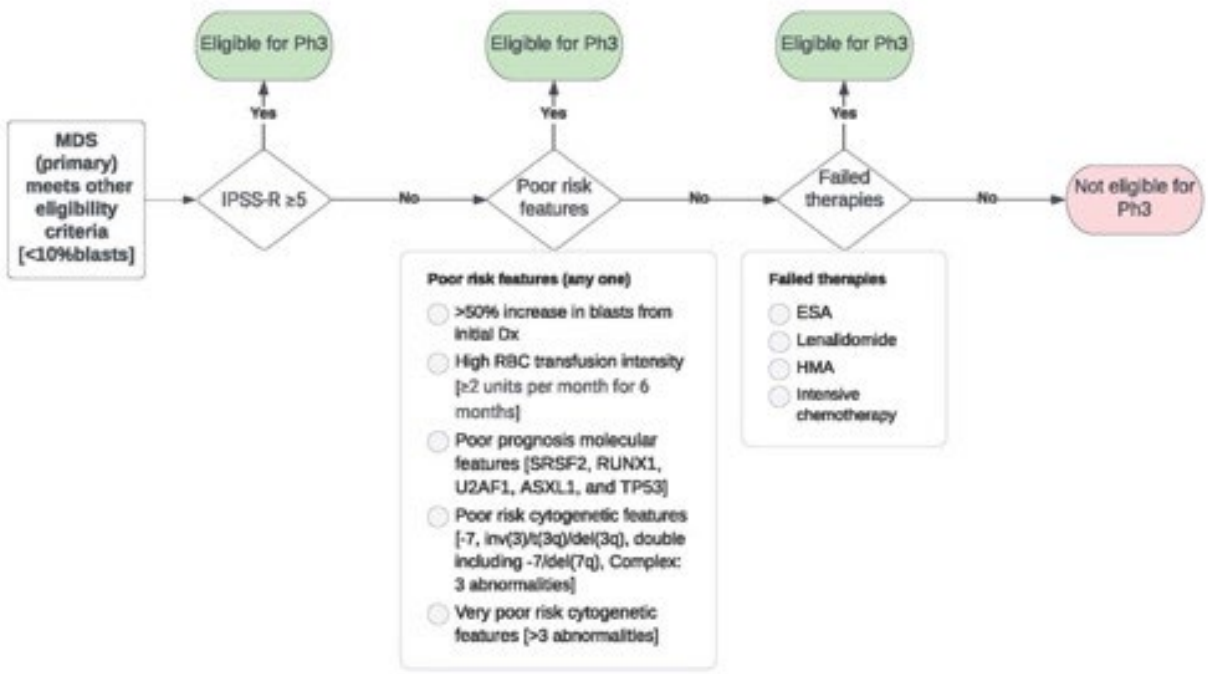
The data and results of the study will be owned solely by the sponsor and shall be confidential information of the sponsor, subject to the investigator's publication rights outlined in the agreement between the investigator/institution and the sponsor regarding the conduct of the clinical study (the "Clinical Study Agreement"). It is understood by the investigator that the sponsor may use the information developed in this clinical study in connection with the development of its compounds and therefore, may disclose it as required to other clinical investigators or regulatory agencies. To allow for the use of the information derived from this clinical study, the investigator understands that he/she has an obligation to provide and disclose test results and all data developed during this study to the sponsor.

Any publication or presentation of the results of this clinical study by the investigator may only be made in strict compliance with the provisions of the Clinical Study Agreement. The investigator should understand that it is not the sponsor's intention to prevent publication of the data generated in the clinical study. However, the sponsor reserves the right to control the form and timing of such publication for commercial reasons.

11.4 International Expert Panel Recommendations: Indications for AlloHSCT for Myelodysplastic Syndrome

The following is adapted from De Witte et al (de Witte 2017).

Figure 11-1 MDS AlloHCT Eligibility Flowchart



11.5 GVHD

11.5.1 aGVHD

11.5.1.1 aGVHD Clinical Grading and Staging

All staging and grading of aGHVD will be performed according to the MAGIC Standardization (Harris 2016).

Guidelines for the assessment of aGVHD and for documentation of signs, symptoms, and testing associated with aGVHD assessment are listed in appendix 11.15.

11.5.1.2 Acute GVHD Response Evaluation

Responses to treatment (eg, corticosteroids) will be assessed as shown in Table 11-1 (MacMillan 2010).

Table 11-1 Response Criteria for Acute GVHD

Complete response (CR)	Complete resolution of acute GVHD symptoms in all organs, without secondary GVHD therapy
Partial response (PR)	Improvement in GVHD stage in all initial GVHD target organs without complete resolution and without worsening in any other GVHD target organs, without secondary GVHD therapy
Very good partial response (VGPR)	Improvement in GVHD in all initial GVHD target organs, with maximum Stage I involvement in one or more organs (except upper gastrointestinal tract), without secondary GVHD therapy
No response (NR)	Same grade of GVHD or progression of GVHD in any organ or death, or the addition of secondary GVHD therapy
Progression	Worsening GVHD in at least 1 organ with or without amelioration in any organ

11.5.1.3 aGVHD Steroid Response

Corticosteroid refractoriness, resistance, dependence and intolerance will be defined as per the EBMT-NIH-CIBMTR Task Force Position Statement (Schoemans 2018), outlined in Table 11-2.

Table 11-2 aGVHD Steroid Response Terminology

Terminology	Criteria
Refractoriness or Resistance	▪ Progression of acute GVHD within 3−5 days of therapy onset with ≥2 mg/kg/day of prednisone; OR ▪ Failure to improve within 5−7 days of treatment initiation; OR ▪ Incomplete response after more than 28 days of immunosuppressive treatment including steroids
Dependence	▪ Inability to taper prednisone below 2 mg/kg/day, OR ▪ A recurrence of acute GVHD activity during steroid taper
Intolerance	▪ Emergence of unacceptable toxicity due to the use of corticosteroids

Adapted from Schoemans 2018.

11.5.2 cGVHD

11.5.2.1 cGVHD Diagnosis

The diagnosis of cGVHD will be based on 2014 International NIH Chronic GVHD Diagnosis and Staging Consensus Working Group criteria and requires at least one diagnostic manifestation of chronic GVHD or at least one distinctive manifestation plus a pertinent biopsy, laboratory or other tests (eg, pulmonary function tests (PFTs), Schirmer's test), evaluation by a specialist

(ophthalmologist, gynecologist) or radiographic imaging showing cGVHD in the same or another organ (Table 11-3) (Jagasia 2015). Biopsy or other testing is encouraged and often valuable to confirm the presence of cGVHD, but it is not always feasible and is not mandatory if the participant has at least 1 of the diagnostic findings of cGVHD.

Guidelines for the assessment of cGVHD and for documentation of signs, symptoms, and testing associated with cGVHD assessment are listed in section 11.17.

Table 11-3 Signs and Symptoms of Chronic GVHD*

Organ or Site	Diagnostic (Sufficient to Establish the Diagnosis of cGVHD)	Distinctive[1] (Seen in cGVHD, but Insufficient Alone to Establish a Diagnosis)
Skin	Poikiloderma Lichen planus-like features Sclerotic features Morphea-like features Lichen sclerosus-like features	Depigmentation Papulosquamous lesions
Nails		Dystrophy Longitudinal ridging, splitting or brittle features Onycholysis Pterygium unguis Nail loss (usually symmetric, affects most nails)
Scalp and body hair		New onset of scarring or nonscarring scalp alopecia (after recovery from chemoradiotherapy) Loss of body hair
Mouth	Lichen planus-like changes	Xerostomia Mucoceles Mucosal atrophy Ulcers Pseudomembranes
Eyes		New onset dry, gritty, or painful eyes Cicatricial conjunctivitis Keratoconjunctivitis sicca Confluent areas of punctate keratopathy
Genitalia	Lichen planus-like features Lichen sclerosis-like features	Erosions Fissures
Females	Vaginal scarring or clitoral/labial agglutination	Ulcers
Males	Phimosis or urethral/meatus scarring or stenosis	
GI Tract	Esophageal web Strictures or stenosis in the upper to mid third of the esophagus	
Lung	Bronchiolitis obliterans diagnosed with lung biopsy Bronchiolitis obliterans syndrome[2]	Air trapping and bronchiectasis on chest CT
Muscles, fascia, joints	Joint stiffness or contractures secondary to fasciitis or sclerosis	Myositis or polymyositis[3]

Abbreviations: cGVHD, chronic graft-versus-host disease; GI, gastrointestinal.

[1] In all cases, infection, drug effect, malignancy, or other causes must be excluded.

[2] Bronchiolitis obliterans syndrome can be diagnostic for lung cGVHD only if distinctive sign or symptom is present in another organ.

[3] Diagnosis of cGVHD requires biopsy.

*Adapted from Jagasia 2015.

11.5.2.2 cGVHD Response Evaluation

cGVHD responses to therapy will be based upon 2014 International NIH Chronic GVHD Diagnosis and Staging Consensus Working Group clinician assessments (Table 11-4) (Lee 2015).

Table 11-4 Response Determination for Chronic GVHD

Organ	Complete Response	Partial Response	Progression
Skin	NIH Skin Score 0 after previous involvement	Decrease in NIH Skin Score by 1 or more points	Increase in NIH Skin Score by 1 or more points, except 0 to 1
Eyes	NIH Eye Score 0 after previous involvement	Decrease in NIH Eye Score by 1 or more points	Increase in NIH Eye Score by 1 or more points, except 0 to 1
Mouth	NIH Modified OMRS 0 after previous involvement	Decrease in NIH Modified OMRS of 2 or more points	Increase in NIH Modified OMRS of 2 or more points
Esophagus	NIH Esophagus Score 0 after previous involvement	Decrease in NIH Esophagus Score by 1 or more points	Increase in NIH Esophagus Score by 1 or more points, except 0 to 1
Upper GI	NIH Upper GI Score 0 after previous involvement	Decrease in NIH Upper GI Score by 1 or more points	Increase in NIH Upper GI Score by 1 or more points, except 0 to 1
Lower GI	NIH Lower GI Score 0 after previous involvement	Decrease in NIH Lower GI Score by 1 or more points	Increase in NIH Lower GI Score by 1 or more points, except from 0 to 1
Liver	Normal ALT, alkaline phosphatase, and Total bilirubin after previous elevation of 1 or more	Decrease by 50%	Increase by 2 x ULN
Lungs	-Normal %FEV1 after previous involvement -If PFTs not available, NIH Lung Symptom Score 0 after previous involvement	-Increase by 10% predicted absolute value of %FEV1 -If PFTs not available, decrease in NIH Lung Symptom Score by 1 or more points	-Decrease by 10% predicted absolute value of %FEV1 -If PFTs not available, increase in NIH Lung Symptom Score by 1 or more points, except 0 to 1
Joints and fascia	Both NIH Joint and Fascia Score 0 and P-ROM score 25 after previous involvement by at least 1 measure	Decrease in NIH Joint and Fascia Score by 1 or more points or increase in P-ROM score by 1 point for any site	Increase in NIH Joint and Fascia Score by 1 or more points or decrease in P-ROM score by 1 point for any site
Global	Clinician overall severity score 0	Clinician overall severity score decreases by 2 or more points on a 0 – 10 scale	Clinician overall severity score increases by 2 or more points on a 0 – 10 scale

ALT, alanine transaminase; FEV1, forced expiratory volume in the first second; GI, gastrointestinal; NIH, National Institutes of Health; OMRS, Oral Mucosa Rating Scale; PFTs, pulmonary function tests; P-ROM, photographic range of motion; ULN, upper limit of normal.

Adapted from Lee 2015.

11.5.2.3 cGVHD Steroid Response

Corticosteroid refractoriness, resistance, dependence, and intolerance will be defined as per the EBMT-NIH-CIBMTR Task Force Position Statement (Schoemans 2018), outlined in Table 11-5.

Table 11-5 cGVHD Steroid Response Terminology

Terminology	Criteria
Refractoriness or Resistance	• Chronic GVHD progression while on prednisone at ≥1 mg/kg/day for 1−2 weeks, OR • Stable GVHD disease while on ≥0.5 mg/kg/day (or 1 mg/kg every other day) of prednisone for 1−2 months
Dependence	• Inability to taper prednisone below 0.25 mg/kg/day (or >0.5 mg/kg every other day) in at least 2 unsuccessful attempts separated by at least 8 weeks
Intolerance	• Emergence of unacceptable toxicity due to the use of corticosteroids

Adapted from Schoemans 2018.

11.6 Revised International Prognostic Scoring System (IPSS-R) for Myelodysplastic Syndromes

The Revised International Prognostic Scoring System (IPSS-R) involves the combination of the scores of 5 main features (Table 11-6) to determine a risk category (Table 11-7) (Greenberg 2012).

Table 11-6 IPSS-R Prognostic Score Values

Prognostic Variable	0	0.5	1	1.5	2	3	4
Cytogenetics*	Very good	—	Good	—	Intermediate	Poor	Very poor
BM blast, %	≤2	—	>2% to <5%	—	5% to 10%	>10%	—
Hemoglobin	≥10	—	8 to <10	<8	—	—	—
Platelets	≥100	50 to <100	<50	—	—	—	—
ANC	≥0.8	<0.8	—	—	—	—	—

Abbreviations: ANC, absolute neutrophil count; BM, bone marrow; IPSS-R, Revised International Prognostic Scoring System.

* Cytogenetic categories:

Very good: -Y, del(11q)

Good: normal, del(5q), del(12p), del(20q), double including del(5q)

Intermediate: del(7q), +8, +19, i(17q), any other single or double independent clones

Poor: −7, inv(3)/t(3q)/del(3q), double including −7/del(7q), complex with 3 abnormalities

Very poor: complex with >3 abnormalities

From Greenberg 2012.

Table 11-7 IPSS-R Prognostic Risk Categories/Scores

Risk Category	Risk Score
Very low	≤1.5
Low	>1.5–3
Intermediate	>3.4–4.5
High	>4.5–6
Very High	>6

From Greenberg 2012.

11.6.1 Therapy-Related MDS

Independent of IPSS-R scoring, therapy-related MDS requires the following disease features to be present:

- History of prior treatment with cytotoxic chemotherapy or radiation therapy.
- Morphologic evidence of significant dysplasia (ie, ≥10 % of erythroid precursors, granulocytes, or megakaryocytes) on the peripheral blood smear or bone marrow examination, in the absence of other causes of dysplasia. In the absence of morphologic evidence of dysplasia, a presumptive diagnosis of MDS can be made in participants with otherwise unexplained refractory cytopenias together with certain genetic abnormalities characteristic of therapy-related MDS.
- Blast count in bone marrow is ≤20 percent.

11.7 DRI Risk Score Assessment

DRI risk score flow charts were adapted from the following references:

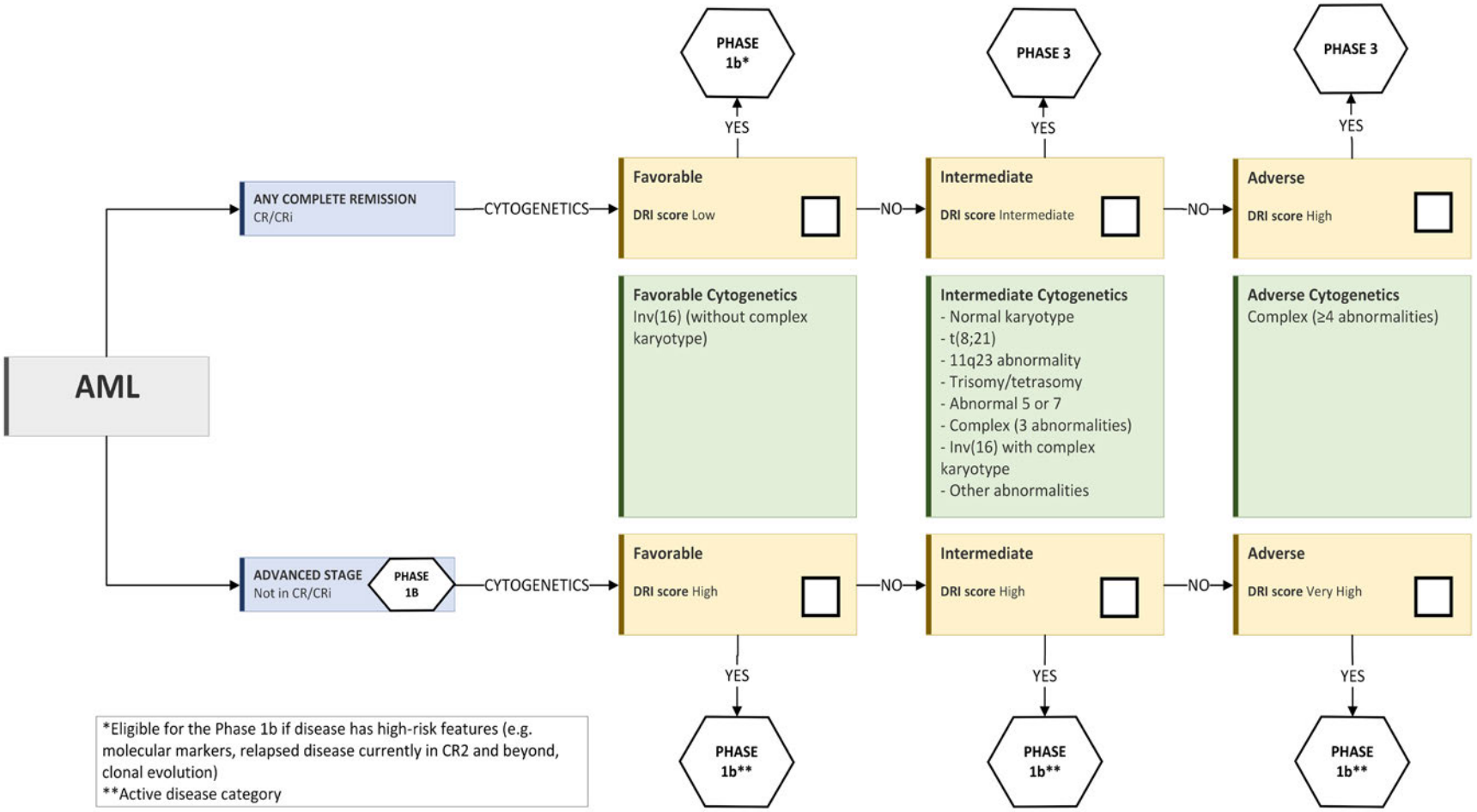
DRI scoring for AML, ALL and MDS. MDS definitions (high and low risk disease): (Armand 2014)

AML cytogenetics: (Armand 2012b)

MDS cytogenetics and stage (early and advanced): (Armand 2010)

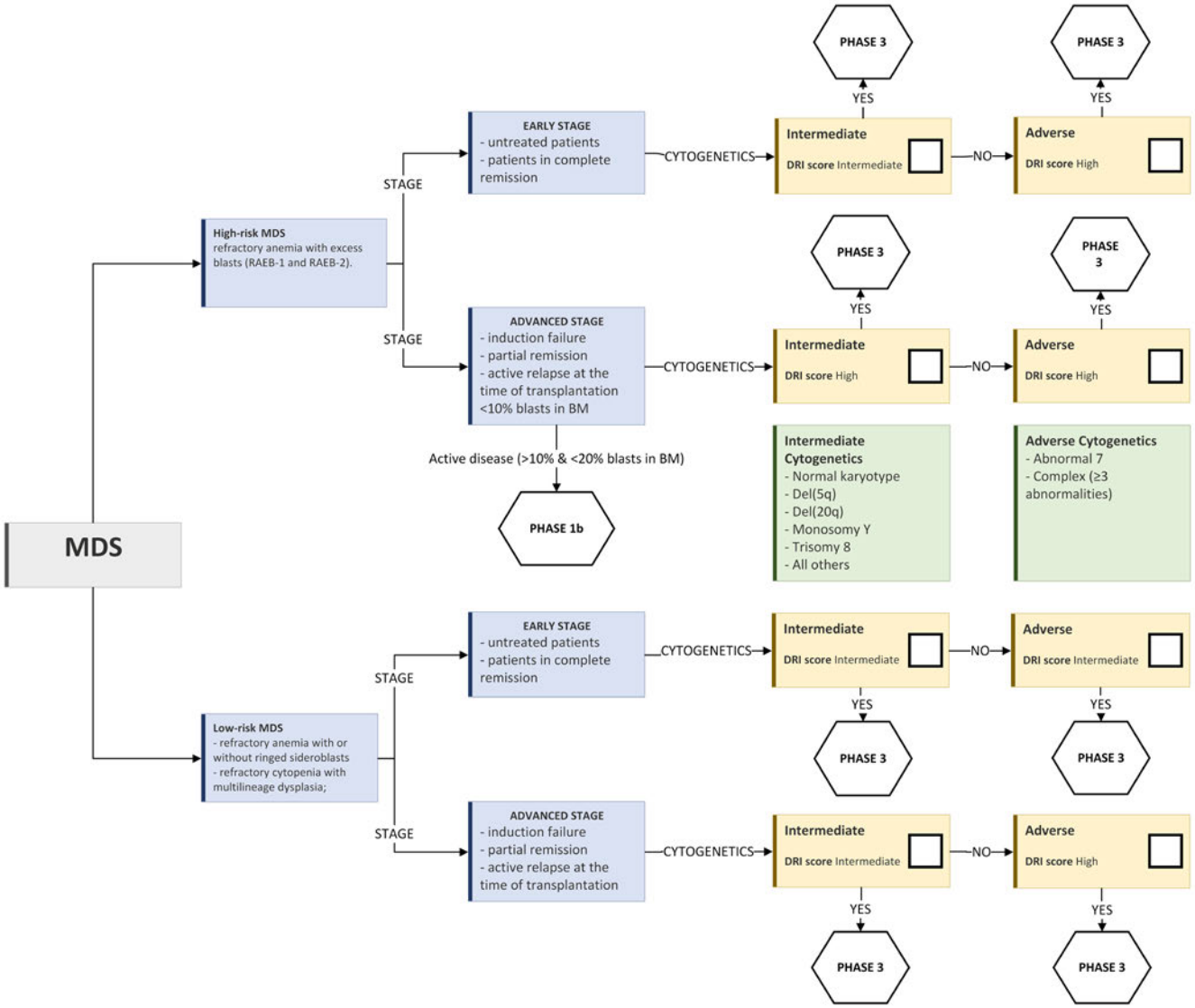
For patients with mixed phenotype acute leukemia/acute leukemia of ambiguous lineage, the DRI Risk Score should be calculated using the flowchart for AML if the leukemic blasts express a preponderance of myeloid markers or the flowchart for ALL if the leukemic blasts express a preponderance of lymphoid markers.

Figure 11-2 DRI AML Scoring Flow Chart



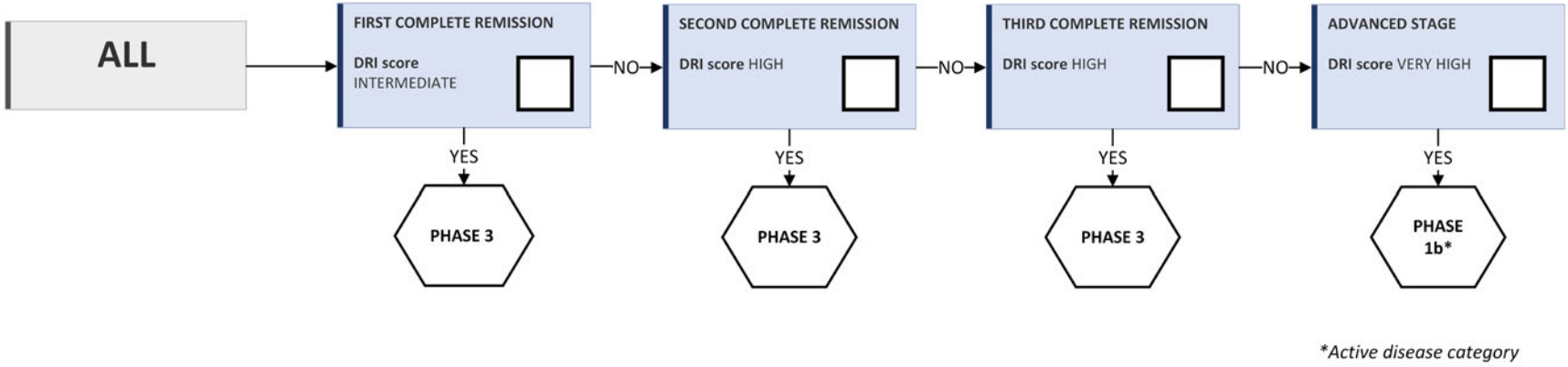
Adapted from Armand 2014 and Armand 2012a

Figure 11-3 DRI MDS Scoring Flow Chart



Adapted from Armand 2014 and Armand 2012a

Figure 11-4 DRI ALL Scoring Flow Chart



Adapted from Armand 2014

11.8 Performance Status Criteria

Karnofsky Status	Karnofsky Grade	ECOG Grade	ECOG Status
Normal, no complaints	100	0	Fully active, able to carry on all pre-disease performance without restriction
Able to carry on normal activities. Minor signs or symptoms of disease	90	1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, eg, light housework, office work
Normal activity with effort	80	1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, eg, light housework, office work
Care for self. Unable to carry on normal activity or to do active work	70	2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours
Requires occasional assistance, but able to care for most of his needs	60	2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours
Requires considerable assistance and frequent medical care	50	3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours
Disabled. Requires special care and assistance	40	3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours
Severely disabled. Hospitalization indicated though death nonimminent	30	4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair
Very sick. Hospitalization necessary. Active supportive treatment necessary	20	4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair
Moribund	10	4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair
Dead	0	5	Dead

From Oken 1982.

11.9 HCT–CI

The HCT–CI is calculated as the sum of the weighted scores for comorbidities present in the subject, as shown in Table 11-8.

Table 11-8 Definitions and Scoring of Comorbidities Included in the HCT-CI

Comorbidity	Definition	Weighted Score
Arrhythmia	Atrial fibrillation or flutter, sick sinus syndrome, or ventricular arrhythmias	1
Cardiac	Coronary artery disease[1], congestive heart failure, myocardial infarction, or EF ≤ 50%	1
Inflammatory bowel disease	Crohn's disease or ulcerative colitis	1
Diabetes	Requiring treatment with insulin or oral hypoglycemics but not diet alone	1
Cerebrovascular disease	Transient ischemic attack or cerebrovascular accident	1
Psychiatric disturbance†	Depression or anxiety requiring psychiatric consult or treatment	1
Hepatic, mild	Chronic hepatitis, bilirubin >ULN to 1.5 x ULN, or AST/ALT >ULN to 2.5 x ULN	1
Obesity	Participants with a body mass index >35 kg/m^2	1
Infection	Requiring continuation of antimicrobial treatment after day 0	1
Rheumatologic	Systemic lupus erythematosus, rheumatoid arthritis, polymyositis, mixed connective tissue disease, or polymyalgia rheumatica	2
Peptic ulcer	Requiring treatment	2
Moderate/severe renal	Serum creatinine >2 mg/dL, on dialysis, or prior renal transplantation	2
Moderate pulmonary	DLCO and/or FEV1 66%-80% or dyspnea on slight activity	2
Prior solid tumor[2]	Treated at any time point in the patient's past history, excluding nonmelanoma skin cancer	3
Heart valve disease	Except mitral valve prolapse	3
Severe pulmonary	DLCO and/or FEV1 ≤65% or dyspnea at rest or requiring oxygen	3
Moderate/severe hepatic	Liver cirrhosis, bilirubin >1.5 x ULN, or AST/ALT >2.5 x ULN	3

Abbreviations: ALT, alanine transaminase; AST, aspartate transaminase; DLCO, diffusing capacity of the lung for carbon monoxide; EF, ejection fraction; forced expiratory volume in the first second; HCT-CI, Hematopoietic Stem Cell Transplant-Specific Comorbidity Index; ULN, upper limit of normal.

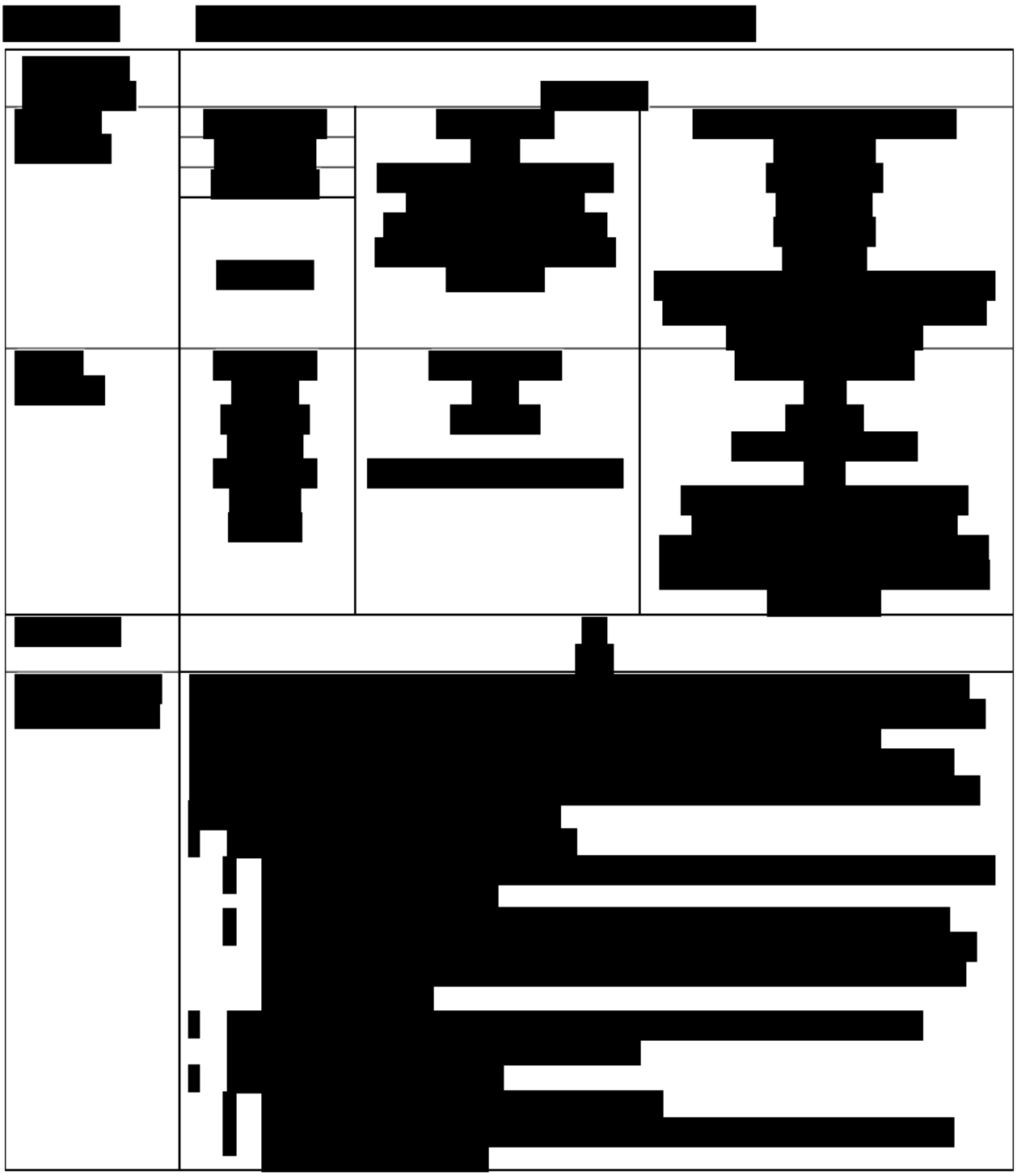
[1] One or more vessel-coronary artery stenosis requiring medical treatment, stent, or bypass graft.

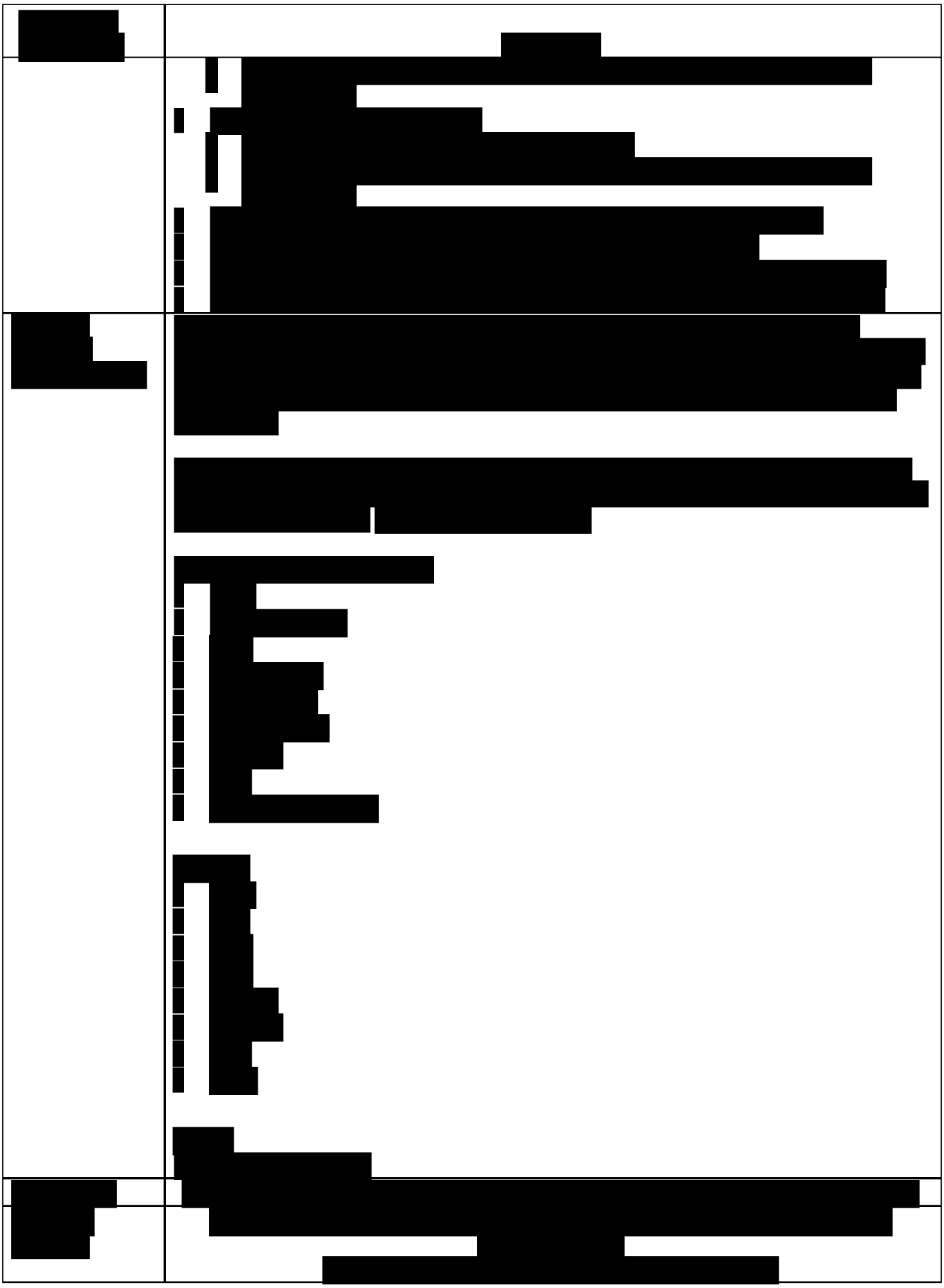
[2] Recent analysis (Shouval et al. 2022), has indicated that prior diagnosis of a solid tumor is not an independent predictor of non-relapse mortality. Therefore, if a participant has a history of a solid tumor that was treated with curative intent ≥ 5 years prior to planned day 0 with no evidence of recurrence of that tumor, the participant may be considered to have a score of zero for this category.

Adapted from Sorror et al. 2005.

11.10 Clinical Laboratory Studies

The tests described in Table 11-9 are to be performed as scheduled in appendix 11.1 and recorded in the CRF. Additional tests may be performed at any time during the study as determined necessary by the investigator, sponsor or required by local regulations. Investigators must document their review of each laboratory report.





[redacted]

11.11 Definition of Woman of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming post-menopausal unless permanently sterile.

Women in the following categories are not considered WOCBP:

- Celibate for at least 3 months (a negative pregnancy test is required for study participation if the participant reports celibacy)
- Premenopausal or postmenopausal female with 1 of the following:
    - Documented hysterectomy
    - Documented bilateral salpingectomy
    - Documented bilateral oophorectomy
    - Note: Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.
- Postmenopausal female
    - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle-stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.
    - Females on HRT and whose menopausal status is in doubt should be considered WOCBP for purposes of this study – eg, such women warrant pregnancy testing at screening.

11.12 Screening Questions for Creutzfeldt-Jakob Disease (CJD)/Variant CJD (vCJD)

All donors should be screened for risk of CJD/vCJD transmission. However, donors determined to be ineligible, based on the results of required testing and/or screening, may nonetheless be included if either apply, as per 21 CFR § 1271.65 2018:

- The donor is a first-degree or second-degree blood relative of the recipient
- Urgent medical need, meaning no comparable human cell product is available and the recipient is likely to suffer death or serious morbidity without the human cell product, as attested by the investigator.

If applicable, the investigator should discuss the risk of CJD/vCJD transmission with the Recipient.

Table 11-10 Countries Considered to be at Risk for Transmission of vCJD

Albania	France	Netherlands (Holland)	Switzerland	Yugoslavia (Federal Republic of):
Austria	Germany	Norway	United Kingdom:	Kosovo,
Belgium	Greece	Poland	England	Montenegro,
Bosnia-Herzegovina	Hungary	Portugal	Northern Ireland,	Serbia
Bulgaria	Ireland (Republic of)	Romania	Scotland, Wales,	
Croatia	Italy	Slovak Republic	the Isle of Man,	
Czech Republic	Liechtenstein	Slovenia	the Channel Islands,	
Denmark	Luxembourg	Spain	Gibraltar or	
Finland	Macedonia	Sweden	the Falkland Islands	

Screening questions:

1. Since 1980, have you ever lived in or traveled to any country considered to be at risk for transmission of vCJD (variant Creutzfeldt-Jakob disease)? (refer to Table 11-9). If no, skip to question #2. If yes, please respond to the following:
   a. From 1980 through 1996, did you spend time that adds up to 3 months or more in the United Kingdom (England, Northern Ireland, Scotland, Wales, the Isle of Man, the Channel Islands, Gibraltar, or the Falkland Islands)?
   b. Since 1980, have you received a transfusion of blood or blood components while in the UK or France?
   c. Since 1980, have you spent time that adds up to 5 years or more (including time spent in the UK between 1980 and 1996) in any country considered to be at risk for transmission of vCJD (variant Creutzfeldt-Jakob Disease)? (refer to Table 11-9)
2. From 1980 through 1996, were you a member of the U.S. military, a civilian military employee, or a dependent of either a member of the U.S. military or civilian military employee?

3. From 1980 through 1990, did you spend a total of 6 months or more associated with a military base in any of the following countries: United Kingdom, Belgium, Netherlands, or Germany?
4. From 1980 through 1996, did you spend a total of 6 months or more associated with a military base in any of the following countries: Spain, Portugal, Turkey, Italy, or Greece?
5. Have any of your blood relatives ever had Creutzfeldt-Jakob Disease?
6. Have you ever received growth hormone made from human pituitary glands?
7. Have you ever received a dura mater (brain covering) graft?

If Donors answer in the affirmative to any of the above questions, they are considered to be at risk of transmitting CJD/vCJD. This fact should be communicated to the Recipient site as a component of the donor screening packet. As noted, Donor blood products may still be used if there is urgent medical need, meaning no comparable human cell product is available and the recipient is likely to suffer death or serious morbidity without the human cell product, as attested by the investigator.

11.13 Definitions of CR, CRi, and Relapse

11.13.1 Definition of CR and CRi (Acute Leukemias)

11.13.1.1 Definition of CR for AML and MPAL

For AML and MPAL, a CR is defined according to FDA draft guidance for industry ("Acute Myeloid Leukemia: Developing Drugs and Biological Products for Treatment (August 2020)" available at https://www.fda.gov/media/140821/download):

1. Bone marrow blasts <5% by morphologic examination
2. Absence of circulating blasts in the peripheral blood by morphologic examination
3. No evidence extramedullary disease
4. ANC >1.0 × 10^9/L (1,000/µL)
5. Platelet count >100 × 10^9/L (100,000/µL)

CRi is defined as meeting all CR criteria except for residual neutropenia (<1.0 × 10^9/L) and/or thrombocytopenia (<100 × 10^9/L).

11.13.1.2 Definition of CR for ALL

For ALL, a CR is defined per the CIBMTR, https://www.cibmtr.org/manuals/fim/1/en/topic/all-response-criteria, accessed 4 December 2021):

1. <5% blasts in the bone marrow
2. Normal maturation of all cellular components in the bone marrow
3. No extramedullary disease (eg, central nervous system, soft tissue disease)

4. ANC >1,000/µL
5. Platelets >100,000/µL
6. Transfusion independence

CRi is defined as meeting all CR criteria except for residual neutropenia ($\leq 1.0 \times 10^9$/L) and/or thrombocytopenia ($\leq 100 \times 10^9$/L).

11.13.2 Definition of Relapse for AML and MPAL

The definition of relapse for AML and MPAL is based on the AML International Working Group recommendations (Döhner 2010), and is defined as the emergence of any of the following after prior achievement of a CR or CRi:

- bone marrow blasts ≥5%; or
- reappearance of blasts in the blood; or
- development of extramedullary disease

11.13.3 Definition of Relapse for ALL

The definition of relapse for ALL is based on the European Working Group for Adult ALL recommendations (Gökbuget 2017), and is defined as the emergence of any of the following after prior achievement of a CR or CRi:

- bone marrow blasts ≥5%; or
- development of extramedullary disease

11.13.4 Response Criteria for Myelodysplatic Syndrome

Myelodysplastic syndrome responses should be graded according to the 2006 IWG guidelines (Cheson 2006).

11.14 Response Criteria for BPDCN

BPDCN responses should be graded according to the methods described in Frankel et al. (Frankel 2014).

11.15 Definition of Relapse for CML

Relapse after alloHCT will be defined as the emergence of BCR-ABL positivity and/or cytogenetic relapse that requires the institution of secondary therapy for CML. This includes the use of donor lymphocyte infusion, tyrosine kinase inhibitors (TKIs), or chemotherapy in response to molecular and/or cytogenetic progression. The date of relapse will be the date in which the molecular and/or cytogenetic progression was identified. The use of TKIs targeting BCR-ABL prophylactically to prevent relapse is not considered a relapse-defining event.

11.16 Precision-T aGVHD Assessment and Reporting Guidelines

The aGVHD Assessment Worksheet begins on the following page.

PRECISION-T
Acute GVHD Target Organ Abnormality Assessment Worksheet

Subject Study ID Code:_____

Date (dd-MON-year): _____

Assessor: _____
(aGVHD should be assessed by the principal investigator or subinvestigators)

Please indicate Study Visit Day (days after transplant) and visit type (in-person, etc.) by checking the appropriate box below:

Days After Transplant	+14	+21	+28	+35	+42	+49	+56	+100	+180	+365	Unscheduled Visit
In-person assessment (strongly preferred)											(Please indicate days after transplant)
Remote/tele-visit assessment:											
Missed visit retrospective assessment:											

Acute GVHD Assessment Timepoints
Evaluation for acute GVHD via a target organ assessment must occur at the protocol mandated assessment schedule, as well as at any visit between scheduled assessments (ie, unscheduled visits) where abnormalities in target organs are identified, from day +14 through day +365. An aGVHD assessment form is not required for unscheduled visits that occur within 7 days of another documented visit unless the participant has new or evolving signs or symptoms of possible acute GVHD.

Hospitalizations outside of the scheduled assessments are considered unscheduled visits, and an aGVHD assessment should be performed upon admission and weekly thereafter for the duration of hospitalization.

Assessment must include completion of the "aGVHD Target Organ Abnormality Assessment Worksheet" by a GVHD provider.The worksheet must be completed as a part of the visit and should not rely on extracting data from the EMR to complete.

All abnormalities in GVHD target organs must be recorded, even if explained by a non-GVHD cause. These should also be reported as adverse events.

Endpoint Adjudication Data
GVHD assessments will be reviewed by the study Endpoint Adjudication Committee. Please additionally provide a copy of the clinic visit note, redacted of any protected health information, for any aGVHD assessment visit where GVHD is considered a potential diagnosis, or abnormalities are identified in any acute GVHD target organ. Pathology reports and radiology reports of studies performed to evaluate for the presence of GVHD must also be provided.

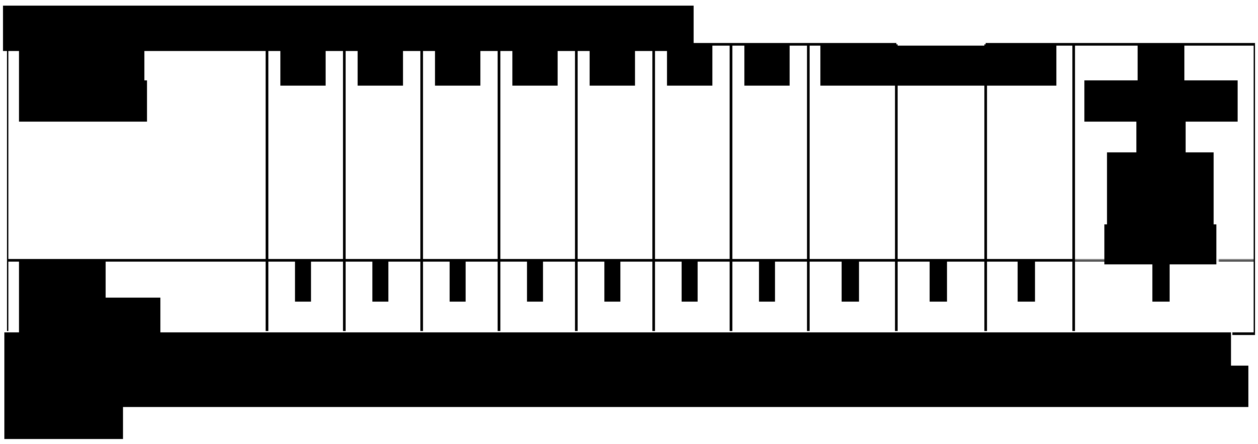
Missed aGVHD Assessment
Every effort should be made to evaluate participants on mandated visit days and during applicable unscheduled visits. However, if a subject is seen at the Transplant center at a protocol mandated visit between day +14 and day +365 anda GVHD assessor does not complete an assessment worksheet at the time of the visit, the PI or a subinvestigator must review the medical record from the visit and complete this form based on the data available. Missed assessments with retrospective evaluation for GVHD should be indicated as such above (page 1).

Remote Visits
In the event a remote visit is required due to the Covid-19 pandemic, the assessment must still be performed. Every effort should be made to conduct a video assessment of the target aGVHD organs.

Diagnosis of aGVHD
As noted above, a clinic note should be provided for any aGVHD assessment time point where GVHD is considered a potential diagnosis, or abnormalities are identified in any acute GVHD target organ. If aGVHD is diagnosed on a given visit, the clinic note should document all pertinent signs and symptoms.

Biopsies of aGVHD Target Organs

Biopsies (eg, skin, liver, etc.) performed to assess for GVHD will be evaluated by a blinded, third-party pathologist in addition to any assessment performed at your local institution. Please refer to the GVHD Biopsy Pathology Manual for detailed instructionsfor slide preparation and shipping.



aGVHD Assessment

All target organ abnormalities and etiologies must be recorded to allow for calculation of stage and grade by the MAGIC standardization (Harris 2016).

SKIN	
Are there any skin changes noted on exam or skin symptoms reported?	☐ Yes (*Proceed to Section A)* ➡ ☐ No (*Proceed to Section C)* ➡ ☐ Not assessed (*Proceed to the next target organ)* ⇨
SECTION A	
A.1. **Onset date (MM/DD/YYYY)**	
A.2. Please indicate **ALL contributing etiologies** for skin changes *If any option(s) other than aGVHD are checked, the skin changes should be submitted as adverse events in the study EDC.*	☐ aGVHD (*Proceed to Section B)* ➡ ☐ Conditioning regimen Drug(s) (specify) (*Proceed to Section C)* ➡ _____ ☐ Other Drug(s) (specify) (*Proceed to Section C)* ➡ _____ ☐ Infection (specify) (*Proceed to Section C)* ➡ _____ ☐ Other (specify) (*Proceed to Section C)* ➡ _____
SECTION B.	
B.1. **Check everything that applies:**	☐ Maculopapular rash ☐ Bullous formation ☐ Desquamation ☐ Generalized erythroderma ☐ Pruritus ☐ Pain ☐ Other (describe)_____

B.2. **Check skin area(s) involved and total %** *Per MAGIC, only areas involved with **active** erythema should be used for determination of BSA staging of GVHD using the "rule of nines"*	Arm(s) ☐ Right (9%) ☐ Left (9%) Leg(s) ☐ Right (18%) ☐ Left (18%) ☐ Chest and abdomen (18%) ☐ Back (18%) ☐ Head (9%) **Total** _____%
SECTION C.	
C.1. Since the last aGVHD assessment completion, does the patient report a **history of skin changes**, not present on exam today, that could represent aGVHD of the skin?	☐ Yes (describe) _____ _____ _____ ☐ No ☐ Not Assessed

SKIN STAGE (MAGIC)		
	☐ **Stage 0**	No active (erythematous GVHD rash)
	☐ **Stage 1**	Maculopapular rash <25% BSA
	☐ **Stage 2**	Maculopapular rash 25 – 50% BSA
	☐ **Stage 3**	Maculopapular rash >50% BSA
	☐ **Stage 4**	Generalized erythroderma plus bullous formation / desquamation >5% BSA

GASTROINTESTINAL TRACT: UPPER GI	
Does the patient report any upper GI symptoms today?	☐ Yes (*Proceed to Section A)* ☐ No (*Proceed to Section C)* ☐ Not assessed (*Proceed to the next organ)*
SECTION A	
A.1. Onset date (MM/DD/YYYY)	
A.2. Please indicate **ALL contributing etiologies** for upper GI symptoms *If any option(s) other than aGVHD are checked, the upper GI symptoms should be submitted as adverse events in the study EDC.*	☐ aGVHD (*Proceed to Section B*) ☐ Conditioning regimen Drug(s) (specify) (*Proceed to Section C)* _____ ☐ Other Drug(s) (specify) (*Proceed to Section C)* _____ ☐ Infection (specify) (*Proceed to Section C)* _____ ☐ Other (specify) (*Proceed to Section C)* _____
SECTION B.	
B.1. Does the patient report **nausea**?	☐ No ☐ Intermittent ☐ Persistent (lasting 3 or more days)
B.2. Does the patient report **vomiting**?	☐ No ☐ Intermittent ☐ Persistent (At least 2 days with at least 2 episodes of vomiting per day)
B.3. Does the patient report **anorexia**?	☐ No ☐ Intermittent ☐ Persistent (weight loss)
B.4. Does the patient report **any other upper GI symptoms**?	☐ No ☐ Yes (specify)_____

SECTION C.	
C.1. Since the last aGVHD assessment completion, does the patient report a **history of upper GI symptoms**, not present on exam today, that could represent aGVHD of the upper GI?	☐ Yes (describe) _____ _____ _____ ☐ No ☐ Not Assessed

UPPER GI STAGE (MAGIC)		
	☐ **Stage 0**	No or intermittent nausea, vomiting or anorexia
	☐ **Stage 1**	Persistent nausea, vomiting or anorexia

GASTROINTESTINAL TRACT: LOWER GI	
Does the patient present with any lower GI symptoms today?	☐ Yes (*Proceed to Section A)* ➡ ☐ No (*Proceed to Section C)* ➡ ☐ Not assessed (*Proceed to the next organ)* ➡
SECTION A	
A.1. Onset date (MM/DD/YYYY)	
A.2. **Please indicate ALL contributing etiologies for the lower GI symptoms.** *If any option(s) other than aGVHD are checked, the lower GI symptoms should be submitted as adverse events in the study EDC.*	☐ aGVHD (*Proceed to Section B)* ➡ ☐ Conditioning regimen Drug(s) (specify) (*Proceed to Section C)* ➡ _____ ☐ Other Drug(s) (specify) (*Proceed to Section C)* ➡ _____ ☐ Infection (specify) (*Proceed to Section C)* ➡ _____ ☐ Other (specify) (*Proceed to Section C)* ➡ _____
SECTION B	
B.1. Record the maximum daily volume and number of episodes of diarrhea, independent of etiology ** Per MAGIC Criteria The "maximum daily volume" is defined as the "highest daily diarrhea volume during the 3 days before its diagnosis" (excluding volumes attributed to bowel preps).*	Maximum daily volume* _____mL ☐ Not recorded Maximum daily number of episodes_____ ☐ Not recorded
B.2. Is **ileus** present?	☐ No ☐ Yes
B.3. Are the stools **grossly bloody**? Only record "yes" if aGVHD is sole etiology. Otherwise, record as an AE. *Per MAGIC, "streaks of blood in the stool due to hemorrhoids or anal fissures or transient hematochezia after endoscopic biopsies" do not constitute grossly bloody stools.*	☐ No ☐ Yes
B.4. Does the patient report **severe abdominal pain**?	☐ No

Per MAGIC, "severe" pain is suggested to be if it "requires the initiation of high doses of narcotic pain medication or a significant increase in ongoing narcotic use and the abdominal pain significantly impacts a patient's performance status as determined by the treating clinician."	☐ Yes
SECTION C.	
C.1. Since the last aGVHD assessment completion, does the patient report a **history of lower GI symptoms**, not present on exam today, that could represent aGVHD of the lower GI?	☐ Yes (describe) _____ _____ _____ ☐ No ☐ Not Assessed

LOWER GI STAGE (MAGIC)		
	☐ **Stage 0**	Adult: <500 mL/day or <3 episodes /day
	☐ **Stage 1**	Adult: 500 – 900 mL/day or 3 - 4 episodes /day
	☐ **Stage 2**	Adult: 1000 – 1500 mL/day or 5 - 7 episodes /day
	☐ **Stage 3**	Adult: >1500 mL/day or >7 episodes /day
	☐ **Stage 4**	Severe abdominal pain with or without ileus or grossly bloody stool (regardless of stool volume)

LIVER	
Are there any abnormal laboratory findings or symptoms present today related to the patient's liver?	☐ Yes (*Proceed to Section A)* ☐ No (*Proceed to the next organ)* ☐ Not assessed (*Proceed to the next organ)*
SECTION A	
A.1. Onset date (MM/DD/YYYY)	
A.2. Maximum Total Bilirubin, mg/dL	
A.3. Maximum AST value, mg/dL	
A.4. **Please indicate ALL contributing etiologies for liver symptoms** *Note: aGVHD should not be selected unless bilirubin has increased since aGVHD diagnosis in another organ.* *Note that these LFT abnormalities should be submitted as adverse events, if deemed to be clinically significant, even if not considered aGVHD-related.*	☐ aGVHD (*Proceed to Section B)* ☐ Conditioning regimen Drug(s) (specify) *(Proceed to Staging)* _____ ☐ Other Drug(s) (specify) *(Proceed to Staging)* _____ ☐ Infection (specify) *(Proceed to Staging)* _____ ☐ Other (specify) *(Proceed to Staging)* _____
SECTION B	
B.1. Was total bilirubin **elevated before** diagnosis of aGVHD?	☐ Yes *(Proceed to next question)* ☐ No *(Proceed to staging)*
B.2. If yes, has total bilirubin **increased further** since diagnosis of aGVHD?	☐ Yes *(Proceed to staging)* ☐ No *(Proceed to next question)*
B.3. Was liver aGVHD confirmed via **biopsy**? *Per MAGIC, if bilirubin levels were elevated before the diagnosis of GVHD in another target organ and do not increase further, do not diagnose liver GVHD in the absence of biopsy confirmation.*	☐ Yes ☐ No

LIVER STAGE (MAGIC)		
		Total bilirubin level
	☐ **Stage 0**	<2 mg/dL
	☐ **Stage 1**	2 - 3 mg/dL
	☐ **Stage 2**	3.1 - 6 mg/dL
	☐ **Stage 3**	6.1 - 15 mg/dL
	☐ **Stage 4**	>15 mg/dL

OTHER ORGANS – aGVHD	
Are there any other signs, symptoms, or laboratory finding that are suggestiveof aGVHD?	☐ Yes (*Proceed to Section A)* ➡ ☐ No (*Proceed to Actions Taken)* ⇨ ☐ Not assessed (*Proceed to Actions Taken)* ⇨
SECTION A	
A.1. Describe other signs symptoms, or laboratory finding(s).	
A.2. Onset date (MM/DD/YYYY)	

ACTIONS TAKEN	
Were any **medications** added or dose-adjusted to treat aGVHD based on today's findings?	☐ No ☐ Yes (specify) _____ _____ _____
If the aGVHD **grade has improved** since the last aGVHD assessment, please provide the **reason**.	☐ Not applicable ☐ aGVHD removed from differential diagnosis ☐ aGVHD resolving with treatment ☐ Other etiology is resolving
Has a **biopsy** to assess for the presence of aGVHD been obtained since the last aGVHD assessment?	☐ No ☐ Yes Provide a PHI-redacted copy of the pathology report(s) and indicate site(s) biopsied, ☐ Liver ☐ Esophagus ☐ Stomach ☐ Colon/Rectum ☐ Skin: List Locations: _____ ☐ Other:_____

Please indicate the <u>overall clinical aGVHD grade</u> (per MAGIC) by checking the appropriate box:

Overall Clinical aGVHD Grade (per MAGIC; based on most severe target organ involvement)	Description
☐ **0**	No stage 1 – 4 of any organ
☐ **I**	Stage 1 - 2 skin without liver, upper GI, or lower GI involvement
☐ **II**	Stage 3 rash and/or stage 1 liver and/or stage 1 upper GI and/or stage lower GI
☐ **III**	Stage 2 - 3 liver and/or stage 2 - 3 lower GI, with stage 0 – 3 skin and/or stage 0 – 1 upper GI
☐ **IV**	Stage 4 skin, liver, or lower GI involvement, with stage 0 – 1 upper GI

11.17 Precision-T cGVHD Assessment and Reporting Guidelines

The cGVHD Assessment Worksheet begins on the following page.

PRECISION-T
Chronic GVHD Assessment Worksheet

Subject Study ID Code: _____

Date (dd-MON-year): _____

Assessor: _____
(cGVHD should be assessed by the principal investigator or subinvestigators)

Please indicate Study Visit Day (days after transplant) and visit type (in-person, etc) by checking the appropriate box below:

Days After Transplant	+56	+100	+180	+270	+365	+545	+730	Unscheduled visit
In-person assessment (strongly preferred)								(Please indicate days post-transplant):
Remote/tele-visit assessment:								
Missed visit retrospective assessment:								

Chronic GVHD Assessment Timepoints
Evaluation for chronic GVHD must occur at the protocol mandated assessment schedule, as well asat any unscheduled visits from day +56 through day +730. Hospitalizations outside of the scheduled assessments are considered unscheduled visits, and a cGVHD assessment should be performed upon admission and weekly thereafter for the duration of hospitalization.

Assessment must include completion of the "cGVHD Assessment Worksheet" by a GVHD provider. The worksheet must be completed as a part of the visit and must not rely on extracting data from the EMR to complete. Please additionally provide a copy of the clinic visit note, redacted of any protected health information, for each clinic visit that includes a protocol-mandated cGVHD assessment.

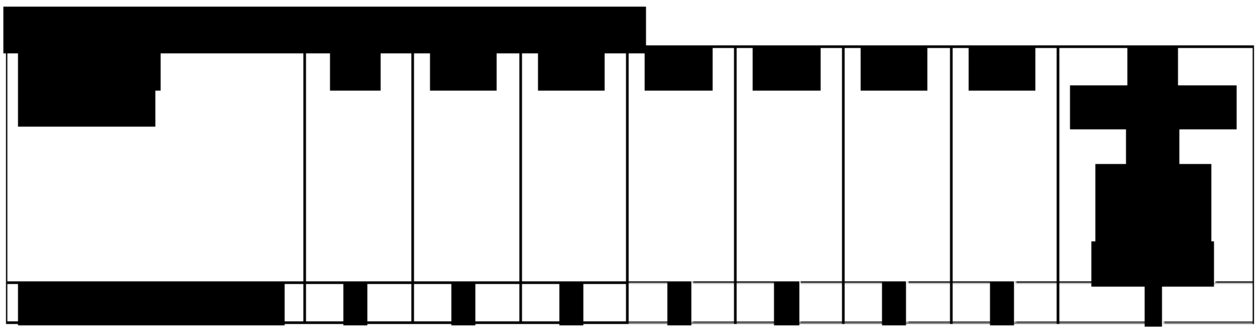
All abnormalities in GVHD target organs must be recorded, even if explained by a non-GVHD cause. These should also be reported as adverse events.

Missed cGVHD Assessment
Every effort should be made to evaluate participants on mandated visit days and during unscheduled visits. However, if a subject is seen at the Transplant center between day +56 and day +730 and a GVHD assessor does not complete an assessment worksheet at the time of the visit, the PI or a subinvestigator must review the medical record from the visit and complete this form based on the dataavailable. Missed assessments with retrospective evaluation for GVHD should be indicated as suchabove (page 1).

Remote Visits
In the event a remote visit is required due to the Covid-19 pandemic, the assessment must still be performed. Every effort should be made to conduct a video assessment of the target cGVHD organs.

Diagnosis of cGVHD
As noted above, a clinic note should be provided for every cGVHD assessment time point. If cGVHD is diagnosed on a given visit, the clinic note should document all pertinent sign andsymptoms.

Biopsies of GVHD Target Organs
In addition to documenting signs and symptoms, any biopsies (eg, skin, liver, etc.) performed to assess for GVHD will be evaluated by a blinded, third-party pathologist in addition to any assessment performed at your local institution. Please refer to the lab leaflet for detailed instructionsfor slide preparation and shipping.



cGVHD raw data, staging, and grading should be collected at time points outlined

above and at all unscheduled visits from day +56 through day +730.

cGVHD Staging and Grading

Grading of chronic GHVD will be performed according to NIH consensus criteria, and this worksheet is adapted from these criteria (Jagasia 2015).

Performance Status %	Karnofsky Performance Score Comments
100	Normal. No complaints. No evidence of disease.
90	Able to carry on normal activity. Minor signs or symptoms of disease.
80	Normal activity with effort. Some signs or symptoms of disease.
70	Care of self. Unable to carry on normal activity or to do active work.
60	Requires occasional assistance, but is able to care for most of his needs.
50	Requires considerable assistance and frequent medical care
40	Disabled. Requires special care and assistance.
30	Severely disabled. Hospitalization is indicated although death not imminent.
20	Hospitalization necessary, very sick active supportive treatment necessary
10	Moribund. Fatal processes progressing rapidly.
0	Dead.

Karnofsky Performance Score (as assessed on this visit):	

	SCORE 0	SCORE 1	SCORE 2	SCORE 3
PERFORMANCE SCORE:	☐ Asymptomatic and fully active (ECOG 0; KPS or LPS 100%)	☐ Symptomatic, fully ambulatory, restricted inly in physically strenuous activity (ECOG 1, KPS or LPS 80 – 90%)	☐ Symptomatic, capable of self-care, >50% of waking hours out of bed (ECOG 2, KPS or LPS 60 – 70%)	☐ Symptomatic, limited self-care, >50% of waking hours in bed (ECOG 3 – 4, KPS or LPS <60%)
SKIN SCORE % BSA				
GVHD features to be scored by BSA:	☐ No BSA involved	☐ 1 – 18% BSA	☐ 19 – 50% BSA	☐ >50% BSA

Check all that apply:

- ☐ Maculopapular rash/erythema
- ☐ Lichen planus-like features
- ☐ Sclerotic features
- ☐ Papulosquamous lesions or ichthyosis
- ☐ Keratosis pilaris-like GVHD

Note: Skin scoring should use both percentage of BSA involved by disease signs and cutaneous features scales. When a discrepancy exists between the percentage of total body surface (BSA) score and the skin feature score, OR if superficial sclerotic features are present (Score 2), but there is impaired mobility or ulceration (Score 3), the higher level should be used for the final skin scoring

Abbreviations: ECOG (Eastern cooperative Oncology Group), KPS (Karnofsky Performance Status), LPS (Lansky Performance Status), BSA (body surface area).

Subject Study ID Code: _____ Date: _____ Study Visit Day (Days After Transplant): _____

	SCORE 0	SCORE 1	SCORE 2	SCORE 3
SKIN FEATURES **SCORE:**	☐ No sclerotic features		☐ Superficial sclerotic features "not hidebound" (able to pinch)	**Check all that apply:** ☐ Deep sclerotic features "Hidebound" (unable to pinch) ☐ Impaired mobility ☐ Ulceration

Other skin GVHD features (not scored by BSA)

Check all that apply:

☐ Hyperpigmentation
☐ Hypopigmentation
☐ Poikiloderma
☐ Severe or generalized pruritus
☐ Hair involvement
☐ Nail involvement
☐ *Abnormality present but explained entirely by non-GVHD documented cause (specify):* _____

MOUTH **Lichen planus-like features present:** ☐ **Yes** ☐ **No**	☐ No symptoms	☐ Mild symptoms **with** disease signs but not limiting oral intake significantly	☐ Moderate symptoms with disease signs **with** partial limitation of oral intake	☐ Severe symptoms with disease signs **with** major limitation of oral intake

☐ *Abnormality present but explained entirely by non-GVHD documented cause (specify):* _____

EYES *Keratoconjunctivitis sicca (KCS) confirmed by ophthalmologist:* ☐ **Yes** ☐ **No** ☐ **Not examined**	☐ No symptoms	☐ Mild dry eye symptoms not affecting ADL (requirement of lubricant eye drops ≤3 x per day)	☐ Moderate dry eye symptoms partially affecting ADL (requiring lubricant eye drops >3 x per day or punctal plugs), **without** new vision impairment due to KCS	☐ Severe dry eye symptoms significantly affecting ADL (special eyeware to relieve pain) **OR** unbale to work because of ocular symptoms **OR** loss of vision due to KCS

☐ *Abnormality present but explained entirely by non-GVHD documented cause (specify):* _____

Abbreviations: ADL (activities of daily life)

Subject Study ID Code: _____ Date: _____ Study Visit Day (Days After Transplant): _____

	SCORE 0	SCORE 1	SCORE 2	SCORE 3
GI TRACT ☐ Esophageal web / proximal stricture or ring ☐ Dysphagia ☐ Anorexia ☐ Nausea ☐ Vomiting ☐ Diarrhea ☐ Weight loss* >5% ☐ Failure to thrive	☐ No symptoms	☐ Symptoms without significant weight loss* (<5%)	☐ Symptoms associated with mild to moderate weight loss* (5% – 15%) **OR** moderate diarrhea without significant interference with daily living	☐ Symptoms associated with severe weight loss* >15%, requires nutritional supplement for most calorie needs **OR** esophageal dilation **OR** severe diarrhea with significant interference with daily living
☐ *Abnormality present but explained entirely by non-GVHD documented cause (specify):* _____ * Weight loss within 3 months				
LIVER	☐ Normal total bilirubin and ALT or AP <3 x ULN	☐ Normal total bilirubin and ALT 3 to 5 x ULN or AP ≥3 x ULN	☐ Elevated total bilirubin but ≤3 mg/dL or ALT >5 x ULN	☐ Elevated total bilirubin but >3 mg/dL
☐ *Abnormality present but explained entirely by non-GVHD documented cause (specify):* _____				
LUNGS** **Symptom score:**	☐ No symptoms	☐ Mild symptoms (shortness of breath after climbing one flight of steps)	☐ Moderate symptoms (shortness of breath after walking on the ground)	☐ Severe symptoms (shortness of breath at rest; requiring O_2)
Lung score: % FEVI ☐ *Pulmonary function tests* ☐ Not performed	☐ FEVI ≥80%	☐ FEVI 60 – 79%	☐ FEVI 40 – 59%	☐ FEVI ≤39%
☐ *Abnormality present but explained entirely by non-GVHD documented cause (specify):* _____				

** Lung scoring should be performed using both the symptoms and FEVI scores wherever possible. FEVI should be used in the final lung function scoring where there is a discrepancy between symptoms and FEVI scores

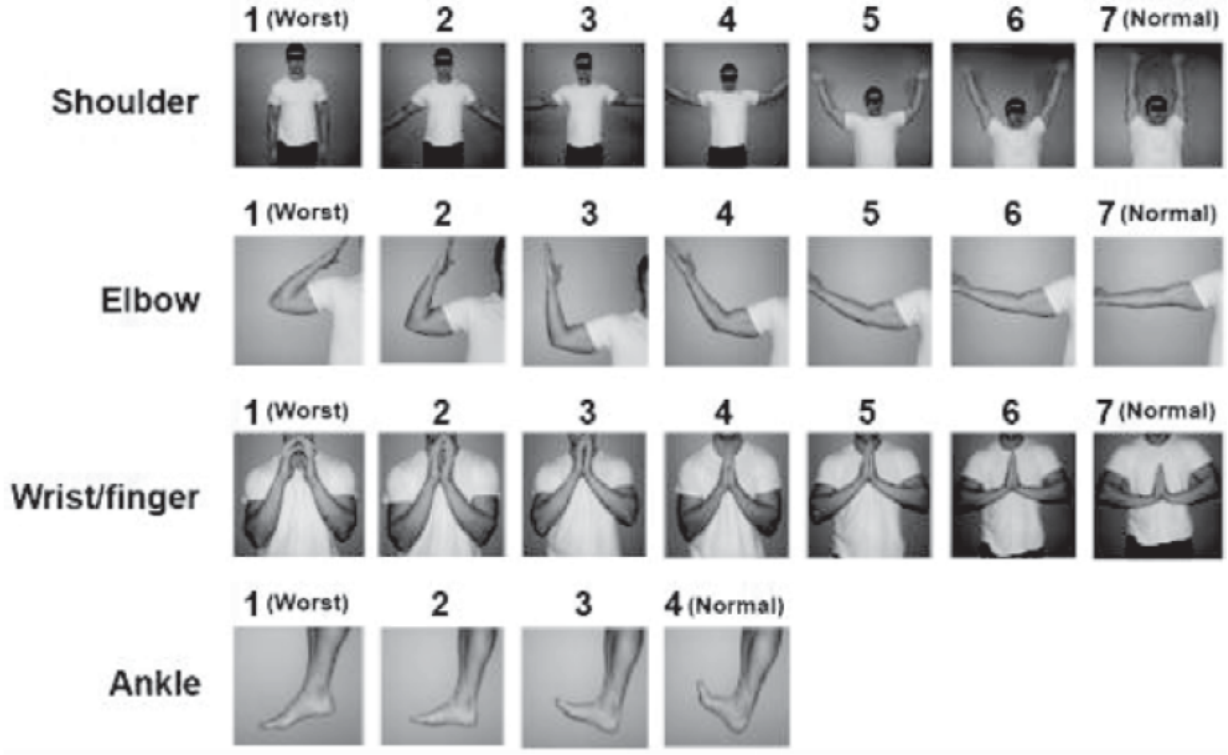
Abbreviations: LFTs: (liver function tests), AP (alkaline phosphatase), ALT (alanine transaminase), ULN (upper limit of normal).

Subject Study ID Code: _____ Date: _____ Study Visit Day (Days After Transplant): _____

	SCORE 0	SCORE 1	SCORE 2	SCORE 3
JOINTS AND FASCIA **<u>P-ROM score</u>** *(See below)* Shoulder (1-7): _____ Elbow (1-7): _____ Wrist/finger (1-7): ____ Ankle (1-4): _____	☐ No symptoms	☐ Mild tightness of arms or legs, normal or mild decreased range of motion (ROM) **AND** not affecting ADL	☐ Tightness of arms or legs **OR** joint contractures, erythema thought due to fasciitis, moderate decrease ROM **AND** mild to moderate limitation of ADL	☐ Contractures **WITH** significant decrease ROM **AND** significant limitation of ADL (unable to tie shoes, button shirts, dress self, etc.)

☐ *Abnormality present but explained entirely by non-GVHD documented cause (specify):* _____

Photographic Range of Motion (P-ROM)



Subject Study ID Code: _____ Date: _____ Study Visit Day (Days After Transplant): _____

	SCORE 0	SCORE 1	SCORE 2	SCORE 3
GENITAL TRACT **Check:** ☐ Male ☐ Female	☐ No signs	☐ Mild signs and females with or without discomfort on exam	☐ Moderate signs and may have symptoms* with discomfort on exam	☐ Severe signs with or without symptoms*

Currently sexually active:
☐ Yes
☐ No

Assessment performed by a gynecologist?
☐ Yes
☐ No

Check all signs that apply:

☐ Lichen planus-like features
☐ Lichen sclerosis-like features
☐ Vaginal scarring (female)
☐ Clitoral/labial agglutination (female)
☐ Labial resorption (female)
☐ Erosions
☐ Fissures
☐ Ulcers
☐ Phimosis (male)
☐ Urethral meatus scarring / stenosis (male)

☐ *Abnormality present but NOT thought to represent GVHD (specify cause):* _____

☐ *Abnormality thought to represent GVHD PLUS other causes (specify cause):* _____

**Genital symptoms are not specific to cGVHD and can represent premature gonadal failure or genital tract infection.*

If a gynecologist is unavailable, external examination may be performed to determine "discomfort on exam" as follows:

a) Spread the labia majora to inspect the vulva for the above signs. Touch the vestibular gland openings (Skene's and Bartholin's), labia minora and majora gently with a q-tip. Vulvar pain elicited by the gentle touch of a q-tip is classified as discomfort on examination. Palpate the vaginal walls with a single digit to detect bands, shortening, narrowing or other signs of vaginal scarring.
b) If the woman is sexually active, determine whether q-tip palpation or gentle palpation of scarred ridges elicits pain similar to that which the woman experiences during intercourse.

Female genitalia: Severity of signs:
1) Mild (any of the following); erythema on vulvar mucosal surfaces, vulvar lichen-planus or vulvar lichen-sclerosis.
2) Moderate (any of the following); erosive inflammatory changes of the vulvar mucosa, fissures in vulvar folds
3) Severe (any of the following); labial fusion, clitoral hood agglutination, fibrinous vaginal adhesions, circumferentialfibrous vaginal banding, vaginal shortening, synechia, dense sclerotic changes, and complete vaginal stenosis.

Male genitalia: Diagnostic features include lichen planus-like or lichen sclerosis-like features and phimosis or urethralscarring or stenosis. Severity of signs:
1) Mild: lichen planus-like feature.
2) Moderate: lichen sclerosis-like feature or moderate erythema.
3) Severe: phimosis or urethral/meatal scarring.

Other indicators, clinical features or complications related to chronic GVHD (check all that apply and assign a score to severity (0-3) based on functional impact where applicable none – 0, mild – 1, moderate – 2, severe – 3):

☐ Ascites (serositis): _____
☐ Pericardial effusion: _____
☐ Pleural effusion(s): _____
☐ Nephrotic syndrome: _____
☐ Myasthenia gravis: _____
☐ Peripheral Neuropathy: ____
☐ Polymyositis: _____
☐ Weight loss >5% without GI symptoms: _____
☐ Eosinophilia >500/µl: _____
☐ Platelets <100,00/µl: _____
☐ Others (specify): _____

Has a biopsy to assess for the presence of GVHD been obtained since the last cGVHD assessment?

☐ NO
☐ YES: If yes, please provide a PHI-redacted copy of the pathology report(s) and indicate sites biopsied:

☐ Skin ☐ Lungs
☐ Mouth ☐ Genital tract
☐ GI tract ☐ Other (specify): _____
☐ Liver

NIH Global/Overall Severity of Chronic GVHD Grading

Mild chronic GVHD:
- 1 or 2 Organs involved with no more than score 1 *plus* Lung score of 0

Moderate chronic GVHD:
- 3 or More organs involved with no more than score 1 **OR**
- At least 1 organ (not lung) with a score of 2 **OR**
- Lung score of 1

Severe chronic GVHD:
- At least 1 organ with a score of 3 **OR**
- Lung score of 2 or 3

Key points:
- *In skin: higher of the 2 scores to be used for calculating global severity.*
- *In lung: FEV1 is used instead of clinical score for calculating global severity.*
- *If the entire abnormality in an organ is noted to be unequivocally explained by a non-GVHD documented cause, that organ is not included for calculation of the global severity.*
- *If the abnormality in an organ is attributed to multifactorial causes*
- *(GVHD plus other causes) the scored organ will be used for calculation of the global severity regardless of the contributing causes (no downgrading of organ severity score).*

Overall GVHD Severity (Opinion of evaluator)	☐ **No GVHD**	☐ **Mild**	☐ **Moderate**	☐ **Severe**

STATISTICAL ANALYSIS PLAN

[redacted]

19 September 2024

Sponsor: Orca Bio, Inc.

Protocol Name: Precision-T

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

[redacted]

Phase 3 Only

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TABLE OF ABBREVIATIONS

Abbreviation	Definition
AE	adverse event
aGVHD	acute graft-versus-host disease
alloHCT	allogeneic hematopoietic cell transplantation
ATC	anatomical therapeutic chemical
cGVHD	chronic graft-versus-host disease
CSR	clinical study report
eCRF	electronic case report form
EDC	electronic data capture
GRFS	graft-versus-host disease-free and relapse-free survival
GVHD	graft-versus-host disease
HSPC	hematopoietic stem and progenitor cell
IPD	important protocol deviation
IRR	infusion-related reaction
ISFS	immunosuppression-free survival
IWRS	interactive web response system
MCID	minimal clinical important difference
NA	not applicable
NRM	nonrelapse mortality
OS	overall survival
PTLD	posttransplantation lymphoproliferative disorder
QoL	quality of life
RFS	relapse-free survival
SOS	sinusoidal obstruction syndrome
TEAE	treatment-emergent adverse event
TMA	thrombotic microangiopathy
VOD	veno-occlusive disease

1 INTRODUCTION

The purpose of this statistical analysis plan (SAP) is to provide details of the statistical analyses for the phase 3 component of the Precision-T study that have been outlined within the Precision-T Protocol [redacted]. The scope of this plan includes the interim and primary analyses. [redacted]

2 STUDY OBJECTIVES

2.1 Primary Objective

The primary objective of the phase 3 component of Precision-T is to compare survival free of moderate-to-severe chronic graft-versus-host disease (cGVHD) between participants eligible for allogeneic hematopoietic stem cell transplantation (alloHCT) who received either Orca-T followed by single-agent tacrolimus or a control consisting of standard-of-care (SoC) unmanipulated allograft followed by tacrolimus plus methotrexate.

2.2 Secondary Objectives

Secondary objectives of the phase 3 component of Precision-T are as follows:

- To compare time to moderate or severe cGVHD between participants undergoing alloHCT with either Orca-T or SoC
- To compare overall survival (OS) between participants undergoing alloHCT with either Orca-T or SoC
- 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

3 STUDY OVERVIEW

3.1 Study Design

The phase 3 component of Precision-T is a randomized, open-label, multicenter study designed to compare the outcomes between participants who receive either Orca-T followed by single -agent tacrolimus or SoC control allograft followed by GVHD prophylaxis with tacrolimus and methotrexate. Participants aged 18 to 65 years with acute leukemia (myeloid, lymphoid, or mixed phenotype) in complete remission with Disease Risk Index (DRI) risk category of intermediate to high or high-risk myelodysplastic syndrome (MDS) who have a human leukocyte antigen (HLA)-matched sibling donor (MSD) or matched unrelated donor (MUD) are eligible for the phase 3 component of the study. Participants enrolled onto the phase 3 component will be randomized in a 1:1 ratio to either the Orca-T or SoC arm, stratified by the following:

- Donor type (HLA-MSD versus HLA-MUD)
- DRI risk category (intermediate risk or high risk)

To ensure the study is designed to isolate the treatment effect of Orca-T as well as reduce the heterogeneity introduced with the use of disparate conditioning regimens prior to Orca-T, the choice of conditioning regimen has been limited to the regimens listed in section 6.3.1.1 of the Precision-T Protocol. The allowed regimens include both total body irradiation (TBI)-based options (TBI/cyclophosphamide [Cy] and TBI/etoposide) and a non-TBI-based option (busulfan/fludarabine/thiotepa [BFT]).

Orca-T is an allogeneic stem cell and T-cell immunotherapy comprising the following cell therapy drug products: purified hematopoietic stem and progenitor cells (HSPCs), purified regulatory T cells (T_{regs}), and purified conventional T cells (T_{cons}). [redacted] As each donor apheresis product contains variable amounts of HSPCs, T_{regs}, and T_{cons}, the actual cell dosage formulated in each drug product is controlled to dose ranges informed by clinical manufacturing data from ongoing clinical studies with Orca-T.

The primary analysis will occur when 56 cGVHD-free survival (cGFS) events are observed. A single interim analysis is planned for when 37 cGFS events (2/3 information fraction) are observed. A data monitoring committee (DMC) will meet at least quarterly to review accumulated safety data, and the DMC will also review the interim analysis results. DMC oversight of trial safety and efficacy data is described in further detail in the Precision-T DMC Charter. The DMC may recommend stopping a component of the study based on their assessment of safety data and may also claim efficacy of Orca-T based on the interim analysis results.

Although the study is an open-label study, the study statistician and programming team will remain blinded to the treatment information of individual participants and may be unblinded after the planned interim analysis to support potential regulatory interactions and/or regulatory filings. The outputs to support regular DMC meetings and the interim analysis will be provided by an external, independent biostatistics/programming team.

3.1.1 Endpoint Adjudication Committee

An independent endpoint adjudication committee (EAC) will perform a blinded determination as to whether the criteria for aGVHD and/or cGVHD have been met for each participant, and the EAC will then grade aGVHD and cGVHD according to Mount Sinai Acute GVHD International Consortium (MAGIC) grading criteria and International National Institutes of Health (NIH) Chronic GVHD Diagnosis and Staging Consensus Working Group criteria, respectively (see sections 11.5.1 and 11.5.2 of the Precision-T Protocol). The EAC will be composed of a minimum of 3 experts in GVHD assessment. The full membership, mandate, and processes of the EAC will be detailed in the EAC Charter. Primary estimands of primary and secondary endpoints with aGVHD or cGVHD components will be based on the assessments from the EAC.

3.2 Sample Size

The primary endpoint of cGFS per EAC is used to evaluate the effect of the experimental regimen for hematopoietic cell transplantation (HCT) against a standard of care. To achieve 90% power with a true hazard ratio (HR) = 0.40 and 1-sided alpha of .025, the required number of events needed is 56 (see Fleming and Harrington 1991, 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.

To account for 5% loss to follow-up in both treatment arms, 174 participants will be randomized.

4 STUDY ENDPOINTS AND COVARIATES

4.1 Study Endpoints/Estimands

4.1.1 Primary Endpoints and Primary Estimand

cGFS is defined as the time from the date of HCT (ie, day 0) 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.

Table 1 Primary Estimand for cGFS

Treatments	Population	Variable (Endpoint)	Population Level Summary
Orca-T versus SoC as randomized	ITT analysis set	cGFS per EAC	*P* value from stratified log-rank test stratified by the randomization stratification factors; hazard ratio from stratified Cox model stratified by the randomization stratification factors
General Censoring Rules			
Participants who received HCT (either SoC or Orca-T) 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 (either SoC or Orca-T) but have no cGVHD assessment after day 0 will be censored at day 0 except that a death within 56 + 3[a] 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 (either SoC or Orca-T) will be censored at randomization with a hypothetical day 0 added at randomization.			
Handling of Intercurrent Events			
ALL intercurrent events (treatment policy): Intercurrent events are considered irrelevant, and all available data will be included for the derivation of cGFS.			
Handling of Missing Assessments			
The rules described below is only apply to participants who received HCT (either SoC or Orca-T) • A participant will be censored at 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 **Note:** • The evaluation of missing cGVHD assessments discussed above for cGFS per the EAC will be based on whether a scheduled cGVHD survey was performed by investigators and nominal visit names (day +56, day +100, etc.) reported by investigators will be used. • The date of the last cGVHD assessment prior to the first missing cGVHD assessment discussed above is defined as below: - In general, it is defined as the date of the last cGVHD survey (scheduled or unscheduled) performed by investigator prior to the first missing scheduled cGVHD survey. - However, if no moderate or severe cGVHD is reported by EAC and the first missing scheduled cGVHD survey occurs between the date of last absence of moderate and severe cGVHD per EAC and the death date, it is defined as the date of last absence of moderate and severe cGVHD per EAC. • If an unscheduled assessment is conducted within 1 month of a missed scheduled assessment, the missed scheduled assessment will not be counted as missing.			

Abbreviations: cGFS, chronic graft-versus-host disease-free survival; cGVHD, chronic graft-versus-host disease; EAC, endpoint adjudication committee; HCT, hematopoietic cell transplantation; ITT, intention to treat; SoC, standard of care.

a Day +56 is the first scheduled cGVHD assessment, with day 0 defined as Orca-T HSPC administration or SoC HCT date, and a 3-day window is allowed for the visit.

4.1.2 Secondary Endpoints and Primary Estimand

4.1.2.1 Secondary Endpoint 2: Time to Moderate or Severe cGVHD

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.

Table 2 Primary Estimand for Time to Moderate or Severe cGVHD

Treatments	Population	Variable (Endpoint)	Population Level Summary
Orca-T versus SoC as randomized	ITT analysis set	Time to first onset of moderate or severe cGVHD per EAC with death as a competing event	*P* value from stratified Gray's (Gray 1988) stratified by randomization stratification factors to assess the equality of cumulative incidence functions between treatment groups; HR with 95% CI from the stratified subdistribution proportional hazards model (Fine and Gray 1999; Zhou et al. 2011) stratified by randomization stratification factors
General Censoring Rules			
Participants who received HCT (either SoC or Orca-T), 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 (either SoC or Orca-T) but have no cGVHD assessment after day 0 will be censored at day 0 except that a death within 56 + 3[a] 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 (either SoC or Orca-T) will be censored at randomization with a hypothetical day 0 added at randomization.			
Handling of Intercurrent Events			
ALL intercurrent events (treatment policy): Intercurrent events are considered irrelevant, and all available data will be included for the derivation of time to moderate or severe cGVHD			
Handling of Missing Assessments			
The rules described below is only apply to participants who received HCT (either SoC or Orca-T) • A participant will be censored at 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. **Note:** • The evaluation of missing cGVHD assessments discussed above for cGFS per the EAC will be based on whether a scheduled cGVHD survey was performed by investigators and nominal visit names (day +56, day +100, etc.) reported by investigators will be used.			

- The date of the last cGVHD assessment prior to the first missing cGVHD assessment discussed above is defined as below:
  - In general, it is defined as the date of the last cGVHD survey (scheduled or unscheduled) performed by investigator prior to the first missing scheduled cGVHD survey.
  - However, if no moderate or severe cGVHD is reported by EAC and the first missing scheduled cGVHD survey occurs between the date of last absence of moderate and severe cGVHD per EAC and the death date, it is defined as the date of last absence of moderate and severe cGVHD per EAC.
- If an unscheduled assessment is conducted within 1 month of a missed scheduled assessment, the missed scheduled assessment will not be counted as missing.

Abbreviations: cGVHD, chronic graft-versus-host disease; CI, confidence interval; EAC, endpoint adjudication committee; HCT, hematopoietic cell transplantation; HR, hazard ratio; ITT, intention to treat; SoC, standard of care.

a Day +56 is the second scheduled cGVHD assessment, with day 0 defined as Orca-T HSPC administration or SoC HCT date, and a 3-day window is allowed for the visit.

4.1.2.2 Secondary Endpoint 3: OS

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

Table 3 Primary Estimand for OS

Treatments	Population	Variable (Endpoint)	Population Level Summary
Orca-T versus SoC as randomized	ITT analysis set	OS	*P* value from stratified log-rank test stratified by the randomization stratification factors; hazard ratio from stratified Cox model stratified by the randomization stratification factors
General Censoring Rules			
Participants who are alive will be censored at the date last known to be alive.			
Handling of Intercurrent Events			
ALL intercurrent events (treatment policy): Intercurrent events are considered irrelevant, and all available data will be included for the derivation of OS.			
Handling of Missing Assessments			
Missing assessments will be disregarded, and all available data will be used for the derivation of OS.			

Abbreviations: ITT, intention to treat; OS, overall survival; SoC, standard of care.

4.1.2.3 Secondary Endpoint 3: GRFS up to 2 Year

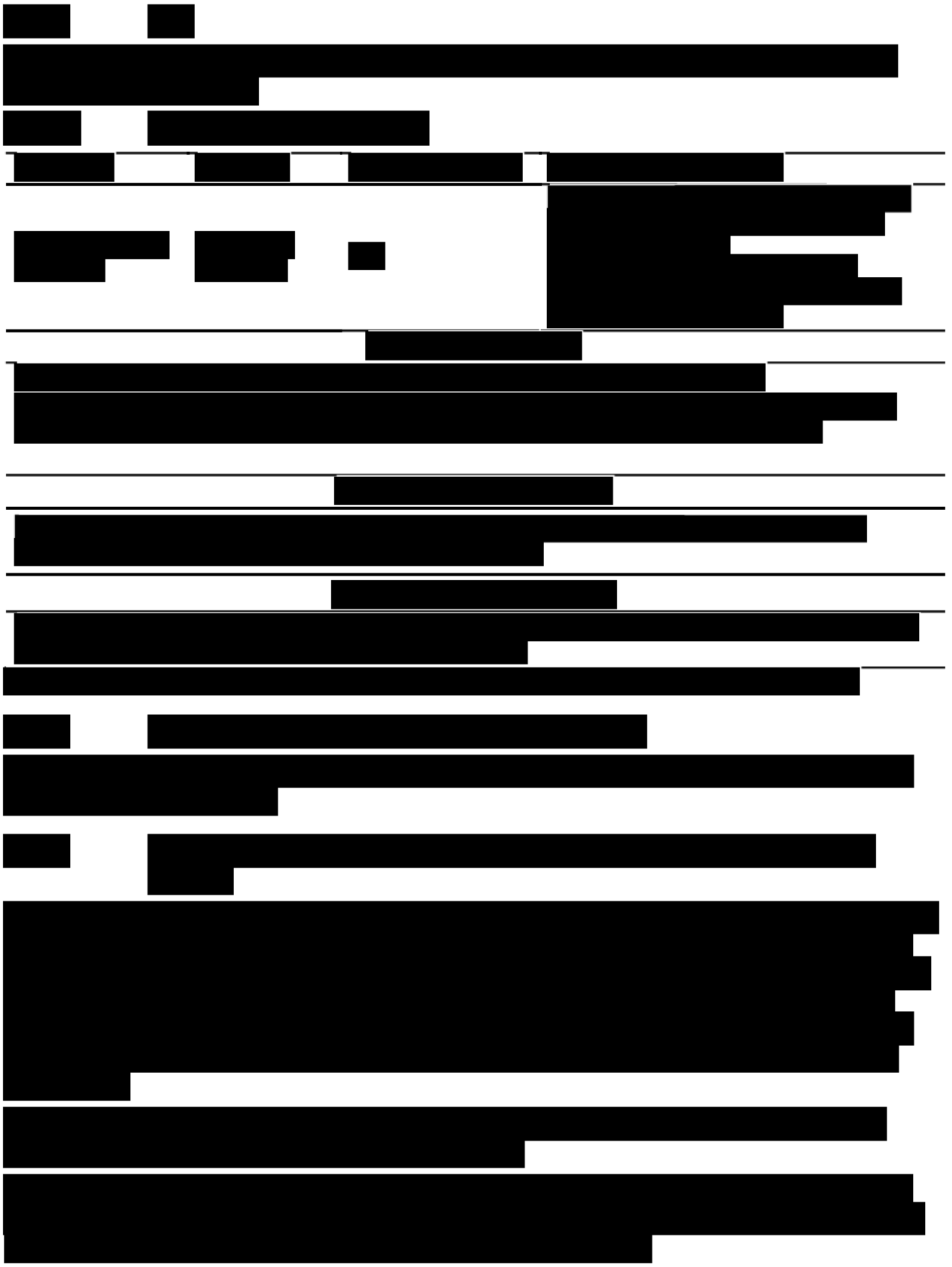
GRFS is defined as the time from HCT to death from any cause, relapse, the first onset of grade 3 or 4 aGVHD (graded per MAGIC criteria), or the first onset of moderate or severe cGVHD (graded per NIH consensus criteria), whichever is earliest, within 2 years from day 0.

Table 4 Primary Estimand for GRFS

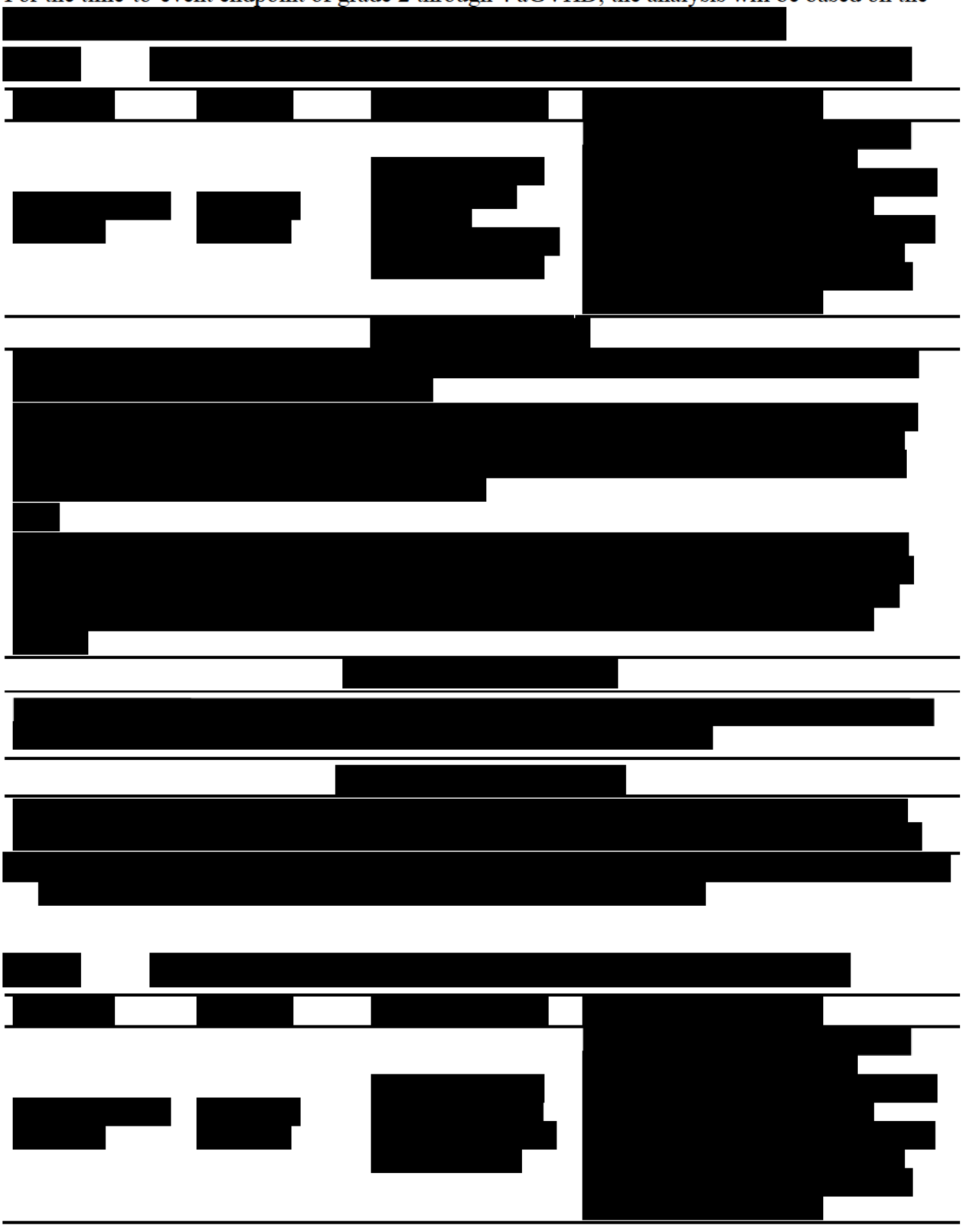
Treatments	Population	Variable (Endpoint)	Population Level Summary
Orca-T versus SoC as randomized	ITT analysis set	GRFS per EAC	*P* value from stratified log-rank test stratified by the randomization stratification factors; hazard ratio from stratified Cox model stratified by the randomization stratification factors

General Censoring Rules
Participants who receive HCT (either SoC or Orca-T) 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 (either SoC or Orca-T) will be censored at randomization with a hypothetical day 0 added at randomization.
Handling of Intercurrent Events
ALL intercurrent events (treatment policy): Intercurrent events are considered irrelevant, and all available data will be included for the derivation of GRFS.
Handling of Missing Assessments
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.

Abbreviations: aGVHD, acute graft-versus-host disease; cGVHD, chronic graft-versus-host disease; EAC, endpoint adjudication committee; HCT, hematopoietic cell transplantation; ITT, intention to treat; SoC, standard of care.



For the time-to-event endpoint of grade 2 through 4 aGVHD, the analysis will be based on the



[redacted]

4.2 Planned Covariates

The analysis to determine if Orca-T is superior to SoC with respect to the primary endpoint of cGFS per EAC will be stratified by the following stratification factors at randomization:

- Donor type (HLA-MSD versus HLA-MUD)
- DRI risk category (intermediate risk or high risk)

The analyses for the primary estimand of the secondary endpoints will also be stratified by these factors.

5 HYPOTHESES AND/OR ESTIMATIONS

The following hypotheses will be tested using the gatekeeping strategy in the order listed below:

1. Primary hypothesis: The null hypothesis is that there is no difference between treatment groups with respect to cGFS per EAC versus the alternative hypothesis that the treatment groups differ. The null hypothesis will be rejected if the *P* value from a 2-sided stratified log-rank test stratified by randomization stratification factors is less than the threshold determined by the alpha spending function specified in section 10.5 at the given analysis (interim or primary analysis).
2. Secondary hypothesis 1: The null hypothesis is that there is no difference between treatment groups with respect to time to moderate or severe cGVHD per EAC versus the alternative hypothesis that the treatment groups differ. The null hypothesis will be rejected if the *P* value from a 2-sided stratified Gray's test (Gray 1988) stratified by the randomization stratification factors is less than the threshold determined by the alpha spending function specified in section 10.5 at a given analysis (interim or primary analysis).
3. Secondary hypothesis 2: The null hypothesis is that there is no difference between treatment groups with respect to OS versus the alternative hypothesis that the treatment groups differ. The null hypothesis will be rejected if the P value from a 2-sided stratified log-rank test stratified by randomization stratification factors is less than the threshold determined by the alpha spending function specified in section 10.5 at a given analysis (interim or primary analysis).
4. Secondary hypothesis 3: The null hypothesis is that there is no difference between treatment groups with respect to GRFS per EAC up to 2 year after alloHCT versus the alternative hypothesis that the treatment groups differ. The null hypothesis will be rejected if the P value derived from a 2-sided stratified log-rank test stratified by randomization stratification factors is less than the threshold determined by the alpha spending function specified in section 10.5 at a given analysis (interim or primary analysis).

6 DEFINITIONS

6.1 General Study-Related Definitions

6.1.1 Participant, Donor, and Recipient

Participant refers specifically to an individual who was randomized in this study to receive Orca-T or SoC HCT. Donor refers specifically to an individual who donated blood that was intended to be used in the HCT. Recipient is also used to refer to an individual who was randomized to receive HCT (ie, participant) as needed to clearly distinguish those individuals from donors.

6.1.2 Baseline

The reference date for time-to-event endpoints is specified in their corresponding definitions.

For analyzing safety data and demographic and baseline disease characteristics, baseline is defined as the last assessment taken prior to the day of the conditioning regimen.

6.1.3 Duration (including time-to-event efficacy endpoints)

The duration between 2 dates (eg, start date and end date) will be calculated as follows unless otherwise specified:

(end date – start date + 1) (in days)

6.1.4 Study Day

The date of SoC HCT or Orca-T HSPC infusion is defined as day 0. Study day will be defined using the date of SoC HCT or Orca-T HSPC infusion (day 0) as a reference and will be defined as follows:

date of interest – date of Orca-T HSPC infusion/SoC HCT

6.1.5 Time-Related Unit Conversion

To calculate years/months/weeks from days, the following formulas will be used:

years = number of days ÷ 365.25
months = number of days ÷ 30.4375 (ie, 365.25/12)
weeks = number of days ÷ 7

Values based on the above computations will be rounded to tenths.

6.1.6 Data Cutoff Date

For the interim and primary analysis triggered by the number of cGFS events per EAC (37 or 56 events, respectively), the cutoff date is the date of the last assessment related to an EAC-confirmed 37th or 56th event, respectively. Due to the EAC review process, there may be more than 37 or 56 adjudicated events prior to the cutoff date. For the interim analysis, exact 37 events will be used, unless multiple events occur on the same day as the 37th event, in which case all events occurring on or before that date will be included. For both data reported in electronic data capture (EDC) system and EAC data, only the data up to the data cutoff date will

be used for the interim analysis. Specifically, if the moderate or severe cGVHD event onset date per EAC, or the last date when the EAC confirmed the absence of moderate or severe cGVHD, falls after the data cutoff date, it will be treated as an absence of moderate or severe cGVHD at the data cutoff date. The actual event date or the last confirmation date will not be used for the derivation of cGFS per EAC. For the primary analysis, all adjudicated events will be included. If more than 37 or 56 events are used for the analysis, the efficacy boundaries (*P* value critical value) will be adjusted correspondingly using the alpha spending function specified in section 10.5.

Comprehensive data cleaning for the interim and primary analysis will only be applied to data collected up to the data cutoff date defined above. A data snapshot will be extracted from the clinical database after the data cutoff date, but only the data collected up to the data cutoff date will be used to create the tables, figures, and listings for the CSR.

Comprehensive data cleaning will be applied to all data collected prior to the final database lock.

6.1.7 Visit Window for Analyses at 1 Year and 2 Years

For the estimands of primary, secondary, exploratory time to event endpoints, the phrase of "within 1 year after/from day 0" or "within 2 years after/from day 0" is used to limit the assessments and/or events included for the derivation of the endpoints.

Specially for cGFS, time to moderate or severe cGVHD, GRFS, and time to grade 2 through grade 4 aGVHD or time to grade 3 or grade 4 aGVHD, where aGVHD and/or cGVHD and/or disease relapse are events, 'within 1 year' and 'within 2 years' are only used to limit the inclusion of death events for the time to event endpoint derivation, whether death is an event or competing event, while including all cGVHD assessments, aGVHD assessments and disease evaluation. This is because the last scheduled aGVHD assessment is planned at the day +365 visit, so aGVHD assessments may occur beyond 1 year but are not expected to occur much later. Similarly, since the last scheduled cGVHD assessment and disease evaluation are planned at the day +730 visit, cGVHD assessments and disease relapse evaluation may occur after 2 years but are not expected to occur much later.

For other time to endpoints where a given AE, other than aGVHD or cGVHD, is an event (eg, grade ≥3 infection), it is noted that no general AE is required to be reported after EOAP which is expected to occur at the 2-year mark but Orca-T related AEs are still required to be reported after it. To have a fair comparison between the two arms, 'within 1 year' and 'within 2 years' are used to limit the inclusion of both death events and the given AE.

Considering the protocol's visit window of ± 21 days for those two visits, "within 1 year after/from day 0" is defined as "within 365 + 21 days after/from day 0' and "within 2 years after/from day 0" is defined as "within 730 + 21 days after day 0". The 21-day window ensures the relevant assessments and events used for the derivation fall within a similar time frame.

6.2 Estimand-Related Definitions

6.2.1 Intercurrent Events

Although the treatment policy will be used for all intercurrent events for the primary estimands for the primary and secondary endpoints, the following intercurrent events will be identified and may be considered for sensitivity or supplementary analyses:

1. Use of donor lymphocyte infusion (DLI) for relapse, chimerism, or other reasons
2. 2nd alloHCT or other cellular therapy (excluding DLI)
3. Changes in GVHD prophylaxis for any reason, including early tapering of tacrolimus
4. Received aGVHD treatment beyond first line (ie, aGVHD treatment beyond corticosteroids)
5. Use of investigational treatment for aGVHD or cGVHD
6. Use of rituximab for any reason including Epstein-Barr virus reactivation
7. Use of ruxolitinib for prevention of disease recurrence
8. Use of imatinib (or other BCR-ABL inhibitors) for prevention of disease recurrence
9. Disease relapse

Intercurrent events of manufacturing failure, harvest failure, and graft failure will be addressed by using the ITT analysis set (primary estimands) and per-protocol analysis set (estimands for supplementary analysis).

6.2.2 Policies Used to Handle Intercurrent Events

Hypothetical policy strategy

A scenario is envisaged in which the intercurrent event would not occur: the value of the variable to reflect the clinical question of interest is the value which the variable would have taken in the hypothetical scenario defined. For this study, by hypothetical policy strategy, relevant assessments/events after the intercurrent event will be excluded from the derivation of the corresponding time-to-event endpoint.

Treatment policy strategy

The occurrence of the intercurrent event is considered irrelevant in defining the treatment effect of interest: the value for the variable of interest is used regardless of whether the intercurrent event occurs.

Treatment policy will be used for the primary estimands for all primary and secondary endpoints, while hypothetical policy may be used for certain intercurrent events for some sensitivity/supplementary analyses.

6.2.3 Disease Relapse and Disease Relapse Date

In general, a participant will be considered to have experienced disease relapse if the disease evaluation eCRF indicates so. The disease relapse date reported in the disease evaluation eCRF will be used as the relapse date. If a participant has started a new anticancer therapy to treat MRD positivity in the absence of disease relapse as defined in the protocol recorded in the disease evaluation eCRF, this participant will be considered to have relapsed at the initialization of the new anticancer therapy. If MRD is negative after randomization or MRD was not tested, this participant will NOT be considered to have relapsed. Initiation of maintenance therapy pre-specified in the eligibility form with or without MRD positivity will not be counted as a relapse. If more than 5 participants are considered to have disease relapse due to positive postrandomization MRD without disease relapse documented in the disease evaluation eCRF, a sensitivity analysis will be conducted by censoring those participants at their last disease assessment.

6.3 Safety-Related Definitions

6.3.1 Treatment-Emergent Period

All adverse events (AEs), serious AEs (SAEs), AEs of special interest (AESIs), aGVHD events, and cGVHD events with an onset during the TEAE period defined in Table 11 will be considered treatment emergent and included in the corresponding AE summary tables. All AEs reported by sites, regardless of whether they are treatment emergent or not, will be listed. A summary table will also be provided for AEs with an onset on or after the conditioning regimen but prior to day 0.

Table 11 also defines the treatment emergent period for laboratory data, concomitant medications, vital signs, and physical examinations. Details on the corresponding analyses are provided in sections 10.6.3, 10.6.4, and 10.6.8.

Table 11 Treatment-Emergent Period

TEAE Period	Safety Data Category
Day 0 to day +100	all AEs, laboratory data, vital signs, physical examinations[a]
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; Hb, hemoglobin; HCT, hematopoietic cell transplantation; PLT, platelets; SAE, serious adverse event, Tbili, total bilirubin.

a For physical exam, eCRF is designed to confirm whether a physical examination took place and the date of the exam; Clinical data from the physical examination will not be formally collected but clinically significant abnormal findings (i.e. adverse events) will be recorded.

6.3.2 AESIs

Analyses of AESIs will be based on sites' reporting of an AE belonging to 1 of the AESI categories listed below. AESIs for Orca-T are as follows:

- Secondary malignancy, including posttransplantation lymphoproliferative disorder (PTLD)
- Grade ≥3 infection
- Graft failure (primary or secondary)
- Thrombotic microangiopathy (TMA)
- VOD/sinusoidal obstruction syndrome (SOS)

6.3.3 Identified and Potential Risks

Identified and potential risks for Orca-T are listed below:

- Identified risks
  - aGVHD
  - cGVHD

  - Graft failure

- Potential risks
  - Batch manufacturing failure
  - Infusion-related reaction (IRR)
  - Hypersensitivity
  - Grade ≥3 infection
  - TMA
  - VOD/SOS
  - Secondary malignancy, including PTLD

For participants who received nonconforming Orca-T batches (ie, batch manufacturing failure), separate summaries of time to neutrophil engraftment, time to platelet engraftment, and the number of participants with primary or secondary graft failure will be provided.

Except for batch manufacturing failure, AESIs and potential/identified risks are defined by a single preferred term (PT), system organ class (SOC), or SMQ. If there is not a relevant SMQ available or available SMQs do not align with the events typically seen in the transplant setting, customized MedDRA queries will be created based on medical review.

Primary graft failure is defined as being alive without recovery of neutrophils (ie, without achieving an ANC ≥500/mm^3 for 3 consecutive days) at day +28 without another identifiable cause such as relapsed/persistent disease. Secondary graft failure is defined as neutrophil engraftment followed by subsequent decline in ANC <500/mm^3 unresponsive to growth factor therapy by day +100 without another identifiable cause such as relapsed/persistent disease. Graft failure includes both primary graft failure and secondary graft failure, which are reported as AEs.

Analysis of IRRs and hypersensitivity require grouping of Medical Dictionary for Regulatory Activities preferred terms (PTs). IRR is defined as treatment-emergent AEs of any MedDRA PT listed in Table 14 with an onset within 24 hours after administration of any Orca-T or SoC infusion. Additional AEs may be added to Table 14 based on medical review of the accumulated data. The final set of AEs will be provided in the CSR.

Hypersensitivity is defined as TEAEs identified within the SMQ of hypersensitivity and the SMQ of anaphylactic reaction with an onset within 24 hours of Orca-T or SoC infusion. The PTs retrieved from the 2 referenced SMQs will be medically reviewed and may be customized to ensure applicability to the TEAEs typically observed in the transplant setting. The final set of PTs for any modified SMQs of hypersensitivity and anaphylaxis will be provided in the summary of clinical safety.

Infection includes all PTs under the SOC “infections and infestations.” For all infection events that are grade ≥3, customized MedDRA queries (Table 15) will be utilized that group events by type of organism (fungal, viral, bacterial, and other). The final PTs included to define each category will be included in the summary of clinical safety.

Secondary malignancy, including PTLD, is defined as AEs included in the SMQ of malignancies that occurred following administration of Orca-T or SoC.

7 ANALYSIS SETS

7.1 Donor Analysis Set

The donor analysis set consists of all donors who complete mobilization and initiate apheresis. The donor analysis set will be used for all summary tables and listing for donors.

7.2 Recipient Analysis Sets

The analysis sets for recipients are defined below:

Analysis Set	Description
ITT analysis set	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.
Per-protocol analysis set	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. Important protocol deviations that may affect evaluation of the efficacy will be defined prior to the data snapshot for the interim analysis and may be updated for the primary analysis.
Safety analysis set	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.

Abbreviations: ITT, intention to treat; SoC, standard of care.

7.3 Subgroup Analyses

Subgroup analyses will be performed on the primary and secondary endpoints using the primary estimand for the subgroups defined below. Additionally, subgroup analyses will also be conducted on the primary and secondary endpoints derived based investigators' assessment on aGVHD and/or cGVHD, as well as possibly on certain efficacy-related exploratory endpoints. Key safety tables, as discussed in section 10.6, may also be repeated for the same subgroups. The subgroups analyzed may include the following or others not listed here:

- 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)

In general, given a subgroup, if number of participants in either arm is less than 5, there is no need to repeat the efficacy tables for that subgroup.

8 INTERIM ANALYSIS

The interim and primary analyses for the primary and secondary endpoints are planned as described in Figure 1.

A single interim analysis is planned to assess the primary endpoint, cGFS, when 37 primary endpoint (cGFS) events per EAC are observed. This represents 2/3 of the expected 56 primary efficacy events at the time of the primary analysis. The efficacy boundary for cGFS will be based on the Lan-DeMets (1983) 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 is .0116 for the interim analysis and .0464 for the primary analysis. Due to the EAC review process, more than 37 or 56 events may be included for the respective analysis. If more than 37 or 56 events are used for the analysis, the efficacy boundaries (*P* value critical value) will be adjusted correspondingly using the alpha spending function.

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

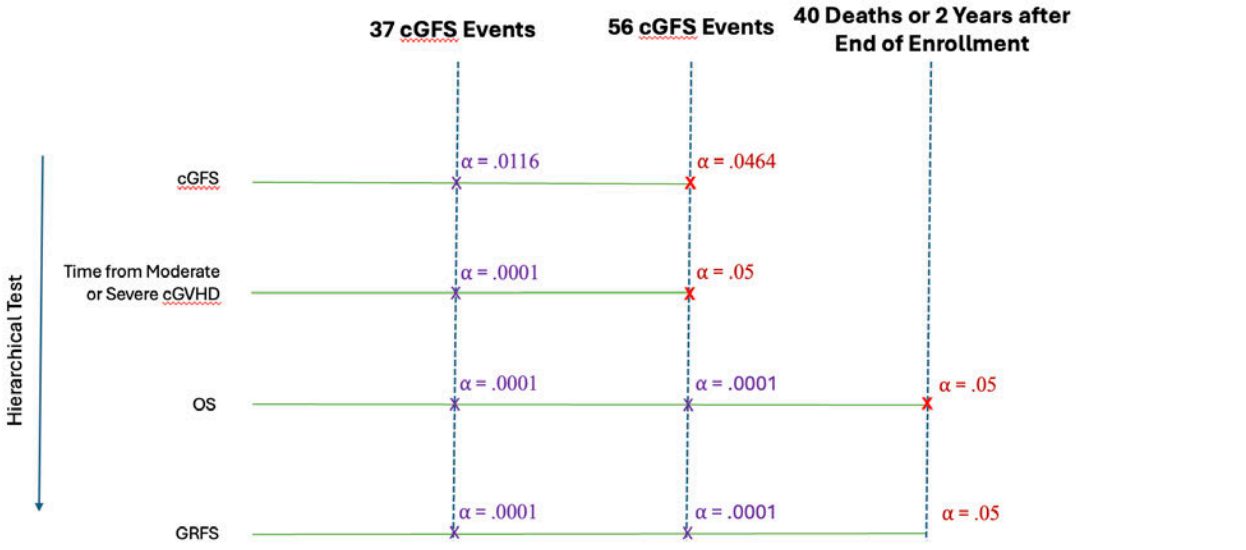
Two interim analyses are planned to assess the second secondary endpoint OS: when 37 primary endpoint (cGFS) events per EAC are observed, when 56 primary endpoint (cGFS) events per EAC are observed, and at the primary analysis for GRFS. The primary analysis for OS will be performed when 40 deaths are observed or 2 years after the end of enrollment, whichever is earlier.Two interim analyses are planned to assess the third secondary endpoint GRFS per EAC: when 37 primary endpoint (cGFS) events per EAC are observed, and when 56 primary endpoint (cGFS) events per EAC are observed. The primary analysis for GRFS per EAC will be performed at the primary analysis of OS.

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

An external, independent DMC will review the efficacy results from the interim analysis when 37 primary endpoint (cGFS) events per EAC are observed. In addition, the DMC will assess safety data approximately every 3 months. The timing of safety reviews may be adjusted to coincide with the DMC meeting to review the efficacy results from the interim analysis. Based on their review of the interim analysis results, the DMC will make a recommendation as to whether efficacy can be claimed early based on the primary endpoint. An independent biostatistics/programming team outside of Orca Bio will perform the DMC-related safety analyses and provide the interim analysis results to the DMC. Further details are provided in the DMC Charter.

It is expected that study enrollment will be complete or close to completion at the interim analysis.

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



α denotes the 2-sided critical p-value at each analysis
The interval between each analysis in the plot may not be proportional to the time interval between each analysis or the information fraction at each analysis

9 DATA SCREENING AND ACCEPTANCE

9.1 General Principles

The objective of the data screening is to assess the quantity, quality, and statistical characteristics of the data relative to the requirements of the planned analyses. The database will be subject to edit checks outlined in the data management plan by Orca Bio Clinical Data Management (CDM). Any critical data issues will be communicated to CDM for resolution before the data snapshot for each of the planned analyses.

9.2 Data Handling and Electronic Transfer of Data

Orca Bio CDM will provide all data to be used in the planned analyses. This study uses Zelta as EDC system.

9.3 Handling of Incomplete Dates

9.3.1 Imputation of Partially Missing Dates of AEs and Concomitant Medications

The original dates reported by sites before any imputation will be used to determine whether an AE or a concomitant medication is treatment emergent or not. If an AE or concomitant medication cannot be determined to be treatment emergent or not due to a missing or partially missing start/end date, the AE or concomitant medication should be considered treatment emergent.

For AEs and concomitant medication, start and stop dates with only the day missing may be imputed when the calculation of the duration of an AE or a concomitant medication is needed. If imputation of an incomplete stop date is required and both the start date and the stop date are incomplete, then the start date will be imputed first.

9.3.1.1 Missing Day Only for Start Date

If the month and year of the incomplete start date are the same as the month and year of day 0, then day 0 will be assigned to the missing day.

If either the year is before the year of day 0 or if both years are the same but the month is before the month of day 0, then the last day of the month will be assigned to the missing day.

If either the year is after the year of day 0 or if both years are the same but the month is after the month of day 0, then the first day of the month will be assigned to the missing day.

Concomitant procedure/surgery date is considered as start date and imputed using the same rule described above.

9.3.1.2 Missing Day Only for Stop Date

If the stop date is the same year and month as the death date, the date of death will be assigned to the missing date; otherwise, the last day of the month will be assigned to the missing day.

9.3.2 Imputation of Partially Missing Dates of Other Datasets

In addition to adverse event, concomitant medication, concomitant procedure/surgery, missing dates with only day missed from other datasets may be imputed if needed for the analysis, for

example, the last contact date in the Survival Status dataset. And in general, the date will be imputed the first day of the month unless such an imputation creates inconsistency within the dataset or cross different datasets.

9.4 Outliers

Any suspected outliers will be investigated by the study team and will be included in the database unless they are determined to be the result of an error or if sufficient supporting evidence or explanation exists to justify their exclusion. Any outliers excluded from the analysis will be discussed in the CSR, including the reasons for exclusion and the impact of their exclusion on the study results.

9.5 Distributional Characteristics

The statistical assumptions for analysis methods will be assessed. For example, the proportional hazards assumption will be visually checked by plotting log(-log(survival)) versus log(time) by treatment. If the assumptions for the distributional characteristics are not met, these will be described, and further analyses may be carried out using data transformations or alternative analysis methods.

The use of transformations or alternative analysis methods will be justified in the CSR.

9.6 Validation of Statistical Analyses

Tables, figures, and listings will be produced with validated programs. Programs will be developed and maintained and output will be verified in accordance with the sponsor's relevant SOP(s). The production environment for statistical analyses consists of the SAS System version 9.4 or later.

10 STATISTICAL METHODS OF ANALYSIS

10.1 General Principles

Data will be pooled across sites for summary analyses unless specified otherwise.

For both efficacy and safety analyses, summary tables will present the data by treatment. The overall summary of TEAEs will present data by conditioning regimen, treatment and separately by disease type, and treatment.

The subgroup analyses described in section 7.3 will evaluate any potential differences in efficacy and safety between different disease types and/or conditioning regimens.

For continuous variables, descriptive statistics will be presented, including the number of participants used in the calculation (n), mean, standard deviation (SD), median, and range (minimum and maximum).

For categorical variables, summaries will reflect frequencies and percentages, with the denominator for percentages being the number of participants in the corresponding analysis set, unless specified otherwise.

Listings will be provided and, if needed, sorted by site and participant number.

10.2 Participant Accountability

The number and percentage of participants who were screened, randomized, received HCT (either Orca-T or SoC), were ongoing at the time of the data cutoff, ended active participation in the study (along with the reasons), and completed study will be summarized by treatment. The number and percentage of participants randomized will be tabulated by the stratification factors and by study site. Key study dates will be presented, including the first participant randomized, last participant randomized, and data cutoff date for analysis.

10.3 Important Protocol Deviations

Important protocol deviations (IPDs) are defined as a subset of protocol deviations that might significantly affect the completeness, accuracy, and/or reliability of the study data or that might significantly affect a participant's rights, safety, or well-being.

IPD categories will be defined by the study team and updated during the IPD reviews throughout the study prior to database lock. These definitions of IPD categories, subcategory codes, and descriptions will be used for the study.

The number and percentage of participants who experience each of the IPDs will be presented. A listing and a summary table by category of all IPDs will be provided.

10.4 Demographic and Baseline Characteristics

Demographic (ie, age, age group [<55 or ≥55], sex, race, and ethnicity) and baseline disease characteristics will be summarized by treatment using descriptive statistics on the ITT analysis set. If multiple races have been reported for a participant, the participant will be categorized as multiple races. The baseline characteristics to be summarized include the following:

- Primary disease

- Donor-recipient relationship: MUD or MSD
- Karnofsky performance status score
- HCT Comorbidity Index (HCT-CI) score (score ≤2 or score ≥3)
- Disease status at transplantation (excluding MDS)
- MRD at baseline (participants with AML or ALL only) (positive or negative)
- IPSS-R prognostic score (MDS only)
- DRI score (intermediate or high)
- Relationship of CMV status between a recipient and the corresponding donor (negative/negative, negative/positive, positive/negative, or positive/positive)
- Relationship of ABO types between donor and recipient (A/A, or, A/AB, etc.)
- Gender match between donor and recipient (gender matched, or gender mismatched)

10.5 Efficacy Analysis

The study will have an overall alpha of .05 with 2-sided testing.

To preserve the overall significance level, statistical testing of the primary and secondary endpoints will follow a hierarchical structure.

First, the primary endpoint of cGFS per EAC will be tested. The critical 2-sided *P* value for cGFS is .0116 for the interim analysis and .0464 for the primary analysis if the interim analysis is based on exactly 37 events out of the total of 56 events using the spending function described in section 8. If the primary endpoint is significant, secondary endpoints will be tested sequentially. For each of the secondary endpoints, if tested, a generalized Haybittle–Peto boundary will be used between the interim and primary analyses. That is, the critical value for the *P* value at each of the interim analyses will be 2-sided .0001, while the critical value at the primary analysis will still be 2-sided .05.

If Orca-T demonstrates superiority to SoC with respect to cGFS per the EAC, the secondary endpoint of time to moderate or severe cGVHD per the EAC will be tested. If Orca-T demonstrates superiority to SoC with respect to time to moderate or severe cGVHD per the EAC, the secondary endpoint of OS will be tested. If Orca-T demonstrates superiority to SoC with respect to OS,GRFS per the EAC up to 2 years will be tested.

The time of the occurrence of 56 cGFS events will be used to define the timing of interim or primary analysis for secondary endpoints as described in section 8, even if the primary efficacy endpoint cGFS has already been assessed as significant at the time of its interim analysis and will not be tested at the primary analysis.

For time-to-event endpoints without competing risks, the presentation will be by treatment and include the number of participants who were censored and the number of participants who experienced the event of interest along with their respective percentages. The Kaplan-Meier method will be applied to estimate event-free probabilities at selected timepoints and quantiles for each treatment arm. Greenwood's formula (Kalbfleish and Prentice 1980) for standard error will be used to calculate confidence intervals (CIs) for the estimated event-free probability. CIs for quartiles of each group will be estimated per Brookmeyer and Crowley (Brookmeyer and Crowley 1982) using a log-log transformation. The analysis will be complemented by the provision of Kaplan-Meier curves by treatment. The *P* value for the hypothesis test for the primary estimand will be calculated from a stratified log-rank test stratified by randomization

stratification factors. In addition, a stratified Cox model stratified by randomization stratification factors will be applied to provide the hazard ratio (HR) between the 2 arms for the primary estimand. For sensitivity analyses, an unstratified log-rank test and unstratified Cox model may be used.

For time-to-event endpoints with a competing event, the presentation will be by treatment arm and include the number of participants who were censored, the number of participants who experienced the event of interest, and the number of participants who experienced a competing event, along with the corresponding percentages. Nonparametric estimation of the cumulative incidence rate by treatment accompanied by the corresponding 95% CI at selected timepoints, considering the presence of competing risk events, will be provided. Curves illustrating cumulative incidence along the time since randomization will also be provided. Gray's test (Gray 1988) will be performed to assess the equality of cumulative incidence functions between treatment groups. The *P* value for the hypothesis test for the primary estimand will be calculated from the stratified Gray's test stratified by randomization stratification factors, and the stratified subdistribution proportional hazards model (Fine and Gray 1999; Zhou et al. 2011) stratified by randomization stratification factors will be used to calculate treatment HR with 95% CI. For sensitivity analyses, an unstratified Gray's test (Gray 1988) and unstratified subdistribution proportional hazards model (Fine and Gray 1999) may be used.

Reverse Kaplan-Meier method (Schemper and Smith, 1996) will be used to provide the median follow time for cGFS, OS, and GRFS.

10.5.1 EAC Output

The EAC will review blinded patient profiles from the clinical database which may include aGVHD/cGVHD assessments; concomitant medication; posttransplantation anticancer therapy; GVHD prophylaxis; hospitalizations; AEs; relevant laboratory test results; ALT, AST, and bilirubin values; CMV viral loads; C diff test results; and PFT results, if performed. Additional source documents will also be provided directly from sites to the EAC as part of the standard dossier contents for cases/events requiring review (EAC Charter version 1.0, section 8).

Instead of providing a by-visit assessment, the EAC will provide an overall GVHD profile to include the whole safety follow-up course, including but not limited to the following:

- Whether or not a participant experienced aGVHD/cGVHD
  - If not, the last documented absence of aGVHD/cGVHD
  - If yes, the worst overall grade/severity and the date of either the onset of a GVHD event of interest or the last date when the participant is free of GVHD events of interest. GVHD events of interest are grade 3 or 4 aGVHD or moderate or severe cGVHD.

The EAC output description above will be used to derive all the related endpoints per EAC. Note that the evaluation of missing cGVHD/aGVHD assessments will also be based on whether a scheduled cGVHD/aGVHD survey was performed by investigators and nominal visit names (day +56, day +100, etc.) reported by investigators will be used for efficacy endpoints per EAC since EAC does not provide by-visit assessments.

10.5.2 Intercurrent Event and Missing Visits for Estimands

10.5.2.1 Intercurrent Event

Treatment policy will be used for all intercurrent events defined in section 6.2 for the primary estimands for all the time-to-event endpoints.

A summary of intercurrent events will be provided by treatment and may include the number and percentage of participants who experienced each of the intercurrent events. Sensitivity/supplementary analyses with hypothetical policies employed for intercurrent events will be performed.

10.5.2.2 Missing Assessments

Primary estimands for cGFS and time to moderate or severe cGVHD will handle the data differently when there is a missing cGVHD assessment(s), and details are provided in Table 1 and Table 2. If an unscheduled assessment is conducted within 1 month of a missed scheduled assessment, the missed scheduled assessment will not be counted as missing.

All events of interest for the time to event endpoints (ie, moderate or severe cGVHD, grade 3 or 4 aGVHD, and relapse) are severe events that are unlikely to be overlooked by investigators or other site personnel or to go unreported by participants. Therefore, sensitivity analyses will be performed by including all events and/or assessments regardless of the extent of missing data. For cGFS and exploratory endpoints, missing assessments will be disregarded and all the assessments and/or events after the missing assessments will be included for the derivation of the endpoints as their primary estimands.

Details are provided in the corresponding estimands.

10.5.3 Analysis of Primary Efficacy Endpoint

A 2-sided stratified log-rank test stratified by the randomization factors will be used to compare cGFS per EAC between the Orca-T group the SoC group. In addition, the HR with a 95% CI will be estimated from a stratified Cox regression model stratified by the randomization factors. The KM summaries described in section 10.5 will be performed by treatment. The primary analysis will be performed on the ITT analysis set using the primary estimand described in Table 1.

Sensitivity and supplementary analyses described in Table 17 will be performed. Those sensitivity and supplementary analyses differ from the primary estimand in 1 or more of the following aspects:

- The per-protocol analysis set will be used instead of the ITT analysis set.
- For GVHD related endpoints, assessments per investigator will be used versus assessments per EAC. To derive endpoints per investigator assessment for aGVHD and/or cGVHD, only the information from the aGVHD/cGVHD survey eCRF will be used, although additional information may be available in adverse event and aGVHD/cGVHD response eCRFs, since the aGVHD/cGVHD survey eCRF provides the most comprehensive evaluation.
- Unstratified analyses will be used instead of stratified ones.
- Hypothetical policy instead of treatment policy will be used to handle intercurrent events.
- Different approaches will be used when there is a missing assessment.

Subgroup analyses will be performed to explore the consistency of the treatment effect for subgroups described in section 7.3. To examine the impact of stratification errors (if any), the primary analysis may be repeated using the values of the stratification values reported on the CRF rather than through Interactive Web Response System (IWRS) if discrepancy between those two is observed.

10.5.4 Analysis of Secondary Efficacy Endpoints

As described in section 10.5, if the primary endpoint is significant, the secondary endpoints will use a fixed sequence algorithm with the endpoints tested in the following order, with a given endpoint tested only if all the previous endpoint tests were significant:

1. cGFS per EAC
2. Time to moderate-to-severe cGVHD per EAC
3. OS
4. GRFS per EAC up to 2 year

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

A generalized Haybittle–Peto boundary will be used between the interim and primary analyses for secondary endpoints. That is, the critical value for the *P* value at each of the interim analyses will be 2-sided .0001, while the primary analysis will maintain the 2-sided critical value of .05.

For time to moderate-to-severe cGVHD per EAC, the primary estimand is provided in Table 2. The *P* value from the stratified Gray's test (Gray 1988) stratified by randomization stratification factors will be used to determine whether the hypothesis test is significant. The analysis approaches for time-to-event endpoints with a competing event described in section 10.5 will be used. Sensitivity and supplementary analyses similar to those for the primary endpoint and described in Table 18 will be performed.

For OS, the primary estimand is provided in Table 3. The *P* value from the stratified log-rank test stratified by randomization stratification factors will be used to determine whether the hypothesis test is significant. KM analysis approaches and Cox models described in section 10.1 will be used. Sensitivity and supplementary analyses described in Table 20 will be performed.

For GRFS per EAC up to 2 year, the primary estimand is provided in Table 4. The P value from the stratified log-rank test stratified by randomization stratification factors will be used to determine whether the hypothesis test is significant. KM analysis approaches and Cox models described in section 10.5 will be used. Sensitivity and supplementary analyses described in Table 19 will be performed.

10.5.5 Analysis of Exploratory Efficacy Endpoints

For each of exploratory endpoints, the corresponding analysis set is defined in section 4.1.3.

For NRM, the primary estimand is provided in Table 5. The descriptive *P* value from the stratified Gray's test (Gray 1988) stratified by randomization stratification factors will be provided. The analysis approaches time to event endpoints with a competing event described in section 10.5 will be used.

For RFS, the primary estimand is provided in Table 6. The descriptive *P* value from the stratified log-rank test stratified by randomization stratification factors will be used to determine whether the hypothesis test is significant. KM analysis approaches and Cox models described in section 10.5 will be used.

Death up to day +100 and death up to day +180 will be summarized.

Time to grade 2 through 4 aGVHD, time to grade 3 or 4 aGVHD, time to grade ≥3 infection, and time to grade ≥4 infection with death as a competing event will be analyzed using approaches described in section 10.5 for time-to-event endpoints with a competing event.

The summary of all grade aGVHD and cGVHD, steroid-refractory aGVHD and steroid-refractory cGVHD, and grade ≥3 mucositis and grade ≥4 mucositis will be provided as part of the safety summary.

For the incidence and timing of neutrophil engraftment, the number of participants who have achieved neutrophil engraftment either by day +28 and by day +100 will be provided by treatment. Summary statistics will also be provided including mean, SD, median, Q1, Q3, and range for days from day 0 to neutrophil engraftment. Similarly, the number of participants who have achieved platelet engraftment by day +50 and by day +100 will be provided with summary statistics. The same summary statistics will also be provided for days from day 0 to platelet engraftment. Additionally, the incidence of platelet transfusions will also be summarized.

The number of participants who received TPN will be summarized by treatment received.

The duration of initial hospitalization due to alloHCT starting from day 0 will be summarized by treatment received, together with the number of participants who are admitted to the ICU and the number of days in the ICU due to alloHCT.

The number of participants who are rehospitalized due to AEs, cumulative duration of rehospitalization due to AEs, number of periods of rehospitalization due to AEs, and average duration of rehospitalization due to AEs will be summarized by treatment received. The same analysis will be performed for number of participants who are admitted to ICU due to AEs, cumulative days in the ICU due to AEs, number of times of admission to the ICU due to AEs, and average days in the ICU per time due to AEs.

The number and percentage of participants who meet criteria for ISFS will be summarized by treatment received.

The absolute number (per µL of peripheral blood) of T cells, NK cells, and B cells in recipients will be summarized by treatment received.

The analysis of health-related QoL endpoints is described in section 10.5.6.

10.5.6 Analysis of Health-Related QoL Endpoints

10.5.6.1 FACT-BMT and EQ-5D-5L

FACT-BMT and EQ-5D-5L will be used for this study, with assessments taken at screening, day +14, day +28, day +56, day +100, day +180, day +270, day +365, and day +730.

EQ-5D-5L

The EQ-5D-5L is a widely used generic measure of health status consisting of 2 parts. The first part (the descriptive system) assesses health in 5 dimensions (mobility, self-care, usual activities, pain/discomfort, anxiety/depression), each of which has 5 levels of response (no problems, slight problems, moderate problems, severe problems, extreme problems/unable to). This part of the EQ-5D questionnaire provides a descriptive profile that can be used to generate a health state profile. The second part of the questionnaire consists of a visual analogue scale (VAS) on which the patient rates his/her perceived health from 0 (the worst imaginable health) to 100 (the best imaginable health).

The measurements from this instrument include EQ-5D-5L dimension responses, EQ VAS, and EQ-5D index. The EQ-5D index will be calculated using United States of America value sets (Pickard et al. 2019; Euro QoL 2022)

FACT-BMT

The FACT-BMT was designed to measure QoL in patients undergoing bone marrow transplantation. It combines the FACT-G, a widely used assessment primarily assessing physical well-being (PWB), social/family well-being (SWB), emotional well-being (EWB), and functional well-being (FWB), with Bone Marrow Transplantation Subscale (BMTS) to measure BMT-specific concerns (McQuellon et al. 1997). The following scores will be derived from the questionnaire:

- PWB score
- SWB score
- EWB score
- FWB score
- BMTS score
- FACT-BMT trial outcome index (TOI)
- FACT-G total score
- FACT-BMT total score

The assessment taken at screening will be the baseline assessment. For each score listed for FACT-BMT and EQ VAS and EQ-5D index, the analysis will be performed on the safety analysis set subjects who have valid baseline value and at least one postbaseline value.

The scores listed for FACT-BMT and EQ VAS and EQ-5D index will be summarized descriptively at each visit for the observed value, change from baseline, and percent change from baseline. EQ-5D-5L dimension response will be summarized by presenting the number of participants and percentage for each level of response by visit. For FACT-BMT total score and EQ-5D index, the number and percentage of participants who have achieved minimal clinical important difference (MCID) will also be provided. MCID here refers to FACT BMT total score change from baseline ≥7 or EQ-5D index change from baseline ≥0.07 (McQuellon et al. 1997; Yost and Eton 2005; Pickard et al. 2007).

For each of the scores listed for FACT-BMT, EQ VAS, and EQ-5D index, a mixed effects model for repeated measures (MMRM) will be performed to compare the between-treatment difference adjusting for correlations across multiple timepoints within a participant and controlling for the baseline value. Adjusted mean difference and 95% CIs will be presented to illustrate the effect of

treatment. Adjusted means and standard error bars will be plotted over time. The MMRM model will include participant, baseline score value, treatment, analysis visit, and treatment-by-visit interaction as explanatory variables. Baseline score value, treatment, visit, and treatment-by-visit interactions will be fixed effects in the model; participants will be treated as a random effect. An unstructured covariance matrix will be used to model the within-subject variance, and the Kenward-Roger approximation will be used to estimate the degrees of freedom. Restricted maximum likelihood (REML) estimation will be used. If the fit of the unstructured covariance structure fails to converge, the following covariance structures will be used in order until convergence is reached: Toeplitz with heterogeneity (TOEPH), autoregressive with heterogeneity (ARH(1)), Toeplitz (TOEP), and autoregressive (AR(1)). If there are still issues with the fit of the model or estimation of the treatment effects, treatment-by-visit interactions will be removed from the model.

PRO questionnaire compliance by visit will be summarized by treatment group.

10.5.6.2 Modified 7-Day Lee cGVHD Symptom Scale

For participants diagnosed with cGVHD, the modified 7-Day Lee cGVHD symptom scale should be completed within 7 days of diagnosis. Thereafter, the modified Lee symptom scale should be completed whenever routine QoL assessments are performed for participants with a history of cGVHD or ongoing cGVHD.

The summary score of the modified 7-Day Lee cGVHD symptom scale (Teh et al. 2020) will be summarized by visit and treatment. A listing will be provided to present all the subscale scores and summary scores.

10.5.7 Biomarker Analysis

Descriptive summaries for the incidence and timing of T-cell, NK and B-cell immune reconstitution parameters will be explored.

10.6 Safety Analyses

10.6.1 Adverse Events

The MedDRA version 26.0 or later will be used to code all AE to a system organ class and a preferred term (PT). AESIs and identified and potential risks are defined in section 6.3. Since aGVHD and cGVHD use different grading criteria, additional safety summaries with aGVHD and/or cGVHD events excluded may be provided when summary statistics on general PTs including aGVHD and/or cGVHD are needed by grade.

Only treatment-emergent AEs as defined in Table 11 will be included in the summary tables. Listings for all AEs and certain categories of AEs will be provided with treatment-emergent records flagged.

[redacted]

10.6.2 Hospitalization

For initial hospitalization due to alloHCT, descriptive summary statistics for duration of hospitalization starting from day 0, the number of participants who are admitted to the ICU, and the number of days in the ICU will be provided by treatment received using the safety analysis set.

For rehospitalization due to AEs, cumulative duration of hospitalization, number of hospitalizations, average duration of hospitalization, number of participants who are admitted to ICU, cumulative days in the ICU, number of times of admission to the ICU, and average days in the ICU per time will be provided by actual treatment group in the safety analysis set.

10.6.3 Laboratory Test Results

Selected laboratory parameters will be summarized using descriptive statistics at scheduled visits by actual treatment group in the safety analysis set.

[redacted]

For laboratory abnormalities, worsening from baseline to worst postbaseline grade per CTCAE version 5.0 or later during the safety follow-up period will be provided, including the

number of participants whose postbaseline worst laboratory assessment has a higher grade than the baseline assessment, and the number of participants whose postbaseline worst grade is grade 3 or 4, together with the percentage. Baseline is defined as the last assessment prior to the day of conditioning regimen. If the laboratory assessment is taken on the same day as the first day of the conditioning regimen, the laboratory assessment is considered to be after the conditioning regimen. The postbaseline refers to the assessments after unmanipulated SoC allograft or Orca-T HSPC transfusion.

Only baseline and treatment emergent laboratory assessments will be included for the summary tables. The treatment emergent period for laboratory data is described in more detail in Table 11.

A listing of the results with CTCAE grade for selected laboratory parameters will be provided. All the laboratory assessments for the selected parameters will be presented in the listings with treatment emergent records flagged.

Laboratory test-related AEs defined by the SMQ of haemorrhage laboratory terms and the SMQof haematopoietic cytopenias will be summarized by SOC, PT, and worst grade (section 10.6.1.1).

10.6.4 Vital Signs

Summary of statistics for temperature, supine systolic blood pressure (BP), supine diastolic BP, pulse, respiratory rate, and pulse oximetry will be provided for 30 minutes and 1 hour assessments following administration of Orca-T HSPC/Treg/Tcon infusion and SoC HCT infusion including baseline assessments. Summary of the number and percentage of participants who have the following outlier vital signs will also be provided:

- Temperature ≥38°C
- Systolic blood pressure (SBP) <90 mmHg

The treatment emergent period for vital signs is described in more detail in Table 11. A listing of vital signs will also be provided with treatment emergent records flagged.

10.6.5 Karnofsky Performance Score

Karnofsky performance score will be summarized for each visit by treatment. Shifts from baseline to the best and worst post-baseline score may be tabulated.

10.6.6 Chimerism

The percentage of donor granulocytes, T cells, B cells, NK cells, and CD34+ cells will be summarized for recipients by treatment and visit. Additional analysis may include visual presentation of the data or summarization of data within a subgroup.

10.6.7 Exposure to Investigational Product

For each of the Orca-T infusions (HSPC, T_{reg}, and T_{con}), summary statistics will be provided by treatment group for the following variables as outlined in CD45+ cell dose/kg, viable cell dose/kg, total CD45+ cell dose (CD45+ cell dose/kg times participant's weight), and viable cell dose (viable cell dose/kg times participant's weight) as shown in Table 12.

Table 12 Orca-T Components (HSPC, T_{reg}, and T_{con}) Dosing Variables

	HSPC	T_{reg}	T_{con}
CD45+ cell dose	CD45+ cell dose/kg	CD45 + cell dose/kg	—
Viable cell dose	% viable HSPC × CD45+ cell dose/kg	% viable T_{reg} and CD45+ cell dose/kg	% viable T-cell dose

Abbreviations: HSPC, hematopoietic stem and progenitor cell; Tcon, conventional T cell; Treg, regulatory T cell.

[redacted]

A listing of total viable cells/kg and total viable cells administered for each participant will be provided for HSPCs, T_{regs}, and T_{cons}.

10.6.8 Exposure to Concomitant Medication/Procedure/Surgery

Data collected in the concomitant medication eCRF includes the following:

1. Protocol-specified treatment including the following:
    a. Conditioning regimen
    b. GVHD prophylaxis medication
    c. GVHD treatment (as applicable)
2. Concomitant medication of special interest including the following:
    a. Immunosuppressive medication that is relevant to GVHD
    b. Medication for prevention of relapse
    c. FLT3, BCR-ABL, or IDH1/2 inhibitors for prevention of relapse
    d. Anticancer medication/treatment for relapse
    e. Antimicrobial prophylaxis/therapy
    f. Premedication for administration of Orca-T or SoC
    g. Any medication/treatment for infusion-related reactions
3. Other/general concomitant medication.

All concomitant medication received from day 0 through 2 year (plus the visit window of 21 days) will be considered treatment emergent and summarized by treatment received by ATC (level 2) and PT as coded by the World Health Organization Drug (WHODRUG) dictionary using safety analysis set.

Additional summary will be provided to concomitant medications of special interest in categories 1 and 2 received from day 0 through 2 year as described below.

10.6.8.1 Conditioning Regimen

Summary statistics will be provided for the following 2 sets of measurements by treatment:

- Total dose for each drug in BFT and TBI-based regimen
- Total dose/kg for each drug in BFT and TBI-based regimen

10.6.8.2 GVHD Prophylaxis

All GVHD prophylaxis medication received by participants from day 0 through 2 years (plus the visit window of 21 days) will be included in the summary. The pharmacokinetic profile of tacrolimus will be evaluated.

10.6.8.3 GVHD Treatment

All GVHD treatment medications received by participants from day 0 through 2 years (plus the visit window of 21 days) will be included in the summary. Summary statistics (the number and percentage) for participants who are steroid responsive and who are steroid refractory will be provided.

Concomitant surgery and procedures after HCT and within 2 years after HCT will also be summarized by treatment received, ATC classification (level 2), and PT (see Table 11).

10.6.8.4 Exposure Response Analysis

An exploratory exposure-response analysis will be performed in the safety analysis set to evaluate the dose-response relationship for each of Orca-T's components. The exposure-related variables (independent variables) and output endpoints (dependent variables) for the analysis are listed in Table 13. Selection of these endpoints is based on the biological plausibility of an effect produced by each component of Orca-T, and only those participants whose drug product meets release specifications will be included in the respective analysis.

Table 13 Planned 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)
T_{regs}	
Total number of viable T_{reg} cells	moderate or severe cGVHD (yes or no) at 1 year
Dose of viable T_{reg} cells/kg	moderate or severe cGVHD (yes or no) at 1 year
T_{cons}	
Total number of viable T_{con} cells	CD3 count over time
Dose of viable T_{con} cells/kg	CD3 count over time

Abbreviations: ANC, absolute neutrophil count; cGVHD, chronic graft-versus-host disease; HSPCs, hematopoietic stem and progenitor cells; Tcons, conventional T cells; Tregs, regulatory T cells

a Neutrophil engraftment is defined as achieving an ANC ≥500/mm3 for 3 consecutive days by day +28. The first of the 3 days is designated the day of engraftment. If ANC never drops below 500/mm3, day +1 is designated the day of engraftment.

Unstratified and stratified Cochran-Mantel-Haenszel test with continuity correction will be conducted for the binary endpoints. The stratification will be the conditioning regimen (TBI vs

non-TBI). For CD3 count over time, longitudinal analysis models will be applied with appropriate covariates.

Additional clinical outcome endpoints and statistical models may be explored for the exposure-response analyses if needed.

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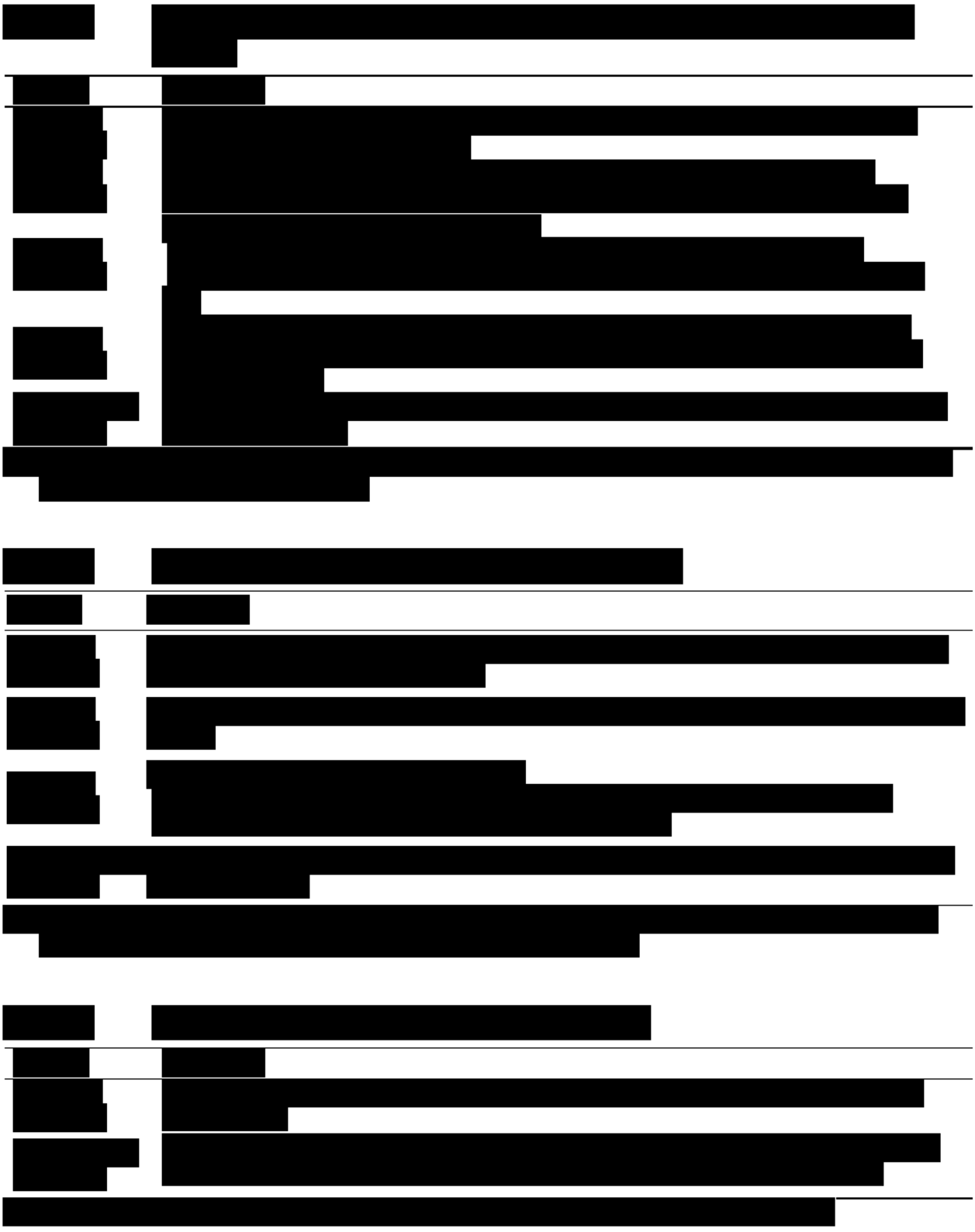
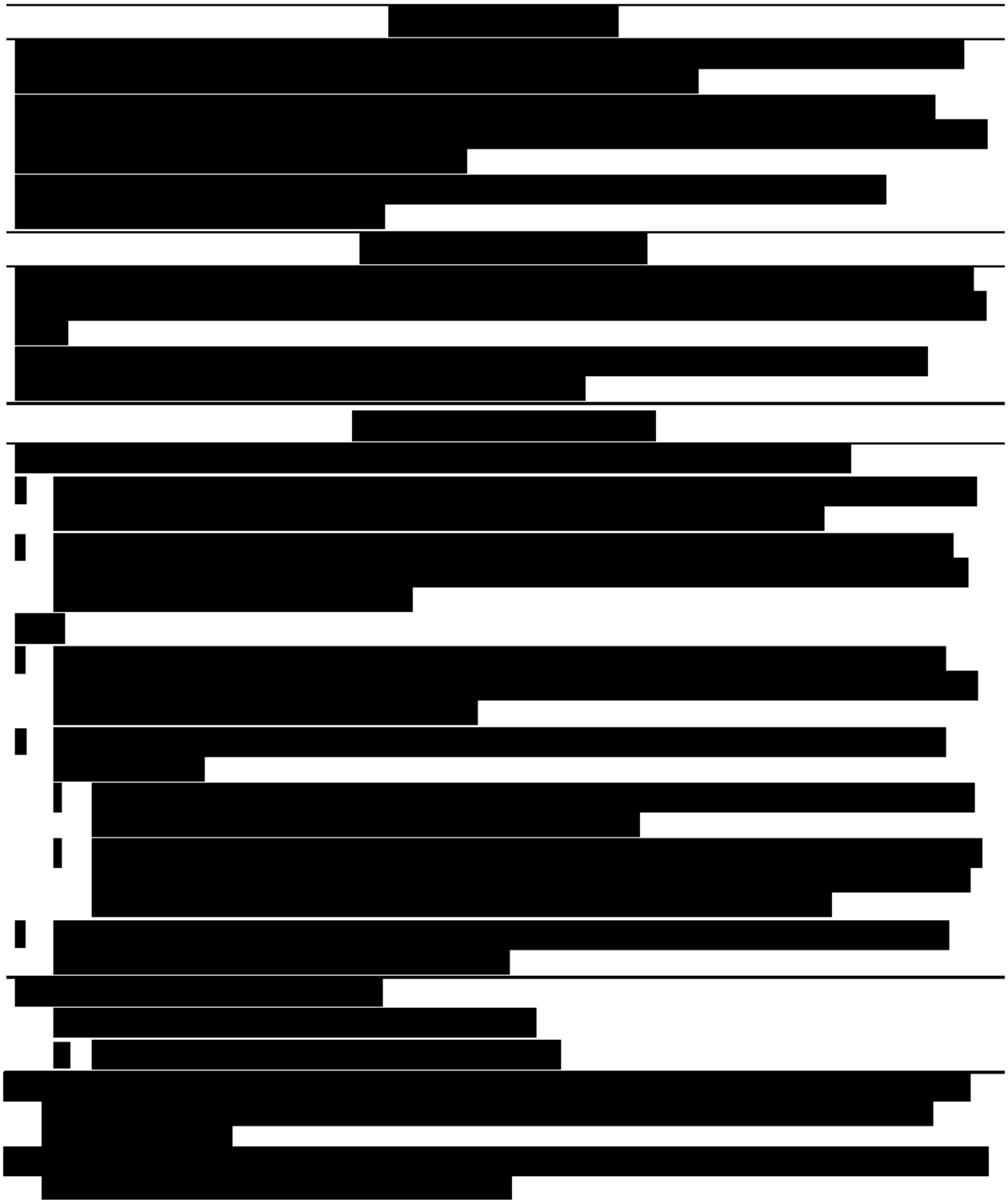
[redacted]





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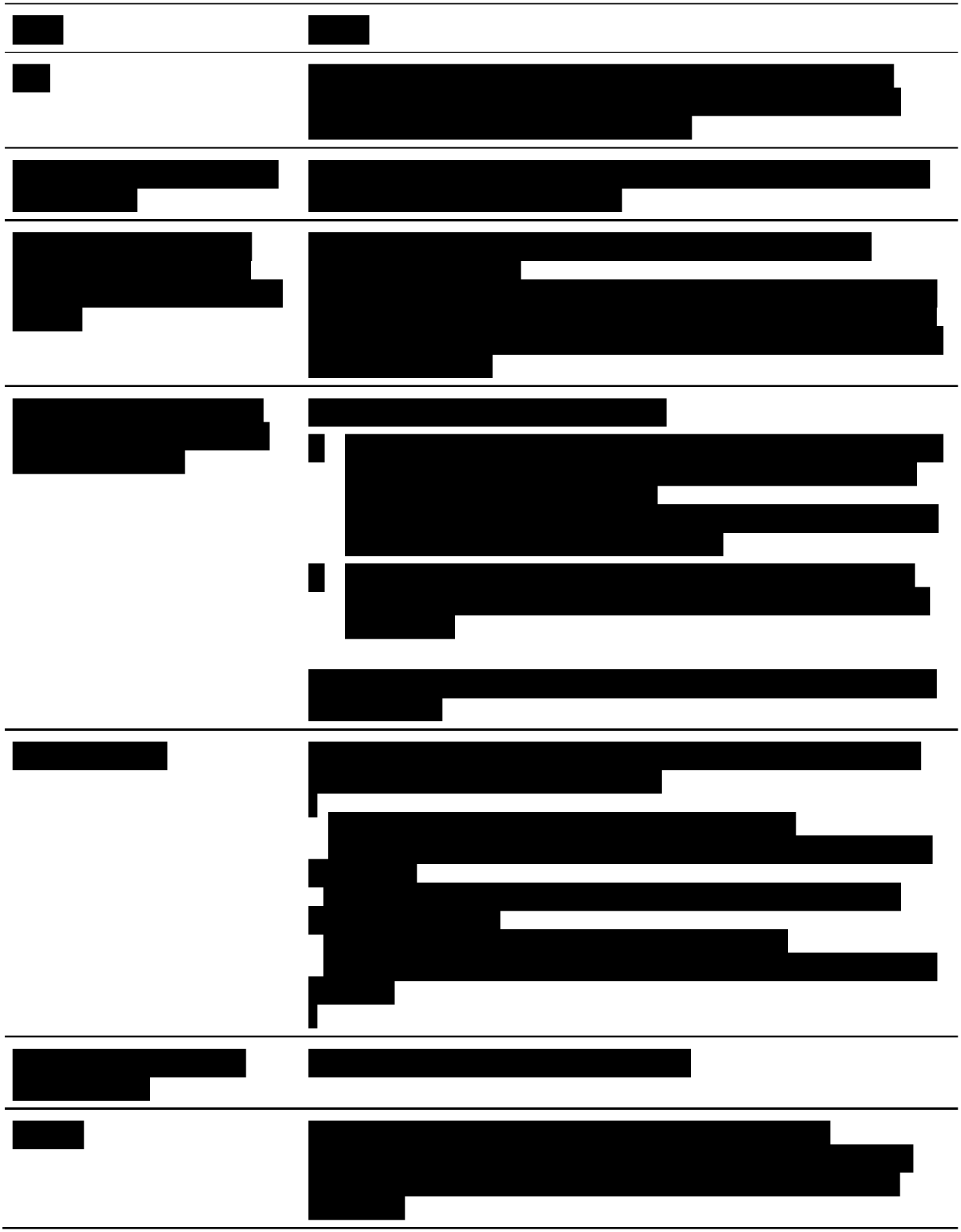
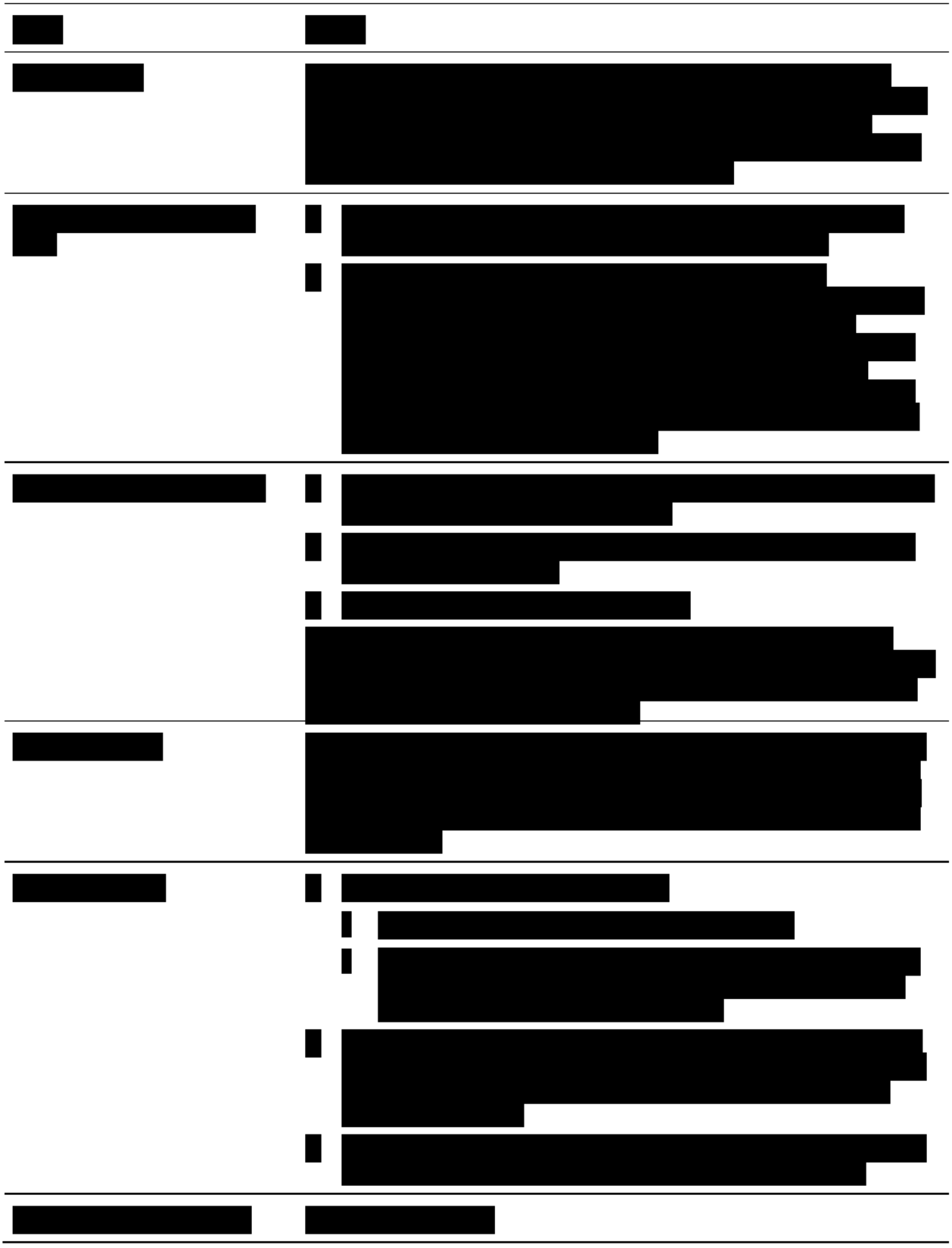




MEMO

Precision-T Phase 3 – Decision to Forgo Interim Analysis and Establish Preliminary Cutoff Date for Primary Analysis for cGFS

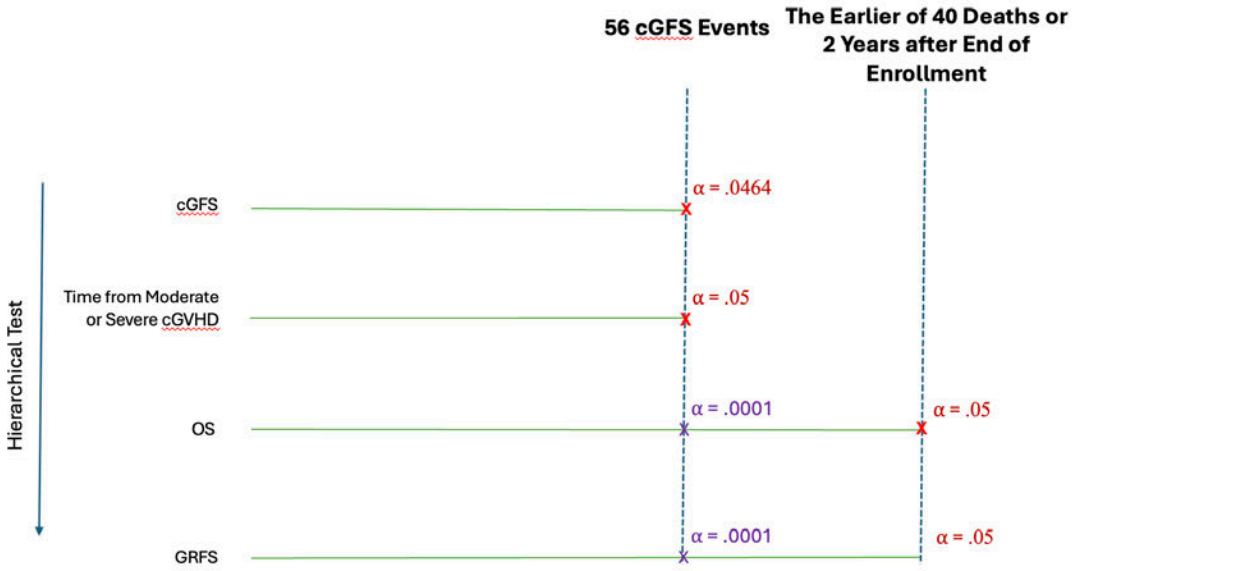
The Precision-T protocol [redacted] and the Statistical Analysis Plan (SAP) [redacted] outlined an interim analysis for the phase 3 component, aimed at evaluating the primary endpoint of moderate or severe chronic graft-versus-host disease (cGVHD)-free survival (cGFS) as determined by the Endpoint Adjudication Committee (EAC). This analysis was to occur after 37 cGFS events per the EAC (defined as the earlier occurrence of death or moderate/severe cGVHD, with moderate/severe cGVHD adjudicated by the EAC) had taken place. The primary analysis for cGFS is planned based on 56 cGFS events per the EAC.

However, cGFS events have been occurring at a faster rate than initially predicted. 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. As a result, the sponsor has decided to forgo the interim analysis for cGFS and proceed directly to the primary analysis for cGFS. In alignment with FDA's comments sent via email on 27 November 2024 and to take a conservative approach, 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. Please refer to Figure 1 in this memo, which supersedes Figure 1 in the Precision-T Phase 3 SAP, version 4.0.

The preliminary data cutoff date for the primary analysis for cGFS is 15 July 2024. All relevant data from the Electronic Data Capture (EDC) system and materials submitted by study sites for visits up to that cutoff date will be reviewed by the EAC. EDC data up to the cutoff date, along with all acute GVHD (aGVHD)/cGVHD outcome data from the EAC will be utilized for the primary analysis. As a result, more than 56 cGFS events per the EAC could be included in the primary analysis.

In the unlikely event that fewer than 56 cGFS events are confirmed by the EAC as of the preliminary cutoff date, a later cutoff date will be implemented to ensure that at least 56 cGFS events per EAC are included in the primary analysis for cGFS.

Figure 1 Planned Analyes for Primary and Secondary Endpoints



α denotes the 2-sided critical p-value at each analysis
The interval between each analysis in the plot may not be proportional to the time interval between each analysis or the information fraction at each analysis