Study Title:	A Phase 1B/2 Study to Evaluate the Safety, Tolerability, Pharmacokinetics, Pharmacodynamics, and Clinical Activity of EQ001 in Subjects with Newly Diagnosed Acute Graft Versus Host Disease
Protocol Number:	EQ001-aGVHD-001
Investigational Product(s):	EQ001
Sponsor:	Equillium, Inc.
Development Phase:	Phase 1b/2
NCT Number:	NCT03763318
Document Version Date:	24 February 2021

CONFIDENTIAL

A PHASE 1B/2 STUDY TO EVALUATE THE SAFETY, TOLERABILITY, PHARMACOKINETICS, PHARMACODYNAMICS, AND CLINICAL ACTIVITY OF EQ001 IN SUBJECTS WITH NEWLY DIAGNOSED ACUTE GRAFT VERSUS HOST DISEASE

CLINICAL STUDY PROTOCOL: EQ001-aGVHD-001

IND Number: 139877

Indication: Acute Graft Versus Host Disease

Sponsor: Equillium Inc.

[redacted]

Confidentiality Statement

SPONSOR SIGNATURE PAGE

A PHASE 1b/2 STUDY TO EVALUATE THE SAFETY, TOLERABILITY, PHARMACOKINETICS, PHARMACODYNAMICS, AND CLINICAL ACTIVITY OF EQ001 IN SUBJECTS WITH NEWLY DIAGNOSED ACUTE GRAFT VERSUS HOST DISEASE

[redacted]

[redacted]

SYNOPSIS

Name of Sponsor Company: Equillium, Inc.	
Name of Finished Product: EQ001	**Name of Active Ingredient:** Itolizumab (Bmab 600)
Title of Study: A Phase 1b/2 Study to Evaluate the Safety, Tolerability, Pharmacokinetics, Pharmacodynamics, and Clinical Activity of EQ001 in Subjects with Newly Diagnosed Acute Graft Versus Host Disease	
Study Centers: Approximately 20 sites in North America. Additional sites and/or countries may be added, depending on subject accrual rates.	
Study Period: Approximately 12 months (2 months of treatment, 10 months follow-up, total of 12 months on study) for Part A and Part B	**Phase of Development:** Phase 1b – Study Part A Phase 2 – Study Part B

Objectives:

The objectives of Part A of the study are to:

Primary

- Determine the safety and tolerability of intravenous (IV) dosing of EQ001 in subjects with newly diagnosed acute graft versus host disease (aGVHD)
- Determine optimal IV dose level(s) of EQ001 in subjects with newly diagnosed aGVHD

Secondary

- To characterize the pharmacokinetics (PK) of EQ001 in subjects with newly diagnosed aGVHD
- [redacted]
- To assess the clinical activity of EQ001 in subjects with newly diagnosed aGVHD

The objectives of Part B of the study are to:

Primary

- To define the clinical activity of EQ001 in subjects with newly diagnosed aGVHD

Secondary

- To further characterize the safety, tolerability, [redacted] in subjects with newly diagnosed aGVHD

Study Design:

This is a multi-center study to evaluate the safety, tolerability, PK, [redacted], and clinical activity of EQ001 in subjects with an initial clinical presentation of aGVHD. The study will enroll up to approximately 100 subjects in two (2) parts:

- Part A – Open-label, cohort based, dose escalation component:

  Part A will enroll approximately 24 subjects in successive cohorts of 3 to 6 adult subjects each to determine the safety, tolerability, pharmacological, and biological activity of ascending IV doses of EQ001. Once an optimal dose is determined in Part A of the study, up to approximately 15 additional subjects will be enrolled at the selected dose in order to collect more data.

- Part B – Randomized, double-blind, placebo-controlled component:

  Part B will enroll approximately 60 additional subjects, randomized in a 2:1 ratio to either active treatment with an optimally defined dose of EQ001 (40) or placebo (20), to determine the safety, tolerability, and clinical activity of EQ001.

Informed consent for participation in the study will be obtained prior to any study-related procedures or assessments. All subjects will be screened for potential participation, and those meeting eligibility criteria will be offered participation in the study. The study will enroll subjects with an initial clinical diagnosis of aGVHD who require systemic immunosuppressive treatment. All subjects will receive standard treatment for aGVHD with systemically administered corticosteroids, prednisone at approximately 1-2 mg/kg/day (or its equivalent) at the time of the first dose of study drug administration. The first dose of study drug must be administered within 72 hours (3 days) of receipt of the subject's initial corticosteroid dose.

Screening assessments will include: a medical history, physical exam, aGVHD organ stages and overall clinical grading[redacted] aGVHD activity index [aGVHD-AI][redacted], vital signs, an electrocardiogram (ECG), laboratory tests (clinical chemistries, hematology, coagulation panel, urinalysis, pregnancy test in females of childbearing potential only and viral serologies), study eligibility check, recording of prior and concomitant medications and treatments and collection of relevant biopsy data.

During the study, subjects will undergo periodic evaluations including physical exams, aGVHD organ stages and overall clinical grading[redacted] aGVHD-AI[redacted] vital signs, ECG, laboratory tests, PK (Part A only)/[redacted] and anti-drug antibody (ADA) sampling, a skin biopsy (optional in Part B only), stool sample (optional in Part B only), recording of concomitant medication usage, adverse event (AE) monitoring, disease progression assessments and collection of relevant biopsy data.

Part A of the study will utilize a standard 3 + 3 dose escalation design until a dose is selected. Cohort enrollment will proceed in a sequential manner to evaluate escalating dose levels of EQ001: Cohort 1 – 0.4 mg/kg, Cohort 2 – 0.8 mg/kg, Cohort 3 – 1.6 mg/kg, and Cohort 4 – 2.4 mg/kg. Dose escalation will proceed if no predefined stopping criteria are met. The dose-limiting toxicity (DLT) assessment period will be the first 29 days of treatment (i.e., Study Days 1 to 29) and will guide dose escalation decisions. Subjects will be considered evaluable for DLT assessment if they have received at least two doses of study drug and completed study assessments through Study Day 29 or received at least one dose of study drug and had a DLT within the first 29 days on study. Enrollment of the next higher dose cohort will not commence until all safety data from all subjects from prior cohorts and all available safety data from the current cohort through Study Day 29 are reviewed by the Data and Safety Monitoring Committee (DSMC) and approval is granted for dose escalation. [redacted]

Part B of the study will be randomized, double blinded, and placebo controlled, and will commence following the completion of Part A and approval by the DSMC. In Part B, up to 60 subjects will be enrolled to better define the safety, tolerability,[redacted], and immunogenicity of EQ001, and to explore the clinical activity of EQ001 in subjects with newly diagnosed aGVHD.

[redacted]

[redacted]

[redacted]

Early Termination Visit:

Subjects that receive at least one dose of study drug should be encouraged to complete all study visits. If a subject does not complete the study to Study Day 85 (eg, subject withdraws from the study or subject enrolls in an alternate clinical trial), the subject will be asked to return for an Early Termination (ET) visit within 28 days of the last dose of study drug administration. The following assessments will be conducted: physical exam, aGVHD organ stages and overall clinical grading, aGVHD-AI disease progression assessment, vital signs, laboratory tests, ECG, PK[redacted] and ADA, AE monitoring, recording of concomitant medications and treatments, and collection of all relevant biopsy data.

Unscheduled Visit:

In addition, if at any time up to Study Day 169, a subject has an unscheduled study visit, all procedures that were conducted at the visit will be collected in the electronic case report form (eCRF) as an unscheduled visit. If a subject experiences disease progression or recurrence, the subject should complete an unscheduled visit that includes disease assessments and grading.

Safety and Long-Term Follow-Up:

All subjects who complete study drug dosing will be evaluated on Study Day 169 for disease progression assessments, aGVHD organ stages and overall clinical grading, aGVHD-AI, PK[redacted], ADA, and AE monitoring .Collection of concomitant medications may be required after Day 85 through Day 169, if requested by the Sponsor for any ongoing safety concerns related to study drug.

During the Long-Term Follow-Up period, the site will phone subjects on Study Days 253 and 337 to collect information on disease status (disease relapse or cGVHD), long-term survival, and safety (eg, recent hospitalization or SAEs).

Dose Modification and Dose Schedule Deviation:

[redacted].

In Part A, if a subject has a DLT during the DLT window (Study Days 1-29), study drug dosing will be discontinued for that subject. Subjects experiencing a DLT will be encouraged to remain in the study and complete the remaining visits; the subjects will not be replaced. If a subject terminates early for a reason other than a toxicity during the DLT window, the subject may be replaced.

In the event of a clinically significant AE that is not a DLT, study drug dosing may be temporarily withheld, and supportive therapy administered, as clinically indicated. If the toxicity resolves to baseline or Grade 1 prior to the next schedule dose, dosing may be continued at the next scheduled dosing visit as follows, with agreement of the Sponsor and/or Medical Monitor:

- at the assigned dose (subjects in Part A or Part B) or
- at the next lower dose level evaluated in Part A (subjects in Part B only)

[redacted]

Data and Safety Monitoring Committee (DSMC), Dose-Limiting Toxicity, and Stopping Criteria:

A DSMC will review all available clinical and laboratory safety data at defined intervals during the conduct of each cohort in Part A and periodically during Part B of the study. The DSMC will make recommendations regarding the continuation, discontinuation, or modification of the study, cohort advancement (during Part A), and progression to Part B of the study.

During Part A of the study, the DSMC will apply the following dose escalation rules. If 0 of the 3 initial evaluable subjects experiences a DLT, then escalation may occur to the next higher dose level. If 1 of the 3 initial subjects

experiences a DLT, then 3 additional subjects will be enrolled at the same dose level for a total of up to 6 evaluable subjects. If 1 out of the 6 subjects experience a DLT, then escalation may proceed to the next higher dose level. If two (2) or more subjects experience a DLT, no additional subjects will be enrolled in the cohort, and the next lower dose level will enroll additional subjects for a total of 6 evaluable subjects.

AEs will be graded by the investigator using the Common Terminology Criteria for Adverse Events (CTCAE) v5.0. Further, the relationship of each AE to the study drug will be assessed by the investigator as related, probably related, possibly related, unlikely related, or not related. [redacted]

- [redacted]
- [redacted]

Subject Stopping Criteria:

Dosing of EQ001 will be permanently discontinued in a subject if any of the following occurs:

During Part A:

- Any DLT
- [redacted]

During Part B:

- Study drug related toxicity that cannot be controlled with supportive care despite 1 dose reduction and/or delay of treatment for up to 1 week
- [redacted]

During any part of the study:

- Withdrawn consent
- Investigator or Sponsor considers that the subject will not benefit from further investigational product
- Pregnancy
- Subject is not able to comply with the study requirements
- Sponsor terminates the study
- A regulatory authority mandates study dosing cessation

Number of Subjects Planned:

Up to approximately 100 subjects with newly diagnosed aGVHD are planned to be enrolled in the study.

Diagnosis and Main Criteria for Inclusion:

Inclusion Criteria:

Subjects must meet all the following inclusion criteria to be eligible for study participation:

1. Male or female subject at least 18 years of age for Part A, and at least 12 years of age for Part B.
2. Recipients of first allogeneic hematopoietic stem cell transplantation (alloHSCT) using myeloablative or non-myeloablative conditioning regimens.
- [redacted]

[redacted]

7. Deemed by the investigator to be likely to comply with the protocol for the duration of subject's enrollment.

Exclusion Criteria:

Subjects meeting any of the following exclusion criteria are not eligible for study participation:

1. Presence of morphologic relapsed primary malignancy, treatment for relapse after alloHSCT was performed, or requirement for rapid immunosuppressive treatment withdrawal for early malignancy relapse.
2. Evidence of graft failure based on cytopenia(s), as determined by the investigator.
3. Evidence of post-transplant lymphoproliferative disease.

[redacted]

[redacted]

14. As determined by the investigator, any medical, psychiatric, or other condition or circumstance that is likely to negatively affect: the subject's participation in this clinical study, the subject's safety, or the reliability of the study data.

Investigational Products, Dosage, and Mode of Administration:

The investigational product is EQ001 (itolizumab [Bmab 600]), a humanized recombinant immunoglobulin G1 (IgG1) monoclonal antibody (mAb) that selectively targets the extracellular scavenger receptor cysteine -rich (Sc) membrane-distal domain 1 of human CD6. [redacted]

Study drug will be administered by IV infusion[redacted].

In Part A of this study, EQ001 doses to be evaluated include 0.4 mg/kg (in Cohort 1), 0.8 mg/kg (in Cohort 2), 1.6 mg/kg (in Cohort 3), and 2.4 mg/kg (in Cohort 4).

In Part B of this study, an optimal dose of EQ001 (as determined in Part A) or placebo will be administered.

Additional cohorts and dose levels during Part A (with a dose change of 100% or less between cohorts) may be explored, based on emerging safety, [redacted] or at the discretion of the Sponsor in consultation with the DSMC and the investigators.

Criteria for Evaluation:

Safety:

Safety will be assessed by physical examinations, vital signs, 12-lead ECGs, laboratory tests [redacted] ADA, and AE monitoring. Prior clinical experience with EQ001 has identified lymphopenia, infusion-related reactions, and fever as potential adverse reactions to study drug administration, and these clinical parameters will be closely monitored in the current study.

Pharmacokinetics:

[redacted] serum for PK will be collected at specified timepoints as outlined in the Schedule of Events [redacted].

[redacted]

Efficacy:

Clinical activity will be assessed by change from baseline in aGVHD organ stages and overall clinical grading, aGVHD-AI, concomitant medication usage and disease progression [redacted].

[redacted]

Statistical Methods:

Data will be summarized using descriptive statistics (n, mean, median, standard deviation, minimum, maximum) for continuous variables and frequencies and percentages for categorical variables. By-subject listings of the data will also be provided.

Analysis Populations:

Safety Population: Consists of all subjects who receive at least one (1) dose of study drug.

PK Analysis Population[redacted] Subjects in the safety population who have at least one (1) measurable post-EQ001 exposure concentration.

[redacted]

Efficacy Population[redacted] Subjects in the safety population who have received at three (3) doses of study drug.

Statistical Analysis:

AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) for the purposes of summarization. Subject incidence of treatment-emergent AEs (TEAEs), treatment-emergent serious AEs (TESAEs), TEAEs leading to treatment discontinuation, and TEAEs with an outcome of death will be summarized by system organ class (SOC) and preferred term (PT). AEs will also be further summarized by worst severity grade and relationship to study drug. [redacted].

Clinical laboratory data will be summarized descriptively including observed values at collection timepoints and change from baseline. All laboratory parameters that can be graded using CTCAE v5.0 will be graded. [redacted]

[redacted]

[redacted]

Safety evaluations may also include changes in the subject's physical examination findings, vital signs, and ECG findings.

[redacted]

A detailed description of data analysis and statistical methods to be used will be outlined separately in a Statistical Analysis Plan (SAP).

TABLE OF CONTENTS

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

ADA	anti-drug antibodies
AE	adverse event
AESI	adverse events of special interest
aGVHD	acute graft versus host disease
aGVHD-AI	acute Graft Versus Host Disease Activity Index
ALC	absolute lymphocyte count
ALCAM	activated leukocyte cell adhesion molecule
alloHSCT	allogeneic hematopoietic stem cell transplantation
ALT	alanine aminotransferase (SGPT)
ANC	absolute neutrophil count
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase (SGOT)
AUC	area under the time-concentration curve
BUN	blood urea nitrogen
CFR	Code of Federal Regulations
cGVHD	chronic graft versus host disease
Cl	Clearance
C_{max}	maximum serum drug concentration
C_{min}	minimum serum drug concentration
CMV	Cytomegalovirus
CRF	case report form
CSR	clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
DLI	donor lymphocyte infusion
DLT	dose-limiting toxicity
DNA	deoxyribonucleic acid
DSMC	Data and Safety Monitoring Committee
EBV	Epstein Barr virus
ECG	Electrocardiogram
eCRF	electronic case report form
EOI	end of infusion
ET	early termination
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GGT	gamma glutamyl transferase
GI	Gastrointestinal
GVHD	graft versus host disease
HBV	hepatitis B virus
Hct	Hematocrit
HCV	hepatitis C virus
Hgb	Hemoglobin
HHV-6	human herpes virus 6
HIPAA	Health Information Portability and Accountability Act

HSCT	hematopoietic stem cell transplantation
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council on Harmonisation
IgG1	immunoglobulin G1
IND	Investigational New Drug
INR	International Normalized Ratio
[redacted]	[redacted]
IRB	Institutional Review Board
IV	Intravenous
IWRS	interactive web response system
LDH	lactic dehydrogenase
LYO	Lyophilization
mAb	monoclonal antibody
MAGIC	Mount Sinai Acute GVHD International Consortium
MedDRA	Medical Dictionary for Regulatory Activities
NAB	neutralizing ADA
NYHA	New York Heart Association
PBMC	peripheral blood mononuclear cell
[redacted]	[redacted]
Ph.Eur.	European Pharmacopoeia
PK	Pharmacokinetics
PT	preferred term
RBC	red blood cells
RNA	ribonucleic acid
SAE	serious adverse event
SAP	Statistical Analysis Plan
SC	Subcutaneous
Sc	scavenger receptor cysteine-rich
SCID	severe combined immune deficiency
SGOT	serum glutamic oxaloacetic transaminase (AST)
SGPT	serum glutamic pyruvic transaminase (ALT)
SOC	system organ class
$t_{½}$	half-life
TCR	T cell receptor
TEAEs	treatment-emergent adverse events
TESAEs	treatment-emergent serious adverse events
Th17	T helper 17
T_{max}	time to maximum serum concentration
ULN	upper limit of normal
USP	United States Pharmacopeia
US	United States
Vd	volume of distribution
WBC	white blood cell (count)

1. INTRODUCTION

1.1. Background

Hematopoietic stem cell transplantation (HSCT) is a potentially curative treatment for both benign and malignant hematologic conditions. Unfortunately, graft versus host disease (GVHD), a syndrome in which donor cells recognize and attack host tissues, remains a major cause of morbidity and mortality following HSCT. GVHD is a systemic inflammatory condition primarily mediated by the transplanted immune system that can lead to severe multi-organ damage. The need for increased and prolonged immunosuppression to treat GVHD, in addition to the immunosuppressive effects of the disease itself, results in poor quality of life for these patients and increases the risk of infection, organ impairment, and death.

Despite prophylactic treatment, acute GVHD (aGVHD) affects 30 to 70% of HSCT recipients, and chronic GVHD (cGVHD) occurs in 20 to 50% of HSCT recipients depending on the type of transplant, patient characteristics, and GVHD prophylaxis regimen [redacted] Historically, aGVHD has been defined as a constellation of signs and symptoms occurring in the first 100 days following HSCT, while cGVHD referred to a somewhat different constellation of signs and symptoms occurring after 100 days. However, a clear distinction between the 2 conditions has been challenged by the recognition of typical signs of aGVHD and cGVHD outside of these delineated periods [redacted] In 2014, the National Institutes of Health released new consensus criteria that refined the definitions of both acute and chronic GVHD, addressing issues of controversies in the overlap between the 2 conditions [redacted] Although aGVHD and cGVHD involve distinct pathological processes (aGVHD has a strong inflammatory component, whereas cGVHD displays more autoimmune and fibrotic features), CD4+ T helper 17 (Th17) cells play a critical role in the pathogenesis of both forms.

1.2. Itolizumab

Itolizumab is a humanized recombinant immunoglobulin G1 (IgG1) monoclonal antibody (mAb) that selectively targets the extracellular scavenger receptor cysteine-rich (Sc) membrane-distal domain 1 of human CD6 [redacted] a co-stimulatory membrane glycoprotein associated with T cell modulation and implicated in several autoimmune and inflammatory diseases, including psoriasis, multiple sclerosis, rheumatoid arthritis, and Sjogren's disease [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

1.6. Rationale for Evaluating EQ001 for the Treatment of aGVHD

As the number of HSCTs continues to increase each year, the importance and need for effective therapies to prevent the occurrence of GVHD and treat both aGVHD and cGVHD and thereby improve outcomes for this potentially curative therapy cannot be over-emphasized. [redacted]

Thus, there is an urgent unmet medical need for development of targeted, safe, and effective treatment strategies for both aGVHD and cGVHD to improve long-term post-transplant outcomes and quality of life for HSCT recipients.

1.7. Rationale for Selection of Starting Dose

A robust body of clinical data exists to inform the selection of a starting dose, and dose regimen, for EQ001 in this study.

[redacted]

2. STUDY OBJECTIVES

2.1. Study Part A

2.1.1. Primary Objectives

The primary objectives of Part A of this study are:

- Determine the safety and tolerability of intravenous (IV) dosing of EQ001 in subjects with newly diagnosed acute graft versus host disease (aGVHD)
- Determine optimal IV dose level(s) of EQ001 in subjects with newly diagnosed aGVHD

2.1.2. Secondary Objectives

The secondary objectives of Part A of this study are as follows:

- To characterize the pharmacokinetics (PK) of EQ001 in subjects with newly diagnosed aGVHD
- [redacted]
- [redacted]
- To assess the clinical activity of EQ001 in subjects with newly diagnosed aGVHD

2.2. Study Part B

2.2.1. Primary Objective

The primary objective of Part B of this study is to define the clinical activity of EQ001 in subjects with newly diagnosed aGVHD.

2.2.2. Secondary Objective

The secondary objective of Part B of this study is to further characterize the safety, tolerability, [redacted] of EQ001 in subjects with newly diagnosed aGVHD.

3. INVESTIGATIONAL PLAN

3.1. Overall Study Design and Plan

This is a multi-center study to evaluate the safety, tolerability, PK, [redacted] and clinical activity of EQ001 in subjects with an initial clinical presentation of aGVHD. The study will enroll up to approximately 100 subjects in two (2) parts [redacted]

- Part A – Open-label, cohort based, dose escalation component:

  Part A will enroll approximately 24 subjects in successive cohorts of 3 to 6 adult subjects each to determine the safety, tolerability, pharmacological, and biological activity of ascending IV doses of EQ001. Once an optimal dose is determined in Part A of the study, up to approximately 15 additional subjects will be enrolled at the selected dose in order to collect more data.

- Part B – Randomized, double-blind, placebo-controlled component:

  Part B will enroll approximately 60 additional subjects, randomized in a 2:1 ratio to either active treatment with an optimally defined dose of EQ001 (40) or placebo (20), to determine the safety, tolerability, and clinical activity of EQ001.

Part A of the study will utilize a standard 3 + 3 dose escalation design until a dose is selected. Cohort enrollment will proceed in a sequential manner to evaluate the escalating dose levels of EQ001 (Section 5.3.1). Dose escalation will proceed as long as no predefined stopping criteria are met. The dose-limiting toxicity (DLT) assessment period will be the first 29 days of treatment (i.e., Study Days 1 to 29) and will guide dose escalation decisions. Subjects will be considered evaluable for DLT assessment if they have received at least two doses of study drug and completed through Study Day 29 or received at least one dose of study drug and had a DLT within the first 29 days on study. Enrollment of the next higher dose cohort will not commence until all safety data from all subjects from prior cohorts and all available safety data from the current cohort through Study Day 29 are reviewed by the Data and Safety Monitoring Committee (DSMC) and approval is granted for dose escalation. An optimal dose of EQ001 will be determined based on all available data, including safety, tolerability, [redacted]. Once a dose is selected, up to approximately 15 additional subjects will be enrolled at the selected dose in order to collect more data.

Part B of the study will be randomized, double blinded, and placebo controlled, and will commence following the completion of Part A and approval by the DSMC. In Part B, approximately 60 subjects will be enrolled to better define the safety, tolerability, [redacted], and to explore the clinical activity of EQ001 in subjects with newly [redacted] aGVHD.

After informed consent has been obtained, all subjects will be screened for potential participation, and those meeting eligibility criteria will be offered participation in the study. The study will enroll subjects with an initial clinical diagnosis of aGVHD requiring systemic immunosuppressive treatment. All subjects must receive their first dose of study drug within 72 hours (3 days) of the subject's initial systemically administered corticosteroid dose.

The systemically administered corticosteroid treatment will be prednisone, at approximately 1-2 mg/kg/day (or its equivalent) at the time of first dose of study drug administration; however, the investigator can adjust dosing as clinically indicated during the study according to the recommended treatment and tapering schedule [redacted]

[redacted]

Subjects in Parts A and B will have the same study assessments except as noted. All subjects will have two (2) months of dosing comprising five (5) doses of study drug, administered IV every fourteen (14) days, and ten (10) months of follow up for a total of twelve (12) months in the study. The follow-up period will consist of a 2-month Safety Follow-Up period (through Day 169) and then an 8-month Long-Term Follow-Up period (through Day 337). [redacted] overview of the study timeline for Part A and Part B, respectively. During the Long-Term Follow-Up period, the site will phone subjects on Study Days 253 and 337 to collect information on disease status (disease relapse or cGVHD), long-term survival, and safety (eg, recent hospitalization or SAEs).

[redacted]

[redacted]

3.2. Data and Safety Monitoring Committee (DSMC), Dose-Limiting Toxicity, and Stopping Criteria

The purpose of the DSMC is to provide an unbiased review of the safety data generated by the clinical trial. An independent DSMC will be established to review clinical trial data prior to dose escalation and during Part B on an as-needed basis. A statistician, serving as a non-voting member to the DSMC, will provide data preparation support to the DSMC. A sponsor representative will also serve as a non-voting member of the DSMC to facilitate sponsor internal planning.

The Chair of the DSMC will be informed by the Protocol Chair or the Sponsor of the potential need for ad hoc meetings and will coordinate such meetings. A formal DSMC Charter will be prepared and finalized prior to study enrollment.

The DSMC will review all available clinical and laboratory safety data at defined intervals during the conduct of each cohort in Part A and periodically during Part B of the study. Based on a review of available data, the DSMC will make recommendations regarding the continuation, discontinuation or modification of the study, cohort advancement (during Part A), and progression to Part B of the study.

During Part A of the study, the DSMC will apply the following dose-escalation rules per cohort.

- For each cohort, if 0 of the 3 initial evaluable subjects experiences a DLT (see Section 3.2.1 for DLT definition), then escalation may occur to the next higher dose level.
- If 1 of the 3 initial subjects experiences a DLT, then 3 additional subjects will be enrolled at the same dose level for a total of up to 6 evaluable subjects.
- If 1 out of the 6 subjects experience a DLT, then escalation may proceed to the next higher dose level.
- If two (2) or more subjects experience a DLT, no additional subjects will be enrolled in the cohort, and the next lower dose level will enroll additional subjects for a total of 6 evaluable subjects.

The Sponsor will apply the following criteria to the determination of optimal dose in Part A of the study:

- Adequate safety without DLT
  and
- [redacted]

If more than one dose meets these criteria, then additional safety, tolerability, PK, [redacted] and efficacy data will be taken into consideration to select a dose.

DSMC decisions regarding advancement to the next higher cohort will be governed by the principle that the study is not intended to define a maximally tolerated dose (MTD). As such, no further dose escalations will occur once the second of two administered dose levels meet the criteria for an optimal dose, even if the observed safety and tolerability profile of the second (higher) dose level supports further dose escalation.

Additional subjects may be enrolled in cohorts if approved by the DSMC to further characterize drug safety, tolerability, or efficacy. Also, the DSMC may recommend modification of the doses to be evaluated, to not initiate specific dose cohorts, to initiation additional dose cohorts, or to terminate the study if it is deemed necessary. Appropriate regulatory approvals will be obtained prior to initiation of any recommended changes by the DSMC, as required.

3.2.1. Dose-Limiting Toxicities

During the 3+3 dose-escalation of Part A, any of the following events that are considered by the investigator to be at least possibly related to the study drug are considered DLTs during the DLT window Study Days 1–29:

- [redacted]
- [redacted]

3.2.2. Subject Stopping Criteria

Dosing of EQ001 will be permanently discontinued in a subject if any of the following occur:

During Part A:

- Any DLT
- [redacted]

During Part B:

- Study drug related toxicity that cannot be controlled with supportive care, despite 1 dose reduction and/or delay of treatment for up to 1 week

[redacted]

During any part of the study:

- Withdrawn consent
- Investigator or Sponsor considers that the subject will not benefit from further investigational product
- Pregnancy
- Subject is not able to comply with the study requirements
- Sponsor terminates the study
- A regulatory authority mandates study dosing cessation

The investigator will classify AEs that are observed in a subject as either expected to occur based on the underlying disease (Section 7.7) and/or are consistent with the AE profile in the current EQ001 Investigator's Brochure, or unexpected based on their prior clinical experience and management of aGVHD patients.

3.2.3. Study Stopping Criteria

The DSMC can recommend stopping the study at any time based on emerging safety data. [redacted]

[redacted]

If the recommendation of the DSMC is to halt study dosing for all subjects or pause enrollment, it can be resumed based on the recommendation of the DSMC after further review of all available safety data and notifications of/submission to appropriate regulatory agencies and institutional review committees, in line with country-specific regulations.

3.3. Rationale for Study Design

The design of this study includes both an open-label (Part A) as well as a double-blinded and placebo-controlled (Part B) component. A two-part study utilizing different designs was chosen to support the attainment of the objectives that are specific to each part of the study.

Part A has been designed to explore the safety and tolerability of ascending dose levels of the IV administration of multiple doses of EQ001. An open-label design is supported by the availability of extensive safety and tolerability data on itolizumab for which to compare the open-label safety data generated in this study. A cohort-based dose escalation design was chosen to rigorously evaluate, and conservatively escalate, IV doses of EQ001. Once a dose is selected in Part A, up to 15 additional subjects will be enrolled at that dose level for additional data.

Part B has been designed to explore the clinical activity of the IV administration of multiple doses of EQ001. A blinded, placebo-controlled design was chosen to provide the most rigorously assessments of efficacy possible in aGVHD.

3.4. Study Duration and Number of Centers

Each subject will have 2 months of treatment and 10 months of follow-up (2 months of safety follow-up and 8 months of long-term follow-up), for a total of 12 months on study.

This study will be conducted at approximately 20 clinical sites in North America. Additional sites and/or countries may be added, depending on subject accrual rates.

4. STUDY POPULATION SELECTION

4.1. Study Population

Each cohort within Part A (dose-escalation), and Part B (double-blind, placebo-controlled), will enroll unique subjects who may not be treated in more than 1 cohort or study part.

[redacted]

4.3. Inclusion Criteria

Subjects must meet all the following inclusion criteria to be eligible for study participation:

1. Male or female subject at least 18 years of age for Part A, and at least 12 years of age for Part B.
2. Recipients of first allogeneic hematopoietic stem cell transplantation (alloHSCT) using myeloablative or non-myeloablative conditioning regimens.

[redacted]

[redacted]

7. Deemed by the investigator to be likely to comply with the planned procedure as required by the protocol for the duration of the study.

4.4. Exclusion Criteria

Subjects meeting any of the following exclusion criteria are not eligible for study participation:

1. Presence of morphologic relapsed primary malignancy, treatment for relapse after alloHSCT was performed, or requirement for rapid immunosuppressive treatment withdrawal for early malignancy relapse.
2. Evidence of graft failure based on cytopenia(s), and as determined by the investigator.
3. Evidence of post-transplant lymphoproliferative disease

[redacted]

[redacted]

14. As determined by the investigator, any medical, psychiatric, or other condition or circumstance that is likely to negatively affect: the subject's participation in this clinical study, the subject's safety, or the reliability of the study data.

5. STUDY TREATMENT(S)

[redacted]

5.2. Study Drug

In Part A, all subjects will receive their cohort assigned dose of EQ001. In Part B, subjects will be randomized in a blinded fashion to either EQ001 or placebo using a 2:1 allocation.

The study drugs are:

- EQ001, containing the active ingredient itolizumab (Bmab 600), a humanized recombinant IgG1 mAb that selectively targets the extracellular Sc membrane-distal domain 1 of human CD6[redacted]
- Placebo is a sterile, clear, colorless, preservative-free solution with the same formulation (minus the drug) as EQ001[redacted]

[redacted]

5.3. Treatment(s) Administered

All subjects will receive standard treatment for aGVHD with systemically administered corticosteroids. All subjects must receive their first dose of study drug within 72 hours (3 days) of the subject's initial systemically administered corticosteroid dose.

The systemically administered corticosteroid treatment will be prednisone, at approximately 1-2 mg/kg/day (or its equivalent) at the time of first dose of study drug administration; [redacted]

5.3.1. Part A

In Part A of this study, EQ001 will be administered every 14 days for two (2) months (5 doses) at the following dose levels:

- Cohort 1: 0.4 mg/kg
- Cohort 2: 0.8 mg/kg
- Cohort 3: 1.6 mg/kg
- Cohort 4: 2.4 mg/kg

[redacted]

See Section 3.1 for additional information regarding dose escalation.

5.3.2. Part B

In Part B of this study, an optimal dose of EQ001 (as identified in Part A) or placebo will be administered in a blinded fashion every 14-days for two (2) months (5 doses). In Part B, study drug will be prepared by an unblinded qualified health care professional (e.g., pharmacist or designee) at the investigative site who is not otherwise associated with the study. Investigators, study site personnel, subjects and the Sponsor and/or designee will be blinded to treatment assignments.

[redacted]

[redacted]

[redacted]

[redacted]

- [redacted]
- [redacted]

[redacted]

5.4. Prior and Concomitant Medication

Prior and concomitant medications and treatments will be collected from the time the subject signs the informed consent through Day 85. After Day 85 through Day 169, collection of concomitant medications may be required if requested by the Sponsor for any ongoing safety concerns related to study drug.

Prior medications will focus on those used for prevention and treatment of GVHD, including prior investigational treatments.

5.4.1. Permitted Therapies

The study will enroll subjects with an initial clinical diagnosis of aGVHD requiring systemic immunosuppressive treatment. All subjects are allowed to remain on their GVHD prophylactic immunosuppressant regimens and/or their ongoing cancer maintenance therapy. The following immunosuppressant agents are permitted:

- [redacted]
- [redacted]
- [redacted]
- [redacted]

5.4.2. Prohibited Therapies

[redacted]

If a determination is made to treat a subject with any these therapies or medications during the study, the Medical Monitor should be informed. Subjects will be asked to remain in the study and complete the remaining visits, but no additional study drug will be administered.

5.5. Treatment Compliance

The study drug will be administered open-label in Part A and in a blinded fashion in Part B at the clinic/facility by a qualified staff member. The date and start and stop times of the infusion will be recorded.

[redacted]

5.7. Enrollment or Randomization and Blinding

It is the responsibility of the investigator to ensure that subjects are eligible to participate in the study prior to enrollment and continue to remain eligible throughout the study. An interactive web response system (IWRS) will be used for the study to ensure study drug inventory, accountability and appropriate cohort allocation and blinded treatment assignment. The site's unblinded Pharmacist or designee will have access to the IWRS and all treatment assignments.

5.7.1. Part A

Part A of the study is open-label. Once informed consent has been obtained, all screening procedures have been assessed, and study eligibility has been confirmed, subjects will be enrolled to receive EQ001 on Study Day 1. The study Pharmacist or designee will access the

IWRS to enroll the subject into the study, receive cohort assignment, dose level, record drug accountability, and request resupply.

5.7.2. Part B

Part B of the study will be randomized, double blinded, and placebo controlled. Subjects will be randomized in a 2:1 ratio to an optimal dose of EQ001 (as determined in Part A) or placebo.

Once informed consent has been obtained, all screening procedures have been assessed, and study eligibility has been confirmed, subjects will be randomized to receive either EQ001 or placebo on Study Day 1. The unblinded study Pharmacist or designee will access the IWRS to randomize the subject into the study, receive the blinded treatment assignment, dose level, record drug accountability, and request resupply.

Investigators, site staff, subjects, and the Sponsor and/or designee will be blinded to treatment assignment. The unblinded pharmacist or designee will be instructed not to divulge the treatment administered of any subject with the blinded site personnel, study subject, caregiver, and/or Sponsor or designee.

The blind should be broken only if knowledge of the subject's treatment allocation would facilitate specific emergency treatment. Unblinding procedures are provided in the Pharmacy Manual. The investigator must contact the Sponsor and/or designee prior to unblinding a subject's treatment assignment. In the event of an emergency when unblinding is necessary and the Sponsor and/or designee could not be contacted, the investigator should contact the Sponsor and/or designee as soon as possible after the unblinding.

[redacted]

[redacted]

[redacted]

Upon completion or termination of the study, all unused and partially used (if allowed by site/institutional procedure to be retained) investigational product must be returned to the Sponsor (or designated agent) unless the Sponsor authorizes the study site to destroy investigational product.

If the Sponsor authorizes the study site to destroy investigational product, the investigator is responsible to ensure that arrangements are made for proper disposal. Written authorization should be issued by the Sponsor; procedures for proper disposal should be established according to applicable regulations, guidelines, and procedures; and appropriate records of the disposal should be documented and forwarded to the Sponsor.

If the study site is unable to destroy the investigational product, the unblinded study monitor will facilitate the return of unused and/or partially used investigational product.

6. STUDY PROCEDURES

Subjects in Parts A and B will have the same study assessments except as noted. The following assessments will be conducted during screening and at selected time points specified in the Schedules of Events [redacted] and in Protocol Section 8. Additional procedures deemed necessary as part of standard of care may be performed at the discretion of the investigator. All missed visits and any performed procedures that are not protocol-specified activities must be documented in the subject's medical record and the appropriate electronic case report form (eCRF).

6.1. Screening and Informed Consent

Before subjects commence any study-specific activities or procedures, the Sponsor requires a copy of the study site's written Institutional Review Board (IRB) approval of the protocol, informed consent form (ICF), and all other subject information and/or recruitment material, if applicable. Each subject (or legally acceptable representative) must sign and date the ICF before participating in study-specific activities.

After the ICF is signed, the subject enters screening. Each subject will be assigned a unique subject number at the time of screening. Subject numbers will be sequential within each study site. If more than one (1) assessment is performed during screening, the initial assessment closest to the enrollment date and time will be used for eligibility. Subjects must have their first dose of study drug within 72 hours (3 days) of their first corticosteroid dose, therefore, sites should consent and start screening subjects as soon as aGVHD is suspected.

This subject number, assigned at the time of screening, will be used to identify the subject throughout the study and must be used on all study documentation related to that subject. The subject identification number will remain constant throughout the entire study; it must not be changed after initial assignment. Each study site will maintain a list identifying all subjects by subject identification number and initials.

After completing the screening period, the subject will be evaluated by the investigator to confirm eligibility. A subject is considered enrolled when the investigator decides that all of the eligibility criteria are met. The investigator will document this decision and date and time in the subject's medical record and the eCRF. Screen failure subjects will be entered into the eCRF. Investigators will maintain a screening log of all potential study candidates that includes limited information about each candidate, dates, and outcome of screening process (e.g., enrolled into study, reason for ineligibility, or withdrawal of consent).

6.2. Demographics and Medical History

Demographic data including sex, age, race, and ethnicity will be collected.

The investigator or designee will collect medical and surgical history that started prior to enrollment, including information on the subject's concurrent medical conditions. All findings will be recorded on the medical history eCRF.

[redacted]

[redacted]

6.3. Physical Exam

The investigator or designee will conduct a complete physical exam during screening and a targeted physical exam at selected time points thereafter. Physical exam finding prior to the first dose of study drug will be recorded on the medical history eCRF page and clinically significant findings after the first dose of study drug will be recorded as AEs.

At a minimum, the complete physical exam should include assessments of the head and neck, skin, nervous system, lungs, cardiovascular system, abdomen, thyroid, lymph nodes, and extremities.

A targeted physical exam will include assessment of any new subject complaints or changes from baseline, including clinical grade of aGVHD at diagnosis and organ involvement at diagnosis, infusion-related reactions, and examinations for potential hypersensitivity reactions.

6.4. Vital Signs

The following vital sign measurements will be performed: systolic and diastolic blood pressure, pulse, respiration rate, and temperature. On dosing days, vital signs will be monitored pre-dose and every 30 minutes (± 5 minutes) [redacted] The subject must be in seated or in a semi-recumbent position in a rested and calm state for at least 10 minutes before vital signs are collected. The position selected for a subject should be the same throughout the study and documented on the vital signs eCRF.

Height will be measured without shoes at screening.

Weight without shoes will be obtained at screening. On dosing days, weight will be collected pre-dose. The weight at screening will be used to calculate all study drug doses unless there has been a change in weight by 20% or greater. An additional subsequent change in dosing will not occur unless there is a change in weight of 20% or more from the new weight that required the dosing change to be made (no longer referencing back to the Screening weight at subsequent doses).

[redacted]

[redacted]

[redacted]

6.7. Biopsy Review

Any relevant tissue biopsy (eg, gastrointestinal, liver, bone marrow, or skin), performed per standard of care to support the clinical diagnosis and/or management of a subject's aGVHD at any time prior to and during the subject's enrolment, should be collected and the clinical data derived from the biopsy entered into the eCRF. Biopsies that were performed prior to and during screening to confirm the diagnosis of aGVHD should be recorded.

6.8. Minimal Residual Disease (MRD)

Assessments of MRD should be captured if they were done anytime from the time of the HSCT through baseline (Day 1).

6.9. Chronic GVHD (cGVHD)

An assessment of cGVHD will be performed during the long-term follow-up visits.

6.10. 12-Lead Electrocardiography

The subject must be in a seated, semi-recumbent, or supine position in a rested and calm state for at least 10 minutes before ECG assessment is conducted. Each 12-lead ECG should be performed prior to blood draws, dosing (if applicable, except for Baseline post-dose ECG), or other invasive procedures.

In Part A, a single ECG will be recorded using the site's standard ECG equipment. The investigator or designated study site physician will review, sign, and date all ECGs. The original ECGs will be retained with the subject's source documents. At the request of the Sponsor, a copy of the original ECG will be made available to the Sponsor. Each ECG should capture QRS, QT, QTc, RR, and PR intervals and be documented on the ECG eCRF.

In Part B, ECGs in triplicate taken over 5 minutes will be recorded using the ECG equipment provided and transmitted to a central ECG reader. The ECG results will be assessed by blinded, independent, central review to evaluate changes in ECG intervals and morphology as compared

with pretreatment ECGs. An ECG manual will be provided. The investigator or designated study site physician will also review, sign, and date all ECGs. The original ECGs will be retained with the subject's source documents.

Any clinically significant abnormal ECG findings will be recorded as AEs.

6.11. Clinical Laboratory Tests

6.11.1. Local Laboratory Parameters

Blood samples will be collected [redacted], Protocol Section 8 and below. All safety laboratory test will be conducted at the local clinic/facility. Samples will be collected pre-dose on study dosing days. Repeat laboratory testing is not required if a test was already performed within the specified time window for collection. Samples may be analyzed for the tests outlined in this protocol and for any additional tests necessary to ensure subject safety. These may include, but are not limited to, investigation of unexpected results. Subjects will be in a seated, semi-recumbent, or supine position during blood collection. [redacted]

[redacted]

6.11.2. Central Laboratory Parameters

Blood, skin biopsy, and stool samples will be collected [redacted] Protocol Section 8 and below from screening through the follow-up visits and submitted to the central laboratories for analysis. [redacted]

6.11.2.1. Pharmacokinetic [redacted]

In Part A only, serum will be assayed for EQ001 concentrations using a validated assay. PK samples will be collected at time points specified below. Based on emerging PK data, the actual collection times may change after discussion between the investigator and Sponsor. [redacted]

- [redacted]
- [redacted]
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- [redacted]
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- [redacted]
- [redacted]

[redacted]

6.11.2.2. Anti-Drug Antibody (ADA) and Neutralizing ADA (NAB)

Serum samples will be obtained for detection of ADA against EQ001 as outlined below and if required a neutralizing ADA assay will be run on the same sample. Samples will be batched and run at the end of Part A and at the end of Part B. [redacted]

- [redacted]

[redacted]

[redacted]

[redacted]

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[redacted]	[redacted]	[redacted]
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[redacted]

[redacted]

[redacted]

6.11.4. Research Use of Stored Human Samples, Specimens, or Data

De-identified data obtained from this study may be shared with other academic institutions after completion of the study. Furthermore, any remaining plasma, blood, and tissue samples may be stored for future analysis to help understand the markers for disease state, progression, and response to treatment as new discoveries emerge. [redacted]

6.12. Removal of Subjects from the Study

At any time, the investigator can remove a subject from the study or stop study drug dosing if deemed necessary for subject safety. The Sponsor also reserves the right to terminate the study at any time. All data normally collected at completion of the study must be collected at the time of the subject's early termination or termination of the study (see Section 8.12 or Section 8.15, as appropriate). If consent has not been withdrawn, AEs will continue to be collected as described in Section 7.

A termination case report form (CRF) page will be completed for every subject enrolled, whether or not the subject completed the study. The reason for any early discontinuation from the study should be indicated on this form. Separate CRF entries will document whether each subject completed all doses of study drug, or if not, the reason a subject terminated study drug early.

The investigator will discuss with the subject/subject's parent(s) or legally acceptable representative(s) the most appropriate way to withdraw to ensure the subject's health. Should a subject (or a legally acceptable representative) request or decide to withdraw consent, all efforts will be made to complete and report the observations as thoroughly as possible up to the date of withdrawal.

7. ADVERSE EVENTS

An AE is any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease or any worsening of a pre-existing condition temporally associated with the use of a study drug, whether or not related to the study drug. AEs that occur after the first dose of EQ001 or during the study treatment and safety follow-up periods will be documented on the AE eCRF. The investigator will assess the AE severity and relationship of the AE to study drug. The investigator will treat the subject as medically required.

Laboratory values that are outside the laboratory reference range should be reported as AEs only if considered clinically significant by the investigator.

From the time of obtaining informed consent through the first administration of study drug, all SAEs and nonserious AEs related to protocol mandated procedures will be recorded on the SAE/AE eCRF. All other untoward medical occurrences observed during screening, including exacerbation or changes in medical history, will be captured on the medical history eCRF. Details on recording and reporting AEs are provided below.

AEs will be collected through Study Day 169 for subjects who complete study drug through Day 57. AEs will be collected through Study Day 85 for subjects who discontinue study drug early. Recent hospitalizations and SAEs, if applicable, will be recorded at the Day 253 and 337 visits.

The investigator's clinical judgment should be used to determine whether a subject is to be withdrawn due to an AE. In the event the subject requests to withdraw from study-related treatment, the subject should be asked to return for all remaining study visits through Study Day 169. In the event a subject is withdrawn from study, an early-termination visit should be completed.

All subjects experiencing AEs while on study drug, including clinically significant abnormal laboratory values, whether or not associated with use of the study drug, must be monitored until the condition returns to normal, returns to the subject's baseline, until the investigator determines the AE has reached a stable outcome and is no longer clinically significant, or the subject is considered lost to follow up.

If consent has not been withdrawn, all deaths should be reported through Study Day 337, even if study drug has been discontinued.

7.1. Severity

All AEs, both serious and non-serious, will be assessed for severity using the Common Terminology Criteria for Adverse Events (CTCAE) v5.0. The CTCAE scale includes unique clinical descriptions of AEs that are categorized by anatomy and/or pathophysiology. Reference the following website:
https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11.pdf

The CTCAE scale displays Grades 1 through 5 with unique clinical descriptions of severity for each AE (including abnormal laboratory values) based on this general guideline provided in the CTCAE scale. For any AEs not covered by CTCAE the conventional definition of severity will be used.

- Grade 1 (Mild) AE: minor; no specific medical intervention; marginal clinical relevance
- Grade 2 (Moderate) AE: minimal intervention; local intervention; noninvasive intervention
- Grade 3 (Severe) AE: significant symptoms requiring hospitalization or invasive intervention
- Grade 4 (Life-threatening or disabling) AE: Complicated by acute, life-threatening complications; need for intensive care or emergent invasive procedure
- Grade 5 Fatal AE

7.2. Relationship

The investigator or qualified sub-investigator is responsible for assessing the relationship to study drug using clinical judgment and the following considerations:

- Related: The AE is definitely related to study medication administration.
- Probably Related: There is a high degree of certainty that the AE is related to study medication administration.
- Possibly Related: The AE could be related either to study medication administration or to concurrent disease/medication.
- Unlikely Related: There is a high degree of certainty that the AE is NOT related to study medication administration.
- Not Related: The AE is clearly due to other causes (e.g., concurrent medication, underlying disease, etc.)

The relationship to study-related procedures (e.g., invasive procedures such as venipuncture) should be assessed using the following considerations:

- Related: The AE is definitely related to study-related procedures.
- Probably Related: There is a high degree of certainty that the AE is related study-related procedures.
- Possibly Related: The AE could be related either to study-related procedures or to concurrent disease/medication.
- Unlikely Related: There is a high degree of certainty that the AE is NOT related to study-related procedures.
- Not Related: The AE is clearly due to other causes (e.g., concurrent medication, underlying disease, etc.).In making a causality assessment of an AE, consideration should be made as to whether or not the event is expected to occur due to the underlying disease based on the investigator's prior clinical experience in the management of aGVHD (see Section 7.5.1).

7.3. Clinical Laboratory Adverse Events

The investigator is responsible for reviewing the results of all laboratory tests as they become available and determining whether an abnormal value in an individual study subject represents a clinically significant change from the subject's baseline value(s). The investigator may repeat the laboratory test or request additional tests to verify the results of the original laboratory tests.

In general, abnormal laboratory findings without clinical significance (based on the investigator's judgment) are not to be recorded as AEs. However, laboratory value changes that require

treatment or adjustment in current therapy are considered AEs. Where applicable, clinical sequelae (not the laboratory abnormality) are to be recorded as the AE.

7.4. Serious Adverse Events

An SAE is defined by federal regulation as any AE occurring at any dose that results in any of the following outcomes:

- death,
- life-threatening AE (Note: A life-threatening AE is one that, in the view of the investigator, places the subject at immediate risk of death from the reaction as it occurred),
- hospitalization or prolongation of existing hospitalization,
- a persistent or significant disability/incapacity, or
- a congenital anomaly/birth defect.

Important medical events that may not result in death, be life threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in subject hospitalization, or the development of drug dependency or drug abuse.

An unexpected AE is any event for which the specificity or severity is not consistent with the AE profile in the current EQ001 Investigator's Brochure.

All SAEs, regardless of cause(s) or relationship to study drug, must be reported within 24 hours to the study Sponsor and/or designee.

7.5. Reporting Adverse Events

7.5.1. Reporting Procedures for Non-Serious Adverse Events

The investigator is responsible for ensuring that all AEs observed by the investigator or designee or reported by the subject are reported using the AE eCRF.

The investigator will assign the following AE attributes:

- AE diagnosis or syndrome(s), if known (if not known, signs or symptoms)
- Dates of onset and resolution (if resolved)
- Severity
- Relatedness to study drug or study-related procedures
- Action taken
- Outcome

Follow-up of non-serious AEs will continue through the last day on the study and/or until a definitive outcome (e.g., resolved, resolved with sequelae, lost to follow-up) is achieved.

When a subject is withdrawn from the study because of a non-serious AE, the Sponsor and/or designee must be notified by e-mail or phone within 48 hours.

7.5.2. Reporting Procedures Serious Adverse Events

The investigator is responsible for ensuring that all SAEs observed by the investigator or reported by the subject are promptly assessed and reported to the Sponsor and/or designee. The investigator must assess whether the SAE is related to study drug or any study-related procedure.

The procedures for reporting SAEs are as follows:

- Record the SAE on the AE eCRF and complete the "Serious Adverse Event Report" form.
- Within 24 hours of the investigator's knowledge of the event, e-mail, fax and/or enter via the electronic CRF the SAE Report form to the attention of the Sponsor and/or designee. Additional contact numbers and AE/SAE reporting instructions will be provided in the Study Manual.
- For fatal or life-threatening events, also e-mail and/or fax copies of hospital case reports, autopsy reports, and other documents, when requested and applicable. Transmission of such documents should occur with personal subject details de-identified, without losing the traceability of a document to the subject identifiers. Transmission of the initial report of the event should not be delayed in order to include these additional documents.
- The Sponsor or/or designee may request additional information from the investigator to ensure the timely completion of accurate safety reports.

The investigator must take all therapeutic measures necessary for resolution of the SAE. Any medications or therapies necessary for treatment of the SAE must be recorded in the event description section of the SAE form and the concomitant medication eCRF.

Follow-up of SAEs will continue through the last day on the study and/or until a definitive outcome (e.g., resolved, resolved with sequelae, lost to follow-up, fatal) is achieved.

While pregnancy is not considered an AE, all cases of fetal drug exposure via a maternal parent as study subject or pregnancy of a partner of a male study subject will be reported immediately to the Sponsor or its designee. Information related to the pregnancy must be documented on a "Pregnancy Confirmation and Outcome" form, provided by the Sponsor or its designee, and the pregnancy should be followed until a definitive outcome has been determined.

Some SAEs will qualify for reporting to the FDA as applicable via the MedWatch reporting system in accordance with FDA and other applicable regulations. The Sponsor or its designee will report SAEs as required to regulatory authorities, investigators in compliance with all reporting requirements according to local regulations and Good Clinical Practice (GCP).

The investigator will notify the appropriate IRB of SAEs occurring at the study site and other AE reports received from the Sponsor, in accordance with local procedures and statutes. The investigator or designee at each study site is responsible for submitting Investigational New

Drug (IND) safety reports (initial and follow-up) and other safety information (e.g., revised Investigator's Brochure) to the IRB and for retaining a copy in the study files.

[redacted]

[redacted]

[redacted]

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8. STUDY ACTIVITIES

Please refer to the Appendices, Section 12, for additional details. [redacted]

- EQ001 T cell stimulation

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8.13. Unscheduled Visit

If at any time up to Study Day 169, a subject has an unscheduled study visit, all procedures that were conducted at the visit will be collected in the eCRF as an unscheduled visit. If a subject experiences disease progression or recurrence, the subject should complete an unscheduled visit that includes disease assessments and grading.

[redacted]

9. PLANNED STATISTICAL METHODS

A detailed description of data analysis and statistical methods to be used will be outlined separately in a Statistical Analysis Plan (SAP).

9.1. General Considerations

Data will be summarized using descriptive statistics (n, mean, median, standard deviation, minimum, maximum) for continuous variables and frequencies and percentages for discrete variables. All data summaries will be displayed by cohort in Part A and by treatment group in Part B. A total column will also be included. By-subject listings of the data will also be provided. All data summaries and listings will be produced using the SAS® software Version 9.3 or higher. A separate SAP will be prepared describing the details of the analyses mentioned below and the analyses of the exploratory efficacy endpoints.

[redacted]

[redacted]

[redacted]

9.3. Analysis Populations

9.3.1. Safety Population

Safety population consists of all subjects who receive any study medication. All data summaries except PK and PD data related summaries will use this population.

9.3.2. Pharmacokinetic Analysis Population [redacted]

Subjects in the safety population who have at least one (1) measurable post-EQ001exposure concentration will be included in the PK analysis population.

[redacted]

[redacted]

9.3.4. Efficacy Population[redacted]

Subjects in the safety population who have received at least three (3) doses of study drug will be included in the efficacy population[redacted]

9.4. Subject Disposition

Subject disposition data will be summarized and will include number and percent of subjects enrolled, number and percent of subjects initiating and completing treatment, number and percent of subjects discontinuing treatment, and the reasons for discontinuation. Subject enrollment by study center and major protocol deviations will also be summarized.

9.5. Demographics and Baseline Characteristics

Demographics and other baseline characteristics will be summarized for the subjects in the safety population. Demographic data will include age, gender, race, and ethnicity. Baseline characteristics data will include (but not limited to) grade of aGVHD at diagnosis, organ involvement at diagnosis, underlying disease resulting in transplant, graft source, conditioning regimen, and prophylaxis regimen.

9.6. Statistical Analysis of Pharmacokinetic Variables

Serum concentrations and PK parameters ([redacted] will be listed and summarized for EQ001 dose cohort using descriptive statistics by treatment for each cohort.

[redacted].

9.7. Safety Analysis

All safety data summaries will use the safety population.

For subjects in Part A, number and percent of subjects experiencing any DLTs will be presented by cohort. A listing of DLTs will also be provided.

AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) and will be graded by the investigator using the CTCAE v5.0 or the current version. Subject incidence of TEAEs, treatment-emergent serious AEs (TESAEs), TEAEs leading to treatment discontinuation and TEAEs with an outcome of death will be summarized by SOC and preferred term (PT). AEs will also be further summarized by worst severity grade and relationship to study drug. [redacted]

Clinical laboratory data will be summarized descriptively, these summaries will include observed values at collection timepoints and change from baseline. All laboratory parameters that can be graded using the CTCAE will be graded. [redacted]

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9.9. Efficacy Analyses

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All efficacy data summaries for Part A will use the safety population, whereas Part B will use the efficacy population for Part B. Clinical activity will be assessed by change from baseline in: aGVHD Organ Stages and Overall Clinical Grading and aGVHD-AI. Corticosteroid and immunosuppressive agent usage will be compared between groups. Overall mortality and nonrelapse-mortality at 12 months, overall response rate (proportion of subjects with a best response of PR or better during the 12-month assessment period compared to last pre-dose assessment) and Kaplan-Meier estimates of progression-free survival will also be calculated. In general, changes from baseline in numeric variables will be compared between the two groups using an analysis of covariance model with baseline value as a covariate. Proportions will be compared between the groups using the Fisher's Exact test. Time to event data will be compared using the log-rank test.

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10. ADMINISTRATIVE CONSIDERATIONS

10.1. Investigator Responsibilities

The investigator is responsible for complying with all local, state, and federal regulations relating to performing clinical research with an investigational product. The investigator is responsible for ensuring that the investigation is conducted according to the signed Investigator Agreement (FDA Form 1572), the approved protocol, and applicable regulations for protecting the rights, safety, and welfare of study subject under the investigator's care. The investigator is additionally responsible for the control of investigational product and for providing accurate and verifiable data to the Sponsor.

The investigator must obtain the Informed Consent and HIPAA authorization of each subject before participation in the study. The investigator must assure initial and continuing review of the study by an IRB that complies with applicable national and local regulations.

The investigator will maintain minutes of meetings with study staff and document training of research study personnel for conduct of the study, including qualifications, experience, and study role.

The investigator will be given a copy of the most current version of the EQ001 Investigator's Brochure and appropriate study process manuals and plans. The investigator is obligated to become familiar with all sections of these documents prior to initiation of the study.

Other investigator responsibilities relative to the IRB include the following:

- Submit to the IRB for review any advertisements that will be used to recruit subjects
- Submit all protocol amendments, revisions of the Investigator's Brochure, or revisions of the Informed Consent to the IRB for review
- If Sponsor notifies the investigator about SAEs reported in other studies associated with this investigational product, report that information to the IRB
- Provide the IRB with any other information it requests before or during the conduct of the study
- Report to the IRB all adverse drug reactions that are serious, unexpected, and related to investigational product
- Maintain a file of study-related information
- Update the IRB on a minimum of a yearly basis

10.2. Institutional Review Board (IRB) Approval

Before initiation of the study at a study site, the protocol, including the final version of the ICF, the subject information sheet (if applicable), and any other relevant study documentation will be submitted to the appropriate IRB. In addition, the IRB must approve all advertising used to recruit subjects for the study. Written approval of the study documentation, including any proposed postings or advertising, must be obtained and sent to the Sponsor or its designee before the study site can be initiated or the study drug can be released to the investigator.

The investigator is responsible for informing the IRB of any amendments to the protocol, ICF, written information provided to subjects, and/or other procedures in accordance with local requirements. The protocol must be re-approved by the IRB upon receipt of amendments, in accordance with applicable law. The investigator must send a copy of the approval letter from the IRB to the Sponsor or its designee.

The investigator will report promptly to the IRB and the Sponsor any new information that may adversely affect the health or safety of past or current subjects or the conduct of the study, including deviations from the protocol or reports of any reportable SAEs, during and for two (2) years after completion of the study.

The investigator should submit written reports of clinical study status to their IRB annually or more frequently if required. A final study notification will also be forwarded to the IRB after the study is completed or in the event of premature termination of the study in accordance with the applicable regulations. After completion of the study, the investigator will provide the IRB with a report of the outcome of the study. Copies of all contact with the IRB should be maintained in the study file. Copies of clinical study status reports (including termination) should be provided to the Sponsor.

10.3. Ethical Conduct of the Study

This study will be conducted in compliance with the protocol; GCP guidelines, including International Council for Harmonisation (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use Guidelines (ICH E6); and FDA regulatory requirements. In addition, the study will be conducted in compliance with any and all current laws, requirements, regulations (including, but not limited to, HIPAA) of local, state, federal and foreign authorities and agencies having jurisdiction over the subject matter and performance of, and the study (referred to herein as "applicable law").

Investigators and all sub-investigators will comply with 21 Code of Federal Regulations (CFR), Part 54, 1998 and similar conflicts of interest laws requiring documentation of financial interests or arrangements with the Sponsor, or proprietary interests in the drug under study. Any required documentation must be provided prior to the investigator's (and any sub-investigator's) participation in the study. The investigator and sub-investigator(s) will notify the Sponsor or its designee of any change in reportable interests during the study and for 1 year following completion of the study. Study completion is defined as the date when the last subject completes all protocol-defined activities.

10.4. Subject Information and Consent

Prior to conducting any study-related procedures, the investigator must obtain written informed consent from each subject or legally authorized representative, in accordance with applicable law. Consent will be documented on a written ICF. The ICF must be approved both by the Sponsor and by the reviewing IRB prior to presenting it to a subject. Each ICF must comply with the ICH GCP Guidelines, FDA requirements, and local regulatory requirements.

Investigators may discuss study availability and the possibility for entry with a potential subject without first obtaining consent. However, informed consent must be obtained and documented prior to initiation of any procedures that are performed solely for the purpose of determining eligibility for research, including withdrawal from current medication(s). The informed consent process should take place under conditions where the subject has adequate time to consider the risks and benefits associated with his/her participation in the study. The investigator or qualified designee must explain to each subject or legally authorized representative the aims, methods, reasonably anticipated benefits, and potential hazards of the study.

Once appropriate essential information has been provided and fully explained in layman's language to the subject by the investigator (or a qualified designee), the approved ICF will be signed and dated by both the subject and the person obtaining consent (investigator or designee), as well as by any other parties required by the IRB. The subject will receive a copy of the signed ICF; the original will be retained in the study files. The investigator must document the consent interview and place the record in the study files. The investigator shall also maintain a log of all subjects who sign the ICF and indicate if the subject was enrolled into the study or reason for non-enrollment.

10.5. Confidentiality

The investigator must assure that subjects' anonymity will be strictly maintained and that their identities are protected from unauthorized parties. Only subject initials, date of birth, another unique identifier (as allowed by local law) and an identification code will be recorded on any form or biological sample submitted to the Sponsor, IRB, or laboratory. Laboratory specimens must be labeled in such a way as to protect subject identity while allowing the results to be recorded to the proper subject. Refer to specific laboratory instructions (or in accordance with local regulations). NOTE: The investigator must keep a screening log showing codes, names, and addresses for all subjects screened and for all subjects enrolled in the study. Subject data will be processed in accordance with all applicable regulations. (Some studies may require double-coding of samples; insert language as appropriate.)

The investigator agrees that all information received from the Sponsor, including but not limited to the Investigator's Brochure, this protocol, CRF/eCRF, the study drug, and any other study information, remain the sole and exclusive property of the Sponsor during the conduct of the study and thereafter. This information is not to be disclosed to any third party (except employees or agents directly involved in the conduct of the study or as required by law) without prior written consent from the Sponsor. The investigator further agrees to take all reasonable precautions to prevent the disclosure by any employee or agent of the study site to any third party or otherwise into the public domain. In compliance with applicable law and/or ICH GCP Guidelines, the investigator will permit the Sponsor's representatives and, when necessary, representatives of the FDA or other regulatory authorities' direct access to any medical records relevant to the study for verification of study-related procedures and data. Direct access includes examining, analyzing, verifying, and reproducing any records and reports that are important to the evaluation of the study.

Investigators will obtain authorization from the subject to permit access to study-related records, including personal information.

The Sponsor will ensure that the use and disclosure of protected health information obtained during the study complies with HIPAA and related privacy laws, including the Health Information Technology for Economic and Clinical Health Act, where these rules are applicable. Authorization is required from each subject (i.e., specific permission granted by such individual to a covered entity for the use or disclosure of an individual's protected health information). The investigator and institution must obtain such waiver/authorization in writing from the subject or legally authorized representative. Valid authorization must meet the implementation specifications under the applicable privacy laws. Authorization may be combined in the ICF (approved by the IRB), or it may be a separate document (approved by the IRB) or provided by the investigator or Sponsor (without IRB approval).

10.6. Study Initiation

Before the study drug can be shipped to the study site and before the study can begin, the following documents must be submitted and received by the Sponsor:

- Original US FDA Form 1572 signed by the investigator
- Documentation of the IRB approval of the protocol and Informed Consent
- A copy of the IRB-approved Informed Consent and HIPAA authorization that will be used
- Copy of current curriculum vitae and medical licenses of the investigator
- A membership list of the IRB
- Investigator's financial disclosure form

The Sponsor will notify the site when the study can begin.

10.7. Case Report Forms and Study Records

The investigator will comply with the requirements for all assessments and data collection for each subject, as specified in the protocol.

During each subject's visit to the clinic, the investigator or qualified designee will record progress notes in the subject's medical record to document all significant observations. At a minimum, these notes will contain the following:

- Documentation of the informed consent process, including any revised consents.
- The date of the visit and the corresponding visit or day in the study schedule.
- General subject status remarks, including any significant medical findings. The severity, frequency, and duration of any AEs and the investigator's assessment of relationship to study drug must also be recorded.
- Any changes in concomitant medications.
- A general reference to the procedures completed.
- The signature (or initials) and date of all clinicians who made an entry in the progress notes.

In addition, any contact with the subject via telephone or other means that provides significant clinical information will also be documented in the progress notes, as described above.

Data for this study will be captured in electronic eCRFs. Study auditing, data entry, verification and validation, and subsequent analysis will be performed by the Sponsor, or its designees, in accordance with GCPs and established Standard Operating Procedures.

Clinical data (including AEs, concomitant medications, and clinical laboratory data) will be entered into a database. The creation and validation of the database, data entry, validation, and verification will be performed according to 21 CFR and other applicable local regulations. The data system includes password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate.

10.8. Study Monitoring

The Sponsor or designee will assign monitors who will perform on site monitoring as frequently as necessary and in accordance with ICH GCP.

Source documents and eCRFs will be reviewed at monitoring visits and any findings will be discussed with the investigational staff. The Sponsor expects that at monitoring visits study documents and staff will be available and a suitable space will be provided for review of the study documents. The monitor will meet with the investigator on a regular basis to provide feedback on the conduct of the study.

For Part B, another monitor who is unblinded to subject treatment assignment will perform on-site monitoring of the drug accountability records.

10.9. Access to Source Documentation

The study may be subject to audit by the Sponsor, its designee, or by regulatory authorities. If such an audit occurs, the investigator must agree to allow access to required subject records. The investigator should notify the Sponsor promptly of regulatory authority audits that are scheduled and must forward copies of any findings or audit reports to the Sponsor promptly.

By signing this protocol, the investigator grants permission to personnel from the Sponsor, its representatives, and appropriate regulatory authorities for on-site monitoring and review of all appropriate study documentation, as well as on-site review of the procedures employed in data collection, where clinically appropriate.

10.10. Study or Study Site Termination

The Sponsor may suspend or stop the study at all centers or at specific study centers due to (but not limited to) the discovery of an unexpected, serious, or unacceptable risk to the subjects enrolled in the study, a decision on the part of the Sponsor to suspend or discontinue development of the product, failure of the investigator to enroll subjects into the study at an acceptable rate, failure of the investigator to comply with regulatory authority or ICH Guidelines, or submission of knowingly false information.

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10.13. Quality Assurance

Authorized representatives of the Sponsor, a regulatory authority, or IRB may visit the study site to perform audits or inspections, including source data verification. The purpose of any such audit or inspection is to systematically and independently examine all study-related activities and documents to determine whether these activities were conducted, and data were recorded, analyzed, and accurately reported according to the protocol, ICH GCP guidelines, and any other applicable regulatory requirements.

The investigator should contact the Sponsor immediately if contacted by a regulatory agency about an inspection.

It is important that the investigator and relevant personnel are available during the possible audits or inspections and that sufficient time is devoted to the process.

10.14. Retention of Data

When the study is completed, the investigator must retain the essential documents for as long as needed to comply with regulatory guidelines and Sponsor requirements. The investigator will notify the Sponsor prior to moving or destroying any of the study documents. It is the responsibility of the Sponsor to inform the investigator/institution as to when these documents no longer need to be retained. The investigator should take measures to prevent any accidental or premature destruction of these documents.

10.15. Study Report and Publications

A clinical study report (CSR) will be prepared and provided to the regulatory agency(ies). The Sponsor will ensure that the report meets the standards set out in the ICH Guideline for Structure and Content of Clinical Study Reports (ICH E3). Note that an abbreviated report may be prepared in certain cases.

Investigators in this study may communicate, orally present, or publish in scientific journals or other scholarly media only after written consent has been obtained from the Sponsor.

The investigator will submit to the Sponsor any proposed publication or presentation along with the respective scientific journal or presentation forum at least 60 days before submission of the publication or presentation.

No such communication, presentation, or publication will include the Sponsor's confidential information (see Section 10.5).

The investigator will comply with the Sponsor's request to delete references to its confidential information (other than the study results) in any paper or presentation and agrees to withhold publication or presentation for an additional 60 days in order to obtain patent protection if deemed necessary.

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