16.1.9 Documentation of Statistical Methods

Statistical Analysis Plan
Protocol Number: GC-652-02

STATISTICAL ANALYSIS PLAN

Trial Sponsor:	Generon (Shanghai) Corporation Ltd.
Protocol Number:	GC-652-02
IND Number:	[redacted]
Investigational Drug:	F-652
Indication:	Gastrointestinal Graft versus Host Disease

Dosage Form/Strength F-652, 45 μg/kg IV

Protocol Title: A Phase IIa Study of Recombinant Human Interleukin-22 IgG2-Fc (F-652) in Combination with Systemic Corticosteroids for the Treatment of Newly Diagnosed Grade II-IV Lower Gastrointestinal Acute Graft-versus-Host Disease (aGVHD) in Hematopoietic Stem Cell Transplantation Recipients

Last Revision Date:	19 March 2020
Version:	1.1
Final Sign-off Date:	
Archive Date:	

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Statistical Analysis Plan
Protocol Number: GC-652-02

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Change Log for Changes Made after the Initial Approval

Revision Date**	Section(s)Modified	Brief Description of Revision(s) or Reason(s) for Revision	Modifications Reviewed and Approved by*
			Sponsor, Everest
17MAR2020	6.2.4	Added details on the stopping date for the definition of treatment emergent AEs	K Dreyer, F Tang
17MAR2020	6.3.3 and 7.5.2	Clarified Immune recovery analysis will performed separately.	K Dreyer, F Tang
17MAR2020	6.4 and 7.7	Clarified PK analysis will performed separately.	K Dreyer, F Tang
17MAR2020	7.4.4	Added details on how to handle special laborotory values (">" or "<")	K Dreyer, F Tang

* Provide person's initial and last name.

** Update the Last Revision Dates on the cover page and the document header.

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GLOSSARY OF ABBREVIATIONS

Abbreviation	Term
aGVHD	Acute Graft-versus-Host Disease
AE	Adverse event
ANC	Absolute neutrophil count
AUC	Area under the curve
BLOQ	Below the limit of quantitation
BMI	Body mass index
BMT	Bone marrow transplant
BPM	Beats per minute
BSA	Body surface area
C_{max}	Concentration Maximum
CBC	Complete Blood Count
CI	Confidence interval
C_L	Clearance
CMV	Cytomegalovirus
CR	Complete response
eCRF	Electronic Case Report Form
CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
ECG	Electrocardiogram
GI	Gastrointestinal
HSCT	Hematopoietic Stem Cell Transplantation
IBMTR	International Bone Marrow Transplant Registry
IV	Intravenous
IWRS	Interactive Web-based Response System
λ_z	Elimination half-life

Abbreviation	Term
MedDRA	Medical Dictionary for Regulatory Activities
MR	Mixed response
NCA	Non-compartmental analysis
NCI	National Cancer Institute
NR	No response
OTC	Over-the-counter
PE	Physical examination
PK	Pharmacokinetics
PR	Partial response
PT	Preferred term
QA	Quality assurance
QC	Quality control
QTcF	Fridericia corrected QT interval
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SI units	International System of Units
SOC	System organ class
SOP	Standard operating procedure
TEAE	Treatment Emergent Adverse Event
TRM	Transplant-related mortality
V_d	Volume of distribution
VGPR	Very good partial response
VS	Vital signs
WHO-DD	World Health Organization Drug Dictionary

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1. INTRODUCTION

This Statistical Analysis Plan (SAP) outlines the statistical methods for the display, summary and analysis of data collected within the scope of Generon (Shanghai) Corporation Ltd. protocol GC-652-02, Protocol Amendment 4.0 dated May 30, 2017. The purpose of this plan is to provide general guidelines from which the analysis will proceed. Nevertheless, deviations from these guidelines must be substantiated by a sound statistical rationale.

The SAP should be read in conjunction with the study protocol and the Case Report Forms (CRFs). This version of the SAP has been developed using the final version of the protocol mentioned above and the study CRFs, Version 4.

This is a Phase IIa open label single arm study to investigate the safety, efficacy, and pharmacokinetics (PK) of F-652 (recombinant human IL-22), administered as an intravenous (IV) infusion once a week for a total of 4 doses at 45 μg/kg, in combination with systemic corticosteroids for the treatment of newly diagnosed grade II-IV lower gastrointestinal (GI) acute graft-versus-host disease (aGVHD) in Hematopoietic Stem Cell Transplantation (HSCT) recipients.

2. STUDY OBJECTIVES AND ENDPOINTS

2.1 Study Objective

The objective of the study is to assess the safety, efficacy and PK of F 652 in combination with systemic corticosteroids for the treatment of newly diagnosed grade II-IV lower GI aGVHD in HSCT recipients. GVHD cytokines and biomarkers will be explored.

2.2 Safety Endpoints

The safety endpoints of this study are the following:

- Adverse event (AE) reporting
- Vital sign (VS) measurements
- Laboratory measurements
- Physical Examination (PE)

2.3 Primary Efficacy Endpoint

- To assess the lower GI aGVHD treatment response rate at Day 28.

2.4 Secondary Efficacy Endpoints

- Lower GI aGVHD treatment response at Days 14 and 56 categorized by complete response (CR), very good partial response (VGPR), partial response (PR), no response (NR)/stable, and progression.
- Overall aGVHD treatment response at Days 14, 28, and 56 categorized by CR, VGPR, PR, mixed response (MR), NR, and progression.
- Discontinuation of immunosuppressive medication at Day 180 and 1 year post initial dosing of F-652.
- Characteristics of immune reconstitution after F-652 treatment.
- Overall survival at 1 year after first infusion of F-652.

2.5 [redacted]

2.6 [redacted]

3. STUDY DESIGN

3.1 Study Design

This Phase IIa open label single arm study will enroll up to 27 subjects to investigate the safety, efficacy, and PK of F-652 (recombinant human IL-22) in combination with systemic corticosteroids for the treatment of newly diagnosed grade II-IV lower GI aGVHD in HSCT recipients. Acute GVHD will be initially diagnosed clinically and staged accordingly.[1] Grading of aGVHD will be based on International Bone Marrow Transplant Registry (IBMTR) criteria[2]. This clinical trial will investigate if the use of F-652 enhances the recovery of the GI tract after aGVHD mediated-injury. The safety endpoints of this study are to assess the incidence of AEs and serious adverse events (SAE), along with other safety. The primary efficacy endpoint is to assess F-652 treatment response at Day 28 in subjects with lower GI aGVHD.

Candidates for this trial will include subjects ≥18 years and ≤80 years of age who are recipients of allogeneic HSCT using bone marrow, peripheral blood stem cells, or umbilical cord blood. Subjects must have stage 1-4 aGVHD of the lower GI tract at screening which will be determined by the maximum stool output in the preceding 3 days. Subjects with concurrent involvement of liver or skin aGVHD will be allowed but not as the sole organ affected. Biopsy of the GI tract is required for GVHD confirmation; however, results are not needed to initiate treatment. If GVHD is not confirmed histologically, treatment with F-652 will be discontinued and the subject will be replaced.

Eligible subjects will be consented and enter the study screening period. During this period, screening samples and tests will be obtained. A GI biopsy will be performed (if not done prior to study entry) for aGVHD disease histologic confirmation. The first dose of F-652 is to occur within 5 days after the subject's initial administration of systemic corticosteroids.

The expected duration of treatment for each subject is 4 weeks. F-652 weekly will be administered once a week for a total of 4 doses. Study enrollment will begin with 16 subjects dosed at 45 μg/kg of F-652. These subjects will be evaluated for treatment response at Day 28. If ≤6 of the first 16 subjects demonstrate a treatment response (i.e., response ≥PR), the clinical trial will be closed due to a lack of

efficacy. If 7 or more subjects of the first 16 subjects have a treatment response, an additional 11 subjects will be required to complete enrollment into the study for a total sample size of 27 subjects (Figure 1).

All subjects will be followed for efficacy through Day 56, safety through Day 180, and subject survival status will be collected at Day 365 (1 year from the date of initial dosing of F-652).

Prior to each dosing of F-652, subjects are required to meet the following criteria: absolute neutrophil count (ANC) ≥500/mm^3, serum creatinine ≤3.0 mg/dl, and all non-hematologic toxicity (except alopecia) attributed to the study drug as probable or greater to resolved to ≤ Grade 1 or returned to the subject's baseline condition. Failure to meet these criteria will result in treatment delay, dose reduction, or withdrawal from the study, as outlined in Protocol Section 3.3.2 (Hold and Stop Rules). A review of excess subject mortality at Day 56 will occur for every 6 subjects accrued into the study.

During the course of the study, systemic corticosteroids (prednisone or methylprednisolone equivalent) will be administered concurrently with F-652. Tapering of corticosteroids is permitted as outlined in Protocol Section 5.2 (Treatment Administrations); however, tapering should result in no less than 0.25 mg/kg/day of prednisone (or IV equivalent) by Day 28, after which tapering may be according to local institutional guidelines.

All subjects should be treated to the institutional allogeneic bone marrow transplant (BMT) standard of care guidelines for prophylaxis against infection. This includes, *Pneumocystis carinii*, Herpes simplex, Herpes Zoster, and fungal infections. Subjects will be closely monitored for cytomegalovirus (CMV) reactivation according to the each local center standard practice.

The study drug will be administered on an inpatient or outpatient basis, depending on the subject's clinical condition. The route of administration of F-652 is IV and will be administered once a week on Days 0, 7, 14, and 21. Following infusion of F-652, vital signs will be obtained and nursing assessment will be performed according to the BMT institutional standard of care. PK sampling will occur as per the schedule listed in the Protocol in Appendix 3 and serum samples to test the immunogenicity of F-652 will be taken. Subjects will be evaluated for grade 3-4 toxicities, graded by the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE). A complete description of the study procedures for each clinical visit is presented in the Protocol in Appendix 1.

GVHD biomarkers will be assessed at baseline and post-treatment. Baseline assessment of GVHD markers in the peripheral blood and GI tissue will be performed at the time of GVHD diagnosis, pending specimen availability. Due to the extensive processing of the peripheral blood for the assessment of GVHD cytokine markers, cytokine samples are optional for subjects participating in this study. The biomarker panel will include ST2 and REG3α whereas the cytokine panel will include IL-21, IL-22, and IL-23 levels. A stool sample will be collected for intestinal microbiota analysis and GVHD biology, including histology and epithelial gene expression, will also be analyzed in biopsy samples from the GI tract as the specimen allows. Post-treatment evaluation of GVHD biomarkers/cytokines in the peripheral blood, stool sample for intestinal microbiota, and GI tract biopsies will be performed approximately 28 days after study drug initiation or at least 3 days after receiving last dose of study drug (subject and sample availability permitting). Sampling may be withheld in subjects who are critically ill.

A study visit schematic is provided in Figure 2 and a complete schedule of study procedures and events are presented in Section 1.1 (Schedule of Procedures and Events).

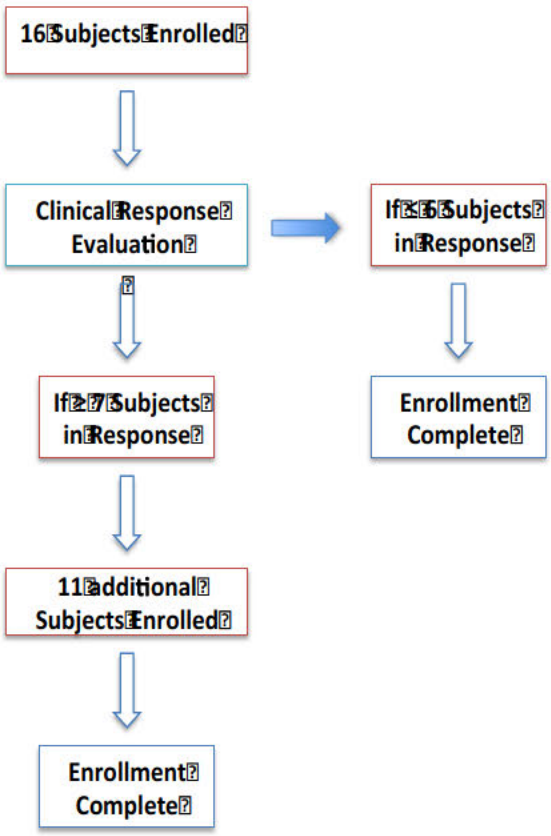
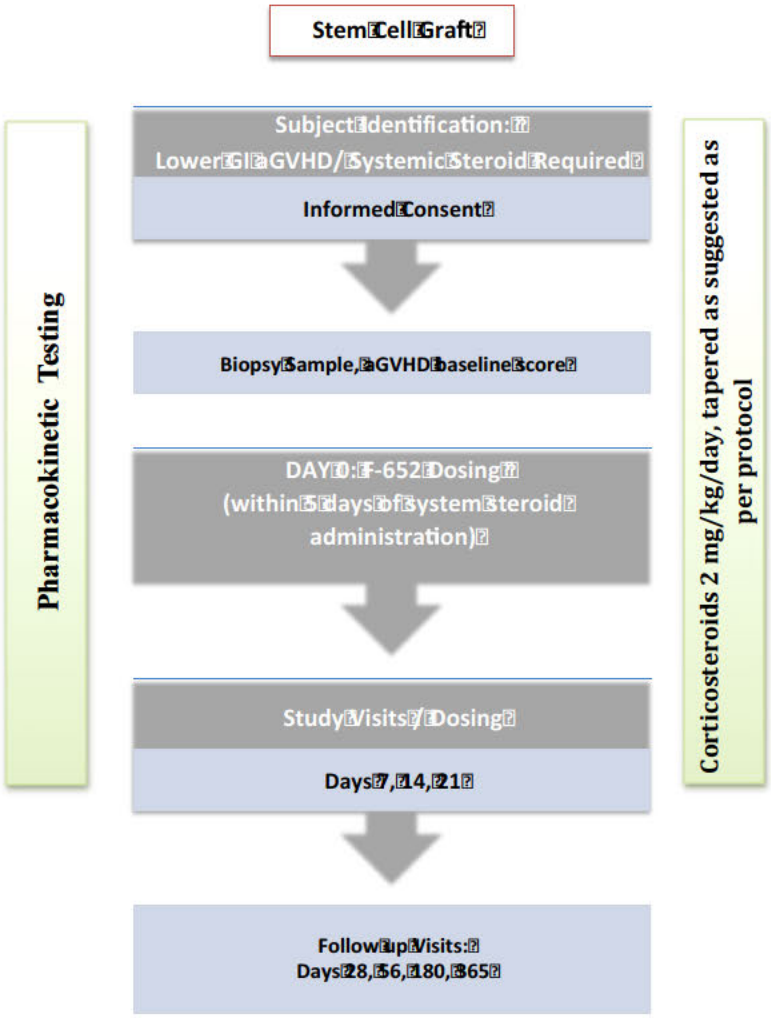


Figure 1 Study Enrollment Schematic



aGVHD = acute Graft-versus-Host Disease; F-652 = recombinant human interleukin-22 IgG2-Fc (F-652); GI = gastrointestinal

Figure 2 Study Visit Schematic

3.2 Schedule of Procedures and Events

Table 1 Schedule of Assessments

Assessments	Screening	Day 0	Day 7	Day 14	Day 21	Day 28*	Day 56	Day 180	Day 365
Window for visit (days)	(5) days		(±) 2	(±) 2	(±) 2	(±) 4	(±) 14	(±) 30	(±) 30
Signing of Informed Consent	X								
Relevant Medical History	X						X	X	X
Body Temperature, Weight, Vital Signs (BP, heart rate, respiratory rate)	X	X	X	X	X	X	X	X	X
Physical examination	X	X				X	X	X	X
CBC[1]	X		X	X	X	X	X		
Blood chemistry[1]	X		X	X	X	X	X		
Urinalysis	X					X			
Immune recovery (per institutional standard)[2]		X				X			
Serum for F-652 antibody testing (pre dosing of F-652)		X	X	X	X	X	X		
ECG	X					X			
Stool C. *Difficile* testing (if not done within 7 days)	X								
Stool microbiota test	X					X			
Pregnancy test[3]	X								
Current therapy and concomitant medications[4]	X	X	X	X	X	X	X	X	X
GI Biopsy[5]	X					X			
[redacted] (see additional schedule)		X	X	X	X	X	X		
Administration of F-652[7] (within 5 days of consent)		X	X	X	X				
Collection of AEs and toxicity assessment[8]	X	X	X	X	X	X	X		
aGVHD blood research samples (cytokine samples optional)		X				X			
Skin biopsy, subject permitting or if skin rash develops during treatment	X			X		X			
GVHD treatment response				X		X	X		
aGVHD evaluation	X		X	X	X	X	X	X	X

Abbreviations: AE = adverse event; aGVHD = acute graft-versus-host disease; BP = blood pressure; CBC = complete blood count; ECG = electrocardiogram; F-652 = recombinant human interleukin-22-IgG2-Fc; GI = gastrointestinal; GVHD = graft-versus-host disease; PK = pharmacokinetics.* End of treatment visit

[1] Blood samples are taken predose at Screening and Days 7, 14, 21, 28, and 56, and at 72 hours post-dose for CRP determination only at Screening and Days 7, 14, and 21.
[2] Immune recovery assessed on Day 0 as baseline and Days 28, post initial dose of F-652. Testing can be withheld if the subject has very low circulating white blood cells.
[3] For females with reproductive potential, serum test.

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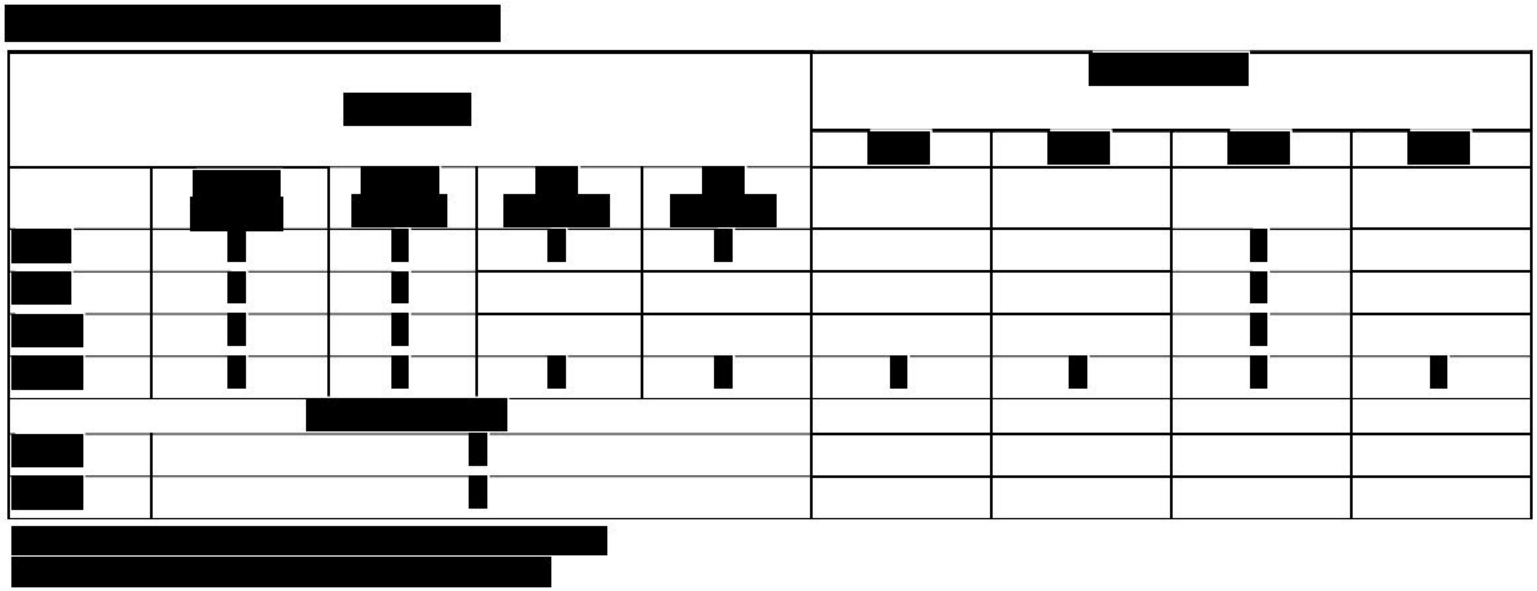
[4] Concomitant medications will be collected at each visit, scheduled or unscheduled. Collection of concomitant medications after Day 56 is required only for subjects with reported SAEs.
[5] Screening: for those subjects where no previous biopsy sample has been taken for GVHD confirmation. Day 28 Biopsy: subject permitting.
[6] See schedule for details**Error! Reference source not found.**.
[7] IV solution prepared per protocol.
[8] Collected at each scheduled or unscheduled visit. All AEs will be collected and documented on the study eCRF page through Study Day 56 (28 days after last dosing of F-652). After Study Day 56, only SAEs deemed possibly, probably, or definitely related to the investigational product are recorded through to the end of the study (Day 365).



3.3 Randomization

There is no randomization as this is a single arm study. An Interactive Web-based Response System (IWRS) with a 24-hour live support help desk will be used to assign subject numbers and to assign study drug. Authorized study site personnel will access the web-based system using a user ID and password. Prior training and a user's manual will be provided to all the study participating sites.

3.4 Hypothesis Testing

In this exploratory Phase IIa study, all statistical tests will be two-sided with no adjustment for multiplicity. All statistical tests and confidence intervals (CI) will use a Type I error rate of 10%. No adjustment will be made for multiple testing.

3.5 Interim Analysis

No interim analysis is planned for this study.

3.5.1 Hold and Discontinuation Rules for the Clinical Trial

Subjects will be closely monitored for clinical deterioration (i.e., disease progression) by the study Investigators, the study Medical Monitor, and the Sponsor's medical expert. In addition to standard toxicities such as alterations in blood chemistries or hematology, this monitoring will also include disease progression and treatment efficacy.

Clinical Trial Termination:

The study includes stopping criteria in the event that excessive Day 56 TRM is observed. The historical rate of TRM deaths is approximately 15-20%.[3] A TRM of 40% at Day 56 would be considered unexpected and an unacceptable number of excess deaths. TRM is defined as death at any time from the commencement of pre-transplant conditioning due to any cause other than disease relapse with the exception of automobile or other accidents.

In this study, there will be an ongoing review for excessive TRM. The study will be stopped for interim evaluation if the number of deaths is 3 or more in the first 5 subjects treated, 4 or more in the first 9 subjects treated, etc. as per Table 3. This evaluation will occur for the subject's Day 56 visit (post their initial F-652 dosing). Subjects removed from the study due to negative biopsy for aGVHD will not be accountable for the mortality rate rule analysis.

Table 3 Stopping criteria for excessive mortality based on a Pocock boundary

Failure Type	Mortality Rate Rule for Study Termination	Death rate in the population	Probability boundary is crossed
Transplant-Related Mortality (day +56)	3 deaths in the first 5 subjects treated	0.15	0.10
	4 deaths in the first 9 subjects treated		
	5 deaths in the first 13 subjects treated	0.40	0.93

	6 deaths in the first 18 subjects treated		
	7 deaths in the first 23 subjects treated		
	8 deaths at any point		

From Ivanova A, Qaqish BF and Schell MJ (2005).[4]

3.6 Sample Size

This study is designed to distinguish between an unpromising Day+28 treatment response rate (Lower GI aGVHD treatment response of Partial Response or better) of 35% and a promising treatment response rate of 60% using a Simon's two-stage optimal design. With a maximum sample of 27 subjects, this study has a type I error of 0.10 and a type II error of 0.10.

4. DATA AND ANALYTICAL QUALITY ASSURANCE

The overall quality assurance (QA) procedures for the study data, statistical programming and analyses are described in the Everest's Standard Operating Procedures (SOPs). Detailed statistical and programming quality control (QC) and QA procedures are documented in the Statistical Analysis and Programming QC/QA Plan.

The study endpoints and analytic approaches are both prospectively defined and documented in the protocol and in this SAP finalized prior to the database lock and data analysis.

5. ANALYSIS POPULATIONS

5.1 Safety Population

All enrolled subjects receiving any study treatment will be included in the Safety Population, which will be used for all safety analyses.

5.2 Efficacy Evaluable Population

All subjects who are eligible and have any post-treatment GVHD evaluation (not strictly limited to treatment response) or have disease progression before a GVHD evaluation can be performed will be included in the Efficacy Evaluable Population, which will be used for all efficacy analyses. Missing aGVHD treatment response will be imputed as non-response for this analysis.

5.3 [redacted]

6. SPECIFICATION OF ENDPOINTS AND VARIABLES

Several analytic variables must be derived from the data as it was collected. This section describes the variables collected, as well as how they will be modified for inclusion in the analyses.

6.1 Demographic and Baseline Characteristics

6.1.1 Demographics and Baseline Characteristics

Demographic parameters collected include:

- Age
- Sex
- Race
- Ethnicity
- Reproductive status

Baseline characteristics include:

- Weight (kg)
- Height (cm)
- Body mass index (BMI) in kg/m^2
- Body surface area (BSA) in m^2
- Days since clinical lower GI aGVHD diagnosis
- Screening aGVHD stage for each target organ (Skin, Lower GI Tract, Upper GI Tract, and Liver) using the modified keystone criteria
- IBMTR Severity Grade
- Type of HSCT (Blood, Bone Marrow, Cord, or Haploidentical)
- CMG IgG serostatus (Positive, Negative, or Equivocal)
- CMG IgM serostatus (Positive, Negative, or Equivocal)
- Physical examination clinically significant abnormalities (Yes or No)

Age, BMI, BSA, and days since clinical lower GI aGVHD diagnosis will be computed as:

Table 4 Data Handling Rules for Demographic Data

Description	Data Handling Rule
Age (years)	Age = integer((date of screening-date of birth)/365.25)
BMI	BMI = Weight (kg) / [Height (cm)/100]^2
BSA	BSA =([Height (cm) x Weight (kg)]/ 3600)$^{1/2}$
Days since clinical lower GI aGVHD diagnosis	Days since clinical lower GI aGVHD diagnosis = Date of screening – Date of Clinical Lower GI aGVHD diagnosis

6.1.2 Medical and Surgery History, Prior Chemotherapy

Medical and surgical history and prior chemotherapy will be collected.

General medical and surgical history will include a description of the diagnosis or procedures, start and end date, and if the condition is still ongoing.

Prior chemotherapy agent name, number of cycles, and date of last dose will be recorded on the eCRF.

6.2 Safety

- AE reporting
- VS measurements
- Laboratory measurements (hematology, serum chemistry, and urinalysis)
- Electrocardiogram (ECG) measurements
- PE

Standard safety parameters include hematology, blood chemistry and urinalysis parameters, vital signs, physical examination, and toxicity management. The National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) v 4.03 will be used to grade potential AEs.

6.2.1 Safety Baseline and Study Day

The baseline of safety measures are the last measure before first dose of F-652.

Study day will be computed from Day 0 as:

Study day = (Date of interest) – (Date of Day 0) + 1

6.2.2 Extent of Exposure to Study Medication

Extent of exposure to study drug (F-652) will be assessed using the following variables:

Table 5 Data Handling Rules for Extent of Exposure to Study Medication Data

Description	Definition/ Data Handling Rule
Number of Treatments	Number of infusions started, regardless of the completion status.
Treatment duration	Treatment duration (days) = Date of last dose of F-652– Date of first dose of F-652 + 1
Total F-652 Received (mg)	The total dosage of F-652 received. The starting dose is 45 μg/kg. Subsequent doses may be reduced, as determined by the Investigator, to 30 μg/kg or 10 μg/kg. The drug administered is at a concentration of 5 mg/mL. Dose infused (mg) can be calculated as (Volume infused (mL) * 5 mg/mL).
Number of Subjects with Doses Interrupted or Discontinued Prematurely (Overall and for each dose)	Number of subjects administered study drug but who had the infusion interrupted or discontinued prematurely.

6.2.3 Prior and Concomitant Medication

Prior and concomitant medications, including BMT/GVHD and systemic corticosteroid medications, will be recorded at screening and during the study. Prior medication is defined as any medication taken before the first dose of F-652. Concomitant medication is defined as any medication taken during the study between the date of the first dose of F-652 and the last study date of the subject, up to the Day 56 visit. Any medications started after the last study date of the subject will not be considered concomitant

medications. After Day 56, only concomitant medications related to a SAE will be documented on the eCRFs and will be considered as post-dose medications.

Any medication which cannot be identified as prior or concomitant will be considered as being in both of the categories that are possible from the available information.

All relevant information, including reason for use, dose, unit, frequency and route, will be recorded for any medication administered or received prior and during the study.

Summaries of all concomitant medications taken during the course of the study will be presented in tabular form using Anatomical Therapeutic Chemical 4 classification codes and preferred drug name via the World Health Organization Drug Dictionary (WHO-DD) with latest version to be specified in the Clinical Study Report. For the summary tables, if a subject has taken a concomitant medication more than once, the subject will be counted only once for the medication.

For medications with incomplete dates, imputation will be used to convert to a complete date. Imputed dates will be used to determine the study day.

Partial medication start dates will be imputed as follows:

1. Only the year is reported: If the subject started receiving study treatment in the year reported, then the date of the first dose of study treatment will be used as the starting date of the medication. Otherwise, January 1 will be used as the start of the medication.
2. The month and year is reported: If the subject started receiving study treatment during the month and year reported, then the date of first dose of study treatment will be used as the starting date of the medication. Otherwise, the first day of the month will be used as the start of the medication.

Partial medication end dates will be imputed for non-ongoing medications as follows:

1. Only the year is reported: If the subject stopped receiving study treatment in the year reported, then the date of the last dose of study treatment will be used as the end date of the medication. Otherwise, December 31 will be used as the end of the medication.
2. The month and year is reported: If the subject stopped receiving study treatment during the month and year reported, then the date of last dose of study treatment will be used as the end date of the medication. Otherwise, the last day of the month will be used as the end of the medication.

The above rules are subject to logical sense, for example, imputed start date should be on or prior to imputed end date.

6.2.4 Adverse Events

Adverse events (AEs) will be collected and coded using the latest version of the Medical Dictionary for Regulatory Activities (MedDRA). Analysis of adverse events will be carried out on the Safety Population.

All AEs from the time of randomization, regardless of suspected causal relationship to the investigational product, will be documented on the AE page(s) of the eCRF up to and including Study Day 56. After Day 56, SAEs deemed possibly, probably, or definitely related to the investigational product are required to be recorded through to the end of the study (Day 365).

A treatment-emergent adverse event (TEAE) is any adverse event that begins on or after first dose of F-652, or is a worsening of a pre-existing medical condition, up to study follow-up Day 56 (or 28 days after last dosing of F-652 if the subject does not have follow-up Day 56). SAEs that start after Day 56 will be considered post-treatment. Incidence of TEAE will be presented overall for all subjects.

The severity of each AE will be classified using the NCI-CTCAE toxicity scale as follows:

- Grade 1 = Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
- Grade 2 = Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental Activities of Daily Living (ADL)
- Grade 3 = Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL
- Grade 4 = Life-threatening consequences; urgent intervention indicated.
- Grade 5 = Death related to AE.

The relationship of each AE will be assessed by the investigator and assigned to 1 of the following categories:

- Unrelated
- Unlikely
- Possible
- Probable
- Definite

An AE will be considered "related" to study drug if the relationship is "possible", "probable" or "definite".

Serious adverse events (SAE) are defined as any adverse events occurring at any dose that suggests a significant hazard, contraindication, side effect, or precaution. SAEs will be collected from the time of study entry until 30 days after completion of the trial or 30 days after premature withdrawal of a subject from the trial.

If the death of a subject is reported at any point during the study, the date of death, autopsy performed (yes/no), and any clarifying information should be collected. The event causing death will be reported as a SAE.

Adverse Events Counting Rules:

1. In the analyses, a subject having the same event (AE preferred term) more than once during the study will be counted only once for that event type.
2. A subject with more than one different adverse event in a particular system organ class (SOC) will be counted only once in the total of subjects experiencing adverse events in that particular SOC.
3. If an event changes in intensity or in seriousness during the study, it will be counted only once with the worst grade and seriousness respectively.
4. If the causal relationship to the study drug is assessed differently, it will be counted only once by considering the "Worst" documented degree of relationship.

Missing values will be treated as missing except for relationship, grade and seriousness of an AE, at which occurrence a "worst case" approach will be taken. Thus, if relationship is missing the AE will be

regarded as related to the study drug, if the grade is missing the grade of the AE will be regarded as severe (Grade 3), if seriousness is missing the AE will be regarded as an SAE.

Events with Irregular Start Dates: All treatment-emergent adverse events will be included in the tabulations regardless the completeness of the onset dates. Partial dates may be imputed when appropriate, as discussed below.

If a partial date is reported for the start of an adverse event, a complete date will be estimated by the following algorithm:

1. Only the year is reported: If the subject started receiving study medication in the prior year, then January 1 will be used as the starting date of the event. If the subject started receiving study medication in the year reported, then the date of the first dose of study medication will be used as the start of the event.
2. The month and year are reported: If the subject started receiving study medication prior to the month and year reported, then the first day of the month will be used as the starting date of the event. If the subject started receiving medication during the month and year reported, then the date of the first dose of study medication will be used as the start of the event.

If a partial date is reported for the end of an adverse event and the adverse event is not continuing, a complete date will be estimated by the following algorithm:

1. Only the year is reported: If the subject started receiving study medication in the prior year, then the date of final study contact with the subject will be used as the end of the adverse event. If the subject started receiving study medication in the year reported, the earlier of December 31 or the date of final study contact with the subject will be used as the end of the adverse event.
2. The month and year are reported: The earlier of the last day of the month or the date of final contact with the subject will be used as the end of the adverse event.

Before the database lock, uncoded events will be assigned the string “UNCODED” as the body system, and the verbatim term will be used as the preferred term, so they can be included in the summary tables. In the final dataset, all the adverse events should have been coded.

6.2.5 Laboratory Data

This study will be conducted in up to 4 clinical centers in North America. Blood samples for hematology, serum chemistry, and serum hCG, as well as stool samples for C. difficile will be collected and analyzed by a local laboratory. Blood samples collected for PK will be analyzed by a central laboratory.

Conversion to the International System of Units

All laboratory data will be stored in the database with the units in which they are originally reported. Laboratory data in summary tables and subject data listings will be presented in the International System of Units (SI units). Laboratory data not reported in SI units will be converted to SI units before further processing or data analysis.

Hematology and blood chemistry data will be graded according to NCI-CTCAE severity grade.

Baseline laboratory parameters (blood chemistry, hematology, and urinalysis) are defined as the subject’s last assessment prior to the first dose of F-652.

Change in laboratory parameters post baseline can be computed as:

Change from baseline = Current Value – Baseline Value

Missing laboratory values will not be imputed for the safety analysis. In case of repeated measurements at a given visit, the latest value will be used for analysis.

6.2.6 Vital Signs

Vital signs are collected at Screening, Days 0, 7, 14, 21, 28, 56, 180, and 365, and include the following parameters:

- Height (cm) (Screening only)
- Weight (kg)
- Temperature (°C)
- Heart rate (beats per minute [BPM])
- Diastolic and systolic blood pressure (mmHg)
- Respiratory rate (beats/minute)

Weight at Days 0, 7, 14, and 21 will be measured once. Temperature, heart rate, blood pressure, and respiratory rate at Days 0, 7, 14, and 21 will be measured 15 minutes after the start of infusion, at the completion of infusion, and 1 hour after the end of infusion. All parameters will be collected one time each at Screening and on Days 28, 56, 180, and 365.

Baseline and change from baseline are defined similarly as in Section 6.2.5.

6.2.7 Electrocardiogram

Standard 12-lead ECG will be measured at screening and Day 28. The following parameters are included:

- PR Interval
- QRS Duration
- QT Interval
- RR Interval
- Heart Rate
- QTc Fridericia Interval (QTcF)

QTcF will be calculated as: $QT/\sqrt[3]{RR}$.

Another version of QTc was also collected from the CRF and will only be listed.

6.2.8 Other Safety Assessments

Other safety assessments include:

- Serum pregnancy test
- Urine pregnancy test
- Physical examination

Any clinically significant abnormalities from physical examination will be reported as medical history if observed at Screening, or as an AE if observed after enrollment.

6.3 Efficacy

The Efficacy Evaluable Population will be used for the efficacy analyses.

Missing aGVHD treatment response will be imputed as non-response for this analysis. Handling of missing values is covered in section 7.1.1.

6.3.1 Study Day

The date of the first dose of F-652 represents Study Day 1.

Study day will be computed from day 1 as:

Study day = (date of interest) – (date of Study Day 1) + 1

6.3.2 Primary Efficacy Variables

- The lower GI aGVHD treatment response rate 28 days following the initiation of therapy will be assessed by examining the proportion of subjects with a CR, VGPR, PR or have NR/stable or progression of lower GI aGVHD symptomatology. Treatment Response will be defined as CR, VGPR, or PR. No Treatment Response will be defined as NR/stable or progression.

6.3.3 Secondary Efficacy Variables

- The lower GI aGVHD treatment response rate at Days 14 and 56 will be assessed by examining the proportion of subjects with a CR, VGPR, PR or have NR/stable or progression of lower GI aGVHD symptomatology. Treatment Response will be defined as CR, VGPR, or PR. No Treatment Response will be defined as NR/stable or progression.
- The overall aGVHD treatment response rate at Days 14, 28, and 56 will be assessed by examining the proportion of subjects with a CR, VGPR, PR, MR, or have NR/stable or progression of overall aGVHD symptomatology. Treatment Response will be defined as CR, VGPR, PR, or MR. No Treatment Response will be defined as NR/stable or progression.
- Discontinuation of immunosuppressive medication at Day 180 and 1 year post initial dosing of F-652 will be assessed by estimating the proportion of subjects who have stopped immunosuppressive medication at Day 180 and 1 year. Immunosuppresive medications will be identified as those collected on the BMT/GVHD Medications CRF and categorized as Immunosuppressants. Subjects who discontinue at Day 180 and at 1 year will be defined as those who have stopped all immunosuppressant medications that were being taken at or after the first dose of F-652.
- Overall survival from the time of the first infusion of F-652 will be calculated as the number of days from the date of the first infusion to the date of death (Date of death – Date of first infusion +1) for subjects who die. Survival time for subjects who do not die will be based on the subject's study completion or discontinuation date (Date of completion/discontinuation – Date of first infusion +1).
- Characteristics of immune reconstitution after F-652 treatment will be evaluated through the B and T lymphocytes recovery and will be measured on Study Days 0 and 28 post-initial dose of F-652. They will be detailed in a separate analysis plan.

6.3.4 [redacted]

[redacted]

6.4 [redacted]

[redacted]

7. STATISTICAL ANALYSIS

7.1 General Data Handling Rules and Definitions

All subjects enrolled will be accounted for in the statistical analysis and presentation of the trial results.

All data collected on case report forms will be provided in listings, except data collected only for confirmation of study entry criteria and for study administrative purposes. If any enrolled subject is found to not have valid documented informed consent, that subject's data will be excluded from the report.

Except where specified, all continuous variables will be summarized with descriptive statistics (the number of non-missing values (n), mean, standard deviation, median, minimum and maximum) and all categorical variables will be summarized with frequency counts and percentages.

7.1.1 Missing Data and Imputation

For the analysis of the primary endpoint, the lower GI aGVHD treatment response rate at Day 28, missing data will be imputed as non-response. The rate and pattern of missing data will be explored and summarized.

Subjects who have reported protocol deviations, which may have a significant impact on the estimation of the PK parameters, will be removed from the PK Population. Subjects with partial serum concentration data will be evaluated to determine whether sufficient data is available for meaningful analysis.

No other data will be imputed in the analysis.

7.1.2 Analysis Visit and Visit Window Definitions

All safety and efficacy data will be analyzed based on the nominal visits and nominal time points. Only if the data from the nominal visit is missing, data from unscheduled visits or an early discontinuation visit for the same nominal visit or time point will be used. Data obtained during unscheduled and early discontinuation visits will be allocated to the scheduled visit corresponding to the visit window they fall in as specified in **Table 6**.

If multiple values are the same number of days away from the target study day, then the latter value will be used. In the unlikely event an unscheduled or early discontinuation visit, associated with a particular visit window, falls either prior to the actual previous nominal visit date or after the subsequent nominal visit date, it will not be used.

Table 6. Time Windows for Efficacy/Safety Assessments

Visit (label)	Time Interval (study day)	Target Time Point (day)
Screening	-5 to -1	-5 to -1
Day 0	1	1
Day 7	6 to 10	8
Day 14	13 to 17	15
Day 21	20 to 24	22
Day 28	25 to 33	29
Day 56	43 to 61	57
Day 180	151 to 211	181
Day 365	336 to 396	366

7.2 Subject Disposition

Disposition tables will be presented for all subjects.

The number and percentage of subjects who did not meet the screening criteria, were enrolled into the study, and completed each of the four doses will be tabulated. The number and percentage of subjects included and excluded from the defined analysis populations and reasons for study discontinuation will also be summarized. Other disposition information, reasons for screen failure and study discontinuation details will be provided in individual subject data listings.

7.3 Demographic and Baseline Characteristics

Demographic and baseline characteristics data will be summarized and tabulated.

Continuous baseline parameters (such as age) will be summarized descriptively. For categorical demographic parameters (such as gender, race, ethnicity) frequencies of subjects will be provided.

All medical history, acute graft-versus-host disease (aGVHD) diagnosis, prior chemotherapy, physical examination (abnormalities only), prior/concomitant medications, BMT/GVHD medications, and systemic corticosteroid administration data collected on the eCRF will be presented in listings.

7.4 Safety Analyses

All safety analysis will be performed on the Safety Population. Safety will be assessed based on AE reporting, physical examination, vital sign measurement, and clinical laboratory test results. Summaries of safety parameters will be presented for all treated subjects.

Wherever applicable for a safety parameter, the last assessment made before the first dose of F-652 will be used as the baseline for all analyses of that safety parameter.

In case of repeated measurements at a given timepoint, the latest value will be used for analysis. Measurements at unscheduled visits will only be listed, unless it is actually a repeat of the scheduled measurement.

7.4.1 Extent of Exposure to Study Medication

Descriptive statistics will be presented for the number of treatments, treatment duration (days), total F-652 received (mg), and number of incompleted doses. Study drug dose, date and time, and volume will be provided in listings.

7.4.2 Concomitant Medications

The number and percent of subjects with concomitant medications will be tabulated by ATC class and preferred term. Other details, including medication verbatim and coding, will be provided in listings. The number and percent of subjects with BMT/GVHD medications will be tabulated by category and drug name, as defined in the CRF. Other details will be provided in listings. The number and percent of subjects with systemic corticosteroid medications will be tabulated by corticosteroid name (Prednisone, Methylprednisolone, and Other). Other details, including other specified corticosteroid names, will be provided in listings.

7.4.3 Adverse Events

Analysis of adverse events will be carried out on the Safety Population. All adverse events will be included in the analyses, summaries, and individual subject data listings.

A TEAE overview summary table will be provided for all treated subjects including the number and percentage of subjects reporting at least one TEAE and the number of TEAEs reported for the following categories:

- Any TEAEs
- Serious TEAEs
- Deaths
- TEAE leading to study drug interruption
- TEAE leading to discontinuation of study drug

7.4.3.1 Incidence of Adverse Events

TEAEs will be summarized by SOC and preferred term (PT). The summary tables will display the total number and percentage of subjects reporting a specific TEAE, and the number of TEAE reported. TEAEs will be presented by SOC sorted alphabetically and PT sorted in decreasing frequency of occurrence.

Summary tables will be prepared for:

- Summary of TEAEs
- All TEAEs
- Serious TEAEs
- Treatment-related TEAEs
- TEAE leading to study drug discontinuation
- TEAEs by maximum severity
- TEAEs by relationship to study drug
- Common TEAEs with > 5% incidence rate
- Post-treatment SAE's

Supporting data listings will be provided, including:

- All adverse events (including any AEs reported in the study)
- Serious adverse events
- Deaths
- Adverse events for subjects who discontinued the study due to AE
- Glossaries of Preferred terms to verbatim by System Organ Class (SOC)

Infusion related reactions details will also be listed.

7.4.4 Laboratory Data

Laboratory values of '>=x' or '<=x' will be taken as the value of x in the analyses. If a laboratory value is prefixed with '>': the available original value +0.001 will be used for table summaries; if a laboratory value is prefixed with '<', then the original value –0.001 will be used in table summaries.

Shift tables from screening visit to the worst post-baseline value will be presented for clinical laboratory measurements (serum chemistry and hematology) for all treated subjects.

All data will be all displayed in subject data listings for all safety subjects.

7.4.5 Vital Signs

Descriptive statistics will be prepared for vital sign measurements, by visit and time (after dose), for actual values and changes from baseline. All data will be all displayed in subject data listings for all safety subjects.

7.4.6 Electrocardiogram

All ECG parameters will be listed.

7.4.7 Other Safety Assessments

Physical examination and pregnancy test results will be presented in listings for all Safety subjects.

7.5 Efficacy Analyses

All testing will be two-sided, with "statistical significance" defined as a corresponding p-value < 0.10.

The analyses of the secondary endpoints will be performed with no adjustment for multiplicity.

7.5.1 Primary Efficacy

The primary endpoint of lower GI aGHVD treatment response rate 28 days following the initiation of therapy will be reported as the proportion of subjects who provide a response as defined as Treatment Response (CR, VGPR, or PR), and No Treatment Response (NR and progression).

7.5.1.1 Sensitivity Analyses

No sensitivity analyses are planned at this time to evaluate the robustness of the primary efficacy results.

7.5.2 Secondary Efficacy

Secondary efficacy endpoints will be analyzed as follows:

- Response to therapy will be explored by examining the proportion of subjects with a Treatment Response (CR, VGPR, or PR), and No Treatment Response (NR/stable or progression) lower GI aGVHD symptomatology at 14 and 56 days post treatment initiation.
- Overall aGVHD response to therapy will be explored by examining the proportion of subjects with a Treatment Response (CR, VGPR, PR, or MR), and No Treatment Response (NR/stable or progression) of aGVHD at Days 14, 28, and 56 post-treatment initiation.
- The proportion of subjects who have stopped immunosuppressive medication at Day 180 and 1 year post initial dosing of F-652 will be estimated.
- Immune recovery will be evaluated through the B and T lymphocytes recovery and will be measured on Study Days 0 and 28 post-initial dose of F-652. Immune recovery data will be analyzed in a separate analysis plan.
- Kaplan-Meier methodology will be used to estimate overall survival from the time of the first infusion of F-652. Subjects who do not die will be censored at the date of completion/discontinuation from the study.

7.6 [redacted]

[redacted]

[redacted]

7.7 [redacted]

[redacted] a

8. CHANGES FROM METHODS PLANNED IN THE PROTOCOL

No changes are planned from the protocol.

9. STATISTICAL SOFTWARE

All analyses will be done using SAS version 9.4.

10. REFERENCES

1. Przepiorka D, Weisdorf D, Martin P, et al. 1994 Consensus Conference on Acute GVHD Grading. Bone Marrow Transplant. 1995;15(6):825-828.
2. Rowlings PA, Przepiorka D, Klein JP, et al. IBMTR Severity Index for grading acute graft-versus-host disease: retrospective comparison with Glucksberg grade. British Journal of Haematology. 1997;97(4):855-864.
3. Levine JE, Logan B, Wu J, et al. Graft-versus-host disease treatment: predictors of survival. Biol Blood Marrow Transplant. 2010;16(12):1693-1699.
4. Ivanova A, Qaqish BF and Schell MJ. (2005). Continuous Toxicity Monitoring in Phase II Trials in Oncology. Biometrics 61, 540-545.

APPENDIX 1 DATA HANDLING RULES

Category	Description	Data Handling Rules
Demographics	Age (years)	Age = integer((date of screening-date of birth)/365.25)
Demographic	BMI	BMI = Weight(kg) / [Height(cm)/100]^2
Demographic	BSA	BSA = ([Height(cm) x Weight(kg)]/ 3600)$^{1/2}$
Demographic	Days since clinical lower GI aGVHD diagnosis	Days since clinical lower GI aGVHD diagnosis = Date of screening – Date of Clinical Lower GI aGVHD diagnosis
Medical History	Any Medical history	flags are none, but data are present, change the flag to "Yes"
Efficacy	Stop day of immunosuppresive medication	= Stop date of immunosuppresive medication – Date of first dose of F-652 + 1
Efficacy	Overall survival time	= Date of completion/discontinuation – Date of first infusion + 1
Extent of Exposure to Study Medication	Actual volume infused	Collected on the CRF in mL, rounded to 1 decimal place.
Safety Lab	Assessment day	Assessment day = (Date of assessment) – (Date of first dose) + 1.
Safety Lab	Change from baseline	Change from baseline = Current Value – Value at last assessment prior to dose 1 treatment.

APPENDIX 2 SAS CODE FOR STATISTICAL ANALYSES

The SAS code for the efficacy endpoint analyses are given below.

Proportion of Subjects with Response- Primary Efficacy Endpoint	proc freq; tables aval/binomial(exact) alpha=0.1; run; Note: Use for Primary Efficacy endpoint, lower GI aGHVD response at day 28.
Proportion of Subjects with Response- Secondary Efficacy Endpoints	proc freq; tables aval/binomial(exact) alpha=0.1; by avisitn; run; Note: Use for Secondary Efficacy endpoints, lower GI aGHVD response at days 14 and 56, overall aGVHD response at days 14, 28, and 56, and proportion of subjects who have stopped immunosuppressive medication at days 180 and 365.
Kaplan Meier Survival Estimate- Secondary	proc lifetest; time survdays*censor(1); run;

Efficacy Endpoint Overall Survival	

APPENDIX 3 MOCKUP TABLES, LISTINGS, AND GRAPHS (TLGS)

Mockup tables, listings, and graphs are presented in a separate document prior to the final signoff of this SAP.

Statistical Analysis Plan
Protocol Number: GC-652-02

APPENDIX 3 SPECIFICATION OF END OF TEXT STANDARD OUTPUT TABLES, LISTINGS, AND FIGURES (TLFs)

A Phase IIa Study of Recombinant Human Interleukin-22 IgG2-Fc (F-652) in Combination with Systemic Corticosteroids for the Treatment of Newly Diagnosed Grade II-IV Lower Gastrointestinal Acute Graft-versus-Host Disease (aGVHD) in Hematopoietic Stem Cell Transplantation Recipients

GC-652-02

Investigational Medicinal Product:	F-652 45 μg/kg IV
Indication:	Gastrointestinal Graft versus Host Disease
Phase:	IIa
Date of Last Revision:	January 20, 2021
Version:	1.1

General Instructions for End-of-Text TFLs

Following are the specifications for end of text standard tables, listings, and figures (TFLs).

Header

The following header should appear at the very top of each page of a table, a listing, or a figure (TLF):

```
Generon (Shanghai) Corporation Ltd                                    F-652
Protocol GC-652-02                                                Page n of N
```

Footer

The following footer should appear at the bottom of each page of a TLF generated in SAS:

Report generated by program:/sasdir/PGNAME.sas Version yyyy-mm-dd hh:mm

where: PGNAME = SAS program name. Version will be replaced by “Draft” or “Final”.

Title

At least three (3) lines should be reserved for the whole title. The first line is for the TLF number (i.e., title index #); the second line is for the actual title (title); and the third line is reserved for the analysis population descriptor (population). All titles should be centered, as shown in the following example:

```
Table 3.1
Demographics
Safety Population
```

Footnotes

- In general, a footnote serves as a brief explanation/clarification/definition/concept of a flag symbol or a character, an abbreviation, a terminology, etc., that appears in or related directly to the displayed content of a TLF. Detailed/technical elaboration of, for example, a mathematical/statistical formula, a statistical term/test, or an algorithm for deriving a parameter value, should be addressed in the text of the statistical analysis plan (SAP).

- All footnotes should follow immediately after a horizontal solid line. There should be one and only one space between the last footnote and the footer.
- When an abbreviation (e.g. TEAE, SAE, etc.) appears first time in the whole set of TLFs for a study, a footnote should be provided at least once; and it is up to the Study Biostatistician, Pharmacokinetic (PK) Scientist, and Study Programmer to decide whether there is a need to repeat the same footnote for the rest of TLFs (if applicable).
- Each line of a complete footnote should end with a period. When a footnote needs more than 1 line, one (1) period is needed.
- Footnotes should be in the format shown in the following example:

```
N = number of subjects in the Safety Population.
n = number of subjects in the specific category.
% = 100 x (n/N).
Baseline is defined as the last assessment before the first dose of the
investigational product.
```

Page Layout

- All output should be in landscape orientation. A margin of 1.5, 1, 1, and 1 inch should be on the top, right, left, and bottom, respectively.
- All efforts should be made to present all treatment groups in one page.
- When 3 or more treatment groups are designed for a study and if it is not possible to fit all of them in one page, the 4th, 5th and 6th treatment groups should be displayed on the 2nd page, etc. The Study Biostatistician will pre-determine the order for the display of the treatment groups.

Page Format

- There should be a solid line at the top of the tables and listings just below the title.
- There should be a solid line just below the column headings that runs completely across the width of the tables and listings.
- There should be a solid line at the bottom of the tables and listings just above the footnote(s) on every page.

Font

- The default font to be used in the actual study tables/listings should be Courier New 8 point which is approximately equivalent to the acceptable font size of Times New Roman 9-10 in accordance with the FDA's guidance on Electronic Common Technical Document Specification.
- The use of Courier New 7 point is optional for some tables/listings and will be determined at the study level by the Study Biostatistician and Study Programmer. However, it is recommended that this option be used primarily for data listings.

Descriptive Statistics

By default, descriptive statistics in this template covers: n, Mean, Median, Standard Deviation (SD), Minimum (Min), and Maximum (Max). Unless otherwise specified in the actual table shells, the mean and median should be displayed to one more decimal place than the original data, the standard deviation, standard error of the mean should be displayed to two more decimal place than the original data.

Rounding for Percentage

Unless specified in the actual table shells for a study, all percentages will be rounded to 1 decimal place in all TLFs.

Unless specified in the actual table shells for a study, p-values will be presented with 4 decimal places.

Alignment of Decimals

- It is recommended that all the decimal places be aligned in summary tables, as shown in the following example:

Decimal Align

```
Mean              xx.xx
SD                xx.xxx
Median            xx.xx
Min, Max       xx.x, xx.x
n                  xxx
```

- When numbers with decimal points are included in brackets (e.g., percentages), have the brackets aligned to the right and then padded to allow for all possible percentages and then the left brackets will also be aligned. For example:

Brackets Align

```
(99.9%)          (xx.x)
( 9.9%)          ( x.x%)
```

- It is recommended that all column entries in a summary tables and listings are aligned to the center.
- Columns for text fields are all left justified. Columns with whole numbers are all right justified.
- For graphs, the lines are distinguishable and that the symbols for each line are appropriate. Legend is consistent across output for treatment names and abbreviations.

Use of N Versus n

- N = total number of subjects in the defined Population.
- n = total number of subjects in the specific category.
- If N is specified in the column heading then any reference to the number of patients in the body should be small n, as shown in the following example:

Demographic Parameter	Treatment Group A (N=XXX)	Treatment Group B (N=XXX)	Total (N=XXX)
Age (years)			
Mean	xx.x	xx.x	xx.x
SD	x.x	x.x	x.x
Median	xx.x	xx.x	xx.x
Min, Max	xx, xx	xx, xx	xx, xx
n	xxx	xxx	xxx

A Note for Subject Data Listings

- Observed Dates/AE Intensity/Relationship to investigational product are used in subject data listings.
- Observed values or raw assessment scores are used in data listings along with their derived values used in analyses, e.g., raw assessment scores and derived total scores.

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Shells for End-of-Text TLFs

1. SUBJECT DISPOSITION

Table 1.1.1
Subject Disposition
All Screened Subjects

	Total (N = XX)	
	n	(%)
Screened	xx	(xx.x)
Screen Failed	xx	(xx.x)
Dose With Study Treatment	xx	(xx.x)
Histologically confirmed GVHD	xx	(xx.x)
Started Dose 1 (Day 0)	xx	(xx.x)
Started Dose 2 (Day 7)	xx	(xx.x)
Started Dose 3 (Day 14)	xx	(xx.x)
Started Dose 4 (Day 21)	xx	(xx.x)
Completed Treatment Period (Day 28)	xx	(xx.x)
Completed Day 56	xx	(xx.x)
Completed Day 180	xx	(xx.x)
Completed the Study(Day 365)	xx	(xx.x)
Early Withdrawal before Completing Treatment Period (Day 28)	xx	(xx.x)
Reason for Discontinuation		
Adverse Event	xx	(xx.x)
Transplant-Related Mortality (TRM)	xx	(xx.x)
Other Adverse Event	xx	(xx.x)
Withdrawal of Consent	xx	(xx.x)
Lost to Follow-up	xx	(xx.x)
Failure to Comply with Protocol Requirements	xx	(xx.x)
Protocol Specified Discontinuation Criteria	xx	(xx.x)
Lower GI aGVHD Not Confirmed Histologically	xx	(xx.x)
Progressive GVHD	xx	(xx.x)
Lack of GVHD Treatment Response	xx	(xx.x)
Requires Tapering of Corticosteroids Before Day 3	xx	(xx.x)
Requires Increase Immunosuppression Therapy Due to Active aGVHD	xx	(xx.x)
Requires > 2 Study Drug Dose Reductions	xx	(xx.x)
Pregnancy	xx	(xx.x)

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Investigator Decision	xx	(xx.x)
Sponsor Decision	xx	(xx.x)
Early Withdrawal after Treatment Period (Day 28)[1]	xx	(xx.x)
Reason for Discontinuation		
Withdrawal of Consent	xx	(xx.x)
Subject Lost-To-Follow-Up	xx	(xx.x)
Subject Deceased	xx	(xx.x)
Subject experiences relapse of primary malignancy or develops new malignancy	xx	(xx.x)
Progression of GVHD	xx	(xx.x)
Subject started new therapy	xx	(xx.x)
Other	xx	(xx.x)
Safety Population	xx	(xx.x)
Efficacy Evaluable Population	xx	(xx.x)
Pharmacokinetic Population	xx	(xx.x)

Safty Population includes all subjects who received any study treatment.
Efficacy Evaluable Population includes all subjects who are eligible and have any post-treatment GVHD evaluation (not strictly limited to treatment response) or have disease progression before a GVHD evaluation can be performed.
Pharmacokinetic Population includes all subjects who received any study treatment and provided sufficient samples for PK parameter estimation.
[1] Subject xxxx completed the treatment period (4 doses of F-652), and discontinued on study day xxx.
N = number of all screened subjects.
n = Number of subjects within a specific category. Percentages are calculated as 100 x (n/N).
Source: Listings 1.1, 1.2, 1.3

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Listing 1.**1**
Listing of Screen Failures and Reason for Failure
All Screened Subjects

Subject ID	Age(yrs)[1]/Sex/Race	Screen Failure?	Date of Informed Consent Signed	Protocol Version	Criteria	Waiver Granted by Sponsor	Reason
xxxxxx	60/M/Caucasian	Yes	yyyy-mm-dd	x	xxxxxxxx	xxx	xxxxxxxx

This table includes all screened subjects who failed any inclusion/exclusion criteria.
[1] Age = age at Screening. M = Male, F = Female.

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Listing 1.2
Subjects Who Prematurely Discontinued the Study
All Enrolled Subjects

Subject ID	Age(yrs)/Sex/Race	Reason for Early Discontinuation	Specified Reason	Date of Discontinuation (Study Day) [1]	Date of Last Contact (Study Day) [2]
xxxxxx	60/F/Caucasian	Adverse Event	Other Adverse Event	yyyy-mm-dd (xx)	yyyy-mm-dd (xx)

[1] Study Day = date of discontinuation – first dose date + 1.
[2] Date of Last Contact is for the subjects lost to Follow-up. Study Day = date of last contact – first dose date + 1.
M = Male, F = Female.

Listing 1.3
Subject Disposition Information
All Screened Subjects

Subject ID	Date of Informed Consent	Date of Completion/Discontinuation/Last Contact (Study Day) [1]	Dates of First/Last Dose of Study Drug (Study Day) [1]	Completed Dose 1/2/3/4?	Safety Population	Efficacy Evaluable Population	[redacted] Population
xxxxxx	yyyy-mm-dd	yyyy-mm-dd (xx)	yyyy-mm-dd(xx)/ yyyy-mm-dd(xx)	Y/Y/Y/N	Yes	No	Yes

[redacted].
[1] Study Day = date of interest – date of dose 1 + 1.

Report generated by program: /sasdir/xxxx.sas

Listing 1.4
GI Biopsy
All Screened Subjects

Subject ID	Date of Completion/Discontinuation /Last Contact (Study Day) [1]	Dates of First/Last Dose of Study Drug (Study Day) [1]	Safety Population	Efficacy Evaluable Population	Visit	GI Biopsy Performed ?	Date of Biopsy	Type of Procedure Performed	aGVHD histologically confirmed?
xxxxxx	yyyy-mm-dd (xx)	yyyy-mm-dd(xx)/ yyyy-mm-dd(xx)	Yes	No	Screening Day 28	Yes	yyyy-mm-dd	Colonscopy	Yes

[1] Study Day = date of interest - date of dose 1 + 1.

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Listing 1.5
Subjects Excluded From Efficacy Evaluable Population
Safety Population

Subject ID	Date of Informed Consent	Date of Completion/Discontinuation/Last Contact (Study Day) [1]	Dates of First/Last Dose of Study Drug (Study Day) [1]	Completed Dose 1/2/3/4?	Efficacy Evaluable Population	Reason For Exclusion
xxxxxx	yyyy-mm-dd	yyyy-mm-dd (xx)	yyyy-mm-dd(xx)/ yyyy-mm-dd(xx)	Y/Y/Y/N	No	Yes

[1] Study Day = date of interest - date of dose 1 + 1.

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2. DEMOGRAPHICS, BASELINE CHARACTERISTICS AND OTHER SUMMARIES

Table 2.1.1
Demographics and Baseline Characteristics
Safety Population

	Total (N=XX)
Age (yrs)	
Mean	xx.x
SD	xx.xx
Median	xx.x
Min, Max	xx, xx
n	xxx
Sex - n(%)	
Female	xx (xx.x)
Childbearing potential[1]	xx (xx.x)
Non-childbearing potential[1]	xx (xx.x)
Male	xx (xx.x)
Race - n(%)	
White	xx (xx.x)
Black or African American	xx (xx.x)
Asian	xx (xx.x)
American Indian or Alaska Native	xx (xx.x)
Native Hawaiian or other Pacific Islander	xx (xx.x)
Other	xx (xx.x)
Ethnicity - n(%)	
Hispanic or Latino	xx (xx.x)
Not Hispanic or Latino	xx (xx.x)
Weight in kg	
Mean	xx.xx
SD	xx.xxx
Median	xx.xx
Min, Max	xx, xx
n	xxx
Height in cm	
Mean	xx.xx

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SD	xx.xxx
Median	xx.xx
Min, Max	xx, xx
n	xxx
BMI in kg/m^2 [2]	
Mean	xx.xx
SD	xx.xxx
Median	xx.xx
Min, Max	xx, xx
n	xxx
BSA in m^2[3]	
Mean	xx.xx
SD	xx.xxx
Median	xx.xx
Min, Max	xx, xx
n	xxx
Days Since Clinical Lower GI aGVHD Diagnosis [4]	
Mean	xx.xx
SD	xx.xxx
Median	xx.xx
Min, Max	xx, xx
N	xxx
Screening aGVHD Stage for Each Target Organ [5]	
Skin – n(%)	
Stage 0	xx (xx.x)
Stage 1	xx (xx.x)
Stage 2	xx (xx.x)
Stage 3	xx (xx.x)
Stage 4	xx (xx.x)
Lower GI Tract – n(%)	
Stage 0	xx (xx.x)
Stage 1	xx (xx.x)
Stage 2	xx (xx.x)
Stage 3	xx (xx.x)
Stage 4	xx (xx.x)
Upper GI Tract – n(%)	
Stage 0	xx (xx.x)
Stage 1	xx (xx.x)

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Liver – n(%)	
Stage 0	xx (xx.x)
Stage 1	xx (xx.x)
Stage 2	xx (xx.x)
Stage 3	xx (xx.x)
Stage 4	xx (xx.x)
IBMTR Severity Grade – n(%) [6]	
I	xx (xx.x)
II	xx (xx.x)
III	xx (xx.x)
IV	xx (xx.x)
Type of HSCT – n(%)	
Blood	xx (xx.x)
Bone Marrow	xx (xx.x)
Cord	xx (xx.x)
Haploidentical	xx (xx.x)
CMV IgG Serostatus – n(%)	
Positive	xx (xx.x)
Negative	xx (xx.x)
Equivocal	xx (xx.x)
CMV IgM Serostatus – n(%)	
Positive	xx (xx.x)
Negative	xx (xx.x)
Equivocal	xx (xx.x)
Physical Examination Clinically Significant Abnormalities – n(%)	
Yes	xx (xx.x)
No	xx (xx.x)
Risk Group [6]	
High Risk	xx (xx.x)
Standard Risk	xx (xx.x)

N = number of subjects in the Safety population.
n = Number of subjects within a specific category. Percentages are calculated as 100 x (n/N).
[1] BMI = Weight(kg) / [(Height(cm)/100)^2].
[2] BSA = ([Height(cm) x Weight(kg)]/ 3600)^1/2.
[3] Days since clinical lower GI aGVHD diagnosis = Date of enrollment – Date since clinical lower GI aGVHD diagnosis.
[4] Screening aGVHD Stage for Each Target Organ: Stages defined using Modified Keystone Criteria in Protocol Appendix 5, Table 2.
[5] IBMTR Severity Grade: Grades defined using IBMTR Severity Index for Grading aGVHD in Protocol Appendix 5, Tables 3.
[6] Risk group based on refined aGVHD Risk Score by MacMillan et al., 2015 April.

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Source: Listing 2.1 to 2.3

Programming Note: Add a row of Missing for any categorical variable with missing values for the baseline characteristic.

Table 2.1.2
Demographics and Baseline Characteristics
Efficacy Evaluable Population

Programmer note: This table is only needed when Efficacy Evaluable≠Safety .

Table 2.1.3
Demographics and Baseline Characteristics
PK Population

Programmer note: This table is only needed when Efficacy Evaluable≠PK .

Listing 2.1
Demographics
Safety Population

Subject ID	Age(yrs)/ Sex/ Race/ Ethnicity	Reproductive Status	Weight (kg)	Height (cm)	BMI (kg/m^2)	BSA (m^2)
xxxx	Xx/F/ Caucasian/ Not Hispanic	Non-childbearing potential	xxx.x	xxx.x	xx.x	xx.x
xxxxxx	Xx/M/ Caucasian/ Hispanic	NA	xxx.x	xxx.x	xx.x	xx.x
xxxxxx	Xx/F/ Caucasian/ Not Hispanic	Childbearing potential	xxx.x	xxx.x	xx.x	xx.x

BMI = Body Mass Index. BSA = Body Surface Area. M = Male, F = Female.

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Listing 2.2
Baseline Characteristics
Safety Population

Subject ID	Days Since Clinical Lower GI aGVHD Diagnosis [1]	Screening aGVHD Stage for Each Target Organ [2]				IBMTR Severity Grade [3]	Type of HSCT	CMV IgG Serostatus	CMV IgM Serostatus	Risk Group	Physical Examination Clinically Significant Abnormalities
		Skin	Lower GI Tract	Upper GI Tract	Liver						
xxxx	xxx.x	Stage 3	Stage 3	Stage 1	Stage 0	0	Bone Marrow	Positive	Equivocal	High Risk	Yes
xxxxx	xxx.x	Stage 2	Stage 4	Stage 0	Stage 4	I	Cord	Negative	Negative	Low Risk	No
xxxxx	xxx.x	Stage 1	Stage 1	Stage 1	Stage 3	IV	Haploidentical	Equivocal	Positive	Low Risk	No

GI = Gastrointestinal. aGVHD = Acute Graft-versus-Host Disease. IBMTR = International Bone Marrow Transplant Registry. HSCT = Hematopoietic Stem Cell Transplantation. CMG = . IgG = Immunoglobulin G. IgM = Immunoglobulin M.
[1] Days Since Clinical Lower GI aGVHD diagnosis = Date of screening – Date of Clinical Lower GI aGVHD diagnosis.
[2] Screening aGVHD Stage for Each Target Organ: Stages defined using Modified Keystone Criteria in Protocol Appendix 5, Table 2.
[3] IBMTR Severity Grade: Grades defined using IBMTR Severity Index for Grading aGVHD in Protocol Appendix 5, Tables 3.

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Listing 2.3
Acute Graft-Versus-Host Disease (aGVHD) Diagnosis
Safety Population

Subject ID	Date of Hematopoietic Stem Cell Transplantation	Type of HSCT	Date of Clinical Lower GI aGVHD Diagnosis	Was Pre-Transplant Cytomegalovirus Serostatus for the Recipient Available?	If Yes, Date of CMV Test	If Yes, CMG IgG	If Yes, CMG IgM
xxxx	yyyy-mm-dd	Bone Marrow	yyyy-mm-dd	Yes	yyyy-mm-dd	Positive	Equivocal
xxxxxx	yyyy-mm-dd	Cord	yyyy-mm-dd	No			
xxxxxx	yyyy-mm-dd	Haploidentical	yyyy-mm-dd	Yes	yyyy-mm-dd	Equivocal	Negative

HSCT = Hematopoietic Stem Cell Transplantation. GI = Gastrointestinal. aGVHD = Acute Graft-versus-Host Disease. CMV = Cytomegalovirus. CMG = . IgG = Immunoglobulin G. IgM = Immunoglobulin M.

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Listing 2.4
Medical and Surgical History (Excluding aGVHD and HSCT)
Safety Population

Subject ID	System Organ Class	Diagnosis or Procedures (Verbatim Term)	Onset Date	Is Condition Still Present? (Yes/No)	End Date
xxxxxx	Drug Allergy	xxxxxxxxxxxxxxxxxxxxx (XXXXXXXXXXXXXXX)	yyyy-mm	No	yyyy-mm

Note to programers: sort by subjid, SOC, onset date and diagnosis

Listing 2.5
Prior Chemotherapy
Safety Population

Subject ID	Any Chemotherapy in the Past 1 Year?	Therapy Code	Agent Name	Number of Cycles	Date of Last Dose	Ongoing at Screening?
xxxxxx	Yes	Chemo/Anthracycline	xxxxxxxxxx	xx		Yes
xxxxxx	Yes	Hormonal	xxxxxxx	xx	yyyy-mm-dd	No

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Listing 2.6
Prior and Concomitant Medications
Safety Population

Subject ID	Drug Name/ Prefered Term/ ATC Class [1]	Start/Stop Date(Ongoing) (Study Day[2])	Dose	Unit	Route	Frequency	Reason for Use (Specify)	Prior/ Concomitant/ Post-dose
xxxxxx	Xxxxxx/ Xxxxxxxxxxxx/ xxxxxxxxxxxxxxxxx	yyyy-mm-dd(-8)/ Ongoing	xxx	xx	xxx	xx	xxxxxx	Yes/No/No
xxxxxx	Xxxxxx/ Xxxxxxxxxxxx/ xxxxxxxxxxxxxxxxx	yyyy-mm-dd(5)/ yyyy-mm-dd(6)	xxx	xx	xxx	xx	Rescue Therapy (Febrile Neutropenia)	Yes/Yes/No

Prior medications are any medications taken prior to the date of first dose of study drug; Concomitant medications are those ongoing at baseline and taken during the study treatment period up to Day 56; Post-dose medications are these taken after the Day 56 visit (or 28 days after the last dose of study drug if no Day 56 visit).
[1] The World Health Organization (WHO) drug dictionary (Version &whodrug) was used to code concomitant medications.
[2] A negative number for study day denotes the number of days prior to the start of the first dose of study drug. Otherwise, study day is Date of interest - date of first dose of study drug + 1.

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Listing 2.7
BMT/GVHD Medications
Safety Population

Subject ID	Category/ Drug Name [1]	Route	Start/Ongoing Or Stop Date	Study Day[2]	Prior/ Concomitant/ Post-dose
xxxxxx	Xxxxxx/ Xxxxxxxxxxxx	xxx	yyyy-mm-dd/ Ongoing	Day 5	Yes/No/No
xxxxxx	Xxxxxx/ Xxxxxxxxxxxx	xxx	yyyy-mm-dd/ yyyy-mm-dd	Day 11	Yes/Yes/No

Prior BMT/GVHD medications are any medications taken prior to the date of first dose of study drug; Concomitant BMT/GVHD medications are those ongoing at baseline and taken during the study treatment period.
[1] The drug categories and drug names specified on the CRF were used to code BMT/GVHD medications.
[2] A negative number for study day denotes the number of days prior to the start of the first dose of study drug. Otherwise, study day is Date of interest - date of first dose of study drug + 1.

Listing 2.8
Systemic Corticosteroid Administration
Safety Population

Subject ID	Corticosteroid Name (Other, Specify) [1]	Start/Stop Date(Ongoing) (Study Day[2])	Dose	Unit	Route	Frequency	Prior/ Concomitant
xxxxxx	Xxxxxxxxxxxx (xxxxxxxxxxxxxxxxxx)	yyyy-mm-dd(-8)/ Ongoing	xxx	xx	xxx	xx	Yes/No
xxxxxx	Xxxxxxxxxxxx	yyyy-mm-dd(5)/ yyyy-mm-dd(6)	xxx	xx	xxx	xx	Yes/Yes

Prior Systemic corticosteroid administration are any medications taken prior to the date of first dose of study drug; Concomitant Systemic corticosteroid administration are those ongoing at baseline and taken during the study treatment period.
[1] The corticosteroid names specified on the CRF were used to report systemic corticosteroid medications.
[2] A negative number for study day denotes the number of days prior to the start of the first dose of study drug. Otherwise, study day is Date of interest − date of first dose of study drug + 1.

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Listing 2.9
Glossary of Medication Classes, Preferred Terms, and Verbatim Terms for Medications
Safety Population

ATC Class	Preferred Term	Verbatim Term
AMIDES	BUPIVACAINE	MARCAINE
	LIDOCAINE	INJECTION LIDOCAINE
		LIDOCAINE

WHO-DDE xxxxx version was used to code medications.

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3. SAFETY ANALYSIS

3.1. EXTENT OF EXPOSURE TO STUDY DRUG

Table 3.1.1
Exposure to Study Drug
Safety Population

	Total (N=XX)
Number of Treatments [1]	
Mean	xx.x
SD	xx.x
Median	xx
Min, Max	xx, xx
n	xxx
Treatment Duration (days)[2]	
Mean	xx.x
SD	xx.x
Median	xx
Min, Max	xx, xx
n	xxx
Total F-652 Received (mg)[3]	
Mean	xx.x
SD	xx.x
Median	xx
Min, Max	xx, xx
n	xxx
Number of Subjects with Doses Interrupted or Discontinued Prematurely	
Any Dose	xx
Dose 1	xx
Dose 2	xx
Dose 3	xx
Dose 4	xx

N = number of subjects in the Safety population. n = number of subjects contributing to summary statistics.
% = Percentages are based on n.
[1] Number of Treatments = Number of infusions started, regardless of the completion status.
[2] Treatment Duration (days) = Date of last dose of F-652- Date of first dose of F-652 + 1.
[3] Total F-652 Received (mg) = The total dosage of F-652 received. The starting dose was 45 µg/kg. Subsequent doses may have been reduced, as determined by the Investigator, to 30 µg/kg or 10 µg/kg. The drug administered was prepared as a 100 mL IV bag. Dose received (mg) was calculated as (Weight in kg * Dose Level in mg/kg) * (Actual Volume Administrated in mL/100 mL).

Source: Listing 3.1.1

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Listing 3.1.1
Study Drug Administration
Safety Population

Subject ID	Dose	Treatment Infusion Date and Start and Stop Times (24 hr clock) /Day [1]	Dose Level	Actual Volume Infused (mL)	Was Study Drug Administration Interrupted or Discontinued Prematurely?	If Yes, Please Indicate Reason(s)	If Infusion Related Reaction or Other Toxicity, Worst CTCAE Grade	If Other Reason, Specify
xxxx	Dose 1	yyyy-mm-dd hh:mm/hh:mm/xx	45 µg/kg	xxx.x	No			
	Dose 2	yyyy-mm-dd hh:mm/hh:mm/xx	45 µg/kg	xxx.x	No			
	Dose 3	yyyy-mm-dd hh:mm/hh:mm/xx	45 µg/kg	xxx.x	No			
	Dose 4	yyyy-mm-dd hh:mm/hh:mm/xx	45 µg/kg	xxx.x	Yes	Infusion Related Reaction	2	
xxxxxx	Dose 1	yyyy-mm-dd hh:mm/hh:mm/xx	45 µg/kg	xxx.x	Yes	Other Toxicity, Other Reason	3	xxxxxxxxxxx
	Dose 2							
	Dose 3							
	Dose 4							

CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events.
[1] Treatment Day = Dosing date - first dose date + 1.

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3.2. CONCOMITANT MEDICATIONS

Table 3.2.1
Concomitant Medications
Safety Population

ATC Class/ Preferred Term	n	Total (N=XX) (%)
Any Concomitant Medications	xx	(xx.x)
ATC Class 1	xx	(xx.x)
Preferred Term1	xx	(xx.x)
Preferred Term2	xx	(xx.x)
……		
ATC Class 2	xx	(xx.x)
Preferred Term1	xx	(xx.x)
Preferred Term2	xx	(xx.x)
……		

The World Health Organization (WHO) drug dictionary (Version &whodrug) was used to code concomitant medications.
Concomitant medication is defined as any medication taken during the study between the date of the first dose of study drug and the last study date of the subject, up to the Day 56 visit.
N = number of subjects in the Safety population.
n = Number of subjects within a specific ATC class or medication. Percentages are calculated as 100 x (n/N).
Multiple uses of a specific medication for a subject were counted once in the frequency for the medication. Likewise, multiple uses within a specific medication class for a subject were counted once in the frequency for the medication class.

Source: Listing 2.6

Programmer note: Classes sorted alphabetically. Medications sorted within classes in decreasing order of frequency in the total group.

Table 3.2.2
Concomitant BMT/GVHD Medications
Safety Population

Category/ Drug Name	n	Total (N=XX) (%)
Any BMT/GVHD Medications	xx	(xx.x)
Antibacterials	xx	(xx.x)
Ciprofloxacin (Cipro)	xx	(xx.x)
Levofloxacin (Levaquin)	xx	(xx.x)
……		
Antifungals	xx	(xx.x)
Voriconazole (Vfend)	xx	(xx.x)
Posaconazole (Noxafil)	xx	(xx.x)
……		

The drug categories and drug names specified on the CRF were used to code BMT/GVHD medications.
Concomitant BMT/GVHD medication is defined as any BMT/GVHD medication taken during the study between the date of the first dose of study drug and the last study date of the subject, up to the Day 56 visit.
N = number of subjects in the Safety population.
n = Number of subjects within a specific category or drug name. Percentages are calculated as 100 x (n/N).
Multiple uses of a specific medication for a subject were counted once in the frequency for the medication. Likewise, multiple uses within a specific medication category for a subject were counted once in the frequency for the medication category.

Source: Listing 2.7

Programmer note: Categories sorted alphabetically. Medications sorted within classes in decreasing order of frequency in the total group.

Table 3.2.3
Concomitant Systemic Corticosteroid Administration
Safety Population

Corticosteroid Name	n	Total (N=XX) (%)
Any Corticosteroid Administration	xx	(xx.x)
Prednisone	xx	(xx.x)
Methylprednisolone	xx	(xx.x)
Other	xx	(xx.x)

The corticosteroid names specified on the CRF were used to report systemic corticosteroid medications.
Concomitant systemic corticosteroid administration is defined as any medication taken during the study between the date of the first dose of study drug and the last study date of the subject, up to the Day 56 visit.
N = number of subjects in the Safety population.
n = Number of subjects within a corticosteroid name. Percentages are calculated as 100 x (n/N).
Multiple uses of a specific medication for a subject were counted once in the frequency for the medication.

Source: Listing 2.8

Programmer note: Medications sorted in decreasing order of frequency in the total group.

3.3. ADVERSE EVENT

Table 3.3.1
Overall Summary of Treatment Emergent Adverse Events
Safety Population

	Total (N = xx) n(%)
Total Subjects with at Least 1 TEAE	xx (xx.x)
Total Number of TEAEs	xx
Total Subjects with at Least 1 TESAE	xx (xx.x)
Total Number of TESAEs	xx
Total Number of Deaths	xxx
Subjects with at least 1 TEAE	
Leading to Study Drug Interruption	xx (xx.x)
Leading to Study Drug Discontinuation	xx (xx.x)

n = Number of subjects within a specific category. Percentages are calculated as 100 x (n/N).
TEAE = any adverse event that begins on or after treatment or is a worsening of a pre-existing medical condition.
TESAE = Treatment Emergent Serious adverse event.

Source: Listing 3.3.1.

Table 3.3.2
Treatment Emergent Adverse Events by System Organ Class and Preferred Term
Safety Population

System Organ Class Preferred Term	Total (N=XX) n (%)	 # of TEAE
Any TEAE	xx (xx.x)	xx
System Organ Class 1	xx (xx.x)	xx
Preferred Term 1	xx (xx.x)	xx
…		
System Organ Class 2	xx (xx.x)	xx
…		

MedDRA version &meddra was used to code adverse events.
n = Number of subjects within a specific category. Percentages are calculated as 100 x (n/N).
TEAE = any adverse event that begins on or after treatment or is a worsening of a pre-existing medical condition.

Source: Listing 3.3.1.

Programmer note: SOCs sorted alphabetically and preferred term (PT) sorted in decreasing frequency of occurrence.

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Table 3.3.3
Treatment Emergent Serious Adverse Events by System Organ Class and Preferred Term
Safety Population

System Organ Class Preferred Term	Total (N = XX) N (%)	 # of SAE
Any SAE	xx (xx.x)	xx
System Organ Class 1	xx (xx.x)	xx
Preferred Term 1	xx (xx.x)	xx
…		
System Organ Class 2	xx (xx.x)	xx
…		

MedDRA version &meddra was used to code adverse events.
SAE = serious adverse event.
n = Number of subjects within a specific category. Percentages are calculated as 100 x (n/N).

Source: Listing 3.3.1.

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Table 3.3.4
Treatment Related Treatment Emergent Adverse Events by System Organ Class and Preferred Term
Safety Population

System Organ Class Preferred Term	Total N = XX (N=XX) n (%)	# of TEAE
Any Treatment Related TEAE	xx (xx.x)	xx
System Organ Class 1	xx (xx.x)	xx
Preferred Term 1	xx (xx.x)	xx
…		
System Organ Class 2	xx (xx.x)	xx
…		

MedDRA version &meddra was used to code adverse events.
n = Number of subjects within a specific category. Percentages are calculated as 100 x (n/N).
Related = possible, probable or definite.
TEAE = any adverse event that begins on or after treatment or is a worsening of a pre-existing medical condition.

Source: Listing 3.3.1.

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Table 3.3.5
Treatment Emergent Adverse Events Leading to Study Drug Discontinuation by System Organ Class and Preferred Term
Safety Population

System Organ Class Preferred Term	Total (N=XX) N (%)	# of TEAE
Any TEAE Leading to Study Drug Discontinuation	xx (xx.x)	xx
System Organ Class 1	xx (xx.x)	xx
Preferred Term 1	xx (xx.x)	xx
…		
System Organ Class 2	xx (xx.x)	xx
…		

MedDRA version &meddra was used to code adverse events.
n = Number of subjects within a specific category. Percentages are calculated as 100 x (n/N).
TEAE = any adverse event that begins on or after treatment or is a worsening of a pre-existing medical condition.

Source: Listing 3.3.1.

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Table 3.3.6
Treatment Emergent Adverse Events by Maximum NCI-CTCAE Grade
Safety Population

System Organ Class Preferred Term NCI-CTCAE Grade	Total (N=XX) n (%)
Any TEAE	xx (xx.x)
System Organ Class 1	xx (xx.x)
Grade 1	xx (xx.x)
Grade 2	xx (xx.x)
Grade 3	xx (xx.x)
Grade 4	xx (xx.x)
Grade 5	xx (xx.x)
Preferred Term 1	xx (xx.x)
Grade 1	xx (xx.x)
Grade 2	xx (xx.x)
Grade 3	xx (xx.x)
Grade 4	xx (xx.x)
Grade 5	xx (xx.x)
Preferred Term 2	xx (xx.x)
Grade 1	xx (xx.x)
Grade 2	xx (xx.x)
Grade 3	xx (xx.x)
Grade 4	xx (xx.x)
Grade 5	xx (xx.x)
…	
System Organ Class 2	
...	

MedDRA version &meddra was used to code adverse events.
NCI-CTCAE version 4.0 was used to grade the severity of adverse events.
If a subject had more than one occurrence of the same event category, only the most severe occurrence was counted.
n = Number of subjects within a specific category. Percentages are calculated as 100 x (n/N).
Grade 1 = Mild; Grade 2 = Moderate; Grade 3 = severe; Grade 4 = Life-threatening/Disabling; Grade 5 = Death.
TEAE = any adverse event that begins on or after treatment or is a worsening of a pre-existing medical condition. CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events.

Source: Listing 3.3.1.

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Table 3.3.7
Treatment Emergent Adverse Events by Relationship to Study Drug
Safety Population

System Organ Class Preferred Term Relationship to Study Drug	Total (N=XX) n (%)
Any TEAE	xx (xx.x)
System Organ Class 1	xx (xx.x)
UNR	xx (xx.x)
UNL	xx (xx.x)
POS	xx (xx.x)
PROB	xx (xx.x)
DEF	xx (xx.x)
Preferred Term 1	
UNR	xx (xx.x)
UNL	xx (xx.x)
POS	xx (xx.x)
PROB	xx (xx.x)
DEF	xx (xx.x)
Preferred Term 2	
UNR	xx (xx.x)
UNL	xx (xx.x)
POS	xx (xx.x)
PROB	xx (xx.x)
DEF	xx (xx.x)
…	
System Organ Class 2	xx (xx.x)
...	

MedDRA version &meddra was used to code adverse events.
If a subject had more than one occurrence of the same event category, only the most treatment-related occurrence was counted.
TEAE = any adverse event that begins on or after treatment or is a worsening of a pre-existing medical condition.
n = Number of subjects within a specific category. Percentages are calculated as 100 x (n/N).
UNR = Unrelated; UNL = Unlikely; POS = Possible; PROB = Probable; DEF = Definite.
Source: Listing 3.3.1.

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Table 3.3.8
Common Treatment Emergent Adverse Events > 5% Incidence Rate by System Organ Class and Preferred Term
Safety Population

System Organ Class Preferred Term	Total (N=XX) n (%)
System Organ Class 1	xx (xx.x)
Preferred Term 1	xx (xx.x)
Preferred Term 2	xx (xx.x)
…	
System Organ Class 2	
...	

MedDRA was version &meddra was used to code adverse events.
TEAE = any adverse event that begins on or after treatment or is a worsening of a pre-existing medical condition.
n = Number of subjects within a specific category. Percentages are calculated as 100 x (n/N).

Source: Listing 3.3.1.

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Table 3.3.9
Post-Treatment Serious Adverse Events by System Organ Class and Preferred Term
Safety Population

System Organ Class Preferred Term	Total (N = XX) N (%)	 # of SAE
Any SAE	xx (xx.x)	xx
System Organ Class 1	xx (xx.x)	xx
Preferred Term 1	xx (xx.x)	xx
…		
System Organ Class 2	xx (xx.x)	xx
…		

MedDRA version &meddra was used to code adverse events.
SAE = serious adverse event.
n = Number of subjects in Preferred Term category. Percentages are calculated as 100 x (n/N).
Post-treatment SAE's are SAEs that start after Day 56

Source: Listing 3.3.1.

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Listing 3.3.1
Adverse Events
Safety Population

Subject ID	Age/ Sex/ Race	Date of First/Last Dose	AE Onset/ Stop Date/Ongoing	AE Onset/ Stop Day	System Organ Class/ Preferred Term/ (Verbatim Term)	CTCAE Grade / Relationship to IMP	SAE?/ TEAE?	Trt. Given	Outcome	Action Taken with Study Drug
xxxxx	xx/x/x	yyyy-mm-dd/ yyyy-mm-dd	yyyy-mm-dd / ongoing	xx/xx	xxxxxxxxxxxx/ xxxxxxxxxxxxxx/ (xxxxxxxxxxx)	Severe/ Not related	Yes/Yes	xxxx	xxxxx	Dose Not Changed

MedDRA version &meddra was used to code adverse events.
A negative number for study day denotes the number of days prior to the start of the first dose. Otherwise, study day is Date of interest - date of first dose + 1.
M = Male, F = Female.

Programmer note: Sort by Site ID, Subject ID, AE Onset Date and AE Resolution Date. If hospitalized, add hospital admission and discharge day, i.e. 3 (Day xx-Day xx).

Listing 3.3.2
Serious Adverse Events
Safety Population

Subject ID	Age/ Sex/ Race	System Organ Class/ Preferred Term/ (VerbatimTerm)	Onset Date (Study day)/ Resolution Date(Study Day)/ ongoing	CTCAE Grade[1] / Relationship to Study Drug	Outcome	Treatment for AE?	Action Taken with Study Drug	Seriousness criteria
xxxxxxx	xx/x/x	XXXXXXXXXXXX/ XXXXXXXXX/ (XXXXXXXXXX)	YYYY-MM-DD (xx) YYYY-MM-DD (xx)	Severe/ Probably related	Recovered /Resolved	Yes	Drug Interrupted Stopped: YYYY-MM-DD hh:mm AE abated Restarted: YYYY-MM-DD hh:mm AE reoccurred	Hospitalization/prolongation. Admission on YYYY-MM-DD Discharged on YYYY-MM-DD
Additional Case Details: xxxxxxxxxxxxxx								
Relevant Diagnostic Tests: xxxxxxxxxxxxxxxxxx								
xxxxxxx	xx/x/x	XXXXXXXXXXXX/ XXXXXXXXX/ (XXXXXXXXXX)	YYYY-MM-DD (xx) ongoing	Severe/ Unlikely related	Not recovered /not resolved	Yes	None	Death on YYYY-MM-DD Autopsy performed
xxxxxxx	xx/x/x	XXXXXXXXXXXX/ XXXXXXXXX/ (XXXXXXXXXX)	YYYY-MM-DD (xx) ongoing	Severe/ Unlikely related	Not recovered /not resolved	Yes	Drug Withdrawn Last dose date YYYY-MM-DD	Life-threatening

A negative number for study day denotes the number of days prior to the start of the first dose. Otherwise, study day is Date of interest - date of first dose + 1.
MedDRA version &meddra was used to code adverse events.
[1] NCI-CTCAE version 4.0 was used to grade the severity of adverse events.
M = Male, F = Female.

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Programmer note: Sort by Site ID, Subject ID, AE Onset Date and AE Resolution Date. If hospitalized, add hospital admission and discharge day, i.e. 3 (Day xx-xx).

Listing 3.3.3
Deaths
Safety Population

Subject ID	Age/ Sex/ Race	Efficacy Evaluable Population?	Date of Death	Study Day of Death	Transplant-Related Mortality (TRM)?	Autopsy Performed?	Date of First/Last Dose
xxxxxx		Yes	YYYY-MM-DD	xx	Yes	Yes	YYYY-MM-DD/YYYY-MM-DD

M = Male, F = Female.

Programmer note: Sort by Site ID, Subject ID, Death date

Listing 3.3.4
Adverse Events for Subjects Who Discontinued the Study Due to AE
Safety Population

Subject ID	System Organ Class/ Preferred Term / (Verbatim Term)	Day of Onset/ Outcome (Resolution Day or Ongoing) / Grade [1]	Relationship to Study Drug/ Action Taken with Study Drug	Serious AE (Yes/No)/ Reason	Treatment Given	Transplant-Related Mortality /Other AE?
xxxxxx	xxxxx/ xxxxx / xxxxxxx	5/ Unknown/ 15/III	Unrelated/ Dose Not Changed	Yes/ Hospitalization/Prolongation of existing hospitalization (Day xx-Day xx)	Yes/No	Other AE

A negative number for study day denotes the number of days prior to the start of the first dose. Otherwise, study day is Date of interest – date of first dose + 1.
MedDRA version &meddra was used to code adverse events. All AEs are listed for a subject who discontinued due to an adverse event.
[1] NCI-CTCAE version 4.0 was used to grade the severity of adverse events.

Programmer note: Sort by Site ID, Subject ID, AE Onset Date and AE Resolution Date. If hospitalized, add hospital admission and discharge day, i.e. 3 (Day xx-Day xx).

Listing 3.3.5
Adverse Events of Special Interest: Toxicity
Safety Population

Subject ID	Study Drug Administration Date (Study Day) [1]	Was Study Drug Administration Delayed or Dose Reduced Due to Toxicity?	Type(s) of Toxicity	If Hematology Toxicity, Blood Counts (ANC)	If Skin Toxicity, Infusion Related Reaction, or Other Toxicity, Worst CTCAE Grade	If Other Toxicity, Specify
xxxxxx	yyyy-mm-dd (5)	Yes	Hematology Toxicity, Infusion Related Reaction	>= 500/mm^3	3	
xxxxxx	yyyy-mm-dd (10)	Yes	Skin Toxicity, Other Toxicity		2, 4	xxxxxxxx

[1] Study day = Date of study drug administration – date of first dose + 1.
[2] Study day = Date of onset of AE – date of first dose + 1.

Programmer note: Sort by Site ID, Subject ID, AE Onset Date and AE Resolution Date. If hospitalized, add hospital admission and discharge day, i.e. 3 (Day xx-Day xx).

Listing 3.3.6
Glossary of System Organ Class, Preferred Term and Verbatim Term for Adverse Event
Safety Population

System Organ Class	Preferred Term	Verbatim Term
CARDIAC DISORDERS	ANGINA PECTORIS	ANGINA PECTORIS
	CARDIAC MURMUR NOS	HEART MURMUR
		CARDIAC MURMUR

3.4. CLINICAL LABORATORY MEASUREMENTS

Table 3.4.1
Shifts from Baseline to Post-baseline Laboratory Abnormality for Hematology Parameters
Safety Population

Laboratory Parameter: Hemoglobin (Unit)

Baseline Grade	Post-Baseline Highest Grade			
	Low	Normal	High	Missing
Low (N=xxx)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx
Normal (N=xxx)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx
High (N=xxx)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx
Any Grade (N=xxx)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx
Low (N=xxx)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx
Normal (N=xxx)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx
High (N=xxx)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx
Any Grade (N=xxx)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx

….Repeat Above for each laboratory test required within Hematology.

Baseline was the subject's last assessment prior to the initiation of study drug (Dose 1).
N = number of subjects who received the treatment and had data in the Baseline category with non-missing data Post-Baseline. n = number of subjects in baseline and post-baseline category. % = 100 x n/N.

Source: Listing 3.4.1.

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Post-hoc Table 3.4.1a
Shifts from Baseline to Post-baseline Laboratory Abnormality for Platelet Count
Safety Population

Programming Note: Follow the shell of 3.4.1.

Table 3.4.2
Shifts from Baseline to Post-baseline Laboratory Abnormality for Chemistry Parameters
Safety Population

Programmer note: Change Source footnote to Listing 3.4.2.

Post-hoc Table 3.4.3
Hematology Parameters of Special Interest: Platelet by Weight Subgroup
Safety Population

Hematology Parameter (unit) Visit Statistics	Subjects with Weight <= xx.x kg (N=XX)	Subjects with Weight > xx.x kg (N=XX)	Total (N=XX)
Platelet (10^9/L)			
Baseline			
Actual Value:			
Mean	xx.x	xx.x	xx.x
SD	xx.x	xx.x	xx.x
Median	xx	xx	xx
Min, Max	xx, xx	xx; xx	xx, xx
n	xxx	xxx	xxx
Day 7			
Actual Value:			
Mean	xx.x	xx.x	xx.x
SD	xx.x	xx.x	xx.x
Median	xx	xx	xx

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Min, Max	xx, xx	xx; xx	xx, xx
n	xxx	xxx	xxx
Change from Baseline:			
Mean	xx.x	xx.x	xx.x
SD	xx.x	xx.x	xx.x
Median	xx	xx	xx
Min, Max	xx, xx	xx; xx	xx, xx
n	xxx	xxx	xxx
… Day 14 …			
…			
…			
…			
… Day 21 …			
…			
… Day 28 …			
Day 56			
Repeat above for all other Hematology lab results			

Post-hoc Figure 3.4.4
Hematology Parameters of Special Interest: Platelet Count by Visit for Subjects with AE Platelet Count Decreased
Safety Population

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Listing 3.4.1
Laboratory Parameters – Hematology by Visit
Safety Population

Hematology Parameter: XXXXXXXXXXXX <unit>

Subject ID	Laboratory Name	Lab ID #	Visit	Date of Collection	Original Result	Original Unit	Standard Result	Change from Baseline [1]	Reference Range (Low – High)	Outside Normal Range (Y/N)
xxxxxx			Screening	yyyy-mm-dd	xx.x	xxxx	xxxx		0 - 5	
			Day 7	yyyy-mm-dd	xx.x	xxxx	xxxx		0 - 5	
			Day 14							
			Day 21							
			Day 28							
			Day 56							
			Unscheduled							

[1] Baseline was the subject's last assessment prior to the initiation of study drug (Dose 1).

Programmer note:
1. Order records by Parameter, subject number, and date of sample.
2. Repeat pages for all hematology parameters.

Listing 3.4.2
Laboratory Parameters – Chemistry by Visit
Safety Population

Programmer note: Similar to Listing 3.4.1.

Listing 3.4.3
Hematology Parameters of Special Interest: Platelet for these subjects with AE Platelet count decreased
Safety Population

Subject ID	Age/ Sex/ Race	Date of First/Last Dose	AE Onset/ Stop Date/Ongoing	CTCAE Grade / Relationship to IMP	SAE?/ TEAE?	Trt. Given	Outcome	Action Taken with Study Drug	Visit	Date of Collection	Platelet (10^9/L)
xxxxx	xx/x/x	yyyy-mm-dd/ yyyy-mm-dd	yyyy-mm-dd / ongoing	Severe/ **Not related**	Yes/Yes	**XXXX**	xxxxx	Dose Not Changed	Screening	yyyy-mm-dd	*xxxx*
									Day 7	yyyy-mm-dd	*xxxx*
									…	…	…

Post-hoc Listing 3.4.4
Hematology Parameters of Special Interest: Platelet Count by Visit for Subjects with AE Platelet Count Decreased
Safety Population

Programmer note: Similar to Listing 3.4.3.

Figure 3.4.3

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Platelet for these subjects with AE Platelet count decreased - Subject xxxx
Safety Population

VITAL SIGNS

Table 0.1
Descriptive Statistics for Vital Signs by Visit and Timepoint
Safety Population

Vital Sign Parameter (unit) Visit Statistics	Total (N=XX)
Temperature (°C)	
Screening	
Actual Value:	
Mean	xx.x
SD	xx.x
Median	xx
Min, Max	xx, xx
n	xxx
Day 0, 15 Minutes After Start of Infusion	
Actual Value:	
Mean	xx.x
SD	xx.x
Median	xx
Min, Max	xx, xx
n	xxx
Change from Baseline:	
Mean	xx.x
SD	xx.x
Median	xx
Min, Max	xx, xx
n	xxx
Day 0, Completion of Infusion	
…	
Day 0, 1 Hour After End of Infusion	
…	
Repeat for Days 7, 14, and 21 for the 3 timepoints above, and for Days 28, 56, 180, 365, and Unscheduled, with no time point.	
Repeat above for	
Heart Rate (beats/min)	
Systolic Blood pressure (mmHg)	
Diastolic Blood pressure (mmHg)	
Respiratory Rate (breaths/min)	

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Repeat for Screening, Days 0, 7, 14, 21, 28, 56, 180, 365, and Unscheduled, with no time point for

Weight (kg)

Repeat for Screening only, with no time point for

Height (cm)

Baseline was the subject's last assessment prior to the initiation of study drug.
N = number of subjects in the Safety Population.
n = number of subjects contributing to summary statistics.
SD = standard deviation.

Source: Listing 3.5.1.

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Listing 0.1
Vital Signs
Safety Population

Subject ID	Date of Assessment (Study Day)[1]	Visit	Time Point	Temperature (°C)	Heart Rate (beats/min)	Systolic Blood Pressure (mmHg)	Diastolic Blood Pressure (mmHg)	Respiratory Rate (breaths/min)	Weight (kg)	Height (cm)
xxxxxx	yyyy-mm-dd (xx)	Screening		xx.x	xxx	xxx	xx	xxx	xx.x	xx.x
		Day 0							xx.x	
			15 Minutes After Start of Infusion	xx.x	xxx	xxx	xx	xxx		
			Completion of Infusion	xx.x	xxx	xxx	xx	xxx		
			1 Hour After End of Infusion	xx.x	xxx	xxx	xx	xxx		
		Day 7							xx.x	
			15 Minutes After Start of Infusion	xx.x	xxx	xxx	xx	xxx		
			Completion of Infusion	xx.x	xxx	xxx	xx	xxx		
			1 Hour After End of Infusion	xx.x	xxx	xxx	xx	xxx		
		…								

[1] Assessment Day = date of assessment - first dose date of study drug + 1.

Programmer note: Include same visits and timepoints listed in table above.

3.5. ECG PARAMETERS

Listing 3.5.1
ECG Results by Visit
Safety Population

Subject ID	Age(yrs)/Sex/Race	Visit	Date of ECG Performed	Parameters (Units)	Results	Any Clinically Significant Abnormalities? (Yes/No)
xxxxxx	60/F/Caucasian	Screening	yyyy-mm-dd			No
		Day 28				
		Unscheduled				

M = Male, F = Female.

Programmer note: Include Heart Rate, PR Interval, RR Interval, QRS, QT, and QTc from CRF, and calculated QTcF.

3.6. OTHER SAFETY ASSESSMENTS

Listing 3.6.1
Pregnancy Test
Safety Population

Subject ID	Age(yrs)/Race	Visit	Performed? (Yes/No)	Pregnancy Test		
				Type	Date	Result
xxxxxx		Screening	Yes	Urine	yyyy-mm-dd	Positive
		Day 28		Serum		
		Unscheduled				

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Listing 3.6.2
Physical Examination
Safety Population

		Physical Examination		
Subject ID	Visit	Performed? (Yes/No)	If Yes, Date	Any Clinically Significant Abnormalities (Yes/No)
xxxxxx	Screening	Yes	yyyy-mm-dd	Yes
	Day 0			
	Day 28			
	Day 56			
	Day 180			
	Day 365			
	Unscheduled			

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Listing 3.6.3
Follow-up Telephone Call
Safety Population

Subject ID	Age(Yrs)/Sex/Race	Date of Call	Was subject contacted by telephone for follow-up?
xxxxxx		yyyy-mm-dd	Yes
xxx-xxx		yyyy-mm-dd	Yes

M = Male, F = Female.

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4. EFFICACY

4.1. PRIMARY EFFICACY ANALYSIS

Table 4.1.1
Lower GI aGVHD Treatment Response Rate at Day 28
Efficacy Evaluable Population

Response	Total (N=XX) n (%)	90% Exact Confidence Interval
Treatment Response	xx (xx.x)	(xx.x, xx.x)
Complete Response	xx (xx.x)	(xx.x, xx.x)
Very Good Partial Response	xx (xx.x)	(xx.x, xx.x)
Partial Response	xx (xx.x)	(xx.x, xx.x)
No Treatment Response	xx (xx.x)	(xx.x, xx.x)
No Response	xx (xx.x)	(xx.x, xx.x)
Progression	xx (xx.x)	(xx.x, xx.x)

Missing aGVHD treatment response was imputed as non-response for this analysis.
N = Number of subjects in the Efficacy Evaluable Population.
n = Number of subjects within a specific category. Percentages are calculated as 100 x (n/N).

Source: Listing 4.2.1

Post-hoc Table 4.1.1a
Lower GI aGVHD Treatment Response Rate at Day 28 by Risk Group
Efficacy Evaluable Population

	High Risk Group (N=xx)		Low Risk Group (N=xx)		Overall (N=xx)	
Response	Total (N=XX) n (%)	90% Exact Confidence Interval	Total (N=XX) n (%)	90% Exact Confidence Interval	Total (N=XX) n (%)	90% Exact Confidence Interval
Treatment Response	xx (xx.x)	(xx.x, xx.x)	xx (xx.x)	(xx.x, xx.x)	xx (xx.x)	(xx.x, xx.x)
Complete Response	xx (xx.x)	(xx.x, xx.x)	xx (xx.x)	(xx.x, xx.x)	xx (xx.x)	(xx.x, xx.x)
Very Good Partial Response	xx (xx.x)	(xx.x, xx.x)	xx (xx.x)	(xx.x, xx.x)	xx (xx.x)	(xx.x, xx.x)
Partial Response	xx (xx.x)	(xx.x, xx.x)	xx (xx.x)	(xx.x, xx.x)	xx (xx.x)	(xx.x, xx.x)
No Treatment Response	xx (xx.x)	(xx.x, xx.x)	xx (xx.x)	(xx.x, xx.x)	xx (xx.x)	(xx.x, xx.x)
No Response	xx (xx.x)	(xx.x, xx.x)	xx (xx.x)	(xx.x, xx.x)	xx (xx.x)	(xx.x, xx.x)
Progression	xx (xx.x)	(xx.x, xx.x)	xx (xx.x)	(xx.x, xx.x)	xx (xx.x)	(xx.x, xx.x)

Missing aGVHD treatment response was imputed as non-response for this analysis.
N = Number of subjects in the Efficacy Evaluable Population.
n = Number of subjects within a specific category. Percentages are calculated as 100 x (n/N).

Source: Listing 4.2.1

Post-hoc Table 4.1.1b
Lower GI aGVHD Treatment Response Rate at Day 28 by Risk Group and Weight Subgroup
Efficacy Evaluable Population

	High Risk Group (N=xx)				Standard Risk Group (N=xx)			
	Weight <= xxx kg		Weight > xxx kg		Weight <= xxx kg		Weight > xxx kg	
Response	Total (N=XX) n (%)	90% Exact Confidence Interval	Total (N=XX) n (%)	90% Exact Confidence Interval	Total (N=XX) n (%)	90% Exact Confidence Interval	Total (N=XX) n (%)	90% Exact Confidence Interval
Treatment Response	xx (xx.x)	(xx.x, xx.x)	xx (xx.x)	(xx.x, xx.x)	xx (xx.x)	(xx.x, xx.x)	xx (xx.x)	(xx.x, xx.x)
Complete Response	xx (xx.x)	(xx.x, xx.x)	xx (xx.x)	(xx.x, xx.x)	xx (xx.x)	(xx.x, xx.x)	xx (xx.x)	(xx.x, xx.x)
Very Good Partial Response	xx (xx.x)	(xx.x, xx.x)	xx (xx.x)	(xx.x, xx.x)	xx (xx.x)	(xx.x, xx.x)	xx (xx.x)	(xx.x, xx.x)

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Partial Response	xx (xx.x)	(xx.x, xx.x)	xx (xx.x)	(xx.x, xx.x)	xx (xx.x)	(xx.x, xx.x)	xx (xx.x)	(xx.x, xx.x)
No Treatment Response	xx (xx.x)	(xx.x, xx.x)	xx (xx.x)	(xx.x, xx.x)	xx (xx.x)	(xx.x, xx.x)	xx (xx.x)	(xx.x, xx.x)
No Response	xx (xx.x)	(xx.x, xx.x)	xx (xx.x)	(xx.x, xx.x)	xx (xx.x)	(xx.x, xx.x)	xx (xx.x)	(xx.x, xx.x)
Progression	xx (xx.x)	(xx.x, xx.x)	xx (xx.x)	(xx.x, xx.x)	xx (xx.x)	(xx.x, xx.x)	xx (xx.x)	(xx.x, xx.x)

Missing aGVHD treatment response was imputed as non-response for this analysis.
N = Number of subjects in the Efficacy Evaluable Population.
n = Number of subjects within a specific category. Percentages are calculated as 100 x (n/N).

Source: Listing 4.2.1

Post-hoc Figure 4.1 – Subject xxxxx
Lower GI aGVHD Treatment Response over Time

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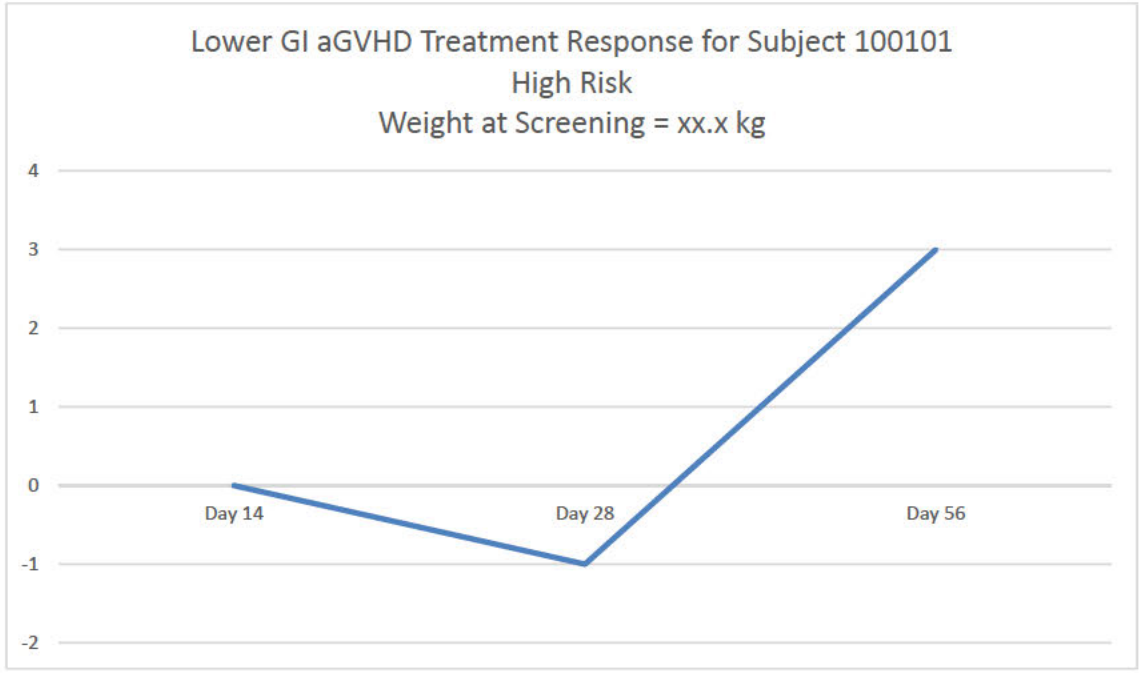

Add Legend: 3=Complete Response; 2=Very Good Partial Response; 1=Partial Response;

0=No Response; -1=Progression

4.2. SECONDARY EFFICACY ANALYSIS

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Table 4.2.1
Lower GI aGVHD Treatment Response Rate at Days 14 and 56
Efficacy Evaluable Population

Response	Total (N=XX) n (%)	90% Exact Confidence Interval
Day 14		
N1	xx	
Treatment Response	xx (xx.x)	(xx.x, xx.x)
Complete Response	xx (xx.x)	(xx.x, xx.x)
Very Good Partial Response	xx (xx.x)	(xx.x, xx.x)
Partial Response	xx (xx.x)	(xx.x, xx.x)
No Treatment Response	xx (xx.x)	(xx.x, xx.x)
No Response	xx (xx.x)	(xx.x, xx.x)
Progression	xx (xx.x)	(xx.x, xx.x)
Day 56		
N1	xx	
Treatment Response	xx (xx.x)	(xx.x, xx.x)
Complete Response	xx (xx.x)	(xx.x, xx.x)
Very Good Partial Response	xx (xx.x)	(xx.x, xx.x)
Partial Response	xx (xx.x)	(xx.x, xx.x)
No Treatment Response	xx (xx.x)	(xx.x, xx.x)
No Response	xx (xx.x)	(xx.x, xx.x)
Progression	xx (xx.x)	(xx.x, xx.x)

N = Number of subjects in the Efficacy Evaluable Population.
n = Number of subjects within a specific category. N1= Number of subjects with Lower GI aGVHD Treatment Response at the visit.
Percentages are calculated as 100 x (n/N1).
Source: Listing 4.2.1

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Pos-hoc Table 4.2.1a
Lower GI aGVHD Treatment Response Rate at Days 14 and 56 by Risk Group
Efficacy Evaluable Population

Pos-hoc Table 4.2.1b
Lower GI aGVHD Treatment Response Rate at Days 14 and 56 by Risk Group and Weight Subgroup
Efficacy Evaluable Population

Table 4.2.2
Overall aGVHD Treatment Response Rate at Days 14, 28, and 56
Efficacy Evaluable Population

Response	Total (N=XX) n (%)	90% Exact Confidence Interval
Day 14		
N1	xx	
Treatment Response	xx (xx.x)	(xx.x, xx.x)
Complete Response	xx (xx.x)	(xx.x, xx.x)
Very Good Partial Response	xx (xx.x)	(xx.x, xx.x)
Partial Response	xx (xx.x)	(xx.x, xx.x)
Mixed Response	xx (xx.x)	(xx.x, xx.x)
No Treatment Response	xx (xx.x)	(xx.x, xx.x)
No Response	xx (xx.x)	(xx.x, xx.x)
Progression	xx (xx.x)	(xx.x, xx.x)
Day 28		
N1	xx	
Treatment Response	xx (xx.x)	(xx.x, xx.x)
Complete Response	xx (xx.x)	(xx.x, xx.x)
Very Good Partial Response	xx (xx.x)	(xx.x, xx.x)
Partial Response	xx (xx.x)	(xx.x, xx.x)
Mixed Response	xx (xx.x)	(xx.x, xx.x)
No Treatment Response	xx (xx.x)	(xx.x, xx.x)
No Response	xx (xx.x)	(xx.x, xx.x)
Progression	xx (xx.x)	(xx.x, xx.x)
Day 56		
N1	xx	

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Treatment Response	xx (xx.x)	(xx.x, xx.x)
Complete Response	xx (xx.x)	(xx.x, xx.x)
Very Good Partial Response	xx (xx.x)	(xx.x, xx.x)
Partial Response	xx (xx.x)	(xx.x, xx.x)
Mixed Response	xx (xx.x)	(xx.x, xx.x)
No Treatment Response	xx (xx.x)	(xx.x, xx.x)
No Response	xx (xx.x)	(xx.x, xx.x)
Progression	xx (xx.x)	(xx.x, xx.x)

N = Number of subjects in the Efficacy Evaluable Population.
n = Number of subjects within a specific category. N1= Number of subjects with Overall aGVHD Treatment Response at the visit.
Percentages are calculated as 100 x (n/N1).
Source: Listing 4.2.1

Post-hoc Table 4.2.2a
Overall aGVHD Treatment Response Rate at Days 14, 28, and 56 by Risk Group
Efficacy Evaluable Population

Post-hoc Table 4.2.2b
Overall aGVHD Treatment Response Rate at Days 14, 28, and 56 by Risk Group and Weight Subgroup
Efficacy Evaluable Population

Table 4.2.3
Discontinuation of Immunosuppressive Medication at Day 180 and 1 Year Post Initial Dosing of F-652
Efficacy Evaluable Population

Discontinuation of Immunosuppressive Medication	Total (N=XX) n (%)	90% Exact Confidence Interval
Day 180		
N1	xx	
Yes	xx (xx.x)	(xx.x, xx.x)
No	xx (xx.x)	(xx.x, xx.x)
1 Year (Day 365)		
N1	xx	
Yes	xx (xx.x)	(xx.x, xx.x)
No	xx (xx.x)	(xx.x, xx.x)

N = number of subjects in the Efficacy Evaluable Population. N1 = number of subjects completed the visit.
n = Number of subjects within a specific category. Percentages are calculated as 100 x (n/N1).
Immunosuppresive medications were identified as those collected on the BMT/GVHD Medications CRF and categorized as Immunosuppressants.
Subjects who discontinued at Day 180 and at 1 year were defined as those who stopped all immunosuppressant medications that were being taken at or after the first dose of F-652.
Source: Listing 4.2.2

Table 4.2.4
Immune Recovery
Efficacy Evaluable Population

B and T Lymphocyte Parameter (unit) Visit Statistics	Total (N=XX)
ALC (Cell/mcL)	
Day 0	
Actual Value:	
Mean	xx.x
SD	xx.x
Median	xx
Min, Max	xx, xx
n	xxx
Day 28	
Actual Value:	
Mean	xx.x
SD	xx.x
Median	xx
Min, Max	xx, xx
n	xxx
Change from Baseline:	
Mean	xx.x
SD	xx.x
Median	xx
Min, Max	xx, xx
n	xxx
Repeat above for all other immune reconstitution panel parameters as listed in SAP section 6.3.3.	

ALC = Absolute Lymphocyte Count. PHA = Phytohemagglutinin-P.
N = number of subjects in the Efficacy Evaluable Population.
n = Number of subjects within a specific category. Percentages are calculated as 100 x (n/N).
Change from baseline values includes only those subjects with both Day 0 and Day 28 values.

Source: Listing 4.2.3.

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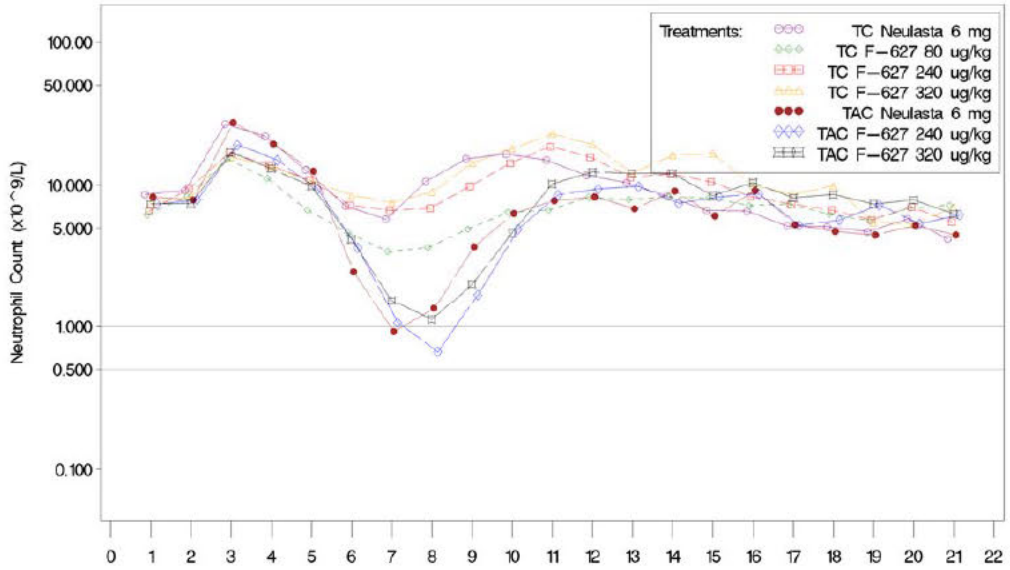
Figure 4.2.1
Mean Absolute Lymphocyte Count (ALC) Over Time
Efficacy Evaluable Population



Programmer note:
1. AXES: Display Day 0 and Day 28 on the X axis (label "Study Day"). Display value on the Y axis in log scale (label "[Name of Parameter] (Unit)"
2. LEGEND: REMOVE LEGEND
3. Graph should have one line.
3. Source: Listing 4.2.3

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Figure 4.2.2
Median Absolute Lymphocyte Count (ALC) Over Time
Efficacy Evaluable Population

Figure 4.2.3
Mean CD45+ Lymphocytes Over Time
Efficacy Evaluable Population

Figure 4.2.4
Median CD45+ Lymphocytes Over Time
Efficacy Evaluable Population

Figure 4.2.5
Mean CD3+ T cells Over Time
Efficacy Evaluable Population

Figure 4.2.6
Median CD3+ T cells Over Time
Efficacy Evaluable Population

Figure 4.2.7
Mean CD3+ Absolute Over Time
Efficacy Evaluable Population

Figure 4.2.8
Median CD3+ Absolute Over Time
Efficacy Evaluable Population

Figure 4.2.9
Mean CD3+4+8- T Subset Over Time
Efficacy Evaluable Population

Figure 4.2.10
Median CD3+4+8- T Subset Over Time
Efficacy Evaluable Population

Figure 4.2.11
Mean CD3+4+8- Absolute Over Time
Efficacy Evaluable Population

Figure 4.2.12
Median CD3+4+8- Absolute Over Time
Efficacy Evaluable Population

Figure 4.2.13

Mean CD4+45RA+ T Subset Over Time
Efficacy Evaluable Population

Figure 4.2.14
Median CD4+45RA+ T Subset Over Time
Efficacy Evaluable Population

Figure 4.2.15
Mean CD4+45RA+ Absolute Over Time
Efficacy Evaluable Population

Figure 4.2.16
Median CD4+45RA+ Absolute Over Time
Efficacy Evaluable Population

Figure 4.2.17
Mean CD3+4-8+ T Subset Over Time
Efficacy Evaluable Population

Figure 4.2.18
Median CD3+4-8+ T Subset Over Time
Efficacy Evaluable Population

Figure 4.2.19
Mean CD3+4-8+ Absolute Over Time
Efficacy Evaluable Population

Figure 4.2.20
Median CD3+4-8+ Absolute Over Time
Efficacy Evaluable Population

Figure 4.2.21
Mean CD3+4+8+ T Subset Over Time
Efficacy Evaluable Population

Figure 4.2.22
Median CD3+4+8+ T Subset Over Time
Efficacy Evaluable Population

Figure 4.2.23
Mean CD3+4+8+ Absolute Over Time
Efficacy Evaluable Population

Figure 4.2.24

Report generated by program: /sasdir/xxxx.sas

Median CD3+4+8+ Absolute Over Time
Efficacy Evaluable Population

Figure 4.2.25
Mean CD3+4-8- T Subset Over Time
Efficacy Evaluable Population

Figure 4.2.26
Median CD3+4-8- T Subset Over Time
Efficacy Evaluable Population

Figure 4.2.27
Mean CD3+4-8- Absolute Over Time
Efficacy Evaluable Population

Figure 4.2.28
Median CD3+4-8- Absolute Over Time
Efficacy Evaluable Population

Figure 4.2.29
Mean CD3-19+ B cells Over Time
Efficacy Evaluable Population

Figure 4.2.30
Median CD3-19+ B cells Over Time
Efficacy Evaluable Population

Figure 4.2.31
Mean CD3-19+ Absolute Over Time
Efficacy Evaluable Population

Figure 4.2.32
Median CD3-19+ Absolute Over Time
Efficacy Evaluable Population

Figure 4.2.33
Mean CD3-56+16+ NK cells Over Time
Efficacy Evaluable Population

Figure 4.2.34
Median CD3-56+16+ NK cells Over Time
Efficacy Evaluable Population

Figure 4.2.35

Mean CD3-56+16+ Absolute Over Time
Efficacy Evaluable Population

Figure 4.2.36
Median CD3-56+16+ Absolute Over Time
Efficacy Evaluable Population

Figure 4.2.37
Mean CD3+56+16+ NKT cells Over Time
Efficacy Evaluable Population

Figure 4.2.38
Median CD3+56+16+ NKT cells Over Time
Efficacy Evaluable Population

Figure 4.2.39
Mean CD3+56+16+ Absolute Over Time
Efficacy Evaluable Population

Figure 4.2.40
Median CD3+56+16+ Absolute Over Time
Efficacy Evaluable Population

Figure 4.2.41
Mean CD3+4+8-/CD3+4-8+ Ratio Over Time
Efficacy Evaluable Population

Figure 4.2.42
Median CD3+4+8-/CD3+4-8+ Ratio Over Time
Efficacy Evaluable Population

Figure 4.2.43
Mean PHA (Phytohemagglutinin-P)Over Time
Efficacy Evaluable Population

Figure 4.2.44
Median PHA (Phytohemagglutinin-P)Over Time
Efficacy Evaluable Population

Report generated by program: /sasdir/xxxx.sas

Table 4.2.6
Overall Survival
Efficacy Evaluable Population

Response	Statistic	Total (N=XX)
Time to Death (Days)	Subjects with the Event	xx (xx.x%)
	Censored	xx (xx.x%)
	Median Time to Response	xxx.x
	90% CI for Median	(xxx.x, xxx.x)
	25th – 75th Percentile	xxx, xxx
	Min – Max	xxx, xxx
	Survival rate (90% CI)	
	Day 28	xx (xx.x%, xx.x%)
	Day 56	xx (xx.x%, xx.x%)
	Day 180	xx (xx.x%, xx.x%)
	Day 365	xx (xx.x%, xx.x%)

N = number of subjects in the Efficacy Evaluable Population.
n = Number of subjects within a specific category. Percentages are calculated as 100 x (n/N).
Time to death is the number of days from the date of the first infusion of F-652 to the date of death (Date of death – Date of first infusion +1) for subjects who die. Subjects who did not die were censored with survival time based on the subject's study completion or discontinuation date (Date of completion/discontinuation – Date of first infusion +1).
Summary statistics are Kaplan-Meier estimates.

Source: Listing 4.2.4.

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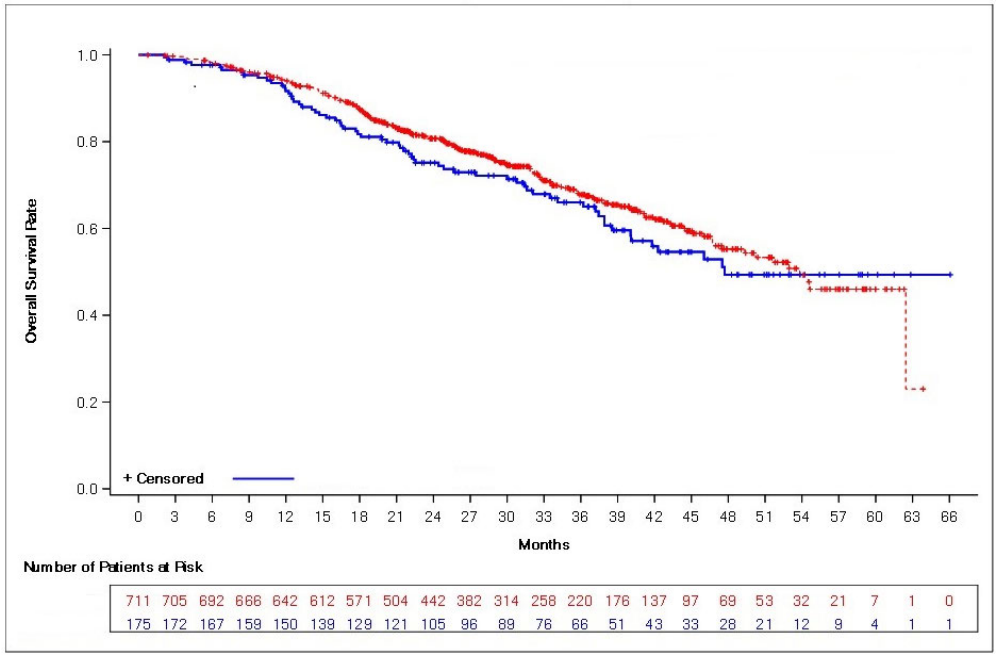
Figure 4.2.45
Kaplan-Meier Plot for Overall Survival
Efficacy Evaluable Population



Programmer note:
1. AXES: Display Days on the X axis, from 0 to 365 (label "Study Day"). Display Overall Survival Rate on the Y axis (label "Overall Survival Rate")
2. LEGEND: No Legend
3. Graph should have one line.
3. Number of Patients at Risk- Change to Number of Subjects. Only include one row of numbers.
3. Source: Listing 4.2.4

Post-hoc Table 4.23.1
Maintenance of Lower GI aGVHD Response at Day 56 in High Risk Group
Efficacy Evaluable Population

Response at Day 28	Treatment Response n (%)	CR n (%)	VGPR n (%)	PR n (%)	NR n (%)	Progression n (%)	Missing n
Treatment Response (N1 = XX)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx
Complete Response (N1 = XX)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx
Very Good Partial Response (N1 = XX)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx
Partial Response (N1 = XX)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx

CR = Complete Response; VGPR = Very Good Partial Response; PR = Partial Response; NR = No Response.
N1 = number of subject with the response at Day 28 who were not missing a response at Day 56.
n = Number of subjects who maintained response at day 56.
Percentages are calculated as 100 x (n/N1)

Post-hoc Table 4.23.2
Maintenance of Lower GI aGVHD Response at Day 56 in Standard Risk Group
Efficacy Evaluable Population

Response at Day 28	Treatment Response	CR n (%)	VGPR n (%)	PR n (%)	NR n (%)	Progression n (%)	Missing n

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	n (%)						
Treatment Response (N1 = XX)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx
Complete Response (N1 = XX)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx
Very Good Partial Response (N1 = XX)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx
Partial Response (N1 = XX)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx

CR = Complete Response; VGPR = Very Good Partial Response; PR = Partial Response;
N1 = number of subject with the response at Day 28 who were not missing a response at Day 56.
n = Number of subjects who maintained response at day 56.
Percentages are calculated as 100 x (n/N1)

Listing 4.2.1
aGVHD Treatment Response by Visit
Efficacy Evaluable Population

Subject ID	Age(yrs)/Sex/Race	Visit	Date of Assessment	Was GVHD Treatment Response Assessed? (Yes/No)	Lower GI aGVHD Treatment Response	Overall aGVHD Treatment Response
xxxxxx	60/F/Caucasian	Day 14	yyyy-mm-dd	Yes	CR	PR
		Day 28				
		Day 56				
		Unscheduled				

CR = Complete Response. VGPR = Very Good Partial Response. PR = Partial Response. MR = Mixed Response. NR = No Response. M = Male, F = Female.

Listing 4.2.2
Discontinuation of Immunosuppressive Medication
Efficacy Evaluable Population

Subject ID	Age(yrs)/Sex/Race	Drug Name	Start Date/ Stop Date/ Study Day [1]	Discontinuation at Day 180? (Yes/No)	Discontinuation at Day 365? (Yes/No)
xxxxxx	60/F/Caucasian		yyyy-mm-dd/ yyyy-mm-dd/ 5	No	Yes

M = Male, F = Female.
[1] Study Day = Date of interest – date of first dose of study drug + 1.

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Listing 4.2.3
Immune Recovery by Visit
Efficacy Population

B and T Lymphocyte Parameter: XXXXXXXXXXX <unit>

Subject ID	Laboratory Name	Lab ID #	Visit	Date of Collection	Result	Unit	Change from Baseline [1]
xxxxxx			Day 0	yyyy-mm-dd	xx.x	xxxx	
			Day 28	yyyy-mm-dd	xx.x	xxxx	

[1] Baseline was the subject's Day 0 value.

Programmer note:
1. Order records by Parameter, subject number, and date of sample.
2. Repeat pages for all B and T Lymphocyte parameters.

Listing 4.2.4
Overall Survival
Efficacy Evaluable Population

Subject ID	Age(yrs)/Sex/Race	Date of First Dose of F-652	Did Subject Die? (Yes/No)	If Subject Died, Date of Death (Study Day) [1]	If Subject Did Not Die, Date of Study Completion/Discontinuation (Study Day) [2]
xxxxxx	60/F/Caucasian	yyyy-mm-dd	Yes	yyyy-mm-dd (xx)	yyyy-mm-dd (xx)

[1] Study Day is the number of days from the date of the first infusion of F-652 to the date of death (Date of death – Date of first infusion +1) for subjects who die.
[2] Study Day is the number of days from the date of the first infustion of F-652 to the date of study completion or discontinuation (Date of completion/discontinuation – Date of first infusion +1) for subjects who do not die.
M = Male, F = Female.

Programmer note: One record per subject for all subjects.

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Post-hoc Listing 4.2.5
Lower GI aGVHD Response in High Risk Group
Efficacy Evaluable Population

Subject ID	Age(yrs)/Sex/Race	Days since Diagnosis	Weight (kg)	Number of Doses Received	Analysis Visit	Response Category
		xx	xx	4		Complete Response
xxxxxx	60/F/Caucasian				Day 14	
					Day 28	Partial Response
					Day 56	
						Etc.

M = Male, F = Female.

Additional Analysis(Just run the SAS procedure and saved the outputs as lst):
1. Run a SAS model with response variable = WK28 response category (continuous -1 to 3 with 0=No Response), independent variables Days since Diagnosis, Weight (kg), Number of Doses Received – see if anything is significant;
2. Run a MMRM model with response variable = response (continuous -1 to 3 with 0=No Response), independent variables Visit (Day 14, 28, 56), Days since Diagnosis, Weight (kg), Number of Doses Received – see if anything is significant;

Post-hoc Listing 4.2.6
Lower GI aGVHD Response in Subjects with a Treatment Response that Subsequently Lost the Response
Efficacy Evaluable Population

Subject ID	Age(yrs)/Sex/Race	Visit	Date of Assessment	Lower GI aGVHD Treatment Response	Overall aGVHD Treatment Response
xxxxxx	60/F/Caucasian	Day 14	yyyy-mm-dd	CR	PR

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Day 28

Day 56

Unscheduled

CR = Complete Response; VGPR = Very Good Partial Response; PR = Partial Response; MR = Mixed Response; NR = No Response.
M = Male, F = Female.

Programming notes:
Similar to Listing 4.2.1

[redacted]

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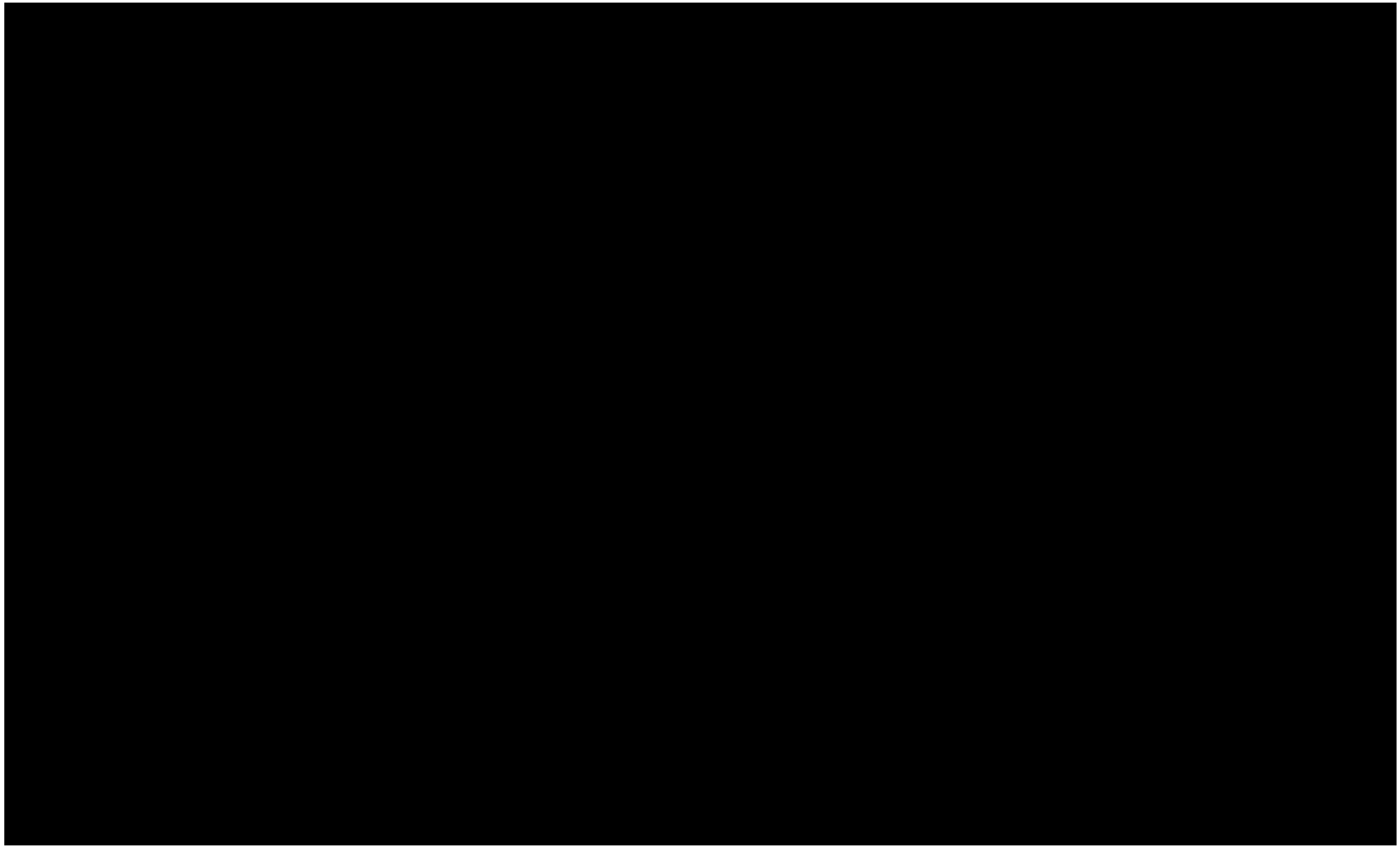
6 [redacted]



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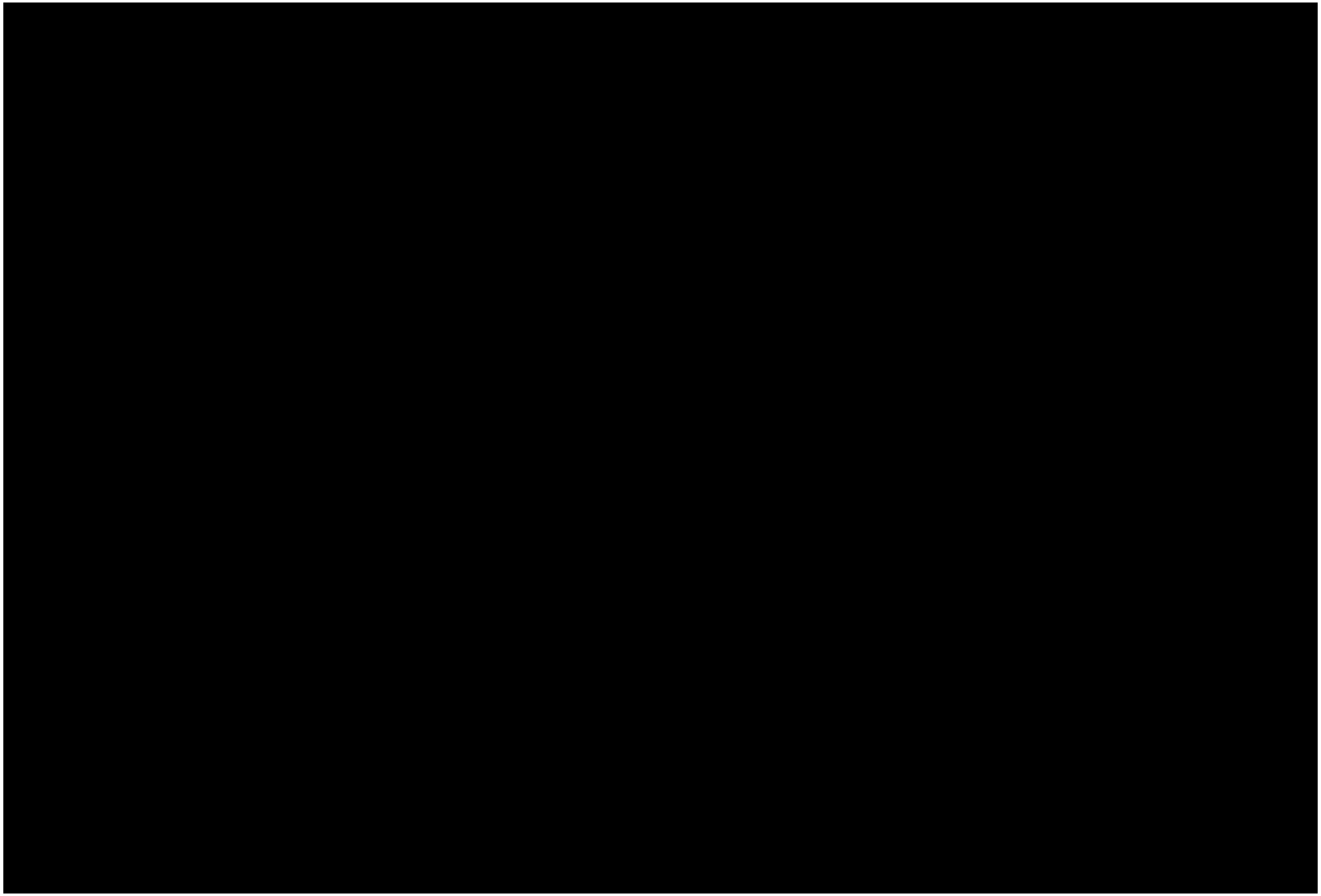

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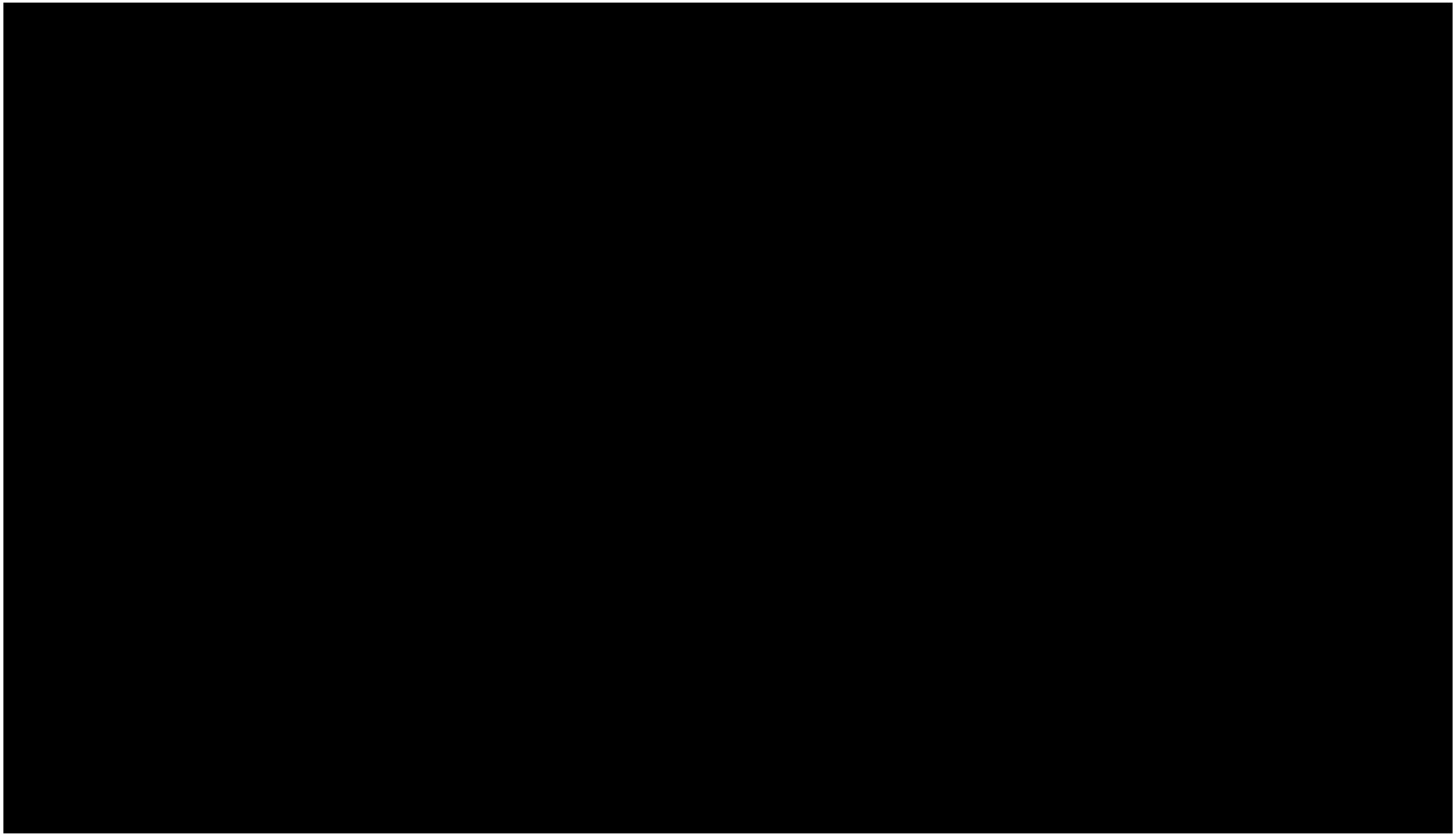

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Statistical Analysis Plan
Protocol Number: GC-652-02

STATISTICAL ANALYSIS PLAN

Trial Sponsor: Generon (Shanghai) Corporation Ltd.
Protocol Number: GC-652-02
IND Number: [redacted]
Investigational Drug: F-652
Indication: Gastrointestinal Graft versus Host Disease

Dosage Form/Strength F-652, 45 µg/kg IV

Protocol Title: A Phase IIa Study of Recombinant Human Interleukin-22 IgG2-Fc (F-652) in Combination with Systemic Corticosteroids for the Treatment of Newly Diagnosed Grade II-IV Lower Gastrointestinal Acute Graft-versus-Host Disease (aGVHD) in Hematopoietic Stem Cell Transplantation Recipients

Last Revision Date: 07 October 2019
Version: 1.0
Final Sign-off Date:
Archive Date:

EVEREST CLINICAL RESEARCH

Statistical Analysis Plan
Protocol Number: GC-652-02

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Generon (Shanghai) Corporation

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09 Oct 2019 — Date

Statistical Analysis Plan
Protocol Number: GC-652-02

Change Log for Changes Made after the Initial Approval

Revision Date**	Section(s)Modified	Brief Description of Revision(s) or Reason(s) for Revision	Modifications Reviewed and Approved by*
			Sponsor, Everest

* Provide person's initial and last name.

** Update the Last Revision Dates on the cover page and the document header.

Statistical Analysis Plan
Protocol Number: GC-652-02

TABLE OF CONTENTS

GLOSSARY OF ABBREVIATIONS

Abbreviation	Term
aGVHD	Acute Graft-versus-Host Disease
AE	Adverse event
ANC	Absolute neutrophil count
AUC	Area under the curve
BLOQ	Below the limit of quantitation
BMI	Body mass index
BMT	Bone marrow transplant
BPM	Beats per minute
BSA	Body surface area
C_{max}	Concentration Maximum
CBC	Complete Blood Count
CI	Confidence interval
C_L	Clearance
CMV	Cytomegalovirus
CR	Complete response
eCRF	Electronic Case Report Form
CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
ECG	Electrocardiogram
GI	Gastrointestinal
HSCT	Hematopoietic Stem Cell Transplantation
IBMTR	International Bone Marrow Transplant Registry
IV	Intravenous
IWRS	Interactive Web-based Response System
λ_z	Elimination half-life

Abbreviation	Term
MedDRA	Medical Dictionary for Regulatory Activities
MR	Mixed response
NCA	Non-compartmental analysis
NCI	National Cancer Institute
NR	No response
OTC	Over-the-counter
PE	Physical examination
PK	Pharmacokinetics
PR	Partial response
PT	Preferred term
QA	Quality assurance
QC	Quality control
QTcF	Fridericia corrected QT interval
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SI units	International System of Units
SOC	System organ class
SOP	Standard operating procedure
TEAE	Treatment Emergent Adverse Event
TRM	Transplant-related mortality
V_d	Volume of distribution
VGPR	Very good partial response
VS	Vital signs
WHO-DD	World Health Organization Drug Dictionary

Statistical Analysis Plan
Protocol Number: GC-652-02

1. INTRODUCTION

This Statistical Analysis Plan (SAP) outlines the statistical methods for the display, summary and analysis of data collected within the scope of Generon (Shanghai) Corporation Ltd. protocol GC-652-02, Protocol Amendment 4.0 dated May 30, 2017. The purpose of this plan is to provide general guidelines from which the analysis will proceed. Nevertheless, deviations from these guidelines must be substantiated by a sound statistical rationale.

The SAP should be read in conjunction with the study protocol and the Case Report Forms (CRFs). This version of the SAP has been developed using the final version of the protocol mentioned above and the study CRFs, Version 4.

This is a Phase IIa open label single arm study to investigate the safety, efficacy, and pharmacokinetics (PK) of F-652 (recombinant human IL-22), administered as an intravenous (IV) infusion once a week for a total of 4 doses at 45 μg/kg, in combination with systemic corticosteroids for the treatment of newly diagnosed grade II-IV lower gastrointestinal (GI) acute graft-versus-host disease (aGVHD) in Hematopoietic Stem Cell Transplantation (HSCT) recipients.

2. STUDY OBJECTIVES AND ENDPOINTS

2.1 Study Objective

The objective of the study is to assess the safety, efficacy and PK of F 652 in combination with systemic corticosteroids for the treatment of newly diagnosed grade II-IV lower GI aGVHD in HSCT recipients. GVHD cytokines and biomarkers will be explored.

2.2 Safety Endpoints

The safety endpoints of this study are the following:

- Adverse event (AE) reporting
- Vital sign (VS) measurements
- Laboratory measurements
- Physical Examination (PE)

2.3 Primary Efficacy Endpoint

- To assess the lower GI aGVHD treatment response rate at Day 28.

2.4 Secondary Efficacy Endpoints

- Lower GI aGVHD treatment response at Days 14 and 56 categorized by complete response (CR), very good partial response (VGPR), partial response (PR), no response (NR)/stable, and progression.
- Overall aGVHD treatment response at Days 14, 28, and 56 categorized by CR, VGPR, PR, mixed response (MR), NR, and progression.
- Discontinuation of immunosuppressive medication at Day 180 and 1 year post initial dosing of F-652.
- Characteristics of immune reconstitution after F-652 treatment.
- Overall survival at 1 year after first infusion of F-652.

2.5 [redacted]

2.6 [redacted]

3. STUDY DESIGN

3.1 Study Design

This Phase IIa open label single arm study will enroll up to 27 subjects to investigate the safety, efficacy, and PK of F-652 (recombinant human IL-22) in combination with systemic corticosteroids for the treatment of newly diagnosed grade II-IV lower GI aGVHD in HSCT recipients. Acute GVHD will be initially diagnosed clinically and staged accordingly.[1] Grading of aGVHD will be based on International Bone Marrow Transplant Registry (IBMTR) criteria[2]. This clinical trial will investigate if the use of F-652 enhances the recovery of the GI tract after aGVHD mediated-injury. The safety endpoints of this study are to assess the incidence of AEs and serious adverse events (SAE), along with other safety. The primary efficacy endpoint is to assess F-652 treatment response at Day 28 in subjects with lower GI aGVHD.

Candidates for this trial will include subjects ≥18 years and ≤80 years of age who are recipients of allogeneic HSCT using bone marrow, peripheral blood stem cells, or umbilical cord blood. Subjects must have stage 1-4 aGVHD of the lower GI tract at screening which will be determined by the maximum stool output in the preceding 3 days. Subjects with concurrent involvement of liver or skin aGVHD will be allowed but not as the sole organ affected. Biopsy of the GI tract is required for GVHD confirmation; however, results are not needed to initiate treatment. If GVHD is not confirmed histologically, treatment with F-652 will be discontinued and the subject will be replaced.

Eligible subjects will be consented and enter the study screening period. During this period, screening samples and tests will be obtained. A GI biopsy will be performed (if not done prior to study entry) for aGVHD disease histologic confirmation. The first dose of F-652 is to occur within 5 days after the subject's initial administration of systemic corticosteroids.

The expected duration of treatment for each subject is 4 weeks. F-652 weekly will be administered once a week for a total of 4 doses. Study enrollment will begin with 16 subjects dosed at 45 μg/kg of F-652. These subjects will be evaluated for treatment response at Day 28. If ≤6 of the first 16 subjects demonstrate a treatment response (i.e., response ≥PR), the clinical trial will be closed due to a lack of

efficacy. If 7 or more subjects of the first 16 subjects have a treatment response, an additional 11 subjects will be required to complete enrollment into the study for a total sample size of 27 subjects (Figure 1).

All subjects will be followed for efficacy through Day 56, safety through Day 180, and subject survival status will be collected at Day 365 (1 year from the date of initial dosing of F-652).

Prior to each dosing of F-652, subjects are required to meet the following criteria: absolute neutrophil count (ANC) $\geq 500/mm^3$, serum creatinine ≤ 3.0 mg/dl, and all non-hematologic toxicity (except alopecia) attributed to the study drug as probable or greater to resolved to $\leq$ Grade 1 or returned to the subject's baseline condition. Failure to meet these criteria will result in treatment delay, dose reduction, or withdrawal from the study, as outlined in Protocol Section 3.3.2 (Hold and Stop Rules). A review of excess subject mortality at Day 56 will occur for every 6 subjects accrued into the study.

During the course of the study, systemic corticosteroids (prednisone or methylprednisolone equivalent) will be administered concurrently with F-652. Tapering of corticosteroids is permitted as outlined in Protocol Section 5.2 (Treatment Administrations); however, tapering should result in no less than 0.25 mg/kg/day of prednisone (or IV equivalent) by Day 28, after which tapering may be according to local institutional guidelines.

All subjects should be treated to the institutional allogeneic bone marrow transplant (BMT) standard of care guidelines for prophylaxis against infection. This includes, *Pneumocystis carinii*, Herpes simplex, Herpes Zoster, and fungal infections. Subjects will be closely monitored for cytomegalovirus (CMV) reactivation according to the each local center standard practice.

The study drug will be administered on an inpatient or outpatient basis, depending on the subject's clinical condition. The route of administration of F-652 is IV and will be administered once a week on Days 0, 7, 14, and 21. Following infusion of F-652, vital signs will be obtained and nursing assessment will be performed according to the BMT institutional standard of care. PK sampling will occur as per the schedule listed in the Protocol in Appendix 3 and serum samples to test the immunogenicity of F-652 will be taken. Subjects will be evaluated for grade 3-4 toxicities, graded by the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE). A complete description of the study procedures for each clinical visit is presented in the Protocol in Appendix 1.

GVHD biomarkers will be assessed at baseline and post-treatment. Baseline assessment of GVHD markers in the peripheral blood and GI tissue will be performed at the time of GVHD diagnosis, pending specimen availability. Due to the extensive processing of the peripheral blood for the assessment of GVHD cytokine markers, cytokine samples are optional for subjects participating in this study. The biomarker panel will include ST2 and REG3α whereas the cytokine panel will include IL-21, IL-22, and IL-23 levels. A stool sample will be collected for intestinal microbiota analysis and GVHD biology, including histology and epithelial gene expression, will also be analyzed in biopsy samples from the GI tract as the specimen allows. Post-treatment evaluation of GVHD biomarkers/cytokines in the peripheral blood, stool sample for intestinal microbiota, and GI tract biopsies will be performed approximately 28 days after study drug initiation or at least 3 days after receiving last dose of study drug (subject and sample availability permitting). Sampling may be withheld in subjects who are critically ill.

A study visit schematic is provided in Figure 2 and a complete schedule of study procedures and events are presented in Section 1.1 (Schedule of Procedures and Events).

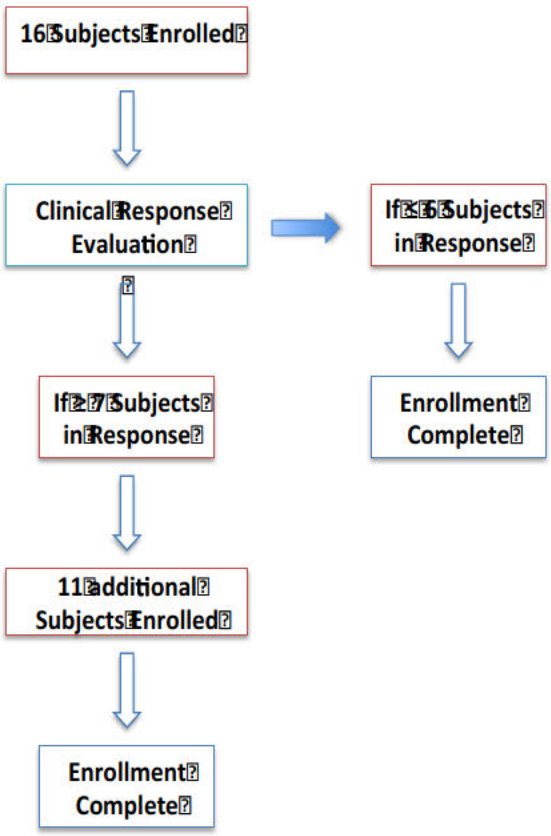
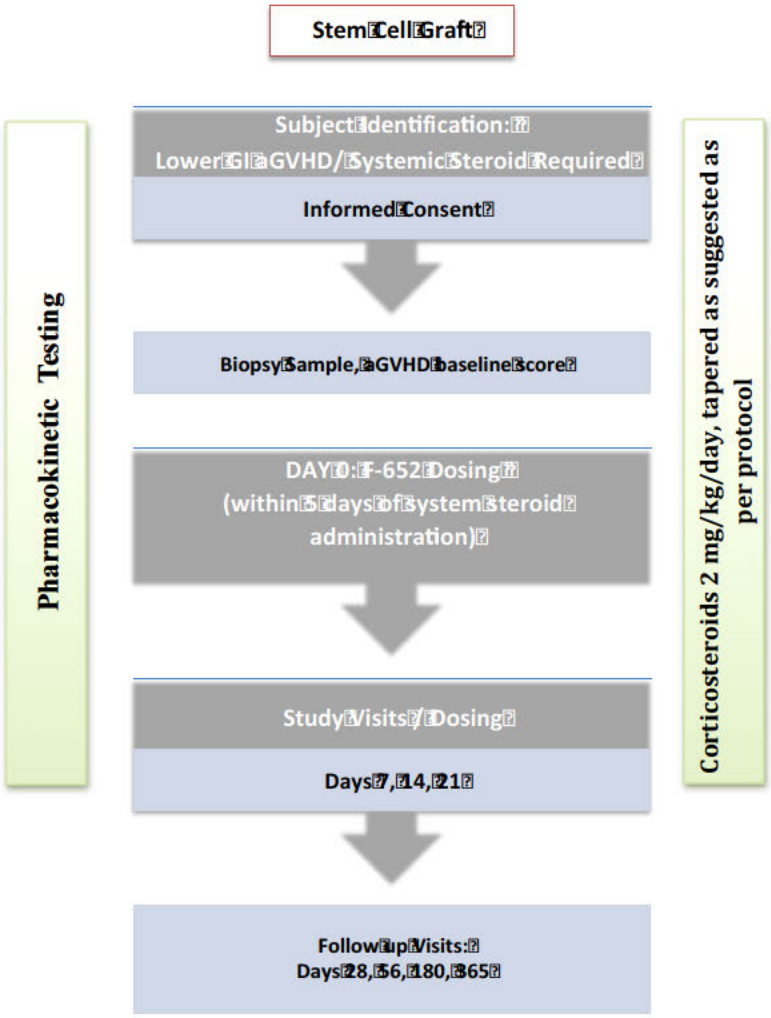


Figure 1 Study Enrollment Schematic



aGVHD = acute Graft-versus-Host Disease; F-652 = recombinant human interleukin-22 IgG2-Fc (F-652); GI = gastrointestinal

Figure 2 Study Visit Schematic

3.2 Schedule of Procedures and Events

Table 1 Schedule of Assessments

Assessments	Screening	Day 0	Day 7	Day 14	Day 21	Day 28*	Day 56	Day 180	Day 365
Window for visit (days)	(5) days		(±) 2	(±) 2	(±) 2	(±) 4	(±) 14	(±) 30	(±) 30
Signing of Informed Consent	X								
Relevant Medical History	X						X	X	X
Body Temperature, Weight, Vital Signs (BP, heart rate, respiratory rate)	X	X	X	X	X	X	X	X	X
Physical examination	X	X				X	X	X	X
CBC[1]	X		X	X	X	X	X		
Blood chemistry[1]	X		X	X	X	X	X		
Urinalysis	X					X			
Immune recovery (per institutional standard)[2]		X				X			
Serum for F-652 antibody testing (pre dosing of F-652)		X	X	X	X	X	X		
ECG	X					X			
Stool C. *Difficile* testing (if not done within 7 days)	X								
Stool microbiota test	X					X			
Pregnancy test[3]	X								
Current therapy and concomitant medications[4]	X	X	X	X	X	X	X	X	X
GI Biopsy[5]	X					X			
[redacted] (see additional schedule)		X	X	X	X	X	X		
Administration of F-652[7] (within 5 days of consent)		X	X	X	X				
Collection of AEs and toxicity assessment[8]	X	X	X	X	X	X	X		
aGVHD blood research samples (cytokine samples optional)		X				X			
Skin biopsy, subject permitting or if skin rash develops during treatment	X			X		X			
GVHD treatment response				X		X	X		
aGVHD evaluation	X		X	X	X	X	X	X	X

Abbreviations: AE = adverse event; aGVHD = acute graft-versus-host disease; BP = blood pressure; CBC = complete blood count; ECG = electrocardiogram; F-652 = recombinant human interleukin-22-IgG2-Fc; GI = gastrointestinal; GVHD = graft-versus-host disease; PK = pharmacokinetics.* End of treatment visit

[1] Blood samples are taken predose at Screening and Days 7, 14, 21, 28, and 56, and at 72 hours post-dose for CRP determination only at Screening and Days 7, 14, and 21.
[2] Immune recovery assessed on Day 0 as baseline and Days 28, post initial dose of F-652. Testing can be withheld if the subject has very low circulating white blood cells.
[3] For females with reproductive potential, serum test.

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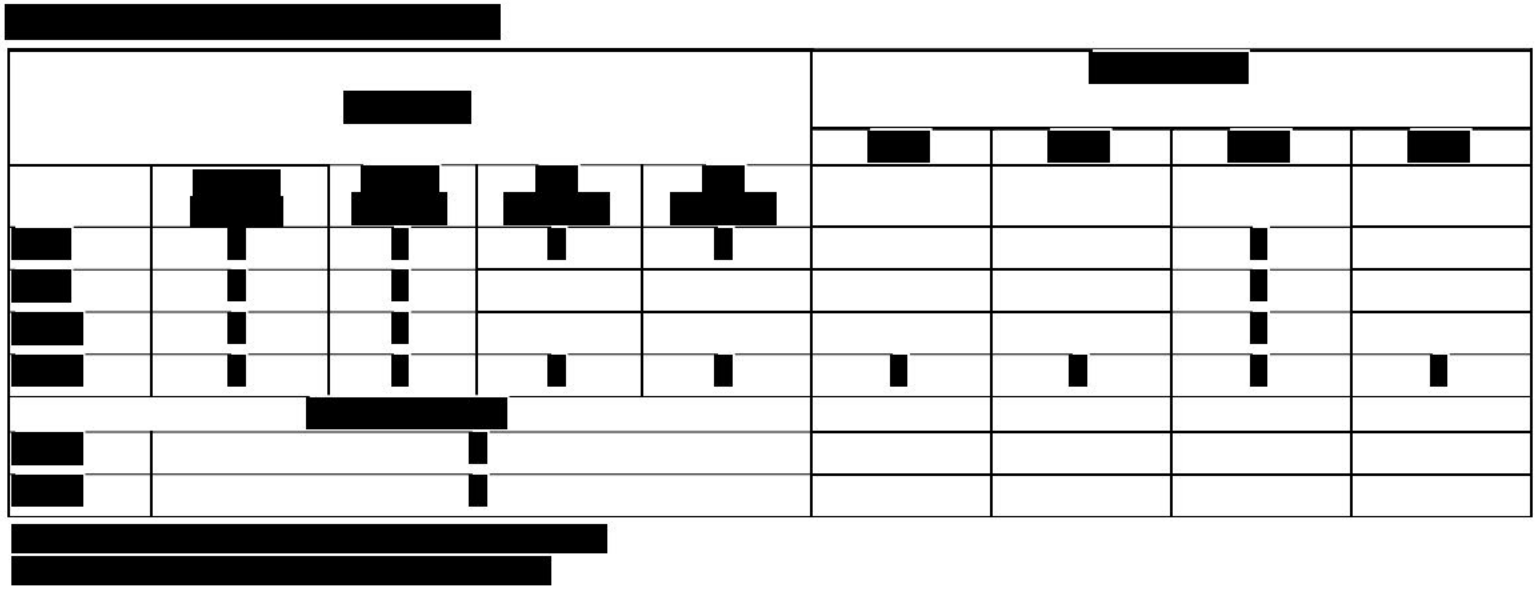
[4] Concomitant medications will be collected at each visit, scheduled or unscheduled. Collection of concomitant medications after Day 56 is required only for subjects with reported SAEs.
[5] Screening: for those subjects where no previous biopsy sample has been taken for GVHD confirmation. Day 28 Biopsy: subject permitting.
[6] See schedule for details**Error! Reference source not found.**.
[7] IV solution prepared per protocol.
[8] Collected at each scheduled or unscheduled visit. All AEs will be collected and documented on the study eCRF page through Study Day 56 (28 days after last dosing of F-652). After Study Day 56, only SAEs deemed possibly, probably, or definitely related to the investigational product are recorded through to the end of the study (Day 365).



3.3 Randomization

There is no randomization as this is a single arm study. An Interactive Web-based Response System (IWRS) with a 24-hour live support help desk will be used to assign subject numbers and to assign study drug. Authorized study site personnel will access the web-based system using a user ID and password. Prior training and a user's manual will be provided to all the study participating sites.

3.4 Hypothesis Testing

In this exploratory Phase IIa study, all statistical tests will be two-sided with no adjustment for multiplicity. All statistical tests and confidence intervals (CI) will use a Type I error rate of 10%. No adjustment will be made for multiple testing.

3.5 Interim Analysis

No interim analysis is planned for this study.

3.5.1 Hold and Discontinuation Rules for the Clinical Trial

Subjects will be closely monitored for clinical deterioration (i.e., disease progression) by the study Investigators, the study Medical Monitor, and the Sponsor's medical expert. In addition to standard toxicities such as alterations in blood chemistries or hematology, this monitoring will also include disease progression and treatment efficacy.

Clinical Trial Termination:

The study includes stopping criteria in the event that excessive Day 56 TRM is observed. The historical rate of TRM deaths is approximately 15-20%.[3] A TRM of 40% at Day 56 would be considered unexpected and an unacceptable number of excess deaths. TRM is defined as death at any time from the commencement of pre-transplant conditioning due to any cause other than disease relapse with the exception of automobile or other accidents.

In this study, there will be an ongoing review for excessive TRM. The study will be stopped for interim evaluation if the number of deaths is 3 or more in the first 5 subjects treated, 4 or more in the first 9 subjects treated, etc. as per Table 3. This evaluation will occur for the subject's Day 56 visit (post their initial F-652 dosing). Subjects removed from the study due to negative biopsy for aGVHD will not be accountable for the mortality rate rule analysis.

Table 3 Stopping criteria for excessive mortality based on a Pocock boundary

Failure Type	Mortality Rate Rule for Study Termination	Death rate in the population	Probability boundary is crossed
Transplant-Related Mortality (day +56)	3 deaths in the first 5 subjects treated	0.15	0.10
	4 deaths in the first 9 subjects treated		
	5 deaths in the first 13 subjects treated	0.40	0.93

	6 deaths in the first 18 subjects treated		
	7 deaths in the first 23 subjects treated		
	8 deaths at any point		

From Ivanova A, Qaqish BF and Schell MJ (2005).[4]

3.6 Sample Size

This study is designed to distinguish between an unpromising Day+28 treatment response rate (Lower GI aGVHD treatment response of Partial Response or better) of 35% and a promising treatment response rate of 60% using a Simon's two-stage optimal design. With a maximum sample of 27 subjects, this study has a type I error of 0.10 and a type II error of 0.10.

4. DATA AND ANALYTICAL QUALITY ASSURANCE

The overall quality assurance (QA) procedures for the study data, statistical programming and analyses are described in the Everest's Standard Operating Procedures (SOPs). Detailed statistical and programming quality control (QC) and QA procedures are documented in the Statistical Analysis and Programming QC/QA Plan.

The study endpoints and analytic approaches are both prospectively defined and documented in the protocol and in this SAP finalized prior to the database lock and data analysis.

5. ANALYSIS POPULATIONS

5.1 Safety Population

All enrolled subjects receiving any study treatment will be included in the Safety Population, which will be used for all safety analyses.

5.2 Efficacy Evaluable Population

All subjects who are eligible and have any post-treatment GVHD evaluation (not strictly limited to treatment response) or have disease progression before a GVHD evaluation can be performed will be included in the Efficacy Evaluable Population, which will be used for all efficacy analyses. Missing aGVHD treatment response will be imputed as non-response for this analysis.

5.3 [redacted]

[redacted]

6. SPECIFICATION OF ENDPOINTS AND VARIABLES

Several analytic variables must be derived from the data as it was collected. This section describes the variables collected, as well as how they will be modified for inclusion in the analyses.

6.1 Demographic and Baseline Characteristics

6.1.1 Demographics and Baseline Characteristics

Demographic parameters collected include:

- Age
- Sex
- Race
- Ethnicity
- Reproductive status

Baseline characteristics include:

- Weight (kg)
- Height (cm)
- Body mass index (BMI) in kg/m^2
- Body surface area (BSA) in m^2
- Days since clinical lower GI aGVHD diagnosis
- Screening aGVHD stage for each target organ (Skin, Lower GI Tract, Upper GI Tract, and Liver) using the modified keystone criteria
- IBMTR Severity Grade
- Type of HSCT (Blood, Bone Marrow, Cord, or Haploidentical)
- CMG IgG serostatus (Positive, Negative, or Equivocal)
- CMG IgM serostatus (Positive, Negative, or Equivocal)
- Physical examination clinically significant abnormalities (Yes or No)

Age, BMI, BSA, and days since clinical lower GI aGVHD diagnosis will be computed as:

Table 4 Data Handling Rules for Demographic Data

Description	Data Handling Rule
Age (years)	Age = integer((date of screening-date of birth)/365.25)
BMI	BMI = Weight (kg) / $[\text{Height (cm)}/100]^2$
BSA	BSA =([Height (cm) x Weight (kg)]/ 3600)$^{1/2}$
Days since clinical lower GI aGVHD diagnosis	Days since clinical lower GI aGVHD diagnosis = Date of screening – Date of Clinical Lower GI aGVHD diagnosis

6.1.2 Medical and Surgery History, Prior Chemotherapy

Medical and surgical history and prior chemotherapy will be collected.

General medical and surgical history will include a description of the diagnosis or procedures, start and end date, and if the condition is still ongoing.

Prior chemotherapy agent name, number of cycles, and date of last dose will be recorded on the eCRF.

6.2 Safety

- AE reporting
- VS measurements
- Laboratory measurements (hematology, serum chemistry, and urinalysis)
- Electrocardiogram (ECG) measurements
- PE

Standard safety parameters include hematology, blood chemistry and urinalysis parameters, vital signs, physical examination, and toxicity management. The National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) v 4.03 will be used to grade potential AEs.

6.2.1 Safety Baseline and Study Day

The baseline of safety measures are the last measure before first dose of F-652.

Study day will be computed from Day 0 as:

Study day = (Date of interest) – (Date of Day 0) + 1

6.2.2 Extent of Exposure to Study Medication

Extent of exposure to study drug (F-652) will be assessed using the following variables:

Table 5 Data Handling Rules for Extent of Exposure to Study Medication Data

Description	Definition/ Data Handling Rule
Number of Treatments	Number of infusions started, regardless of the completion status.
Treatment duration	Treatment duration (days) = Date of last dose of F-652– Date of first dose of F-652 + 1
Total F-652 Received (mg)	The total dosage of F-652 received. The starting dose is 45 μg/kg. Subsequent doses may be reduced, as determined by the Investigator, to 30 μg/kg or 10 μg/kg. The drug administered is at a concentration of 5 mg/mL. Dose infused (mg) can be calculated as (Volume infused (mL) * 5 mg/mL).
Number of Subjects with Doses Interrupted or Discontinued Prematurely (Overall and for each dose)	Number of subjects administered study drug but who had the infusion interrupted or discontinued prematurely.

6.2.3 Prior and Concomitant Medication

Prior and concomitant medications, including BMT/GVHD and systemic corticosteroid medications, will be recorded at screening and during the study. Prior medication is defined as any medication taken before the first dose of F-652. Concomitant medication is defined as any medication taken during the study between the date of the first dose of F-652 and the last study date of the subject, up to the Day 56 visit. Any medications started after the last study date of the subject will not be considered concomitant

medications. After Day 56, only concomitant medications related to a SAE will be documented on the eCRFs and will be considered as post-dose medications.

Any medication which cannot be identified as prior or concomitant will be considered as being in both of the categories that are possible from the available information.

All relevant information, including reason for use, dose, unit, frequency and route, will be recorded for any medication administered or received prior and during the study.

Summaries of all concomitant medications taken during the course of the study will be presented in tabular form using Anatomical Therapeutic Chemical 4 classification codes and preferred drug name via the World Health Organization Drug Dictionary (WHO-DD) with latest version to be specified in the Clinical Study Report. For the summary tables, if a subject has taken a concomitant medication more than once, the subject will be counted only once for the medication.

For medications with incomplete dates, imputation will be used to convert to a complete date. Imputed dates will be used to determine the study day.

Partial medication start dates will be imputed as follows:

1. Only the year is reported: If the subject started receiving study treatment in the year reported, then the date of the first dose of study treatment will be used as the starting date of the medication. Otherwise, January 1 will be used as the start of the medication.
2. The month and year is reported: If the subject started receiving study treatment during the month and year reported, then the date of first dose of study treatment will be used as the starting date of the medication. Otherwise, the first day of the month will be used as the start of the medication.

Partial medication end dates will be imputed for non-ongoing medications as follows:

1. Only the year is reported: If the subject stopped receiving study treatment in the year reported, then the date of the last dose of study treatment will be used as the end date of the medication. Otherwise, December 31 will be used as the end of the medication.
2. The month and year is reported: If the subject stopped receiving study treatment during the month and year reported, then the date of last dose of study treatment will be used as the end date of the medication. Otherwise, the last day of the month will be used as the end of the medication.

The above rules are subject to logical sense, for example, imputed start date should be on or prior to imputed end date.

6.2.4 Adverse Events

Adverse events (AEs) will be collected and coded using the latest version of the Medical Dictionary for Regulatory Activities (MedDRA). Analysis of adverse events will be carried out on the Safety Population.

All AEs from the time of randomization, regardless of suspected causal relationship to the investigational product, will be documented on the AE page(s) of the eCRF up to and including Study Day 56. After Day 56, SAEs deemed possibly, probably, or definitely related to the investigational product are required to be recorded through to the end of the study (Day 365).

A treatment-emergent adverse event (TEAE) is any adverse event that begins on or after first dose of F-652, or is a worsening of a pre-existing medical condition, up to Day 56. SAEs that start after Day 56 will be considered post-treatment. Incidence of TEAE will be presented overall for all subjects.

The severity of each AE will be classified using the NCI-CTCAE toxicity scale as follows:

- Grade 1 = Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
- Grade 2 = Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental Activities of Daily Living (ADL)
- Grade 3 = Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL
- Grade 4 = Life-threatening consequences; urgent intervention indicated.
- Grade 5 = Death related to AE.

The relationship of each AE will be assessed by the investigator and assigned to 1 of the following categories:

- Unrelated
- Unlikely
- Possible
- Probable
- Definite

An AE will be considered "related" to study drug if the relationship is "possible", "probable" or "definite".

Serious adverse events (SAE) are defined as any adverse events occurring at any dose that suggests a significant hazard, contraindication, side effect, or precaution. SAEs will be collected from the time of study entry until 30 days after completion of the trial or 30 days after premature withdrawal of a subject from the trial.

If the death of a subject is reported at any point during the study, the date of death, autopsy performed (yes/no), and any clarifying information should be collected. The event causing death will be reported as a SAE.

Adverse Events Counting Rules:

1. In the analyses, a subject having the same event (AE preferred term) more than once during the study will be counted only once for that event type.
2. A subject with more than one different adverse event in a particular system organ class (SOC) will be counted only once in the total of subjects experiencing adverse events in that particular SOC.
3. If an event changes in intensity or in seriousness during the study, it will be counted only once with the worst grade and seriousness respectively.
4. If the causal relationship to the study drug is assessed differently, it will be counted only once by considering the "Worst" documented degree of relationship.

Missing values will be treated as missing except for relationship, grade and seriousness of an AE, at which occurrence a "worst case" approach will be taken. Thus, if relationship is missing the AE will be regarded as related to the study drug, if the grade is missing the grade of the AE will be regarded as severe (Grade 3), if seriousness is missing the AE will be regarded as an SAE.

Events with Irregular Start Dates: All treatment-emergent adverse events will be included in the tabulations regardless the completeness of the onset dates. Partial dates may be imputed when appropriate, as discussed below.

If a partial date is reported for the start of an adverse event, a complete date will be estimated by the following algorithm:

1. Only the year is reported: If the subject started receiving study medication in the prior year, then January 1 will be used as the starting date of the event. If the subject started receiving study medication in the year reported, then the date of the first dose of study medication will be used as the start of the event.
2. The month and year are reported: If the subject started receiving study medication prior to the month and year reported, then the first day of the month will be used as the starting date of the event. If the subject started receiving medication during the month and year reported, then the date of the first dose of study medication will be used as the start of the event.

If a partial date is reported for the end of an adverse event and the adverse event is not continuing, a complete date will be estimated by the following algorithm:

1. Only the year is reported: If the subject started receiving study medication in the prior year, then the date of final study contact with the subject will be used as the end of the adverse event. If the subject started receiving study medication in the year reported, the earlier of December 31 or the date of final study contact with the subject will be used as the end of the adverse event.
2. The month and year are reported: The earlier of the last day of the month or the date of final contact with the subject will be used as the end of the adverse event.

Before the database lock, uncoded events will be assigned the string "UNCODED" as the body system, and the verbatim term will be used as the preferred term, so they can be included in the summary tables. In the final dataset, all the adverse events should have been coded.

6.2.5 Laboratory Data

This study will be conducted in up to 4 clinical centers in North America. Blood samples for hematology, serum chemistry, and serum hCG, as well as stool samples for C. difficile will be collected and analyzed by a local laboratory. Blood samples collected for PK will be analyzed by a central laboratory.

Conversion to the International System of Units

All laboratory data will be stored in the database with the units in which they are originally reported. Laboratory data in summary tables and subject data listings will be presented in the International System of Units (SI units). Laboratory data not reported in SI units will be converted to SI units before further processing or data analysis.

Hematology and blood chemistry data will be graded according to NCI-CTCAE severity grade.

Baseline laboratory parameters (blood chemistry, hematology, and urinalysis) are defined as the subject's last assessment prior to the first dose of F-652.

Change in laboratory parameters post baseline can be computed as:

Change from baseline = Current Value – Baseline Value

Missing laboratory values will not be imputed for the safety analysis. In case of repeated measurements at a given visit, the latest value will be used for analysis.

6.2.6 Vital Signs

Vital signs are collected at Screening, Days 0, 7, 14, 21, 28, 56, 180, and 365, and include the following parameters:

- Height (cm) (Screening only)
- Weight (kg)
- Temperature (°C)
- Heart rate (beats per minute [BPM])
- Diastolic and systolic blood pressure (mmHg)
- Respiratory rate (beats/minute)

Weight at Days 0, 7, 14, and 21 will be measured once. Temperature, heart rate, blood pressure, and respiratory rate at Days 0, 7, 14, and 21 will be measured 15 minutes after the start of infusion, at the completion of infusion, and 1 hour after the end of infusion. All parameters will be collected one time each at Screening and on Days 28, 56, 180, and 365.

Baseline and change from baseline are defined similarly as in Section 6.2.5.

6.2.7 Electrocardiogram

Standard 12-lead ECG will be measured at screening and Day 28. The following parameters are included:

- PR Interval
- QRS Duration
- QT Interval
- RR Interval
- Heart Rate
- QTc Fridericia Interval (QTcF)

QTcF will be calculated as: $QT/\sqrt[3]{RR}$.

Another version of QTc was also collected from the CRF and will only be listed.

6.2.8 Other Safety Assessments

Other safety assessments include:

- Serum pregnancy test
- Urine pregnancy test
- Physical examination

Any clinically significant abnormalities from physical examination will be reported as medical history if observed at Screening, or as an AE if observed after enrollment.

6.3 Efficacy

The Efficacy Evaluable Population will be used for the efficacy analyses.

Missing aGVHD treatment response will be imputed as non-response for this analysis. Handling of missing values is covered in section 7.1.1.

6.3.1 Study Day

The date of the first dose of F-652 represents Study Day 1.

Study day will be computed from day 1 as:

Study day = (date of interest) – (date of Study Day 1) + 1

6.3.2 Primary Efficacy Variables

- The lower GI aGVHD treatment response rate 28 days following the initiation of therapy will be assessed by examining the proportion of subjects with a CR, VGPR, PR or have NR/stable or progression of lower GI aGVHD symptomatology. Treatment Response will be defined as CR, VGPR, or PR. No Treatment Response will be defined as NR/stable or progression.

6.3.3 Secondary Efficacy Variables

- The lower GI aGVHD treatment response rate at Days 14 and 56 will be assessed by examining the proportion of subjects with a CR, VGPR, PR or have NR/stable or progression of lower GI aGVHD symptomatology. Treatment Response will be defined as CR, VGPR, or PR. No Treatment Response will be defined as NR/stable or progression.
- The overall aGVHD treatment response rate at Days 14, 28, and 56 will be assessed by examining the proportion of subjects with a CR, VGPR, PR, MR, or have NR/stable or progression of overall aGVHD symptomatology. Treatment Response will be defined as CR, VGPR, PR, or MR. No Treatment Response will be defined as NR/stable or progression.
- Discontinuation of immunosuppressive medication at Day 180 and 1 year post initial dosing of F-652 will be assessed by estimating the proportion of subjects who have stopped immunosuppressive medication at Day 180 and 1 year. Immunosuppresive medications will be identified as those collected on the BMT/GVHD Medications CRF and categorized as Immunosuppressants. Subjects who discontinue at Day 180 and at 1 year will be defined as those who have stopped all immunosuppressant medications that were being taken at or after the first dose of F-652.
- Characteristics of immune reconstitution after F-652 treatment will be evaluated through the B and T lymphocytes recovery and will be measured on Study Days 0 and 28 post-initial dose of F-652. Graphical and summary measures will be used to describe the CD3+CD4+, CD3+CD8+, and CD19+ populations. The entire immune reconstitution panel consists of the following:
  - ALC (absolute lymphocyte count) (Cell/mcL)
  - CD45+ Lymphocytes (%)
  - CD3+ T cells (%)
  - CD3+ Absolute (Cell/mcL)

- CD3+4+8- T Subset (%)
- CD3+4+8- Absolute (Cell/mcL)
- CD4+45RA+ T Subset (%)
- CD4+45RA+ Absolute (Cell/mcL)
- CD3+4-8+ T Subset (%)
- CD3+4-8+ Absolute (Cell/mcL)
- CD3+4+8+ T Subset (%)
- CD3+4+8+ Absolute (Cell/mcL)
- CD3+4-8- T Subset (%)
- CD3+4-8- Absolute (Cell/mcL)
- CD3-19+ B cells (%)
- CD3-19+ Absolute (Cell/mcL)
- CD3-56+16+ NK cells (%)
- CD3-56+16+ Absolute (Cell/mcL)
- CD3+56+16+ NKT cells (%)
- CD3+56+16+ Absolute (Cell/mcL)
- CD3+4+8-/CD3+4-8+ Ratio
- PHA (Phytohemagglutinin-P) (CPM)

- Overall survival from the time of the first infusion of F-652 will be calculated as the number of days from the date of the first infusion to the date of death (Date of death – Date of first infusion +1) for subjects who die. Survival time for subjects who do not die will be based on the subject's study completion or discontinuation date (Date of completion/discontinuation – Date of first infusion +1).

6.3.4 [redacted]

[redacted]

- [redacted]

6.4 [redacted]

- [redacted]

[redacted]

- [redacted]

[redacted]

- [redacted]

[redacted]

7. STATISTICAL ANALYSIS

7.1 General Data Handling Rules and Definitions

All subjects enrolled will be accounted for in the statistical analysis and presentation of the trial results.

All data collected on case report forms will be provided in listings, except data collected only for confirmation of study entry criteria and for study administrative purposes. If any enrolled subject is found to not have valid documented informed consent, that subject's data will be excluded from the report.

Except where specified, all continuous variables will be summarized with descriptive statistics (the number of non-missing values (n), mean, standard deviation, median, minimum and maximum) and all categorical variables will be summarized with frequency counts and percentages.

7.1.1 Missing Data and Imputation

For the analysis of the primary endpoint, the lower GI aGVHD treatment response rate at Day 28, missing data will be imputed as non-response. The rate and pattern of missing data will be explored and summarized.

Subjects who have reported protocol deviations, which may have a significant impact on the estimation of the PK parameters, will be removed from the PK Population. Subjects with partial serum concentration data will be evaluated to determine whether sufficient data is available for meaningful analysis.

No other data will be imputed in the analysis.

7.1.2 Analysis Visit and Visit Window Definitions

All safety and efficacy data will be analyzed based on the nominal visits and nominal time points. Only if the data from the nominal visit is missing, data from unscheduled visits or an early discontinuation visit for the same nominal visit or time point will be used. Data obtained during unscheduled and early discontinuation visits will be allocated to the scheduled visit corresponding to the visit window they fall in as specified in **Table 6**.

If multiple values are the same number of days away from the target study day, then the latter value will be used. In the unlikely event an unscheduled or early discontinuation visit, associated with a particular visit window, falls either prior to the actual previous nominal visit date or after the subsequent nominal visit date, it will not be used.

Table 6. Time Windows for Efficacy/Safety Assessments

Visit (label)	Time Interval (study day)	Target Time Point (day)
Screening	-5 to -1	-5 to -1
Day 0	1	1
Day 7	6 to 10	8
Day 14	13 to 17	15
Day 21	20 to 24	22
Day 28	25 to 33	29

Day 56	43 to 61	57
Day 180	151 to 211	181
Day 365	336 to 396	366

7.2 Subject Disposition

Disposition tables will be presented for all subjects.

The number and percentage of subjects who did not meet the screening criteria, were enrolled into the study, and completed each of the four doses will be tabulated. The number and percentage of subjects included and excluded from the defined analysis populations and reasons for study discontinuation will also be summarized. Other disposition information, reasons for screen failure and study discontinuation details will be provided in individual subject data listings.

7.3 Demographic and Baseline Characteristics

Demographic and baseline characteristics data will be summarized and tabulated.

Continuous baseline parameters (such as age) will be summarized descriptively. For categorical demographic parameters (such as gender, race, ethnicity) frequencies of subjects will be provided.

All medical history, acute graft-versus-host disease (aGVHD) diagnosis, prior chemotherapy, physical examination (abnormalities only), prior/concomitant medications, BMT/GVHD medications, and systemic corticosteroid administration data collected on the eCRF will be presented in listings.

7.4 Safety Analyses

All safety analysis will be performed on the Safety Population. Safety will be assessed based on AE reporting, physical examination, vital sign measurement, and clinical laboratory test results. Summaries of safety parameters will be presented for all treated subjects.

Wherever applicable for a safety parameter, the last assessment made before the first dose of F-652 will be used as the baseline for all analyses of that safety parameter.

In case of repeated measurements at a given timepoint, the latest value will be used for analysis. Measurements at unscheduled visits will only be listed, unless it is actually a repeat of the scheduled measurement.

7.4.1 Extent of Exposure to Study Medication

Descriptive statistics will be presented for the number of treatments, treatment duration (days), total F-652 received (mg), and number of incompleted doses. Study drug dose, date and time, and volume will be provided in listings.

7.4.2 Concomitant Medications

The number and percent of subjects with concomitant medications will be tabulated by ATC class and preferred term. Other details, including medication verbatim and coding, will be provided in listings. The number and percent of subjects with BMT/GVHD medications will be tabulated by category and

drug name, as defined in the CRF. Other details will be provided in listings. The number and percent of subjects with systemic corticosteroid medications will be tabulated by corticosteroid name (Prednisone, Methylprednisolone, and Other). Other details, including other specified corticosteroid names, will be provided in listings.

7.4.3 Adverse Events

Analysis of adverse events will be carried out on the Safety Population. All adverse events will be included in the analyses, summaries, and individual subject data listings.

A TEAE overview summary table will be provided for all treated subjects including the number and percentage of subjects reporting at least one TEAE and the number of TEAEs reported for the following categories:

- Any TEAEs
- Serious TEAEs
- Deaths
- TEAE leading to study drug interruption
- TEAE leading to discontinuation of study drug

7.4.3.1 Incidence of Adverse Events

TEAEs will be summarized by SOC and preferred term (PT). The summary tables will display the total number and percentage of subjects reporting a specific TEAE, and the number of TEAE reported. TEAEs will be presented by SOC sorted alphabetically and PT sorted in decreasing frequency of occurrence.

Summary tables will be prepared for:

- Summary of TEAEs
- All TEAEs
- Serious TEAEs
- Treatment-related TEAEs
- TEAE leading to study drug discontinuation
- TEAEs by maximum severity
- TEAEs by relationship to study drug
- Common TEAEs with > 5% incidence rate
- Post-treatment SAE's

Supporting data listings will be provided, including:

- All adverse events (including any AEs reported in the study)
- Serious adverse events
- Deaths
- Adverse events for subjects who discontinued the study due to AE
- Glossaries of Preferred terms to verbatim by System Organ Class (SOC)

Infusion related reactions details will also be listed.

7.4.4 Laboratory Data

For analysis purposes, the study visit/timepoint will be recalculated from the date of the first dose collected from Study Drug Administration eCRF page.

Shift tables from screening visit to the worst post-baseline value will be presented for clinical laboratory measurements (serum chemistry and hematology) for all treated subjects.

All data will be all displayed in subject data listings for all safety subjects.

7.4.5 Vital Signs

Descriptive statistics will be prepared for vital sign measurements, by visit and time (after dose), for actual values and changes from baseline. All data will be all displayed in subject data listings for all safety subjects.

7.4.6 Electrocardiogram

All ECG parameters will be listed.

7.4.7 Other Safety Assessments

Physical examination and pregnancy test results will be presented in listings for all Safety subjects.

7.5 Efficacy Analyses

All testing will be two-sided, with "statistical significance" defined as a corresponding p-value < 0.10.

The analyses of the secondary endpoints will be performed with no adjustment for multiplicity.

7.5.1 Primary Efficacy

The primary endpoint of lower GI aGHVD treatment response rate 28 days following the initiation of therapy will be reported as the proportion of subjects who provide a response as defined as Treatment Response (CR, VGPR, or PR), and No Treatment Response (NR and progression).

7.5.1.1 Sensitivity Analyses

No sensitivity analyses are planned at this time to evaluate the robustness of the primary efficacy results.

7.5.2 Secondary Efficacy

Secondary efficacy endpoints will be analyzed as follows:

- Response to therapy will be explored by examining the proportion of subjects with a Treatment Response (CR, VGPR, or PR), and No Treatment Response (NR/stable or progression) lower GI aGVHD symptomatology at 14 and 56 days post treatment initiation.
- Overall aGVHD response to therapy will be explored by examining the proportion of subjects with a Treatment Response (CR, VGPR, PR, or MR), and No Treatment Response (NR/stable or progression) of aGVHD at Days 14, 28, and 56 post-treatment initiation.
- The proportion of subjects who have stopped immunosuppressive medication at Day 180 and 1 year post initial dosing of F-652 will be estimated.

- Immune recovery will be evaluated through the B and T lymphocytes recovery and will be measured on Study Days 0 and 28 post-initial dose of F-652. Graphical and summary measures will be used to describe the CD3+CD4+, CD3+CD8+, and CD19+ populations for each of the measurements in the reconstitution panel.
- Kaplan-Meier methodology will be used to estimate overall survival from the time of the first infusion of F-652. Subjects who do not die will be censored at the date of completion/discontinuation from the study.

7.6 [redacted]

7.7 [redacted]

8. CHANGES FROM METHODS PLANNED IN THE PROTOCOL

No changes are planned from the protocol.

9. STATISTICAL SOFTWARE

All analyses will be done using SAS version 9.4.

10. REFERENCES

1. Przepiorka D, Weisdorf D, Martin P, et al. 1994 Consensus Conference on Acute GVHD Grading. Bone Marrow Transplant. 1995;15(6):825-828.
2. Rowlings PA, Przepiorka D, Klein JP, et al. IBMTR Severity Index for grading acute graft-versus-host disease: retrospective comparison with Glucksberg grade. British Journal of Haematology. 1997;97(4):855-864.
3. Levine JE, Logan B, Wu J, et al. Graft-versus-host disease treatment: predictors of survival. Biol Blood Marrow Transplant. 2010;16(12):1693-1699.
4. Ivanova A, Qaqish BF and Schell MJ. (2005). Continuous Toxicity Monitoring in Phase II Trials in Oncology. Biometrics 61, 540-545.

APPENDIX 1 DATA HANDLING RULES

Category	Description	Data Handling Rules
Demographics	Age (years)	Age = integer((date of screening-date of birth)/365.25)
Demographic	BMI	BMI = Weight(kg) / [Height(cm)/100]^2
Demographic	BSA	BSA = ([Height(cm) x Weight(kg)]/ 3600)$^{1/2}$
Demographic	Days since clinical lower GI aGVHD diagnosis	Days since clinical lower GI aGVHD diagnosis = Date of screening – Date of Clinical Lower GI aGVHD diagnosis
Medical History	Any Medical history	flags are none, but data are present, change the flag to "Yes"
Efficacy	Stop day of immunosuppresive medication	= Stop date of immunosuppresive medication – Date of first dose of F-652 + 1
Efficacy	Overall survival time	= Date of completion/discontinuation – Date of first infusion + 1
Extent of Exposure to Study Medication	Actual volume infused	Collected on the CRF in mL, rounded to 1 decimal place.
Safety Lab	Assessment day	Assessment day = (Date of assessment) – (Date of first dose) + 1.
Safety Lab	Change from baseline	Change from baseline = Current Value – Value at last assessment prior to dose 1 treatment.

APPENDIX 2 SAS CODE FOR STATISTICAL ANALYSES

The SAS code for the efficacy endpoint analyses are given below.

Proportion of Subjects with Response- Primary Efficacy Endpoint	proc freq; tables aval/binomial(exact) alpha=0.1; run; Note: Use for Primary Efficacy endpoint, lower GI aGHVD response at day 28.
Proportion of Subjects with Response- Secondary Efficacy Endpoints	proc freq; tables aval/binomial(exact) alpha=0.1; by avisitn; run; Note: Use for Secondary Efficacy endpoints, lower GI aGHVD response at days 14 and 56, overall aGVHD response at days 14, 28, and 56, and proportion of subjects who have stopped immunosuppressive medication at days 180 and 365.
Kaplan Meier Survival Estimate- Secondary	proc lifetest; time survdays*censor(1); run;

Efficacy Endpoint Overall Survival	

APPENDIX 3 MOCKUP TABLES, LISTINGS, AND GRAPHS (TLGS)

Mockup tables, listings, and graphs are presented in a separate document prior to the final signoff of this SAP.