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Clinical Study Protocol: GC-652-02

Study 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**
Study Number:	GC-652-02
Study Phase:	IIa
Product Name:	F-652
IND Number:	[redacted]
Indication:	Gastrointestinal Graft versus Host Disease
Investigators:	Multicenter
Sponsor:	Generon (Shanghai) Corporation Building 9, 787 Kangqiao Road, Shanghai, PRC 201315 Tel: 8621-61760866 Fax: 8621-61760865
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Name of Principal Investigators:	Doris M. Ponce, M.D. Alan Hanash, M.D., PhD. Juliet N. Barker, MBBS. Memorial Sloan Kettering Cancer Center 1275 York Avenue, New York, NY 10065
Protocol Date:	30 May 2017 Version: Amendment 4

INTRODUCTORY AND CONFIDENTIALITY STATEMENT

This protocol has been prepared according to the International Conference on Harmonisation (ICH) Harmonised Tripartite Guidelines for Good Clinical Practice issued in June 1996, with an implication date of January 17, 1997 and Food and Drug Administration (FDA) Good Clinical Practice (GCP) guidelines and Code of Federal Regulations (CFR): 21 CFR 312, 21 CFR 50, 21 CFR 56.

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PRINCIPAL INVESTIGATOR'S STATEMENT

I, the undersigned, have reviewed this protocol, including appendices, and I agree to conduct the clinical study as described (subject to any amendments). Any changes in procedure will only be made if necessary to protect the safety, rights or welfare of study subjects.

I agree to conduct in person or to supervise the study. I agree to ensure that all who assist me in the conduct of the study are aware of their obligations.

Site Investigator:	**Site Number:**
……..	…….
Signature	Date

Sponsor Approval and Medical Expert for the Trial:

Tom Tang, MD,
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……. ……30 May 2017……

Signature Date

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STUDY SYNOPSIS

Protocol Number:	GC-652-02
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 in Hematopoietic Stem Cell Transplantation Recipients
Study Phase:	Phase IIa
Name of Product:	F-652
Name of Active Ingredient:	Recombinant human interleukin (IL)-22 and human immunoglobulin (Ig) IgG2-Fc fusion protein (rhIL-22 IgG2 Fc).
Indication:	Gastrointestinal (GI) Acute Graft-versus-Host Disease (aGVHD) in Hematopoietic Stem Cell Transplantation (HSCT) Recipients.
Sponsor:	Generon (Shanghai) Corporation Building 9, 787 Kang Qiao Road, Shanghai, PRC 201315 Tel: 8621-61760866 Fax: 8621-61760865
Name of Sponsor Contact:	Tom Tang, MD Generon (Shanghai) Corporation
Name of Principal Investigators:	Doris M. Ponce, M.D. Alan Hanash, M.D., PhD Juliet N. Barker, MBBS Memorial Sloan Kettering Cancer Center 1275 York Avenue, New York, NY 10065
Test Product, Dose, and Mode of Administration:	F-652 is to be administered intravenously (IV) once a week for a total of 4 doses at 45 μg/kg each. Dose reduction is permitted depending on individual subject safety and tolerability. Reduced doses permitted in de-escalation order: 30 μg/kg and then 10 μg/kg.
Concurrent Control:	No concurrent control
Objectives and Study Endpoints:	**Objective:** The objective of the study is to assess the safety, efficacy, and pharmacokinetics (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. **Safety Endpoints:** 1. Adverse event (AE) reporting. 2. Vital sign measurements 3. Laboratory measurements 4. Physical Examination **Primary Efficacy Endpoint:** To assess the lower GI aGVHD treatment response rate at Day 28. **Secondary Efficacy Endpoints:**

	1. 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. 2. Overall aGVHD treatment response at Days 14, 28, and 56 categorized by CR, VGPR, PR, mixed response (MR), NR/stable, and progression. 3. Discontinuation of immunosuppressive medication at Day 180 and 1 year post initial dosing of F-652. 4. Characteristics of immune reconstitution after F-652 treatment. 5. Overall survival at 1 year after first infusion of F-652. 
Study Design:	This is a Phase IIa single arm open-label study to investigate the safety, efficacy, and PK of F-652 in combination with systemic corticosteroids in subjects who have undergone HSCT and have newly diagnosed grade II-IV lower GI aGVHD. The HSCT may be derived from bone marrow, peripheral blood stem cells, or cord blood. The PK of F-652 in this subject population will be investigated and the immunogenicity for F-652 will be tested. Subjects may be replaced if subject withdrawal is not related to safety or treatment responses. During the course of the study, F-652 will be administered in conjunction with systemic corticosteroids, as per the standard of care for subjects with lower GI aGVHD. Prednisone will be given at a dose of 2 mg/kg/day (or IV equivalent) and tapered as suggested per protocol. A dose of 45 µg/kg F-652 will be administered IV once per week at a rate of 100 mL/hour for one hour for 4 doses. Subjects will be followed for efficacy through Day 56, for safety through Day 180, and subject survival status will be collected at Day 365. 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 patients. During the course of a subject's therapy, dose reduction may occur on an individual basis as per protocol.
Study Site:	This study will be conducted in up to 4 clinical centers in North America.
Subject Population:	The study population may consist of up to 27 male and female subjects with newly diagnosed Grade II-IV lower GI aGVHD.
Eligibility:	Eligible subjects will be between ≥18 to ≤80 years of age who are recipients of HSCT and are newly diagnosed with grade II-IV lower GI aGVHD.[1] Minimum criteria for lower GI aGVHD includes diarrhea of greater than 500 mL/day. If stool volume is not quantified in mL, each episode of diarrhea will be estimated at a volume of 200 mL. Subjects with aGVHD affecting other organs (e.g. skin,

	liver) will be allowed if grade II-IV lower GI aGVHD is concurrently present. Subjects will have an absolute neutrophil count (ANC) ≥500/mm^3 and serum creatinine ≤3 mg/dL. A biopsy of the GI tract is required for study entry; 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 withdrawn and replaced in the study. The severity of aGVHD will be graded using the International Bone Marrow Transplant Registry (IBMTR) criteria.
Duration of Treatment:	The duration of study treatment will be a total of approximately 4 weeks with a screening phase and a post treatment phase. All post treatment visits are scheduled after the initial F-652 treatment. Clinical assessments will occur during the screening period (up to 5 days), study entry (Day 0, first dose of F-652), and on Days 7, 14, 21, 28, 56, 180, and 365. Clinical visits will also occur according to the PK sampling schedule. PK sampling will occur on dosing Days 0, 7, 14, and 21 as follows (all post-dose sampling time points are after the start of the infusion): Day 0: 60 min pre-dose and post-dose 30 min, 1 hr, 8 hr, and 72 hrs. Days 7 and 14: 60 min pre-dose and post dose 30 min and 72 hrs. Days 21: 60 min pre-dose and post-dose 30 min, 1 hr, 8 hr, 24 hrs, 48 hrs, 72 hrs, and 96 hrs. PK sampling will occur during follow-up on Days 28 and 56 as follows: Days 28 and 56: during the visit. [redacted].
Subject Assignment:	All eligible subjects will be given open label F-652. There will be no randomization in this single arm study.
Efficacy Assessments:	The efficacy of F-652 in combination with systemic corticosteroids for the treatment of grade II-IV lower GI aGVHD will be assessed by evaluating therapy response rate by Day 28.
Safety Assessments:	• AEs and serious adverse events (SAEs) • Vital signs • Clinical laboratory tests (to include hematology, serum chemistry, and urinalysis) • Physical examination
Data Analyses:	• Safety analysis will be assessed by a review of all safety parameters including AEs, SAEs, laboratory safety parameters, and vital signs. • Efficacy will be evaluated by treatment response along with immunosuppressive use and overall survival. In addition, GVHD biomarkers and cytokines will be explored. • Non-compartmental analysis of PK parameters, such as C_{max} and AUC will be performed.
Date	30 May 2017

1 INTRODUCTION

1.1 Acute GVHD and Current Therapy

Acute graft versus host disease (aGVHD) is a frequent and, at times, unpredictable and severe complication of hematopoietic stem cell transplantation (HSCT).[2-4] Organs affected in GVHD include the skin, liver, and/or the gastrointestinal (GI) tract, and is a common cause of transplant-related mortality (TRM).[2,5] While calcineurin-inhibitor based GVHD prophylaxis has decreased the incidence and mortality associated with aGVHD, it provides inadequate protection since this disease commonly affects more than 50% of HSCT recipients.[6,7] Although several clinical factors have been associated with aGVHD risk, such as recipients of sex-mismatched HSCT, donor-recipient human leukocyte antigen-mismatch, peripheral blood stem cell graft and myeloablative conditioning,[8,9] and omission of anti-thymocyte globulin (ATG) in the conditioning regimen,[10] it is currently unknown which patients will develop this complication post-allograft. Ponce et al. demonstrated that GVHD frequently occurs after unmodified unrelated donor and cord blood transplantation; the incidence of grade II-IV aGVHD at Day 100 was found to be 56% and 55%, respectively.[11] GVHD was the most common cause of transplant-related death in T-replete and T-cell depleted unrelated donor and cord blood transplant recipients. In this study and others, the GI tract was the organ most commonly associated with lethal GVHD.[12-14] These findings support the investigation of new GVHD treatment strategies specifically targeting the GI tract.

The standard treatment for grade II-IV aGVHD is systemic corticosteroids at a daily dose of 2 mg/kg.[15] However, treatment with systemic corticosteroids is non-target specific and can be associated with several and potential life-threatening side effects including lethal infections.[16] Approximately 50% of the patients will not achieve a sustained complete response (CR) to therapy with corticosteroids,[6] and for those patients who fail to respond or are unable to maintain aGVHD control upon tapering corticosteroid therapy, escalation of immunosuppressive therapy is necessary.[17,18] While several immunosuppressive agents can be added for second-line therapy, such as ATG, alemtuzumab, monoclonal antibodies against CD3, tumor-necrosis factor (TNF)-α inhibitor and pentostatin,[19-24] they are usually associated with a very low durable CR rate and profound immunosuppression that may cause severe sequelae of infection and abrogation of graft-versus-tumor effect increasing the risk of disease relapse or progression.[25,26] If clinical response is achieved to these agents, duration of remission is typically short. Therefore, survival is poor in corticosteroid-resistant aGVHD and approximately only 15% of the patients will be alive after 2 years.[27] Thus, the ideal treatment of aGVHD is one that can preserve overall immunity and have low risk of infection complications while maintaining graft-versus-tumor effect to preserve the protection against malignant relapse.

Better understanding of the mechanisms involved in the development of aGVHD could potentially reveal a targeted-specific therapy. Acute GVHD is caused by the allorecognition of host antigens by donor lymphocytes. The affected host organs may initially undergo injury from the direct toxicity of the conditioning regimen, which also leads to local entry of microbial products such as endotoxin or bacterial DNA. This injury and the subsequent signals generated by cytokines and microbial products could be the initial trigger for the production of further inflammatory cytokines which induce more efficient antigen processing and presentation by local dendritic cells (DC). This consequently leads to recruitment and activation of alloreactive naïve donor T-cells in secondary lymphoid tissues and proliferation. End-organ damage to targeted tissue (GI tract, skin, and liver) is subsequently mediated by the direct cytotoxic actions of activated donor effector T-cells as well as the actions of local cytokines. In animal models, cytokines up-regulation or down-regulation have been identified

as a manifestation of aGVHD.[12,28-30] In the GI tract specifically, inflammatory cytokines can promote tissue injury causing an alteration of the intestinal stem cell (ISC) and progenitor cell niche that may result in gut GVHD.[31,32] However, there is currently no treatment available to promote the recovery of the epithelial tissue that has been damaged by GVHD.

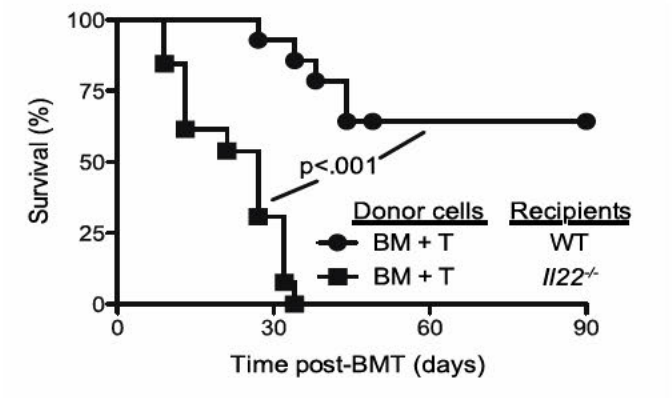
GVHD involves complex interactions between innate and adaptive immunity, culminating in tissue damage by inflammatory mediators and cellular effectors. Acute GVHD is a proinflammatory process mediated in part by donor T-cells. Cytokines and chemokines influence T-cell differentiation pathways and trafficking to GVHD target organs and also mediate direct tissue damage. Notably, in murine studies, proinflammatory cytokines expressed in GVHD have been reported to regulate homing molecule expression on alloreactive donor activated T-cells.[33-35] At Memorial Sloan Kettering Cancer Center (MSKCC), Hanash et al evaluated the effects of interleukin (IL)-21 signaling in donor T-cells in a murine model of bone marrow transplant.[31] Using IL-21 receptor deficient donor T-cells they demonstrated that abrogation of IL-21 signaling led to decreased GVHD mortality and GI GVHD pathology. IL-21 receptor deficient T-cells showed decreased gut infiltration and reduction in inflammatory cytokine production within the mesenteric lymph nodes. IL-23 has similarly been implicated in experimental GI GVHD. This cytokine is produced by antigen presenting cells post-bone marrow treatment (BMT),[35] and has been reported as a major regulator of IL-22 production.[36-38] Donor bone marrow deficient in IL-23 reduced GI GVHD compared with animals receiving wild-type grafts. In DCs purified from the colon, levels of IL-23 and its receptor were elevated, but not at other GVHD target sites. Increased interferon (IFN)-γ CD4+ T-cells appear to mediate these inflammatory effects.[35]

New insights into the roles played by cytokines in GVHD biology may provide novel targets for the prevention and treatment of aGVHD.

1.1.1 Recombinant Human IL-22 (F-652) and Reduction of GVHD

IL-22 is an IL-10-family cytokine produced by innate lymphoid cells (ILCs) and T-cells.[39,40] The IL-22 receptor is present in many epithelial tissues and expression of IL-22 reduces the severity of multiple experimental injury models including colitis, hepatitis, and thymic radiation injury.[41-43] Murine models of allogeneic HSCT have provided clinically relevant experimental systems for assessing mechanisms of immune-mediated intestinal damage and regeneration.[44-46] Hanash et al studied the role of IL-22 in murine gut GVHD.[32] They showed that intestinal IL-22 can be produced by intestinal lamina propia ILCs post-BMT, but that GI GVHD leads to loss of gut ILCs and impaired IL-22 production due to the elimination of IL-22 producing cells by the donor immune system. Deficiency of IL-22 led to increased GVHD in HSCT recipients (Figure 1). Additionally, mice deficient for IL-22 demonstrated increased gut pathology due to GVHD including intestinal crypt apoptosis, depletion of ISCs in the small intestine, and loss of epithelial integrity.

Figure 1. Post-BMT ISC Survival Curve in IL-22-Deficient Mice



BM = bone marrow; BMT = bone marrow transplant; IL = interleukin; T = T cells; WT = wild type.

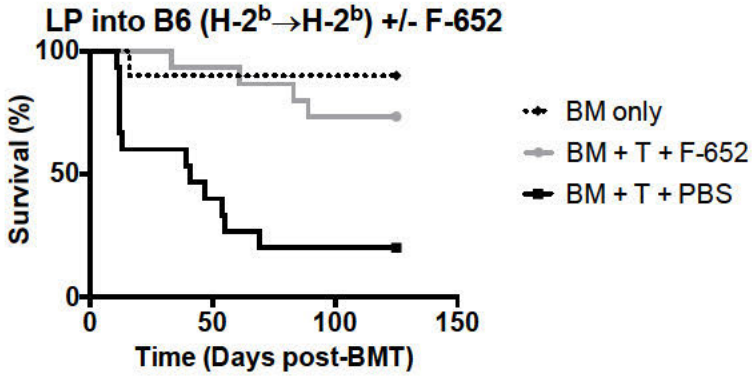
The role of IL-22 as a supportive growth factor for the ISC compartment was evaluated in an *ex vivo* ISC function model.[47] Murine small intestine crypts were isolated and cultured in the presence or absence of recombinant murine (rm)IL-22. Culturing crypts with rmIL-22 for 7 days led to the growth of substantially larger organoids than those cultured with epidermal growth factor (EGF), Noggin and R-spondin-1 alone. Increased organoid size was apparent as early as 5 days after culture. In addition, culture with IL-22 led to increased perimeter size and surface area of large intestinal organoids. ISCs are located within the crypt buds that grow during organoid development and IL-22 culture led to significantly greater crypt budding in both small and large intestine organoids, suggesting structural evidence of stem cell compartment regeneration. Additionally, F-652, a recombinant human (rh)IL-22 dimer/Fc fusion protein, was able to increase the size of murine small and large intestinal organoids, suggesting a translational potential for this compound. IL-22 led to increased organoid size, crypt budding, and STAT3 activation.

The effect of IL-22 in tissue damage was evaluated *in vivo* in a clinically relevant major histocompatibility complex (MHC)-matched (minor histocompatibility antigen-mismatched) allogeneic BMT murine model.[47] Recipients transplanted with T-cells to induce GVHD were treated with rmIL-22 or phosphate-buffered saline (PBS) starting 7 days post-BMT. These mice treated with IL-22 demonstrated reduced histopathologic evidence of gut GVHD, including less apoptosis within crypt epithelium. IL-22 treatment led to reduced pathology despite an intact alloimmune response. IL-22 also did not limit the ability of donor T-cells to clear A20 lymphoma in BMT recipients challenged with tumor at the time of transplant. This argued that IL-22 could reduce gut GVHD pathology without inducing immunosuppression, in contrast to all current prophylactic or therapeutic clinical interventions for GVHD.

Reduced numbers of ISCs,[32,48] and niche-forming Paneth cells[49,50] have been described in mice with GVHD. The effect of IL-22 on the ISC compartment was assessed by the administration of rmIL-22 to ISC reporter mice with GVHD. There was an increase in the number of $Lgr5^+$ (mitotically active) ISCs in mice treated with rmIL-22 compared to mice treated with PBS. Lgr5-GFP+ cells expressed increased Ki-67 after *in vivo* treatment with rmIL-22, indicating that the treatment augmented proliferation of the ISC pool. Paneth cells are thought to provide a supportive microenvironment for Lgr5+ ISCs through delivery of Wnt and EGF signals to crypt base columnar stem cells.[51] However, IL-22 treatment did not change the number of Paneth cells or Paneth cell-derived growth factors in small intestine epithelium, suggesting a direct effect of IL-22 on ISCs and progenitor cells. Mertelsmann et al also evaluated the impact of recombinant human IL-22 (F-652) administration on systemic

GVHD[47] and found a reduction in overall GVHD mortality following F-652 administration in recipients of MHC-matched allogeneic HSCT (Figure 2).

Figure 2. Post-BMT Survival Curve



BM = bone marrow; BMT = bone marrow transplant; PBS = phosphate buffered saline; T = T-Cells.

F-652 is a recombinant fusion protein containing human IL-22 and human immunoglobulin G2 (IgG2)-Fc produced in CHO cells in serum-free cultures. This molecule dimer has an improved pharmacological stability due to its Fc-fusion protein. This molecule was developed by Generon (Shanghai) Corporation.

In summary of the experimental models, IL-22 leads to increased recovery of ISCs from immune-mediated pathology by acting on ISCs to accelerate regeneration of the ISC pool. IL-22 augmented proliferation of Lgr5+ ISCs murine model (*in vivo* and *ex vivo*), which resulted in epithelial recovery. Thus, IL-22 provides a critical link between innate immunity and intestinal biology for maintenance of the structural integrity of the epithelial barrier.

1.1.2 Clinical Studies and Previous Human Usage

A Phase I randomized double-blind, placebo-controlled, single dose escalating study of F-652 was conducted in healthy male volunteers for the evaluation of the safety, tolerability, and pharmacokinetics (PK) of this drug. A total of 40 subjects were enrolled in the study. F-652 was administered [redacted] vs. placebo. Safety evaluations were conducted during the study including adverse events (AEs), physical examination, clinical safety laboratory (hematology, biochemistry, coagulation panel, immunological test, urinalysis), vital signs, and 12-lead electrocardiogram (ECG). PK endpoints were derived from the serum concentration-time profile of F-652 and included the following: total exposure (area under the plasma concentration vs. time curve [AUC]), maximum serum concentration (C_{max}), time at maximum concentration (t_{max}), last measurable serum concentration, time at last measurable concentration, clearance (C_L), volume of distribution (V_d), elimination half-life (λ_z), accumulation ratio (R_{ac}), and dose proportionality.

A total of 41 treatment-emergent adverse events (TEAEs) were reported in 23 subjects (58%). All TEAEs reported were mild or moderate in severity. There were no severe or life-threatening AEs, or any serious adverse events (SAEs) reported. Twenty-six TEAEs were considered related to F-652. Fewer TEAEs were reported following F-652 dosing via IV compared to [redacted] dose level. TEAEs reported following [redacted] dosing were all mild in severity, while 3 moderate events were reported following [redacted] dosing. This indicated that the study subjects better tolerated IV dosing. The number of TEAEs reported increased with IV dose, increasing above what was observed for placebo at

the [redacted] dose groups. Further, the number of moderate TEAEs reported increased with dose, and compared to IV placebo. The most frequently reported related TEAEs were dry skin (12 events reported by 12 subjects occurring locally after SC administration and more widely after IV dosing) and eye pruritus (3 events reported by 3 subjects following IV dosing). These showed improvement with the use of moisturizer cream and saline containing ocular drops, respectively.

When AEs were assessed according to dosing, the [redacted] had a delayed injection site reaction (2 mild, 4 moderate) consistent of dry skin, erythema, and rash. The [redacted] was associated with dry skin (1 moderate, 2 mild), skin allergic reaction (1 moderate), eye pruritus (1 moderate), while at an [redacted] it was associated with AEs of with dry skin (2 mild, 5 moderate), erythema (1 moderate), and eye pruritus (1 mild, 3 moderate). Reviews of laboratory test results, vital signs, and ECG parameters revealed no trends or changes over time following dosing with F-652 at any SC or IV dose.

[redacted]

Table 1.1.2. Summary of Related TEAEs for IV Infusion

Adverse Event	IV (N=24) S (%) E
Dry skin	10 (25.0%) 10
Eye pruritus	3 (7.5%) 3
Rash erythematous	2 (5.0%) 2
Chills	1 (2.5%) 1
Infusion related reaction	1 (2.5%) 1
Headache	1 (2.5%) 1
Somnolence	1 (2.5%) 1
Dermatitis allergic	1 (2.5%) 1

Note: Data is presented as S (%) E where S is the number of subjects, % is the percentage of subjects; E is the number of events.

1.1.3 Potential Risks and Benefits

A similar AE profile associated with F-652 is anticipated in this study as seen in the previous human experience, detailed in the Section 1.1.2. Given this safety profile, F-652 may enhance treatment response and contribute to the survival of this patient population and thus, may prove to be a beneficial treatment. The size of this Phase IIa trial should provide initial qualitative estimates of the effects of the F-652 in the treatment of grade II-IV lower GI aGVHD critical to the planning of subsequent trial(s).

2 STUDY OBJECTIVES

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 Study Endpoints

Safety Endpoints

The safety endpoints of this study are the following:

- AE reporting
- Vital sign measurements
- Laboratory measurements
- Physical Examination

Primary Efficacy Endpoint

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

Secondary Efficacy Endpoints

- Lower GI aGVHD treatment response at Days 14 and 56 categorized by 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.

Pharmacokinetic Endpoints

- Total exposure (AUC)
- C_{max}
- Other parameters, such as C_L, V_d, and λ_z maybe estimated.

3 INVESTIGATIONAL PLAN

3.1 Overall 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[52]. 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 SAEs, 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 patients (Figure 3).

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: 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 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 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 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.

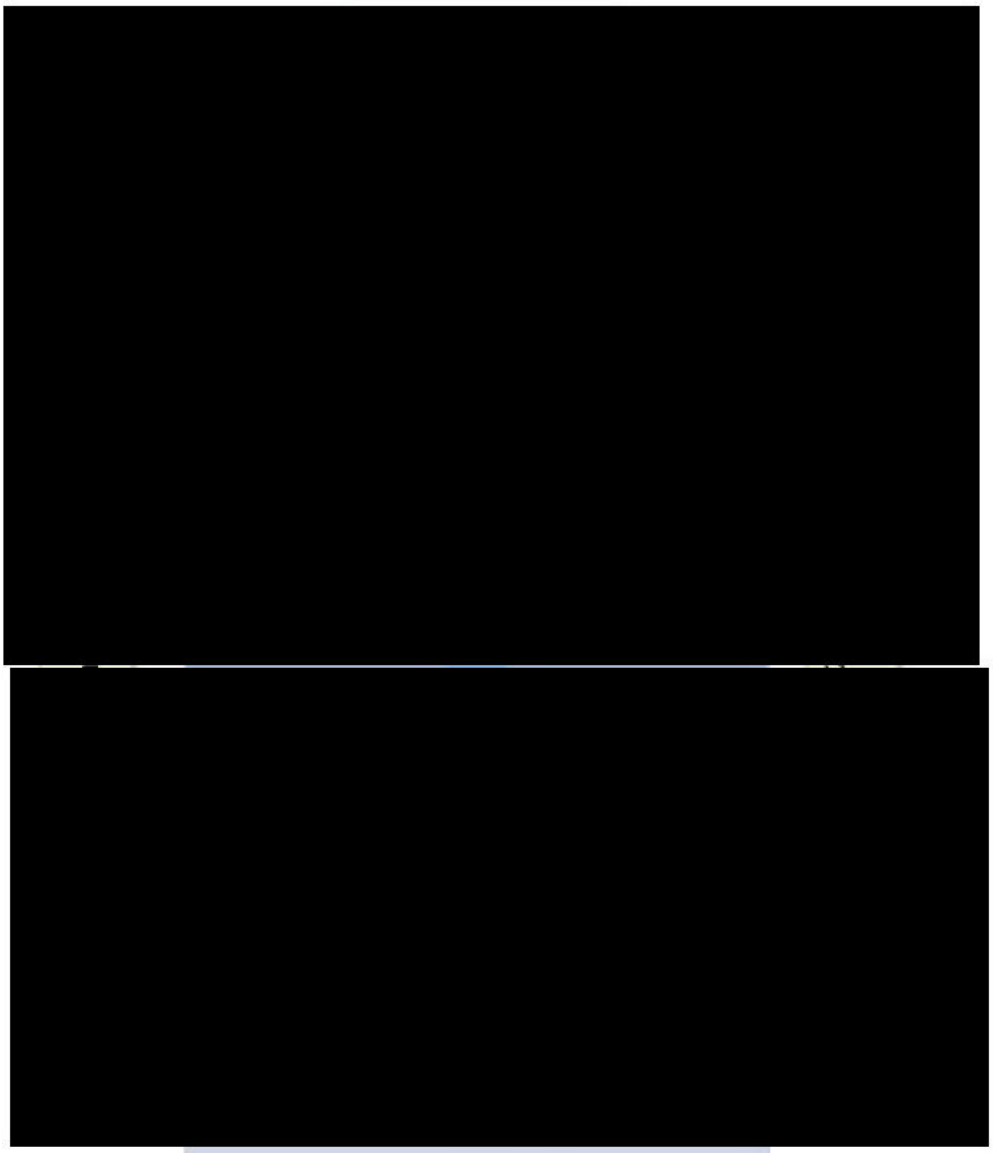
The study drug will be administered on an inpatient or outpatient basis, depending on the subject's clinical condition. The route of administration of F-652 is IV and will be administered once a week on Days 0, 7, 14, and 21. Following infusion of F-652, vital signs will be obtained and nursing assessment will be performed according to the BMT institutional standard of care. PK sampling will occur as per the schedule listed in 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 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 patients who are critically ill.

A study visit schematic is provided in Figure 4 and a complete schedule of study procedures and events are presented in Appendix 2 (Schedule of Procedures and Events).

Figure 3. [redacted]

Figure 4. [redacted]



aGVHD = acute Graft-versus-Host Disease.

3.2 Rationale for Study Design

Acute GVHD is a frequent complication following HSCT and a leading cause of TRM. The mainstay of treatment of aGVHD is corticosteroids. Although effective for some, the overall initial response rate is only 50% which decreases to 42% when the GI tract is affected. GI aGVHD produces direct epithelial tissue injury causing intestinal damage and inflammation. Murine models have shown that GI aGVHD particularly targets the ISC compartment and results in the loss of ILCs. These ILCs produce cytokine IL-22, which mediates a variety of protective effects including maintenance of tissue homeostasis, epithelial barrier integrity, and inducer of antimicrobial peptides in the GI tract. However, with the loss of ILCs in GI aGVHD, the production of IL-22 is impaired. While there is no current approved therapy that enhances the recovery of the human intestinal damage caused by aGVHD, treatment with IL-22 *in vivo* has emerged as a novel therapy in murine GI aGVHD. These studies have demonstrated that IL-22 administration promoted healing of the GI tract through its trophic effects on the intestinal epithelium and increased the ISC recovery.

This study is designed to determine the efficacy, safety, tolerability, and PK of F-652 in subjects with lower GI grade II-IV aGVHD. Based on the safety profile of F-652 observed in the Phase I trial and the lack of serious side effects and toxicity observed, this trial has been designed for the treatment of lower GI aGVHD with F-652 at a dose of 45 µg/kg in combination with systemic corticosteroids.

All subjects will be dosed with single administration of 45 µg/kg of F-652 weekly for a total of 4 doses. Safety of the subjects will be monitored throughout the study. An assessment of a subject's ability to continue treatment before each dosing of F-652 will be made, with a dose reduction permitted (Section 5.2.1.1), as determined by the treating physician. The potential benefits of F-652 for the treatment of aGVHD in a clinical setting are to be evaluated in order to determine if expansion of F-652 in a clinical program is warranted. The design of this study ensures an incremental evaluation of subjects with aGVHD to ensure subject safety.

3.2.1 F-652 Dosing

The dose chosen, 45 µg/kg, was the highest dose of F-652 tested in healthy male subjects with a demonstrated tolerable safety profile. The most common TEAEs identified were dry skin and eye pruritus. The PK results from the previous study indicated a once a week treatment regimen administered for 4 weeks, is appropriate. Study drug preparation is detailed in Appendix 4.

3.3 Study Duration and Dates

3.3.1 Duration of Subject Participation

The duration of the study participation consists of an initial screening period, followed by 4 weeks of treatment, and 4 post-treatment clinical visits (Days 28, 56, 180, and Day 365). Prior to study admission, there is a screening period of up to 5 days for the completion of the study consent form, the collection of medical history, signs and symptoms, laboratory tests, and biopsy sampling. After completion of therapy, subsequent evaluations will consist of a physical exam, blood tests, aGVHD assessment, and a post-treatment GI biopsy (as permitted by subject).

Subjects will be required to provide samples for the PK and immunogenicity evaluation of F-652. PK sampling will occur as per the schedule listed in Appendix 3.

3.3.2 Hold and Stop Rules

3.3.2.1 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%.[53] 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 3.3.2.1. 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 3.3.2.1. 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).[54]

3.3.2.2 Reasons for Subject Study Drug Discontinuation

A subject may withdraw from the trial at any time at his/her own request, or he/she may be withdrawn at any time at the discretion of the Investigator or Sponsor for safety, behavioral, or administrative reasons. The list of reasons for subject withdrawal is provided in Section 7.9.1.

3.3.3 End of Treatment and Follow-up Visits

All subjects will receive an End of Treatment assessment on Day 28. Subjects withdrawing from the study early will have their End of Treatment assessment visit and will be asked to

participate in a follow-up phone call. All AEs and concomitant medications will be recorded through 28 days after the last dose of study drug (Study Day 56) and only related SAEs (and associated concomitant medications)will be recorded through its stabilization, resolution, or the end of the study.

For subjects completing treatment, follow up visits will occur on Days 56, 180, and 365 from the first dose of F-652. The 365-day follow up visit will evaluate the subject's general health and aGVHD status. Subjects will be discharged from the study following the Day 365 Follow-up Visit.

4 STUDY POPULATION SELECTION

4.1 Study Population

The study population will consist of adult male and female subjects aged ≥18 to ≤80 years of age with newly diagnosed stage I-IV lower GI aGVHD[1] following allogeneic HSCT.

Eligible subjects must meet all entry criteria prior to receiving study medication, except for histologic confirmation of disease, as outlined below. If lower GI aGVHD is not confirmed histologically, the subject will be withdrawn from the study and replaced.

4.2 Inclusion Criteria

Each subject must meet the following criteria to be enrolled in this study:

1. Age ≥18 years and ≤80.
2. Newly diagnosed stage 1-4 lower GI aGVHD[1] with a minimum stool volume >500 mL/day (determined by the maximum stool output in the preceding 3 days) following allogeneic HSCT using bone marrow or peripheral blood stem cells, or cord blood.
3. Subjects are willing to undergo a biopsy to confirm lower GI aGVHD. Biopsy results are not needed to initiate treatment. However, if aGVHD is not confirmed histologically, treatment with F-652 will be discontinued.
4. Female subjects of childbearing potential who: agree to practice 2 effective methods of contraception at the same time from the time of signing the informed consent form (ICF) through 90 days after the last dose of study drug, OR are postmenopausal for at least 1 year before the screening visit, OR are surgically sterile, OR agree to practice true abstinence when this is in line with the preferred and usual lifestyle of the subject (periodic abstinence and withdrawal are not acceptable methods of contraception).
5. Male subjects, even if surgically sterilized (i.e. status post-vasectomy) must agree to one of the following: agree to practice effective barrier contraception during the entire study treatment period and through 90 days after the last dose of study drug, OR agree to practice true abstinence when this is in line with the preferred and usual lifestyle of the subject (periodic abstinence and withdrawal are not acceptable methods of contraception).
6. Have adequate renal function (Serum creatinine ≤3 mg/dL).
7. ANC ≥500/mm^3.
8. Show evidence of a personally signed and dated informed consent document indicating that the subject (or legally acceptable representative) has been informed of all pertinent aspects of the trial.

4.3 Exclusion Criteria

Subjects who meet any of the following criteria will be excluded from the study.

1. Evidence of relapse or progression of hematologic malignancy at the time of study enrollment.
2. Active uncontrolled infection. Subjects with a controlled infection receiving definitive therapy for 48 hours prior to enrollment are eligible.
3. Subjects requiring vasopressors or mechanical ventilation.
4. Subjects who have received previous systemic corticosteroids for the treatment of acute GI GVHD for longer than 5 days. Subjects who were treated with systemic corticosteroids for aGVHD for a prior allogeneic HSCT ≥12 months ago are eligible.

5. Subjects who received any corticosteroid therapy (for non-GVHD) at doses >0.5 mg/kg/day prednisone (or IV equivalent) within 7 days prior to the onset of GVHD therapy.
6. Subjects who developed aGVHD after unplanned donor lymphocyte infusion.
7. Subjects with chronic GVHD features (i.e., acute/chronic GVHD overlap syndrome or classical chronic GVHD).
8. History of psoriasis.
9. History of epithelial malignancies including melanoma or any carcinomas.
10. History or diagnosis of mantle cell lymphoma or anaplastic large cell lymphoma.
11. Subject is pregnant or breast-feeding.
12. Evidence of current uncontrolled cardiovascular conditions, including uncontrolled hypertension, uncontrolled cardiac arrhythmias, symptomatic congestive heart failure, unstable angina, or myocardial infarction within the past 6 months.
13. The subject or guardian is unable to give informed consent or unable to comply with the treatment protocol including appropriate supportive care, follow-up, and research tests.
14. The subject has tested positive for the Clostridium difficile toxin within 7 days of study entry.
15. Cytotoxic, biologic, or investigational agents are not permitted throughout the study. These include, but are not limited to, antithymocyte globulin, alemtuzumab, rituximab, photopheresis, and thalidomide. Subjects who participated in any other investigational drug trial or had exposure to any other investigational agent, device or procedure, within 4 weeks prior to screening and throughout the entire trial, except for trials of investigational drugs administered prophylactically for GVHD or CMV post allogeneic HSCT. In this exception, the other investigational drug must be discontinued upon enrolling (i.e., screening/sign ICF) into this study.
16. Any serious medical or psychiatric illness that could, in the Investigator's opinion, potentially interfere with the completion of treatment according to this protocol.

5 STUDY TREATMENTS

5.1 Description of Treatments

5.1.1 Study Drug: F-652 (Recombinant human IL-22)

The drug product (DP) was manufactured by [redacted] under Good Manufacturing Practice (GMP) for pharmaceutical products.

[redacted]

5.1.2 Preparation [redacted]

[redacted]

5.2 Treatments Administered

5.2.1 F-652

Treatment will be administered IV on an inpatient and/or outpatient basis depending on the subject's clinical condition. Dose reduction of F-652 is described in Section 5.2.1.1. No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the subject's aGVHD.

The treatment program will consist of 4 doses of F-652 administered weekly (every 7 days). Treatment, if all doses are given on time, will occur on Days 0, 7, 14, and 21. Doses can be administered ± 2 days to accommodate scheduling (see Table 5.2.1.1).

Table 5.2.1.1. F-652 administration schedule

Dose number	Day of treatment
Dose 1	Day 0
Dose 2	Day 7 (± 2)
Dose 3	Day 14 (± 2)
Dose 4	Day 21 (± 2)

Doses may be delayed up to 2 weeks awaiting toxicity resolution. Delay beyond 2 weeks for resolution of toxicity related to the study drug will mandate dose reduction or removal of the subject from the study.

[redacted]

Safety criteria for stopping doses: If an adverse reaction occurs during the administration of F-652, the infusion may be slowed or stopped at the discretion of the PI. If the infusion is slowed or temporary stopped, the total infusion time should not exceed 3 hours. The adverse reaction must be recorded on the AE page of the electronic Case Report Form (eCRF). Subjects will be carefully observed during each infusion. Subjects will remain under observation for 1 hour after the infusion.

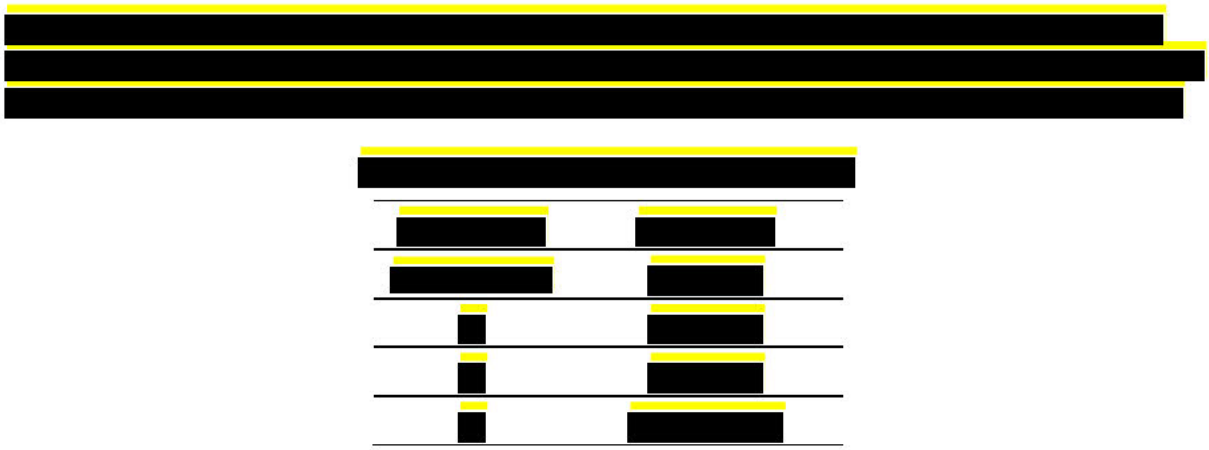
5.2.1.1 Pre-Treatment Criteria and Dose Modification Guidelines

Subjects should meet the criteria outlined below before initiation into the next treatment cycle. If the subject does not meet the criteria, dosing should be delayed for up to 1 week. At the end of that time, the subject should be re-evaluated to determine whether the criteria have been met. If the subject continues to fail to meet the criteria, therapy should be delayed and evaluated as necessary for the potential resumption of treatment. The maximum delay before treatment should be permanently discontinued will be 2 weeks from last dose or at the discretion of the PI.

Criteria for continuation to next treatment dose:

- ANC $\geq$500/mm^3
- Serum creatinine $\leq$3.0 mg/dL
- All other non-hematologic toxicities attributed as probable or definite related to the study drug must resolved to $\leq$grade 1 or to the subject's baseline condition.

[redacted]



5.2.2 Systemic Corticosteroids

All subjects enrolled in this trial must be initiated on prednisone at a dose of 2 mg/kg/day. Patients may receive IV methylprednisolone at prednisone comparable dosing and may be administered as in divided doses. Concomitant use of poorly absorbable corticosteroids (i.e. budesonide/beclomethasone) will be allowed in combination with systemic corticosteroids and the study drug. Patients must be maintained on 2 mg/kg/day of prednisone (or comparable dose of methylprednisolone) for 3 days following the first dose of F-652 and the dose must not be tapered to less than 0.25 mg/kg/day of prednisone or 0.2 mg/kg/day methylprednisolone by Day 28. Corticosteroids can otherwise be tapered per institutional practice.

Recommended Corticosteroids Taper for Responders:

- Days 0-7: 2 mg/kg/day of prednisone (or IV equivalent) divided once or twice a day.
- Days 8-15: 1.5 mg/kg/day of prednisone (or IV equivalent)
- Days 16-21: 1 mg/kg/day of prednisone (or IV equivalent)
- Days 22-28: 0.5 mg/kg/day of prednisone (or IV equivalent)
- Days 29-35: 0.25 mg/kg/day of prednisone (or IV equivalent)

5.2.3 Prophylaxis Against Infection

Subjects will be treated according to the institutional allogeneic BMT standard of care guidelines and will be given prophylaxis against the following: 1) *Pneumocystis carinii*, 2) Herpes simplex and Herpes Zoster, and 3) fungal infections. Subjects should be closely monitored for reactivation of CMV. Clinically significant CMV viremia will be treated according to local institutional standard practice.

5.2.4 Supportive Care

Subjects will receive supportive care according to the local institutional standard practice. Blood transfusion and growth factors may be provided based on institutional practices and should be clearly recorded in the eCRF.

5.3 [redacted]

[redacted]

5.4 Investigational Product at Study Site

Study medication will be shipped to each institution. The IWRS will be used to monitor the inventory level of the investigational drug supply at clinical sites and for subject number assignment and study medication dispensing. The Investigator is responsible for monitoring the inventory of medication supplies to ensure sufficient supply for the site. The study monitors will also verify the drug accountability during each site-monitoring visit. At the end of the study, all study drug supplies will be returned to the Sponsor/designee by the study monitor for each site.

5.5 Test Article Accountability

The Investigator will maintain accurate records for the receipt of all study medication. In addition, accurate records will be kept regarding when and how much study medication is dispensed and used by each subject in the study. Drug accountability and distribution of drug will be done at each visit as needed during the course of the study. Reasons for deviation from the expected dispensing regimen must also be recorded. Inventory at each site will be monitored by the IWRS system and replenished when necessary. A storage temperature log is also to be maintained for documentation of proper storage conditions. Malfunctions must be reported to the Sponsor immediately. The clinical supplies for this study must be maintained under adequate security and stored under conditions specified on the label.

5.6 Investigational Product at Study Site at Study Conclusion

At completion of the study, all study medication will be reconciled by the designee and then returned, retained, or destroyed according to applicable country regulations. Prior to any

action being taken with study medication after the study is completed, the Investigator will contact the Sponsor or the contracted research organization for approval of such action.

5.7 Selection and Timing of Dose for Each Subject

Once a subject has met the eligibility criteria, dosing will commence as specified in Section 5.2.

5.8 Method of Assigning Treatment to Subjects

Study site personnel will assign the investigational drug to each subject via IWRS. The IWRS system will identify which study drug vial is to be used for reconstitution and administered to a subject using its unique identification number.

6 TRIAL PROCEDURES

Trial procedures and scheduling are listed in detail in: Appendix 1 (Trial Procedures and Study Activities) and Appendix 2 (Schedule of Procedures and Events).

6.1 Measures to Avoid Bias

6.1.1 Randomization

There is no randomization as this is a single arm study. An 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.

6.1.2 Blinding

There is no blinding in this single arm study trial.

6.1.3 Simultaneous Utilization of All Arms

There is only one treatment arm in this study.

6.2 Concomitant Therapy

1) All subjects enrolled in this trial will receive corticosteroids. The dose of prednisone (or IV equivalent) is 2 mg/kg/day as therapy for aGVHD. Tapering is permitted as outlined in Section 5.2.2. All concomitant therapies through Day 56 should be recorded in the subject's eCRF; after Day 56, only concomitant medications administered in relation to or for an SAE are collected.

6.2.1 Approved Medications

Use of concomitant anti-infective agents for prophylaxis or treatment of infection(s) is permitted and will follow the institutional guidelines.

[redacted]

Subjects may be switched to an alternate immunosuppressive regimen as clinically indicated or based on side effects at the discretion of the Investigator. As applicable, drug levels of [redacted] should be obtained at Screening and just before dosing on Days 7, 14, and 21, as well as the End of Treatment Visit. This will be done for monitoring and dose adjustment per standard of care, or more frequently as needed. These immunosuppressant medications may result in a variety of drug interactions which may require dose adjustments.

6.2.2 Change from Baseline in Medications

Systemic corticosteroid therapy may be tapered, as indicated in Section 5.2.2. No tapering of systemic immunosuppression will be allowed sooner than Study Day 3. Taper after Study Day 3 is allowed at the discretion of the treating physician. The treating physician may adjust tacrolimus, CSA, MMF, and sirolimus medications, as necessary.

6.3 Restrictions

6.3.1 Medications Not Permitted

Besides those medications specified in the exclusion criteria (see Section 4.3), addition of other systemic immunosuppression agents would result in subject withdrawal from the study. Cytotoxic, biologic, or investigational agents are not permitted throughout the study.

6.4 Treatment Compliance

Subject compliance will be monitored by obtaining the study medication accountability inventory and a record of any delayed doses, along with a list of concomitant medications according to the institutional policy, at each visit.

7 STUDY PROCEDURES

7.1 Informed Consent

The Investigator will obtain and document an ICF for each subject screened in this study. Prior to the initiation of any study procedures, all subjects will be informed in writing of the nature of the protocol and investigational therapy, its possible hazards, and their right to withdraw at any time, and will sign a form indicating their consent to participate. The subject's medical records should contain written documentation indicating that informed consent was obtained. The ICF must be reviewed and approved by the Investigator's designated Institutional Review Board (IRB)/Independent Ethics Committee (IEC) and by the Sponsor. The ICF should include all the elements as outlined in Section 4.8.10 of the ICH guideline for GCP (E6).

7.2 Medical History

Medical history will be collected at screening evaluation and clinical symptomatology will be assessed by subject interview at each scheduled visit post-initial dose of F-652 therapy. Concomitant medications, dose of corticosteroids, illnesses, AEs, and participation in other investigational drug studies will also be recorded. If other unscheduled activities are performed up to Study Day 56, such as physical examination or laboratory studies, the results should be recorded in the subject's eCRF.

7.3 Physical Examination

Physical examination including height and body weight will be performed at screening. Height will be recorded at screening only; if it is not possible to measure height at screening, a historical record of height may be used (e.g., height as measured at hospital admission). Physical exam will be done on visit Days 0, 28, 56, 180, and 365 post-initial dose of F-652 therapy. Any change from baseline will be evaluated and assessed by the Investigator. Any clinically significant findings from an abbreviated physical exam for any unscheduled visit up to Study Day 56, as deemed necessary by medical staff must be included in the eCRFs.

7.4 Vital Signs

Blood pressure, heart rate, body temperature, and respiratory rate will be measured according to Appendix 2 (Schedule of Procedures and Events) or following early termination of the study. If multiple vital signs measurements are taken for a subject on the day of a study visit, the results of the first vital signs measurement of the day will be recorded on the CRFs. Vital signs are to be taken 15 minutes after the start of infusion, at the completion of infusion, and 1 hour after the end of the infusion for each dose of F-652.

7.5 Clinical Laboratory Tests

Blood will be collected to assess hematology and serum chemistry profiles at screening and on Days 0, 7, 14, 21, 28, and 56 as per Appendix 2 (Schedule of Procedures and Events). For each subject, all clinical laboratory assessments will be reported in the eCRF.

Immunogenicity serum samples will be taken on Days 0, 7, 14, 21, 28, and 56, pre-dosing of F-652, where applicable. All immunogenicity samples will be shipped to the Sponsor or its agent, as directed in the study laboratory manual.

In the event of multiple laboratory assessments are performed for a subject on the day of a study visit during the course of the SOC, the results of the most complete laboratory assessment will be recorded on the CRFs.

7.5.1 Laboratory Parameters

Subjects will be in a seated or supine position during blood collection. In the event of abnormal clinical laboratory values, the Investigator will make a judgment whether or not the abnormality is clinically significant. Clinical laboratory tests will include those listed in Table 7.5.1.1.

Table 7.5.1.1. List of Laboratory Tests

Hematology:

- Hematocrit (Hct)
- Hemoglobin (Hgb)
- Mean corpuscular volume (MCV)
- Platelet count
- Red blood cell (RBC) count
- White blood cell (WBC) count with differential

Other:

Chemistry:

- Albumin
- Alkaline phosphatase (ALP)
- ALT
- AST
- C-reactive protein (CRP)
- Blood urea nitrogen (BUN)
- Calcium (Ca)
- Carbon dioxide (CO_2)
- Chloride (Cl)
- Creatinine
- Glucose
- Fibrinogen
- Lactate dehydrogenase (LDH)
- Phosphorus
- Potassium (K)
- Sodium (Na)
- Total bilirubin
- Direct bilirubin
- Total cholesterol
- Total protein
- Triglycerides

7.5.1.1 Sample Collection, Storage, and Shipping

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, as per the schedule of events in Appendix 2 (Schedule of Procedures and Events). Blood, stool, and skin research samples for exploratory analyses will be shipped according to details in a provided laboratory manual. A separate laboratory manual will be provided by the central laboratory for blood samples collected for PK analysis and will be performed according to the schedule presented in Appendix 3).

7.5.1.2 Blood Volume

Total blood volume for all research tests will be approximately 200 mL.

7.5.2 Urinalysis

Urinalysis parameters for clinical laboratory tests will be obtained at screening and Day 28 and will include the following assessments:

appearance	occult blood
bilirubin	pH
glucose	protein
ketones	specific gravity
leukocyte esterase	urobilinogen

7.5.3 Assessment of aGVHD

A complete assessment of aGVHD will be conducted at Screening (baseline) and at Study Visit Days 7, 14, 21, 28, 56, 180, and 365 post-initial dose of F-652 therapy.

7.6 Efficacy Assessments

The aim of this 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 allogeneic HSCT recipients. The efficacy primary endpoint is to assess the lower GI aGVHD response rate at Day 28.

7.6.1 Methods and Timing for Assessing Acute Graft-Versus-Host Disease (aGVHD)

Acute GVHD will be diagnosed clinically and staged according to modified Keystone criteria (Appendix 5). Grading of aGVHD will be based on IBMTR criteria[52] (Appendix 5). Biopsy samples will be obtained prior to therapy initiation for confirmation of clinical diagnosis. Acute GVHD assessments will be obtained at Screening (baseline) and on Days 7, 14, 21, 28, 56, 180, and 365 post-initial dose of F-652 therapy.

Responses to aGVHD therapy will be determined using published definitions[6] of GVHD response and will be assessed on Days 14, 28, and 56.

Acute lower GI GVHD Response Criteria:

Scoring of CR, VGPR, PR, progression, and NR will be in comparison to the participant's lower GI aGVHD stage prior to treatment with F-652. Response will be based on the following response definitions:

- CR: stage of 0 for all aGVHD symptomatology in the lower GI tract with no additional intervening aGVHD therapy.
- VGPR: tolerating food or enteral feeding, predominantly formed stools, no overt GI bleeding or abnormal cramping.
- PR: improvement by at least 1 stage in lower GI aGVHD symptomatology with no additional intervening therapy for their GVHD.
- Progression**:** deterioration in lower GI tract aGVHD.
- NR/stable: absence of any improvement in aGVHD stage. Subjects receiving secondary therapy (including need to re-escalate corticosteroid dose to

≥2.5 mg/kg/day of prednisone (or methylprednisolone equivalent) will be classified as non-responders.

Response for All Organs Involved with aGVHD:

Treatment response defined as CR, VGPR, PR, MR, progression, and NR will be in comparison to the subject's aGVHD stage prior to treatment with F-652. Response will be based on the following response definitions:

- CR: stage of 0 of all aGVHD symptomatology in all GVHD target organs with no additional intervening GVHD therapy.
- VGPR: tolerating food or enteral feeding, predominantly formed stools, no overt GI bleeding or abnormal cramping, no more than occasional nausea or vomiting.
- PR: improvement in aGVHD stage in all initial GVHD target organs without complete resolution and without worsening in any other GVHD target organs
- MR: improvement in 1 or more GVHD target organs with deterioration in another organ manifesting symptoms of aGVHD or development of symptoms of aGVHD in a new organ.
- Progression: worsening of GVHD in at least 1 organ without any improvement in others.
- NR/stable: absence of any improvement in aGVHD stage. Subjects receiving secondary therapy (including need to re-escalate corticosteroid dose to ≥2.5 mg/kg/day of prednisone [or methylprednisolone equivalent of 2 mg/kg/day]) will be classified as non-responders.

Treatment Failure:

The following will be considered as treatment failures:

- NR/stable after 14 days of therapy.
- Progression after 7 days of therapy.
- Administration of additional systemic therapy for aGVHD (or re-escalation of corticosteroids dose to ≥ 2.5 mg/kg/day of prednisone (or methylprednisolone equivalent)
- TRM

7.7 Safety Assessments

7.7.1 Standard Safety Parameters

Standard safety parameters include hematology, blood chemistry, urinalysis, vital signs, physical examination, and symptom/toxicity assessment as outlined in Section 7 and according to the schedule of events presented in Appendix 2 (Schedule of Procedures and Events).

The NCI CTCAE will be used to grade potential AEs (see Section 7.7.3.3).

7.7.2 Adverse Events Assessments

7.7.2.1 Procedures for Eliciting Reports of and Recording Adverse Events and Inter-current Illnesses

The Investigator is to document on the eCRFall directly observed AEs and all AEs spontaneously reported by the trial subject through Study Day 56 (or approximately 28 days after last dose of study drug). After Study Day 56, only 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).

Each trial subject will be questioned about AEs at each clinic visit. AEs can be discovered by observing the subject, questioning the subject objectively, and/or receiving an unsolicited complaint from the subject. For all study visits, up to and including a subject's Day 56 study visit,, a history of any AEs occurring since the last visit are to be recorded in the study the eCRF pages. Only SAEs deemed possibly, probably, or definitely related to the investigational product are required to be recorded from study Day 56 through to the end of the study (Day 365). Specimens are to be collected for specified laboratory tests as needed and results will be reviewed. Physical examinations will be performed as appropriate.

7.7.2.2 Timing and Duration of Follow-up of Subjects after Adverse Events Reported

The subject is routinely followed up for 4 weeks after termination of drug dosing for identification of potential AEs. Any Grade 3 or 4 AEs or SAE is to be followed until it has resolved or stabilized. Sponsor must be advised of all Grade 3 or 4 AEs within one week of their identification and of all SAEs within 24 hours of identification. Subjects will be followed until the AE resolves or stabilizes.

7.7.3 Defining, Grading, and Reporting Adverse Events

7.7.3.1 Adverse Events

All AEs, whether observed by researchers or reported by subjects, regardless of treatment group or suspected causal relationship to the investigational product(s), 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).

For all AEs, the Investigator must obtain information adequate to determine the cause and outcome of the AE and to assess whether it meets the criteria for classification as an SAE, which require immediate notification to Sponsor and its designated representative (see Section 7.7.3.7). The Investigator is required to assess causality and record that assessment on the eCRF. Follow-up of the AE after the date of therapy discontinuation is required if the AE or its sequelae persist. Follow-up is required until the event or its sequelae is resolved and/or stabilized at a level acceptable to the Investigator and the Sponsor clinician and safety officer.

DEFINITION

An AE is any occurrence or worsening (from baseline) of an undesirable or unintended sign, symptom (including an abnormal laboratory finding), or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. Worsening of underlying disease will not be considered to be an AE, since it will be

classified as a treatment failure. Pregnancy will not be considered to be an AE, but will be collected separately. However if the resultant child has a birth defect, this will be considered to be an SAE.

Throughout the study, the Investigator must record all AEs on the eCRF through Study Day 56, regardless of the severity or relationship to study medication or procedure. The Investigator should treat subjects with AEs appropriately and observe them at suitable intervals until the events resolve or stabilize.

AEs will be regarded as 'pre-treatment' if they occur between the Screening Visit (signing of ICF) and the time of administration of the first dose of study medication. All events reported following the first study medication administration will be recorded as treatment emergent AEs (TEAE). AEs that are unresolved at the time of study termination will be followed until they resolve or stabilize.

7.7.3.2 Serious Adverse Events

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

- Death: A death occurring during the study or which comes to the attention of the Investigator during the protocol-defined follow-up after the completion of therapy, whether or not considered treatment-related, must be reported.
- Life-threatening: Any adverse therapy experience that places the subject, in the view of the Investigator, at immediate risk of death from the reaction as it occurred.
- Inpatient hospitalization (i.e. the event required at least a 24-hour hospitalization or prolonged hospitalization beyond the expected length of stay). Hospitalization admissions and/or surgical operations scheduled to occur during the study period, but planned prior to study entry are not considered SAEs if the illness or disease existed before the person was enrolled in the trial, provided that it did not deteriorate in an unexpected manner during the trial.
- Persistent or significant disability/incapacity.
- Congenital anomaly/birth defect.

Additionally, any AEs occurring at any dose that suggests a significant hazard, contraindication, side effect, or precaution may be considered an SAE. This includes, but may not be limited to any of the following events:

- Spontaneous abortion or death of the infant within 1 month of birth.
- An event that required intervention to prevent permanent impairment or damage.

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

Pregnancy is NOT considered an SAE (see Section 7.7.3.8).

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 an event meets any of the criteria listed above, it must be reported on the eCRFs as an SAE regardless of its presumed relationship to the study drug. However, after Study Day 56, only SAEs deemed possibly, probably, or definitely related to the investigational product are required to be reported through to the end of the study (Day 365).

7.7.3.3 Severity and Grading

Toxicity grades are assigned by the study site to indicate the severity of AEs occurring in study participants. To do this, the NCI CTCAE grading system will be used in AE reporting. The purpose of using the CTCAE system is to provide a standard language to describe toxicities, to facilitate tabulation and analysis of the data, and to facilitate the assessment of the clinical significance of all AEs. AEs should be recorded and graded 1 to 5 according to the CTCAE grades provided below:

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.

*Activities of Daily Living (ADL):

*Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

**Self-care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

If an AE term cannot be found in the CTCAE, the AE should be graded based on the verbiage provided for the grades above.

7.7.3.4 Relationship

The relationship between an AE and an investigational product is determined by the site Investigator and recorded on the appropriate eCRF and/or SAE Report Form. The CTCAE provides the following descriptors and definitions. (See Table 7.7.3.1.)

The Investigator's determination of drug-relatedness (attribution) for each AE should be recorded in the source documentation.

For additional information, please consult the CTCAE and the Common Toxicity Criteria Document at the following URL: http://ctep.cancer.gov/reporting/ctc.html.

Table 7.7.3.1. Attribution of Adverse Events

"Unrelated" Category Code:		
Code	Descriptor	Definition
1	Unrelated	The AE is clearly not related to the investigational agent(s).
2	Unlikely	The AE is doubtfully related to the investigational agent(s).
"Related" Category Codes:[1]		
Code	Descriptor	Definition
3	Possible	The AE may be related to the investigational agent(s).
4	Probable	The AE is likely related to the investigational agent(s).
5	Definite	The AE is clearly related to the investigational agent(s).

[1] For regulatory reporting purposes, only SAEs that meet the definition of "related" and are unexpected will be reported in an expedited manner.

7.7.3.5 Clinical Significance

A clinically significant change from baseline may be recorded as an AE if deemed appropriate by the PI or Sponsor.

7.7.3.6 Clinical Laboratory Adverse Events

The criteria for determining whether an abnormal objective test finding should be reported as an AE are as follows:

1. Test result is associated with accompanying symptoms, and/or
2. Test result requires additional diagnostic testing or medical/surgical intervention, and/or
3. Test result leads to a change in trial dosing or discontinuation from the study, significant additional concomitant drug treatment, or other therapy, and/or
4. Test result is considered to be an AE by the Investigator or Sponsor.

Any grade 3-4 laboratory abnormalities (except for hematologic abnormalities if present at baseline) are considered to be AEs independent of associated signs or symptoms. Any abnormal test result that is determined to be an error does not require reporting as an AE.

NCI CTCAE will be used to grade the severity of laboratory abnormalities.

7.7.3.7 Reporting Adverse Events (Serious and Non-serious)

Each AE is to be classified by the Investigator as serious or non-serious. This classification determines the reporting procedures to be followed.

SAEs are reportable from the time that the subject enters into the clinical trial up to and including 30 calendar days after the last administration of the investigational product. Any SAE occurring more than 30 calendar days after completion of the study must be promptly reported if a causal relationship to study drug is suspected.

If an SAE occurs, the Generon Safety Officer and/or his/her agent are to be notified within 24 hours of awareness of the event by the Investigator. In particular, if the SAE is fatal or life-threatening, notification must be made to the Generon Safety Officer or his/her agent immediately, irrespective of the extent of available AE information. This time frame also applies to additional new information (follow-up) on previously forwarded SAE reports.

In the rare event that the Investigator does not become aware of the occurrence of an SAE immediately (e.g., if an outpatient trial subject initially seeks treatment elsewhere), the Investigator is to report the event within 24 hours after learning of it and document the time of his/her first awareness of the AE.

For all SAEs, the Investigator is obligated to provide information to the Generon Safety Officer and his/her agent in accordance with the time frames for reporting specified above. In addition, Generon study clinician or the Generon Safety Officer may request an Investigator to obtain specific follow-up information in an expedited fashion. This information may be more detailed than that captured on the AE eCRF. This will include a description of the AE in sufficient detail to allow for a complete medical assessment of the case and independent determination of possible causality. Information on other possible causes of the event, such as concomitant medications and illnesses must be provided. In the case of a subject death, a summary of available autopsy findings must be submitted as soon as possible to Generon Safety Officer and his/her designated representative.

The Investigator’s causality assessment must be included in all reports of SAEs. An Investigator’s causality assessment is the determination of whether there exists a reasonable possibility that the investigational product caused or contributed to an AE. If the Investigator’s final determination is that causality is unknown and the Investigator cannot determine whether the event is related to study drug, then the event will be handled as “related to study drug” for reporting purposes. If the Investigator's causality assessment is "unknown but not related to study drug", this should be clearly documented on study records. In addition, if the Investigator determines the AE is associated with trial procedures, the Investigator must record this causal relationship in the source documents and eCRF, as appropriate and report such an assessment in accordance with the SAE reporting requirements.

It should be noted that the form for collection of SAE information is not the same as the AE eCRF. Where the same data are collected, the forms must be completed in a consistent manner. For example, the same AE term should be used on both forms. AEs should be reported using concise medical terminology on the eCRFs as well as on the form for collection of SAE information.

If a subject begins a new therapy (i.e., is discontinued from the study and completes the end of study assessment), the AE reporting period will end at the time of the new treatment is started. Death must be reported if it occurs within 30 days after the date of last dose of investigational product, irrespective of any intervening treatment.

Since the study population (patients with aGVHD) is expected to have a relatively high background of AEs, anticipated AEs that are serious will not be reported in an expedited manner to the FDA, as they are anticipated to occur at a frequency independent of drug exposure. Examples include events related to the disease/condition under study (e.g., symptoms, disease progression), events unlikely to be related to the underlying disease or condition under investigation but common in the study population independent of drug

therapy, and events anticipated from any background treatment. These events do not warrant expedited reporting as individual cases because it is not possible, based on a single case, to determine that there is a reasonable possibility that the drug caused the event. An IND safety report will be submitted only if an aggregate analysis indicates that such events are occurring more frequently than expected in the drug treatment group.

7.7.3.8 Exposure *In Utero*

For investigational products within clinical trials and for marketed products, an *exposure in-utero* (EIU) occurs if a female becomes, or is found to be pregnant either while receiving or having been exposed to (e.g., environmental toxin) an investigational medication or product, or the female becomes or is found to be pregnant after discontinuing and/or being exposed to the investigational medication or product.

If any trial subject becomes or is found to be pregnant while receiving an investigational medication/product, the Investigator must submit this information to the Generon Safety Officer or sponsor designee (using the SAE reporting contact fax number) on a Pregnancy Report Form. This must be done irrespective of whether an AE has occurred, and within 24 hours of awareness of the pregnancy.

The information submitted should include the anticipated date of delivery (see below for information related to induced termination of pregnancy).

The Investigator will follow the subject until completion of the pregnancy or until pregnancy termination (i.e., induced abortion) and then notify Generon (Shanghai) Corporation Medical Officer or Sponsor's designee of the outcome.

The Investigator will provide this information as a follow up to the initial Pregnancy Report Form. The reason(s) for an induced abortion should be specified. A pregnancy report is not created when an ectopic pregnancy report is received since this pregnancy is not usually viable. Rather, an SAE is to be submitted with the event of ectopic pregnancy.

If the outcome of the pregnancy meets the criteria for immediate classification as a SAE (i.e., spontaneous abortion, stillbirth, neonatal death, or congenital anomaly [including that in an aborted fetus, stillbirth or neonatal death]), the Investigator should follow the procedures for reporting SAEs.

In the case of a live birth, the "normality" of the newborn can be assessed at the time of birth (i.e., no minimum follow-up period of a presumably normal infant is required before a Pregnancy Report Form can be completed). The "normality" of an aborted fetus can be assessed by gross visual inspection, unless pre-abortion test findings are suggestive of a congenital anomaly.

Additional information about pregnancy outcomes that are classified as SAEs follows:

- "Spontaneous abortion" includes miscarriage and missed abortion.
- All neonatal deaths that occur within 1 month of birth should be reported, without regard to causality, as SAEs. In addition, any infant death after 1 month that the Investigator assesses as possibly related to the in utero exposure to the investigational medication should be reported.

7.7.4 Toxicity (Adverse Event) Management

Subjects should receive full supportive care per institutional guidelines including blood products, antibiotics, and antiemetics at the discretion of the provider. Suggested guidelines for potential toxicities are detailed in the subsections below, including when and how long study drug should be withheld and when subjects should be discontinued from the study.

Re-initiation of the study drug that was withheld cannot occur until drug-related toxicity (probably or definitely related) decreases to ≤grade 1 or baseline condition. Subjects who require >14 days recovering from a potential drug-related toxicity will be taken off study treatment. Dose modification or delay may occur in the setting of lower grade toxicity if the Investigator believes that is in the interest of a subject safety. In the event of a grade 1-2 toxic event, re-treatment with F-652 is permitted in the presence of the toxicity.

If a probably related or definitely related AE occurs again after resumption of study drug, subject will hold drug until resolution to ≤grade 1 or baseline condition and then resume study drug at a reduce dose as outlined in Table 7.7.4.3**Error! Reference source not found.**. If resolution of an initial AE takes >7 days but ≤14 days and has no other explanation, then the study drug will be restarted at a reduced dose upon resolution ≤grade 1 or baseline condition. If resolution of an initial AE takes >7 days and has an alternative explanation not related to study, F-652 may be restarted at the original dose at the discretion of the Investigator. If resolution of an initial AE takes >14 days and has no other explanation, then the subject will be removed from the study treatment.

Study drug will be held immediately at the identification of a study-related SAE. If an SAE resolves to CTCAE ≤grade 1 or baseline in ≤7 days, then a subject may resume study drug at the original dose. If an SAE does not resolve but is determined to be unrelated to study drug, treatment can be restarted at the original dose at the discretion of the Investigator.

7.7.4.1 Hematologic Toxicity

Blood counts should be checked at each treatment visit. Granulocyte colony stimulating factor (G-CSF) is not routinely included in the care of these subjects but can be used at the discretion of the Investigator. G-CSF treatment is strongly recommended if ANC <1000 mm^3.

No primary prophylactic use of white blood cell growth factor support is recommended, but may be used as secondary prophylaxis at the discretion of the Investigator.

Hematology toxicity related to F-652 treatment should be managed as outlined in Table 7.7.4.1**Error! Reference source not found.**.

Table 7.7.4.1. Hematology Toxicity Management

Blood Counts (ANC/mm^3)	**Administer % of Full Dose**
≥500	100%
<500 and subject afebrile (temp <38.0ºC)	Hold F-652 and give G-CSF support. Give 100% of dose once ANC >500 mm^3.
<500 and subject febrile (≥38ºC)	Hold F-652. Treatment of neutropenic fever per institutional guidelines. Restart at full dose after 1 week if ANC >500 mm^3 (G-CSF support is allowed).

7.7.4.2 Skin Toxicity

Skin dryness was the most common side effect reported with F-652 use. Skin erythema was also observed, but was less common. Baseline skin findings including rash should be documented prior to initiation of each treatment dose. Given that the differential diagnosis also includes skin aGVHD, histologic evaluation is recommended for assessment of etiology at any grade of presentation. Skin toxicity related to F-652 treatment is to be managed as outlined in Table 7.7.4.2**Error! Reference source not found.**.

Table 7.7.4.2. Skin Toxicity Management

Skin Rash	Administer % of Full DoseF-652 dose	Comments
Grade 1	100%	Obtain skin biopsy, start topical corticosteroids and/or moisturizer
Grade 2 Scattered but not generalized erythema	100%	Obtain skin biopsy, start topical corticosteroids and/or moisturizer
Grade 3 Generalized erythroderma, ulcerative dermatitis or skin changes with pain interfering with function	Withhold dose until toxicity is ≤Grade 1 or has returned to baseline. If subject has a second grade 3 toxicity or if resolution of the first takes >7 days, withhold dose until toxicity is ≤grade 1, then reduce dose by one dose level and resume treatment.	Obtain skin biopsy. If a 3rd Grade 3 event occurs, subjects will be discontinued from the study.
Grade 4 Life-threatening, disabling	Withhold dose until toxicity is ≤grade 1, then reduce dose by one dose level and resume treatment, or discontinue at the discretion of the PI after discussion with treating physician.	Obtain skin biopsy. If a 2nd Grade 4 event occurs, subjects will be discontinued from the study.

7.7.4.3 Other Toxicities

All other Grade 3-4 toxicities (except hematologic and skin) considered probably or definitely related to F-652 should be managed as outlined in Table 7.7.4.3**Error! Reference source not found.**.

Table 7.7.4.3. Other Toxicity Management

Toxicity	Administer % of Full DoseF-652 dose	Comments
Grade 1	100%	
Grade 2	100%	
Grade 3	Withhold dose until toxicity is ≤grade 1 or has returned to baseline. If subject has a second grade 3 toxicity or if resolution of the first takes >7 days, withhold dose until toxicity grade is ≤1, then reduce dose by one dose level and resume treatment.	If a 3rd Grade 3 event occurs, subjects will be discontinued from the study.
Grade 4	Withhold dose until toxicity is ≤grade 1 or has returned to baseline, then reduce dose by one dose level and resume treatment, or discontinue at the discretion of the PI after discussion with treating physician.	If a 2nd Grade 4 event occurs, subjects will be discontinued from the study.

7.8 Concomitant Medication Assessments

All concomitant medications (over the counter or prescribed) taken by subjects during the screening period and throughout the duration of the study will be documented in the patient's medical/source records. Concomitant medications are to be recorded in the eCRFs as described below, up to Study Day 56. Common medications typical for treatment of aGVHD and/or transplant are to be documented on the "Common aGVHD/Transplant Medications" eCRF and will include the medication name and start/stop date of the medication regardless of dose changes. All other medications not common to aGVHD/transplant therapy are to be documented on the "Concomitant Medication" eCRF page and must include medication name, indication (reason for use), start/stop date, dose, route, and frequency.

After Study Day 56, only concomitant medications related to a SAE will be documented on the eCRFs.

7.9 Removal of Subjects from the Trial or Study Drug

A subject may withdraw from the trial at any time at his/her own request, or he/she may be withdrawn at any time at the discretion of the Investigator or Sponsor for safety, behavioral, or administrative reasons. The Investigator will document the reason for a subject's withdrawal from the study.

7.9.1 Criteria for Subject Withdrawal

The following are criteria for subject discontinuation from the study:

1. Subject withdraws study consent.
2. Subject is found to be ineligible for the protocol as per the Inclusion/Exclusion criteria.
3. Subject's lower GI acute GVHD is not confirmed histologically.
4. Subject has aGVHD progression after 7 days of therapy (dose 2) or at any subsequent point or NR/stable aGVHD after 14 days of therapy (dose 3). The Investigator may withdraw the subject from the study and treat the subject per the standard of care.
5. Subject requires more than 2 investigational drug (F-652) dose reductions.
6. Failure of the subject to comply with protocol requirements.
7. Subject is initiated on protocol-prohibited medications.
8. Exhibition of unacceptable toxicity (adverse event), which would make it difficult or dangerous to comply with further protocol requirements such as study visits, blood draws, etc.
9. Subject experiences an acute infection that is either not identified or controlled by the next scheduled infusion.
10. Subject develops serious infusion reaction (such as bronchospasm with wheezing or requires ventilatory support) or serum sickness-like reactions manifesting 1 to 14 days after drug administration.
11. Subject experiences a recurrent Grade 4 AE related to study treatment.
12. Subject develops malignancy, including skin cancer or relapse of the disease for which the allogeneic HSCT was performed.
13. Subject requires tapering of systemic corticosteroids (<2 mg/kg/day) before Study Day 3.
14. Subject requires an increase in their current immunosuppression therapy or the addition of systemic immunosuppression therapies due to active aGVHD.
15. There are changes in medical status of the subject such that the Investigator believes that subject safety will be compromised or that it would be in the best interest of the subject to stop participation in the study.

16. Death of the subject.
17. Subjects with a test consistent with pregnancy such as a positive beta-hCG.
18. Subject is lost to follow-up.

7.9.2 Procedures for Subject Withdrawal

At the time of study withdrawal, subjects, if capable, will be asked to complete all of the procedures that would normally be performed at the Day 28 (End of Treatment) assessment. Collection of research/exploratory samples is at the discretion of the Investigator. If the End of Treatment Visit for early withdrawal overlaps with another study visit (within 1-2 days), only one set of laboratory and research samples will be collected during the visit. If the End of Treatment Visit occurs between regularly planned study visits, a 1-2 day window is allowed for the visit and sample collection relative to the withdrawal date. All assessments for the visit must be completed and samples collected prior to the subject starting a new treatment. Withdrawn subjects will have a 30-day follow-up phone call after their last clinical assessment.

7.9.3 Replacements for Withdrawn Subjects

Subjects withdrawn from the study due to a failure of aGVHD histologic confirmation will be replaced.

7.9.4 Follow-Up of Withdrawn Subjects

At the time of withdrawal from study, the reasons for the withdrawal should be ascertained and recorded. If it is for a medical procedure, the outcome should be recorded.

If the subject withdraws consent to continue in the study, the subject will be requested at a minimum to participate in a post-treatment follow-up phone call (30 days after the last dose). If the subject declines, no further evaluations are to be performed and no attempts should be made to contact the subject or collect additional data. If the subject is withdrawn from the study prior to initiation of the study drug, no follow-up will be conducted.

If a subject does not return for scheduled visits, every effort should be made to re-establish contact. Attempts made to reach the subject should be clearly documented. If the subject cannot be contacted, every effort should be made to document subject outcome as far as possible.

7.9.5 Documentation

For any subject who withdraws, the date and the reason for the withdrawal must be recorded on the appropriate eCRF.

8 QUALITY CONTROL AND ASSURANCE

During trial conduct, Generon or its agents will conduct periodic monitoring visits to ensure that the protocol and GCP are being followed. The monitors may review source documents to confirm that the data recorded on eCRFs are accurate. The investigators and institutions will allow Generon's monitors or its agents and appropriate regulatory authorities direct access to source documents to perform this verification.

The trial sites may be subject to review by the IRB/IEC, quality assurance audits performed by Generon, and/or inspection by appropriate regulatory authorities from the US or other countries.

Investigators and their relevant personnel must be available during the monitoring visits and audits or inspections. Sufficient time must be devoted to these inspections.

The Investigator is required to keep accurate records to ensure the conduct of the study is fully documented. The Investigator is required to ensure that all eCRFs are complete and accurate for every subject entered in the trial.

The Sponsor is responsible for regular inspection of the conduct of the trial, for verifying adherence to the protocol, and for confirming the completeness, consistency, and accuracy of all documented data.

9 PLANNED STATISTICAL METHODS

9.1 General Considerations

Detailed methodology for summary and statistical analyses of the data collected in this trial will be documented in a Statistical Analysis Plan (SAP), which will be signed and maintained by the Sponsor. This document will expand upon and may modify the plans outlined in the protocol; however, any major modifications of the primary endpoint definition and/or its analysis will also be reflected in a protocol amendment. In this exploratory Phase IIa study, all statistical tests will be two-sided with no adjustment for multiplicity.

Descriptive summaries of variables will be provided where appropriate. For continuous variables, the number of non-missing values (n) and the median, mean, standard deviation, minimum, and maximum will be summarized. For categorical variables, the number and percent of each variable will be summarized. All collected data will be presented in listings.

9.2 Determination of Sample Size

As described in Section 9.6.1, this study is designed to distinguish between an unpromising Day+28 treatment response rate of 35% and a promising treatment response rate of 60% using a Simon's two-stage optimal design. With a maximum sample of 27 patients, this study has a type I error of 0.10 and a type II error of 0.10.

9.3 Analysis Populations

Three study populations are defined for the study: a Safety Population, an Efficacy Evaluable Population, and a PK Population. Additional study populations may be defined to further explore study data. Any additional study populations will be defined in either the SAP or in the final clinical study report.

9.3.1 Safety Population

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

9.3.2 Efficacy Evaluable Population

All subjects who receive study treatment and provide at least one post-treatment assessment for aGVHD treatment response 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.

9.3.3 Pharmacokinetic Population

All subjects who receive study treatment and provide sufficient samples for PK parameter estimation will be included in the PK Population, which will be used for all PK analyses. 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.

9.4 Demographics and Baseline Characteristics

All baseline subject characteristics and demographic data (including age, height, weight, race, ethnicity), medical history, physical examination (abnormalities only), and prior/concomitant medications will be listed for all subjects. Demographic data will be summarized and tabulated.

9.5 Study Endpoints

Study endpoints are provided in Section 2.2.

9.6 Statistical Methods

9.6.1 Safety Analysis

Safety will be assessed based on AE reporting, physical examination, vital sign measurement, and clinical laboratory test results.

AEs will be tabulated by body system and preferred term according to a standardized thesaurus (Medical Dictionary for Regulatory Activities [MedDRA]). The severity of AEs will be classified using the NCI-CTCAE toxicity scale as detailed in Section 7.7.3.3. Summaries will be provided in separate tables for SAEs, treatment-related AEs, and AEs leading to study discontinuation. AEs will also be summarized by maximum severity and relationship to the study drug for each treatment group and overall.

Concomitant medications including baseline medications will be tabulated by subject with drug category and preferred term.

Physical examination findings will be provided as subject listings. Descriptive statistics for vital sign measurements, by treatment and time (after dose) will be provided. Hematological data and blood chemistry will be graded according to NCI CTCAE severity grade. Shift tables from the screening visit to the end of study visit will be presented for clinical laboratory measurements (serum chemistry, hematology, and urinalysis).

9.6.2 Primary Efficacy Analysis

The primary endpoint of 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 in Appendix 6.

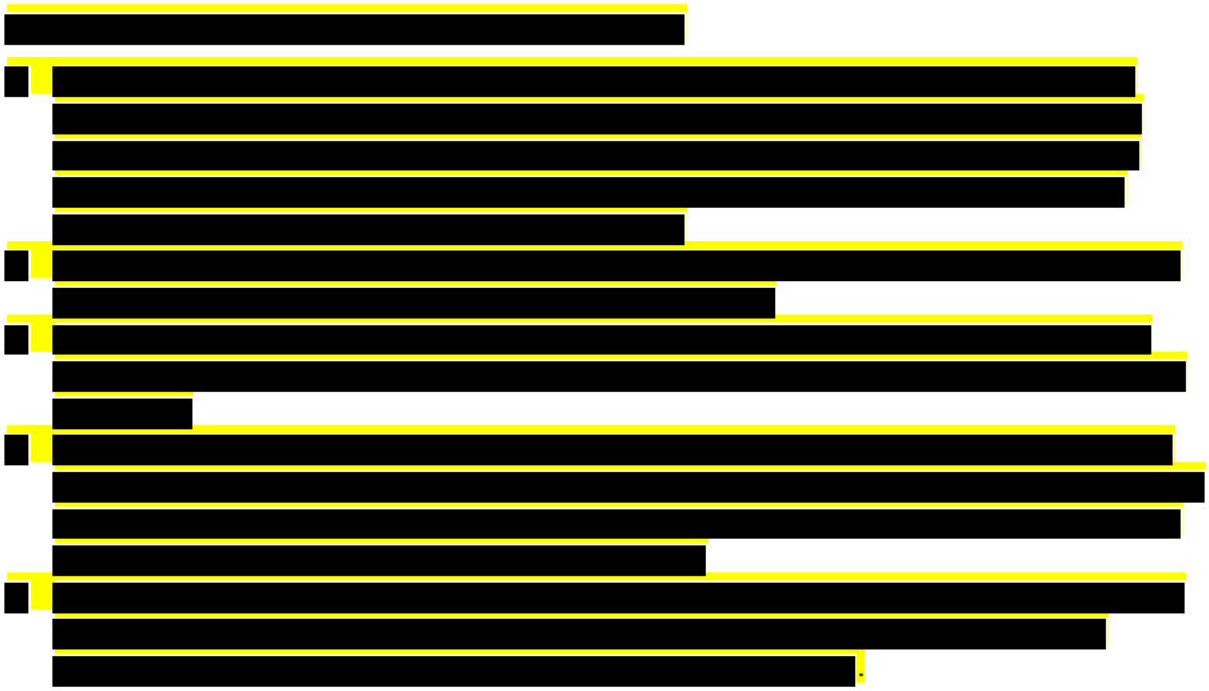
9.6.3 Secondary Efficacy Analysis

Secondary efficacy endpoints will be analyzed as follows:

1. Response to therapy will be explored by examining the proportion of subjects with a CR, VGPR, PR or have NR/stable or progression of lower GI aGVHD symptomatology at 14 and 56 days post treatment initiation.
2. Overall aGVHD response to therapy will be explored by examining the proportion of subjects with a CR, VGPR, PR, MR, NR/stable or who have progression of aGVHD at Days 14, 28, and 56 post-treatment initiation.
3. The proportion of subjects who have stopped immunosuppressive medication at Day 180 and 1 year will be estimated.
4. 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.

5. Kaplan-Meier methodology will be used to estimate overall survival from the time of the first infusion.

9.6.4 [redacted]



9.6.5 Pharmacokinetics Analysis

PK profiles will be evaluated by the Sponsor and will include graphs of plasma F-652 concentration-time profiles for individual subjects and for means. Non-compartmental PK methods will be used to estimate PK parameters of interest.

9.6.6 Criteria for Termination and Sponsor Discontinuation Criteria

Premature termination of this clinical trial may occur because of a regulatory authority decision, change in opinion of the IRB/IEC, drug safety problems, or at the discretion of Generon. In addition, Generon retains the right to discontinue development of F-652 at any time.

Generon reserves the right to discontinue the trial prior to inclusion of the intended number of subjects, but intends only to exercise this right for valid scientific or administrative reasons. After such a decision, the Investigator must contact all participating subjects within a time period set by Generon. As directed by Generon, all trial materials must be collected and all eCRFs completed to the greatest extent possible.

9.6.7 Level of Significance

All statistical tests and confidence intervals will use a Type I error rate of 10%. No adjustment will be made for multiple testing.

9.6.8 Procedure for Accounting for Missing, Unused and Spurious Data

For the primary efficacy analysis, missing data will be imputed as non-response. No other data will be imputed in the analysis.

10 ADMINISTRATIVE CONSIDERATIONS

10.1 Investigators and Study Administrative Structure

The PI and study staff has the responsibility of maintaining a comprehensive and centralized filing system containing all study-related documentation. These files must be available for inspection by the sponsor, representatives of the sponsor, the IRB/IEC, and regulatory authorities (i.e., FDA or international regulatory authorities) at any time, and should consist of the following elements:

- Subject files, supporting source documentation from the medical record including laboratory data and the ICF.
- Regulatory files, containing the protocol with all amendments and Investigator signature pages, copies of all other regulatory documentation, and all correspondence between the site and the IRB/IEC and Sponsor; and drug accountability files, including a complete account of the receipt and disposition of the study medication (test article).

Records are to be available for 2 years after marketing application approval, or if the application is not approved or never submitted, 2 years after the last shipment and delivery of the material and the appropriate competent regulatory authorities are notified. The Sponsor will provide written notification when it is appropriate for the Investigator to discard the study-specific documents referenced above.

10.2 Institutional Review Board (IRB) or Independent Ethics Committee (IEC) Approval

It is the responsibility of the Investigator to obtain prior approval of the trial protocol, protocol amendments, ICFs, and other relevant documents (e.g., advertisements) if applicable, from the IRB/IEC. All correspondence with the IRB/IEC should be retained in the Investigator File. Copies of IRB/IEC approvals should be forwarded to Generon or its designees.

The only circumstance in which an amendment may be initiated prior to IRB/IEC approval is where the change is necessary to eliminate apparent immediate hazards to the subjects. In that event, the Investigator must notify the IRB/IEC and Generon or its designees in writing within 5 working days after the implementation.

10.3 Ethics

10.3.1 Treatment Considerations

The final study protocol, including the final version of the ICF, must be approved or given a favorable opinion in writing by an IRB or IEC as appropriate. The Investigator must submit written approval to the Sponsor or its designee before he or she can enroll any subject into the study.

The PI is responsible for informing the IRB or IEC of any amendment to the protocol in accordance with local requirements. In addition, the IRB or IEC must approve all advertising used to recruit subjects for the study. The protocol must be re-approved by the IRB or IEC upon receipt of amendments and annually, as local regulations require.

The PI is also responsible for providing the IRB/IEC with reports of any reportable serious adverse drug reactions from any other study conducted with the investigational product. The Sponsor or its designee will provide this information to the PI.

Progress reports and notifications of serious adverse drug reactions will be provided to the IRB or IEC according to local regulations and guidelines.

10.3.2 Ethical Conduct of the Study

The trial will be performed in accordance with the protocol, International Conference on Harmonisation (ICH) GCP guidelines, and applicable local regulatory requirements and laws.

10.4 Subject Information and Consent

The ICF must be agreed to by Generon and the IRB/IEC and must be in compliance with ICH-GCP, local regulatory requirements, and legal requirements.

The Investigator must ensure that each trial subject, or his/her legally acceptable representative, is fully informed about the nature and objectives of the trial and possible risks associated with participation. The Investigator will obtain written ICF each subject or the subject's legally acceptable representative before any study-specific activity is performed. The ICF used in this trial, and any changes made to it during the course of the trial, must be approved by both the IRB/IEC and Sponsor before use. The Investigator will retain a copy of each subject's signed consent form.

A Sponsor recommended sample informed consent form will be provided to the investigational site as a separate document. Modifications to the consent required by ethics committee/IRB should be reviewed by the Sponsor.

10.5 Subject Confidentiality

All information obtained during the conduct of the study with respect to the subjects' state of health will be regarded as confidential. This is detailed in the written information provided to the subject. An agreement for disclosure of any such information will be obtained in writing and is included in both copies of the ICF signed by the subject. The study data shall not be disclosed to a third party without the written consent of the sponsor.

10.6 Study Monitoring

The Sponsor or a sponsor representative will visit the study center periodically to monitor adherence to the protocol, compliance with ICH guidelines, adherence to applicable regulations, and the maintenance of adequate and accurate clinical records. eCRFs will be reviewed to ensure that key safety and efficacy data are collected and recorded as specified by the protocol. The monitor will be permitted to access subjects' complete medical records, laboratory data, and other source documentation as needed to monitor the trial appropriately.

10.7 Case Report Forms and Study Records

Each site is responsible for collecting and maintaining the source documentation describing the clinical information.

eCRFs are required and should be completed in a timely manner for each included subject. The completed original eCRFs are the sole property of Generon and should not be made

available in any form to third parties, except for authorized representatives of Generon or appropriate regulatory authorities, without written permission from Generon.

It is the Investigator's responsibility to ensure completion and to review and approve all eCRFs. eCRFs must be signed by the Investigator or by an authorized staff member. These signatures serve to attest that the information contained on the eCRFs is correct and complete. At all times, the Investigator has final personal responsibility for the accuracy and authenticity of all clinical and laboratory data entered on the eCRFs. Subject source documents are the physician's subject records maintained at the trial sites. In most cases, the source documents will be the hospital's or the physician's charts. In cases where the source documents are the hospital or the physician's charts, the information collected on the eCRFs must match those charts.

All information recorded in the electronic Case Report Forms must be documented in the source document. To leave as is implies that the Investigator may document directly into the eCRF and not record in the clinic record. If a policy or standard operating procedure requires the present language, it must be specified what information can be documented directly into the eCRF.

10.7.1 Electronic Case Report Forms

eCRFs are to be completed using the iDataFax electronic data capture system. Sites will receive training and guidelines for appropriate eCRF completion.

All eCRFs should be completed by designated, trained, data entry personnel or the study coordinator as appropriate. The eCRF should be reviewed and electronically signed and dated by the Investigator.

In addition, at the end of the study, the Investigator will receive subject data for his or her site in a read-only format on a compact disc that must be kept with the study records.

10.8 Protocol Interpretation and Compliance

To ensure accurate interpretation and implementation of the study, the procedures and endpoints defined in the protocol will be carefully reviewed by the PI and his or her staff prior to the time of study initiation. The Sponsor and PI will follow all reasonable means to resolve any differences of opinion of matters of eligibility, toxicity and other endpoints. In the event that a resolution cannot be reached then one or both parties may seek to terminate the study following the provisions outlined in the Clinical Trials Agreement.

10.9 Access to Source Documentation

The PI and the Investigator’s institution must permit trial-related monitoring, audits, IRB/IEC review, and regulatory inspections by providing direct access to source data/documents.

10.10 Data Generation and Analysis

The eCRF data will be verified by a series of computerized edit checks, and all relevant data queries will be resolved on an ongoing basis. When the eCRFs are complete, they will be reviewed and signed by the Investigator. All elements of data entry (i.e., time, date, verbatim text, and the person performing the data entry) are recorded in an electronic audit trail to allow all data changes in the database to be monitored and maintained in accordance with federal regulations.

10.11 Records Retention and Retention of Data

To enable evaluations and/or audits from regulatory authorities or Generon, the Investigator agrees to keep complete records, including the identity of all participating subjects (sufficient information to link records, e.g., eCRFs and hospital records), all original signed ICFs, copies of all eCRFs, source documents, and detailed records of treatment disposition. The records must be retained by the Investigator according to ICH and local regulations as well as the Clinical Trials Agreement.

If the Investigator relocates, retires, or for any reason withdraws from the trial, Generon should be notified in advance. The trial records must be transferred to an acceptable designee, such as another Investigator, another agreed-upon institution, or to Generon. The Investigator must obtain written permission from Generon before disposing of any records, even if retention requirements have been met.

10.12 Financial Disclosure

The Sponsor, Generon, will provide adequate insurance for trial conduct.

10.13 Publication and Disclosure Policy

Publication of study results is discussed in the Clinical Trials Agreement. All publications to be submitted to scientific journals or presentations to be given at scientific meetings must be submitted to the Generon (Shanghai) Corporation at least one month prior to submission. Planned presentations must include all slides. This includes presentations given at the presenter's own institution (such as Grand Rounds). However, presentations given to the study team are not required to be approved in advance.

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Appendix 1 Trial Procedures and Study Activities

Screening (begins with consent):

- Informed Consent is signed
- Registration of Subject into the IWRS system
- Relevant Medical history
- Listing of all treatments and current therapies over the past 1 month and any chemotherapy regimens in the past 1 year from the date of informed consent
- Concomitant medications
- Physical examination
- Height and body weight
- Vital Signs *(BP and heart rate, respiratory rate, body temperature)*
- Complete blood count (CBC) with Differential
- Blood chemistry *(Sodium, Potassium, BUN, Serum Creatinine, Chloride, Carbon Dioxide, Calcium, Phosphorus, Glucose, Bilirubin total and direct, ALT, AST, ALP, CRP, LDH, Albumin, Fibrinogen, Total Protein, Total Cholesterol, Triglycerides)*
- Urinalysis
- ECG-12 lead
- Stool sample for *C. diff testing (if not tested in the last 7 days)*
- Stool sample for microbiota testing
- aGVHD baseline scoring and grading *(by IBMTR scoring system)*
- GI evaluation and biopsy*: flexible sigmoidoscopy (preferred) or colonoscopy and upper endoscopy, according to local center practice.
- Skin biopsy for evaluation of rash, optional in the absence of rash
- Collection of adverse events (AEs)
- Serum pregnancy test as appropriate

* If no biopsy for GI aGVHD confirmation has been performed before study entry. GI evaluation to be done within 5 days of initial systemic corticosteroid administration

Study Day 0, Initial Dose of F-652 (to be within 5 days of initial systemic corticosteroid administration):

- Body weight
- Physical examination
- Vital Signs *(BP and heart rate, respiratory rate, body temperature). Vital signs are to be taken 15 min. after the start of F-652 infusion, at the completion, and 1 hour after the end of the initial infusion*.
- Serum sample for F-652 antibody testing (prior to administration of F-652)
- PK testing samples
- Collection of AEs and toxicity assessments
- Concomitant medications
- Administration of F-652
- aGVHD blood research samples (cytokine samples optional)

Study Days 7*, 14*, and 21*:

- Body weight

- Collect vital signs *(BP and heart rate, respiratory rate, body temperature). Vital signs are to be taken 15 min. after the start of F-652 infusion, at the completion, and 1 hour after the end of the initial infusion*.
- CBC with Differentials
- Blood chemistry *(Sodium, Potassium, BUN, Serum Creatinine, Chloride, Carbon Dioxide, Calcium, Phosphorus, Glucose, Bilirubin total and direct, ALT, AST, ALP, CRP, LDH, Albumin, Fibrinogen, Total Protein, Total Cholesterol, Triglycerides)*
- Serum sample for F-652 antibody testing (prior to administration of F-652)
- PK testing samples *(see schedule for Day 21+ sampling)*
- Collection of AEs and toxicity assessments
- Concomitant medications
- Administration of F-652
- aGVHD scoring and grading *(by IBMTR scoring system)*
- Skin biopsy if rash develops during treatment, optional in the absence of rash (Day 14)
- aGVHD treatment response *(only for visit Day 14)*

*Actual study day may vary as per the allowed window for visit due to each subject's individual schedule.

Study Day 28* (End of Treatment Visit):

- Body weight
- Physical examination
- Collect vital signs *(BP and heart rate, respiratory rate, body temperature)*
- CBC with Differential
- Blood chemistry *(Sodium, Potassium, BUN, Serum Creatinine, Chloride, Carbon Dioxide, Calcium, Phosphorus, Glucose, Bilirubin total and direct, ALT, AST, ALP, CRP, LDH, Albumin, Fibrinogen, Total Protein, Total Cholesterol, Triglycerides)*
- Serum sample for F-652 antibody testing
- Urinalysis
- PK testing samples
- Collection of AEs and toxicity assessments
- Concomitant medications
- aGVHD scoring and grading *(by IBMTR scoring system)*
- aGVHD treatment response
- aGVHD blood research samples (cytokine samples optional)
- Stool sample for microbiota testing
- Skin biopsy if rash develops during treatment, optional in the absence of rash
- ECG-12 lead
- GI evaluation and biopsy*: *flexible sigmoidoscopy (preferred) or colonoscopy and upper endoscopy with biopsy according to local center practice. (1 sample required, subject permitting, 4 others collected).*

*Actual study day may vary as per the allowed window for visit due to each subject's individual schedule.

Study Follow up Day 56*:

- Relevant medical history
- Body weight
- Physical examination
- Collect vital signs *(BP and heart rate, respiratory rate and body temperature)*
- CBC with Differential
- Blood chemistry (*Sodium, Potassium, BUN, Serum Creatinine, Chloride, Carbon Dioxide, Calcium, Phosphorus, Glucose, Bilirubin total and direct, ALT, AST, ALP, CRP, LDH, Albumin, Fibrinogen, Total Protein, Total Cholesterol, Triglycerides)*
- Serum sample for F-652 antibody testing
- Current therapy and concomitant medications
- Collection of AEs and toxicity assessments
- aGVHD scoring and grading *(by IBMTR scoring system)*
- aGVHD treatment response
- PK testing sample

*Actual study day may vary as per the allowed window for visit due to each subject's individual schedule.

Study Follow up Days 180 and 365*:

- Relevant medical history
- Body weight
- Physical examination
- Collect vital signs *(BP, heart rate, respiratory rate, body temperature)*
- aGVHD scoring and grading *(by IBMTR scoring system)*
- SAEs (possibly, probably, or definitely related to the investigational drug)
- Current therapy and concomitant medications (only for subjects with SAEs reported after Day 56)

*Actual study day may vary as per the allowed window for visit due to each subject's individual schedule.

Appendix 2 Schedule of Procedures and Events

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			
PK Testing[6] (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: aGVHD = acute graft-versus-host disease; BP = blood pressure; ECG = electrocardiogram; 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 patient has very low circulating white blood cells.

[3] For females with reproductive potential, serum test.

[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 (Appendix 3).

[7] Intravenous (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).

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Appendix 4 [redacted]

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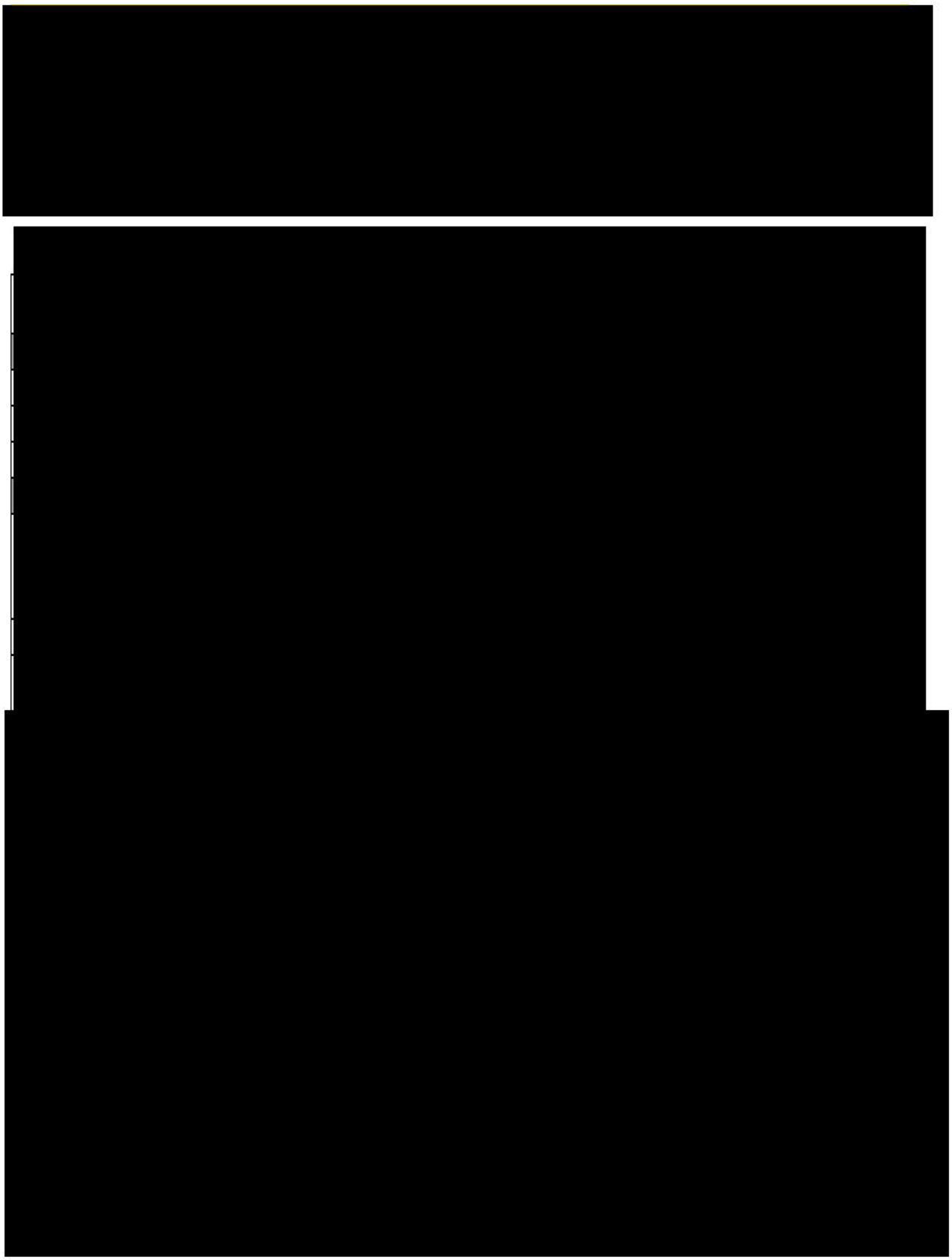

Appendix 5 aGVHD Diagnosis and Grading Tables

Appendix Table 2. Modified Keystone Criteria

	Stage 0	Stage 1	Stage 2	Stage 3	Stage 4
Skin	No Rash	Rash <25% BSA	25-50% BSA	>50% BSA	Generalized erythroderma with bullae and/ or desquamation
GI Tract*	≤500 ml/day stool volume	501-1000 ml/day stool volume	1001-1500 ml/day stool volume	>1500 ml/day stool volume	Severe abdominal pain +/- ileus, with or without hematochezia
Upper GI		Severe nausea, vomiting, or anorexia			
Liver	Total bilirubin <2.0 mg/dL	2.1-3 mg/dl	3.1-6 mg/dl	6.1-15 mg/dl	>15 mg/dl

Abbreviations: BSA = body surface area; GI = gastrointestinal
* If stool sample is not quantified in mL, each episode of diarrhea will be estimated to be a volume of 200 mL.

Appendix Table 3. IBMTR Severity Index for Grading aGVHD

	Skin	Liver	GI
I	Stage 1	0	0
II	Stage 2	Stage 1-2	Stage 1-2
III	Stage 3	Stage 3	Stage 3
IV	Stage 4	Stage 4	Stage 4

Appendix 6 Criteria for Therapeutic Response/Outcome Assessment

Acute lower GI GVHD Response Criteria:

- Complete Response (CR): stage of 0 of all aGVHD symptomatology in the lower GI tract with no additional intervening GVHD therapy.
- Very good partial response (VGPR): tolerating food or enteral feeding, predominantly formed stools, no overt GI bleeding or abnormal cramping.
- Partial Response (PR): improvement by at least 1 stage in lower GI GVHD symptomatology with no additional intervening therapy for their GVHD.
- No Response (NR)/stable: absence of any improvement in GVHD stage. Subjects receiving secondary therapy (including need to re-escalate corticosteroid dose to ≥2.5 mg/kg/day of prednisone (or methylprednisolone equivalent) will be classified as non-responders.
- Progression**:** deterioration in lower GI tract.

Response for All Organs Involved with Acute GVHD:

- Complete Response (CR): stage of 0 of all aGVHD symptomatology in all GVHD target organs with no additional intervening GVHD therapy.
- Very good partial response (VGPR): tolerating food or enteral feeding, predominantly formed stools, no overt GI bleeding or abnormal cramping, no more than occasional nausea or vomiting.
- Partial response (PR): improvement in GVHD stage in all initial GVHD target organs without complete resolution and without worsening in any other GVHD target organs.
- Mixed response (MR): improvement in 1 or more GVHD target organs with deterioration in another organ manifesting symptoms of GVHD or development of symptoms of GVHD in a new organ.
- No response (NR)/stable: absence of any improvement in GVHD stage. Subjects receiving secondary therapy (including need to re-escalate corticosteroid dose to ≥2.5 mg/kg/day of prednisone or methylprednisolone equivalent) will be classified as non-responders.
- Progression: deterioration in at least 1 organ without any improvement in others.

Treatment Failure:

The following will be considered as treatment failures:

- NR/stable after 14 days of therapy.
- Progression after 7 days of therapy.
- Administration of additional systemic therapy for GVHD (or re-escalation of corticosteroid dose to ≥2.5 mg/kg/day of prednisone (or methylprednisolone equivalent)
- Transplant-related mortality (TRM)

Discontinuation of Immunosuppressive Medications.

- Discontinuation of immunosuppression will be assessed over time. The date of discontinuation of corticosteroids will be recorded. In addition, dates for discontinuation of all other systemic immunosuppressive medications (including CSA, tacrolimus, sirolimus, etc.) for treatment or prevention of aGVHD will be assessed.

Transplant related mortality (TRM)

- 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. The incidence of TRM at Day 56 is the primary safety endpoint.

Appendix 7 List of Abbreviations and Definitions of Terms

λ_z	Elimination half-life
ADL	Activities of daily living
AE	Adverse event
aGVHD	Acute Graft-versus-Host Disease
ALP	Alkaline Phosphatase
ALT (SGOT)	Alanine aminotransferase
ANC	Absolute neutrophil counts
AST (AGPT)	Aspartate aminotransferase
ATG	Anti-thymocyte globulin
AUC	Area under the plasma concentration vs. time curve
BMT	Bone marrow transplant
BUN	Blood Urea Nitrogen
C_{max}	Concentration Maximum
CBC	Complete Blood Count
CFR	Code of Federal Regulations
C_L	Clearance
CMV	Cytomegalovirus
CR	Complete response
CRP	C-reactive Protein
CSA	Cyclosporine
CTCAE	Common Terminology Criteria for Adverse Events
D5W	5% dextrose in water
DC	Dendritic cell
DP	Drug product
DS	Drug substance
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EIU	*Exposure in utero*
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GI	Gastrointestinal
GMP	Good Manufacturing Practices

hCG	Human chorionic gonadotropin
Hgb	Hemoglobin
HSCT	Hematopoietic stem cell transplantation
IBMTR	International Bone Marrow Transplant Registry
ICF	Informed consent form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IL	Interleukin
ILC	Innate lymphoid cell
IND	Investigational New Drug
IRB	Institutional Review Board
ISC	Intestinal stem cell
IV	Intravenous
IWRS	Interactive web based response system
MedDRA	Medical Dictionary for Regulatory Activities
MHC	Major histocompatibility complex
MMF	Mycophenolate mofetil
MR	Mixed response
NCI	National Cancer Institute
NR	No response
PI	Principal Investigator
PK	Pharmacokinetics
PR	Partial response
rh	Recombinant human
rm	Recombinant murine
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
$t_{1/2}$	Half-life
t_{max}	Maximum concentration (of a drug in bloodstream)
TEAE	Treatment-emergent adverse event
TRM	Transplant-related mortality
V_d	Volume of distribution
VGPR	Very Good Partial Response