



CLINICAL STUDY PROTOCOL

Study Title: A Phase 2, Randomized, Double-Blind, Placebo-Controlled Study to Assess the Efficacy and Tolerability of Entospletinib, a Selective SYK Inhibitor, in Combination with Systemic Corticosteroids as First-Line Therapy in Subjects with Chronic Graft Versus Host Disease (cGVHD)

Sponsor: Gilead Sciences, Inc.
333 Lakeside Drive
Foster City, CA 94404

IND Number: 129907
EudraCT Number: 2015-004572-30
Clinical Trials.gov Identifier: NCT02701634

Indication: Chronic Graft Versus Host Disease (cGVHD)

Protocol ID: GS-US-406-1840

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PROTOCOL SYNOPSIS
Gilead Sciences, Inc.
333 Lakeside Drive
Foster City, CA 94404

Study Title:	A Phase 2, Randomized, Double-Blind, Placebo-Controlled Study to Assess the Efficacy and Tolerability of Entospletinib, a Selective SYK Inhibitor, in Combination with Systemic Corticosteroids as First-Line Therapy in Subjects with Chronic Graft Versus Host Disease (cGVHD)
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Study Centers Planned:	Approximately 30 centers in the North America, Europe, Asia and Australia
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Objectives:	<p>The primary objective is:</p> <p>To evaluate the effect of ENTO on the best overall response rate (BORR) as assessed by the NIH cGVHD Activity Assessment (NCAA) by 24 weeks in the setting of add-on to systemic corticosteroids as part of first-line therapy for cGVHD</p> <p>The key secondary objectives are:</p> <ul style="list-style-type: none">• To evaluate the effect of ENTO on the skin domain of the Lee Symptom Scale (LSS) (Appendix 6) at 24 weeks• To evaluate the effect of ENTO on the mouth domain of the LSS at 24 weeks• To evaluate the effect of ENTO on the eyes domain of the LSS at 24 weeks• To evaluate the effect of ENTO on the total score of the LSS at 24 weeks <p>Additional secondary objectives include:</p> <ul style="list-style-type: none">• To evaluate the effect of ENTO on duration of response (DOR)• To evaluate the effect of ENTO on dose reduction of corticosteroids
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- To evaluate the effect of ENTO on initiation of second-line therapy for cGVHD
- To evaluate the effect of ENTO on progression of cGVHD
- To evaluate the safety and tolerability of ENTO

Exploratory objectives include:

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P
D

[Redacted text]

[Redacted text]

[Redacted text]

[Redacted text]

Study Design:

Randomized, double-blind, placebo-controlled, multicenter study to evaluate the efficacy and safety of ENTO (Treatment Arm 1) vs. placebo (Treatment Arm 2) in combination with systemic corticosteroids for subjects with cGVHD.

An interim analysis for futility is planned when approximately 50% of subjects have been on study for 24 weeks. The primary endpoint will be evaluated when all subjects complete 24 weeks of treatment. Duration and quality of response will be evaluated up to 48 weeks of blinded treatment.

After 48 weeks, subjects who are still on investigational treatment (ENTO or PTM) and are eligible to remain on study will have the option to receive open-label extension (OLE) with ENTO and attend visits per the schedule of assessments (Table 6-1) for an additional 96 weeks.

Subjects who complete the study through Week 48 and do not wish to participate in the OLE will be required to return to the clinic after completion of study drug for a 30-Day Follow-up Visit.

Number of Subjects Planned:

Approximately 100 subjects. Randomization will be stratified by 1) calcineurin inhibitor or mycophenolate mofetil (MMF) use (no vs. yes) and 2) moderate vs. severe cGVHD as determined by the NIH cGVHD Diagnosis and Staging Criteria (NCDSC) at the Screening visit.

Target Population:

Adult males or non-pregnant, non-lactating, female subjects with cGVHD

Duration of Treatment:	48 weeks in the double-blind, placebo-controlled period. After 48 weeks subjects who are still on investigational treatment (ENTO or PTM) and are eligible to remain on study will have the option to receive OLE with ENTO and attend visits per the schedule of assessments (Table 6-1) for an additional 96 weeks.
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Diagnosis and Main Eligibility Criteria:	The following are a summary of the key criteria:
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Key Inclusion Criteria:

- Male or non-pregnant, non-lactating, female subjects
- 18-75 years of age, inclusive at Screening
- Newly diagnosed cGVHD defined by:
 - a) At least 100 days after receiving any allogeneic hematopoietic stem cell transplant
 - AND
 - b) Receiving a new course of systemic corticosteroids (1.0 mg/kg/day or prednisone equivalent) as first-line cGVHD therapy for at least 1 day and no more than 21 days prior to first dose of ENTO/Placebo
 - AND
 - c) Moderate to severe cGVHD as assessed by NCDSC with at least three organ systems involved OR one organ system with a score of 2 OR lung organ score = 1 ([Appendix 2](#))
- Subjects who have undergone transplant for hematologic malignancy are required to be in complete remission.
- Have either a normal ECG or one with abnormalities that are considered clinically insignificant by the investigator in consultation with the Sponsor

Key Exclusion Criteria:

- Uncontrolled infection within 4 weeks prior to Randomization
 - History of the following therapies in the post-transplant period:
 - B cell depleting biologic agents
 - CD19 CAR-T cells based therapies
 - BTK/SYK/JAK/PI3K inhibitors
 - Phototherapy-unless administered for acute GVHD
-

- Treatment of cGVHD with anti-thymocyte globulins (ATG), or campath within 60 days of Screening visit unless used for treatment of acute GVHD
- Severe organ dysfunction manifested during Screening period:
 - Requiring supplemental oxygen at more than 2 L/min
 - Uncontrolled arrhythmia or heart failure

Study Procedures/
Frequency:

Eligible subjects will be randomized 1:1 to Treatment Arm 1 or Treatment Arm 2 to receive study drug for 48 weeks. Following Screening and Baseline/Day 1 Visits, subjects will return for study visits at Weeks: 2, 4, 8, 12, 16, 20, 24, 30, 36, 42 and 48. Subjects that participate in the OLE will return for visits at Weeks: 50, 52, 56, 60, 64, 72 and visits every 12 weeks thereafter. During the OLE, the maximum period of co-administration of ENTO with Cyclosporine, Tacrolimus or MMF should not exceed 3 months. Subjects who do not wish to participate in the OLE will have a 30-day Follow-Up visit after their week 48 visit.

NOTE for subjects receiving tacrolimus, cyclosporine or MMF:

For subjects receiving these medicines at enrolment and are continuing on these medicines, the blood levels of tacrolimus, cyclosporine or the active metabolite of MMF (MPA) will be monitored at Baseline/Day 1 (prior to starting ENTO or placebo-to-match [PTM]), on Day 2 or Day 3 and Day 6 or Day 7 after initiating ENTO or PTM, and at the end of Week 2 and Week 50 study visit. Beyond these time points, concentration monitoring for tacrolimus, and cyclosporine should follow the treating institution's protocol and therapeutic range for monitoring these medicines. For subjects who initiate these medicines while already receiving ENTO, concentration monitoring for tacrolimus, cyclosporine and MPA should follow the treating institution's protocol and therapeutic range for monitoring these medicines. When a concentration sample is taken at a local lab in accordance with the treating institution's protocol for monitoring these medications, a sample may also be requested for central lab analysis.

At Screening the NIH cGVHD Diagnosis and Staging Criteria (NCDSC) ([Appendix 3](#)) will be administered. At Baseline/Day1 and Weeks 4, 8, 12, 16, 20, 24, 30, 36, 42, 48, 56, 60, 64, 72, every 12 weeks thereafter and Early Study Drug Discontinuation (ESDD) the NCAA ([Appendix 5](#)), and the LSS ([Appendix 6](#)) will be administered. Serological screening for HIV antibody (Ab), hepatitis B antigen, hepatitis C Antibody will be collected at the Screening visit. For subjects with hematologic malignancy, assessments of residual disease will be followed per the institutional guidelines.

Blood and urine will be collected at all study visits per the schedule of assessments (Table 6-1).

Blood for selected biomarkers will be collected at all study visits per the Schedule of Assessments (Table 6-1).

PPD

Test Product, Dose, and Mode of Administration:

Treatment Arm 1: ENTO 400 mg twice daily: 2 X 200 mg tablets twice daily, for subjects currently on proton pump inhibitors (PPI)*

Treatment Arm 2: Placebo-to-match (PTM) twice daily

Both treatment arms will be administered orally without food (in a fasted state) for 48 weeks.

*For subjects **NOT** currently taking a PPI, the dose will be adjusted to ENTO 200 mg twice daily: 1 X 200 mg tablet orally twice daily without food (in a fasted state) for 48 weeks.

Reference Therapy, Dose, and Mode of Administration:

Systemic corticosteroids at a dose and route consistent with first-line therapy for newly diagnosed cGVHD.

Systemic corticosteroids will be administered per provided treatment schema.

Criteria for Evaluation:

Safety:

Safety evaluations include documentation of AEs, physical examination, vital signs, ECGs, and clinical laboratory evaluations.

Efficacy:

The primary endpoint is BORR by 24 weeks, as assessed by the NCAA, in the setting of add-on therapy to systemic corticosteroids as part of first-line therapy for cGVHD.

The key secondary endpoints are:

- Change from Baseline in the skin domain of the LSS at 24 weeks
 - Change from Baseline in the mouth domain of the LSS at 24 weeks
 - Change from Baseline in the eyes domain of LSS at 24 weeks
 - Change from Baseline in the total score of the LSS at 24 weeks
-

Other secondary endpoints include:

- DOR
- Proportion of subjects who achieve at least 50% reduction in systemic corticosteroid dose relative to baseline
- Proportion of subjects who initiate second-line therapy for cGVHD
- Failure-free-survival (FFS)
- Safety and tolerability of ENTO

Exploratory endpoints of this study include:

P	
P	
D	

Pharmacokinetics: PK blood sampling will occur at Weeks 2 through Week 48 and then every 12 weeks thereafter.

Statistical Methods: The primary endpoint of BORR by 24 weeks is defined as the proportion of subjects who achieve a complete or partial response (CR or PR) within 24 weeks, as assessed by the NCAA. A CR is achieved when all signs and symptoms of cGVHD have resolved. A PR is achieved when an objective response is observed in any organ system without progression in another organ system, and no additional systemic therapy is needed.

The primary analysis for BORR will be performed in the intent-to-treat (ITT) Analysis Set, which includes all subjects who were randomized. Response rate will be summarized by count and percent of subjects with each ordinal response (CR, PR, and CR + PR). A stratified Cochran-Mantel-Haenszel (CMH) Chi-square test will be performed to compare BORR between ENTO and PTM by 24 weeks. The difference in response rates between treatment groups and the corresponding 95% CIs will be presented.

Change from Baseline in the LSS scores will be analyzed using a mixed model repeated measures (MMRM) model. Duration of response (DOR) will be analyzed using the Kaplan-Meier method.

A sequential testing strategy will be implemented to preserve the overall type I error rate across the primary and key secondary endpoints of the study at a 2-sided significance level of 0.05. If the primary hypothesis is rejected, the key secondary endpoints will be sequentially tested at the 2-sided 0.05 significance level in the following order: (1) change from Baseline in the skin domain of the LSS, (2) change from Baseline in the mouth domain of the LSS, (3) change from Baseline in the eyes domain of the LSS, and (4) change from Baseline in the total score of the LSS. If a null hypothesis is not rejected, formal sequential testing will stop and only nominal significance will be cited for the remaining endpoints.

With 40 subjects per treatment group, there is 75% power to detect a 30% improvement in response rate at the 2-sided 0.05 significance level using a Fisher's exact test, assuming a placebo response rate of 50%. A total of 100 subjects (50 per treatment group) will be enrolled assuming a 20% dropout rate.

Safety data will be listed by subject and summarized by treatment and frequency of event/abnormality or descriptive statistical summaries, as appropriate. The endpoints to be evaluated will include AEs, physical examination, clinical laboratory test findings, ECG abnormalities and interval measurements, and vital signs measurements.

An external multidisciplinary data monitoring committee (DMC) will review the progress of the study, perform interim reviews of safety data at regular intervals approximately every 3 months, and perform an interim review of efficacy data for futility when approximately 50% of subjects have been on study for 24 weeks, as described in the DMC Charter. The DMC will provide recommendations to Gilead as to whether the nature, frequency, and severity of adverse effects associated with study treatment warrant the early termination of the study in the best interests of the participants, whether the study should continue as planned, or the study should continue with modifications.

This study will be conducted in accordance with the guidelines of Good Clinical Practice (GCP) including archiving of essential documents.

GLOSSARY OF ABBREVIATIONS AND DEFINITION OF TERMS

aGVHD	Acute Graft Versus Host Disease
ADL	Activities of daily living
AKT	Protein kinase B
ALT	alanine aminotransferase
AML	acute myeloid leukemia
APC	antigen presenting cell
AST	aspartate aminotransferase
ATG	anti-thymocyte globulins
AUC	area under curve versus time
BAFF	B cell Activating Factor
BCMA	B cell maturation antigen
BCR	B cell receptor
BCRP	breast cancer resistance protein
BLNK	B cell linker protein
BLQ	below limit of quantitation
BTK	Bruton's tyrosine kinase
BORR	best overall response rate
cGMP	Current Good Manufacturing Practice
CI	confidence interval
cGVHD	Chronic Graft Versus Host Disease
Clast	last observed quantifiable concentration
CL	systemic clearance following IV administration
CLL	chronic lymphocytic leukemia
Cmax	maximum observed serum/plasma/peripheral blood mononuclear (PBMC) concentration of drug
Ctau	concentration at the end of the dosing interval
CONMED	concomitant medication
CPK	creatine phosphokinase
CR	complete response
CRF	case report form(s)
CRO	contract (or clinical) research organization
CRP	C-reactive protein
CTCAE	Common Terminology Criteria for Adverse Events
DSPH	Drug Safety and Public Health
DMC	Data Monitoring Committee
DOR	duration of response
E2	Estradiol
ECG	Electrocardiogram

eCRF	electronic case report form(s)
ENTO	Entospletinib
ENTO BIS-MSA	Entospletinib bismesylate monohydrate
ENTO MSA	Entospletinib methanesulfonate
ENTO SSD	Entospletinib spray-dried dispersion tablet
ERK	Extracellular signal regulated kinase
ESR	erythrocyte sedimentation rate
ET	early termination
FDA	(United States) Food and Drug Administration
FFS	failure-free survival
FSH	follicle-stimulating hormone
cGVHD	Chronic Graft Versus Host Disease
GCP	Good Clinical Practice (Guidelines)
GGT	Gamma-glutamyl transferase
GVHD	Graft Versus Host Disease
GSI	Gilead Sciences, Inc.
Hb	Hemoglobin
HBV	Hepatitis B virus
hCG	human chorionic gonadotropin
HCV	hepatitis C virus
HDL	high-density lipoprotein
HDPE	high-density polyethylene
hERG	human-ether-a-go-go related gene
HIV	Human immunodeficiency virus
HSCT	hematopoietic stem cell transplant
IB	investigator's brochure
ICF	informed consent form
ICH	International Conference on Harmonisation
IEC	independent ethics committee
IgG	immunoglobulin G
IgM	immunoglobulin M
IMP	Investigational Medicinal Product
IND	Investigational New Drug (Application)
IRB	institutional review board
ITT	intent-to-treat
IUD	intrauterine device
IV	Intravenous
IxRS	interactive voice/web response system
JAK	janus kinase
LDL	low-density lipoprotein

LLN	lower limit of the normal range
LLOQ	lower limit of quantitation
LOCF	last observation carried forward
LOEL	lowest observed effect level
LOQ	limit of quantitation
LSS	Lee Symptom Scale
MAD	multiple ascending dose
MAP	mitogen-activated protein
MedDRA	Medical Dictionary for Regulatory Activities
MK2	MAP kinase activated protein kinase-2
MMF	mycophenolate mofetil
MMP9	Matrix metalloproteinase-9
MMRM	mixed model repeated measures
µm	Micro millimeter
NDA	New Drug Application
NCAA	NIH cGVHD Activity Assessment
NCDSA	NIH cGVHD Diagnosis and Staging Criteria
NIH	National Institute of Health
NOAEL	no observable adverse effect level
NRI	non-responder imputation
PE	physical examination
PFT	pulmonary function tests
PI3K	phosphatidylinositol-4,5-bisphosphate 3-kinase
PK	Pharmacokinetic
PP	per-protocol
PR	pulse rate
PPI	proton pump inhibitor
PTM	placebo-to-match
Q1	first quartile
Q3	third quartile
QTcF	Quantum Tunnelling Composite Fridericia
RA	rheumatoid arthritis
RNA	ribonucleic acid
SAD	single ascending dose
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SEM	standard error of measure
SOC	System Organ Class
SUSAR	Suspected Unexpected Serious Adverse Reaction

SYK	Spleen tyrosine kinase
TACI	Transmembrane activator and CAML interactor
TLC	total lung capacity
t _{max}	the time (observed time point) of C _{max}
t _{1/2}	an estimate of the terminal elimination half-life of the drug in serum/plasma/PBMC, calculated by dividing the natural log of 2 by the terminal elimination rate constant (λ_z)
UGT1A1	uridine disphosphate glucuronosyltransferase 1A1
ULN	upper limit of the normal range
US	United States
V _z	apparent volume of distribution following IV administration
WBC	White blood cell
WHO	World Health Organization
λ_z	terminal phase rate constant

1. INTRODUCTION

1.1. Background

1.1.1. Background on Chronic Graft Versus Host Disease

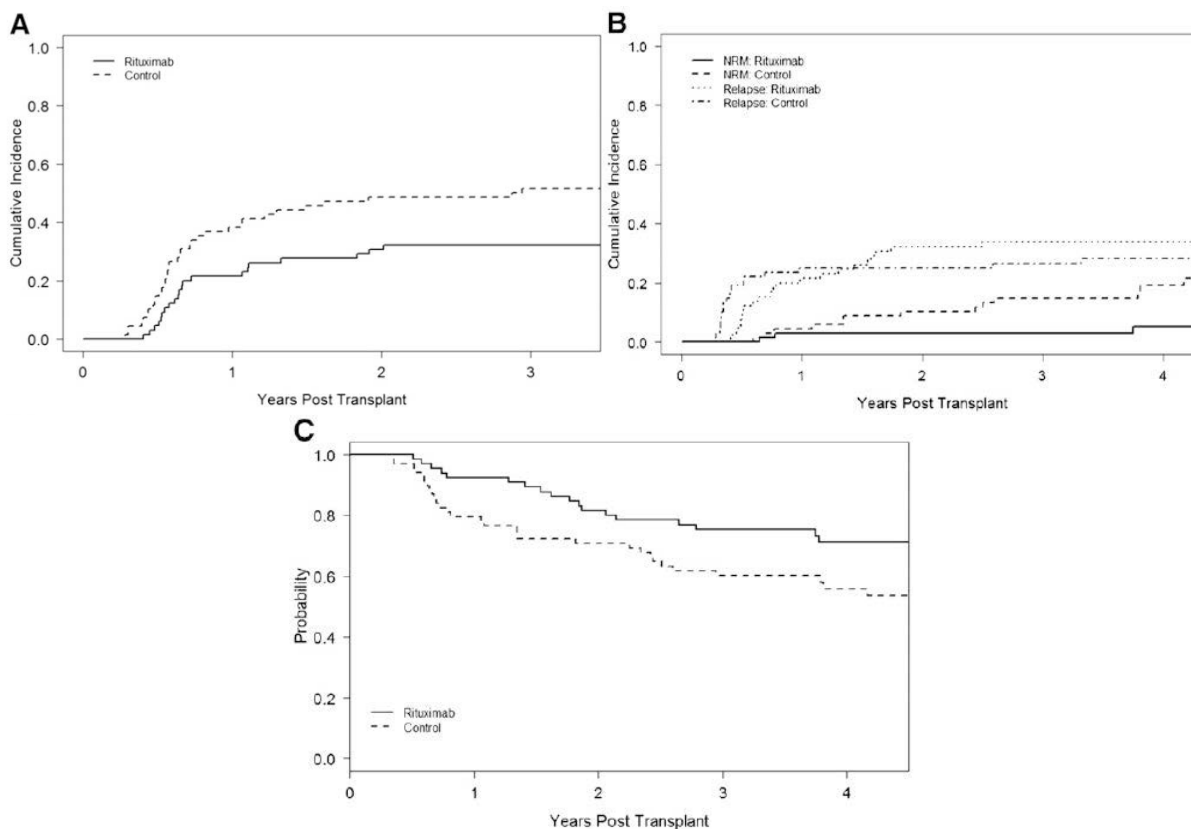
Chronic Graft Versus Host Disease (cGVHD) is a disease observed in recipients of allogeneic hematopoietic stem cells, where the new immune system is reconstituted without complete tolerance to the host and begins to attack multiple organ systems including eyes, skin, mucosa, lungs, gut, and liver. Classic acute GVHD (aGVHD) occurs in episodes with donor cell engraftment before 100 days post-transplant and is thought to be mediated by donor T cells. Acute GVHD is observed in 35-50% of patients receiving hematopoietic stem cell transplant (HCT) {[Jacobsohn et al 2007](#)}. Acute GVHD is a risk factor for developing cGVHD, but cGVHD can develop without history of aGVHD. Chronic GVHD occurs in 35-70% of patients receiving allogeneic transplants. In the U.S., the incidence of cGVHD is estimated at ~3000-5000 patients per year, with prevalence at approximately 10,000 {[Vigorito et al 2009](#)}. Initial therapy for cGVHD consists of high dose systemic corticosteroids, however 50 to 60% of patients fail to have a complete response to this line of therapy.

No agents are currently approved for cGVHD. A combination of calcineurin inhibitors, mTOR inhibitors and mycophenolate mofetil (MMF) are frequently added as second-line therapy with an initial response rate of 20-70% {[Flowers et al 2015](#)}. The majority of responses are not durable, and cGVHD is associated with a 5-year mortality of 30-50% {[Blazar et al 2012](#)}. Current immunosuppressive treatments also increase the rate of life-threatening infections and cancer relapse due to presumably the loss of graft versus tumor effect. The absence of effective therapies is attributed to the limited understanding of disease pathophysiology and limited directed development by industry.

1.1.1.1. Role of SYK in cGVHD

Unlike aGVHD which is believed to be mediated by allo-reactive T cells; the current biological and clinical evidence implicates that dysregulated B cell homeostasis is involved in establishment of the chronic phase of GVHD. B cell depletion in the peri-HSCT period is correlated with a reduction in the incidence of cGVHD. In addition, antibodies against minor histocompatibility antigens have been associated with the occurrence of cGVHD. In murine models of cGVHD, donor B cell alloantibodies have been shown to be responsible for the pathogenesis of the disease. A single open label study with the CD20 B cell depleting agent -rituximab- evaluated the potential of prophylactic therapy for development of cGVHD post-transplant period {[Cutler et al 2013](#)}. This study demonstrated clinically relevant differences in the cumulative incidence of cGVHD and overall survival ([Figure 1-1](#)).

Figure 1-1. cGVHD prophylaxis with rituximab.
(A) Cumulative incidence of cGVHD.
(B) Non-relapse mortality & GVHD recurrence.
(C) Overall survival



In a subsequent study, subjects with steroid-refractory cGVHD received open-label rituximab {Cutler et al 2006} and an overall response rate of 70% was observed. This is in comparison to an expected response rate of ~50% for those receiving standard of care alone {Cutler et al 2013, Inamoto et al 2014}. These efficacy data with rituximab in cGVHD represent clinical validation that therapy targeting B cells in this disease indication is effective. However, treatment of cGVHD with rituximab is suboptimal. The treatment effect is not durable as altered B cell populations recover {Sarantopoulos et al 2011}, and non-selective depletion of B cells results in complications such as hypogammaglobulinemia {Cutler et al 2013}. Targeting the pathogenic B cell subpopulation that drives cGVHD may therefore yield enhanced efficacy and safety.

Emerging data also indicates that alterations in B cell homeostasis play a pathogenic role in cGVHD {Sarantopoulos et al 2015}. In healthy individuals, newly generated B cells emerge from the bone marrow as transitional B cells and must complete maturation and selection in the periphery {Wardemann et al 2003}. About 40% of these newly emerged B cells are auto reactive. Transitional B cells are dependent upon both BAFF (B cell Activating Factor) and BCR signaling for their differentiation/maturation and survival. Low BAFF levels facilitate deletion

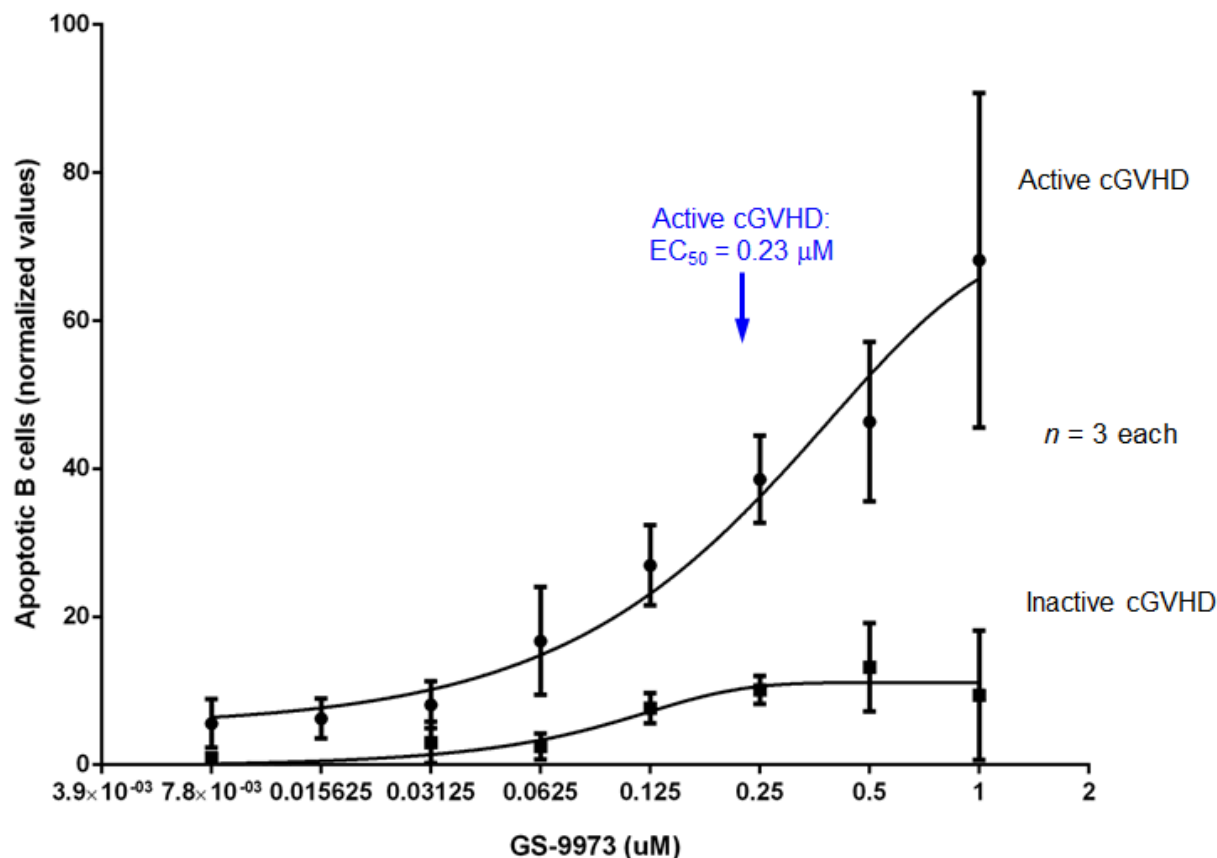
of autoreactive B cells. Following HSCT, donor B cell reconstitution occurs in the presence of a high foreign antigen load and high BAFF levels. This unique setting promotes the survival of activated, potentially allo- and auto-reactive B cells that would normally undergo negative selection. These donor-derived B cells can react with recipient tissue, facilitate tissue damage, produce inflammatory cytokines and serve as antigen presenting cell (APCs). Importantly, patients with cGVHD treated with anti-CD20 who have persistent B cell lymphopenia after treatment experience worsening symptoms, suggesting that both high BAFF levels and limited capacity to generate sufficient native and transitional B cells contribute to the abnormal B cell homeostasis that underlies the disease pathology. High numbers of native and transitional B cells protect from cGVHD development, possibly by binding and decreasing BAFF levels. These results further support the hypothesis that normal B cell homeostasis is required for protection from cGVHD.

As described, BAFF and B cell receptor (BCR) signaling play critical roles in the establishment of B cell homeostasis by regulating the auto-reactive B cell population. Patients with cGVHD have significantly increased BAFF levels versus B cell numbers {[Sarantopoulos et al 2011](#)}. Circulating CD27+ B cell subsets are increased and have high expression levels of the BAFF receptors. These cells are present in patients with autoimmune disease, but are absent in healthy individuals. These CD27+ cells are able to constitutively produce IgG and potentially mediate anti-recipient tissue responses. In the cGVHD murine model, elevated BAFF was shown to maintain B cells in a state of heightened sensitivity to antigen stimulation following BCR stimulation. This observation led to the hypothesis that B cells of cGVHD patients become more sensitive to antigen stimulation via BCR stimulation, resulting in loss of peripheral tolerance and survival of autoreactive B cell clones. In vitro studies in human B cells from cGVHD patients vs. those without cGVHD, revealed that cGVHD B cells have increased proliferative responses to BCR stimulation and reduced apoptosis {[Allen et al 2012](#)}.

A mechanistic understanding of BAFF and BCR signaling in cGVHD is currently being investigated and highlights that therapeutic kinase inhibition may benefit cGVHD patients with altered B cell homeostasis. The aberrant B cell survival in cGVHD patients is postulated to involve BAFF signaling via a SYK-AKT-ERK axis {[Allen et al 2012](#)}. Following HSCT, peripheral B cells isolated from cGVHD patients signal through protein kinase B and ERK and have decreased expression of the proapoptotic molecule, BIM, resulting in heightened metabolism and resistance to apoptosis {[Allen et al 2012](#)}. Importantly, B cells from cGVHD patients also have increased proliferative responses to BCR stimulation, with concomitant elevations in B cell linker protein (BLNK) and SYK phosphorylation compared to patients without cGVHD {[Allen et al 2014](#)}. Pharmacologically blocking SYK kinase activity with fostamatinib in vitro in cGVHD donor B cells, prevented BCR hyper-responsiveness of B cells to BCR stimulation with anti-IgM {[Allen et al 2014](#)}. Inhibition of Burton's tyrosine kinase (BTK) activity by ibrutinib blocked PLC- gamma 2 activation in cGVHD patient B cells; impacting survival of cGVHD B cells in a BTK dependent manner {[Dubovsky et al 2014](#), [Miklos et al 2015](#)}. These data suggest that BAFF and BCR cooperate to prime cGVHD B cells for survival and antigen responsiveness by lowering the threshold for BCR activation in cGVHD. Blockade of BCR signaling, therefore, could be of therapeutic benefit by reestablishing normal B cell homeostasis. Therefore, both SYK and BTK inhibition have potential to modulate aberrant

B cell function in cGVHD. In contrast to SYK, there are no published data to indicate that BTK is activated in cGVHD patient samples. Preliminary unpublished data from the Sarantopoulos Lab at Duke University with ENTO in the same assay with active cGVHD patient samples demonstrates a dose-dependent effect of ENTO to induce apoptosis of B cells vs. in samples from patients without active cGVHD (Figure 1-2).

Figure 1-2. Entospletinib Induces Apoptosis in B Cells from cGVHD Patients



In summary, failed induction of B cell tolerance after HSCT is postulated to underlie the pathophysiology of human cGVHD. Factors contributing to impaired tolerance induction include post-HSCT lymphopenia, persistent allo-antigen stimulation, and high BAFF levels, all of which contribute to hyper-responsive BCR pathways. SYK inhibition of cGVHD B cell subsets could antagonize the pro-survival signaling and result in pathogenic B cell deletion that could help reestablish B cell homeostasis.

1.2. Entospletinib (ENTO)

For further information refer to the ENTO Investigator's Brochure (IB).

1.2.1. Preclinical Pharmacology and Toxicology

Entospletinib (ENTO) was evaluated in a standard battery of safety pharmacology studies to assess potential effects on central nervous, cardiovascular, and respiratory systems. ENTO had no effect on central nervous and respiratory system parameters evaluated in rats. In a cardiovascular safety pharmacology study in dogs, small increases in heart rate (up to a 25% increase) were observed in male dogs given ENTO at 15, 50, or 150 mg/kg. While the higher heart rates were considered ENTO related, the relevance of these changes to humans is not known. Due to the observed increases in heart rate, a no observed effect level (NOEL) was not identified and the lowest observed effect level was 15-mg/kg. ENTO had no effect on ECGs or arterial blood pressure values at oral doses up to 150 mg/kg, the highest dose tested. Consistent with the lack of effect on ECG parameters, ENTO has no meaningful effect on the human-ether-a-go-go related gene (hERG), indicating that ENTO would not be expected to induce clinical QT prolongation.

The toxicity of ENTO has been characterized in animal genotoxicity, embryo-fetal reproductive toxicity, and phototoxicity studies. Recently published data demonstrated that species-specific GI toxicity and lymphoid changes, similar to that which was observed following ENTO administration to dogs, can occur in dogs but not rats, cynomolgus monkeys, or humans treated with p38 map kinase and mitogen-activated protein (MAP) kinase activated protein kinase-2 (MK2) small molecule kinase inhibitors that inhibit pathways that overlap with SYK signaling pathways {[Morris et al 2010](#)}. Oral administration of ENTO to rats for up to 26 weeks or cynomolgus monkeys for up to 39 weeks showed no evidence of GI toxicity or lymphoid changes at exposures which overlapped with or exceeded those that resulted in acute toxicity in dogs. Furthermore, ENTO (administered as Entospletinib methanesulfonate (ENTO MSA)) has been previously investigated in healthy human subjects at doses up to 1200 mg twice a day for 7 days and in subjects with rheumatoid arthritis (RA) at doses up to 900 mg twice a day for 26 days and no evidence of GI or lymphoid toxicity was observed in these clinical studies. Therefore, the relevance of these findings to humans is not known.

ENTO inhibits uridine disphosphate glucuronosyltransferase 1A1 (UGT1A1) with an IC_{50} of 2 μ M. This enzyme is involved in glucuronidation of bilirubin, and inhibitors of UGT1A1 have the potential to produce increased levels of total and indirect (unconjugated) bilirubin in the circulation {[Zhang et al 2005](#)}.

ENTO is considered non-genotoxic and administration of ENTO did not result in skin reactions indicative of phototoxicity in mice.

Administration of ENTO to pregnant female rats and rabbits from implantation to the closure of the hard palate (International Conference on Harmonisation [ICH] Harmonised Tripartite Guideline stages C to D) resulted in dose-dependent developmental findings including increased incidence of early and late fetal resorptions and reduced fetal weights, and delays in ossification of the forelimb phalanges (rats and rabbits) and metacarpals (rabbits only). These fetal findings occurred at ENTO doses that caused maternal toxicity as demonstrated in both studies by dose-dependent decreases in body weight gain and/or body weight loss and decreased food consumption of the dams. Maternal toxicity was also demonstrated in these studies at doses that did not result in developmental findings.

1.2.1.1. Non Clinical Pharmacology

For further information refer to ENTO Investigator's Brochure (IB).

1.2.1.2. Toxicology

In vitro and in vivo nonclinical studies were conducted to examine the potential toxicity of ENTO. In vivo studies were conducted in rats and dogs. Oral administration is proposed for the initial clinical trials; therefore, multiple-dose studies with ENTO were conducted via the oral route (gavage).

Based on the totality of the data from the standard battery of in vitro and in vivo genotoxicity studies, ENTO is considered non-genotoxic.

Further details can be found in the ENTO IB.

1.2.2. Clinical Trials of Entospletinib (ENTO)

To date, 16 clinical studies have been initiated with ENTO including a total of 566 subjects (including 328 healthy subjects, 7 subjects with RA, 76 subjects with CLL, 155 subjects with NHL; 26 subjects receiving placebo in Phase 1 and Phase 2 clinical studies. Of the 540 subjects receiving ENTO in these studies, ENTO has generally been well tolerated.

Positive results have been reported from a Phase 2 clinical trial with the putative SYK inhibitor fostamatinib showing objective anti-tumor responses in chronic lymphocytic leukemia (CLL) and Non-Hodgkin's lymphoma (NHL) subjects {[Friedberg et al 2010](#)}. These responses occurred despite off target toxicities that limited drug exposure. ENTO is a highly selective inhibitor of SYK and hence has the potential for an improved efficacy and tolerability profile in subjects with hematologic malignancies.

ENTO is being evaluated in an ongoing Phase 2 clinical trial in subjects with relapsed or refractory CLL/NHL. A Phase 1b/2 clinical trial is being conducted for subjects with ENTO monotherapy and in combination with chemotherapy in subjects with acute myeloid leukemia (AML) and acute lymphocytic leukemia (ALL).

ENTO has been studied in single and multiple ascending dose studies in 304 healthy subjects, 7 subjects with rheumatoid arthritis who were on stable doses of methotrexate, 80 subjects with CLL and 95 subjects with NHL. Of these subjects, 460 received ENTO and 26 received placebo. In Pharmacokinetic (PK) studies at steady state in healthy subjects, ENTO was well tolerated when given in a fasted state for 7 days at doses of 25, 75, 200, 600, 900, and 1200 mg twice daily (GS-US-245-0101) and when given in a fed state for 6 days at doses of 100 and 900 mg twice daily (GS-US-245-0106), for 4 days at doses of 200 and 600 mg twice daily (GS-US-339-0101), and at 1200 mg twice daily for 5 days (GS-US-339-0109). Exposure, as measured by AUC and maximum concentration C_{max} , did not increase appreciably at doses above 600 mg under fasted condition.

To provide a margin for inter-patient variability, a dose of 900 mg twice daily was chosen for the study of subjects with rheumatoid arthritis receiving stable doses of methotrexate in Study GS-US-245-0101. A dose of 900 mg ENTO twice daily was given in a fasted state for 26 days in 7 subjects. The median AUC_{tau} in these subjects was similar to that of the healthy subjects. In general, this dose was well tolerated. One subject developed reversible, Grade 2 alkaline phosphatase and transaminase elevations starting 7 days after her last dose of ENTO, concurrent with new onset of a bronchopneumonia. One other subject reported not feeling well and experienced hot flashes, fever, shivers, rash, headache, dizziness, and fainting 1 day after her last dose of ENTO with reversible Grade 1 alkaline phosphatase and Grade 3 transaminase elevations which peaked 1 week later. While these events are potentially confounded by concurrent illnesses, hepatic enzymes will be closely monitored during this study.

Consistent with the known inhibition of UGT1A1 by ENTO, 8 of the 178 healthy subjects developed asymptomatic indirect bilirubin elevations (6 Grade 1, 1 Grade 2 and 1 Grade 3) that resolved following discontinuation of the drug. Three of the 7 subjects with rheumatoid arthritis who received ENTO for 26 days developed asymptomatic indirect bilirubin elevations (2 Grade 1, 1 Grade 3) which improved despite continued dosing.

Common AEs from an on-going Phase 2 study evaluating chronic administration of ENTO monotherapy in 186 subjects with hematologic malignancies are fatigue (53.2%), nausea (45.2%), diarrhea (38.7%), decreased appetite (24.7%), constipation (23.7%), cough (21.0%), and headache (21.0%) as of 21 November 2014. One out of a total of 201 subjects (0.5%) experienced pneumonitis in this monotherapy study as of 11 March 2015.

1.2.3. Interaction with Proton Pump Inhibitors

In Study GS-US-245-1222, omeprazole co-administration reduced ENTO AUC_{tau} by 59% following ENTO BIS-MSA 400 mg BID (solid dispersion formulation). Available solubility and clinical PK data strongly imply that the observed interaction between ENTO and PPIs is due to elevated gastric pH, leading to reduced ENTO absorption. ENTO solubility is known to be highly pH-dependent, with aqueous solubility of 10 mg/mL at pH 2 but <0.15 mg/mL at pH \geq 3.0, suggesting that PPIs are likely to reduce ENTO absorption due to increased gastric pH. In Study GS-US-245-1222, the ENTO terminal elimination half-life was similar when ENTO was administered alone (median [Q1, Q3] 14.89 [11.86, 21.36] hours) or with omeprazole (13.65 [10.49, 17.04] hours), demonstrating that the reduced ENTO exposure observed with omeprazole is likely a result of reduced absorption, rather than a result of altered elimination. Furthermore, omeprazole is a known inhibitor of CYP2C19 {[Angiolillo et al 2011](#)} however in vitro studies did not identify a role of CYP2C19 in ENTO metabolism. In addition, CYP inhibition by omeprazole would be expected to result in increased drug exposure of susceptible substrates, whereas significantly decreased ENTO exposure was observed with omeprazole co-administration in healthy volunteer studies.

Please refer to Section 1.4 of the protocol for further discussion of the dosing implications of PPI co-administration with ENTO in this study.

1.3. Rationale for This Study

Given the emerging role of B cells in cGVHD (abnormal response to BAFF, errors in B cell reconstitution/differentiation, BCR signaling via SYK or BTK, failed induction of B cell tolerance), ENTO, in a dose responsive manner, induces ex vivo apoptosis of a population of B cells present only in patients with active cGVHD, and the proof-of-concept studies with rituximab demonstrating that B cell targeted therapy shows benefit in cGVHD (see Section 1.1.1.1), Gilead is pursuing an investigation into whether ENTO is an effective treatment for cGVHD. Study GS-US-406-1840 is designed to evaluate the efficacy and tolerability of ENTO in addition to systemic corticosteroids in subjects at the time of initial diagnosis of cGVHD requiring treatment. Safety reviews will be performed in real time and will include evaluations of clinical laboratory abnormalities, relapse of primary malignancy, physical examinations, vital signs and AE reporting.

1.4. Rationale for Dose Selection

Since the target coverage necessary to achieve efficacy in subjects cannot be established in ex vivo experiments or animal models, the objective for dose selection is to achieve >50% target inhibition (% inhibition in stimulated CD63+ basophils) at trough. At 200 mg twice daily of ENTO BIS-MSA, the degree of inhibition of CD63+ cells is ~50% at steady state C_{trough} . However, the majority of cGVHD subjects are administered proton pump inhibitors (PPIs), which would be expected to decrease target inhibition below 50% at this dose. At an ENTO BIS-MSA dose of 400 mg twice daily in the presence of a PPI, target inhibition at C_{trough} is ~50%. Thus, the selected dose in cGVHD is 400 mg twice daily of ENTO in patients currently taking a PPI, and 200 mg twice daily of ENTO in patients not currently taking a PPI.

Furthermore, ENTO has a safety profile that is acceptable for subjects receiving treatment for malignancy (including cGVHD subjects). In studies with ENTO, the rate of Grade 3 or 4 AST/ALT elevations is between 10-14%, and these events are reversible with interruption of dosing. Reversible episodes of elevated indirect bilirubin (\geq Grade 1) occur in ~11% of subjects.

1.5. Risk/Benefit Assessment for the Study

Chronic GVHD remains a highly morbid disease with a high mortality rate, and given the cumulative safety data in healthy volunteers and patients with hematologic malignancies, the safety profile of ENTO is expected to be similar in cGVHD patients. ENTO is immunomodulatory, and even though ENTO has not been associated with an increased rate of infections in clinical studies in hematologic malignancy, serious infections are events of interest in this population as patients with cGVHD have a high rate of infections. Any immunomodulatory agent has a theoretical risk of decreasing the graft versus tumor effect, and malignancy relapse is also an event of interest in this study. However, as SYK inhibition affects primarily B cell function and not T-cell function, loss of the graft versus tumor effect is not expected as a result of treatment with ENTO. ENTO is associated with transaminase elevations and bilirubin increases, but these episodes have been reversible. The evaluation of safety of ENTO administration in the cGVHD population is facilitated in this study with the inclusion of a placebo control group.

Refer to the IB for full details of prior and ongoing pre-clinical and clinical studies including summary safety and efficacy data.

1.6. Compliance

This study will be conducted in compliance with this protocol, Good Clinical Practice (GCP), and all applicable regulatory requirements.

2. OBJECTIVES

The primary objective is:

To evaluate the effect of ENTO on the best overall response rate (BORR) as assessed by the cGVHD Activity Assessment (NCAA) by 24 weeks in the setting of add-on to systemic corticosteroids as part of first-line therapy for cGVHD

The key secondary objectives are:

- To evaluate the effect of ENTO on the skin domain of the Lee Symptom Scale (LSS) ([Appendix 6](#)) at 24 weeks
- To evaluate the effect of ENTO on the mouth domain of the LSS at 24 weeks
- To evaluate the effect of ENTO on the eyes domain of the LSS at 24 weeks
- To evaluate the effect of ENTO on the total score of the LSS at 24 weeks

Additional secondary objectives include:

- To evaluate the effect of ENTO on duration of response (DOR)
- To evaluate the effect of ENTO on dose reduction of corticosteroids
- To evaluate the effect of ENTO on initiation of second-line therapy for cGVHD
- To evaluate the effect of ENTO on progression of cGVHD
- To evaluate the safety and tolerability of ENTO

Exploratory objectives include:

P	
P	
D	

3. STUDY DESIGN

3.1. Endpoints

The primary endpoint of this study is:

- The primary endpoint is BORR as assessed by the NCAA by 24 weeks in the setting of add-on to systemic corticosteroids as part of first-line therapy for cGVHD

The key secondary endpoints are:

- Change from Baseline in the skin domain of the LSS at 24 weeks
- Change from Baseline in the mouth domain of the LSS at 24 weeks
- Change from Baseline in the eyes domain of the LSS at 24 weeks
- Change from Baseline in the total score of the LSS at 24 weeks

Other secondary endpoints include:

- DOR
- Proportion of subjects who achieve at least 50% reduction in systemic corticosteroid dose relative to baseline
- Proportion of subjects who initiate second-line therapy for cGVHD
- Failure-free survival (FFS)
- Safety and tolerability of ENTO

Exploratory endpoints of this study include:

P	
P	
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I	
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3.2. Study Design

This protocol describes a randomized, double-blind, placebo-controlled multicenter study to evaluate the efficacy and safety of ENTO (Treatment Arm 1) vs. placebo (Treatment Arm 2) in combination with systemic corticosteroids for subjects with cGVHD.

A total of 100 eligible subjects will be randomized in a 1:1 manner to ENTO (Treatment Arm 1) or placebo-to-match (PTM) (Treatment Arm 2), and treated for 48 weeks during the blinded phase. Randomization will be stratified by the following 2 factors at the Baseline/Day 1 Visit:

Stratification Factor	Stratification Levels
Calcineurin inhibitor or MMF use	Yes vs. No
Disease severity as determined by the 2014 NIH Consensus cGVHD criteria	Moderate cGVHD: <ul style="list-style-type: none">• ≥ 1 organ with score = 2, or• ≥ 3 organs with score = 1, or• lung score = 1 Severe cGVHD: <ul style="list-style-type: none">• any organ score = 3 or• lung score ≥ 2

The final analysis for BORR is planned when all subjects have been on study for 24 weeks. All subjects will be followed up to 48 weeks for DOR evaluation. At the Week 48 visit, subjects who are still on investigational treatment (ENTO or PTM) and are eligible to remain on study will have the option to receive open-label extension (OLE) with ENTO. This OLE offers patients who are deriving a benefit from ENTO or those with no alternative treatments the opportunity for further therapy for a serious and life threatening disease.

An external multidisciplinary data monitoring committee (DMC) will review the progress of the study, perform interim reviews of safety data at regular intervals approximately every 3 months, and perform an interim review of efficacy data for futility when approximately 50% of subjects have been on study for 24 weeks, as described in the DMC Charter. The first DMC meeting will be conducted after the 20th subject has been on study for 4 weeks. The DMC will provide recommendations to Gilead as to whether the nature, frequency, and severity of adverse effects associated with study treatment warrant the early termination of the study in the best interests of the participants, whether the study should continue as planned, or the study should continue with modifications.

3.3. Study Treatments

After 48 weeks of blinded treatment, subjects who are still on investigational treatment (ENTO or PTM) and are eligible to remain on study will have the option to receive open-label extension (OLE) with ENTO and attend visits per the schedule of assessments (Table 6-1) for an additional 96 weeks.

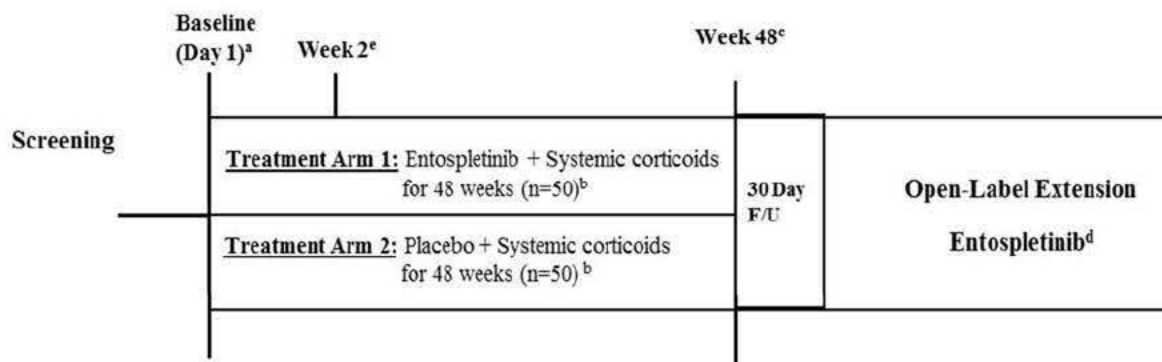
Subjects who provide written informed consent and meet all eligibility criteria will be randomized in a 1:1 fashion to either Treatment Arm 1 or Treatment Arm 2.

Subjects will return for study visits at Weeks: 2, 4, 8, 12, 16, 20, 24, 30, 36, 42 and 48. At the Week 48 visit subjects who are still on investigational treatment (ENTO or PTM) and are eligible to remain on study will have the option to participate in the OLE. If subjects elect not to enroll in the OLE phase of the trial, they will return for a 30-day follow-up visit.

Subjects that will continue in the OLE phase of the trial will return for the following study visits at Weeks: 50, 52, 56, 60, 64, 72 and visits every 12 weeks thereafter. **NOTE for subjects receiving tacrolimus, cyclosporine or MMF:** For subjects receiving these medicines at enrolment and are continuing on these medicines, the blood levels of tacrolimus, cyclosporine or the active metabolite of MMF (MPA) will be monitored at baseline/Day 1 (prior to starting ENTO or PTM), on Day 2 or Day 3 and Day 6 or Day 7 after initiating ENTO or PTM, and at the end of Week 2 and Week 50 study visit. Beyond these time points, concentration monitoring for tacrolimus, cyclosporine and MPA should follow the treating institution's protocol and therapeutic range for monitoring these medicines. For subjects who initiate these medicines while already receiving ENTO or PTM, concentration monitoring for tacrolimus, cyclosporine and MPA should follow the treating institution's protocol and therapeutic range for monitoring these medicines. When a concentration sample is taken at a local lab in accordance with the treating institution's protocol for monitoring these medications, a sample may also be requested for central lab analysis.

PPD

Figure 3-1. Study Schema



- a Following the Baseline/ Day 1 visit subjects will return to the clinic for visits at Weeks 2, 4, 8, 12, 16, 20, 24, 30, 36, 42 and 48.
- b For subjects receiving tacrolimus, cyclosporine or MMF the blood levels of tacrolimus, cyclosporine or the active metabolite of MMF (MPA) will be monitored at baseline/Day 1 (prior to starting ENTO or PTM), on day 2 or day 3 and day 6 or day 7 after initiating ENTO or PTM, and at the end of Week 2 and Week 50 study visit. Beyond these time points, concentration monitoring for tacrolimus, cyclosporine and MPA should follow the treating institutions protocol and therapeutic range for monitoring these medicines
- c Subjects who complete the study through Week 48 and do not wish to continue to participate in the OLE phase of the trial will be required to return to the clinic 30 days after the completion of study drug for a 30-Day Follow-up visit
- d After Week 48, subjects who are still on investigational treatment (ENTO or PTM) and are eligible to remain on study will have the option to receive OLE for an additional 96 weeks. Subjects will attend visits at Weeks: 50, 52, 56, 60, 64, 72 and every 12 weeks thereafter.

- e The initial taper of prednisone from the starting dose of 1.0 mg/kg/day (or equivalent) may be attempted 14 days after co-administration with ENTO/Placebo if there is evidence of improvement in cGVHD

3.4. Discontinuation Criteria

Subject participation may be discontinued in the following instances:

- Intercurrent illness that would, in the judgment of the investigator, affect assessments of clinical status to a significant degree.
- Unacceptable toxicity, or toxicity that, in the judgment of the investigator, compromises the ability to continue study-specific procedures or is considered to not be in the subject's best interest
- Relapse of primary disease
- Severity of cGVHD requiring therapy that is not allowed as concomitant therapy on study (for example JAK inhibitor/BTK inhibitor /mTOR inhibitors/ any cell depletion agent/ phototherapy)
- Subject request to discontinue for any reason
- Subject noncompliance
- Pregnancy during the study; refer to [Appendix 8](#)
- Discontinuation of the study at the request of Gilead, a regulatory agency or an Institutional Review Board or Independent Ethics Committee (IRB/IEC)

3.5. Biomarker Testing

3.5.1. Biomarker Samples to Address the Study Objectives:

Blood will be collected in this study and will be used to evaluate the effect of ENTO on markers relevant to cGVHD and/or the SYK pathway. The specific biomarkers may include, but are not limited to the following: cytokines, cell subset analysis, pathway markers, and/or other B-cell activating factor, B-cell function immunoglobulin levels, and/or antigen-specific B cell responses.

Because biomarker science is a rapidly evolving area of investigation, and adverse events in particular are difficult to predict, it is not possible to specify prospectively all tests that will be done on the specimens provided. The testing outlined below is based upon the current state of scientific knowledge. It may be modified during or after the end of the study to remove tests no longer indicated and/or to add new tests based upon the growing state of art knowledge.

The samples obtained for the study may be stored for 15 years after the end of the study.

3.5.2. Optional Future Research

PPD



3.5.3. Optional Sub-study to study cellular turnover {Emson et al 2013, Ladell et al 2008, Messmer et al 2005}

PPD



4. SUBJECT POPULATION

4.1. Number of Subjects and Subject Selection

Approximately 100 subjects who meet the inclusion/exclusion criteria will be enrolled.

4.2. Inclusion Criteria

Subjects must meet all of the following inclusion criteria to be eligible for participation in this study.

- 1) The ability to understand and sign a written informed consent form, which must be obtained prior to initiation of study procedures
- 2) 18-75 years of age, inclusive at Screening
- 3) Newly diagnosed cGVHD defined by:
 - a) At least 100 days after receiving any allogeneic hematopoietic stem cell transplant
AND
 - b) Receiving a new course of systemic corticosteroids (1.0 mg/kg/day or prednisone equivalent) as first-line cGVHD therapy for at least 1 day and no more than 21 days prior to first dose of ENTO/Placebo
AND
 - c) Moderate to severe cGVHD as assessed by NCDSC with at least three organ systems involved OR one organ system with a score of 2 OR lung organ score = 1 ([Appendix 2](#))
- 4) Subjects who have undergone transplantation for benign indications are eligible for the study. Complete remission is required for subjects who have undergone transplantations for hematologic malignancies.
- 5) Have either a normal ECG or one with abnormalities that are considered clinically insignificant by the investigator in consultation with the Sponsor
- 6) A negative serum pregnancy test is required for female subjects (unless permanently sterile or greater than two years post-menopausal)
- 7) A female subject is eligible to enter the study if it is confirmed that she is:
 - a) Not pregnant or nursing
 - b) Of non-childbearing potential (i.e., women who have had a hysterectomy, have had both ovaries removed or medically documented ovarian failure, or are postmenopausal)

women > 54 years of age with cessation (for ≥ 12 months) of previously occurring menses), or

- c) Of childbearing potential (as defined in [Appendix 8](#)) and agrees to utilize a highly effective protocol-specified contraceptive method or be non-heterosexually active or practice sexual abstinence from Screening throughout the duration of study treatment and for 30 days following the last study drug dose
- 8) Male subjects of childbearing potential who engage in heterosexual intercourse must agree to use protocol specified method(s) of contraception as described in [Appendix 8](#).
- 9) Both female and male subjects of childbearing potential who are receiving mycophenolate mofetil (MMF) must agree to utilize contraceptive measures in accordance with the current MMF SmPC and the precautions for ENTO outlined in [Appendix 8](#), whichever is stricter.

4.3. Exclusion Criteria

Subjects who meet any of the following exclusion criteria are not to be enrolled in this study.

- 1) Uncontrolled infection within 4 weeks prior to Randomization
- 2) History of the following therapies in the post-transplant period:
 - a) B cell depleting biologic agents
 - b) CD19 CAR-T cells based therapies
 - c) BTK/SYK/JAK/PI3K inhibitors
 - d) Phototherapy-unless administered for aGVHD
- 3) Treatment of cGVHD with anti-thymocyte globulins (ATG), or campath within 60 days of Screening visit unless used for treatment of acute GVHD
- 4) Severe organ dysfunction manifest during Screening period:
 - a) Requiring supplemental oxygen at more than 2L/min
 - b) Uncontrolled arrhythmia or heart failure
 - c) Creatinine clearance (Cockcroft-Gault) < 30 mL/min
- 5) Known hypersensitivity to the Investigational Medicinal Product (IMP), the metabolites, or formulation excipient.
- 6) Laboratory abnormalities including:

- a) Human immunodeficiency virus (HIV) antibody, hepatitis B surface antigen or hepatitis C antibody positive (Subjects with positive HCV antibody and without detectable HCV RNA are permitted to enroll)
 - b) Aspartate aminotransferase (AST)/Alanine aminotransferase (ALT) ≥ 2 X upper limit of normal (ULN) unless deemed to be secondary to Liver GVHD
 - c) Total bilirubin ≥ 2 X ULN unless deemed to be secondary to Liver GVHD
- 7) Positive serum pregnancy test (for female subjects)
 - 8) Any other clinical condition or prior therapy that, in the opinion of the investigator, would make the subject unsuitable for the study or unable to comply with dosing requirements
 - 9) Participation in any other clinical trial without prior approval from the sponsor is prohibited while participating in this trial
 - 10) Current alcohol or substance abuse judged by the investigator to potentially interfere with subject compliance or subject safety
 - 11) Subjects receiving ongoing therapy with any of the following medications in the [Table 5-2](#).

5. INVESTIGATIONAL MEDICINAL PRODUCTS

5.1. Randomization, Blinding and Treatment Codes

Subjects will be assigned a screening number at the time of consent. The Randomization and Baseline/Day 1 visit cannot occur until the Investigator has received the results of the Screening tests and subject eligibility has been confirmed.

Once eligibility has been confirmed, each subject will be assigned a unique subject number. Once a subject number has been assigned to a subject, it will not be reassigned to any other subject. Prior to or during the Baseline/Day 1 visit, the investigator or designee will randomize the subject using an Interactive Web Response System (IWRS). Subjects will be randomized in a 1:1 ratio to Treatment Arm 1 or Treatment Arm 2. The IWRS will assign blinded study drug bottle numbers at each study visit (except Weeks 2, 30 and 42). Study drug will be dispensed to the subject in a blinded fashion until Week 48. Randomization will be stratified by the following 2 factors at the Screening and Baseline/Day1 Visit:

Stratification Factor	Stratification Levels
Calcineurin inhibitor or MMF use	Yes vs. No
Disease severity as determined at Screening by the NIH cGVHD Staging and Diagnosis Criteria (NCSDC) Global Severity Score	Moderate cGVHD: ≥ 1 organ with score = 2, or ≥ 3 organs with score = 1, or lung score = 1 Severe cGVHD: any organ score = 3 or lung score ≥ 2

All Baseline/Day 1 tests and procedures must be completed prior the administration of the first dose of the study drug. The subject must complete the Baseline procedures prior to randomization and drug dispensation. Initiation of treatment with the study drug must take place within 24 hours after the Baseline/Day 1 visit.

5.1.1. Procedures for Breaking Treatment Codes

In the event of a medical emergency where breaking the blind is required to provide medical care to the subject, the investigator may obtain treatment assignment directly from the IXRS system for that subject. Gilead recommends but does not require that the investigator contact the Gilead medical monitor before breaking the blind. Treatment assignment should remain blinded unless that knowledge is necessary to determine subject emergency medical care. The rationale for unblinding must be clearly explained in source documentation and on the case report form/ electronic case report form (eCRF), along with the date on which the treatment assignment was obtained. The investigator is requested to contact the Gilead medical monitor promptly in

case of any treatment unblinding. Blinding of study treatment is critical to the integrity of this clinical trial and therefore, if a subject's treatment assignment is disclosed to the investigator, the subject will have study treatment discontinued. All subjects will be followed until study completion unless consent to do so is specifically withdrawn by the subject.

Gilead Drug Safety and Public Health (DSPH) may independently unblind cases for expedited reporting of suspected unexpected serious adverse reactions (SUSARs).

5.2. Description and Handling of Study Drug

5.2.1. Formulation

ENTO is available as 200-mg strength tablets. ENTO 200 mg tablets are blue, plain-faced, capsule-shaped, film-coated tablets. Each tablet contains the equivalent of 200 mg Entospletinib free base in the form of Entospletinib bismesylate monohydrate (ENTO BIS-MSA). In addition to the active ingredient, ENTO tablets contain the following inactive ingredients: methanesulfonic acid, hydroxypropyl methylcellulose, mannitol, microcrystalline cellulose, crospovidone, poloxamer 188, silicon dioxide, magnesium stearate, polyethylene glycol, polyvinyl alcohol, talc, titanium dioxide, and FD&C blue #2 aluminum lake.

Placebo-to-match (PTM) tablets 200 mg are blue, plain-faced, capsule-shaped, film-coated tablets. Each tablet contains the following inactive ingredients: lactose monohydrate, microcrystalline cellulose, crospovidone, magnesium stearate, polyethylene glycol, polyvinyl alcohol, talc, titanium dioxide, and FD&C blue #2 aluminum lake.

5.2.2. Packaging and Labeling

ENTO (GS-9973) 200-mg and PTM tablets are packaged in white, high-density polyethylene (HDPE) bottles. Each bottle contains 60 tablets, silica gel desiccant, and polyester packing material. Each bottle is enclosed with a white, continuous thread, child-resistant polypropylene screw cap with an induction-sealed and aluminum-faced liner.

Study drug(s) to be distributed to centers in the US and other participating countries shall be labeled to meet applicable requirements of the United States Food and Drug Administration (FDA), EU Guideline to Good Manufacturing Practice - Annex 13 (Investigational Medicinal Products), and/or other local regulations.

5.2.3. Storage and Handling

Study drug (ENTO and PTM) should be stored at controlled room temperature of 25°C (77°F); excursions are permitted between 15°C and 30°C (59°F and 86°F). Storage conditions are specified on the label. Until dispensed to the subjects, all bottles of study drugs should be stored in a securely locked area, accessible only to authorized site personnel. To ensure the stability and proper identification, study drug(s) should not be stored in a container other than the container in which they were supplied.

Consideration should be given to handling, preparation, and disposal through measures that minimize drug contact with the body. Appropriate precautions should be followed to avoid direct eye contact or exposure through inhalation when handling.

5.3. Dosage and Administration

ENTO and PTM tablets will be provided by Gilead Sciences.

ENTO or PTM should be taken under fasted conditions. Fasting is defined as no food or liquids other than water for 2 hours pre- and 1 hour post-dose. Subjects unable to swallow tablets should contact Gilead Medical Monitor for guidance. If vomiting occurs within 30 minutes after IMP administration and undissolved tablets are present in the vomitus, the subject should take another dose.

Study medication will be adjusted for whether the subject is taking a proton pump inhibitor (PPI) per the following table, both at study entry and throughout the study.

PPI status	ENTO or PTM dose
Subject is taking PPI	400 mg (2 x 200 mg tablet) twice daily
Subject is NOT taking PPI	200 mg (1 x 200 mg tablet) twice daily

5.4. Prior and Concomitant Medications

Systemic corticosteroids are required at study entry. Administration and taper recommendations are below:

- **Prednisone:** administered initially as a single early morning dose of 1.0 mg/kg/day [or equivalent (Adults: maximum dose 100 mg)]. If due to formulation of prednisone tablets 1.0 mg/kg/day is not possible, we allow a range of 0.90 to 1.10 mg/kg/day.
- Prednisone therapy continues at the initial dose until there is objective evidence of improvement in manifestations of cGVHD (ie, a PR or better), minimum of 14 days of co-administration of ENTO/Placebo and prednisone.
- The initial taper of prednisone from the starting dose of 1.0 mg/kg/day (or equivalent) may be attempted 14 days after co-administration with ENTO/Placebo if there is evidence of improvement in cGVHD
- If exacerbation or recurrence of cGVHD is evident at any step of the taper, the dose of prednisone should be increased promptly by 2 levels, with daily administration for 2 to 4 weeks, followed by resumption of alternate-day administration. Please see [Table 5-1](#) for tapering.

Table 5-1. Tapering of Prednisone after reaching PR/CR

Week	Dose, mg/kg body weight (example for 80kg patient in mg)
0	1.0 once a day (80)
1-3	1.0/0.5 (to begin within 1 week after objective improvement, alternating days) (80/40/80)
4-5	0.5 once a day (40)
6-7	0.5 every other day (40/0/40)
8-9	0.25 every other day (20/0/20)
10	0.1 every other day (10/0/10) with ultimate goal of complete discontinuation of Prednisone

- Inhaled and topical steroids (eg, Budesonide/ Beclomethasone) are not considered second-line therapy and are permitted throughout the duration of the study. Addition of the aforementioned agents will be recorded in the eCRF for posterior analysis.
- Local organ-specific treatment (eg, eye drops) will be recorded in the eCRF and assessment of response after local organ-specific treatment will be based on the NCAA.

Co- Administration of ENTO with Other Classes of Immunosuppressant Agents during OLE:

- During the extension phase (post 96 weeks of study) or OLE, for patients who are eligible to remain on study, the maximum period of co-administration of ENTO with Cyclosporine, Tacrolimus or MMF should not exceed 3 months. The sponsor envisions that if the subject has stable or refractory disease, they should be transitioned to other forms of therapies within this 3 month period.

Disallowed Medications:

Published clinical data suggests that the combination of ENTO with Idelalisib resulted in an unexpected pneumonitis syndrome attributed to excessive mammalian target of rapamycin–like activity. Although pneumonitis has been reported with all mTOR inhibitors, the exact incidence of this toxicity seems to vary widely from study to study. Therapeutic inhibition of kinases involved within the BCR signaling cascade is an emerging field, and many questions remain and for this reason, the co-administration of SYK inhibitors with PI3K inhibitors is strongly discouraged.

In vivo and in vitro data indicates that ENTO is a substrate of CYP2C9 and CYP3A. Co-administration of CYP2C9 inhibitors or inducers may increase or decrease ENTO exposure, respectively. As such, co-administration of moderate and strong CYP3A and CYP2C9 inducers and strong CYP2C9 inhibitors are prohibited in this study. Caution should be exercised when co-administering drugs that are moderate inhibitors of CYP2C9 (eg fluconazole, voriconazole or amiodarone) as they may increase ENTO exposure. Administration of strong and moderate CYP3A and CYP2C9 inducers, and strong CYP2C9 inhibitors, is also prohibited for 2 weeks prior to study drug administration. Examples of strong CYP2C9 inhibitors and moderate/strong

CYP3A and CYP2C9 inducers, PI3K inhibitors, and other medications that are prohibited in this study are provided in [Table 5-2](#)

Table 5-2. Examples of Prohibited Agents

Drug Class	Examples of Prohibited Agents (but not limited to)
mTOR inhibitor	Everolimus, sirolimus
Any cell depleting antibody	Rituxan®
Phototherapy	Phototherapy
BTK agents	Ibrutinib
JAK inhibitors	Tofacitinib, ruxolitinib
Moderate CYP3A/2C9 inducers	Bosentan, modafinil, nafcillin, ritonavir, efavirenz, thioridazine, lopinavir, etravirine, lersivirine, talviraline, tipranavir/ritonavir, semagacestat
Strong CYP3A/2C9 inducers	Rifampin, mitotane, avasimibe, phenytoin, carbamazepine, enzalutamide, St John's Wort, rifabutin, phenobarbital
Strong CYP2C9 inhibitors	Miconazole (systemic)
PI3K inhibitors	Idelalisib
Herbal/Natural Supplements	St. John's Wort

Use with Caution:

In vitro data indicates that Entospletinib has the potential to inhibit several transporters and the metabolizing enzyme UGT1A1, which may affect the plasma concentrations of substrates of these transporters and/or enzyme. Caution should be exercised when co-administering medications that are transported by OATP1B1, OATP1B3, MATE1, P-gp and BCRP or metabolized by UGT1A1; dose adjustment or switching to an alternative medication may be necessary if clinically indicated. A list of sensitive substrates of this enzyme and/or transporters is provided below; any use of these medicines should be discussed with the medical monitor.

Table 5-3. List of Sensitive Substrates of UGT1A1, OATP1B1, OATP1B3, P-gp and BCRP

Transporter	Substrate
P-gp	Aliskiren, aldosterone, ambrisentan, colchicine, dasatinib, dabigatran etexilate, dexamethasone, digoxin, diltiazem, domperidone, etoposide, fexofenadine, imatinib, itraconazole, ivermectin, loperamide, lapatinib, maraviroc, methylprednisolone, nilotinib, posaconazole, quinidine, ranolazine, saxagliptin, sitagliptin, sparfloxacin, talinolol, tolvaptan, topotecan, vinblastine
BCRP	Methotrexate, mitoxantrone, imatinib, irinotecan, lapatinib, rosuvastatin, sulfasalazine, topotecan
OATP1B1	Atrasentan, atorvastatin, ezetimibe, fluvastatin, glyburide, SN-38 (active metabolite of irinotecan), rosuvastatin, simvastatin acid, pitavastatin, pravastatin, repaglinide, valsartan, olmesartan
OAPT1B3	Atorvastatin, rosuvastatin, pitavastatin, telmisartan, valsartan, olmesartan
UGT1A1	Acetaminophen, atorvastatin, bopiramine, carvedilol, clofibrate, ezetimibe, flavopiridol, gemfibrozil, genistein, nalorphine, naltrexone, naringenin, raloxifene, SN-38, simvastatin, telmisartan, troglitazone

In a study in healthy volunteers, Entospletinib 400 mg twice daily increased rosuvastatin exposure by approximately 3-4-fold, which may theoretically increase the risk of rhabdomyolysis. In reviewing the safety of subjects whom have received a statin with Entospletinib there have been no reports of rhabdomyolysis nor a different adverse events profile, but in the interest of caution, the following restrictions apply to the use of HMG-CoA reductase inhibitors with Entospletinib:

HMG-CoA reductase inhibitor	Dose Adjustment Required
Atorvastatin	Maximum dose 20 mg QD
Rosuvastatin	Maximum dose 10 mg QD
Pravastatin	Maximum dose 20 mg QD
Simvastatin	Maximum dose 20 mg QD
Lovastatin	Maximum dose 20 mg QD
Fluvastatin	Maximum dose 20 mg QD

5.5. Opportunistic Infections and Prophylactic Regimens

Patients with ongoing cGVHD or continued use of immunosuppressive therapy should be considered as immune deficient and at risk for significant infectious complications. Thus, prophylaxis for opportunistic infection according to institutional treatment standards are mandated. For additional questions please refer to IDSA guidelines {[Tomblyn et al 2009](#)}. Specifically, CMV surveillance is mandated and in case of clinical infection or the need for preemptive CMV treatment, investigational treatment must be discontinued.

5.6. Accountability for Investigational Medicinal Product

The investigator is responsible for ensuring adequate accountability of all used and unused IMP. This includes acknowledgement of receipt of each shipment of IMP (quantity and condition). All used and unused IMP dispensed to subjects must be returned to the site.

Study drug accountability records will be provided by Gilead Sciences (or equivalent documentation maintained by the study site) to:

- Record the date received and quantity of IMP bottles
- Record the date, subject number, subject initials, the IMP bottle number dispensed
- Record the date, quantity of used and unused IMP returned, along with the initials of the person recording the information.

5.6.1. Investigational Medicinal Product Return or Disposal

IMP return and disposal will be performed as outlined in Section [9.1.6](#).

6. STUDY PROCEDURES

The study procedures to be conducted for each subject enrolled in the study are presented in tabular form in the schedule of assessment and described in the text that follows.

The investigator must document any deviation from protocol procedures and notify the sponsor or contract research organization (CRO).

6.1. Subject Enrollment and Treatment Assignment

It is the responsibility of the Investigator to ensure that each subject is eligible for the study before enrollment in the study. Please refer to Section [5.1](#) for details about randomization and treatment assignment.

6.2. Study Assessments

Study procedures are outlined in [Table 6-1](#).

Table 6-1. Schedule of Assessments

Visit	Screening ^a	Baseline/ Day1 ^c	END OF WEEK ^b																Every 12 Weeks	30 Day Follo w-up
			2 ^t	4	8	12	16	20	24	30	36	42	48/ ESDD ^d	50	52	56	60	64	72	
Visit Window	-30 days	0	±3	±3	±3	±3	±3	±3	±3	±5	±5	±5	±5	±3	±3	±3	±3	±3	±5	±5
Written Informed Consent	X																			
Medical History	X																			
Smoking Status	X	X		X	X	X	X	X	X	X	X	X	X		X	X	X	X	X	
Complete Physical Exam	X	X				X			X				X							
Symptom-Directed Physical Exam ^e			X	X	X		X	X		X	X	X		X	X	X	X	X	X	X
Serum Pregnancy Test ^f	X																			
Urine Pregnancy test ^f		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Serum FSH ^f	X																			
NIH cGVHD Diagnosis and Staging Criteria ^u	X																			
NIH cGVHD Activity Assessment (NCAA) Form A with spirometry ^g		X ^g		X	X	X	X	X	X ^g	X	X	X	X ^g			X	X	X	X	
NIH cGVHD Activity Assessment (NCAA) Form B ^h		X		X	X	X	X	X	X	X	X	X	X			X	X	X	X	
Lee Symptom Scale (LSS) ^h		X		X	X	X	X	X	X	X	X	X	X			X	X	X	X	

Visit	Screening ^a	Baseline/ Day1 ^c	END OF WEEK ^b																Every 12 Weeks	30 Day Follo w-up
			2 ^t	4	8	12	16	20	24	30	36	42	48/ ESDD ^d	50	52	56	60	64	72	
Visit Window	-30 days	0	±3	±3	±3	±3	±3	±3	±3	±5	±5	±5	±5	±3	±3	±3	±3	±3	±5	±5
Primary disease assessment per institutional guidelines	X								X				X							
Height	X																			
Vital Signs & Weight ⁱ	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Hematology ^j	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Chemistry ^k	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Urine Analysis ^l	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Metabolic Panel	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
HIV-1, HBV, & HCV Serology ^m	X																			
12 lead ECG-performed supine	X								X				X							
PK ⁿ			X	X	X	X	X	X	X	X	X	X	X				X		X	
Monitoring of calcineurin inhibitors and MPA ^o		X	X											X						
Biomarkers ^p	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
PFT ^s	X								X				X							
Randomize		X																		
Drug Dispensing ^q		X		X	X	X	X	X	X		X		X		X	X	X		X	
Written Informed Consent for OLE													X							

Visit	Screening ^a	Baseline/ Day1 ^c	END OF WEEK ^b																Every 12 Weeks	30 Day Follo w-up
			2 ^t	4	8	12	16	20	24	30	36	42	48/ ESDD ^d	50	52	56	60	64	72	
Visit Window	-30 days	0	±3	±3	±3	±3	±3	±3	±3	±5	±5	±5	±5	±3	±3	±3	±3	±3	±5	±5
Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Medications ^r	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

- a Evaluations to be completed within 30 days prior to Day 1.
- b All study visits are to be scheduled relative to the Day 1 visit date.
- c Initiation of treatment with the study drug must take place within 24 hours after the Baseline/Day 1 Visit
- d Early Study Drug Discontinuation visit to occur within 72 hours of last dose of study drug
- e Symptom-directed physical exam as needed
- f FSH: For female subject post-menopausal for less than two years, if FSH < 40 mIU/ mL a serum pregnancy test will be required. Women determined to be of child bearing potential will have a serum pregnancy test performed at screening. All subsequent visits will have a urine test, and positive urine pregnancy tests will be confirmed with a serum test. During OLE, urine pregnancy test will be performed every 4 weeks starting with end of visit Week 64.
- g NCAA Form A ([Appendix 5](#)) with spirometry measures will be completed by the Investigator or Sub-I. In the OLE this will be assessed at Weeks 56, 60, 64, 72 and every 12 weeks thereafter. NCAA should also be performed at the time of initiation of second-line therapy. Walk test to be performed at Baseline/Day 1, Weeks 24 and 48/ESDD when medically feasible. Trained study personnel may complete spirometry and walk test portion.
- h LSS ([Appendix 6](#)) and the NCAA Form B ([Appendix 5](#)) is to be completed by the subject. The subject is to read the questionnaire by himself/herself and write/mark answers directly onto the questionnaire. In the OLE this will be assessed at Weeks 56, 60, 64, 72 and every 12 weeks thereafter. The LSS and the NCAA Form B should also be administered at the time of initiation of second-line therapy.
- i Vital sign measurements include blood pressure, pulse, respiration rate, weight and temperature
- j Complete blood count (CBC) with differential platelet count
- k Chemistry profile: alkaline phosphatase, AST, ALT, GGT, total bilirubin, direct and indirect bilirubin, total protein, albumin, LDH, CPK, bicarbonate, BUN, calcium, chloride, creatinine, glucose, phosphorous, magnesium, potassium, sodium, uric acid, and amylase and (reflex lipase testing is performed in subjects with total amylase > 1.5 ULN)
- l Urine collection for urinalysis and urine pregnancy test (if applicable)
- m Subjects with positive HCV antibody and without detectable HCV RNA are permitted to enroll
- n Randomly timed PK sampling. Sites should enter the time of the last dose of study medication in the eCRF for sample reconciliation. PK samples will be drawn at Week 60 and every 12 weeks in the OLE.
- o For subjects receiving tacrolimus, cyclosporine or MMF the blood levels of tacrolimus, cyclosporine or the active metabolite of MMF (MPA) will be monitored at baseline/Day 1 (prior to starting ENTO or PTM), on day 2 or day 3 and day 6 or day 7 after initiating ENTO or PTM, and at the end of Week 2 and Week 50 study visit. Beyond these time points, concentration monitoring for tacrolimus, cyclosporine and MPA should follow the treating institutions protocol and therapeutic range for monitoring these medicines
- p Assessments may include but are not limited to: cytokines, cell subset analysis, pathway markers, and/or other B-cell activating factor, B-cell function, immunoglobulin levels, and/or antigen-specific B cell response. Timepoints may differ depending on the specific biomarker and will be outlined in the Central Lab Manual.
- q At visit 2, 30, 42 and (OLE visit 50), study drug will not be dispensed at these visits
- r Will include the following: systemic corticosteroid dose, other immunosuppressive, antimicrobials, PPI

- s PFTs will include spirometry with bronchodilator, and diffusing capacity of the lungs for carbon monoxide (DLCO). PFTs will be done at ESDD, if ESDD visit greater than 12 weeks from Baseline. Any PFT done within 30 days prior to randomization can be used in lieu of Screening PFT.
- t The initial taper of prednisone from the starting dose of 1.0 mg/kg/day (or equivalent) may be attempted 14 days after co-administration with ENTO/Placebo if there is evidence of improvement in cGVHD
- u Local lab results may be used to establish diagnosis of liver cGVHD

6.2.1. Screening Visit

Written informed consent must be obtained from each subject before initiation of any visit procedures. After a subject has provided informed consent, the investigator and other study personnel (listed on the Form FDA 1572) will determine if the subject is eligible for participation in the study. Subjects will be screened within 30 days before the Baseline/Day 1 visit to determine eligibility for the participation in the study. This assessment will include review of the Inclusion/Exclusion criteria and completion of all Screening visits procedures as outlined in [Table 6-1](#).

Screening visit procedures will include the following for all subjects that provide informed consent: vital signs (including height and weight), medical history, smoking status, complete physical examination, 12-lead ECG (performed supine), concomitant medications, serum pregnancy test (for women of child bearing potential), serum FSH (if applicable), primary malignancy assessment (if applicable), complete the NCDSC (local lab results may be used to establish diagnosis of liver cGVHD), blood draws for the following tests: hematology, chemistry, metabolic panel, HIV-1, HBV, and HCV serology unless specified otherwise. Urine will be collected for urinalysis.

Pulmonary function tests (PFTs) will be required at Screening: spirometry with bronchodilator and diffusing capacity of the lungs for carbon monoxide (DLCO). Per institutional guidelines Investigators may seek specialist examination for PFTs, ocular and gynecological involvement, and other items as described in the NCDSC.

Subjects meeting all of the inclusion criteria and none of the exclusion criteria will return to the clinic within 30 days from the Screening visit for randomization into the study.

From the time of obtaining informed consent through the first administration of investigational medicinal product, record all serious adverse events (SAEs), as well as any adverse events related to protocol-mandated procedures on the adverse events case report form (eCRF). All other untoward medical occurrences observed during the screening period, including exacerbation or changes in medical history are to be captured on the medical history eCRF. See Section 7. for additional details.

6.3. Baseline/Day 1 Visit

The following evaluations are to be completed at the Baseline/Day 1 visit. The Investigator must confirm subject eligibility prior to randomization. Initiation of treatment with the study drug must take place within 24 hours after the Baseline/Day 1 visit.

Baseline/Day 1 visit procedures will include the following: review of adverse events and concomitant medication use. Sites will obtain: vital signs (including weight), complete physical exam, smoking status, primary malignancy assessment (if applicable), NCAA and LSS. Blood will be collected for the following tests: hematology, chemistry, metabolic panel, Blood specimens for selected biomarkers will be collected at Baseline, and urine for urine pregnancy test (if applicable) and urine analysis.

NCAA Form A should be completed by the Investigator or Sub-Investigator; trained study personnel may complete the spirometry and walk test portion. The NCAA Form B and the LSS should be completed by the subject. Subject is to read questionnaire by himself/herself and write/mark answers directly on the questionnaire.

Eligible subjects will be randomized in the IXRS to obtain the subject number. Study drug will be dispensed in a blinded fashion. Subjects should initiate dosing of study drug within 24 hours of the Baseline/Day 1 visit.

ENTO or PTM should be taken under fasted conditions. Fasting is defined as no food or liquids other than water for 2 hours pre- and 1 hour post-dose. Subjects should be instructed not to bite or chew the tablets. In case of breakage of the tablets in the oral cavity, additional water should be taken as a rinse. Subject should be counseled on the importance of taking study medication daily and to return study medication bottles to each visit.

6.4. Treatment Assessments (Weeks 2-48 and OLE)

Evaluations listed in [Table 6-1](#) are to be completed at the end of Weeks: 2, 4, 8, 12, 16, 20, 24, 30, 36, 42 and 48 in blinded fashion. For subjects continuing in the OLE the evaluations listed in [Table 6-1](#) are to be completed at the end of Weeks: 50, 52, 56, 60, 64, 72 and every 12 weeks thereafter up to Week 144 or, until unacceptable toxicity, withdrawal of consent by subject or withdrawal from study by investigator, or until ENTO becomes commercially available.

Study visits are to be completed within ± 3 days, for Weeks 2-24, and Weeks 50-64. Study visits are to be completed within ± 5 days for Weeks 30-48 and Weeks 72-144. **NOTE for subjects receiving tacrolimus, cyclosporine or MMF:** For subjects receiving these medicines at enrolment and are continuing on these medicines, the blood levels of tacrolimus, cyclosporine or the active metabolite of MMF (MPA) will be monitored at baseline/Day 1 (prior to starting ENTO or PTM), on Day 2 or Day 3 and Day 6 or Day 7 after initiating ENTO or placebo-to-match (PTM), and at the end of Week 2 and Week 50 study visit. Beyond these time points, concentration monitoring for tacrolimus, cyclosporine and MPA should follow the treating institution's protocol and therapeutic range for monitoring these medicines. For subjects who initiate these medicines while already receiving ENTO, concentration monitoring for tacrolimus, cyclosporine and MPA should follow the treating institution's protocol and therapeutic range for monitoring these medicines. When a concentration sample is taken at a local lab in accordance with the treating institution's protocol for monitoring these medications, a sample may also be requested for central lab analysis.

At all visits the following will occur: review of adverse events (AEs) and changes in concomitant medications, vital signs (including weight), primary malignancy assessment (if applicable), blood for hematology, chemistry, metabolic panel, and urine for: pregnancy test (if applicable), and urinalysis. PPD

PFTs will be required at on treatment Weeks 24 and 48 only: spirometry with bronchodilator and diffusing capacity of the lungs for carbon monoxide (DLCO)

ECG will be performed at on treatment Weeks 24 and 48 only.

Blood specimens for selected biomarkers will be collected at Screening, Baseline and at Weeks: 2, 4, 8, 12, 16, 20, 24, 30, 36, 42, 48, 50, 52, 56, 60, 64, 72, every 12 weeks thereafter, 30 Day Follow-up and ESDD (if applicable). The timepoints may differ depending on the specific biomarker and will be outlined in the Central Lab manual.

PK blood draws will be collected at Weeks 2, 4, 8, 12, 16, 20, 24, 30, 36, 42 and 48 and Week 60 and every 12 weeks in the OLE.

Smoking status will be collected at Weeks 4, 8, 12, 16, 20, 24, 30, 36, 42, 48, 52, 56, 60, 64, 72 and every 12 weeks thereafter.

Women determined to be of child bearing potential will have a urine test as listed in [Table 6-1](#) and every 4 weeks during the OLE starting with Week 64.

Complete physical exam will be performed at Weeks 12, 24 and 48, symptom directed physical exam will be completed as needed at all other visits.

NCAA Form A with spirometry should be completed by the Investigator or Sub-Investigator at all study visits (except Week 2) and during the OLE at Weeks 56, 60, 64, 72 and every 12 weeks thereafter. The NCAA Form A should also be performed at the time of initiation of second-line therapy. Situations where subjects have comorbid or irreversible conditions that may interfere with response assessment, the check box on the NCAA indicating that the abnormality is entirely explained by a non-GVHD documented cause should be marked. Organ-specific response measures may be delayed until the following visit to allow for resolution of a non-GVHD issue. All other organs should still be scored. A 2 min or 6 min walk test should be performed at Baseline/Day 1, Weeks 24 and 48/ESDD, when medically feasible. Trained study personnel may complete spirometry and walk test portion of NCAA Form A.

LSS and NCAA Form B should be completed by the subject. The Subject is to read the questionnaire by himself/herself and write/mark answers directly on the questionnaire. The PROs will be completed at all study visits (except Week 2) and during the OLE will be assessed at Weeks 56, 60, 64, 72 and every 12 weeks thereafter. One question has been added to the LSS which asks which two domains are most impactful to the subject.

Document study drug dispensation and accountability for all study drugs dispensed. No study drug will be dispensed at Weeks 2, 30, 42 and 50, drug accountability must be done at dispensing visits.

6.5. Post-treatment Assessments

6.5.1. Unscheduled Visit

A subject should attend an unscheduled visit if requested by the Sponsor or the investigator. The assessments performed are at the investigator's discretion.

For subjects that initiate second line therapy during the study, every attempt should be made to collect the NCAA and LSS at an unscheduled visit and to keep the subject in the study and study related follow-up procedures should be continued.

6.5.2. Early Study Drug Discontinuation (ESDD)

If the subject discontinues study drug prior to the end of study, the subject will be asked to return to the clinic within 72 hours of stopping study drug for the Early Study Drug Discontinuation Visit. The subject will be asked to continue attending the schedule study visits through Week 48. Subjects who ESDD will not be eligible for the OLE phase of the study.

At the ESDD visit, any evaluations showing abnormal results indicating that there is a possible or probable causal relationship with the study drug, should be repeated weekly (or as often as deemed prudent by the investigator) until the abnormality is resolved, returns to baseline, or is otherwise explained.

Evaluation listed in [Table 6-1](#) will be completed at the ESDD visit.

The following will be conducted at the ESDD: review of adverse events (AEs) and changes in concomitant medications, vital signs (including weight), complete physical exam, primary malignancy assessment (if applicable), blood for hematology, chemistry, metabolic panel, selected biomarkers and urine for: pregnancy test (if applicable), and urinalysis. The NCAA and LSS will be assessed.

PFTs will be required at ESDD: spirometry with bronchodilator and diffusing capacity of the lungs for carbon monoxide (DLCO).

6.6. 30 Day Follow-Up Visit

Subjects who complete through Week 48 visit and who do not wish to participate in the OLE phase of the study will return to the clinic 30 days after the completion of study drug for the 30-Day follow-up visit. Subjects who complete the OLE will return to the clinic 30 days after the completion of study drug for the 30-Day follow-up visit

Subjects who permanently discontinue study drug and refuse to continue in the study will be asked to return to the clinic 30 days after the completion of the ESDD visit for the 30-Day follow-up visit.

For the purpose of scheduling a 30-Day follow-up visit, a ± 5 days window may be used. [Table 6-1](#) lists all procedures to be completed at the 30-Day Follow-up visit.

6.7. End of Study

The definition of the end of the trial is the last visit of the last participant on the trial.

6.8. Vital Signs

Vital sign measurements include blood pressure, pulse, respiration rate, weight and temperature.

Height will be measured at the Screening visit only.

6.9. Biomarker Sample Collection

Blood for selected biomarkers may include, but not limited to, cytokines, B-cell activating factor, B-cell function, SYK pathway markers, immunoglobulin levels, and/or antigen-specific B cell responses. Please refer to [Table 6-1](#) for collection timepoints. Samples may be stored for up to 15 years.

6.10. Clinical Laboratory Tests/Assessments

Blood and urine samples will be collected as outlined in [Table 6-1](#). All labs will be done centrally, local lab results may be used to establish diagnosis of liver cGVHD.

- Hematology profile: completed blood count (CBC) with differential and platelet count
- Chemistry profile: alkaline phosphatase, AST, ALT, total bilirubin, direct and indirect bilirubin, total protein, albumin, CPK, bicarbonate, BUN, calcium, chloride, creatinine, glucose, phosphorus, magnesium, potassium, sodium, uric acid
- Metabolic assessments: lipid panel (total cholesterol, HDL, direct LDL, and triglycerides).
- Immunoglobulin levels: Immunoglobulin A-E
- Serum and biomarker storage sample for possible additional clinical testing (if subject agrees)
- Urine pregnancy test (females of child bearing potential only); positive urine pregnancy tests will be confirmed with a serum test.
- Urinalysis

6.11. Criteria for Discontinuation of Study Treatment

Study medication may be discontinued in the following instances:

- Intercurrent illness that would, in the judgment of the investigator, affect assessments of clinical status to a significant degree following resolution of intercurrent illness, the subject may resume study dosing at the discretion of the investigator.
- Unacceptable toxicity, or toxicity that, in the judgment of the investigator, compromises the ability to continue study-specific procedures or is considered to not be in the subject's best interest
- Relapse of primary disease
- Severity of cGVHD requiring therapy that is not allowed as concomitant therapy on study

- Subject request to discontinue for any reason
- Subject noncompliance
- Pregnancy during the study; refer to [Appendix 8](#)
- Discontinuation of the study at the request of Gilead, a regulatory agency or an institutional review board or independent ethics committee (IRB/IEC)

If the investigator considers discontinuing study medication for any reason other than those listed above, such as sustained complete remission of cGVHD for more than 3 months, then tapering to discontinue ENTO can be considered and should follow the schedule listed below:

Starting Dose	Action
400 mg twice daily	200 mg, twice daily, for 2 weeks
	200 mg once daily for 2 weeks
	200 mg, once daily, every other day for 2 weeks
	Stop Study Medication
200 mg twice daily	200 mg once daily for 2 weeks
	200 mg, once daily, every other day for 2 weeks
	Stop Study Medication

7. ADVERSE EVENTS AND TOXICITY MANAGEMENT

7.1. Definitions of Adverse Events, Adverse Reactions, and Serious Adverse Events

7.1.1. Adverse Events

An adverse event (AE) is any untoward medical occurrence in a clinical study subject administered a medicinal product, which does not necessarily have a causal relationship with the treatment. An AE can therefore be any unfavorable and/or unintended sign, symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. AEs may also include pre- or post-treatment complications that occur as a result of protocol specified procedures, lack of efficacy, overdose, drug abuse/misuse reports, or occupational exposure. Pre-existing events that increase in severity or change in nature during or as a consequence of participation in the clinical study will also be considered AEs.

An AE does not include the following:

- Medical or surgical procedures such as surgery, endoscopy, tooth extraction, and transfusion. The condition that led to the procedure may be an adverse event and must be reported.
- Pre-existing diseases, conditions, or laboratory abnormalities present or detected before the screening visit that do not worsen
- Situations where an untoward medical occurrence has not occurred (eg, hospitalization for elective surgery, social and/or convenience admissions)
- Overdose without clinical sequelae (see Section 7.6.2.2)
- Any medical condition or clinically significant laboratory abnormality with an onset date before the consent form is signed and not related to a protocol-associated procedure is not an AE. It is considered to be pre-existing and should be documented on the medical history eCRF.

7.1.2. Serious Adverse Events

A **serious adverse event** (SAE) is defined as an event that, at any dose, results in the following:

- Death
- Relapse of primary disease
- Life-threatening (Note: The term “life-threatening” in the definition of “serious” refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe.)
- In-patient hospitalization or prolongation of existing hospitalization

- Persistent or significant disability/incapacity
- A congenital anomaly/birth defect
- A medically important event or reaction: such events may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent one of the other outcomes constituting SAEs. Medical and scientific judgment must be exercised to determine whether such an event is a reportable under expedited reporting rules. Examples of medically important events include intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; and development of drug dependency or drug abuse. For the avoidance of doubt, infections resulting from contaminated medicinal product will be considered a medically important event and subject to expedited reporting requirements.

7.1.3. Clinical Laboratory Abnormalities and Other Abnormal Assessments as Adverse Events or Serious Adverse Events

Laboratory abnormalities without clinical significance are not recorded as AEs or SAEs. However, laboratory abnormalities (eg, clinical chemistry, hematology, and urinalysis) that require medical or surgical intervention or lead to IMP interruption, modification, or discontinuation must be recorded as an AE, as well as an SAE, if applicable. In addition, laboratory or other abnormal assessments (eg, electrocardiogram, x-rays, vital signs) that are associated with signs and/or symptoms must be recorded as an AE or SAE if they meet the definition of an AE or SAE as described in Sections 7.1.1 and 7.1.2. If the laboratory abnormality is part of a syndrome, record the syndrome or diagnosis (eg, anemia), not the laboratory result (ie, decreased hemoglobin).

For specific information on handling of clinical laboratory abnormalities in this study, please refer to Section 7.4.1.

7.2. Assessment of Adverse Events and Serious Adverse Events

The investigator or qualified sub investigator is responsible for assessing AEs and SAEs for causality and severity, and for final review and confirmation of accuracy of event information and assessments.

7.2.1. Assessment of Causality for Study Drugs and Procedures

The investigator or qualified sub investigator is responsible for assessing the relationship to IMP therapy using clinical judgment and the following considerations:

- **No:** Evidence exists that the adverse event has an etiology other than the IMP. For SAEs, an alternative causality must be provided (eg, pre-existing condition, underlying disease, intercurrent illness, or concomitant medication).
- **Yes:** There is reasonable possibility that the event may have been caused by the investigational medicinal product.

It should be emphasized that ineffective treatment should not be considered as causally related in the context of adverse event reporting.

The relationship to study procedures (eg, invasive procedures such as venipuncture or biopsy) should be assessed using the following considerations:

- **No:** Evidence exists that the adverse event has an etiology other than the study procedure.
- **Yes:** The adverse event occurred as a result of protocol procedures, (eg, venipuncture)

7.2.2. Assessment of Severity

The severity of AEs will be graded using the modified CTCAE, version 4.03. For each episode, the highest grade attained should be reported.

If a CTCAE criterion does not exist, the investigator should use the grade or adjectives: Grade 1 (mild), Grade 2 (moderate), Grade 3 (severe), Grade 4 (life-threatening) or Grade 5 (fatal) to describe the maximum intensity of the adverse event. For purposes of consistency with the CTCAE, these intensity grades are defined in [Table 7-1](#) and [Appendix 7](#).

Table 7-1. Grading of Adverse Event Severity

Grade	Adjective	Description
Grade 1	Mild	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
Grade 2	Moderate	Local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL
Grade 3	Severe	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL
Grade 4	Life-threatening	Urgent intervention indicated
Grade 5	Death	Death related AE

* Activities of Daily Living (ADL) Instrumental ADL refer to opening 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

Table 7-2. Grading of Adverse Event Severity: Upper Respiratory

The only modification to the CTCAE criteria has been the addition of a Grade 1 upper respiratory infection as follows:

CTCAE v4.0 Term	Grade 1*	Grade 2	Grade 3	Grade 4	Grade 5	CTCAE v4.03 AE Term Definition
Upper respiratory infection	Mild symptoms; symptomatic relief (cough suppressant, decongestant, etc.)	Moderate symptoms; oral intervention indicated (e.g., antibiotic, antifungal, antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic, endoscopic, or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death	A disorder characterized by an infectious process involving the upper respiratory tract (nose, paranasal sinuses, pharynx, larynx, or trachea).

The distinction between the seriousness and the severity of an adverse event should be noted. Severe is a measure of intensity; thus, a severe reaction is not necessarily a serious reaction. For example, a headache may be severe in intensity, but would not be classified as serious unless it met one of the criteria for serious events listed in Section 7.1.2.

7.3. Investigator Requirements and Instructions for Reporting Adverse Events and Serious Adverse Events to Gilead

Requirements for collection prior to study drug initiation:

After informed consent, but prior to initiation of study medication, the following types of events should be reported on the case report form (eCRF): all SAEs and adverse events related to protocol-mandated procedures.

Adverse Events

Following initiation of study medication, collect all AEs, regardless of cause or relationship, until 30-days after last administration of study IMP must be reported to the eCRF database as instructed.

All AEs should be followed up until resolution or until the adverse event is stable, if possible. Gilead Sciences may request that certain AEs be followed beyond the protocol defined follow up period.

Serious Adverse Events

All SAEs, regardless of cause or relationship, that occurs after the subject first consents to participate in the study (ie, signing the informed consent) and throughout the duration of the study, including the protocol-required post treatment follow-up period, must be reported to the

eCRF database and Gilead Drug Safety and Public Health (DSPH) as instructed. This also includes any SAEs resulting from protocol-associated procedures performed after informed consent is signed.

Any SAEs and deaths that occur within 30-days of the last dose of study IMP, regardless of causality, should also be reported.

Investigators are not obligated to actively seek SAEs after the protocol defined follow up period however, if the investigator learns of any SAEs that occur after study participation has concluded and the event is deemed relevant to the use of IMP, he/she should promptly document and report the event to Gilead DSPH.

- All AEs and SAEs will be recorded in the eCRF database within the timelines outlined in the eCRF completion guideline.

Electronic Serious Adverse Event (eSAE) Reporting Process

- Site personnel record all SAE data in the eCRF database and from there transmit the SAE information to Gilead DSPH within 24 hours of the investigator's knowledge of the event. Detailed instructions can be found in the eCRF completion guidelines.
- If for any reason it is not possible to record the SAE information electronically, ie, the eCRF database is not functioning, record the SAE on the paper serious adverse event reporting form and submit within 24 hours as described above.
- As soon as it is possible to do so, any SAE reported via paper must be transcribed into the eCRF Database according to instructions in the eCRF completion guidelines.
- If an SAE has been reported via a paper form because the eCRF database has been locked, no further action is necessary.
- All AEs and SAEs will be recorded in the eCRF database within the timelines outlined in the eCRF completion guideline.
- For fatal or life-threatening events, copies of hospital case reports, autopsy reports, and other documents are also to be submitted by e-mail or fax when requested and applicable. Transmission of such documents should occur without personal subject identification, maintaining the traceability of a document to the subject identifiers.
- Additional information may be requested to ensure the timely completion of accurate safety reports.
- Any medications necessary for treatment of the SAE must be recorded onto the concomitant medication section of the subject's eCRF and the event description section of the SAE form.

7.4. Gilead Reporting Requirements

Depending on relevant local legislation or regulations, including the applicable US FDA Code of Federal Regulations, the EU Clinical Trials Directive (2001/20/EC) and relevant updates, and other country-specific legislation or regulations, Gilead may be required to expedite to worldwide regulatory agencies reports of SAEs, serious adverse drug reactions (SADRs), or suspected unexpected serious adverse reactions (SUSARs). In accordance with the EU Clinical Trials Directive (2001/20/EC), Gilead or a specified designee will notify worldwide regulatory agencies and the relevant IEC in concerned Member States of applicable SUSARs as outlined in current regulations.

Assessment of expectedness for SAEs will be determined by Gilead using reference safety information specified in the investigator's brochure or relevant local label as applicable.

All investigators will receive a safety letter notifying them of relevant SUSAR reports associated with any study IMP. The investigator should notify the IRB or IEC of SUSAR reports as soon as is practical, where this is required by local regulatory agencies, and in accordance with the local institutional policy.

7.4.1. Clinical Laboratory Abnormalities and Other Abnormal Assessments as Adverse Events or Serious Adverse Events Toxicity Management

- All clinical events and clinically significant laboratory toxicities will be managed according to uniform guidelines detailed in [Appendix 7](#).
- Grade 3 and 4 clinically significant laboratory abnormalities should be confirmed by repeat testing within 3 calendar days of receipt of results and before investigational medicinal product discontinuation, unless such a delay is not consistent with good medical practice.
- Clinical events and clinically significant laboratory abnormalities will be graded according to the Table for Modified CTCAE 4.03 for Severity of Adverse Events and Laboratory Abnormalities.
- When restarting investigational medicinal product following resolution of the adverse event, the investigational medicinal product should be restarted at full dose or modified dose that is dependent upon discussion with the Gilead Sciences Medical Monitor.
- Any recurrence of the investigational medicinal product-related Grade 3 or 4 clinical or clinically significant laboratory adverse event following dose interruption mandates permanent discontinuation of investigational medicinal product.
- Any questions regarding toxicity management should be directed to the Gilead Sciences Medical Monitor.

7.4.2. Grades 1 and 2 Laboratory Abnormality or Clinical Event

Continue investigational medicinal product at the discretion of the investigator.

7.4.3. Grade 3 Laboratory Abnormality or Clinical Event

- For Grade 3 clinically significant laboratory abnormality or clinical event, investigational medicinal product may be continued if the event is considered to be unrelated to investigational medicinal product.
- For a Grade 3 clinical event, or clinically significant laboratory abnormality confirmed by repeat testing, that is considered to be related to investigational medicinal product, investigational medicinal product should be withheld until the toxicity returns to \leq Grade 2. If a laboratory abnormality recurs to \geq Grade 3 following rechallenge with investigational medicinal product and is considered related to investigational medicinal product, then investigational medicinal product should be permanently discontinued and the subject managed according to local practice. Recurrence of laboratory abnormalities considered unrelated to investigational medicinal product may not require permanent discontinuation.

7.4.4. Grade 4 Laboratory Abnormality or Clinical Event

- For a Grade 4 clinical event or clinically significant Grade 4 laboratory abnormality confirmed by repeat testing that is considered related to investigational medicinal product, investigational medicinal product should be permanently discontinued and the subject managed according to local practice. The subject should be followed as clinically indicated until the laboratory abnormality returns to baseline or is otherwise explained, whichever occurs first. A clinically significant Grade 4 laboratory abnormality that is not confirmed by repeat testing should be managed according to the algorithm for the new toxicity grade.

Investigational medicinal product may be continued without dose interruption for a clinically non-significant Grade 4 laboratory abnormality (e.g., Grade 4 CK after strenuous exercise or triglyceride elevation that is nonfasting or that can be medically managed) or a clinical event considered unrelated to investigational medicinal product.

7.5. Toxicity Management

Concentration Monitoring of Calcineurin Inhibitors and Mycophenolate Mofetil

ENTO has been shown in vitro to inhibit the drug transporters organic anion transporting polypeptides 1B1 and 1B3 (OATP1B1 / OATP1B3), P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP), as well as the drug metabolizing enzyme glucuronosyltransferase UGT1A1. Due to the involvement of these pathways in the disposition of the calcineurin inhibitors tacrolimus and cyclosporine, and the active (mycophenolic acid [MPA]) and inactive metabolites of mycophenolate mofetil, Entospletinib may potentially affect the exposure of these medicines.

For subjects receiving these medicines, the blood levels of tacrolimus, cyclosporine or the active metabolite of MMF (MPA) will be monitored at baseline/Day 1 (prior to starting ENTO), on day 2 or day 3 and day 6 or day 7 after initiating ENTO or PTM, and at the end of Week 2 and Week 50 study visit. Beyond these time points, concentration monitoring for tacrolimus,

cyclosporine and MPA should follow the treating institution's protocol and therapeutic range for monitoring these medicines. When a concentration sample is taken at local lab, in accordance with the treating institution's protocol for monitoring these medications, a sample may also be requested for central lab analysis.

7.6. Special Situations Reports

7.6.1. Definitions of Special Situations

Special situation reports include all reports of medication error, abuse, misuse, overdose, reports of adverse events associated with product complaints, and pregnancy reports regardless of an associated AE.

Medication error is any unintentional error in the prescribing, dispensing, or administration of a medicinal product while in the control of the health care provider, subject, or consumer.

Abuse is defined as persistent or sporadic intentional excessive use of a medicinal product by a subject.

Misuse is defined as any intentional and inappropriate use of a medicinal product that is not in accordance with the protocol instructions or the local prescribing information.

An overdose is defined as an accidental or intentional administration of a quantity of a medicinal product given per administration or cumulatively which is above the maximum recommended dose as per protocol or in the product labelling (as it applies to the daily dose of the subject in question). In cases of a discrepancy in drug accountability, overdose will be established only when it is clear that the subject has taken the excess dose(s). Overdose cannot be established when the subject cannot account for the discrepancy except in cases in which the investigator has reason to suspect that the subject has taken the additional dose(s).

Product complaint is defined as complaints arising from potential deviations in the manufacture, packaging, or distribution of the medicinal product.

7.6.2. Instructions for Reporting Special Situations

7.6.2.1. Instructions for Reporting Pregnancies

The investigator should report pregnancies in female study subjects that are identified after initiation of study medication and throughout the study, including the post study drug follow-up period, to Gilead DSPH using the pregnancy report form within 24 hours of becoming aware of the pregnancy.

Refer to Section [7.3](#) and the eCRF completion guidelines for full instructions on the mechanism of pregnancy reporting.

The pregnancy itself is not considered an AE nor is an induced elective abortion to terminate a pregnancy without medical reasons.

Any premature termination of pregnancy (eg, a spontaneous abortion, an induced therapeutic abortion due to complications or other medical reasons) must be reported within 24 hours as an SAE. The underlying medical reason for this procedure should be recorded as the AE term.

A spontaneous abortion is always considered to be an SAE and will be reported as described in Sections 7.1.1 and 7.1.2. Furthermore, any SAE occurring as an adverse pregnancy outcome post study must be reported to Gilead DSPH.

The subject should receive appropriate monitoring and care until the conclusion of the pregnancy. The outcome should be reported to Gilead DSPH using the pregnancy outcome report form. If the end of the pregnancy occurs after the study has been completed, the outcome should be reported directly to Gilead DSPH. Gilead DSPH contact information is as follows:
Email: Safety_FC@gilead.com and Fax: +1 (650) 522-5477.

Pregnancies of female partners of male study subjects exposed to Gilead or other study drugs must also be reported and relevant information should be submitted to Gilead DSPH using the pregnancy and pregnancy outcome forms within 24 hours. Monitoring of the subject should continue until the conclusion of the pregnancy. If the end of the pregnancy occurs after the study has been completed, the outcome should be reported directly to Gilead DSPH, fax number +1 650 522-5477 or email Safety_FC@gilead.com.

Refer to [Appendix 8](#) for Pregnancy Precautions, Definition for Female of Childbearing Potential, and Contraceptive Requirements.

7.6.2.2. Reporting Other Special Situations

All other special situation reports must be reported on the special situations report form and forwarded Gilead DSPH within 24 hours of the investigator becoming aware of the situation. These reports must consist of situations that involve study IMP and/or Gilead concomitant medications, but do not apply to non-Gilead concomitant medications.

Special situations involving non-Gilead concomitant medications do not need to be reported on the special situations report form; however, for special situations that result in AEs due to a non-Gilead concomitant medication, the AE should be reported on the AE form.

Any inappropriate use of concomitant medications prohibited by this protocol should not be reported as “misuse,” but may be more appropriately documented as a protocol deviation.

Refer to Section 7.3 and the eCRF completion guidelines for full instructions on the mechanism of special situations reporting.

All clinical sequelae in relation to these special situation reports will be reported as AEs or SAEs at the same time using the AE eCRF and/or the SAE report form. Details of the symptoms and signs, clinical management, and outcome will be reported, when available.

8. STATISTICAL CONSIDERATIONS

8.1. Analysis Objectives and Endpoints

8.1.1. Analysis Objectives

The primary objective is:

To evaluate the effect of ENTO on BORR as assessed by the NCAA by 24 weeks in the setting of add-on to systemic corticosteroids as part of first-line therapy for cGVHD

The key secondary objectives are:

- To evaluate the effect of ENTO on the skin domain of the LSS at 24 weeks
- To evaluate the effect of ENTO on the mouth domain of the LSS at 24 weeks
- To evaluate the effect of ENTO on the eyes domain of the LSS at 24 weeks
- To evaluate the effect of ENTO on the total score of the LSS at 24 weeks

Additional secondary objectives include:

- To evaluate the effect of ENTO on DOR
- To evaluate the effect of ENTO on dose reduction of corticosteroids
- To evaluate the effect of ENTO on initiation of second-line therapy for cGVHD
- To evaluate the effect of ENTO on progression of cGVHD
- To evaluate the safety and tolerability of ENTO
- Exploratory objectives include:

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8.1.2. Primary Endpoint

The primary endpoint is BORR by 24 weeks, defined as the proportion of subjects who achieve a complete or partial overall response (CR or PR) as assessed by the NCAA within 24 weeks, in the setting of add-on therapy to systemic corticosteroids as part of first-line therapy for cGVHD.

At each assessment time point, organ-specific responses will be determined according to [Appendix 4](#). An overall time point response across all involved organs will then be determined according to [Table 8-1](#). The best overall response across all time points up to 24 weeks will be used to calculate BORR by 24 weeks.

Table 8-1. Criteria for time point response determination

Response Category	Response Criteria
Complete response (CR)	Resolution of all cGVHD manifestations in each organ or site as described in the NCAA organ response determination table
Partial response (PR)	Improvement of at least 1 organ or site, without progression in any other organ or site as described in the NCAA organ response determination table.
Stable disease (SD)	Neither sufficient improvement to qualify for a PR nor sufficient decline to qualify for a PD
Progressive disease (PD)	<ul style="list-style-type: none"> Worsening of signs and symptoms in any organ or site as described in the NCAA organ response determination table, taking the current best overall response as reference that is not a flare. A flare is defined as acute worsening of signs and symptoms in any organ or site that occurs at least 4 weeks after PR/CR is achieved, which lasts ≤ 4 weeks. <p>OR</p> <ul style="list-style-type: none"> Increase in systemic corticosteroid dose to \geq baseline dose (1 mg/kg/day) <p>OR</p> <ul style="list-style-type: none"> Initiation of systemic immunosuppressive therapy other than systemic corticosteroids

8.1.3. Secondary Endpoint

The key secondary endpoints are:

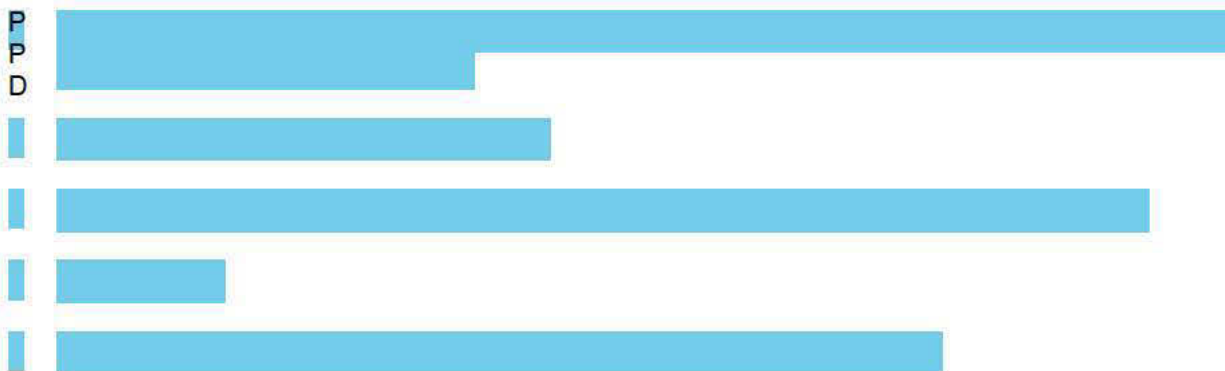
- Change from baseline in the skin domain of the LSS at 24 weeks
- Change from baseline in the mouth domain of the LSS at 24 weeks
- Change from baseline in the eyes domain of the LSS at 24 weeks
- Change from baseline in the total score of the LSS at 24 Weeks

Other secondary endpoints include:

- DOR, defined as the time from the documentation of BORR to the documentation of PD as defined in Table 8-1. Note that a flare does *not* constitute an end to response.
- Proportion of subjects who achieve at least 50% reduction in systemic corticosteroid dose relative to baseline, where % reduction is calculated as (systemic corticosteroid dose at 24 weeks – baseline systemic corticosteroid dose) / baseline systemic corticosteroid dose
- Proportion of subjects who initiate second-line therapy for cGVHD, defined as receiving any therapy besides systemic corticosteroids or study drug for the treatment of cGVHD. Inhaled and topical steroids are not considered second-line therapy.
- Failure-free survival (FFS), defined as the time from randomization to the earliest of first documentation of systemic therapy change, nonrelapse mortality, or recurrent malignancy
- Safety and tolerability of ENTO

8.1.4. Other Endpoints of Interest

Exploratory endpoints include:



8.2. Analysis Conventions

All individual subject data will be listed as measured. All statistical summaries and analyses will be performed using SAS® software (SAS Institute, Cary, North Carolina, USA).

In general, data will be described and summarized by relevant treatment arm, analysis set, and time point. As appropriate, changes from baseline to each subsequent time point will be described and summarized by treatment arm. Graphical techniques (eg, Kaplan-Meier curves, waterfall plots, etc.) may be used when such methods are appropriate and informative.

Summary tables for continuous variables will contain the following statistics: N (number in analysis set), n (number with data), mean, standard deviation (SD), 95% confidence intervals (CIs) on the mean, median, minimum, first quartile (Q1), third quartile (Q3), and maximum.

Summary tables for categorical variables will include: N, n, percentage, and 95% CIs on the percentage.

Subjects with discrepancies between the stratification factor values at randomization and the actual values as documented on data review will be categorized in the analyses according to the actual values.

Unless otherwise specified, all statistical tests will be 2-sided.

8.2.1. Analysis Sets

8.2.1.1. Efficacy

The primary analysis set for efficacy analyses will be the Intent-to-Treat (ITT), which includes data from all randomized subjects, with treatment assignments designated according to randomization.

Selected efficacy endpoints may also be evaluated using the Per-Protocol (PP) analysis set, which includes all randomized subjects who received at least one dose of study drug, did not violate any major entry criteria, and did not have any major protocol deviations.

8.2.1.2. Safety

The primary analysis set for safety analyses will be the Safety Analysis Set, which includes data from all subjects who received at least one dose of study drug, with treatment assignments designated according to actual treatment received. All data collected up to the last dose of study drug plus 30 days will be included in the safety summaries.

8.2.1.3. Pharmacokinetics (PK)

The PK Analysis Set will include data from subjects in the Safety Analysis Set who have the necessary baseline and on-study measurements to provide interpretable results for the specific parameters of interest.

8.3. Data Handling Conventions

Missing data can have an impact upon the interpretation of the trial results. In general, values for missing data will not be imputed unless methods for handling missing data are specified.

Where appropriate, safety data for subjects that did not complete the study will be included in summary statistics.

- If a subject received study drug, the subject will be included in the summary of AEs according to the treatment received; otherwise, if the subject is not dosed then they will be excluded from the summary.
- If safety laboratory results for a subject are missing for any reason at a time point, the subject will be excluded from the calculation of summary statistics for that time point. If the subject is missing a pre-dose value, then the subject will be excluded from the calculation of summary statistics for the pre-dose value and the change from pre-dose values.

Values for missing safety laboratory data will not be imputed; however, a missing Baseline/Day 1 result will be replaced with a screening result, if available. If no pre-treatment safety laboratory value is available, the Baseline/Day 1 value will be assumed to be normal (ie, no grade [Grade 0]) in the summary of graded laboratory abnormalities. Values for missing vital signs data will not be imputed; however, a missing Baseline/Day 1 result will be replaced with a screening result, if available.

Laboratory data that are continuous in nature but are less than the lower limit of quantitation (LOQ) or above the upper LOQ will be imputed as follows:

- A value that is 1 unit less than the LOQ will be used for calculation of descriptive statistics if the data is reported in the form of “<x” (x is considered the LOQ). For example, if the values are reported as <50 and <5.0, then values of 49 and 4.9 will be used for calculation of summary statistics, respectively.
- A value that is 1 unit above the LOQ will be used for calculation of descriptive statistics if the data is reported in the form of “>x” (x is considered the LOQ). For example, if the values are reported as >50 and >5.0, then values of 51 and 5.1 will be used for calculation of summary statistics, respectively.
- The LOQ will be used for calculation of descriptive statistics if the data is reported in the form of “≤ x” or “≥ x” (x is considered as the LOQ).

PK concentration values that are below the limit of quantitation (BLQ) will be presented as “BLQ” in the concentration data listing. Values that are BLQ will be treated as 0 at pre-dose time points, and one-half the value of the lower limit of quantitation (LLOQ) at post-baseline time points, where LLOQ is corrected for the dilution factor (ie, reported LLOQ/dilution factor) for determination of summary and order statistics.

The following conventions will be used for the presentation of summary and order statistics:

- If at least 1 subject has a concentration value of BLQ for the time point, the minimum value will be displayed as “BLQ”
- If more than 25% of the subjects have a concentration value of BLQ for a given time point, the minimum and Q1 values will be displayed as “BLQ”
- If more than 50% of the subjects have a concentration value of BLQ for a given time point, the minimum, Q1, and median values will be displayed as “BLQ”
- If more than 75% of the subjects have a concentration value of BLQ for a given time point, the minimum, Q1, median, and Q3 values will be displayed as “BLQ”
- If all subjects have concentration values of BLQ for a given time point, all order statistics (minimum, Q1, median, Q3, and maximum) will be displayed as “BLQ”

PK parameters that are BLQ will be imputed as one-half LLOQ before log transformation or statistical model fitting.

8.4. Demographic Data and Baseline Characteristics

Demographic data and baseline characteristics will be summarized by treatment group and overall using standard descriptive statistics for the ITT Analysis Set.

Demographic data will include: age, gender, race, and ethnicity.

Baseline characteristics will include: body weight, height, body mass index, and other covariates as necessary.

The number (proportion of subjects) in each stratum will also be summarized.

8.5. Efficacy Analysis

8.5.1. Primary Analysis

The primary endpoint is BORR by 24 weeks in the setting of add-on therapy to systemic corticosteroids as part of first-line therapy for cGVHD. The primary analysis will test the null hypothesis that there is no difference in response rate between ENTO + systemic corticosteroids and placebo + systemic corticosteroids versus the alternative hypothesis that there is a difference.

Response rate will be summarized by count and percent of subjects with each ordinal response (CR, PR, and CR + PR). A stratified Cochran-Mantel-Haenszel (CMH) Chi-square test for association will be performed to compare BORR between ENTO and PTM by 24 weeks. The difference in response rates between treatment groups and the corresponding 95% CIs will be presented.

8.5.2. Secondary Analyses

A sequential testing strategy will be implemented to preserve the overall type I error rate across the primary and key secondary endpoints of the study at a 2-sided significance level of 0.05. The primary endpoint analysis will serve as the gatekeeper for the key secondary endpoint analyses, ie, the primary efficacy endpoint must be met before the key secondary efficacy endpoints can be tested. The key secondary endpoints included in this sequential testing approach are (1) change from baseline in the skin domain of the LSS at 24 weeks, (2) change from baseline in the mouth domain of the LSS at 24 weeks, (3) change from baseline in the eyes domain of LSS at 24 weeks, and (4) change from baseline in the total score of the LSS at 24 weeks.

If the primary hypothesis is rejected, the key secondary endpoints will be sequentially tested at the 2-sided 0.05 significance level in the order listed above. If a null hypothesis is not rejected, formal sequential testing will stop and only nominal significance will be cited for the remaining endpoints.

The key secondary endpoints will be analyzed using a MMRM model that includes all available data at baseline and all post-baseline visits. The model will include terms for baseline value, stratification factor, treatment, visit, and treatment-by-visit interaction. The Kenward-Roger approximation will be used to estimate the denominator degrees of freedom and adjust standard

errors. Treatment comparisons will be generated within the MMRM model based on the linear contrast of the least square means at all-time points. Adjusted means and 95% CIs will be presented by treatment group. Plots of mean (\pm SE) change from baseline over time will be provided by treatment group. Additional sensitivity analyses to further evaluate the impact of missing data may be performed and will be specified in the statistical analysis plan (SAP).

Other secondary endpoints will be analyzed as follows:

DOR and FFS will be analyzed using the Kaplan-Meier (KM) method and stratified logrank test. Kaplan-Meier summary statistics (median, 95% CI for median, and 25th, 75th percentiles) and number and percentage of events will be presented by treatment group. A stratified Cox proportional hazards model will be used to estimate the hazard ratio and corresponding 95% CI. A KM survival plot will also be provided. Data for subjects who do not experience an event will be censored at the date of last visit.

Proportion of subjects with at least 50% reduction in systemic corticosteroid dose relative to baseline and proportion of subjects who initiated second-line therapy for cGVHD will be analyzed similarly to the primary endpoint.

8.5.3. Exploratory Analyses

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8.5.4. Interim Analysis

An interim analysis for futility is planned when approximately 50% of subjects have been on study for 24 weeks. The futility analysis will be performed on BORR by 24 weeks in the ITT Analysis Set. A non-binding futility rule will be implemented. Based upon the analysis results, the DMC may recommend terminating the study for lack of efficacy if the predictive power of obtaining a statistically significant result at the final analysis given the observed interim data is $\leq 5\%$. A 2-sided alpha of 0.001 will be allocated to this futility interim; following the Haybittle-Peto approach {[Haybittle 1971](#), [Peto et al 1976](#)}, the final analysis alpha level is 0.05 (2-sided).

8.5.5. Final Analysis

The final analysis for BORR is planned when all subjects have been on study for 24 weeks. Duration and quality of response will continue to be assessed up to 48 weeks.

8.6. Safety Analysis

All safety data collected on or after the date that ENTO/PTM was first administered up to the date of last dose of ENTO/PTM plus 30 days will be summarized by treatment group (according to the treatment received). Data for the pre-treatment period will be included in data listings.

8.6.1. Extent of Exposure

A subject's extent of exposure to ENTO will be generated from the study drug administration eCRF page. Exposure data will be summarized by treatment group.

8.6.2. Adverse Events

Clinical and laboratory adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). System Organ Class (SOC), High-Level Group Term (HLGT), High-Level Term (HLT), Preferred Term (PT), and Lower-Level Term (LLT) will be attached to the clinical database.

Events will be summarized on the basis of the date of onset for the event. A treatment-emergent adverse event is defined as any adverse event with onset date on or after the date of first dose of study drug up to 30 days after permanent study drug discontinuation, or any adverse events leading to premature study drug discontinuation. Summaries (number and percentage of subjects) of treatment-emergent adverse events (by SOC and PT) will be provided by treatment group.

8.6.3. Laboratory Evaluations

Selected laboratory data (using conventional units) will be summarized using only observed data. Data and change from baseline at all scheduled time points will be summarized.

Graded laboratory abnormalities will be defined using modified CTCAE 4.03. Maximum post-baseline grade will be summarized by count and percentage of subjects with each grade.

Incidence of treatment-emergent laboratory abnormalities, defined as values that increase at least one toxicity grade from baseline at any time post-baseline, will be summarized by treatment group. If baseline data are missing, then any graded abnormality (ie, at least a Grade 1) will be considered treatment-emergent.

Laboratory abnormalities that occur before the first dose of study drug or after the subject has been discontinued from treatment for at least 30 days will be included in data listings.

8.6.4. Other Safety Evaluations

Individual data for 12-lead ECG, vital signs measurements will be listed by subject and summarized by treatment group by incidence of events/abnormalities or descriptive statistical summaries (n, mean, SD, median, Q1, Q3, minimum, and maximum), as appropriate. In comparison to pre-treatment (either Screening or pre-dose on Day 1) values, vital signs measurements and ECG findings will additionally be summarized using predetermined, clinically relevant thresholds.

8.7. Pharmacokinetic Analysis

Concentrations will be listed by subject and summarized using descriptive statistics (eg, n, arithmetic mean, geometric mean, % coefficient of variation [CV], SD, median, Q1, Q3, minimum, and maximum).

8.8. Biomarker Analysis

Descriptive statistics of baseline and change in biomarkers will be provided at each sampling time for all subjects and by treatment.

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8.9. Sample Size

With 40 subjects per treatment group, there is 75% power to detect a 30% improvement in response rate at a 2-sided 0.05 significance level using Fisher's exact test, assuming a placebo response rate of 50%. A total of 100 subjects (50 per treatment group) will be enrolled assuming a 20% dropout rate.

8.10. Data Monitoring Committee

An external multidisciplinary data monitoring committee (DMC) will review the progress of the study, perform interim reviews of safety data at regular intervals approximately every 3 months, and perform an interim review of efficacy data for futility when approximately 50% of subjects have been on study for 24 weeks, as described in the DMC Charter. The DMC will provide recommendations to Gilead as to the whether the nature, frequency, and severity of adverse effects associated with study treatment warrant the early termination of the study in the best interests of the participants, whether the study should continue as planned, or the study should continue with modifications.

The DMC's specific activities will be defined by a mutually agreed charter, which will define the DMC's membership, conduct and meeting schedule.

While the DMC will be asked to advise Gilead regarding future conduct of the study, including possible early study termination, Gilead retains final decision-making authority on all aspects of the study.

9. RESPONSIBILITIES

9.1. Investigator Responsibilities

9.1.1. Good Clinical Practice

The investigator will ensure that this study is conducted in accordance with the principles of the Declaration of Helsinki (as amended in Edinburgh, Tokyo, Venice, Hong Kong, and South Africa), International Conference on Harmonisation (ICH) guidelines, or with the laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the study subject. These standards are consistent with the European Union Clinical Trials Directive 2001/20/EC and Good Clinical Practice Directive 2005/28/EC.

The investigator will ensure adherence to the basic principles of Good Clinical Practice, as outlined in 21 CFR 312, subpart D, “Responsibilities of Sponsors and investigators,” 21 CFR, part 50, 1998, and 21 CFR, part 56, 1998.

The investigator and all applicable sub investigators will comply with 21 CFR, Part 54, 1998, providing documentation of their financial interest or arrangements with Gilead, or proprietary interests in the investigational drug under study. This documentation must be provided prior to the investigator’s (and any sub investigator’s) participation in the study. The investigator and sub investigator agree to notify Gilead of any change in reportable interests during the study and for 1 year following completion of the study. Study completion is defined as the date when the last subject completes the protocol-defined activities.

9.1.2. Institutional Review Board (IRB)/Independent Ethics Committee (IEC) Review and Approval

The investigator (or sponsor as appropriate according to local regulations) will submit this protocol, informed consent form, and any accompanying material to be provided to the subject (such as advertisements, subject information sheets, or descriptions of the study used to obtain informed consent) to an . The investigator will not begin any study subject activities until approval from the IRB/EC has been documented and provided as a letter to the investigator.

Before implementation, the Investigator will submit to and receive documented approval from the IRB/EC any modifications made to the protocol or any accompanying material to be provided to the subject after initial IRB/EC approval, with the exception of those necessary to reduce immediate risk to study subjects.

9.1.3. Informed Consent

The investigator is responsible for obtaining written informed consent from each individual participating in this study after adequate explanation of the aims, methods, objectives, and potential hazards of the study and before undertaking any study-related procedures. The investigator must use the most current IRB/EC approved consent form for documenting

written informed consent. Each informed consent (or assent as applicable) will be appropriately signed and dated by the subject or the subject's legally authorized representative and the person conducting the consent discussion, and also by an impartial witness if required by the IRB/EC.

9.1.4. Confidentiality

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

The investigator agrees that all information received from Gilead, including but not limited to the investigator brochure, this protocol, eCRF, the IMP, and any other study information, remain the sole and exclusive property of Gilead during the conduct of the study and thereafter. This information is not to be disclosed to any third party (except employees or agents directly involved in the conduct of the study or as required by law) without prior written consent from Gilead. The investigator further agrees to take all reasonable precautions to prevent the disclosure by any employee or agent of the study site to any third party or otherwise into the public domain.

9.1.5. Study Files and Retention of Records

The investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented and the study data to be subsequently verified. These documents should be classified into at least the following two categories: (1) investigator's study file, and (2) subject clinical source documents.

The investigator's study file will contain the protocol/amendments, eCRF and query forms, and governmental approval with correspondence, informed consent, drug records, staff curriculum vitae and authorization forms, and other appropriate documents and correspondence.

The required source data should include sequential notes containing at least the following information for each subject:

- Subject identification (name, date of birth, gender);
- Documentation that subject meets eligibility criteria, ie, history, physical examination, and confirmation of diagnosis (to support inclusion and exclusion criteria);
- Documentation of the reason(s) a consented subject is not enrolled
- Participation in study (including study number);

- Study discussed and date of informed consent;
- Dates of all visits;
- Documentation that protocol specific procedures were performed;
- Results of efficacy parameters, as required by the protocol;
- Start and end date (including dose regimen) of IMP, including dates of dispensing and return;
- Record of all adverse events and other safety parameters (start and end date, and including causality and severity);
- Concomitant medication (including start and end date, dose if relevant; dose changes);
- Date of study completion and reason for early discontinuation, if it occurs.

All clinical study documents must be retained by the investigator until at least 2 years or according to local laws, whichever is longer, after the last approval of a marketing application in an ICH region (ie, United States, Europe, or Japan) and until there are no pending or planned marketing applications in an ICH region; or, if no application is filed or if the application is not approved for such indication, until 2 years after the investigation is discontinued and regulatory authorities have been notified. Investigators may be required to retain documents longer if specified by regulatory requirements, by local regulations, or by an agreement with Gilead. The investigator must notify Gilead before destroying any clinical study records.

Should the investigator wish to assign the study records to another party or move them to another location, Gilead must be notified in advance.

If the investigator cannot provide for this archiving requirement at the study site for any or all of the documents, special arrangements must be made between the investigator and Gilead to store these records securely away from the site so that they can be returned sealed to the investigator in case of an inspection. When source documents are required for the continued care of the subject, appropriate copies should be made for storage away from the site.

9.1.6. Case Report Forms

For each subject consented, an eCRF will be completed by an authorized study staff member whose training for this function is documented according to study procedures. eCRF should be completed on the day of the subject visit to enable the sponsor to perform central monitoring of safety data. The Eligibility Criteria eCRF should be completed only after all data related to eligibility have been received. Subsequent to data entry, a study monitor will perform source data verification within the EDC system. Original entries as well as any changes to data fields will be stored in the audit trail of the system. Prior to database lock (or any interim time points as described in the clinical data management plan), the investigator will use his/her log in credentials to confirm that the forms have been reviewed, and that the entries accurately reflect

the information in the source documents. The eCRF capture the data required per the protocol schedule of events and procedures. System-generated or manual queries will be issued to the investigative site staff as data discrepancies are identified by the monitor or internal Gilead staff, who routinely review the data for completeness, correctness, and consistency. The site coordinator is responsible for responding to the queries in a timely manner, within the system, either by confirming the data as correct or updating the original entry, and providing the reason for the update (e.g. data entry error). At the conclusion of the trial, Gilead will provide the site with a read-only archive copy of the data entered by that site. This archive must be stored in accordance with the records retention requirements outlined in Section 9.1.5.

9.1.7. IMP Destruction

Gilead recommends that used and unused IMP supplies be returned to the shipping facility from which it came for eventual destruction. The study monitor will provide instructions for return. If return is not possible, the study monitor will evaluate each study center's IMP disposal procedures and provide appropriate instruction for destruction of unused IMP supplies. If the site has an appropriate standard operating procedure (SOP) for drug destruction as determined by Gilead QA, the site may destroy used (empty or partially empty) and unused IMP supplies in accordance with that site's approved SOP. A copy of the site's approved SOP will be obtained for central files.

If IMP is destroyed on site, the investigator must maintain accurate records for all IMP destroyed. Records must show the identification and quantity of each unit destroyed, the method of destruction, and the person who disposed of the IMP. Upon study completion, copies of the IMP accountability records must be filed at the site. Another copy will be returned to Gilead.

The study monitor will review IMP supplies and associated records at periodic intervals.

9.1.8. Inspections

The investigator will make available all source documents and other records for this trial to Gilead's appointed study monitors, to IRB/EC, or to regulatory authority or health authority inspectors.

9.1.9. Protocol Compliance

The investigator is responsible for ensuring the study is conducted in accordance with the procedures and evaluations described in this protocol.

9.2. Sponsor Responsibilities

9.2.1. Protocol Modifications

Protocol modifications, except those intended to reduce immediate risk to study subjects, may be made only by Gilead. The investigator must submit all protocol modifications to the IRB/EC in accordance with local requirements and receive documented IRB/EC approval before modifications can be implemented.

9.2.2. Study Report and Publications

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

Investigators in this study may communicate, orally present, or publish in scientific journals or other scholarly media only after the following conditions have been met:

The results of the study in their entirety have been publicly disclosed by or with the consent of Gilead in an abstract, manuscript, or presentation form or the study has been completed at all study sites for at least 2 years

The investigator will submit to Gilead any proposed publication or presentation along with the respective scientific journal or presentation forum at least 30 days before submission of the publication or presentation.

No such communication, presentation, or publication will include Gilead's confidential information (see Section 9.1.4).

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

9.3. Joint Investigator/Sponsor Responsibilities

9.3.1. Payment Reporting

Investigators and their study staff may be asked to provide services performed under this protocol, e.g. attendance at Investigator's Meetings. If required under the applicable statutory and regulatory requirements, Gilead will capture and disclose to Federal and State agencies any expenses paid or reimbursed for such services, including any clinical trial payments, meal, travel expenses or reimbursements, consulting fees, and any other transfer of value.

9.3.2. Access to Information for Monitoring

In accordance with regulations and guidelines, the study monitor must have direct access to the investigator's source documentation in order to verify the accuracy of the data recorded in the eCRF.

The monitor is responsible for routine review of the eCRF at regular intervals throughout the study to verify adherence to the protocol and the completeness, consistency, and accuracy of the data being entered on them. The monitor should have access to any subject records needed to verify the entries on the eCRF. The investigator agrees to cooperate with the monitor to ensure that any problems detected through any type of monitoring (central, on site) are resolved.

9.3.3. Access to Information for Auditing or Inspections

Representatives of regulatory authorities or of Gilead may conduct inspections or audits of the clinical study. If the investigator is notified of an inspection by a regulatory authority the investigator agrees to notify the Gilead medical monitor immediately. The investigator agrees to provide to representatives of a regulatory agency or Gilead access to records, facilities, and personnel for the effective conduct of any inspection or audit.

9.3.4. Study Discontinuation

Both the sponsor and the investigator reserve the right to terminate the study at any time. Should this be necessary, both parties will arrange discontinuation procedures and notify the appropriate regulatory authority(ies), IRBs, and IECs. In terminating the study, Gilead and the investigator will assure that adequate consideration is given to the protection of the subjects' interests.

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11. APPENDICES

- Appendix 1. Investigator Signature Page
- Appendix 2. For Screening: NIH cGVHD Diagnosis and Staging Criteria, Global Severity Score {Jagasia et al 2015}
- Appendix 3. For Screening: NIH cGVHD Diagnosis and Staging Criteria (NCDSC) Form {Jagasia et al 2015}
- Appendix 4. For Baseline + Subsequent Visits: Response Determination for the NIH cGVHD Activity Assessment (NCAA) {Lee et al 2015}
- Appendix 5. For Baseline + Subsequent Visits: Chronic GVHD Activity Assessment- Clinician
- Appendix 6. For Baseline + Subsequent Visits: Lee Symptom Scale {Lee et al 2002}
- Appendix 7. Grading of Adverse Event Severity
- Appendix 8. Pregnancy Precautions, Definition for Female of Childbearing Potential, and Contraceptive Requirements
- Appendix 9. Schedule of Assessments for the Optional Cellular Turnover Sub-study*

Appendix 1. Investigator Signature Page

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STUDY ACKNOWLEDGEMENT

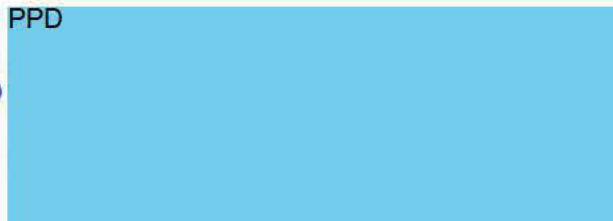
A Phase 2, Randomized, Double-Blind, Placebo-Controlled Study to Assess the Efficacy and Tolerability of Entospletinib, a Selective SYK Inhibitor, in Combination with Systemic Corticosteroids as First-Line Therapy in Subjects with Chronic Graft Versus Host Disease (cGVHD)

GS-US-406-1840 PROTOCOL Amendment 2.0 (Global): 31 August 2016

This protocol has been approved by Gilead Sciences, Inc. The following signature documents this approval.

A. MARIO D. MARCONDES MD PhD
Name (Printed) Mario Marcondes, MD,
PhD

PPD



09/02/2016
Date

INVESTIGATOR STATEMENT

I have read the protocol, including all appendices, and I agree that it contains all necessary details for me and my staff to conduct this study as described. I will conduct this study as outlined herein and will make a reasonable effort to complete the study within the time designated.

I will provide all study personnel under my supervision copies of the protocol and access to all information provided by Gilead Sciences, Inc. I will discuss this material with them to ensure that they are fully informed about the drugs and the study.

Principal Investigator Name (Printed)

Signature

Date

Site Number

Appendix 2. For Screening: NIH cGVHD Diagnosis and Staging Criteria, Global Severity Score {[Jagasia et al 2015](#)}

Mild chronic GVHD

1 or 2 Organs involved with no more than score 1
plus
Lung score 0

Moderate chronic GVHD

3 or More organs involved with no more than score 1
OR
At least 1 organ (not lung) with a score of 2
OR
Lung score 1

Severe chronic GVHD

At least 1 organ with a score of 3
OR
Lung score of 2 or 3

Key points:

In skin: higher of the 2 scores to be used for calculating global severity.

In lung: FEV1 is used instead of clinical score for calculating global severity.

If the entire abnormality in an organ is noted to be unequivocally explained by a non-GVHD documented cause, that organ is not included for calculation of the global severity.

If the abnormality in an organ is attributed to multifactorial causes (GVHD plus other causes) the scored organ will be used for calculation of the global severity regardless of the contributing causes (no downgrading of organ severity score).

Appendix 3. For Screening: NIH cGVHD Diagnosis and Staging Criteria (NCDSC) Form {Jagasia et al 2015}

	SCORE 0	SCORE 1	SCORE 2	SCORE 3
PERFORMANCE SCORE: <div style="border: 1px solid black; width: 50px; height: 20px; display: inline-block;"></div> KPS ECOG LPS	<input type="checkbox"/> Asymptomatic and fully active (ECOG 0; KPS or LPS 100%)	<input type="checkbox"/> Symptomatic, fully ambulatory, restricted only in strenuous activity (ECOG 1, KPS or LPS 80-90%)	<input type="checkbox"/> Symptomatic, ambulatory, capable of self-care, >50% of waking hours out of bed (ECOG 2, KPS or LPS 60-70%)	<input type="checkbox"/> Symptomatic, limited self-care, >50% of waking hours in bed (ECOG 3-4, KPS or LPS <60%)
SKIN† <div style="border: 1px solid black; width: 50px; height: 20px; display: inline-block;"></div> SCORE % BSA <u>GVHD features to be scored by BSA:</u> Check all that apply: <input type="checkbox"/> Maculopapular rash/erythema <input type="checkbox"/> Lichen planus-like features <input type="checkbox"/> Sclerotic features <input type="checkbox"/> Papulosquamous lesions or ichthyosis <input type="checkbox"/> Keratosis pilaris-like GVHD	<input type="checkbox"/> No BSA involved	<input type="checkbox"/> 1-18% BSA	<input type="checkbox"/> 19-50% BSA	<input type="checkbox"/> >50% BSA
SKIN FEATURES SCORE:	<input type="checkbox"/> No sclerotic features		<input type="checkbox"/> Superficial sclerotic features "not hidebound" (able to pinch)	Check all that apply: <input type="checkbox"/> Deep sclerotic features <input type="checkbox"/> "Hidebound" (unable to pinch) <input type="checkbox"/> Impaired mobility <input type="checkbox"/> Ulceration
<u>Other skin GVHD features (NOT scored by BSA)</u> Check all that apply: <input type="checkbox"/> Hyperpigmentation <input type="checkbox"/> Hypopigmentation <input type="checkbox"/> Poikiloderma <input type="checkbox"/> Severe or generalized pruritus <input type="checkbox"/> Hair involvement <input type="checkbox"/> Nail involvement <input type="checkbox"/> Abnormality present but explained entirely by non-GVHD documented cause (specify):				
MOUTH <u>Lichen planus-like features present:</u> <input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Abnormality present but explained entirely by non-GVHD documented cause (specify):	<input type="checkbox"/> No symptoms	<input type="checkbox"/> Mild symptoms with disease signs but not limiting oral intake significantly	<input type="checkbox"/> Moderate symptoms with disease signs with partial limitation of oral intake	<input type="checkbox"/> Severe symptoms with disease signs on examination with major limitation of oral intake

Figure 1. Organ scoring of chronic GVHD. ECOG indicates Eastern Cooperative Oncology Group; KPS, Karnofsky Performance Status; LPS, Lansky Performance Status; BSA, body surface area; ADL, activities of daily living; LFTs, liver function tests; AP, alkaline phosphatase; ALT, alanine aminotransferase; ULN, normal upper limit. *Weight loss within 3 months. †Skin scoring should use both percentage of BSA involved by disease signs and the cutaneous features scales. When a discrepancy exists between the percentage of total body surface (BSA) score and the skin feature score, OR if superficial sclerotic features are present (Score 2), but there is impaired mobility or ulceration (Score 3), the higher level should be used for the final skin scoring. ‡To be completed by specialist or trained medical providers (see Supplemental Figure). **Lung scoring should be performed using both the symptoms and FEV1 scores whenever possible. FEV1 should be used in the final lung scoring where there is discrepancy between symptoms and FEV1 scores.

	SCORE 0	SCORE 1	SCORE 2	SCORE 3
EYES	<input type="checkbox"/> No symptoms	<input type="checkbox"/> Mild dry eye symptoms not affecting ADL (requirement of lubricant eye drops ≤ 3 x per day)	<input type="checkbox"/> Moderate dry eye symptoms partially affecting ADL (requiring lubricant eye drops > 3 x per day or punctal plugs), WITHOUT new vision impairment due to KCS	<input type="checkbox"/> Severe dry eye symptoms significantly affecting ADL (special eyewear to relieve pain) OR unable to work because of ocular symptoms OR loss of vision due to KCS
<i>Keratoconjunctivitis sicca (KCS) confirmed by ophthalmologist:</i>	<input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Not examined			
<input type="checkbox"/> Abnormality present but explained entirely by non-GVHD documented cause (specify):				
GI Tract	<input type="checkbox"/> No symptoms	<input type="checkbox"/> Symptoms without significant weight loss* ($< 5\%$)	<input type="checkbox"/> Symptoms associated with mild to moderate weight loss* (5-15%) OR moderate diarrhea without significant interference with daily living	<input type="checkbox"/> Symptoms associated with significant weight loss* $> 15\%$, requires nutritional supplement for most calorie needs OR esophageal dilation OR severe diarrhea with significant interference with daily living
Check all that apply:				
<input type="checkbox"/> Esophageal web/proximal stricture or ring				
<input type="checkbox"/> Dysphagia				
<input type="checkbox"/> Anorexia				
<input type="checkbox"/> Nausea				
<input type="checkbox"/> Vomiting				
<input type="checkbox"/> Diarrhea				
<input type="checkbox"/> Weight loss $\geq 5\%$ *				
<input type="checkbox"/> Failure to thrive				
<input type="checkbox"/> Abnormality present but explained entirely by non-GVHD documented cause (specify):				
LIVER	<input type="checkbox"/> Normal total bilirubin and ALT or AP < 3 x ULN	<input type="checkbox"/> Normal total bilirubin with ALT ≥ 3 to 5 x ULN or AP ≥ 3 x ULN	<input type="checkbox"/> Elevated total bilirubin but ≤ 3 mg/dL or ALT > 5 ULN	<input type="checkbox"/> Elevated total bilirubin > 3 mg/dL
<input type="checkbox"/> Abnormality present but explained entirely by non-GVHD documented cause (specify):				
LUNGS**				
Symptom score:	<input type="checkbox"/> No symptoms	<input type="checkbox"/> Mild symptoms (shortness of breath after climbing one flight of steps)	<input type="checkbox"/> Moderate symptoms (shortness of breath after walking on flat ground)	<input type="checkbox"/> Severe symptoms (shortness of breath at rest; requiring O_2)
Lung score:	<input type="checkbox"/> FEV1 $\geq 80\%$	<input type="checkbox"/> FEV1 60-79%	<input type="checkbox"/> FEV1 40-59%	<input type="checkbox"/> FEV1 $\leq 39\%$
% FEV1 <input type="text"/>				
Pulmonary function tests				
<input type="checkbox"/> Not performed				
<input type="checkbox"/> Abnormality present but explained entirely by non-GVHD documented cause (specify):				

Figure 1. (continued).

	SCORE 0	SCORE 1	SCORE 2	SCORE 3
JOINTS AND FASCIA	<input type="checkbox"/> No symptoms	<input type="checkbox"/> Mild tightness of arms or legs, normal or mild decreased range of motion (ROM) AND not affecting ADL	<input type="checkbox"/> Tightness of arms or legs OR joint contractures, erythema thought due to fasciitis, moderate decrease ROM AND mild to moderate limitation of ADL	<input type="checkbox"/> Contractures WITH significant decrease of ROM AND significant limitation of ADL (unable to tie shoes, button shirts, dress self etc.)
<u>P-ROM score</u> (see below) Shoulder (1-7): ____ Elbow (1-7): ____ Wrist/finger (1-7): ____ Ankle (1-4): ____				
<input type="checkbox"/> Abnormality present but explained entirely by non-GVHD documented cause (specify): _____				
GENITAL TRACT (See Supplemental figure [†])	<input type="checkbox"/> No signs	<input type="checkbox"/> Mild signs [†] and females with or without discomfort on exam	<input type="checkbox"/> Moderate signs [†] and may have symptoms with discomfort on exam	<input type="checkbox"/> Severe signs [†] with or without symptoms
<input type="checkbox"/> Not examined Currently sexually active <input type="checkbox"/> Yes <input type="checkbox"/> No				
<input type="checkbox"/> Abnormality present but explained entirely by non-GVHD documented cause (specify): _____				
Other indicators, clinical features or complications related to chronic GVHD (check all that apply and assign a score to severity (0-3) based on functional impact where applicable none – 0, mild – 1, moderate – 2, severe – 3)				
<input type="checkbox"/> Ascites (serositis) ____	<input type="checkbox"/> Myasthenia Gravis ____			
<input type="checkbox"/> Pericardial Effusion ____	<input type="checkbox"/> Peripheral Neuropathy ____	<input type="checkbox"/> Eosinophilia > 500/μl ____		
<input type="checkbox"/> Pleural Effusion(s) ____	<input type="checkbox"/> Polymyositis ____	<input type="checkbox"/> Platelets <100,000/μl ____		
<input type="checkbox"/> Nephrotic syndrome	<input type="checkbox"/> Weight loss >5%* without GI symptoms	<input type="checkbox"/> Others (specify): _____		
Overall GVHD Severity (Opinion of the evaluator)	<input type="checkbox"/> No GVHD	<input type="checkbox"/> Mild	<input type="checkbox"/> Moderate	<input type="checkbox"/> Severe
Photographic Range of Motion (P-ROM)				

Figure 1. (continued).

Supplement Figure – Genital Tract Chronic Graft-versus-Host Assessment and Scoring Form

Name: _____ Date of birth: _____ Assessment date: _____

	SCORE 0	SCORE 1	SCORE 2	SCORE 3
GENITAL TRACT	<input type="checkbox"/> No signs	<input type="checkbox"/> Mild signs and females may have symptoms* WITH discomfort on exam	<input type="checkbox"/> Moderate signs and may have symptoms* with discomfort on exam	<input type="checkbox"/> Severe signs with or without symptoms *
<u>Check:</u> <input type="checkbox"/> Male <input type="checkbox"/> Female				
<u>Currently sexually active:</u> <input type="checkbox"/> Yes <input type="checkbox"/> No				
<u>Check all signs that apply:</u>				
<input type="checkbox"/> Lichen planus-like features	<input type="checkbox"/> Erosions			
<input type="checkbox"/> Lichen sclerosis-like features	<input type="checkbox"/> Fissures			
<input type="checkbox"/> Vaginal scarring (female)	<input type="checkbox"/> Ulcers			
<input type="checkbox"/> Clitoral/labial agglutination (female)	<input type="checkbox"/> Phimosis (male)			
<input type="checkbox"/> Labial resorption (female)	<input type="checkbox"/> Urethral meatus scarring/ stenosis (male)			
<input type="checkbox"/> Abnormality present but <u>NOT</u> thought to represent GVHD (specify cause): _____				
<input type="checkbox"/> Abnormality thought to represent GVHD <u>PLUS</u> other causes(specify cause): _____				

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

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

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

Female genitalia: Severity of signs:

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

Male genitalia: Diagnostic features include lichen planus-like or lichen sclerosis-like features and phimosis or urethral scarring or stenosis. Severity of signs:

- 1) Mild: lichen planus-like feature;
- 2) Moderate: lichen sclerosis-like feature or moderate erythema;
- 3) Severe: phimosis or urethral/meatal scarring.

Biopsy obtained: <input type="checkbox"/> Yes <input type="checkbox"/> No	Site biopsied: _____	GVHD confirmed by histology: <input type="checkbox"/> Yes <input type="checkbox"/> No
Change from previous evaluation: <input type="checkbox"/> No prior or current GVHD <input type="checkbox"/> Improved <input type="checkbox"/> Stable <input type="checkbox"/> Worse <input type="checkbox"/> N/A (baseline)		

Completed by (print name): _____

Date form completed: _____

**Appendix 4. For Baseline + Subsequent Visits:
Response Determination for the NIH cGVHD Activity Assessment (NCAA) {Lee et al 2015}**

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

ULN indicates upper limit of normal.

Appendix 5. For Baseline + Subsequent Visits: Chronic GVHD Activity Assessment- Clinician

FORM A

Current Patient Weight: _____ Today's Date: _____ MR#/Name: _____

CHRONIC GVHD ACTIVITY ASSESSMENT- CLINICIAN


























Health Care Provider Global Ratings: 0=none 1=mild 2=moderate 3=severe	Where would you rate the severity of this patient's chronic GvHD symptoms on the following scale, where 0 is cGVHD symptoms that are not at all severe and 10 is the most severe cGVHD symptoms possible: <div style="display: flex; justify-content: space-around; align-items: center;"> 0 1 2 3 4 5 6 7 8 9 </div> <div style="display: flex; justify-content: space-between; align-items: center;"> 10 cGVHD symptoms severe cGVHD not at all severe Most symptoms possible </div>	Since the last assessment would you say that this patient's cGVHD is +3= Very much better +2= Moderately better +1= A little better 0= About the same -1= A little worse -2= Moderately worse -3= Very much worse							
Mouth	Erythema	None	0	Mild erythema or moderate erythema (<25%)	1	Moderate (≥25%) or Severe erythema (<25%)	2	Severe erythema (≥25%)	3
	Lichenoid	None	0	Lichen-like changes (<25%)	1	Lichen-like changes (25-50%)	2	Lichen-like changes (>50%)	3
	Ulcers	None	0			Ulcers involving (≤20%)	3	Severe ulcerations (>20%)	6
		Total score for all mucosal changes							
Gastrointestinal-Esophageal • Dysphagia OR Odynophagia	0= no esophageal symptoms 1=Occasional dysphagia or odynophagia with solid food or pills <u>during the past week</u> 2=Intermittent dysphagia or odynophagia with solid foods or pills, but not for liquids or soft foods, <u>during the past week</u> 3=Dysphagia or odynophagia for almost all oral intake, <u>on almost every day of the past week</u>								
Gastrointestinal-Upper GI • Early satiety OR • Anorexia OR • Nausea & Vomiting	0= no symptoms 1=mild, occasional symptoms, with little reduction in oral intake <u>during the past week</u> 2=moderate, intermittent symptoms, with some reduction in oral intake <u>during the past week</u> 3=more severe or persistent symptoms throughout the day, with marked reduction in oral intake, <u>on almost every day of the past week</u>								
Gastrointestinal-Lower GI • Diarrhea	0= no loose or liquid stools <u>during the past week</u> 1= occasional loose or liquid stools, on some days <u>during the past week</u> 2=intermittent loose or liquid stools throughout the day, <u>on almost every day of the past week, without requiring intervention to prevent or correct volume depletion</u> 3=voluminous diarrhea <u>on almost every day of the past week, requiring intervention to prevent or correct volume depletion</u>								

Lungs (Liters and % predicted) • Bronchiolitis Obliterans	FEV1	FVC	Single Breath DLCO (adjusted for hemoglobin)		TLC	RV
Liver Values	Total serum bilirubin mg/dL	ULN mg/dL	ALT U/L	ULN U/L	Alkaline Phosphatase U/L	ULN U/L
Baseline Values	Total Distance Walked in 2 or 6 Mins: 6 min <input type="checkbox"/> 2 min <input type="checkbox"/>		Karnofsky or Lansky	Platelet Count K/uL	Total WBC K/uL	Eosinophils %
	<input type="checkbox"/> Abnormality present but explained entirely by non-GVHD documented cause (specify site/alternate cause): _____ <input type="checkbox"/> Abnormality present but explained entirely by non-GVHD documented cause (specify site/alternate cause): _____ <input type="checkbox"/> Abnormality present but explained entirely by non-GVHD documented cause (specify site/alternate cause): _____					

CHRONIC GVHD ACTIVITY ASSESSMENT- CLINICIAN (FORM A)

	SCORE 0	SCORE 1	SCORE 2	SCORE 3
SKIN <u>GVHD features to be scored by BSA:</u> Check all that apply: <input type="checkbox"/> Maculopapular rash / erythema <input type="checkbox"/> Lichen planus-like features <input type="checkbox"/> Sclerotic features <input type="checkbox"/> Papulosquamous lesions or ichthyosis <input type="checkbox"/> Keratosis pilaris-like	<input type="checkbox"/> No BSA involved	<input type="checkbox"/> 1-18% BSA	<input type="checkbox"/> 19-50% BSA	<input type="checkbox"/> >50% BSA
<input type="checkbox"/> Abnormality present but explained entirely by non-GVHD documented cause (specify): _____				
SKIN FEATURES SCORE:	<input type="checkbox"/> No sclerotic features		<input type="checkbox"/> Superficial sclerotic features “not hidebound” (able to pinch)	Check all that apply: <input type="checkbox"/> Deep sclerotic features <input type="checkbox"/> “Hidebound” (unable to pinch) <input type="checkbox"/> Impaired mobility <input type="checkbox"/> Ulceration
If skin features score = 3, BSA% of non-moveable sclerosis/fasciitis _____ How would you rate the severity of this patient’s skin and/or joint tightening on the following scale, where 0 is not at all severe and 10 is the most severe symptoms possible: <div style="display: flex; justify-content: space-between; width: 100%;"> 0 1 2 3 4 5 6 7 8 9 10 </div> <div style="display: flex; justify-content: space-between; width: 100%;"> Symptoms not at all severe Most severe symptoms possible </div>				

EYES	<input type="checkbox"/> No symptoms symptoms	<input type="checkbox"/> Mild dry eye symptoms not affecting ADL (requirement of lubricant eye drops ≤ 3 x per day)	<input type="checkbox"/> Moderate dry eye symptoms partially affecting ADL (requiring lubricant eye drops > 3 x per day or punctal plugs), WITHOUT new vision impairment due to KCS	<input type="checkbox"/> Severe dry eye symptoms significantly affecting ADL (special eyewear to relieve pain) OR unable to work because of ocular symptoms OR loss of vision due to KCS
<input type="checkbox"/> Abnormality present but explained entirely by non-GVHD documented cause (specify): _____				
LUNGS	<input type="checkbox"/> No symptoms	<input type="checkbox"/> Mild symptoms (shortness of breath after climbing one flight of steps)	<input type="checkbox"/> Moderate symptoms (shortness of breath after walking on flat ground)	<input type="checkbox"/> Severe symptoms (shortness of breath at rest; requiring O ₂)
<input type="checkbox"/> Abnormality present but explained entirely by non-GVHD documented cause (specify): _____				
JOINTS AND FASCIA	<input type="checkbox"/> No symptoms	<input type="checkbox"/> Mild tightness of arms or legs, normal or mild decreased range of motion (ROM) AND not affecting ADL	<input type="checkbox"/> Tightness of arms or legs OR joint contractures, erythema thought due to fasciitis, moderate decrease ROM AND mild to moderate limitation of ADL	<input type="checkbox"/> Contractures WITH significant decrease of ROM AND significant limitation of ADL (unable to tie shoes, button shirts, dress self etc.)
<input type="checkbox"/> Abnormality present but explained entirely by non-GVHD documented cause (specify): _____				

	1 (Worst)	2	3	4	5	6	7 (Normal)	
Shoulder								<input type="checkbox"/> Not done
	1 (Worst)	2	3	4	5	6	7 (Normal)	
Elbow								<input type="checkbox"/> Not done
	1 (Worst)	2	3	4	5	6	7 (Normal)	
Wrist/finger								<input type="checkbox"/> Not done
	1 (Worst)	2	3	4 (Normal)				
Ankle								<input type="checkbox"/> Not done

FORM B

Today's Date: _____ MR#/Name: _____

CHRONIC GVHD ACTIVITY ASSESSMENT-PATIENT SELF REPORT

Symptoms		As Bad As You Can Imagine										
Please rate how severe the following symptoms have been in the <u>last seven days</u> . Please fill in the circle below from 0 (symptom has not been present) to 10 (the symptom was as bad as you can imagine it could be) for each item.		Not Present										
		0	1	2	3	4	5	6	7	8	9	10
Your skin itching at its WORST?		<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Your skin and/or joint tightening at their WORST?		<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Your mouth sensitivity at its WORST?		<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Your genital discomfort at its WORST? (Women – vagina, vulva, or labia) (Men – penis)		<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Eyes	What is your main complaint with regard to your eyes?											
	Please rate how severe this symptom is, from 0 (not at all severe) to 10 (most severe):							0 1 2 3 4 5 6 7 8 9 10				

Patient Global Ratings:

1. Overall, do you think that your chronic graft versus host disease is mild, moderate or severe?

1= mild
2=moderate
3=severe

2. Please circle the number indicating how severe your chronic graft versus host disease symptoms are, where 0 is cGvHD symptoms that are not at all severe and 10 is the most severe chronic GvHD symptoms possible.

0 1 2 3 4 5 6 7 8 9 10

cGvHD symptoms
not at all severe

Most severe cGvHD
symptoms possible

3. Compared to a month ago, overall would you say that your cGvHD symptoms are:

+3= Very much better
+2= Moderately better
+1=A little better
0= About the same
-1=A little worse
-2=Moderately worse
-3=Very much worse

Appendix 6. For Baseline + Subsequent Visits: Lee Symptom Scale {Lee et al 2002}

By circling one (1) number per line, please indicate how much you have been bothered by the following problems in the past 7 days:

SKIN:		Not at all	Slightly	Moderately	Quite a bit	Extremely
1.	Abnormal skin color.....	0	1	2	3	4
2.	Rashes.....	0	1	2	3	4
3.	Thickened skin.....	0	1	2	3	4
4.	Sores on skin.....	0	1	2	3	4
5.	Itchy skin.....	0	1	2	3	4

EYES AND MOUTH:		Not at all	Slightly	Moderately	Quite a bit	Extremely
6.	Dry eyes.....	0	1	2	3	4
7.	Need to use eye drops frequently..	0	1	2	3	4
8.	Difficulty seeing clearly.....	0	1	2	3	4
9.	Need to avoid certain foods due to mouth pain.....	0	1	2	3	4
10.	Ulcers in mouth.....	0	1	2	3	4
11.	Receiving nutrition from an intravenous line or feeding tube....	0	1	2	3	4

BREATHING:		Not at all	Slightly	Moderately	Quite a bit	Extremely
12.	Frequent cough.....	0	1	2	3	4
13.	Colored sputum.....	0	1	2	3	4
14.	Shortness of breath with exercise..	0	1	2	3	4
15.	Shortness of breath at rest.....	0	1	2	3	4
16.	Need to use oxygen.....	0	1	2	3	4

EATING AND DIGESTION:	Not at all	Slightly	Moderately	Quite a bit	Extremely
17. Difficulty swallowing solid foods....	0	1	2	3	4
18. Difficulty swallowing liquids.....	0	1	2	3	4
19. Vomiting.....	0	1	2	3	4
20. Weight loss.....	0	1	2	3	4
MUSCLES AND JOINTS:	Not at all	Slightly	Moderately	Quite a bit	Extremely
21. Joint and muscle aches.....	0	1	2	3	4
22. Limited joint movement.....	0	1	2	3	4
23. Muscle cramps.....	0	1	2	3	4
24. Weak muscles.....	0	1	2	3	4
ENERGY:	Not at all	Slightly	Moderately	Quite a bit	Extremely
25. Loss of energy.....	0	1	2	3	4
26. Need to sleep more/take naps.....	0	1	2	3	4
27. Fevers.....	0	1	2	3	4
MENTAL AND EMOTIONAL:	Not at all	Slightly	Moderately	Quite a bit	Extremely
28. Depression.....	0	1	2	3	4
29. Anxiety.....	0	1	2	3	4
30. Difficulty sleeping.....	0	1	2	3	4

Summary of the Lee Symptom Scale

Which 2 of the following organs/systems have you found to affect you the most in the last seven days:

- 1) Skin
- 2) Eyes
- 3) Mouth
- 4) Breathing
- 5) Eating and Digestion
- 6) Muscles and Joints
- 7) Energy
- 8) Mental and Emotional

Appendix 7. Grading of Adverse Event Severity

Grade	Adjective	Description
Grade 1	Mild	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
Grade 2	Moderate	Local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL
Grade 3	Severe	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL
Grade 4	Life-threatening	Urgent intervention indicated
Grade 5	Death	Death related AE

* Activities of Daily Living (ADL) Instrumental ADL refer to opening 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

Appendix 8. Pregnancy Precautions, Definition for Female of Childbearing Potential, and Contraceptive Requirements

1) Definitions

ENTO is contraindicated in pregnancy as animal studies in rats and rabbits have shown that study drug is teratogenic. Pregnancy must be excluded before the start of treatment with study drug and prevented thereafter by reliable contraceptive methods. Pregnancy tests will be performed regularly throughout this study per [Table 6-1](#). Please refer to the latest version of the investigator's brochure for additional information.

a) Definition of Childbearing Potential

For the purposes of this study, a female born subject is considered of childbearing potential following the initiation of puberty (Tanner stage 2) until becoming post-menopausal, unless permanently sterile or with medically documented ovarian failure.

Women are considered to be in a postmenopausal state when they are ≥ 54 years of age with cessation of previously occurring menses for ≥ 12 months without an alternative cause. In addition, women of any age with amenorrhea of ≥ 12 months may also be considered postmenopausal if their follicle stimulating hormone (FSH) level is in the postmenopausal range and they are not using hormonal contraception or hormonal replacement therapy.

Permanent sterilization includes hysterectomy, bilateral oophorectomy, or bilateral salpingectomy in a female subject of any age.

b) Definition of Male Fertility

For the purposes of this study, a male born subject is considered fertile after the initiation of puberty unless permanently sterile by bilateral orchidectomy or medical documentation.

2) Contraception Requirements for Female Subjects

a) Study Drug Effects on Pregnancy and Hormonal Contraception

ENTO is contraindicated in pregnancy as there is a strong suspicion of human teratogenicity/fetotoxicity in early pregnancy based on non-clinical data. In addition, ENTO has insufficient data to exclude the possibility of a clinically relevant interaction with hormonal contraception that results in reduced contraception efficacy; therefore, contraceptive steroids are not recommended as a contraceptive method either solely or as a part of a contraceptive regimen. Please refer to the latest version of the investigator's brochure for additional information.

b) Contraception Requirements for Female Subjects of Childbearing Potential

The inclusion of female subjects of childbearing potential requires the use of highly effective contraceptive measures. They must also not rely on hormone-containing contraceptives as a form of birth control during the study. They must have a negative serum pregnancy test at

screening and a negative pregnancy test on the Baseline/Day 1 Visit. Pregnancy tests will be performed on the protocol-specified schedule thereafter. Female subjects must agree to one of the following methods to avoid pregnancy from Screening until 30 days from the last dose of ENTO:

- Complete abstinence from intercourse of reproductive potential. Abstinence is an acceptable method of contraception only when it is in line with the subject's preferred and usual lifestyle.

Or

- Consistent and correct use of 1 of the following methods of birth control listed below.
 - a) Intrauterine device (IUD) with a failure rate of <1% per year
 - b) Tubal sterilization
 - c) Essure micro-insert system (provided confirmation of success 3 months after procedure)
 - d) Vasectomy in the male partner (provided that the partner is the sole sexual partner and had confirmation of surgical success 3 months after procedure)

Female subjects must also refrain from egg donation and in vitro fertilization during treatment and until at least 30 days from the last dose of ENTO.

3) Contraception Requirements for Male Subjects

It is theoretically possible that a relevant systemic concentration may be achieved in a female partner from exposure of the male subject's seminal fluid. Therefore, male subjects with female partners of childbearing potential must use condoms during treatment and until 90 days from the last dose of ENTO. Additional contraception recommendations should also be considered if the female partner is not pregnant.

Male subjects must also refrain from sperm donation during treatment and until at least 90 days from the last dose of ENTO.

4) Unacceptable Birth Control Methods

Birth control methods that are unacceptable include periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea method (LAM). Female condom and male condom should not be used together.

5) Procedures to be Followed in the Event of Pregnancy

Subjects will be instructed to notify the investigator if they become pregnant at any time during the study, or if they become pregnant within 30 days of last study drug dose. Subjects who

become pregnant or who suspect that they are pregnant during the study must report the information to the investigator and discontinue study drug immediately. Subjects whose partner has become pregnant or suspects she is pregnant during the study must report the information to the investigator. Instructions for reporting pregnancy, partner pregnancy, and pregnancy outcome are outlined in Section 7.6.

PPD

