# STATISTICAL ANALYSIS PLAN

**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)

**Name of Test Drug:** Entospletinib

**Study Number:** GS-US-406-1840

**Protocol Version (Date):** Amendment 3.0 (30 January 2017)

**Analysis Type:** Interim and Final

**Analysis Plan Version:** Version 2.0

**Analysis Plan Date:** 11 May 2018

**Analysis Plan Author(s):** PPD

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**CONFIDENTIAL AND PROPRIETARY INFORMATION**
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<table>
<thead>
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<th>Abbreviation</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>BORR</td>
<td>best overall response rate</td>
</tr>
<tr>
<td>CI</td>
<td>confidence interval</td>
</tr>
<tr>
<td>cGVHD</td>
<td>chronic Graft Versus Host Disease</td>
</tr>
<tr>
<td>CMH</td>
<td>Cochran-Mantel-Haenszel</td>
</tr>
<tr>
<td>CPK</td>
<td>creatine phosphokinase</td>
</tr>
<tr>
<td>CR</td>
<td>complete response</td>
</tr>
<tr>
<td>CRF</td>
<td>case report form(s)</td>
</tr>
<tr>
<td>DMC</td>
<td>Data Monitoring Committee</td>
</tr>
<tr>
<td>DOR</td>
<td>duration of response</td>
</tr>
<tr>
<td>EBV</td>
<td>Epstein-Barr Virus</td>
</tr>
<tr>
<td>ECG</td>
<td>electrocardiogram</td>
</tr>
<tr>
<td>eCRF</td>
<td>electronic case report form(s)</td>
</tr>
<tr>
<td>ENTO</td>
<td>entospletinib</td>
</tr>
<tr>
<td>FSH</td>
<td>follicle-stimulating hormone</td>
</tr>
<tr>
<td>GGT</td>
<td>gamma-glutamyl transferase</td>
</tr>
<tr>
<td>GVHD</td>
<td>Graft Versus Host Disease</td>
</tr>
<tr>
<td>Hb</td>
<td>hemoglobin</td>
</tr>
<tr>
<td>HBV</td>
<td>hepatitis B virus</td>
</tr>
<tr>
<td>HCV</td>
<td>hepatitis C virus</td>
</tr>
<tr>
<td>HIV</td>
<td>human immunodeficiency virus</td>
</tr>
<tr>
<td>ITT</td>
<td>intent-to-treat</td>
</tr>
<tr>
<td>IWRS</td>
<td>interactive web response system</td>
</tr>
<tr>
<td>KM</td>
<td>Kaplan-Meier</td>
</tr>
<tr>
<td>LLOQ</td>
<td>lower limit of quantitation</td>
</tr>
<tr>
<td>LOQ</td>
<td>limit of quantitation</td>
</tr>
<tr>
<td>LSS</td>
<td>Lee Symptom Scale</td>
</tr>
<tr>
<td>MedDRA</td>
<td>Medical Dictionary for Regulatory Activities</td>
</tr>
<tr>
<td>MMF</td>
<td>mycophenolate mofetil</td>
</tr>
<tr>
<td>MMRM</td>
<td>mixed model repeated measures</td>
</tr>
<tr>
<td>NCAAA</td>
<td>NIH cGVHD Activity Assessment</td>
</tr>
<tr>
<td>NIH</td>
<td>National Institute of Health</td>
</tr>
<tr>
<td>PCP</td>
<td>Phencyclidine</td>
</tr>
<tr>
<td>PFT</td>
<td>pulmonary function tests</td>
</tr>
<tr>
<td>PK</td>
<td>pharmacokinetic</td>
</tr>
<tr>
<td>PPI</td>
<td>proton pump inhibitor</td>
</tr>
<tr>
<td>PTM</td>
<td>placebo-to-match</td>
</tr>
<tr>
<td>Q1</td>
<td>first quartile</td>
</tr>
<tr>
<td>Q3</td>
<td>third quartile</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Definition</td>
</tr>
<tr>
<td>-------------</td>
<td>------------------------------------------------</td>
</tr>
<tr>
<td>RNA</td>
<td>ribonucleic acid</td>
</tr>
<tr>
<td>SAE</td>
<td>serious adverse event</td>
</tr>
<tr>
<td>SAP</td>
<td>statistical analysis plan</td>
</tr>
<tr>
<td>SD</td>
<td>standard deviation</td>
</tr>
<tr>
<td>SOC</td>
<td>System Organ Class</td>
</tr>
<tr>
<td>SYK</td>
<td>spleen tyrosine kinase</td>
</tr>
<tr>
<td>ULN</td>
<td>upper limit of the normal range</td>
</tr>
<tr>
<td>WBC</td>
<td>white blood cell</td>
</tr>
<tr>
<td>WHO</td>
<td>World Health Organization</td>
</tr>
</tbody>
</table>
1. INTRODUCTION

This statistical analysis plan (SAP) describes the statistical analysis methods and data presentations to be used in tables, figures, and listings (TFLs) for the planned interim and final analyses for Study GS-US-406-1840. This SAP is based on Protocol Amendment 3 dated 30 January 2017 and the electronic case report form (eCRF). The SAP was finalized before the final analysis. The changes made after the finalization of the SAP will be documented in the CSR.

1.1. Study Objectives

The primary objective of this study is:

- To evaluate the effect of entospletinib (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

The key secondary objectives of this study are:

- To evaluate the effect of ENTO on the skin domain of the Lee Symptom Scale (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 are:

- 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:
1.2. Study Design

This is 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 in subjects with cGVHD. An interim analysis for futility is planned when approximately 50% of subjects have been on study for 24 weeks, or have discontinued the study before 24 weeks, or have achieved a response prior to reaching 24 weeks. The primary endpoint will be evaluated when all subjects complete 24 weeks of treatment. Duration and type of response (complete or partial) will be evaluated for up to 48 weeks of blinded treatment. After 48 weeks, subjects who are still on investigational treatment (ENTO or placebo-to-match [PTM]) and are eligible to remain on study will have the option to participate in an open-label extension (OLE) to receive ENTO and attend visits per the schedule of assessments (Appendix 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. This OLE offers patients who are deriving a benefit from ENTO and have no alternative treatments the opportunity for further therapy for a serious and life threatening disease.

Figure 1. Study Schema

- Baseline (Day 1)
- Week 48
- Screening
- ≤30 days prior to Baseline

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 institution's 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, all subjects 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.
The study consists of the following visits:

- Screening
- Baseline/Day 1
- Treatment Assessments (weeks 2-48 and OLE)
- Unscheduled
- Early Study Drug Discontinuation (ESDD)
- 30 Day Follow-Up

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.

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

- 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.

1.3. Sample Size and Power

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.
2. TYPE OF PLANNED ANALYSIS

2.1. Data Monitoring Committee Analyses

An external multidisciplinary Data Monitoring Committee (DMC) will review the progress of the study and perform interim reviews of safety and efficacy data for futility in order to protect subject welfare and preserve study integrity. The DMC is to recommend to the sponsor 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 whether the study should continue with modifications.

The DMC will meet at designated intervals every 5 month after the first 20 subjects have been on study for 8 weeks to review accumulated safety data. The DMC will also review 1 formal interim analysis for futility when approximately 50% of subjects have been on study for 24 weeks or have discontinued the study before 24 weeks, or have achieved a response prior to reaching 24 weeks.

The DMC’s role and responsibilities and the scope of analysis to be provided to the DMC are detailed in a mutually agreed upon charter, which defines the DMC membership, meeting logistics, and meeting frequency.

2.2. Interim Analysis

The DMC is primarily responsible for reviewing safety data. Efficacy data will be reviewed only during the formal interim futility analysis after approximately 50% of subjects have been on study for 24 weeks, or have discontinued the study before 24 weeks, or have achieved a response prior to reaching 24 weeks. A non-binding futility rule will be implemented which is based on the predictive probability of success.

The predictive probability of success is defined as the probability of achieving statistical significance (two sided p-value < 0.05) and a ≥ 30% difference in the BORR between the ENTO and placebo group at the study completion given the data observed at the interim.

If the predictive probability of success is > 30%, the study will continue. If the predictive probability of success is ≤ 30%, the totality of the data including the DOR, response rate at Week 24, and safety data will be reviewed by the DMC to make a thorough risk-benefit assessment. The VP of Clinical Research and the VP of Biometrics at Gilead may review the interim futility analysis results to make subsequent decisions based on the DMC recommendations.

A 2-sided alpha of 0.001 will be allocated to this interim futility analysis; following the Haybittle-Peto approach, the week 24 analysis alpha level will be 0.05 (2-sided).
2.3. Final Analysis

Due to early termination of the study by sponsor for lack of efficacy based on the interim futility analysis results, the final analysis of the data will be performed after all enrolled subjects have finished their follow-up/early-termination visit after the last dose of study drug, outstanding data queries have been resolved or adjudicated as unresolvable, and data have been cleaned and finalized.
3. **GENERAL CONSIDERATIONS FOR DATA ANALYSES**

Analysis results will be presented using descriptive statistics. For categorical variables, the number and percentage of subjects in each category will be presented; for continuous variables, the number of subjects (n), mean, standard deviation (SD) or standard error (SE), median, first quartile (Q1), third quartile (Q3), minimum, and maximum will be presented. Time-to-event endpoints will be summarized using median and quartiles of the Kaplan-Meier (KM) estimates.

3.1. **Analysis Sets**

Analysis sets define which subjects are included in an analysis. The assignment of subjects to analysis sets will be done before the study is unblinded for analysis. A summary of the number and percentage of subjects in each analysis set will be provided by treatment group and in total as part of the subject disposition summary.

3.1.1. **Intent-to-Treat (ITT) Analysis Set**

The Intent-to-Treat (ITT) Analysis Set includes all subjects who were randomized into the study, and will be analyzed according to treatment randomized. This is the primary analysis set for all efficacy analyses and summaries of demographics and baseline characteristics, unless otherwise specified.

A subset of the ITT Analysis Set will be utilized for the interim futility analysis, which includes subjects who have been on study for 24 weeks or have discontinued the study before 24 weeks, or have achieved a response prior to reaching 24 weeks.

3.1.2. **Safety Analysis Set**

The Safety Analysis Set includes data from all subjects who received at least 1 dose of study drug, with treatment assignments designated according to actual treatment received. All data collected up to earlier of the last dose of study drug plus 30 days or first dose of OLE will be included in the safety summaries. The Safety Analysis Set will be used for analyses and summaries of exposure of study drug, corticosteroids, prior and concomitant medication, laboratory data, vital signs, and AEs.

3.1.3. **Pharmacokinetics (PK) Analysis Set**

The Pharmacokinetic (PK) Analysis Set will include all randomized subjects who took at least 1 dose of study drug and have at least 1 non-missing post-dose concentration value reported by the PK laboratory. This is the primary analysis set for all PK analyses.

3.2. **Subject Grouping**

For analyses based on the ITT Analysis Set, subjects will be grouped according to the treatment to which they were randomized. For analyses based on the Safety Analysis Set, subjects will be grouped according to the randomized treatment except when their actual treatment differs from randomized treatment for the entire treatment duration. In this case, subjects will be grouped based on actual treatment received.
For the PK Analysis Set, subjects will be grouped according to the actual treatment they received.

3.3. Strata and Covariates

Subjects will be randomly assigned to treatment groups via the interactive web response system (IWRS) in a 1:1 ratio using a stratified randomization schedule. Stratification will be based on the following factors:

- calcineurin inhibitor or mycophenolate mofetil (MMF) use (no vs. yes) at Screening
- moderate vs. severe cGVHD as determined by the NIH cGVHD Diagnosis and Staging Criteria (NCDSC) at the Screening

If there are discrepancies in stratification factor values between the IWRS and the clinical database, the baseline values recorded in the clinical database will be used for analyses. Both stratification factor values can be defined based on questionnaire data collected at the screening visit, and concomitant medicine data.

Efficacy endpoints will be evaluated using stratification factors as covariates or stratification variables for analyses.

3.4. Examination of Subject Subgroups

Due to early termination of the study by the sponsor, no pre-specified subgroup analyses for efficacy and safety will be conducted.

3.5. Multiple Comparisons

Due to early termination of the study by the sponsor, no formal statistical comparisons will be done.

3.6. Missing Data and Outliers

3.6.1. Missing Data

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. The handling of missing or incomplete dates is described in Section 7.1.5.2 for AE onset, in Section 6.3 for efficacy, in Section 7.4 for prior and concomitant medications, and in Section 7.1.5.2 for missing last dose date.

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) 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.

- 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.

SAS code to calculate the LSS score and handle missing data are provided in Appendix 6.

3.6.2. **Outliers**

Outliers will be identified during the data management and data analysis process. All data will be included in the data analysis.

3.7. **Data Handling Conventions and Transformations**

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.

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

- A value that is 1 unit less than the lower 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 upper 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 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.

3.8. Analysis Visit Windows

3.8.1. Definition of Study Day

Study day is the day relative to the randomization date. Study Day 1 is defined as the randomization day.

Study day will be calculated from the date of randomization and defined as:

- Post-randomization: (assessment date) – (date of Study Day 1) + 1

- Prior to randomization: (assessment date) – (date of Study Day 1).

3.8.2. Analysis Visit Windows

Subject visits might not occur on protocol-specified days. Therefore, for the purpose of analysis, observations will be assigned to analysis windows.

The analysis windows are provided in Table 1.

<table>
<thead>
<tr>
<th>Nominal Visit</th>
<th>Analysis Visit</th>
<th>Nominal Day</th>
<th>Lower Limit</th>
<th>Upper Limit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>Baseline</td>
<td>1</td>
<td>n/a</td>
<td>1</td>
</tr>
<tr>
<td>Week 2</td>
<td>Week 2</td>
<td>14</td>
<td>2</td>
<td>21</td>
</tr>
<tr>
<td>Week 4</td>
<td>Week 4</td>
<td>28</td>
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<td>42</td>
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<tr>
<td>Week 8</td>
<td>Week 8</td>
<td>56</td>
<td>43</td>
<td>70</td>
</tr>
<tr>
<td>Week 12</td>
<td>Week 12</td>
<td>84</td>
<td>71</td>
<td>98</td>
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<tr>
<td>Nominal Visit</td>
<td>Analysis Visit</td>
<td>Nominal Day</td>
<td>Lower Limit</td>
<td>Upper Limit</td>
</tr>
<tr>
<td>---------------</td>
<td>----------------</td>
<td>-------------</td>
<td>-------------</td>
<td>-------------</td>
</tr>
<tr>
<td>Week 16</td>
<td>Week 16</td>
<td>112</td>
<td>99</td>
<td>126</td>
</tr>
<tr>
<td>Week 20</td>
<td>Week 20</td>
<td>140</td>
<td>127</td>
<td>154</td>
</tr>
<tr>
<td>Week 24</td>
<td>Week 24</td>
<td>168</td>
<td>155</td>
<td>189</td>
</tr>
<tr>
<td>Week 30</td>
<td>Week 30</td>
<td>210</td>
<td>190</td>
<td>231</td>
</tr>
<tr>
<td>Week 36</td>
<td>Week 36</td>
<td>252</td>
<td>232</td>
<td>273</td>
</tr>
<tr>
<td>Week 42</td>
<td>Week 42</td>
<td>294</td>
<td>274</td>
<td>315</td>
</tr>
<tr>
<td>Week 48</td>
<td>Week 48</td>
<td>336</td>
<td>316</td>
<td>343</td>
</tr>
</tbody>
</table>

**Table 2. Analysis Visit Windows for Double-Blind Phase ECG Only**

<table>
<thead>
<tr>
<th>Nominal Visit</th>
<th>Analysis Visit</th>
<th>Nominal Day</th>
<th>Lower Limit</th>
<th>Upper Limit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>Baseline</td>
<td>1</td>
<td>n/a</td>
<td>1</td>
</tr>
<tr>
<td>Week 24</td>
<td>Week 24</td>
<td>168</td>
<td>2</td>
<td>252</td>
</tr>
<tr>
<td>Week 48</td>
<td>Week 48</td>
<td>336</td>
<td>253</td>
<td>420</td>
</tr>
</tbody>
</table>

Vital signs, weight, ECG and safety laboratory data collected after last dose date of any study drug will be summarized up to last dose date plus 30 days, and labeled as “FU-30 Day”. For any subjects on ENTO from baseline to Week 48 who decided to enroll into the OLE phase, there will not be a 30 day follow up visit. An unscheduled visit prior to the first dosing of study drug may be included in the calculation of the baseline value, if applicable. The nominal day of “FU-30 Day” is the last dose date plus 30 days. The lower limit of window for “FU-30 Day” is the upper limit of last on drug visit window plus 1, while the upper limit is Follow-Up Day 30.

Follow-Up Day 1 is the date of the last dose of study drug plus 1.

<table>
<thead>
<tr>
<th>Nominal Visit</th>
<th>Analysis Visit</th>
<th>Nominal Follow-Up Day</th>
<th>Lower Limit in Follow-Up Day</th>
<th>Upper Limit in Follow-Up Day</th>
</tr>
</thead>
<tbody>
<tr>
<td>FU-30 Day</td>
<td>FU-30 Day</td>
<td>30</td>
<td>1</td>
<td>30</td>
</tr>
</tbody>
</table>

### 3.8.3. Selection of Data in the Event of Multiple Records in an Analysis Visit Window

Depending on the statistical analysis method, single values may be required for each analysis window. For example, change from baseline by visit usually requires a single value, whereas a time-to-event analysis would not require 1 value per analysis window.
If multiple valid, nonmissing, continuous measurements exist in an analysis window, records will be chosen based on the following rules if a single value is needed:

- In general, the baseline value will be the last nonmissing value on or prior to the first dose date of study drug, unless otherwise specified. If multiple measurements occur on the same day, the last nonmissing value prior to the time of first dose of study drug will be considered as the baseline value. If these multiple measurements occur at the same time or the time is not available, the average of these measurements (for continuous data) will be considered the baseline value.

- For postbaseline visits:
  - The record closest to the nominal day for that visit will be selected.
  - If there are 2 records that are equidistant from the nominal day, the later record will be selected.
  - If there is more than 1 record on the selected day, the average will be taken, unless otherwise specified.

If multiple valid, nonmissing, categorical measurements exist in an analysis window, records will be chosen based on the following rules if a single value is needed:

- For baseline, the last available record on or prior to the date of the first dose of study drug will be selected. If there are multiple records with the same time or no time recorded on the same day, the value with the lowest severity will be selected (eg, normal will be selected over abnormal for safety ECG findings).

- For postbaseline visits:
  - The record closest to the nominal day for that visit will be selected.
  - If there are 2 records that are equidistant from the nominal day, the later record will be selected.
  - If there is more than 1 record on the selected day, the value with the worst severity will be taken (eg, abnormal will be selected over normal for safety ECG findings), unless otherwise specified.
4. SUBJECT DISPOSITION

4.1. Subject Enrollment and Disposition

A summary of subject enrollment will be provided by treatment group for each country, investigator and overall. The summary will present the number and percentage of subjects enrolled. For each column, the denominator for the percentage calculation will be the total number of subjects analyzed for that column.

A similar enrollment table will be provided by randomization stratum. The denominator for the percentage of subjects in the stratum will be the total number of enrolled subjects within that stratum. If there are discrepancies in the value used for stratification assignment between the IWRS and the clinical database, the value collected in the clinical database will be used for the summary. A listing of subjects with discrepancies in the value used for stratification assignment between the IWRS and the clinical database at the time of data finalization will be provided.

A listing of subject enrollment will be provided to describe site, subject number, subject stratification, informed consent date, first screening date, and randomization date.

A summary of subject disposition will be provided by treatment group and overall. This summary will present:

- Number of subjects screened
- Number of subjects randomized (ITT Analysis Set)
- Number and percentage of subjects randomized and treated with study drug (Safety Analysis Set)
- Number and percentage of randomized subjects in the PK Analysis Sets
- Number and percentage of randomized subjects who discontinued study drug, and the reasons for study drug discontinuation
- Number and percentage of randomized subjects who discontinued from the study, and the reasons for study discontinuation

No inferential statistics will be generated.
A listing of subject disposition for all randomized subjects will be generated to describe subject number, randomized study drug (ENTO or placebo) assignment, actual study drug assignment, first dose date, last dose date, duration of study drug treatment, reason for study drug and study discontinuation. A separate listing of reasons for screen failure will be provided by screening ID number in ascending order.

4.2. **Extent of Study Drug Exposure and Adherence**

Extent of exposure to study drug will be examined by assessing the total duration of exposure to study drug and the level of adherence to the study drug specified in the protocol.

4.2.1. **Duration of Exposure to Study Drug**

Duration of exposure is defined as (last dose date – first dose date + 1), regardless of temporary interruptions in study drug administration, and will be expressed in weeks (recorded to 1 decimal place, eg, 4.5 weeks).

Duration of exposure to study drug will be summarized using descriptive statistics (n, mean, SD, median, Q1, Q3, minimum, and maximum) and as the number and percentage of subjects exposed for at least 4, 8, 12, 24, 36 and 48 weeks.

Summaries will be provided by treatment group for the Safety Analysis Set. No inferential statistics will be provided.

4.2.2. **Adherence to Study Drug**

A separate by-subject listing of study drug administration and drug accountability will be provided by subject ID number (in ascending order) and visit (in chronological order).

Adherence will be determined by the reporting of doses taken as documented on the study drug administration eCRF.

Adherence to study drug (%) is defined as (total days on drug) / [Last dose date – First dose date + 1]. Subjects are defined as treatment compliant if they achieved at least 80% adherence. The total number of doses administered will also be summarized.

Descriptive statistics for adherence and total number of doses taken (n, mean, SD, median, Q1, Q3, minimum, and maximum) along with the number and percentage of subjects belonging to adherence categories (eg, < 80%, ≥ 80%) will be provided by treatment group for the Safety Analysis Set. Adherence will also be listed.
4.3. Protocol Deviations

Subjects who did not meet the eligibility criteria for study entry, but enrolled in the study will be summarized regardless of whether they were exempted by the sponsor or not. The summary will present the number and percentage of subjects who did not meet at least 1 eligibility criterion and the number of subjects who did not meet specific criteria by treatment group based on all enrolled subjects. A by-subject listing will be provided for those subjects who did not meet at least 1 eligibility (inclusion or exclusion) criterion. The listing will present the eligibility criterion (or criteria if more than 1 deviation) that subjects did not meet and related comments, if collected.

Protocol deviations occurring after subjects entered the study are documented during routine monitoring. The number and percentage of subjects with important protocol deviations by deviation reason will be summarized by treatment group for the ITT Analysis Set. A by-subject listing will be provided for those subjects with any protocol deviation.
5. **BASELINE CHARACTERISTICS**

5.1. **Demographics**

Subject demographic variables (ie, age, sex, race, ethnicity and region) will be summarized by treatment group and overall using descriptive statistics for age, and using number and percentage of subjects for sex, race, ethnicity and region. Age at baseline is calculated in years at randomization date was made. The summary of demographic data will be provided for the ITT Analysis Set.

5.2. **Other Baseline Characteristics**

In addition to the randomization stratification factors listed in Section 3.3, the following demographic and baseline characteristics will be summarized by treatment group for the overall population:

- Age and Age group (≥ 65 years or < 65 years)
- Gender (male or female)
- Race
- Region
- Ethnicity (Hispanic/Latino, not Hispanic/Latino, or not permitted)
- Height
- Weight
- BMI
- Clinician symptom severity score (Appendix 3, Form A, row 1, box 2)
- Health care provider global ratings (Appendix 3, Form A, row 1, box 1)
- Total score of Lee Symptom Scale
- Skin domain score of the Lee Symptom Scale
- Mouth domain score of the Lee Symptom Scale
- Eyes domain score of the Lee Symptom Scale

5.3. **Medical History**

General medical history data will be collected at screening and listed but not coded.
6. EFFICACY ANALYSES

6.1. Definition of the Primary Efficacy 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 (Appendix 3) 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 2. An overall time point response across all involved organs will then be determined according to Table 3. The best overall response across all time points up to 24 weeks will be used to calculate BORR by 24 weeks.

Table 3. Criteria for time point response determination

<table>
<thead>
<tr>
<th>Response Category</th>
<th>Response Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete response (CR)</td>
<td>Resolution of all cGVHD manifestations in each organ or site as described in the NCAA organ response determination table</td>
</tr>
<tr>
<td>Partial response (PR)</td>
<td>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.</td>
</tr>
<tr>
<td>Stable disease (SD)</td>
<td>Neither sufficient improvement to qualify for a PR nor sufficient decline to qualify for a PD</td>
</tr>
</tbody>
</table>
| Progressive disease (PD)* | • Worsening of signs and symptoms in any organ or site as described in-the NCAA organ response determination table, taking the baseline as reference.  
  OR  
  • Increase in systemic corticosteroid dose to ≥ baseline dose (1 mg/kg/day)  
  OR  
  • Initiation of systemic immunosuppressive therapy other than systemic corticosteroids |

* 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.

6.2. Statistical Hypothesis for the Primary Efficacy Endpoint

The primary analysis will test the null hypothesis (H0) that there is no difference in BORR between ENTO and placebo versus the alternative hypothesis (H1) that there is a difference. Formally,

$$H_0: R_1 = R_0 \text{ vs. } H_1: R_1 \neq R_0,$$

where R1 and R0 are the BORR rate for ENTO and placebo treatment groups, respectively.
6.3. Analysis of the Primary Efficacy Endpoint

The primary analysis for BORR will be performed in the 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, CR or PR, SD and PD). A stratified Cochran-Mantel-Haenszel (CMH) Chi-square test will be performed to compare BORR (CR + PR) between ENTO and placebo-to-match (PTM) by 24 weeks. The difference in response rates between treatment groups and the corresponding 95% CIs will be presented.

If the entire NIH questionnaire is missing, then the organ and subject level statuses are missing. Missing individual NIH domain scores, for example, skin score, will lead to missing status for skin domain. In such a case, the subject level status will be based on the remaining available domain statuses. This is equivalent to imputing the missing domain status as ND or NA.

6.4. Secondary Efficacy Endpoints

6.4.1. Definition of Secondary Efficacy Endpoints

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:

- Duration of response, defined as the time from the documentation of BORR to the documentation of PD as defined in Table 3. Note that a flare does not constitute an end to response. A sensitivity analysis for DOR could consider a flare does constitute an end to response.

- Proportion of subjects who ever 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, non-relapse mortality, or recurrent malignancy
Safety and tolerability of ENTO

6.4.2. Analysis Methods for Secondary Efficacy Endpoints

The key secondary endpoints will be analyzed using a two sample z-test at week 24.

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. DOR will be analyzed only on subjects who responded.

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

Line plot of change from baseline in each domain and total of LSS will be done.

6.5. Exploratory Endpoints

6.5.1. List of Exploratory Endpoints

<table>
<thead>
<tr>
<th>PPD</th>
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6.5.2. Analysis Methods for Exploratory Endpoints

<table>
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<tr>
<th>PPD</th>
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6.6. Changes From Protocol-Specified Efficacy Analyses

<table>
<thead>
<tr>
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</tbody>
</table>
7. SAFETY ANALYSES

7.1. Adverse Events and Deaths

7.1.1. Adverse Event Dictionary

Clinical and laboratory adverse events (AEs) will be coded using the current version of MedDRA 20.1. System organ class (SOC), high-level group term (HLGT), high-level term (HLT), preferred term (PT), and lower-level term (LLT) will be provided in the AE dataset.

7.1.2. Adverse Event Severity

Adverse events are graded by the investigator as Grade 1, 2, 3, 4, or 5 according to toxicity criteria specified in the protocol. The severity grade of events for which the investigator did not record severity will be categorized as “missing” for tabular summaries and data listings. The missing category will be listed last in summary presentation.

Severity of adverse events will be determined by the investigator as mild, moderate, or severe. The severity of events for which the investigator did not record severity will be categorized as “missing” for tabular summaries and data listings. The missing category will be listed last in summary presentation.

7.1.3. Relationship of Adverse Events to Study Drug

Related AEs are those for which the investigator selected “Related” on the AE case report form (CRF) to the question of “Related to Study Treatment.” Relatedness will always default to the investigator’s choice, not that of the medical monitor. Events for which the investigator did not record relationship to study drug will be considered related to study drug for summary purposes. However, by-subject data listings will show the relationship as missing.

7.1.4. Serious Adverse Events

Serious adverse events (SAEs) will be identified and captured as SAEs if AEs met the definitions of SAE specified in the study protocol. Serious adverse events captured and stored in the clinical database will be reconciled with the SAE database from the Gilead Drug Safety and Public Health Department before data finalization.

7.1.5. Treatment-Emergent Adverse Events

7.1.5.1. Definition of Treatment-Emergent Adverse Events

Treatment-emergent adverse events (TEAEs) for the double-blind phase are defined as 1 or both of the following:
• Any AEs with an onset date on or after study drug or placebo start date and no later than earlier of 30 days after permanent discontinuation of study drug or placebo, or first dose date of ENTO in OLE phase, if any.

• Any AEs leading to premature discontinuation of study drug or placebo in the double-blind phase.

Treatment-emergent adverse events (TEAEs) for OLE phase are defined as 1 or both of the following:

• Any AEs with an onset date on or after the OLE ENTO first dose date and no later than 30 days after permanent discontinuation of ENTO

• Any AEs leading to premature discontinuation of study drug or placebo in OLE.

7.1.5.2. Incomplete Dates

If the onset date of the AE is incomplete and the AE stop date is not prior to the first dosing date of study drug, then the month and year (or year alone if month is not recorded) of onset determine whether an AE is treatment emergent. The event is considered double blind phase treatment emergent if both of the following 2 criteria are met:

• The AE onset is the same as or after the month and year (or year) of the first double blind dosing date of study drug

• The AE onset date is the same as or before the month and year (or year) of the date corresponding to 30 days after the date of the last dose of study drug or placebo, or date of first study drug dose of OLE if any

The event is considered OLE phase treatment emergent if both of the following 2 criteria are met:

• The AE onset is the same as or after the month and year (or year) of the first OLE dosing date of study drug

• The AE onset date is the same as or before the month and year (or year) of the date corresponding to 30 days after the date of the last dose of study drug

An AE with completely missing onset and stop dates, or with the onset date missing and a stop date later than the first dosing date of study drug, will be considered to be treatment emergent. In addition, an AE with the onset date missing and incomplete stop date with the same or later month and year (or year alone if month is not recorded) as the first dosing date of study drug will be considered treatment emergent.
If the last study drug dosing date is missing, the latest date among the study drug end date, clinical visit date, laboratory sample collection date, weight and vital signs assessment date that occurred during the on-treatment period will be used.

7.1.6. **Summaries of Adverse Events and Deaths**

Treatment-emergent AEs will be summarized based on the Safety Analysis Set.

A brief summary of AEs will show, by treatment group, the number and percentage of subjects who (1) had any treatment-emergent AE, (2) had any Grade 3 or 4 treatment-emergent AE, (3) had any treatment-emergent treatment-related AE, (4) had any Grade 3 or 4 treatment-emergent treatment-related AE, (5) had any treatment-emergent SAE, (6) had any treatment-emergent treatment-related SAE, (7) had any treatment-emergent AE leading to permanent study drug discontinuation, (8) had any treatment-emergent SAE leading to permanent study drug discontinuation, (9) died during study.

Summaries (n and percentage of subjects) of treatment-emergent AEs (by SOC and PT) will be provided by treatment group using the Safety Analysis Set as follows:

- Summary of AEs
- All treatment-emergent AEs
- All treatment-emergent AEs by preferred term
- All Grade 3 or higher treatment-emergent AEs
- All Grade 3 or higher treatment-emergent AEs by preferred term
- All treatment-emergent treatment-related AEs
- All treatment-emergent treatment-related AEs by preferred term
- All Grade 3 or higher treatment-emergent treatment-related AEs
- All Grade 3 or higher treatment-emergent treatment-related AEs by preferred term
- All treatment-emergent SAEs
- All treatment-emergent SAEs by preferred term
- All treatment-emergent AEs leading to permanent study drug discontinuation
- All treatment-emergent AEs leading to permanent study drug discontinuation by preferred term
• All deaths

Multiple events will be counted once only per subject in each summary. For data presentation, SOC will be ordered alphabetically with PT sorted by decreasing total frequency. For summaries by severity grade, the most severe event will be selected. In addition to the presentation by SOC and PT, summaries of treatment-emergent AEs may be presented by PT only, ordered by decreasing total frequency.

In addition to the by-treatment summaries, data listings will be provided for the following:

• All AEs (with a variable indicating whether the event is treatment-emergent, treatment-related, SAE)

• All Grade 3 and 4 AEs (with a variable indicating whether the event is treatment-emergent, treatment-related, SAE)

• All SAEs (with a variable indicating whether the event is treatment-emergent, treatment-related)

• All Deaths (with a variable indicating whether the event is treatment-emergent, treatment-related, SAE)

All AEs leading to study drug discontinuation (with a variable indicating whether the event is treatment-related, SAE)

Tables of AE will be based on double-blind data. OLE AE will be included in the listings with a column indicating whether the AE was reported during the OLE phase.

Any AE, lab result, or vital sign occurring on or after the date of the first dose of OLE ENTO and no later than 30 days after permanent discontinuation of ENTO is deemed belonging to the OLE phase.

7.1.7. Additional Analysis of Adverse Events

The following categories of AEs of special interest will be summarized (number and percentage) by treatment group.

• Relapse of primary disease/chimerism

• CMV reactivation

• PJP (Pneumocystis Jiroveci Pneumonia)

• EBV reactivation

• Interstitial lung disease
7.2. Laboratory Evaluations

Laboratory data collected during the study will be analyzed and summarized using both quantitative and qualitative methods. Summaries of laboratory data will be provided for the Safety Analysis Set. The analysis will be based on values reported in conventional units. When values are below the LLOQ, they will be listed as such, and the closest imputed value will be used for the purpose of calculating summary statistics. Hemolized test results will not be included in the analysis, but will be listed.

A listing for laboratory test results will be provided by subject ID number and visit in chronological order for hematology and serum chemistry separately. Values falling outside of the relevant reference range will be flagged in the data listings, as appropriate. No inferential statistics will be generated.

7.2.1. Summaries of Numeric Laboratory Results

Descriptive statistics (n, mean, SD, median, Q1, Q3, minimum, and maximum) will be provided by treatment group for each laboratory test specified in the study protocol as follows:

- Baseline values
- Values at each post-baseline assessment
- Change from baseline at each post-baseline assessment

A baseline laboratory value will be defined as the last measurement obtained on or prior to the date/time of first dose of study drug. Change from baseline to a post baseline visit will be defined as the visit value minus the baseline value. Laboratory test results collected at unscheduled visits will be included for the baseline. The mean, median, Q1, Q3, minimum, and maximum will be displayed to the reported number of digits; SD to the reported number of digits plus 1.

In the case of multiple values in an analysis window, data will be selected for analysis as described in Section 3.8.3.

Tables of lab results will be based on double-blind data. OLE lab results will be included in the listings with a column indicating whether the lab result was reported during the OLE phase.

7.2.2. Graded Laboratory Values

The criteria specified in the study protocol will be used to grade laboratory results as Grade 0, mild (Grade 1), moderate (Grade 2), severe (Grade 3), or potentially life threatening (Grade 4). Grade 0 includes all values that do not meet criteria for an abnormality of at least Grade 1. Some laboratory tests have criteria for both increased and decreased levels; analyses for each direction (ie, increased, decreased) will be presented separately.
7.2.2.1. Treatment-Emergent Laboratory Abnormalities

Double blind phase treatment-emergent laboratory abnormalities are defined as values that increase at least 1 toxicity grade from baseline at any post-baseline time point, up to and including the earlier of the date of last dose of study drug plus 30 days, or the first dose of OLE study drug if any.

OLE phase treatment-emergent laboratory abnormalities are defined as values that increase at least 1 toxicity grade from OLE day 1 (first OLE dose date) at any post-OLE day 1 time point, up to and including the date of last dose of OLE study drug plus 30 days.

If the relevant baseline laboratory value is missing, any abnormality of at least Grade 1 observed within the timeframe specified above will be considered treatment emergent.

7.2.2.2. Treatment-Emergent Marked Laboratory Abnormalities

Double blind phase treatment-emergent marked laboratory abnormalities are defined as values that increase from baseline by at least 3 toxicity grades at any post-baseline time point, up to and including the earlier of the date of the last dose of study drug plus 30 days, or the first dose of OLE study drug if any.

OLE phase treatment-emergent marked laboratory abnormalities are defined as values that increase from OLE day 1 (first OLE dose date) by at least 3 toxicity grades at any post-OLE day 1 time point, up to and including the date of the last dose of study drug plus 30 days.

If the relevant baseline laboratory value is missing, any Grade 3 or 4 values observed within the timeframe specified above will be considered treatment-emergent marked abnormalities.

7.2.2.3. Summaries of Laboratory Abnormalities

The following summaries (number and percentage of subjects) for treatment-emergent laboratory abnormalities will be provided by lab test and treatment group; subjects will be categorized according to the most severe post-baseline abnormality grade for a given lab test:

- Treatment-emergent laboratory abnormalities
- Treatment-emergent Grade 3 and 4 laboratory abnormalities
- Treatment-emergent marked laboratory abnormalities

For all summaries of laboratory abnormalities, the denominator is the number of subjects in the Safety Analysis Set with non-missing post-baseline values in the given study period.

A listing of all Grade 3 or 4 laboratory abnormalities will be provided by subject ID number and visit in chronological order. A column will indicate if the laboratory abnormality is treatment-emergent. This listing will include all test results that were collected throughout the study for the lab test of interest, with all applicable severity grades displayed.
7.3. **Body Weight and Vital Signs**

Body weight and vital signs (heart rate, systolic and diastolic blood pressure, body temperature, and respiratory rate) at baseline and each post-baseline assessment, and change from baseline in body weight and vital signs will be summarized for the Safety Analysis Set using descriptive statistics (n, mean, SD, median, Q1, Q3, minimum, and maximum) by treatment group. In the case of multiple values in an analysis window, data will be selected for analysis as described in Section 2. No formal statistical testing is planned. Only double-blind phase data will be summarized in tables. Both double-blind and OLE phase data will be included in listings.

7.4. **Prior Medications and Concomitant Medications**

Medications collected at screening and during the study will be coded using the current version of the World Health Organization (WHO) Drug dictionary. The medications will be categorized as prior or concomitant using the following definitions:

- Prior medications: any medications that were stopped before the study drug start date
- Concomitant medications: any medications initially taken on or after the study drug start date and up to 30 days after permanent discontinuation of study drug.

7.4.1. **Prior Medications**

Prior medications will be summarized by Anatomical Therapeutic Chemical (ATC) drug class and preferred name (using number and percent of subjects) by treatment group and overall. A subject reporting the same medication more than once will be counted only once when calculating the number and percentage of subjects who received that medication. The summary will be ordered by descending overall frequency of ATC drug classes and then by preferred names within an ATC drug class. For drugs with the same frequency, sorting will be done alphabetically.

Summaries will be based on the Safety Analysis Set. No inferential statistics will be generated.

For purposes of analysis, any medication with a stop date that is prior to or on the study drug start date will be included in the summary of prior medications. If a partial stop date is entered, then any medication with the month and year (if day is missing) or year (if day and month are missing) prior to the study drug start date will be included in the prior medications summary.

All prior medications (other than per-protocol study drugs) will be provided in a listing sorted by subject ID number and administration date in chronological order.

7.4.2. **Concomitant Medications**

Use of concomitant medications up to 30 days after permanent study drug discontinuation will be summarized by ATC drug class and preferred name (using number and percent of subjects) by treatment group. A subject reporting the same medication more than once will be counted only
once when calculating the number and percentage of subjects who received that medication. The summary will be ordered by descending active treatment group frequency of ATC medical classes and then by preferred names within an ATC drug class. For drugs with the same frequency, sorting will be done alphabetically.

Summaries will be based on the Safety Analysis Set. No inferential statistics will be generated.

For purposes of analysis, any medication with a stop date that is on or prior to the initial study drug dosing date or a start date that is after the last study drug dosing date plus 30 days will be excluded from a concomitant medication summary. If a partial stop date is entered, any medication with the month and year (if day is missing) or year (if day and month are missing) prior to the initial study drug dosing date will be excluded from the concomitant medication summary. If a partial start date is entered, then any medication with the month and year (if day is missing) or year (if day and month are missing) after the study drug stop date plus 30 days will be excluded from the concomitant medication summary. Medications with completely missing dates will be included in the concomitant medication summary.

All concomitant medications (other than per-protocol study drugs) will be provided in a listing sorted by subject ID number and administration date in chronological order.

7.5. Electrocardiogram Results

7.5.1. Investigator Electrocardiogram Assessment

Individual data for 12-lead ECG will be listed by subject and summarized by treatment group by incidence of events/abnormalities

7.6. Biomarker Analysis

No biomarker analyses are planned within the scope of this analysis plan. There will be a separate Biomarker Analysis Plan (BAP).

7.7. Changes From Protocol-Specified Safety Analyses

There are no deviations from the protocol-specified safety analyses.
8. PHARMACOKINETIC ANALYSES

The following tables will be provided:

- ENTO pharmacokinetic sampling details by subject including deviations in scheduled and actual draw times and procedures
9. REFERENCES

No citations
10. SOFTWARE

# SAP REVISION

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<tr>
<th>Revision Date</th>
<th>Section</th>
<th>Summary of Revision</th>
<th>Reason for Revision</th>
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<td>24 APR 2018</td>
<td>2.3</td>
<td>Week 14 Analysis deleted</td>
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<td>2.4</td>
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<td>24 APR 2018</td>
<td>3.1.2</td>
<td>Deleted the definition of Safety Analysis Set for OLE phase</td>
<td>Study discontinuation due to lack of efficacy and very few OLE AE occurrences</td>
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<td>Deleted the MMRM analysis for LSS. Moved the language of Lab value missing from section 3.7</td>
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<td>24 APR 2018</td>
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<td>Added “for All Except ECG” at the end of title of Table 1</td>
<td>To clarify the windows apply to all endpoints but ECG</td>
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<td>Added the missing imputation when the entire NIH questionnaire is missing</td>
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12. APPENDIX

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<td>Schedule of Assessments</td>
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<sup>a</sup> Screening performed anytime during the specified window.  
<sup>1</sup> Baseline performed anytime during the specified day prior to treatment initiation.  
<sup>b</sup> Assessments performed in the week specified.  
<sup>d</sup> Assessments performed in the 48 hours prior to Day 42.
## END OF WEEK b

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<td>X</td>
</tr>
<tr>
<td>Written Informed Consent for OLE</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

\( ^a \) Screening
\( ^b \) Baseline/Day 1
\( ^c \) Every 12 Weeks
\( ^d \) 48/ESDD
\( ^e \) 30 Day Follow-up

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### Evaluations to be completed within 30 days prior to Day 1.
1. All study visits are to be scheduled relative to the Day 1 visit date.
2. Initiation of treatment with the study drug must take place within 24 hours after the Baseline/Day 1 Visit
3. Early Study Drug Discontinuation visit to occur within 72 hours of last dose of study drug
4. Symptom-directed physical exam as needed
5. 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.
6. LSS (Appendix 4) and the NCAA Form B (Appendix 3) 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.
7. VITAL sign measurements include blood pressure, pulse, respiration rate, weight and temperature
8. Complete blood count (CBC) with differential platelet count
9. 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)
10. Urine collection for urinalysis and urine pregnancy test (if applicable)
11. Subjects with positive HCV antibody and without detectable HCV RNA are permitted to enroll
12. 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.
13. 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
14. 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.
15. At visit 2, 30, 42 and (OLE visit 50) drug accountability only, study drug will not be dispensed at these visits
16. Will include the following: systemic corticosteroid dose, other immunosuppressive, antimicrobials, PPI
17. 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.
## Appendix 2. For Baseline + Subsequent Visits: Response Determination for the NIH cGVHD Activity Assessment (NCAA)

<table>
<thead>
<tr>
<th>Organ</th>
<th>Complete Response</th>
<th>Partial Response</th>
<th>Progression</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin</td>
<td>NIH Skin Score 0 after previous involvement</td>
<td>Decrease in NIH Skin Score by 1 or more points</td>
<td>Increase in NIH Skin Score by 1 or more points, except 0 to 1</td>
</tr>
<tr>
<td>Eyes</td>
<td>NIH Eye Score 0 after previous involvement</td>
<td>Decrease in NIH Eye Score by 1 or more points</td>
<td>Increase in NIH Eye Score by 1 or more points, except 0 to 1</td>
</tr>
<tr>
<td>Mouth</td>
<td>NIH Modified OMRS 0 after previous involvement</td>
<td>Decrease in NIH Modified OMRS by 2 or more points</td>
<td>Increase in NIH Modified OMRS by 2 or more points</td>
</tr>
<tr>
<td>Esophagus</td>
<td>NIH Esophagus Score 0 after previous involvement</td>
<td>Decrease in NIH Esophagus Score by 1 or more points</td>
<td>Increase in NIH Esophagus Score by 1 or more points, except 0 to 1</td>
</tr>
<tr>
<td>Upper GI</td>
<td>NIH Upper GI Score 0 after previous involvement</td>
<td>Decrease in NIH Upper GI Score by 1 or more points</td>
<td>Increase in NIH Upper GI Score by 1 or more points, except 0 to 1</td>
</tr>
<tr>
<td>Lower GI</td>
<td>NIH Lower GI Score 0 after previous involvement</td>
<td>Decrease in NIH Lower GI Score by 1 or more points</td>
<td>Increase in NIH Lower GI Score by 1 or more points, except from 0 to 1</td>
</tr>
<tr>
<td>Liver</td>
<td>Normal ALT, alkaline phosphatase, and Total bilirubin after previous elevation of 1 or more</td>
<td>Decrease by 30%</td>
<td>Increase by 2 × ULN</td>
</tr>
<tr>
<td>Lungs</td>
<td>- Normal %FEV1 after previous involvement</td>
<td>- Increase by 10% predicted absolute value of %FEV1</td>
<td>- Decrease by 10% predicted absolute value of %FEV1</td>
</tr>
<tr>
<td></td>
<td>- If PFTs not available, NIH Lung Symptom Score 0 after previous involvement</td>
<td>- If PFTs not available, decrease in NIH Lung Symptom Score by 1 or more points</td>
<td>- If PFTs not available, increase in NIH Lung Symptom Score by 1 or more points</td>
</tr>
<tr>
<td>Joints and fascia</td>
<td>Both NIH joint and Fascia Score 0 and P-ROM score 25 after previous involvement</td>
<td>Decrease in NIH joint and Fascia Score by 1 or more points or increase in P-ROM score by 1 point for any site</td>
<td>Increase in NIH joint and Fascia Score by 1 or more points or decrease in F-ROM score by 1 point for any site</td>
</tr>
<tr>
<td>Global</td>
<td>Clinician overall severity score 0</td>
<td>Clinician overall severity score decreases by 2 or more points on a 0-10 scale</td>
<td>Clinician overall severity score increases by 2 or more points on a 0-10 scale</td>
</tr>
</tbody>
</table>

ULN indicates upper limit of normal
Appendix 3. 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:

<table>
<thead>
<tr>
<th>Rating</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0=none</td>
<td>None</td>
</tr>
<tr>
<td>1=mild</td>
<td>Mild</td>
</tr>
<tr>
<td>2=moderate</td>
<td>Moderate (≤25%)</td>
</tr>
<tr>
<td>3=severe</td>
<td>Severe (&gt;25%)</td>
</tr>
</tbody>
</table>

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:

- Erythema
  - None
  - Mild erythema or moderate erythema (≤25%)

- Lichenoid
  - None
  - Lichen-like changes (≤25%)

- Ulcers
  - None
  - Ulcers involving (≤20%)

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

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Rating</th>
</tr>
</thead>
<tbody>
<tr>
<td>Erythema</td>
<td>0</td>
</tr>
<tr>
<td>Mild erythema</td>
<td>1</td>
</tr>
<tr>
<td>Moderate (≤25%)</td>
<td>2</td>
</tr>
<tr>
<td>Severe (&gt;25%)</td>
<td>3</td>
</tr>
<tr>
<td>Lichen-like changes</td>
<td>1</td>
</tr>
<tr>
<td>Lichen-like changes (25-50%)</td>
<td>2</td>
</tr>
<tr>
<td>Ulcers involving (≤20%)</td>
<td>3</td>
</tr>
</tbody>
</table>

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 during the past week
  - 2= Intermittent dysphagia or odynophagia with solid foods or pills, but not for liquids or soft foods, during the past week
  - 3=Dysphagia or odynophagia for almost all oral intake, on almost every day of the past week

Gastrointestinal Upper GI

- Early satiety OR Anorexia OR Nausea & Vomiting
  - 0= no symptoms
  - 1=mild, occasional symptoms, with little reduction in oral intake during the past week
  - 2=moderate, intermittent symptoms, with some reduction in oral intake during the past week
  - 3=more severe or persistent symptoms throughout the day, with marked reduction in oral intake, on almost every day of the past week

Gastrointestinal Lower GI

- Diarrhea
  - 0= no loose or liquid stools during the past week
  - 1= occasional loose or liquid stools, on some days during the past week
  - 2= Intermittent loose or liquid stools throughout the day, on almost every day of the past week, without requiring intervention to prevent or correct volume depletion
  - 3= Voluminous diarrhea on almost every day of the past week, requiring intervention to prevent or correct volume depletion
<table>
<thead>
<tr>
<th>Lungs (Liters and % predicted)</th>
<th>FEV1</th>
<th>FVC</th>
<th>Single Breath DLCO (adjusted for hemoglobin)</th>
<th>TLC</th>
<th>RV</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Bronchiolitis Obliterans</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Liver Values</th>
<th>Total serum bilirubin</th>
<th>ULN</th>
<th>ALT</th>
<th>ULN</th>
<th>Alkaline Phosphatase</th>
<th>ULN</th>
<th>U/L</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>mg/dL</td>
<td></td>
<td>U/L</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Baseline Values</strong></td>
<td>Total Distance Walked in 2 or 6 Mins:</td>
<td></td>
<td>Kamofsky or Lansky</td>
<td>Platelet Count</td>
<td>Total WBC</td>
<td>Eosinophils</td>
<td>%</td>
</tr>
<tr>
<td></td>
<td>6 min</td>
<td>2 min</td>
<td></td>
<td>K/uL</td>
<td>K/uL</td>
<td>%</td>
<td></td>
</tr>
</tbody>
</table>

- Abnormality present but explained entirely by non-GVHD documented cause (specify site/alternate cause):__________________________
- Abnormality present but explained entirely by non-GVHD documented cause (specify site/alternate cause):__________________________
- Abnormality present but explained entirely by non-GVHD documented cause (specify site/alternate cause):__________________________
- Abnormality present but explained entirely by non-GVHD documented cause (specify site/alternate cause):__________________________
### CHRONIC GVHD ACTIVITY ASSESSMENT - CLINICIAN (FORM A)

<table>
<thead>
<tr>
<th></th>
<th>SCORE 0</th>
<th>SCORE 1</th>
<th>SCORE 2</th>
<th>SCORE 3</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>SKIN</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>GVHD features to be scored by BSA:</em></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>□ Maculopapular rash / erythema</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>□ Lichen planus-like features</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>□ Sclerotic features</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>□ Papillomatous lesions or ichthyosis</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>□ Keratosis pilaris-like</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>□ Abnormality present but explained entirely by non-GVHD documented cause (specify):</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**SKIN FEATURES SCORE:**

|         |         |         |         |         |
| □ No sclerotic features |         |         |         |         |

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:

<table>
<thead>
<tr>
<th></th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptoms not at all severe</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Most severe symptoms possible</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### EYES

<table>
<thead>
<tr>
<th>SCORE 0</th>
<th>SCORE 1</th>
<th>SCORE 2</th>
<th>SCORE 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>□ No symptoms symptoms</td>
<td>□ Mild dry eye symptoms not affecting ADL</td>
<td>□ Moderate dry eye symptoms partially affecting ADL</td>
<td>□ Severe dry eye symptoms significantly affecting ADL</td>
</tr>
<tr>
<td></td>
<td>(requirement of lubricant eye drops ≤ 3 x per day)</td>
<td>(requiring lubricant eye drops &gt; 3 x per day or punctal plugs), WITHOUT new vision impairment due to KCS</td>
<td>(special eyewear to relieve pain) OR unable to work because of ocular symptoms OR loss of vision due to KCS</td>
</tr>
</tbody>
</table>

- □ Abnormality present but explained entirely by non-GVHD documented cause (specify): ____________

### LUNGS

<table>
<thead>
<tr>
<th>SCORE 0</th>
<th>SCORE 1</th>
<th>SCORE 2</th>
<th>SCORE 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>□ No symptoms</td>
<td>□ Mild symptoms (shortness of breath after climbing one flight of steps)</td>
<td>□ Moderate symptoms (shortness of breath after walking on flat ground)</td>
<td>□ Severe symptoms (shortness of breath at rest; requiring O₂)</td>
</tr>
</tbody>
</table>

- □ Abnormality present but explained entirely by non-GVHD documented cause (specify): ____________

### JOINTS AND FASCIA

<table>
<thead>
<tr>
<th>SCORE 0</th>
<th>SCORE 1</th>
<th>SCORE 2</th>
<th>SCORE 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>□ No symptoms</td>
<td>□ Mild tightness of arms or legs, normal or mild decreased range of motion (ROM) AND not affecting ADL</td>
<td>□ Tightness of arms or legs OR joint contractures, erythema thought due to fasciitis, moderate decrease ROM AND mild to moderate limitation of ADL</td>
<td>□ Contractures WITH significant decrease of ROM AND significant limitation of ADL (unable to tie shoes, button shirts, dress self etc.)</td>
</tr>
</tbody>
</table>

- □ Abnormality present but explained entirely by non-GVHD documented cause (specify): ____________

---

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**FORM B**

TODAY'S DATE: ___________________________  MR#/NAME: ___________________________

**CHRONIC GVHD ACTIVITY ASSESSMENT-PATIENT SELF REPORT**

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Not Present</th>
<th>As Bad As You Can Imagine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Please rate how severe the following symptoms have been in the last seven days. 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.</td>
<td>0 1 2 3 4 5 6 7 8 9 10</td>
<td>0 1 2 3 4 5 6 7 8 9 10</td>
</tr>
<tr>
<td>Your skin itching at its WORST?</td>
<td>0 0 0 0 0 0 0 0 0 0 0</td>
<td>0 0 0 0 0 0 0 0 0 0 0</td>
</tr>
<tr>
<td>Your skin and/or joint tightening at their WORST?</td>
<td>0 0 0 0 0 0 0 0 0 0 0</td>
<td>0 0 0 0 0 0 0 0 0 0 0</td>
</tr>
<tr>
<td>Your mouth sensitivity at its WORST?</td>
<td>0 0 0 0 0 0 0 0 0 0 0</td>
<td>0 0 0 0 0 0 0 0 0 0 0</td>
</tr>
<tr>
<td>Your genital discomfort at its WORST? (Women – vagina, vulva, or labia) (Men – penis)</td>
<td>0 0 0 0 0 0 0 0 0 0 0</td>
<td>0 0 0 0 0 0 0 0 0 0 0</td>
</tr>
<tr>
<td>Eyes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>What is your main complaint with regard to your eyes?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Please rate how severe this symptom is, from 0 (not at all severe) to 10 (most severe):</td>
<td>0 1 2 3 4 5 6 7 8 9 10</td>
<td></td>
</tr>
</tbody>
</table>
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 4. For Baseline + Subsequent Visits: Lee Symptom Scale

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

<table>
<thead>
<tr>
<th>SKIN:</th>
<th>Not at all</th>
<th>Slightly</th>
<th>Moderately</th>
<th>Quite a bit</th>
<th>Extremely</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Abnormal skin color</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>2. Rashes</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>3. Thickened skin</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>4. Sores on skin</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>5. Itchy skin</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>BREATHING:</th>
<th>Not at all</th>
<th>Slightly</th>
<th>Moderately</th>
<th>Quite a bit</th>
<th>Extremely</th>
</tr>
</thead>
<tbody>
<tr>
<td>12. Frequent cough</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>13. Coloered sputum</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>14. Shortness of breath with exercise</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>15. Shortness of breath at rest</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>16. Need to use oxygen</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>EATING AND DIGESTION:</td>
<td>Not at all</td>
<td>Slightly</td>
<td>Moderately</td>
<td>Quite a bit</td>
<td>Extremely</td>
</tr>
<tr>
<td>---------------------</td>
<td>------------</td>
<td>----------</td>
<td>------------</td>
<td>-------------</td>
<td>-----------</td>
</tr>
<tr>
<td>17. Difficulty swallowing solids</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>18. Difficulty swallowing liquids</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>19. Vomiting</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>20. Weight loss</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>MUSCLES AND JOINTS:</th>
<th>Not at all</th>
<th>Slightly</th>
<th>Moderately</th>
<th>Quite a bit</th>
<th>Extremely</th>
</tr>
</thead>
<tbody>
<tr>
<td>21. Joint and muscle aches</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>22. Limited joint movement</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>23. Muscle cramps</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>24. Weak muscles</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>ENERGY:</th>
<th>Not at all</th>
<th>Slightly</th>
<th>Moderately</th>
<th>Quite a bit</th>
<th>Extremely</th>
</tr>
</thead>
<tbody>
<tr>
<td>25. Loss of energy</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>26. Need to sleep more/take naps</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>27. Fevers</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>MENTAL AND EMOTIONAL:</th>
<th>Not at all</th>
<th>Slightly</th>
<th>Moderately</th>
<th>Quite a bit</th>
<th>Extremely</th>
</tr>
</thead>
<tbody>
<tr>
<td>28. Depression</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>29. Anxiety</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>30. Difficulty sleeping</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>
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 5. Predictive Probability of Success Calculation

Notation

Let

- $n_1=$ number of patients in treatment group
- $n_0=$ number of patients in control group
- $n_{i1}=$ number of patients who stayed in trial at least 24 weeks or who stayed less than 24 weeks but responded already at interim in treatment group
- $n_{o1}=$ number of patients who stayed in trial at least 24 weeks or who stayed less than 24 weeks but responded already at interim in control group
- $n_{i11}=$ number of responders at interim in treatment group
- $n_{o11}=$ number of responders at interim in control group
- $x_1=$ number of new responders after interim and at week 24 analysis in treatment group
- $x_0=$ number of new responders after interim and at week 24 analysis in control group

Predictive probability of success

Predictive probability of success is defined as the probability of obtaining a statistically significant 30% difference favorable result at the week 24 analysis (at 2-sided alpha level $\alpha$), accounting for uncertainty about the true treatment effect given the data observed at the interim, and assuming that future data is subject to sampling variation given any possible true effect.

Predictive probability of success can be calculated as:

$$
\sum_{x_1=0}^{n_{i1}} \sum_{x_0=0}^{n_{o0}} \left( \frac{n_{i11} + x_1}{n_{i1}} > \left( \frac{n_{o11} + x_0}{n_0} + 0.3 \right) \right) \{ pvalue(x_1, x_0) < 0.05 \} f(n_1 - n_{i1}, x_1, n_{i11} + 1, n_{i1} - n_{i11} + 1) f(n_1 - n_{i1}, x_1, n_{o11} + 1, n_{i1} - n_{o11} + 1)
$$

where function $f$ is the probability density function of Beta-Binomial Distribution

$$
f(n, x, a, b) = \binom{n}{x} \frac{\Gamma(x+a)\Gamma(n-x+b)}{\Gamma(n+a+b)} \frac{\Gamma(a+b)}{\Gamma(a)\Gamma(b)}
$$

where $\Gamma$ is gamma function.
For Programming

/********************************************************* /
/* Predictive probability of success Macro: */
/********************************************************* /
/* Calculates the probability of statistical significance at final */
/* analysis given data observed at interim */
/********************************************************* /
/* Input Parameters: */
/* n1 = sample size in treatment group */
/* n0 = sample size in control group */
/* n1l = sample size stayed at least 24 weeks or less than 24 weeks but */
/* responded at interim in treatment group */
/* n10 = sample size stayed at least 24 weeks or less than 24 weeks but */
/* responded at interim in control group */
/* n1ll = responders at interim in treatment group */
/* n10l = responders at interim in control group */
/* alpha = 2-sided alpha level at week 24 analysis */
/********************************************************* /

%macro PP_calc(n1,n0,n1l,n10,n1ll,n10l,alpha);
proc iml;
    n1=&n1; /*sample size in treatment group*/
    n0=&n0; /*sample size in control group*/
    n1l=&n1l; /*sample size stayed at least 24 weeks or less than 24 weeks but responded at interim in treatment group*/
    n10=&n10; /*sample size stayed at least 24 weeks or less than 24 weeks but responded at interim in control group*/
    n1ll=&n1ll; /*responders at interim in treatment group*/
    n10l=&n10l; /*responders at interim in control group*/

    cl=(n1-n1l); /*rest patients who are potential to have week 24 responses in treatment group*/
    al=n1ll+1;
    bl=n1l-n1ll+1;
    c0=(n0-n10); /*rest patients who are potential to have week 24 responses in treatment group*/
    a0=n10l+1;
    b0=n10-n10l+1;

    pm=j(cl+1,c0+1,0);
    fd=j(4*(cl+1)*(c0+1),4,0); /*data output for fisher's exact test*/
    do x1=0 to cl;
        p1=comb(cl,x1)*beta(x1+al,cl-xl+bl)/beta(al,bl); /*the probability to observe x1 more responders in treatment group*/
        do x0=0 to c0;
            pass=(x1*(c0+1)+x0)*4;
            p0=comb(c0,x0)*beta(x0+a0,c0-x0+b0)/beta(a0,b0); /*the probability to observe x0 more responders in control group*/
    ```
pm=p1*p0; /*the probability to observe x1 more responders in treatment group and x0 more responders in control group*/
fd[(pass+1):(pass+4),2]=repeat(pm,4,1);

fd[(pass+1),1]=nill+x1; /*count of treatment responses at final*/
fd[(pass+2),1]=n1-nill-x1; /*count of treatment non-responses at final*/
fd[(pass+3),1]=ni01+x0; /*count of control responses at final*/
fd[(pass+4),1]=n0-ni01-x0; /*count of control non-responses at final*/

su=((nill+x1)/n1>(ni01+x0)/n0+0.3); /*marker if treatment is superior 30%*/
fd[(pass+1):(pass+4),3]=repeat(su,4,1);

rn=x1*(c0+1)+x0+1; /*replicate number*/
fd[(pass+1):(pass+4),4]=repeat(rn,4,1);
end;
end;

indicator=repeat(t({1 1 0 0 1 0 1 0}), (c1+1)*(c0+1), 1);

fm=fd||indicator;
varNames="count" "pm" "su" "rep" "group" "response";
create mydata from fm [colname=varNames];
append from fm;
close mydata;
quit;

proc sort data=mydata;
by rep;
run;
proc freq data=mydata;
by rep;
tables group*response/exact cmh;
weight count;
ods output FishersExact=fx; /*output fisher's exact test result*/
run;
data fx1;
set fx;
if Name='XP2_FISH';
keep rep Nvalue1;
run;

proc sort data=fx1;
by rep;
run;
data mydatatal;
merge mydata fx1;
by rep;
if first.rep;
fp=(Nvalue1<alpha)*pm*su; /*if the fisher's exact test is significant and treatment is superior*/
drop count group response;
run;

proc means data=mydata1 sum; /*add the probability together*/
var fp;
run;
%mend;

/* Sample macro call */
%PP_calc(n1=50,n0=50,nil=25,ni0=25,nill=20,ni0l=10,alpha=0.05);
Appendix 6. Lee Score Symptom SAS Code and Note

For Programming

data newdata;
  set olddata;
  ************************************************************

  *** Lee chronic GVHD symptom scales
  ************************************************************
  array oldsx{30} sx1-sx30;
  array newsx{30}
    b3a b3b b3c b3d b3e b3f b3g b3h b3i b3j b3k b3l b3m b3n b3o
    b3p b3q b3r b3s b3t b3u b3v b3w b3x b3y b3z b3aa b3bb b3cc
  b3dd;
  do i = 1 to 30;
    newsx{i}=oldsx{i};
    if newsx{i} not in (0,1,2,3,4) then newsx{i}=.;
  end;
  if nmiss(b3a,b3b,b3c,b3d,b3e) le 2 then
    sx_skin=mean(b3a,b3b,b3c,b3d,b3e)*25;
  if nmiss(b3n,b3u,b3v,b3w,b3x,b3y,b3z) le 3 then
    sx_energy=mean(b3n,b3u,b3v,b3w,b3x,b3y,b3z)*25;
  if nmiss(b3l,b3m,b3o,b3p,b3aa) le 2 then
    sx_lung=mean(b3l,b3m,b3o,b3p,b3aa)*25;
  if nmiss(b3f,b3g,b3h) le 1 then sx_eye=mean(b3f,b3g,b3h)*25;
  if nmiss(b3k,b3g,b3r,b3s,b3t) le 2 then
    sx_nutrition=mean(b3k,b3g,b3r,b3s,b3t)*25;
  if nmiss(b3i,b3j) le 1 then sx_mouth=mean(b3i,b3j)*25;
  if nmiss(b3bb,b3cc,b3dd) le 1 then sx_psych=mean(b3bb,b3cc,b3dd)*25;
  if nmiss(sx_skin,sx_energy,sx_lung,sx_eye,sx_nutrition,sx_mouth,sx_psych) le 3
    then
    sx_sum=mean(sx_skin,sx_energy,sx_lung,sx_eye,sx_nutrition,sx_mouth,sx_psych);
  label
    sx_skin = "Lee symptom skin scale (0-100)"
    sx_energy = "Lee symptom energy scale (0-100)"
    sx_lung = "Lee symptom lung scale (0-100)"
    sx_eye = "Lee symptom eye scale (0-100)"
    sx_nutrition = "Lee symptom nutrition scale (0-100)"
    sx_psych = "Lee symptom psychological scale (0-100)"
    sx_mouth = "Lee symptom mouth scale (0-100)"
    sx_sum = "Lee symptom overall summary scale (0-100)";
  drop i
    b3a b3b b3c b3d b3e b3f b3g b3h b3i b3j b3k b3l b3m b3n b3o
    b3p b3q b3r b3s b3t b3u b3v b3w b3x b3y b3z b3aa b3bb b3cc
  b3dd;
run;

proc print data=newdata noobs;
run;

Code Translation:

Define q1 as the value for question 1, so does q2, q3,..., q30.

If value of q1-q30 is not 0,1,2,3,4 then the value is set to be missing.

If number of missingness in q1,q2,q3,q4,q5 <=2, then skin scale=mean(q1,q2,q3,q4,q5)*25. Otherwise missing.
Here mean(q1,q2,q3,q4,q5) is defined as sum of non-missing values divided by the number of non-missing values.
Specifically, if nothing is missing, then mean(q1,q2,q3,q4,q5)=(q1+q2+q3+q4+q5)/5
if q1 is missing, q2-q5 are non-missing, then mean(q1,q2,q3,q4,q5)=(q2+q3+q4+q5)/4
if q1 and q2 are missing, then mean(q1,q2,q3,q4,q5)=(q3+q4+q5)/3

If number of missingness in q14,q21,q22,q23,q24,q25,q26 <=3 then energy scale=mean(q14,q21,q22,q23,q24,q25,q26)*25. Otherwise missing.
If number of missingness in q12,q13,q15,q16,q27 <=2 then lung scale=mean(q12,q13,q15,q16,q27)*25. Otherwise missing.
If number of missingness in q6,q7,q8 <=1 then eye scale=mean(q6,q7,q8)*25. Otherwise eye scale is missing.
If number of missingness in q11,q17,q18,q19,q20 <=2 then nutrition scale=mean(q11,q17,q18,q19,q20)*25. Otherwise missing.
If number of missingness in q9, q10 <=1 then mouth scale=mean(q9,q10)*25. Otherwise missing.
If number of missingness in q28,q29,q30 <=1 then psychological scale=mean(q28,q29,q30)*25. Otherwise missing.
If number of missingness in skin, energy, lung, eye, nutrition, mouth and psychological <=3 then overall summary scale=mean(skin, energy, lung, eye, nutrition, mouth, psychological scale), otherwise missing.

The range of skin, energy, lung, eye, nutrition, mouth, psychological and overall scale is 0-100.