BMT CTN Protocol 1501 Statistical Analysis Plan (SAP)

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Table of Contents

Protocol

BMT CTN #1501 is titled “A Randomized, Phase II, Multicenter, Open Label, Study Evaluating Sirolimus and Prednisone in Participants with Refined Minnesota Standard Risk, Ann Arbor 1/2 Confirmed Acute Graft-Versus-Host Disease”.

1. General Review of Study Design and Process

1.1 Study Objectives

BMT CTN protocol #1501 is a Phase II randomized, open label, multicenter trial designed to identify whether sirolimus is a potential alternative to prednisone (standard of care) as an up-front treatment for participants with standard-risk acute GVHD defined per clinical and biomarker-based risk stratification.

1.1.1 Primary Objective

The primary objective is to assess the rate of complete response (CR)/partial response (PR) on day 28 post-randomization in participants with standard-risk acute GVHD defined by both clinical and Ann Arbor (AA) 1/2 risk status.

1.1.2 Secondary Objectives

The secondary objectives of the study are to assess:

- The proportion of participants with an acute GVHD response on Day 28 (CR or PR) and who are on a prednisone (or prednisone dose-equivalent corticosteroid) dose of 0.25mg/kg/day or less.
- Proportions of participants with CR, PR, mixed response, no response, and progression among surviving participants at Day 14, 28 and 56.
- Treatment failure (treatment failure defined as: no response, progression, administration of additional therapy for GVHD beyond primary therapy, or mortality) at Day 14, 28, and 56
- Incidence of chronic GVHD by 6 and 12 months post-randomization.
- Incidence of systemic infections within 6 months of randomization.
- Freedom from acute GVHD progression, chronic GVHD, malignancy relapse, and mortality at 6 months and 12 months post-randomization.
- Disease-free and overall survival at 6 and 12 months post randomization.
- GVHD-free survival at 6 and 12 months post-randomization.
- Non-relapse mortality at 6 and 12 months post-randomization.

1.1.3 Exploratory Objectives

The exploratory objectives of the study are to assess:

- Cumulative steroid dose (prednisone-equivalent) through Day 56 post randomization.

- Use of topical (skin, GI) agents for acute GVHD therapy at baseline and during the study's duration.
- Incidence of discontinuation of immune suppression, and immune suppression discontinuation without GVHD or disease progression/recurrence by Days 56, 180, and 365 post-therapy.
- Incidence of EBV-associated lymphoproliferative disorder or EBV reactivation requiring therapy
- Incidence of corticosteroid- and sirolimus-associated complications (collected in all participants):
- Incidence of hyperglycemia (defined as a random glucose >200mg/dL or fasting glucose >126mg/dL) and use of diabetes therapy (use of insulin and/or oral medications to control and/or maintain glucose levels) at baseline, Day 28 and Day 56.
- Hip Flexor and Quadriceps Strength score via handheld dynamometer at baseline, Day 56, and 6 months post-randomization
- Two Minute Walk Test score at baseline, Day 56, and 6 months post-randomization
- 5-time Sit-to-Stand Test score at baseline, Day 56, and 6 months post-randomization
- Adult Myopathy Assessment Tool (AMAT) score at baseline, Day 56, and 6 months post-randomization
- Incidence of hyperlipidemia as measured by fasting lipid panel at baseline, Days 28, 56 and 180 post-randomization.
- Incidence of post-transplant thrombotic microangiopathy (TMA) by 6 months post-randomization.
- Proportion of participants requiring therapy for CMV-reactivation by day 56 post-randomization.
- Change in patient-reported outcomes from enrollment to Day 56, 6 months and 12 months.
- MD Anderson Symptom Inventory (MDASI) score at baseline, Day 56, 6 months, and 12 months post-randomization
- FACT-BMT score at baseline, Day 56, 6 months, and 12 months post-randomization
- MOS Short Form 36 (SF-36) score at baseline, Day 56, 6 months, and 12 months post-randomization
- PedsQL (Pediatric participants) score at baseline, Day 56, 6 months, and 12 months post-randomization
- A secondary descriptive analysis will evaluate all study outcomes in AA3 participants.

1.2 Study Design and Procedures

1.2.1 Primary Hypothesis and Primary Endpoint

The primary hypothesis of the study is that sirolimus treatment will achieve a comparable or superior rate of complete response (CR)/partial response (PR) in the treatment of standard-risk acute GVHD compared to prednisone treatment.

The primary endpoint is the rate of CR/PR of acute GVHD on Day 28 post-randomization in participants with standard-risk acute GVHD defined by clinical and AA1/2 risk status.

1.2.2 Accrual Plan and Randomization

The target sample size of the study is 120 participants with AA1/2 biomarker status. It is expected that 80% of all randomized participants will have AA1/2 status. This requires 150 total participants to be randomized in order to obtain the targeted number of AA1/2 participants.

The estimated accrual period is 2 years.

Participants will be randomized to sirolimus or prednisone treatment in a 1:1 ratio. Randomization is stratified by treatment center using permuted blocks of randomly chosen sizes of 2 or 4.

1.2.3 Duration of Follow-up

Participants will be followed for 28 days from the time of randomization for the primary endpoint. Participants will be followed for 1 year from the time of randomization for other endpoints.

The final analysis report will include the actual accrual and follow up status of the study with the actual timeline upon the study closure.

1.3 Study Population

This study will consist of participants with newly diagnosed standard-risk acute GVHD, per refined Minnesota Risk Criteria[1], following allogeneic hematopoietic cell transplantation. All donor sources and conditioning regimens are allowed. Participants must be able to tolerate oral or enterically-administered medication. No previous systemic immune suppressive therapy for treatment of acute GVHD is allowed except topical corticosteroid use. Detailed inclusion and exclusion criteria for study participants can be found in the protocol.

1.4 Treatment Description

Treatment will be initiated as soon as possible within the 24 hours following randomization. Sirolimus is administered as either tablets or an oral solution, beginning with a loading dose followed by maintenance doses determined by routinely measured trough sirolimus levels. Sirolimus therapy is continued at maintenance levels until Day 56 post randomization, after which the decision to taper dosage is at the discretion of the

treating physician. Prednisone is administered as either tablets or an oral solution at a starting dose of 2 mg/kg/day or 200mg, whichever is lower, for a minimum of 72 hours, after which the choice to taper dosage is at the discretion of the treating physician.

1.5 Response Variables and Data Collection Time Points

The response variables for this study include the primary, secondary, and safety endpoints. The primary endpoint is CR/PR at Day 28. Secondary endpoints include:

- CR/PR at Day 28 with steroid dose of 0.25mg/kg/day or less
- Disease response
- Treatment failure
- Chronic GVHD
- Systemic infection
- Event-free survival
- Overall survival
- Disease-free survival
- GVHD-free survival
- Non-relapse mortality
- Steroid dose
- Topical steroid therapy
- Discontinuation of immune suppression
- EBV-associated lymphoproliferative disorder
- Hyperglycemia
- Functional myopathy
- Hyperlipidemia
- Thrombotic microangiopathy
- CMV reactivation
- Patient-reported outcomes

Safety endpoints included mortality, toxicity, and adverse events. Safety monitoring will be conducted per protocol schedule as described in Section 2.4 of this SAP. Adverse events will be reported per the BMT CTN (Manual of Procedures) MOP.

Definitions for each endpoint are described in detail in the protocol and in section 4 of this SAP.

Participants are required to complete both pre-randomization and post-randomization assessments. Pre-randomization assessments must be performed prior to and as close as possible to the participant's enrollment / randomization on the trial. Post-randomization assessments occur weekly up to Day 56 and then occur at Day 90, 180,

and 365 post-randomization. Data from these evaluations are collected on calendar-driven clinical forms. Deaths, infections, hospitalizations, and adverse events are reported on event-driven clinical forms.

2. General Statistical Considerations

2.1 Sample Size and Power Calculations

The primary hypothesis is that sirolimus treatment will result in a comparable or superior CR/PR rate at Day 28 compared to prednisone treatment. As this is the first trial prospectively assessing sirolimus treatment in a multicenter setting, the trial is not designed to declare non-inferiority formally but rather to estimate the difference in response rates between the sirolimus arm and the prednisone (or standard of care) arm. In lieu of a formal hypothesis test, the difference in response rates between the two arms will be estimated with a 90% confidence interval.

Background data on treatment with sirolimus is available for 27 standard risk (Minnesota Criteria) participants. The overall CR/PR rate in the population was 88.9% (95% CI 77.0%, 100.0%). If patients receiving any level of prednisone are considered failures, the observed CR/PR rate was 55.6% (95% CI 36.8%-74.3%). Considering background data from BMT CTN 0802[2], a phase III acute GVHD treatment trial, data were available for 95 placebo treated participants meeting the standard risk criteria at GVHD onset. The response rate in that population was 64.2% (95% CI 54.6%-73.9%). Note that PR was not formally adjudicated by the Endpoint Review Committee for BMT CTN 0802. Instead, a response of Better Grade (compared to grade at diagnosis) was adjudicated and is considered here as a surrogate for PR. While the point estimates differ slightly, the confidence intervals for the two populations are overlapping. Table 2.1 shows the lower bound of a 90% asymptotic confidence interval given two scenarios: 1) success rate of 60% in each arm and 2) success rate of 60% in the prednisone arm and 50% in the sirolimus arm (sirolimus response rate is 10% lower).

Table 2.1: Lower Bound of Asymptotic 90% Confidence Interval for Difference in Response Rates Between Sirolimus and Prednisone Arms, Assuming Equal Rates (60%) and a 10% Lower Response Rate in the Sirolimus Arm with a 25% Inflation Due to Biomarker Results

Randomized	Analyzed (AA1/2)	N Analyzed Per Arm	Lower Bound of 90% CI Assuming Equal Rates*	Lower Bound of 90% CI Assuming Sirolimus Rate is 10% Lower*
125	100	50	-16%	-26%
150	120	60	-15%	-25%
175	140	70	-14%	-24%
200	160	80	-13%	-23%
225	180	90	-12%	-22%
250	200	100	-12%	-22%

* Difference calculated as Sirolimus response rate minus Prednisone response rate.

The number randomized is determined under the assumption that 80% of randomized participants will have biomarker results indicating standard risk disease (AA1 or 2). Note that 60 analyzable participants per arm (150 randomized) will result in a lower bound of 15% if the success rates in the two populations are equivalent. If sirolimus is 10% worse than the prednisone arm, the lower bound of the confidence interval will exceed 15%. The difference in Day 28 CR/PR rates across the two arms will be reported with its associated 90% confidence interval, however no pre-planned difference or width of confidence interval will be used to indicate failure of either arm or serve as a requirement for consideration of secondary endpoints (i.e. formal non-inferiority will not be declared in this trial). A key secondary endpoint is the proportion of participants in CR/PR with a steroid dose of ≤0.25 mg/kg by Day 28. Of the 95 placebo participants, 22.1% (95% CI 13.8% - 30.5%) achieved a CR/PR by Day 28 and were receiving ≤0.25 mg/kg. This estimate may not be reliable, however, as the taper for BMT CTN 0802 suggested a minimum of 0.25 mg/kg on Day 28; as such, this may be an underestimate of the true rate. Using the upper end of the confidence interval, sixty participants per arm would provide 80.6% power (two-sided 5% type 1 error rate) to test for a difference of 25% between the two groups (30% Prednisone vs. 55% Sirolimus).

2.2 Handling Missing Data

Because the primary endpoint, aGVHD response at Day 28 post-randomization, is evaluable after a short time, we expect very little to no impact of missing data on its analysis. Furthermore, since all endpoints will be evaluable within 1 year of randomization, we do not expect missingness to affect their analyses appreciably. An Endpoint Review Committee will adjudicate data on the primary endpoint to resolve this endpoint for participants with missing data. Any remaining missing values which are not able to be adjudicated will be excluded from the analyses. If any participants have missing data on the primary endpoint, a sensitivity analysis that treats missing responses as failures for aGVHD response will be conducted to examine the robustness of analysis results.

Based on previous BMT CTN studies and other clinical research, it is expected that the data collected on patient reported outcomes will not be complete. Logistic models will be constructed to investigate whether specific patient, clinical, or other variables are predictive of this missingness. If this is the case, inverse probability weighting will be employed to adjust for covariate-dependent missingness in comparing patient reported outcomes between treatment groups.

2.3 Multiple Comparisons

The treatment groups are not being compared on the primary endpoint using a formal hypothesis test, so there is no need to specify a significance level for the primary analysis. Since this is a phase II trial with many secondary and exploratory endpoints, no explicit control for multiplicity will be incorporated; rather a significance level of 5% will be used for all comparisons on these outcomes.

2.4 Interim Analyses

There will be no interim analyses for efficacy or futility as this is a small phase II study.

2.5 Safety Monitoring Guidelines

Monitoring of two key safety endpoints will be conducted monthly, and if rates significantly exceed pre-set thresholds, the NHLBI will be notified in order that the DSMB can be advised. The stopping guidelines serve as trigger for consultation with the DSMB for additional review. The key safety endpoints for this study are: 1) failure of sirolimus therapy and 2) overall mortality. Both endpoints will be monitored among AA 1/2 participants only; failure of sirolimus therapy will be monitored in the sirolimus arm only.

Failure of sirolimus therapy is defined as the addition of a systemic immune suppressive therapy beyond prednisone among those participants originally treated with sirolimus. The rate of sirolimus failure will be monitored up to 42 days post-randomization. At least three events must be observed in order to trigger review. The expected probability of 42 day sirolimus failure is approximately 25-30% (derived from primary sirolimus monotherapy data, as well as anticipated rate of secondary therapy use beyond prednisone in prior BMT CTN aGVHD therapy trials)[2,3].

Each month, the null hypothesis that the 42-day sirolimus failure rate is less than or equal to 25% is tested using a binomial sequential probability ratio test (SPRT). This sequential testing procedure conserves type I error at 5% across all monthly examinations for the sirolimus arm. The SPRT can be represented graphically. At each monthly interim analysis, the number of evaluable participants on study is plotted against the total number of treatment failures. The continuation region of the SPRT is defined by two parallel lines. Only the upper boundary will be used for monitoring in order to protect against excessive 42 day sirolimus failure. If the graph crosses the upper boundary, the SPRT rejects the null hypothesis, and concludes that there are more events than predicted by the number of evaluable participants on study. Otherwise, the SPRT continues until enrollment is complete. Only failures that occur on or before the patient has been followed for 42 days are counted.

The boundaries for the binary SPRT were constructed by setting the null rate of sirolimus failure to be 25% versus an alternative of 50% for 42 day sirolimus failure. To construct the boundary, the nominal type I and type II errors were set to be 10% and 5% respectively. The upper boundary is defined by a slope of 0.37 and an upper intercept of 2.05. Since the upper boundary alone is being used, the actual type I error of the binomial SPRT will be less than the nominal value without a substantial increase in type II error for the alternatives of interest (i.e. sirolimus therapy failure rates higher than expected). Table 2.2 illustrates the number of observed events required to cross the boundary for the binomial SPRT.

Table 2.2: Safety Monitoring Guidelines for Failure of Sirolimus Therapy

Number of Evaluable Participants	Number of Events on or Prior to Day 42
4-5	4
6-7	5
8-10	6
11-13	7
14-16	8
17-18	9
19-21	10
22-24	11
25-26	12
27-29	13
30-32	14
33-35	15
36-37	16
38-40	17
41-43	18
44-45	19
46-48	20
49-51	21
52-54	22
55-56	23
57-59	24
60	25

No monitoring of secondary therapy delivered beyond prednisone will be performed in the prednisone arm, as this treatment is considered standard care.

Day 56 overall mortality is the second key safety endpoint. This endpoint will be monitored within each treatment arm using an extension of the (SPRT) for censored exponential data[4]. Unlike the binary SPRT which assesses the event rate in the number of evaluable participants, the censored exponential SPRT considers the number of events relative to the total time at risk on the study. The SPRT is represented graphically with the number of events on the y-axis and the total time at risk on the x-axis. The upper boundary of the SPRT will be used to guard against excess mortality. This procedure assumes an exponential distribution for overall mortality during the first 56 days, with follow-up time censored at 56 days.

Based on background data for standard risk acute GVHD participants, the expected Day 56 overall mortality is 13.1%. As this estimate includes AA3 participants in addition to AA1/2, to be conservative, the null for the monitoring bound will be set at 10%. An SPRT contrasting 10% vs 25% Day 56 overall mortality results in decision boundaries with a common slope of 1.18 and an upper intercept of 2.29 based on nominal type 1 and type II errors of 9% and 10%, respectively, with the type I and II errors selected based on the simulation study and the actual operating characteristics of the SPRT shown in Table 2.3

that assumed uniform accrual of 60 individuals over a 24 month time period, and exponential time to failure after randomization.

TABLE 2.3: Operating Characteristics of Censored Exponential SPRT of Day 56 Overall Mortality from a Simulation Study with 10,000 Replications

True 56-Day Rate	10%	15%	20%	25%
Probability Reject Null	0.053	0.281	0.641	0.888
Mean Month Stopped	25.2	22.1	16.8	12.0
Mean # Endpoints in 56 Days	5.8	7.6	7.9	7.0
Mean # Participants Enrolled	58.2	51.6	40.4	29.6

If the true Day 56 overall mortality rate is in line with the expected rate (i.e. 10%), then the stopping guideline has a 5% probability of being triggered. If the true overall mortality rate is higher than expected (i.e. 25% by Day 56), then the stopping guideline has an 89% probability of being triggered (on average 12 months after opening when 30 participants have been enrolled).

2.6 Timing of Analysis

A data lock will be used for the primary analysis. The data lock will occur upon the completion of ERC adjudication on the study data and completion of related data quality assurance. An ERC Charter will define the scope of ERC review as well as the timeline for the data adjudication. The data lock will include the mature data on the primary and key secondary endpoints for the study participants. If the first lock occurs prior to the completion of 1 year of follow-up on all study participants, a second data lock will be performed in order to permit analysis of secondary endpoints requiring extended follow-up.

2.7 Software

All analyses will be conducted using SAS 9.4 or higher software and R version 3.1.0 or higher.

2.8 Analysis Populations

2.8.1 Primary Analysis Population

Participants will be analyzed according to the intent to treat (ITT) principle for this study, i.e. according to the treatment groups to which they were randomized, regardless of whether the assigned treatment was administered. Any participant who receives a treatment randomization number will be considered to have been randomized. Since the primary interest of this study is treatment in participants with standard risk acute GVHD, the primary analysis population will consist of all randomized AA1/2 participants with treatment classified per the ITT principle.

The primary analysis for the primary, secondary, and exploratory endpoints will use the primary analysis population. A secondary analysis of the primary endpoint will be

performed, classifying participants by the initial treatment actually given. Another secondary analysis will consider primary and key secondary outcomes for all randomized AA3 participants classified per the ITT principle. An analysis of safety endpoints will also be conducted using the safety analysis population as described below. Analyses of each endpoint and population used will follow the analysis plan as described below in section 4 of this SAP.

If a participant is deemed not eligible for the study after study registration or randomization occurs, he will be excluded from all analysis populations.

2.8.2 Safety Analysis Population

The reporting of serious adverse events will be consistent with standard BMT CTN procedures with the addition of any anticipated SAE related to sirolimus or prednisone therapy. All reported serious adverse events potentially associated with a study drug will be carefully examined with respect to the severity and relationship to the study drug. The type and severity of adverse events will be described. Safety data will be summarized using Medical Dictionary for Regulatory Activities (MeDRA) Coding Version 20.0 or above.

The safety analysis population will be the same as the primary analysis population: all randomized AA1/2 participants categorized according to ITT.

2.9 General Analysis Guidelines

Continuous variables will be described using the mean, standard deviation, median, and range. Categorical variables will be described using frequencies and proportions. All statistical tests will be two-sided at a 0.05 significance level unless otherwise specified.

Any changes to the planned analyses and addition of any ad-hoc analyses will be documented in the final analysis report with justification given for the changes. If it is a change to analysis of an existing endpoint, the change should be clearly stated in the exhibit. If a new endpoint or analysis is performed, it should be included as a supplemental exhibit.

3. Participant Characteristics and Compliance

3.1 Demographics and Baseline Characteristics

Descriptive statistics for demographics and baseline characteristics of participants and donors will be presented by treatment group. Characteristics to be examined are: age, gender, race/ethnicity, performance status, primary disease, risk status, transplant conditioning regimen characteristics, donor type, HLA matching, graft source, initial GVHD prophylaxis delivered, donor and recipient CMV status, acute GVHD organ staging and overall grade at enrollment, and topical steroid therapy use.

Data on performance status, primary disease, risk status, conditioning regimen characteristics, donor type, HLA matching, graft source, initial GVHD prophylaxis, and

donor and recipient CMV status will be retrieved from the CIBMTR database. All other variables will be collected on clinical forms.

3.2 Participant Compliance

A table listing significant protocol deviations/violations will be provided with treatment assignments indicated. Compliance with protocol interventions will be evaluated as appropriate. Premature withdrawals will be described for each case.

A consort diagram will be provided to illustrate study accrual, participant disposition, and follow up.

The number of participants evaluated will be described in the tables and figures for each analysis.

4. Analysis Plan

4.1 Analysis of the Primary Endpoint

The primary endpoint for this study is complete response/partial response (CR/PR) of acute GVHD to therapy at Day 28 post-randomization. No formal hypothesis test will be performed. Instead, the difference in response rates between the two arms will be estimated with a 90% confidence interval.

Acute GVHD response is categorized as complete response (CR), partial response (PR), mixed response (MR), no response (NR), and progression and is scored relative to the participant's acute GVHD status (organ staging) entered on the day of randomization. Response categories are defined as follows:

- **Complete response (CR)**: A stage of 0 for the GVHD grading in all evaluable organs. For example, for a response to be scored as CR at Day 28, the participant must still be in CR on that day and have had no intervening additional therapy for an earlier progression, PR or NR.
- **Partial response (PR)**: Improvement in one or more organs involved with GVHD symptoms without progression in others.
- **Mixed response (MR)**: Improvement in one or more organs with either deterioration in another organ manifesting symptoms of GVHD or development of symptoms of GVHD in a new organ.
- **Progression**: Deterioration in at least one organ without any improvement in others.
- **No response (NR)**: Absence of any improvement or progression

Patients receiving secondary therapy (including need to re-escalate steroid dose to ≥ 2.5 mg/kg/day of prednisone [or methylprednisolone equivalent of 2 mg/kg/day]) will be classified as non-responders. Patients who are assigned to the sirolimus arm who require initiation of systemic corticosteroids for the treatment of acute GVHD will be considered as non-responders for purposes of the primary endpoint assessment.

Participants that have died prior to Day 28 will be treated as nonresponders in the analysis.

The reference for response evaluation is the GVHD organ staging reported at enrollment. The response rate (CR/PR) at Day 28 will be estimated using frequencies in each treatment group. A 90% Wald confidence interval for the difference in rates of the treatment groups will be computed.

In a secondary analysis, rates of Day 28 CR/PR and their 95% confidence intervals will be estimated for each treatment group by donor type, graft source, and HLA mismatch (matched vs. mismatched). As the numbers for these subgroup analyses will be small, the intent is not to declare differences between subgroups formally, but rather to identify potential differences that may need to be considered in future trials.

4.2 Analysis of the Secondary Endpoints

Since this is a phase II trial with many secondary and exploratory endpoints, no explicit control for multiplicity will be incorporated; rather a significance level of 5% will be used for all comparisons on these outcomes.

4.2.1 Proportion of Participants with CR/PR and Steroid Dose 0.25 mg/kg/day or Less

This is a refined endpoint of CR/PR and the use of a prednisone equivalent steroid dose of 0.25 mg/kg/day or less. The rates of CR/PR and steroid dose 0.25 mg/kg/day or less will be estimated within each arm and compared between arms using the Z test for binomial proportions (or Barnard's Exact Unconditional Test[5] as appropriate). Methylprednisone is considered to be 1.25 times as potent as prednisone, while prednisolone is dose-equivalent to prednisone. Note that use of prednisone below the threshold on the sirolimus arm will not be considered a failure for this endpoint. Participants that have died prior to Day 28 will be treated as nonreponders in the analysis.

4.2.2 Disease Response

The rates of complete response, partial response, mixed response, no response, and progression among surviving participants at Day 14, 28, and 56 will be estimated for each treatment group and compared between groups using Pearson's chi-square test (or Fisher's Exact Test as appropriate).

4.2.3 Treatment Failure

Treatment failure is a composite endpoint comprised of death, no response, progression, administration of additional therapy beyond primary therapy for GVHD [(or re-escalation of steroid dose to ≥ 2.5 mg/kg/day of prednisone (or methylprednisolone equivalent of 2 mg/kg/day) or initiation of corticosteroids for the treatment of acute GVHD for participants assigned to the sirolimus arm] at Days 14, 28, and 56. Proportions of treatment failures for the treatment arms will be estimated and compared at Days 14, 28

and 56 using the Z test for comparing binomial proportions (or Barnard's Exact Unconditional Test as appropriate).

4.2.4 Chronic GVHD

Chronic GVHD is defined by NIH Consensus Criteria. Cumulative incidence of chronic GVHD per this Criteria will be estimated for each treatment arm using the Aalen-Johansen estimator[6] and compared between arms using Gray's test[7], treating death and relapse as competing risks. Estimates and confidence intervals will be provided at 6 and 12 months post-randomization.

4.2.5 Systemic Infections

Frequencies of infections will be tabulated by site of disease, date of onset, and severity. The time to first serious infection (Grade 2 or 3 per BMTCTN MOP) will be estimated for each treatment arm using the Aalen-Johansen estimator and compared between arms using Gray's test, treating death as the competing risk. For the definition of infection severity, see the BMT CTN Manual of Procedures.

4.2.6 Event-Free Survival

Event-free survival is a composite endpoint of acute GVHD progression, chronic GVHD, malignancy relapse, and mortality.

Malignancy relapse is defined as follows:

Relapse is defined by either morphological or cytogenetic evidence of acute leukemia or MDS consistent with pre-transplant features, or radiologic evidence of lymphoma, documented or not by biopsy. Progression of disease applies to participants with lymphoproliferative diseases (lymphoma or chronic lymphocytic leukemia) not in remission prior to transplantation. The event is defined as increase in size of prior sites of disease or evidence of new sites of disease, documented or not by biopsy.

Acute leukemia and MDS – Relapse will be diagnosed when there is:

- Reappearance of leukemia blast cells in the peripheral blood; or,
- >5% blasts in the bone marrow, not attributable to another cause (e.g. bone marrow regeneration).
- The appearance of previous or new dysplastic changes (MDS specific) within the bone marrow with or without falling donor chimerism; or
- The development of extramedullary leukemia or leukemic cells in the cerebral spinal fluid; or
- The reappearance of cytogenetic abnormalities present prior to transplantation.

Lymphoproliferative Diseases – Relapse or progression will be diagnosed when there is:

- Appearance of any new lesion more than 1.5 cm in any axis during or at the end of therapy, even if other lesions are decreasing in size. Increased FDG uptake in a previously unaffected site will only be considered relapsed or progressive disease after confirmation with other modalities. In participants with no prior history of pulmonary lymphoma, new lung nodules identified by CT are mostly benign. Thus, a therapeutic decision should not be made solely based on the PET without histologic confirmation.
- At least a 50% increase from nadir in the sum of the product diameters of any previously involved nodes, or in a single involved node, or the size of other lesions (e.g., splenic or hepatic nodules). To be considered progressive disease, a lymph node with a diameter of the short axis of less than 1.0 cm must increase by 50% and to a size of 1.5 x 1.5 cm or more than 1.5 cm in the long axis.

  Lesions should be PET positive if observed in a typical FDG-avid lymphoma or the lesion was PET positive before therapy unless the lesion is too small to be detected with current PET systems (<1.5 cm in its long axis by CT).
- In addition to the criteria above, participants with CLL who present in complete remission prior to transplantation may fulfill the relapse definition if there is reappearance of circulating malignant cells that are phenotypically characteristic of CLL.

*** Institution of any therapy to treat persistent, progressive or relapsed malignancy, including the withdrawal of immunosuppressive therapy or donor lymphocyte infusion, will be considered evidence of relapse/progression regardless7 of whether the criteria described above were met.**

Event-free survival within each treatment group will be described using the Kaplan-Meier estimator, with event time being the earliest time a patient met one of the various criteria for failure. Participants not meeting a failure criterion will be censored at time of last follow-up. Estimates and confidence intervals will be calculated at 6 and 12 months post-randomization.

4.2.7 Overall Survival (OS)

Death from any cause will be considered an event for this endpoint. A participant's event time will be censored if lost to follow up. OS at 6 and 12 months will be described using the Kaplan-Meier estimator and 95% confidence intervals will be computed.

4.2.8 Disease-free Survival (DFS)

Disease-free survival is a composite endpoint of the events death and relapse of the underlying malignancy. A participant's event time will be censored if lost to follow up. DFS at 6 and 12 months will be described using the Kaplan-Meier estimator and 95% confidence intervals will be computed.

4.2.9 GVHD-free Survival

GVHD-free survival is a composite endpoint of the events death, acute GVHD, and chronic GVHD. The proportion of participants alive and GVHD free at 6 and 12 months

post-randomization will be estimated and compared between treatment groups using the Z test for comparing binomial proportions (or Barnard's Exact Unconditional Test as appropriate).

4.2.10 Non-relapse Mortality (NRM)

Non-relapse mortality (NRM) consists of deaths due to any cause other than relapse of the underlying malignancy. The cumulative incidence of non-relapse mortality will be estimated for each treatment group using the Aalen-Johansen estimator and groups will be compared using Gray's test, treating relapse as a competing risk. Estimates and confidence intervals will be provided at 6 and 12 months post-randomization.

4.3 Analysis of the Exploratory Endpoints

Since this is a phase II trial with many secondary and exploratory endpoints, no explicit control for multiplicity will be incorporated; rather a significance level of 5% will be used for all comparisons on these outcomes.

4.3.1 Steroid Dose

Doses of methylprednisolone will be converted to prednisone equivalents by multiplying the methylprednisolone dose by 1.25, while doses of prednisolone are considered equivalent to prednisone. The prednisone dose for each patient at Days 7, 14, 21, 28, 35, 42, 49, and 56 will be recorded. Prednisone doses for each patient will be converted to mg/kg. For participants that weigh over 100kg, maximal starting dose of prednisone will be 200mg (or 2mg/kg based on a modified starting weight of 100kg). For calculation of subsequent prednisone doses/kg on subsequent measures, the modified starting weight of 100kg will be used. The cumulative prednisone dose for each patient at Day 56 will be calculated by adding the doses (end of each week's dose) for each of the first eight weeks of treatment, divided by the number of days of survival during this interval. This mean steroid dose will be described for each treatment group by median and range and will be compared between groups using the Wilcoxon Rank Sum test.

4.3.2 Topical Therapy

The proportion of participants using either topical skin or topical GI steroids at randomization will be estimated for each treatment group. Among participants entering with no topical therapy usage at baseline, the proportion of participants initiating new topical treatment will be described for each treatment group and compared between groups using the Z test for comparing binomial proportions (or Barnard's Exact Unconditional Test as appropriate).

4.3.3 Discontinuation of Immune Suppression

The dates of discontinuation of corticosteroids and other systemic immune suppressive medications will be recorded. Cumulative incidence of immune suppression discontinuation will be described using the Aalen-Johansen estimator and curves will be compared using Gray's test, treating death as the competing risk. Estimates and

confidence intervals will be provided at Day 56 and at 6 and 12 months post-randomization. A refined endpoint of complete immune suppression discontinuation together with freedom from any GVHD or malignancy progression/recurrence will also be examined, treating death, GVHD, and malignancy progression/recurrence as competing risks. Its cumulative incidence for each treatment arm will be described using the Aalen-Johansen estimator; curves will be compared using Gray's test, treating death as the competing risk; and estimates and confidence intervals will be provided at Day 56 and at 6 and 12 months post-randomization.

4.3.4 EBV-associated lymphoproliferative disorder

The cumulative incidence of EBV-associated lymphoproliferative disorder or EBV reactivation therapy will be described using the Aalen-Johansen estimator, treating death as the competing risk. Cumulative incidence curves will be compared between treatments using Gray's test.

4.3.5 Hyperglycemia

Hyperglycemia is defined as a random glucose >200mg/dL or fasting glucose >126mg/dL and use of diabetes therapy, i.e. use of insulin and/or oral medications to control and/or maintain glucose level. The incidence of hyperglycemia and use of diabetes therapy at baseline, Day 28, and Day 56 will be estimated and compared between arms using a Z-test for comparing binomial proportions (or Barnard's Exact Unconditional Test as appropriate).

4.3.6 Functional Myopathy

The change from baseline in functional myopathy score at Day 56 and 6 months post-randomization will be evaluated.

Functional Myopathy measures considered are:

- Hip Flexor and Quadriceps Strength via handheld dynamometer
- Two Minute Walk Test
- 5-time Sit-to-Stand
- Adult Myopathy Assessment Tool (AMAT)

These measures will be described for each treatment group at baseline, Day 56, and 6 months using medians and ranges. Change from baseline within treatment group will be assessed using a Wilcoxon Signed Rank test at each timepoint. Change from baseline at each timepoint will be compared between treatment groups using a Wilcoxon Rank Sum test.

4.3.7 Hyperlipidemia

Prevalence of hyperlipidemia as measured by fasting lipid panel and/or use of lipid-lowering agents at baseline, Days 28, 56 and 180 post-randomization will be compared between groups at each timepoint using a Z-test for binomial proportions (or Barnard's

Exact Unconditional Test as appropriate). For each of the measured components of the fasting lipid panel (e.g. total cholesterol, LDL, HDL, and triglycerides), the proportion of patients in each study arm with measurements outside of normal range (abnormally high for total cholesterol, LDL, and triglycerides; abnormally low for HDL) will also be compared in this manner.

4.3.8 Thrombotic microangiopathy

The proportion of participants experiencing thrombotic microangiopathy by 6 months post-randomization will be estimated and compared between treatment groups using the Z test for comparing binomial proportions (or Barnard's Exact Unconditional Test as appropriate).

4.3.9 CMV reactivation

The proportion of participants with previous CMV exposure (either donor or recipient was previously CMV+) requiring new systemic treatment for an increasing CMV PCR level per institutional practice (participants receiving only standard of care viral prophylaxis will not be included in this assessment) by Day 56 post-randomization will be compared between treatment groups using a Z-test for comparing binomial proportions (or Barnard's Exact Unconditional Test as appropriate).

4.3.10 Patient-Reported Outcomes

Patient-Reported Outcomes (PROs) assessed include the MDASI (MD Anderson Symptom Inventory), FACT-BMT, and MOS Short Form-36 (or PedsQL for pediatric participants) at enrollment and at Day 56, 6 months, and 12 months post-randomization. These will be scored per the recommendations of the developers. PROs at each time point will be summarized using simple descriptive statistics (mean, standard deviation, median, and range). PROs among survivors at each time point will be compared between treatment arms in an initial analysis using two sample t tests. The missing data pattern of the PRO measurements may be examined using graphical techniques and logistic regression models conditional on survival where, at each time point, estimates of the difference in PROs between the treatment groups conditional on survival would be obtained using inverse probability of censoring weighting with independent estimating equations to account for missing data.

4.3.11 Secondary Analysis of AA3 Participants

A secondary analysis will assess study outcomes for AA3 participants by treatment group (note that participants with missing biomarker results will be excluded). Due to the small number of AA3 participants expected, this analysis will be descriptive only as we are unlikely to have power to detect differences between the groups.

5. Template of Proposed Table/Figure/Listing (TFL) Shells

Table/Figure/Listing titles and layout are for illustration purposes only, and may not be the final layout or wording chosen for publications or presentations. Actual format of the

tables and figures may differ and will be subject to change in the final analysis report and/or publication. See the Appendix of this SAP for the exhibit titles and shells.

6. References

[1] MacMillan ML, Robin M, Harris AC, et al. A refined risk score for acute graft-versus-host disease that predicts response to initial therapy, survival, and transplant-related mortality. *Biology of Blood and Marrow Transplantation*. 2015, 21(4):761-767.

[2] Bolanos-Meade J, Logan BR, Alousi AM, et al. Phase 3 clinical trial of steroids/mycophenolate mofetil vs steroids/placebo as therapy for acute GVHD: BMT CTN 0802. *Blood*. 2014, 124:3221-3227.

[3] Pidala J, Tomblyn M, Nishihori T, et al. Sirolimus demonstrates activity in the primary therapy of acute graft-versus-host disease without systemic glucocorticoids. *Haematologica*. 2011, 96:1351-1356.

[4] Haggstrom G. Sequential Tests for Exponential Population and Poisson Processes. *Rand Corporation*. 1979.

[5] Barnard GA. A New Test for 2× 2 Tables. *Nature*. 1945, 156:177.

[6] Aalen OO and Johansen S. An empirical transition matrix for non-homogeneous Markov chains based on censored observations. *Scandinavian Journal of Statistics*. 1978, 141-150.

[7] Gray RJ. A class of K-sample tests for comparing the cumulative incidence of a competing risk. *The Annals of Statistics*. 1988, 1141-1154.

Appendix

Exhibit 1501-1: Participant Disposition and Follow-Up

A consort diagram will be provided showing the number of participants, study assignment, and compliance with each phase of the protocol as applicable. A table will be provided with descriptive statistics on length of follow-up by assigned treatment arm.

Exhibit 1501-2: Participant Demographics and Baseline Characteristics

Baseline characteristics and demographics will be described by frequencies and percentages for categorical covariates, and mean, standard deviation, median, and range for continuous covariates. The following covariates will be included:

- Treatment group assignment
- Gender
- Ethnicity
- Race
- Patient age
- Karnofsky performance score
- Primary Disease
- Disease Status
- Conditioning regimen
- Conditioning regimen intensity
- Donor type
- Graft source
- HLA match score
- GVHD Prophylaxis at Transplant
- Donor/Recipient CMV Status
- Acute GVHD grade at enrollment
- Acute GVHD organ staging at enrollment
- Topical steroid use at enrollment
- Ann Arbor biomarker status

Other baseline covariates will be summarized at the request of the investigators.

	Treatment Arm		
	Sirolimus (N=) N (%)	**Prednisone (N=) N (%)**	**Total (N=) N (%)**
Gender			
Female			
Male			
Ethnicity			
Hispanic or Latino			
Not Hispanic or Latino			
Unknown			

	Treatment Arm		
	Sirolimus (N=) N (%)	**Prednisone (N=) N (%)**	**Total (N=) N (%)**
Not Answered			
Race			
American Indian/Alaskan Native			
Asian			
Hawaiian/Pacific Islander			
Black or African American			
White			
More than One Race			
Other, Specify			
Unknown			
Not Answered			
Age, years			
Mean (Std Dev)			
Median (Range)			
Ann Arbor Biomarker Status			
1			
2			
3			
Missing			
Karnofsky Performance Score			
90 - 100			
Less than 90			
Primary Disease			
Acute Lymphoblastic Leukemia (ALL)			
Acute Myelogenous Leukemia (AML)			
Chronic Myelogenous Leukemia (CML)			
Other Leukemia			
Myelodysplastic/Myeloprolifterative Disorders (MDS/MPN)			
Non-Hodgkin Lymphoma (NHL)			
Hodgkin Lymphoma			
Plasma Cell Disorder/Multiple Myeloma			
Inherited Abnormalities Erythrocyte Differention or Function			
Disease Status			
Complete remission (CR)			

	Treatment Arm		
	Sirolimus (N=) N (%)	**Prednisone (N=) N (%)**	**Total (N=) N (%)**
Partial remission (PR)			
Stable disease (SD)			
Conditioning Regimen[1]			
ATG + FLUD + MEL			
BU + ATG + clofarabine			
BU + ATG + FLUD			
BU + ATG + FLUD + vorinostat			
BU + FLUD			
BU + FLUD + THIO			
CY + BU			
CY + BU + FLUD			
FLUD + MEL			
TBI +CY			
TBI + CY + FLUD			
TBI + FLUD			
Conditioning Regimen Intensity			
Myeloablative			
Non-myeloablative or Reduced Intensity			
Donor Type			
Related Donor			
Unrelated Donor			
Graft Source			
Bone Marrow			
Peripheral Blood			
Cord Blood			
HLA Match Score			
Bone marrow or peripheral blood 8/8			
Bone marrow or peripheral blood 7/8			
Bone marrow or peripheral blood <= 6/8			
Cord blood 6/6			
Cord blood 5/6			
Cord blood <= 4/6			
Missing			
GVHD Prophylaxis at Transplant			

	Treatment Arm		
	Sirolimus (N=) N (%)	**Prednisone (N=) N (%)**	**Total (N=) N (%)**
Post-CY + Other(s)			
TAC + MMF +- Other(s) (except post-CY)			
TAC + MTX +- Other(s) (except MMF, post-CY)			
CSA + MMF +- Other(s) (except post-CY)			
CSA + MTX +- Other(s) (except MMF, post-CY)			
Donor/Recipient CMV Status			
Pos/Pos			
Pos/Neg			
Neg/Pos			
Neg/Neg			
Acute GVHD Grade at Enrollment			
0			
I			
II			
III			
IV			
Acute GVHD Skin Organ Stage at Enrollment			
0			
1			
2			
3			
4			
Acute GVHD Upper GI Organ Involvement at Enrollment			
Yes			
No			
Acute GVHD Lower GI Organ Stage at Enrollment			
0			
1			
2			
3			
4			
Acute GVHD Liver Organ Stage at Enrollment			
0			

	Treatment Arm		
	Sirolimus (N=) N (%)	**Prednisone (N=) N (%)**	**Total (N=) N (%)**
1			
2			
3			
4			
Topical Steroid Use at Enrollment			
Yes			
No			

[1] ATG = antithymocyte globulin, BU = Busulfan, FLUD = Fludarabine, CY = Cyclophosphamide, MEL = Melphalan, TBI = Total body irradiation, THIO = Intrathecal thiotepa

Exhibit 1501-3: Complete Response / Partial Response at Day 28

The primary endpoint is complete response/partial response (CR/PR) of acute GVHD to therapy at Day 28 post-randomization. Participants that have died prior to Day 28 or receive secondary therapy are treated as nonresponders in the analysis.

Acute GVHD Response at Day 28 by Treatment Group		
	Sirolimus (N=) N (%)	**Prednisone (N=) N (%)**
Complete Response (CR)	XX (XX.X%)	XX (XX.X%)
Partial Response (PR)	XX (XX.X%)	XX (XX.X%)
Mixed Response (MR)	XX (XX.X%)	XX (XX.X%)
No Response (NR)	XX (XX.X%)	XX (XX.X%)
Progression	XX (XX.X%)	XX (XX.X%)
Dead	XX (XX.X%)	XX (XX.X%)
Not Evaluable	XX	XX

Day 28 CR/PR Rates				
	N Evaluable	**Estimate**	**Standard Error**	**90% CI**
Sirolimus	XX	XX.X%	XX.X%	(XX.X%, XX.X%)
Prednisone	XX	XX.X%	XX.X%	(XX.X%, XX.X%)
Difference (Sirolimus – Prednisone)	XX	XX.X%	XX.X%	(XX.X%, XX.X%)

Clarify the population for the endpoint (n=?). If n is not the same as the primary endpoint, explain why (e.g. patient not evaluable, missing data, etc.) Give details of not evaluable if the definition is not pre-specified in the protocol.

Exhibit 1501-4: Complete Response / Partial Response and Steroid Dose 0.25/mg/kg/day or Less at Day 28

This is a refined endpoint of CR/PR and the use of a prednisone equivalent steroid dose of 0.25 mg/kg/day or less. Methylprednisone is considered to be 1.25 times as potent as prednisone, while prednisolone is dose-equivalent to prednisone. Note that use of prednisone below the threshold on the sirolimus arm is not considered a failure for this endpoint. Participants that have died or received secondary therapy prior to Day 28 are treated as nonreponders in the analysis.

Day 28 CR/PR and Steroid Dose 0.25/mg/kg/day or Less by Treatment Group			
	Sirolimus (N=) N (%)	**Prednisone (N=) N (%)**	**P-value***
Yes	XX (XX.X%)	XX (XX.X%)	X.XXX
No	XX (XX.X%)	XX (XX.X%)	
Not Evaluable	XX	XX	

* *Clarify test used (Z test of binomial proportions or Barnard's Exact)*

Rates of Day 28 CR/PR with Steroid Dose 0.25/mg/kg/day or Less				
	N Evaluable	**Estimate**	**Standard Error**	**95% CI**
Sirolimus	XX	XX.X%	XX.X%	(XX.X%, XX.X%)
Prednisone	XX	XX.X%	XX.X%	(XX.X%, XX.X%)

Clarify the population for the endpoint (n=?). If n is not the same as the primary endpoint, explain why (e.g. patient not evaluable, missing data, etc.) Give details of not evaluable if the definition is not pre-specified in the protocol.

Exhibit 1501-5: Disease Response

Acute GVHD Response Among Surviving Patients by Treatment Group				
Assessment Time Point		**Sirolimus (N=) N (%)**	**Prednisone (N=) N (%)**	**P-value***
Day 14	Complete Response (CR)	XX (XX.X%)	XX (XX.X%)	X.XXX
	Partial Response (PR)	XX (XX.X%)	XX (XX.X%)	
	Mixed Response (MR)	XX (XX.X%)	XX (XX.X%)	
	No Response (NR)	XX (XX.X%)	XX (XX.X%)	
	Progression	XX (XX.X%)	XX (XX.X%)	
	Not Evaluable	XX	XX	
Day 28	Complete Response (CR)	XX (XX.X%)	XX (XX.X%)	X.XXX
	Partial Response (PR)	XX (XX.X%)	XX (XX.X%)	
	Mixed Response (MR)	XX (XX.X%)	XX (XX.X%)	
	No Response (NR)	XX (XX.X%)	XX (XX.X%)	
	Progression	XX (XX.X%)	XX (XX.X%)	
	Not Evaluable	XX	XX	
Day 56	Complete Response (CR)	XX (XX.X%)	XX (XX.X%)	X.XXX
	Partial Response (PR)	XX (XX.X%)	XX (XX.X%)	
	Mixed Response (MR)	XX (XX.X%)	XX (XX.X%)	
	No Response (NR)	XX (XX.X%)	XX (XX.X%)	
	Progression	XX (XX.X%)	XX (XX.X%)	
	Not Evaluable	XX	XX	

* *Clarify tests used (Chi square with 4 d.f. or Fisher's Exact)*

Clarify the population for the endpoint (n=?). If n is not the same as the primary endpoint, explain why (e.g. patient not evaluable, missing data, etc.) Give details of not evaluable if the definition is not pre-specified in the protocol.

Exhibit 1501-6: Treatment Failure

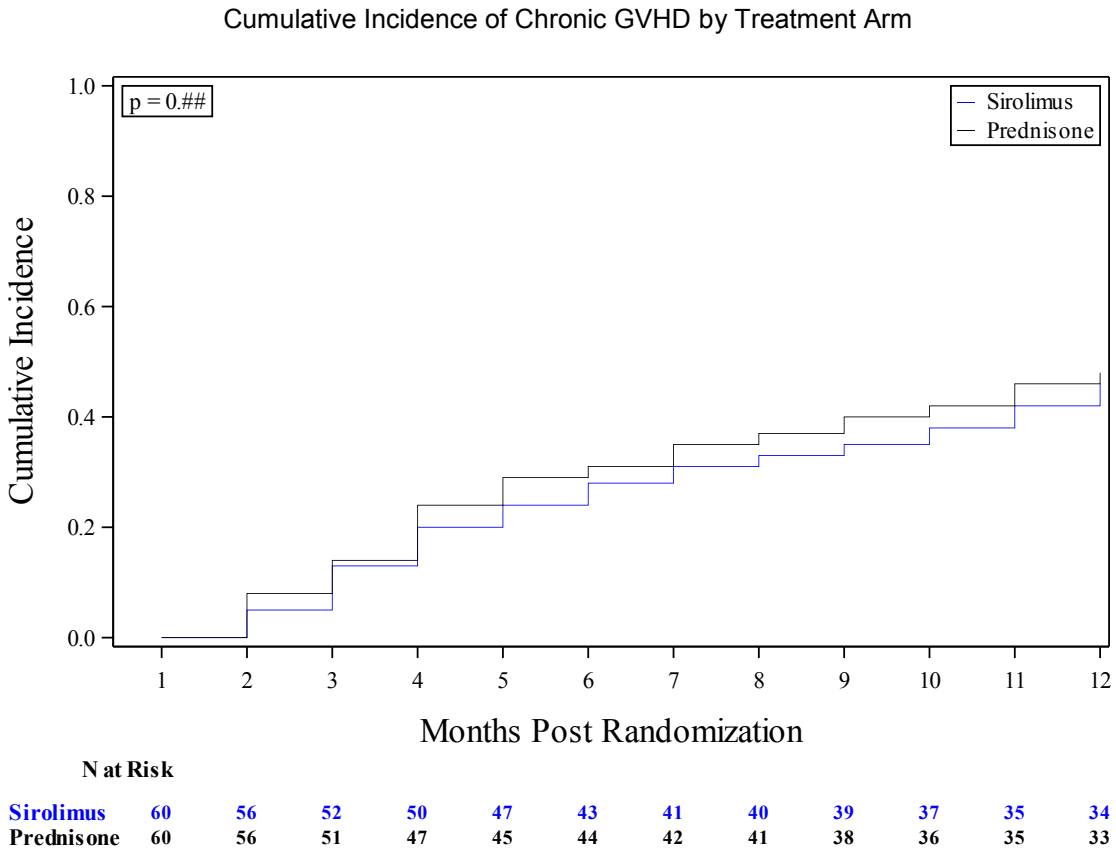
Treatment failure is defined as death, no response, progression, administration of additional therapy beyond primary therapy for GVHD [(or re-escalation of steroid dose to ≥ 2.5 mg/kg/day of prednisone (or methylprednisolone equivalent of 2 mg/kg/day) or initiation of corticosteroids for the treatment of acute GVHD for participants assigned to the sirolimus arm].

Treatment Failure by Treatment Group				
Assessment Time Point		**Sirolimus (N=) N (%)**	**Prednisone (N=) N (%)**	**P-value***
Day 14	Yes	XX (XX.X%)	XX (XX.X%)	X.XXX
	No	XX (XX.X%)	XX (XX.X%)	
	Not Evaluable	XX	XX	
Day 28	Yes	XX (XX.X%)	XX (XX.X%)	X.XXX
	No	XX (XX.X%)	XX (XX.X%)	
	Not Evaluable	XX	XX	
Day 56	Yes	XX (XX.X%)	XX (XX.X%)	X.XXX
	No	XX (XX.X%)	XX (XX.X%)	
	Not Evaluable	XX	XX	

* *Clarify tests used (Z test of binomial proportions or Barnard's Exact)*

Clarify the population for the endpoint (n=?). If n is not the same as the primary endpoint, explain why (e.g. patient not evaluable, missing data, etc.) Give details of not evaluable if the definition is not pre-specified in the protocol.

Exhibit 1501-7: Chronic GVHD



* P-value from Gray's test. Death and relapse are treated as competing risks.

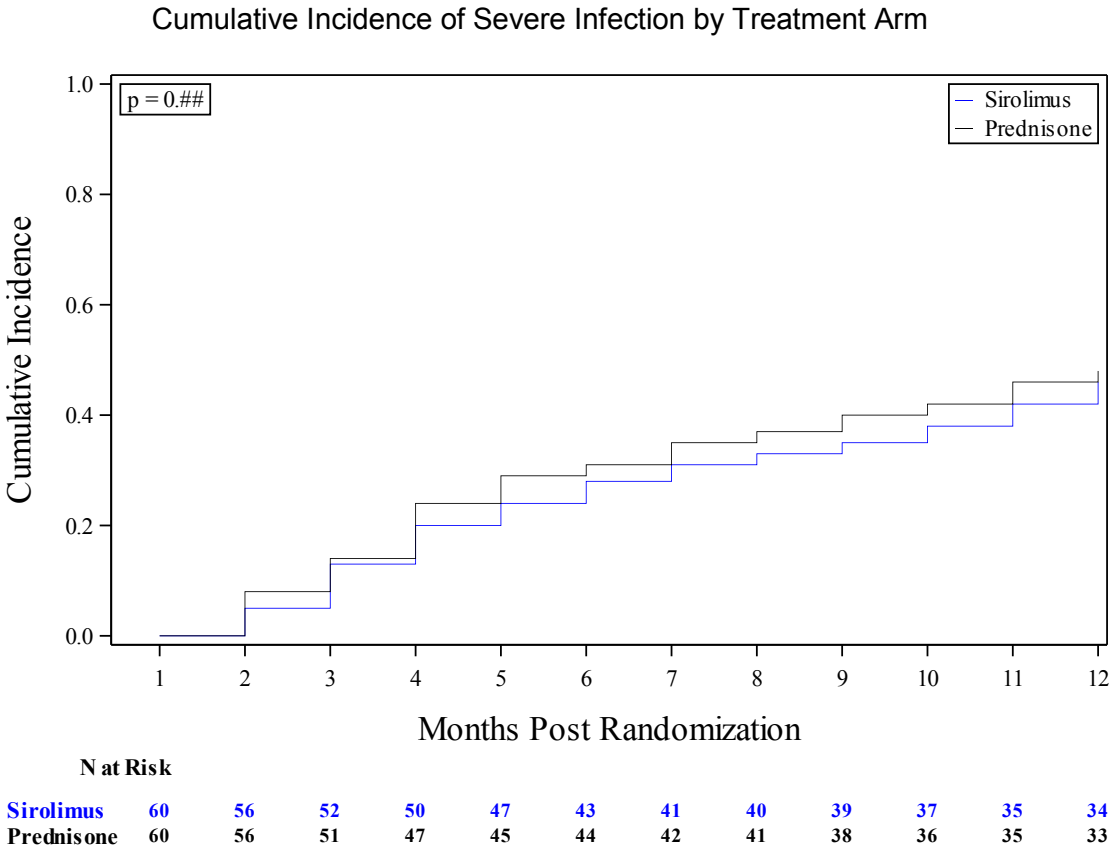
Maximum Severity of Chronic GVHD at 1 Year Post-Randomization by Treatment Group		
Severity	**Sirolimus (N=) N (%)**	**Prednisone (N=) N (%)**
No cGVHD	XX (XX.X%)	XX (XX.X%)
Mild	XX (XX.X%)	XX (XX.X%)
Moderate	XX (XX.X%)	XX (XX.X%)
Severe	XX (XX.X%)	XX (XX.X%)

Cumulative Incidence Estimates and 95% Confidence Intervals for Chronic GVHD		
Time post-randomization	**Sirolimus**	**Prednisone**
6 months	XX.X (XX.X, XX.X)	XX.X (XX.X, XX.X)
12 months	XX.X (XX.X, XX.X)	XX.X (XX.X, XX.X)

Clarify the population for the endpoint (n=?). If n is not the same as the primary endpoint, explain why (e.g. patient not evaluable, missing data, etc.)

Exhibit 1501-8: Systemic Infections

Number of Infections Reported by Treatment Group			
		Sirolimus (N=) N (%)	**Prednisone (N=) N (%)**
Site	Blood/Buffy Coat	XX (XX.X%)	XX (XX.X%)
	Disseminated - Generalized, Isolated at 2 or More Distinct Sites	XX (XX.X%)	XX (XX.X%)
	Brain	XX (XX.X%)	XX (XX.X%)
	Spinal Cord	XX (XX.X%)	XX (XX.X%)
	Meninges and CSF	XX (XX.X%)	XX (XX.X%)
	…	XX (XX.X%)	XX (XX.X%)
	[omitted 37 categories]	XX (XX.X%)	XX (XX.X%)
	…	XX (XX.X%)	XX (XX.X%)
	Spleen	XX (XX.X%)	XX (XX.X%)
	Other Unspecified	XX (XX.X%)	XX (XX.X%)
Time of Onset Post-Randomization	Median days (range)	XX (XX.X-XX.X)	XX (XX.X-XX.X)
	0-90 days	XX (XX.X%)	XX (XX.X%)
	91-180 days	XX (XX.X%)	XX (XX.X%)
	181-270 days	XX (XX.X%)	XX (XX.X%)
	271-365 days	XX (XX.X%)	XX (XX.X%)
Severity	Grade 2 (Moderate)	XX (XX.X%)	XX (XX.X%)
	Grade 3 (Severe / Life Threatening)	XX (XX.X%)	XX (XX.X%)



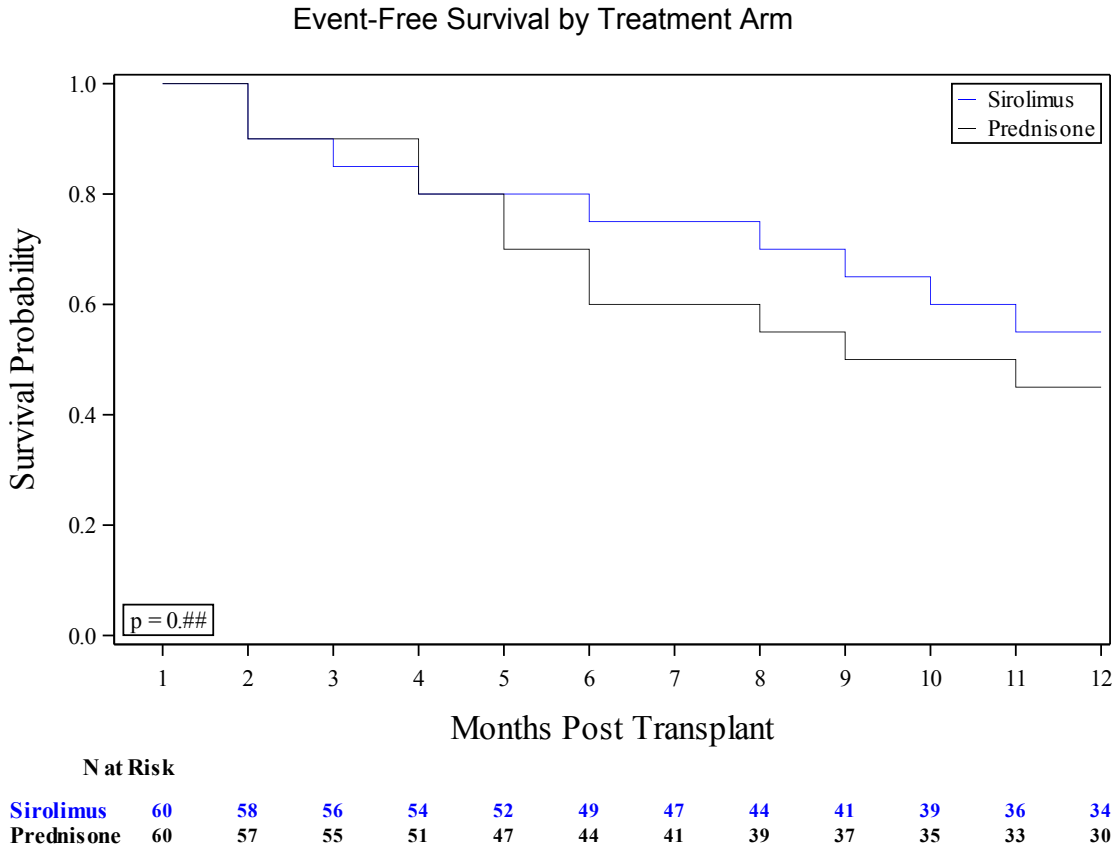
* P-value from Gray's test. Death is treated as the competing risk.

Cumulative Incidence Estimates and 95% Confidence Intervals for Severe Infection		
Time post-randomization	**Sirolimus**	**Prednisone**
6 months	XX.X (XX.X, XX.X)	XX.X (XX.X, XX.X)
12 months	XX.X (XX.X, XX.X)	XX.X (XX.X, XX.X)

Clarify the population for the endpoint (n=?). If n is not the same as the primary endpoint, explain why (e.g. patient not evaluable, missing data, etc.)

Exhibit 1501-9: Event-Free Survival

Event-free survival is a composite endpoint of acute GVHD progression, chronic GVHD, malignancy relapse, and mortality.



* P-value from log rank test.

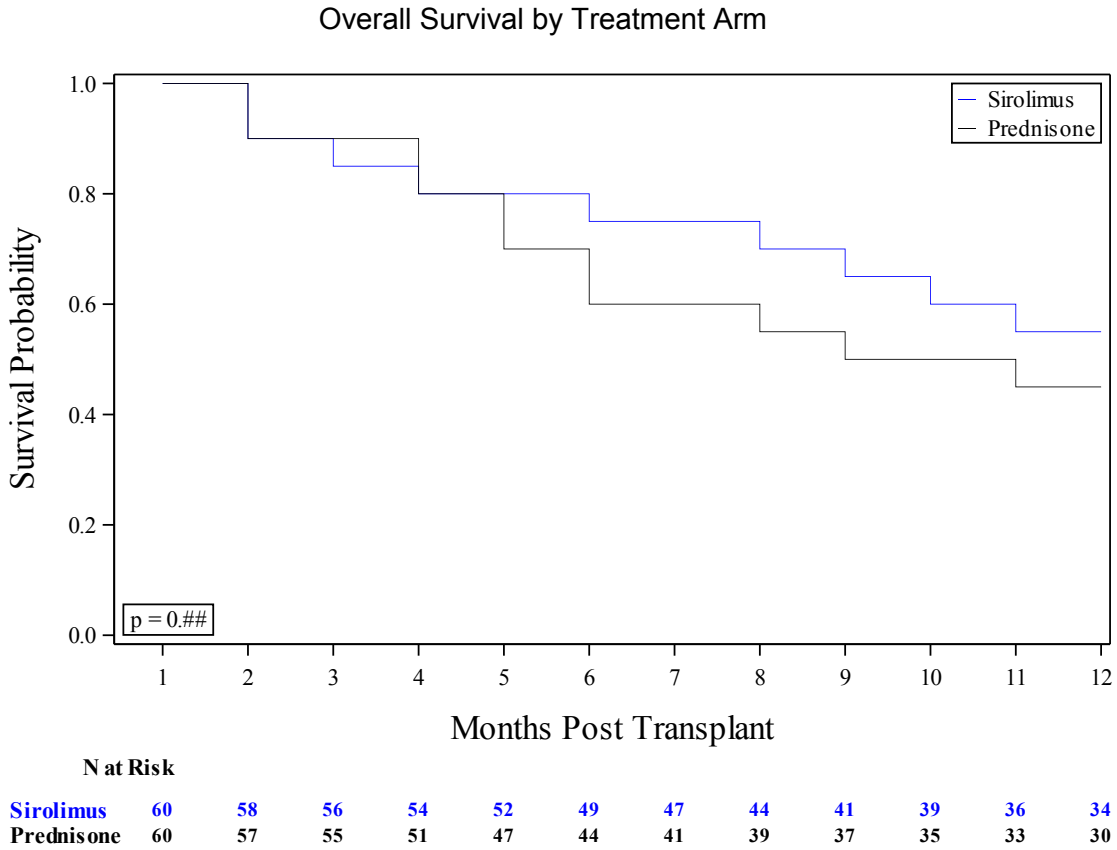
Kaplan Meier Estimates of Event-Free Survival		
	Sirolimus	**Prednisone**
6 months	XX.X (XX.X, XX.X)	XX.X (XX.X, XX.X)
12 months	XX.X (XX.X, XX.X)	XX.X (XX.X, XX.X)

Follow-up time for Event-Free Survival		
	Sirolimus	**Prednisone**
Median days (range)	XX.X (XX.X, XX.X)	XX.X (XX.X, XX.X)

Details need to be added if any lost to follow-up.

Clarify the population for the endpoint (n=?). If n is not the same as the primary endpoint, explain why (e.g. patient not evaluable, missing data, etc.)

Exhibit 1501-10: Overall Survival



* P-value from log rank test.

Kaplan Meier Estimates of Overall Survival		
	Sirolimus	**Prednisone**
6 months	XX.X (XX.X, XX.X)	XX.X (XX.X, XX.X)
12 months	XX.X (XX.X, XX.X)	XX.X (XX.X, XX.X)

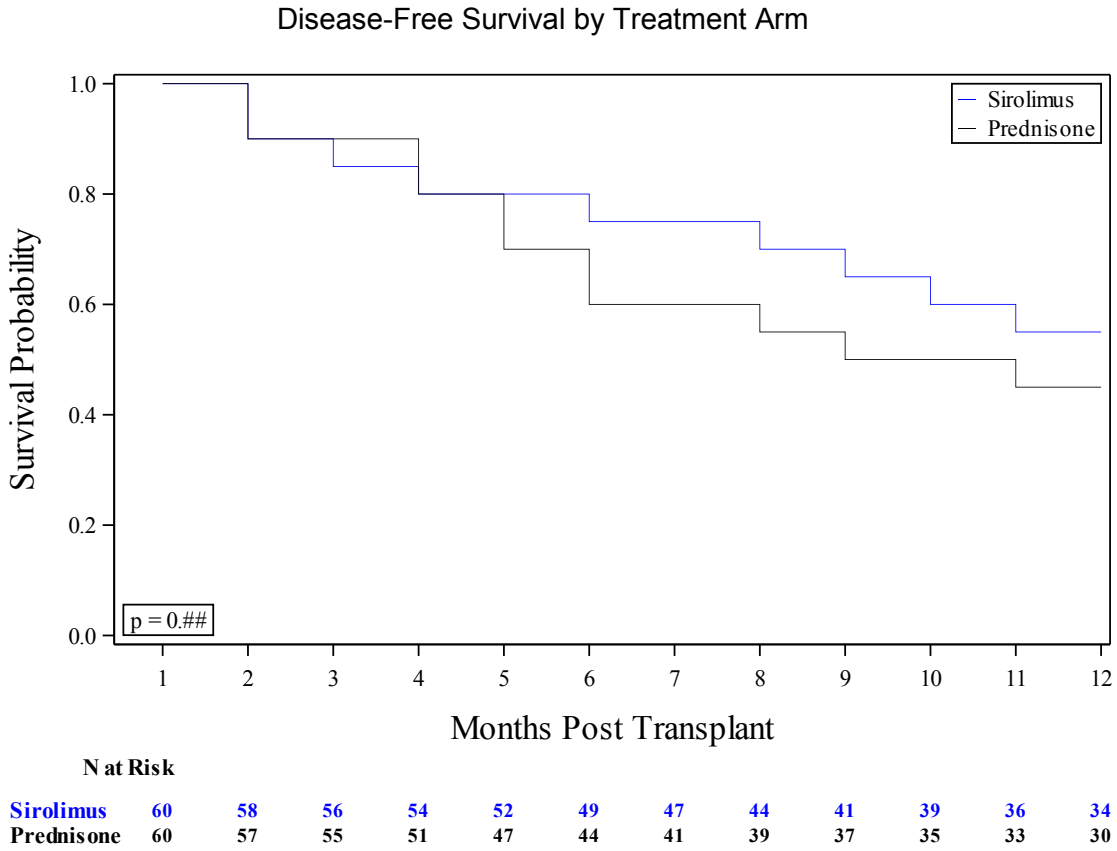
Follow-up time for Overall Survival		
	Sirolimus	**Prednisone**
Median days (range)	XX.X (XX.X, XX.X)	XX.X (XX.X, XX.X)

Details need to be added if any lost to follow-up.

Clarify the population for the endpoint (n=?). If n is not the same as the primary endpoint, explain why (e.g. patient not evaluable, missing data, etc.)

Exhibit 1501-11: Disease-Free Survival

Disease-free survival is a composite endpoint of the events death and relapse of the underlying malignancy.



* P-value from log rank test.

Kaplan Meier Estimates of Disease-Free Survival		
	Sirolimus	**Prednisone**
6 months	XX.X (XX.X, XX.X)	XX.X (XX.X, XX.X)
12 months	XX.X (XX.X, XX.X)	XX.X (XX.X, XX.X)

Follow-up time for Disease -Free Survival		
	Sirolimus	**Prednisone**
Median days (range)	XX.X (XX.X, XX.X)	XX.X (XX.X, XX.X)

Details need to be added if any lost to follow-up.

Clarify the population for the endpoint (n=?). If n is not the same as the primary endpoint, explain why (e.g. patient not evaluable, missing data, etc.)

Exhibit 1501-12: GVHD-free Survival

GVHD-free survival is a composite endpoint of the events death, acute GVHD, and chronic GVHD.

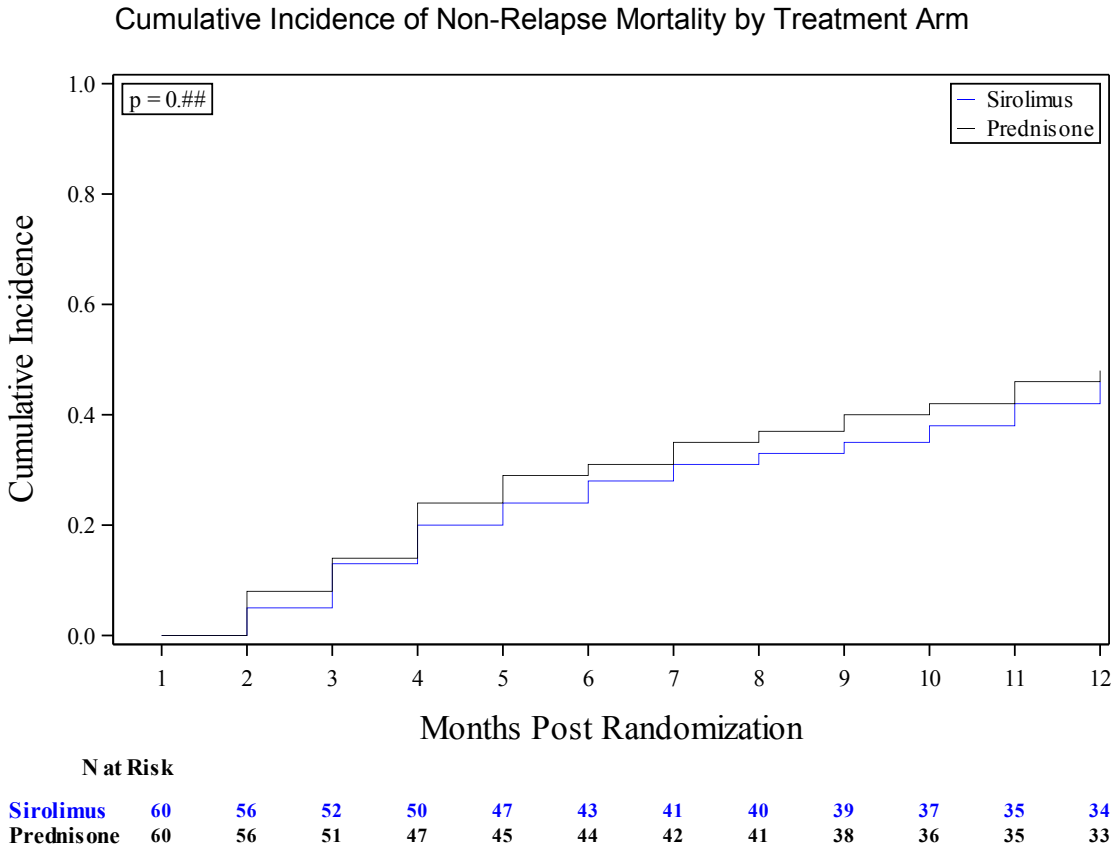
GVHD-free Survival by Treatment Group				
Assessment Time Point		**Sirolimus (N=) N (%)**	**Prednisone (N=) N (%)**	**P-value***
6 months	Yes	XX (XX.X%)	XX (XX.X%)	X.XXX
	No	XX (XX.X%)	XX (XX.X%)	
	Not Evaluable	XX	XX	
12 months	Yes	XX (XX.X%)	XX (XX.X%)	X.XXX
	No	XX (XX.X%)	XX (XX.X%)	
	Not Evaluable	XX	XX	

* *Clarify test used (Z test of binomial proportions or Barnard's Exact)*

Clarify the population for the endpoint (n=?). If n is not the same as the primary endpoint, explain why (e.g. patient not evaluable, missing data, etc.)

Exhibit 1501-13: Non-relapse Mortality

Non-relapse mortality (NRM) consists of deaths due to any cause other than relapse of the underlying malignancy.



* P-value from Gray's test. Relapse is treated as the competing risk.

Cumulative Incidence Estimates and 95% Confidence Intervals for Non-relapse Mortality		
Time post-randomization	**Sirolimus**	**Prednisone**
6 months	XX.X (XX.X, XX.X)	XX.X (XX.X, XX.X)
12 months	XX.X (XX.X, XX.X)	XX.X (XX.X, XX.X)

Clarify the population for the endpoint (n=?). If n is not the same as the primary endpoint, explain why (e.g. patient not evaluable, missing data, etc.)

Exhibit 1501-14: Steroid Dose

The cumulative prednisone-equivalent dose of steroids through Day 56 is described here. Doses of methylprednisolone will be converted to prednisone equivalents by multiplying the methylprednisolone dose by 1.25, while doses of prednisolone are considered equivalent to prednisone. Prednisone doses for each patient will be converted to mg/kg. For participants that weigh over 100kg, maximal starting dose of prednisone will be 200mg (or 2mg/kg based on a modified starting weight of 100kg). For calculation of subsequent prednisone doses/kg on subsequent measures, the modified starting weight of 100kg will be used. Cumulative prednisone dose for each patient at Day 56 is calculated by adding the doses (end of each week's dose) for each of the first eight weeks of treatment, divided by the number of days of survival during this interval.

Cumulative Steroid Dose at Day 56 by Treatment Group			
	Sirolimus (N=)	**Prednisone (N=)**	**P-value***
Median (range)	XX.X (XX.X, XX.X)	XX.X (XX.X, XX.X)	X.XXX

* *Wilcoxon Rank Sum test*

Clarify the population for the endpoint (n=?). If n is not the same as the primary endpoint, explain why (e.g. patient not evaluable, missing data, etc.) Give details of not evaluable if the definition is not pre-specified in the protocol.

Exhibit 1501-15: Topical Therapy

Topical therapy consists of the use of either topical skin or topical GI steroids.

Topical Therapy Use at Baseline by Treatment Group		
	Sirolimus (N=) N (%)	**Prednisone (N=) N (%)**
Yes	XX (XX.X%)	XX (XX.X%)
No	XX (XX.X%)	XX (XX.X%)

Topical Therapy Use Post-Randomization Among Participants Free of Topical Therapy at Baseline by Treatment Group			
	Sirolimus (N=) N (%)	**Prednisone (N=) N (%)**	**P-value***
Yes	XX (XX.X%)	XX (XX.X%)	X.XXX
No	XX (XX.X%)	XX (XX.X%)	

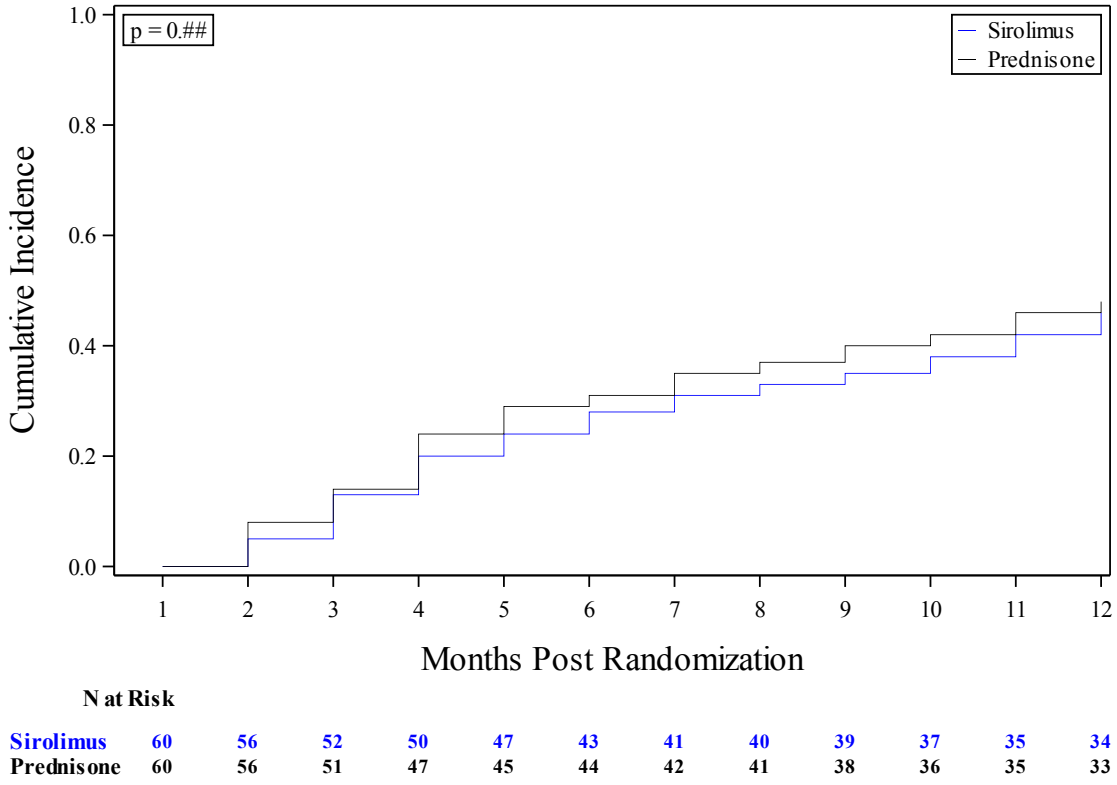
* *Clarify test used (Z test of binomial proportions or Barnard's Exact)*

Clarify the population for the endpoint (n=?). If n is not the same as the primary endpoint, explain why (e.g. patient not evaluable, missing data, etc.) Give details of not evaluable if the definition is not pre-specified in the protocol.

Exhibit 1501-16: Discontinuation of Immune Suppression

Discontinuation of immune suppression consists of discontinuation of corticosteroids and other systemic immune suppressive medications.

Cumulative Incidence of Discontinuation of Immune Suppression by Treatment Arm



N at Risk

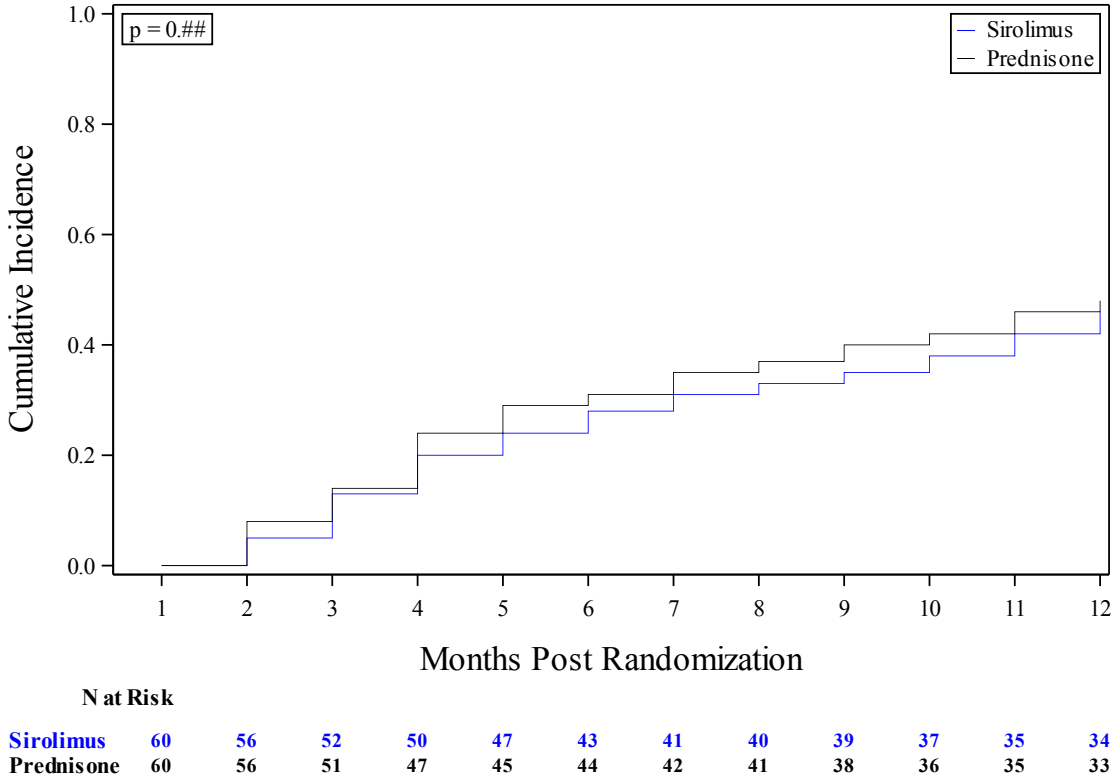
Sirolimus	**60**	**56**	**52**	**50**	**47**	**43**	**41**	**40**	**39**	**37**	**35**	**34**
Prednisone	**60**	**56**	**51**	**47**	**45**	**44**	**42**	**41**	**38**	**36**	**35**	**33**

* P-value from Gray's test. Death is treated as the competing risk.

Cumulative Incidence Estimates and 95% Confidence Intervals for Discontinuation of Immune Suppression		
Time post-randomization	**Sirolimus**	**Prednisone**
Day 56	XX.X (XX.X, XX.X)	XX.X (XX.X, XX.X)
6 months	XX.X (XX.X, XX.X)	XX.X (XX.X, XX.X)
12 months	XX.X (XX.X, XX.X)	XX.X (XX.X, XX.X)

GVHD- and relapse-free discontinuation of immune suppression is a refined endpoint consisting of complete immune suppression discontinuation together with freedom from any GVHD or malignancy progression/recurrence.

Cumulative Incidence of GVHD- and Relapse-free Discontinuation of Immune Suppression by Treatment Arm

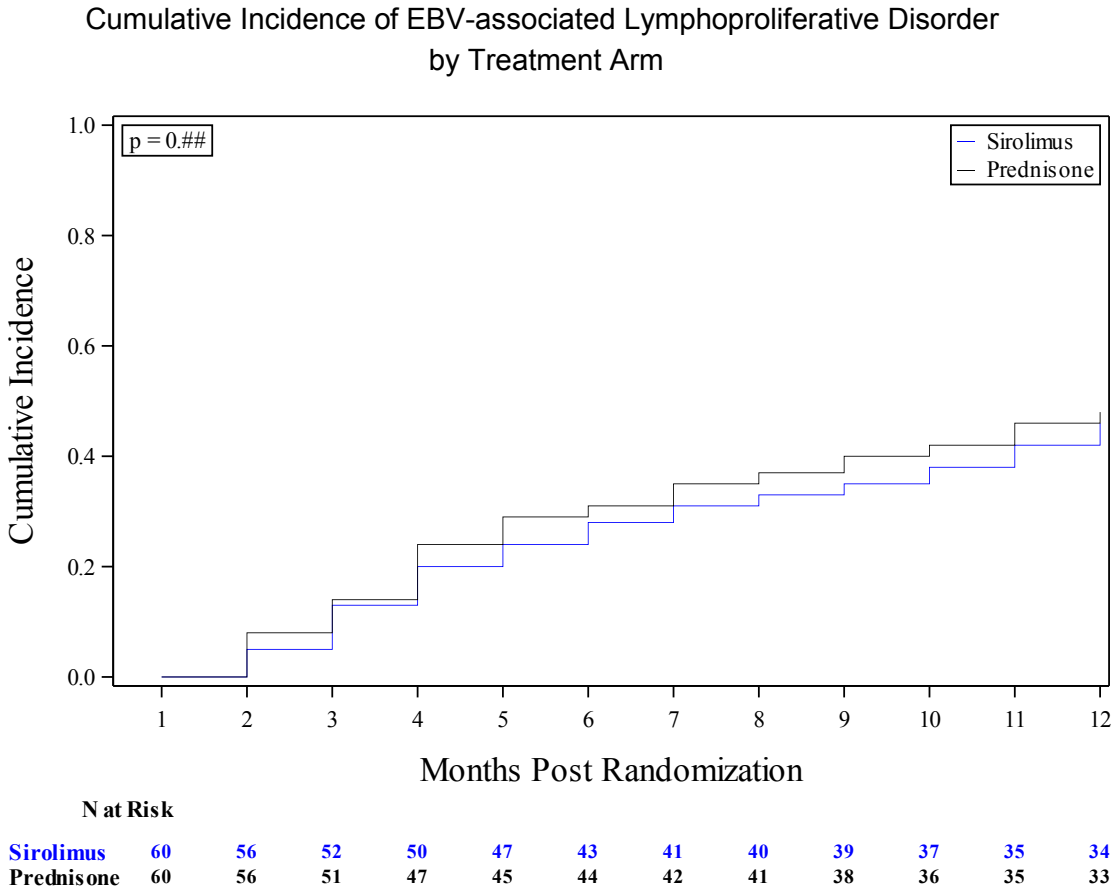


* P-value from Gray's test. Death is treated as the competing risk.

Cumulative Incidence Estimates and 95% Confidence Intervals for GVHD- and Relapse-free Discontinuation of Immune Suppression		
Time post-randomization	**Sirolimus**	**Prednisone**
Day 56	XX.X (XX.X, XX.X)	XX.X (XX.X, XX.X)
6 months	XX.X (XX.X, XX.X)	XX.X (XX.X, XX.X)
12 months	XX.X (XX.X, XX.X)	XX.X (XX.X, XX.X)

Clarify the population for the endpoint (n=?). If n is not the same as the primary endpoint, explain why (e.g. patient not evaluable, missing data, etc.)

Exhibit 1501-16: EBV-associated Lymphoproliferative Disorder



* P-value from Gray's test. Death is treated as the competing risk.

Cumulative Incidence Estimates and 95% Confidence Intervals for EBV-associated Lymphoproliferative Disorder		
Time post-randomization	**Sirolimus**	**Prednisone**
6 months	XX.X (XX.X, XX.X)	XX.X (XX.X, XX.X)
12 months	XX.X (XX.X, XX.X)	XX.X (XX.X, XX.X)

Clarify the population for the endpoint (n=?). If n is not the same as the primary endpoint, explain why (e.g. patient not evaluable, missing data, etc.)

Exhibit 1501-17: Hyperglycemia

Hyperglycemia is defined as a random glucose >200mg/dL or fasting glucose >126mg/dL and use of diabetes therapy, i.e. use of insulin and/or oral medications to control and/or maintain glucose level.

Hyperglycemia by Treatment Group				
Assessment Time Point		**Sirolimus (N=) N (%)**	**Prednisone (N=) N (%)**	**P-value***
Baseline	Yes	XX (XX.X%)	XX (XX.X%)	---
	No	XX (XX.X%)	XX (XX.X%)	
	Not Evaluable	XX	XX	
Day 28	Yes	XX (XX.X%)	XX (XX.X%)	X.XXX
	No	XX (XX.X%)	XX (XX.X%)	
	Not Evaluable	XX	XX	
Day 56	Yes	XX (XX.X%)	XX (XX.X%)	X.XXX
	No	XX (XX.X%)	XX (XX.X%)	
	Not Evaluable	XX	XX	

* *Clarify test used (Z test of binomial proportions or Barnard's Exact)*

Exhibit 1501-18: Functional Myopathy

Functional myopathy measures considered are:

- Hip Flexor and Quadriceps Strength via handheld dynamometer
- Two Minute Walk Test
- 5-time Sit-to-Stand
- Adult Myopathy Assessment Tool (AMAT)

Functional Myopathy Scores by Treatment Group								
Measure	**Assessment Time**	**Sirolimus (N=)**			**Prednisone (N=)**			**Treatment Comparison p-value[2]**
		N	**Median (Range)**	**p-value[1]**	**N**	**Median (Range)**	**p-value[1]**	
Hip Flexor and Quadriceps Strength	Baseline	XX	XX.X (XX.X, XX.X)	-	XX	XX.X (XX.X, XX.X)	-	-
	Day 56	XX	XX.X (XX.X, XX.X)	X.XXX	XX	XX.X (XX.X, XX.X)	X.XXX	X.XXX
	6 months	XX	XX.X (XX.X, XX.X)	X.XXX	XX	XX.X (XX.X, XX.X)	X.XXX	X.XXX
Two Minute Walk Test	Baseline	XX	XX.X (XX.X, XX.X)	-	XX	XX.X (XX.X, XX.X)	-	-
	Day 56	XX	XX.X (XX.X, XX.X)	X.XXX	XX	XX.X (XX.X, XX.X)	X.XXX	X.XXX
	6 months	XX	XX.X (XX.X, XX.X)	X.XXX	XX	XX.X (XX.X, XX.X)	X.XXX	X.XXX
5-time Sit-to-Stand	Baseline	XX	XX.X (XX.X, XX.X)	-	XX	XX.X (XX.X, XX.X)	-	-
	Day 56	XX	XX.X (XX.X, XX.X)	X.XXX	XX	XX.X (XX.X, XX.X)	X.XXX	X.XXX
	6 months	XX	XX.X (XX.X, XX.X)	X.XXX	XX	XX.X (XX.X, XX.X)	X.XXX	X.XXX
Adult Myopathy Assessment Tool	Baseline	XX	XX.X (XX.X, XX.X)	-	XX	XX.X (XX.X, XX.X)	-	-
	Day 56	XX	XX.X (XX.X, XX.X)	X.XXX	XX	XX.X (XX.X, XX.X)	X.XXX	X.XXX

	6 months	XX	XX.X (XX.X, XX.X)	X.XXX	XX	XX.X (XX.X, XX.X)	X.XXX	X.XXX

[1] Wilcoxon Signed Rank test comparing score change from baseline within treatment

[2] Wilcoxon Rank Sum test comparing score changes from baseline between treatments

Clarify the population for the endpoint (n=?). If n is not the same as the primary endpoint, explain why (e.g. patient not evaluable, missing data, etc.)

Exhibit 1501-19: Hyperlipidemia

Hyperlipidemia Status at Randomization by Treatment Group				
Condition		**Sirolimus (N=) N (%)**	**Prednisone (N=) N (%)**	**P-value***
Hyperlipidemia	Yes	XX (XX.X%)	XX (XX.X%)	X.XXX
	No	XX (XX.X%)	XX (XX.X%)	
	Not Evaluable	XX	XX	
High Total Cholesterol	Yes	XX (XX.X%)	XX (XX.X%)	X.XXX
	No	XX (XX.X%)	XX (XX.X%)	
	Not Evaluable	XX	XX	
High LDL	Yes	XX (XX.X%)	XX (XX.X%)	X.XXX
	No	XX (XX.X%)	XX (XX.X%)	
	Not Evaluable	XX	XX	
Low HDL	Yes	XX (XX.X%)	XX (XX.X%)	X.XXX
	No	XX (XX.X%)	XX (XX.X%)	
	Not Evaluable	XX	XX	
High Triglycerides	Yes	XX (XX.X%)	XX (XX.X%)	X.XXX
	No	XX (XX.X%)	XX (XX.X%)	
	Not Evaluable	XX	XX	

Hyperlipidemia Status at Day 28 by Treatment Group				
Condition		**Sirolimus (N=) N (%)**	**Prednisone (N=) N (%)**	**P-value***
Hyperlipidemia	Yes	XX (XX.X%)	XX (XX.X%)	X.XXX
	No	XX (XX.X%)	XX (XX.X%)	
	Not Evaluable	XX	XX	
High Total Cholesterol	Yes	XX (XX.X%)	XX (XX.X%)	X.XXX
	No	XX (XX.X%)	XX (XX.X%)	
	Not Evaluable	XX	XX	
High LDL	Yes	XX (XX.X%)	XX (XX.X%)	X.XXX
	No	XX (XX.X%)	XX (XX.X%)	
	Not Evaluable	XX	XX	
Low HDL	Yes	XX (XX.X%)	XX (XX.X%)	X.XXX
	No	XX (XX.X%)	XX (XX.X%)	

	Not Evaluable	XX	XX	
High Triglycerides	Yes	XX (XX.X%)	XX (XX.X%)	X.XXX
	No	XX (XX.X%)	XX (XX.X%)	
	Not Evaluable	XX	XX	

Hyperlipidemia Status at Day 56 by Treatment Group				
Condition		**Sirolimus (N=) N (%)**	**Prednisone (N=) N (%)**	**P-value***
Hyperlipidemia	Yes	XX (XX.X%)	XX (XX.X%)	X.XXX
	No	XX (XX.X%)	XX (XX.X%)	
	Not Evaluable	XX	XX	
High Total Cholesterol	Yes	XX (XX.X%)	XX (XX.X%)	X.XXX
	No	XX (XX.X%)	XX (XX.X%)	
	Not Evaluable	XX	XX	
High LDL	Yes	XX (XX.X%)	XX (XX.X%)	X.XXX
	No	XX (XX.X%)	XX (XX.X%)	
	Not Evaluable	XX	XX	
Low HDL	Yes	XX (XX.X%)	XX (XX.X%)	X.XXX
	No	XX (XX.X%)	XX (XX.X%)	
	Not Evaluable	XX	XX	
High Triglycerides	Yes	XX (XX.X%)	XX (XX.X%)	X.XXX
	No	XX (XX.X%)	XX (XX.X%)	
	Not Evaluable	XX	XX	

Hyperlipidemia Status at Day 180 by Treatment Group				
Condition		**Sirolimus (N=) N (%)**	**Prednisone (N=) N (%)**	**P-value***
Hyperlipidemia	Yes	XX (XX.X%)	XX (XX.X%)	X.XXX
	No	XX (XX.X%)	XX (XX.X%)	
	Not Evaluable	XX	XX	
High Total Cholesterol	Yes	XX (XX.X%)	XX (XX.X%)	X.XXX
	No	XX (XX.X%)	XX (XX.X%)	
	Not Evaluable	XX	XX	
High LDL	Yes	XX (XX.X%)	XX (XX.X%)	X.XXX

	No	XX (XX.X%)	XX (XX.X%)	
	Not Evaluable	XX	XX	
Low HDL	Yes	XX (XX.X%)	XX (XX.X%)	X.XXX
	No	XX (XX.X%)	XX (XX.X%)	
	Not Evaluable	XX	XX	
High Triglycerides	Yes	XX (XX.X%)	XX (XX.X%)	X.XXX
	No	XX (XX.X%)	XX (XX.X%)	
	Not Evaluable	XX	XX	

[*] *Clarify tests used (Z test of binomial proportions or Barnard's Exact)*

Clarify the population for the endpoint (n=?). If n is not the same as the primary endpoint, explain why (e.g. patient not evaluable, missing data, etc.) Give details of not evaluable if the definition is not pre-specified in the protocol.

Exhibit 1501-20: Thrombotic Microangiopathy

Thrombotic Microangiopathy at 6 Months Post-randomization by Treatment Group			
	Sirolimus (N=) N (%)	**Prednisone (N=) N (%)**	**P-value***
Yes	XX (XX.X%)	XX (XX.X%)	X.XXX
No	XX (XX.X%)	XX (XX.X%)	
Not Evaluable	XX	XX	

* *Clarify test used (Z test of binomial proportions or Barnard's Exact)*

Clarify the population for the endpoint (n=?). If n is not the same as the primary endpoint, explain why (e.g. patient not evaluable, missing data, etc.)

Exhibit 1501-21: CMV Reactivation

CMV reactivation is evidenced by the requirement of new systemic treatment for an increasing CMV PCR level per institutional practice.

CMV Reactivation by Day 56 by Treatment Group			
	Sirolimus (N=) N (%)	**Prednisone (N=) N (%)**	**P-value***
Yes	XX (XX.X%)	XX (XX.X%)	X.XXX
No	XX (XX.X%)	XX (XX.X%)	

* *Clarify test used (Z test of binomial proportions or Barnard's Exact)*

Clarify the population for the endpoint (n=?). If n is not the same as the primary endpoint, explain why (e.g. patient not evaluable, missing data, etc.) Give details of not evaluable if the definition is not pre-specified in the protocol.

Exhibit 1501-22: Patient-Reported Outcomes

Patient-Reported Outcomes (PROs) assessed include the MDASI (MD Anderson Symptom Inventory), FACT-BMT, and MOS Short Form-36 (or PedsQL for pediatric participants) and are scored per the recommendations of the developers.

MDASI Score by Treatment Group							
Assessment Time	**Sirolimus (N=)**			**Prednisone (N=)**			
	N	**Mean (SD)**	**Median (Range)**	**N**	**Mean (SD)**	**Median (Range)**	**P-value***
Baseline	XX	XX.X (XX.X)	XX.X (XX.X, XX.X)	XX	XX.X (XX.X)	XX.X (XX.X, XX.X)	X.XXX
Day 56	XX	XX.X (XX.X)	XX.X (XX.X, XX.X)	XX	XX.X (XX.X)	XX.X (XX.X, XX.X)	X.XXX
6 months	XX	XX.X (XX.X)	XX.X (XX.X, XX.X)	XX	XX.X (XX.X)	XX.X (XX.X, XX.X)	X.XXX
12 months	XX	XX.X (XX.X)	XX.X (XX.X, XX.X)	XX	XX.X (XX.X)	XX.X (XX.X, XX.X)	X.XXX

FACT-BMT Score by Treatment Group							
Assessment Time	**Sirolimus (N=)**			**Prednisone (N=)**			
	N	**Mean (SD)**	**Median (Range)**	**N**	**Mean (SD)**	**Median (Range)**	**P-value***
Baseline	XX	XX.X (XX.X)	XX.X (XX.X, XX.X)	XX	XX.X (XX.X)	XX.X (XX.X, XX.X)	X.XXX
Day 56	XX	XX.X (XX.X)	XX.X (XX.X, XX.X)	XX	XX.X (XX.X)	XX.X (XX.X, XX.X)	X.XXX
6 months	XX	XX.X (XX.X)	XX.X (XX.X, XX.X)	XX	XX.X (XX.X)	XX.X (XX.X, XX.X)	X.XXX
12 months	XX	XX.X (XX.X)	XX.X (XX.X, XX.X)	XX	XX.X (XX.X)	XX.X (XX.X, XX.X)	X.XXX

MOS-SF36 Score by Treatment Group							
Assessment Time	**Sirolimus (N=)**			**Prednisone (N=)**			
	N	**Mean (SD)**	**Median (Range)**	**N**	**Mean (SD)**	**Median (Range)**	**P-value***
Baseline	XX	XX.X (XX.X)	XX.X (XX.X, XX.X)	XX	XX.X (XX.X)	XX.X (XX.X, XX.X)	X.XXX
Day 56	XX	XX.X (XX.X)	XX.X (XX.X, XX.X)	XX	XX.X (XX.X)	XX.X (XX.X, XX.X)	X.XXX
6 months	XX	XX.X (XX.X)	XX.X (XX.X, XX.X)	XX	XX.X (XX.X)	XX.X (XX.X, XX.X)	X.XXX
12 months	XX	XX.X (XX.X)	XX.X (XX.X, XX.X)	XX	XX.X (XX.X)	XX.X (XX.X, XX.X)	X.XXX

PedsQL Score by Treatment Group							
Assessment Time	**Sirolimus (N=)**			**Prednisone (N=)**			
	N	**Mean (SD)**	**Median (Range)**	**N**	**Mean (SD)**	**Median (Range)**	**P-value***
Baseline	XX	XX.X (XX.X)	XX.X (XX.X, XX.X)	XX	XX.X (XX.X)	XX.X (XX.X, XX.X)	X.XXX
Day 56	XX	XX.X (XX.X)	XX.X (XX.X, XX.X)	XX	XX.X (XX.X)	XX.X (XX.X, XX.X)	X.XXX
6 months	XX	XX.X (XX.X)	XX.X (XX.X, XX.X)	XX	XX.X (XX.X)	XX.X (XX.X, XX.X)	X.XXX
12 months	XX	XX.X (XX.X)	XX.X (XX.X, XX.X)	XX	XX.X (XX.X)	XX.X (XX.X, XX.X)	X.XXX

* Independent sample t-test

The missing data pattern of the PRO measurements will be examined using graphical techniques and logistic regression models conditional on survival. At each time point, estimates of the difference in PROs between the treatment groups conditional on survival will be obtained using inverse probability of censoring weighting with independent estimating equations to account for missing data.

Logistic Models of Probability of Missing [PRO score]					
Assessment Time	**Effect**	**N**	**Odds ratio**	**95% CI**	**p-value**
Baseline	**Treatment**				
	Prednisone	XX	1.000	-	-
	Sirolimus	XX	X.XXX	(X.XXX, X.XXX)	X.XXX
	Covariate 1				
	Level 1	XX	1.000	-	-
	…	XX	X.XXX	(X.XXX, X.XXX)	X.XXX
	Level K	XX	X.XXX	(X.XXX, X.XXX)	X.XXX
	Covariate 2				
	Level 1	XX	1.000	-	-
	…	XX	X.XXX	(X.XXX, X.XXX)	X.XXX
	Level K	XX	X.XXX	(X.XXX, X.XXX)	X.XXX
	…				
Day 56	**Treatment**				
	Prednisone	XX	1.000	-	-
	Sirolimus	XX	X.XXX	(X.XXX, X.XXX)	X.XXX
	Covariate 1				
	Level 1	XX	1.000	-	-
	…	XX	X.XXX	(X.XXX, X.XXX)	X.XXX
	Level K	XX	X.XXX	(X.XXX, X.XXX)	X.XXX
	Covariate 2				
	Level 1	XX	1.000	-	-
	…	XX	X.XXX	(X.XXX, X.XXX)	X.XXX
	Level K	XX	X.XXX	(X.XXX, X.XXX)	X.XXX
	…				
6 months	**Treatment**				
	Prednisone	XX	1.000	-	-
	Sirolimus	XX	X.XXX	(X.XXX, X.XXX)	X.XXX
	Covariate 1				
	Level 1	XX	1.000	-	-
	…	XX	X.XXX	(X.XXX, X.XXX)	X.XXX
	Level K	XX	X.XXX	(X.XXX, X.XXX)	X.XXX
	Covariate 2				
	Level 1	XX	1.000	-	-
	…	XX	X.XXX	(X.XXX, X.XXX)	X.XXX
	Level K	XX	X.XXX	(X.XXX, X.XXX)	X.XXX
	…				
12 months	**Treatment**				
	Prednisone	XX	1.000	-	-
	Sirolimus	XX	X.XXX	(X.XXX, X.XXX)	X.XXX
	Covariate 1				
	Level 1	XX	1.000	-	-
	…	XX	X.XXX	(X.XXX, X.XXX)	X.XXX
	Level K	XX	X.XXX	(X.XXX, X.XXX)	X.XXX
	Covariate 2				

	Level 1	XX	1.000	-	-
	…	XX	X.XXX	(X.XXX, X.XXX)	X.XXX
	Level K	XX	X.XXX	(X.XXX, X.XXX)	X.XXX
	…				

Inverse Probability of Missingness Weighting-adjusted [PRO score] by Treatment Group					
Assessment Time	**Sirolimus (N=)**		**Prednisone (N=)**		
	Mean	**95% CI**	**Mean**	**95% CI**	**P-value**
Baseline	XX.X	(XX.X, XX.X)	XX.X	(XX.X, XX.X)	X.XXX
Day 56	XX.X	(XX.X, XX.X)	XX.X	(XX.X, XX.X)	X.XXX
6 months	XX.X	(XX.X, XX.X)	XX.X	(XX.X, XX.X)	X.XXX
12 months	XX.X	(XX.X, XX.X)	XX.X	(XX.X, XX.X)	X.XXX

* Estimates were obtained by fitting GEE using an identity working correlation matrix, with robust standard errors used to compute 95% confidence intervals and obtain p-values from Wald tests of mean comparisons.

Clarify the population for the endpoint (n=?). If n is not the same as the primary endpoint, explain why (e.g. patient not evaluable, missing data, etc.)

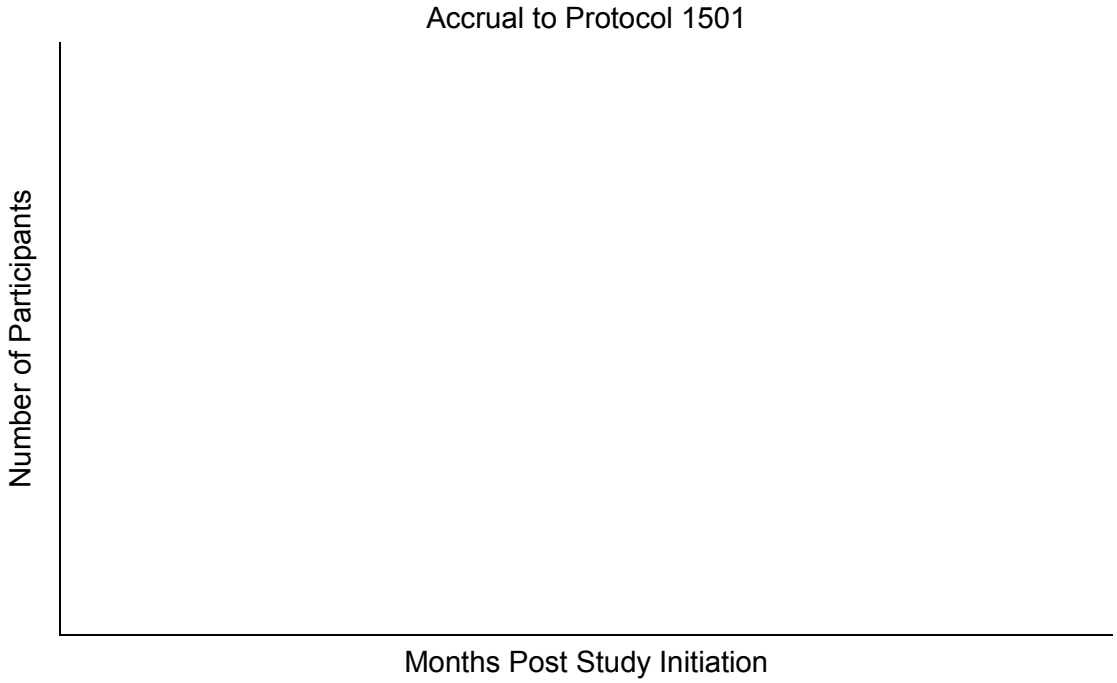
Exhibit 1501-23: Incidence of Toxicities of Grade 3-5

Toxicities by System Organ Class		
Toxicity	**Sirolimus (N=) N (%)**	**Prednisone (N=) N (%)**
Grade 3-5 Oral Mucositis	XX (XX.X%)	XX (XX.X%)
Grade 3-5 Cystitis noninfective	XX (XX.X%)	XX (XX.X%)
Grade 3-5 Acute kidney injury	XX (XX.X%)	XX (XX.X%)
Grade 3-5 Chronic kidney disease	XX (XX.X%)	XX (XX.X%)
Grade 3-5 Hemorrhage	XX (XX.X%)	XX (XX.X%)
Grade 3-5 Hypotension	XX (XX.X%)	XX (XX.X%)
Grade 3-5 Hypertension	XX (XX.X%)	XX (XX.X%)
Grade 3-5 Cardiac arrhythmia	XX (XX.X%)	XX (XX.X%)
Grade 3-5 Left ventricular systolic dysfunction	XX (XX.X%)	XX (XX.X%)
Grade 3-5 Somnolence	XX (XX.X%)	XX (XX.X%)
Grade 3-5 Seizure	XX (XX.X%)	XX (XX.X%)
Grade 3-5 Thrombotic thrombocytopenic purpura	XX (XX.X%)	XX (XX.X%)
Grade 3-5 Capillary leak syndrome	XX (XX.X%)	XX (XX.X%)
Grade 3-5 Hypoxia	XX (XX.X%)	XX (XX.X%)
Grade 3-5 Dyspnea	XX (XX.X%)	XX (XX.X%)
Grade 3-4 ALT	XX (XX.X%)	XX (XX.X%)
Grade 3-4 AST	XX (XX.X%)	XX (XX.X%)
Grade 3-4 Bilirubin	XX (XX.X%)	XX (XX.X%)
Grade 3-4 Alkaline Phosphatase	XX (XX.X%)	XX (XX.X%)
Received Dialysis? – Yes	XX (XX.X%)	XX (XX.X%)
Abnormal Liver Function? – Yes	XX (XX.X%)	XX (XX.X%)

Supplemental Exhibit 1501-1: Enrollment

A table will be provided showing actual monthly accrual for each participating center from study initiation to accrual closure.

A figure will be provided showing projected and actual accrual from study initiation to accrual closure.



Supplemental Exhibit 1501-2: Significant Protocol Deviations

A listing of significant protocol deviations will be provided to describe each deviation.

Supplemental Exhibit 1501-3: Primary Cause of Death

A table summarizing the primary cause of death by treatment group will be provided.

Supplemental Exhibit 1501-4: Adverse Events

A table summarizing the MedDRA-coded System Organ Class (SOC) of the adverse events reported will be provided by treatment group.

Supplemental Exhibit 1501-5: Serious or Grades 3-5 Adverse Events

A table summarizing the SOC of the serious or Grades 3-5 adverse events will be provided by treatment group.

Supplemental Exhibit 1501-6: Safety Monitoring (Safety Endpoints)

Figure of SPRT to illustrate safety monitoring / stopping guidelines.