Statistical Analysis Plan

A Multicenter Open-Label Phase 1b/2 Study of Ibrutinib in Steroid Dependent or Refractory Chronic Graft Versus Host Disease

Protocol PCYC-1129-CA

Version: 1.0

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Confidentiality Statement

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ABBREVIATIONS

AE	adverse event
ALT	alanine aminotransferase
ANC	absolute neutrophil count
AST	aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
cGVHD	chronic graft versus host disease
CI	Confidence interval
CNS	central nervous system
CR	complete response
CRF	case report form
CTCAE v. 4.03	Common Terminology Criteria for Adverse Events version 4.03
CYP	cytochrome P450
DLT	dose limiting toxicity
DOR	Duration of response
eCcr	estimated creatinine clearance
ECG	Electrocardiogram
EDC	electronic data capture
FDA	Food and Drug Administration
FFS	failure free survival
ILD	Interstitial Lung Disease
IRRC	Independent Response Review Committee
MedDRA	Medical Dictionary for Regulatory Activities
MTD	maximum tolerated dose
NCI	National Cancer Institute
NIH	National Institutes of Health
PCYC	Pharmacyclics, LLC
PR	partial response
RP2D	recommended phase 2 dose
SAE	serious adverse event
SAP	Statistical Analysis Plan
SD	stable disease
SI	Système international d'unités
SMQ	Standardized MedDRA Query
SOC	System Organ Class
TEAE	Treatment emergent adverse event
ULN	upper limit of normal
WHO	World Health Organization

1. Introduction

Study PCYC-1129-CA is a Phase 1b/2 open-label study designed to evaluate the safety and efficacy of ibrutinib in subjects with steroid-dependent/refractory chronic graft versus host disease (cGVHD).

Phase 1b will begin with the evaluation of the 420 mg/day dose level of ibrutinib with the potential for subsequent dose reductions if dose limiting toxicities (DLTs) are detected. A modified 3+3+3 design will be used to determine a safe dose to carry forward to Phase 2 of the study (recommended Phase 2 dose [RP2D]).

Phase 2 will evaluate the efficacy of the RP2D of ibrutinib determined in Phase 1b. Subjects will be given ibrutinib continuously along with any pre-existing immunosuppressants for cGVHD and followed for signs of progression/resolution of cGVHD.

The purpose of this statistical analysis plan (SAP) is to provide a comprehensive description of the statistical analyses for efficacy and safety data that have been outlined within the protocol of Study PCYC-1129-CA (Amendment 2, dated 21 October 2015). The analyses will be executed by the Biometrics department of Pharmacyclics unless otherwise specified.

This plan does not cover the pharmacokinetic or pharmacodynamic analyses and biomarker analysis, which will be performed and reported by the separate groups of Pharmacyclics.

1.1 Study Objectives

1.1.1 Primary Objective

The primary objective of the Phase 1b part of the study is to evaluate the safety and tolerability of ibrutinib in subjects with steroid dependent/refractory cGVHD.

The primary objective of the Phase 2 part of the study is to evaluate the clinical efficacy of ibrutinib in steroid dependent/refractory cGVHD by measuring best overall cGVHD response (National Institutes of Health [NIH]-defined complete response and partial response).

1.1.2 Secondary Objectives

Phase 1b:

- To evaluate the clinical efficacy of ibrutinib in steroid dependent/refractory cGVHD by measuring:

  Best overall cGVHD response (complete and partial response per NIH-defined cGVHD criteria)

  Rate of sustained response for at least 5 months

  Duration of response (DOR)

  Corticosteroid requirement changes over time

  Change in symptom burden measured by the Lee cGVHD Symptom Scale

Phase 2:

- To evaluate the clinical efficacy of ibrutinib in steroid dependent/refractory cGVHD by measuring:

  Rate of sustained response for at least 5 months

  Duration of response (DOR)

  Corticosteroid requirement changes over time

  Change in symptom burden measured by the Lee cGVHD Symptom Scale
- To evaluate the safety and tolerability of ibrutinib in steroid dependent/refractory cGVHD

1.1.3 Exploratory Objectives

The exploratory objective covered by this analysis plan is:

- To evaluate the clinical efficacy of ibrutinib by measuring failure free survival at 6 and 12 months

1.2 Study Design

The study will be conducted in two phases.

Phase 1b will begin with the evaluation of the safety of once daily dose (420 mg) ibrutinib with the potential for subsequent dose reductions if DLTs are detected. A modified 3+3+3 design will be used to determine a safe dose to carry forward to Phase 2 of the study. Once the RP2D is determined, Phase 2 will commence.

Phase 2 will evaluate the efficacy of the RP2D of ibrutinib determined in Phase 1b. Subjects will be given ibrutinib continuously along with their pre-existing immunosuppressant for cGVHD and followed for signs of progression/resolution of cGVHD. Approximately 34 subjects will be enrolled in Phase 2 to reach approximately 40 subjects (Phase 1b + Phase 2 subjects) treated at the RP2D.

1.3 Dosage and Administration

Three dose levels of ibrutinib may be tested: 140 mg/day, 280 mg/day, and 420 mg/day. The starting dose level is 420 mg/day and the dose level might be modified based on the DLTs.

The decision to proceed with a RP2D or to reduce the dose will be made in a Dose Level Review Meeting by the Sponsor in conjunction with the investigators after careful consideration of all available safety and laboratory information.

Following the establishment of the RP2D, the Phase 2 portion of the study will begin enrolling additional subjects.

1.4 Sample Size Justification

The Phase 1b part of the study is a modified 3+3+3 dose-finding design that is described in the protocol.

With a sample size of 40 subjects receiving the RP2D, and assuming an overall cGVHD response rate of 50%, the study is expected to have at least 90% power to show the efficacious treatment effect (the lower bound of 95% confidence interval [CI] of the response rate >25%).

1.5 Randomization and Blinding

As an open-label, single arm study, there will be no randomization or blinding of subjects.

2. Study Populations

Safety Population includes all subjects who receive at least 1 dose of ibrutinib from either Phase 1 or Phase 2 portion of the study.

All Treated Population includes all subjects who receive at least 1 dose of RP2D of ibrutinib from either the Phase 1 or Phase 2 portion of the study.

Since the Phase 1 part of the study confirmed that the first dose level is safe for cGVHD subjects and is used as RP2D, the safety population is the same as the all treated population. Therefore, the All Treated Population will be used as the primary analysis population.

Subject 003-201 was excluded from the All Treated Population because the subject had laboratory evidence of a relapse of underlying disease (AML) that was drawn before the first dose of study drug but results were available after the start of ibrutinib. The separate listings will be provided for this subject.

Response Evaluable Population includes all subjects who are in the all treated population and have an evaluable response assessment.

Response evaluable population is used for sensitivity analysis population. It will be used to evaluate dose exposure and best overall cGVHD response.

2.1 Subgroups

Subgroup analysis will be performed on the primary efficacy endpoint as well as TEAEs to assess the effect of the following factors (subgroups that have high levels of imbalance will be omitted):

1. Age (<65 vs. ≥65)
2. Gender (male vs. female).

3. General Analysis Considerations

3.1 Definitions

3.1.1 Study Day

Study day will be calculated in reference to the first dose of study drug. Study Day 1 corresponds to the date that the subject takes the first dose of study drug.

For dates before Study Day 1:

Study Day n = Date of assessment/event – Date of Study Day 1

For dates on or after Study Day 1:

Study Day n = Date of assessment/event – Date of Study Day 1 + 1 day

There will not be a Study Day 0.

3.1.2 Baseline Value

Unless otherwise specified, the baseline value is defined as the last valid measurement on or prior to the first dose of study drug

3.1.3 Postbaseline Value

The postbaseline value is defined as a measurement taken after the first dose of study drug.

For subjects with a valid, nonzero baseline value:

Change from baseline = postbaseline value – baseline value;

% change from baseline = (change from baseline/baseline)*100.

3.1.4 Duration of Treatment

Duration of treatment will be calculated from the date of the first dose of study drug to the date of the last dose of study drug, as follows:

Duration of treatment = date of last dose of study drug – date of first dose of study drug + 1 day.

3.1.5 Time on Study

Time on Study will be calculated from the date of the first dose of study drug to the study exit date or the last known alive date if the subjects are still in the study, as follows:

Time on Study = study exit date/last known alive date – date of first dose of study drug + 1 day.

For subjects who did not take the study drug, Time on Study is calculated from the date of enrollment to the study exit date.

3.1.6 Age

Age in years will be the subject age at the date of enrollment.

3.1.7 Dose Intensity

Dose intensity (mg/day) is defined as the ratio of total dose received in mg and treatment duration in days.

3.1.8 Relative Dose Intensity

Relative dose intensity (%) is defined as the percentage of total cumulative dose administered (mg) versus the total expected dose (mg). Total cumulative dose administered is the sum of daily dose taken over the whole study course; and total expected dose (mg) is the product of the duration of the treatment (day) and the protocol assigned daily dose. Relative dose intensity is calculated by total cumulative dose administered / total expected dose × 100%.

3.1.9 Estimate Creatinine Clearance Rate

Estimated creatinine clearance rate (eCcr) will be calculated using the Cockcroft-Gault formula

$$eCcr(mL/\min) = \frac{(140 - Age) \times Weight\ \ (kg) \times [0.85\ \ if\ \ Female]}{72 \times Serum\ \ Creatinine\ \ (mg/dL)}$$

When serum creatinine is measured in μmol/L, the formula is

$$eCcr(mL/\min) = \frac{(140 - Age) \times Weight\ \ (kg) \times C}{Serum\ \ Creatinine\ \ (\mu mol/L)}$$

using a constant *C* of 1.23 for men and 1.04 for women.

In this calculation, if weight is not measured at the same visit as creatinine, the weight measured prior and closest to the creatinine collection time will be used.

3.1.10 Absolute neutrophil count

Absolute neutrophil count (ANC) is calculated by

ANC = (% neutrophil+% bands) × White blood cell / 100

where white blood cell is in 10^9/L.

3.2 Visit Windows

Visit windows have been given in the Time and Events Schedule of the protocol. For by-visit analysis, visit will be used to associate assessment with a scheduled visit and will be created in reference to the date of first dose of study drug to assign visit number based on evaluation date. Details for target date for each scheduled visit and time interval between scheduled visits are provided in 20.

- If more than one assessment falls into a given visit window, the non-missing one closest to the target date will be used. If two assessments are equally close to the target day, the earlier assessment will be used.

3.3 Missing and Incomplete Data

In order to achieve the goal of a well-conducted clinical study according to Good Clinical Practice, every effort will be made to collect all data. However, despite best efforts, it may be inevitable that some data may be missing or incomplete. In the subject data listing, the available data, including partial data will be presented as they are recorded on the case report forms (CRFs).

Time-to-event or duration-of-event endpoints will be based on the study day rather than visit number or visit label. No imputation of missing values will be performed for efficacy data unless otherwise specified.

No imputation of missing values for safety data will be performed unless otherwise specified.

3.3.1 Missing Date of the Last Dose of Study drug

When the date of the last dose of the study drug is missing for a subject in the All Treated Population, all efforts should be made to obtain the date from the Investigator. If it is still missing after all efforts are made, the information will not be imputed. The subject might be excluded from some analyses due to the missing information.

3.3.2 Missing Date Information for Safety Endpoints

For missing or partial start and end dates for AEs, medical history, prior therapy and concomitant medication, no imputation will be performed. However, a conservative approach will be taken when performing the related analyses. If the available information is not enough to judge whether an event or a therapy duration has overlapped with study treatment duration, events reported on AE pages will be taken as treatment emergent AEs, events reported on medical history page will be treated as prior medical condition, prior or concomitant therapy will be considered as continuing therapy which started prior to first study treatment.

However, an intermediate imputation of partial dates may be taken in order to calculate the study day for AEs, medical history, prior therapy and concomitant medications. This is just for estimation of the timing of events relative to the study course. All missing or partial dates should remain the same values as they were recorded on the CRFs. The intermediate imputation rules are:

If only day is missing, then the 15th of that month will be used.

If only year is present, then June 30th will be used.

If such imputed date for prior therapies or initial diagnosis is on or after the date of the first dose of study drug, then date of the first dose – 1 day will be used. If such imputed date for the start or end of subsequent therapies is before date of last dose of study drug, then date of last dose of study drug +1 day will be assumed. If an imputed start date of prior or subsequent therapy is after the end date, the end date will be used. If an imputed end date of prior or subsequent therapy is before its start date, the start date will be used.

If an imputed AE start date is in the same month and year as the first dose date of study drug but on an earlier date, the first dose date will be used. If an imputed AE start date is

in the same month and year as the date of 30 days post the last dose of study drug but on a later date, the date of 30 days post the last dose will be used. If an imputed AE start date is after the AE end date, the AE end date will be used.

If the imputed date is for an AE end date and is after the death date, then the death date will be used, or if the imputed AE end date is before the AE start date, then the AE start date will be used.

The average daily use of corticosteroid will be used to evaluate the treatment effect. All efforts should be made to obtain the date from the Investigator. If it is still missing after all efforts are made, the information might be imputed with a conservative approach. If a date was missed in the middle of other corticosteroid uses, we might need to fill this dose to the whole gap between the records with imputation.

3.4 Conventions

Continuous variables will be summarized with descriptive statistics (mean, standard deviation, median, quartiles, minimum, and maximum). Standard deviation can be replaced by standard error for special requirement. Categorical variables will be summarized using frequencies and percentages.

In efficacy analysis, month is calculated by cycle (28 days). For the analysis other than efficacy, the following rules will be used for the days to months/years conversion:

- 1 month = 30.4375 days;
- 1 year = 365.25 days.

All data collected on the CRF will be presented in data listings upon request by the Regulatory agency. All statistical analyses will be performed using SAS® version 9.2 or higher.

4. Subject Information

4.1 Subject Enrollment

Subject enrollment will be summarized by study center as based on all enrolled subjects.

4.2 Subject Disposition

The information will be summarized as follows for subject disposition:

- Subject status for the study
- Reason for study termination for subjects who were off the study
- Time on study
- Subject status for the study drug
- Reason for study treatment discontinuation for subjects who discontinued study drugs

4.3 Important Protocol Deviations

In general, protocol violations/deviations will be reviewed by the study team during the study, and important protocol deviations will be determined based on the review. The information of important protocol deviations will be generated based on the review outcome for all subjects.

4.4 Demographics and Baseline Characteristics

All demographic and baseline characteristics will be summarized for the all treated population.

The demographics include:

- Age
- Gender, race, and ethnicity

The baseline characteristics include:

- Weight and height
- Estimated creatinine clearance rate (eCcr)
- Estimated creatinine clearance rate groups (< 30 mL/min; 30 – < 60 mL/min, >= 60 mL/min)
- Baseline hemoglobin and platelets

4.5 Baseline Disease Characteristics and Baseline Medications

The history information related to the disease will be summarized. The key baseline characteristics include:

- Months from Last Transplantation to Enrollment, which is defined as the time period between the last transplantation and enrollment
- Months from Initial cGVHD Diagnosis Date, which is defined as the time period between the initial cGVHD diagnosis and enrollment
- Months from Transplantation to initial cGVHD diagnosis date
- Karnofsky performance status score at baseline
- Number of prior cGVHD treatment regimens
- Organs involved in cGVHD

4.6 Concomitant Medications

Reported medications will be coded to a generic name and an Anatomical Therapeutic Chemical (ATC) class according to World Health Organization (WHO) Drug dictionary and will be summarized.

Medication that was taken before the first dose of the study drug is called prior medication. Concomitant medications are defined as medications that were taken between the date of the first dose of study drug and the date of the last dose of study drug.

Concomitant medications will be summarized by therapeutic class and preferred term. The summary of usage of CYP3A inhibitors as well CYP3A inducers will be provided separately.

The summary of usage of anticoagulants and antiplatelets will also be provided.

Subsequent cGVHD therapies taken after the start of study drug will be summarized separately.

4.7 Extent of Study drug Exposure

The exposure to study drugs will be summarized. The following parameters will be summarized when applicable:

- Duration of treatment
- Cumulative dose received on study
- Dose intensity
- Relative dose intensity
- Dose reduction due to AE
- Dose interruption with 7 days or more due to AE

5. Efficacy Analysis

Unless specified otherwise, all information from the Phase 1b and Phase 2 parts of the study will be combined for efficacy analysis. The primary population used to evaluate efficacy is All Treated Population and where applicable, the response evaluable analysis set will be used as a sensitivity analysis to assess the robustness of the results.

5.1 Primary Endpoint

The primary efficacy endpoint is the best overall cGVHD response rate during the study based on investigator assessments. To assess the primary endpoint, the study used the 2005 NIH Consensus Panel Response criteria with two modifications based on the updated 2014 NIH Consensus Panel Response criteria: 1) "Not Evaluable" can be used for assessments where there is another non-cGVHD cause for the abnormalities documented and 2) a change in cGVHD organ score from 0 to 1 is no longer considered progression as is the case per the 2005 NIH cGVHD Response Criteria.

Best overall cGVHD response rate is defined as the proportion of subjects who achieve a NIH-defined complete response or partial response. The response rate and its 95% confidence interval (CI) will be calculated based on the exact test for binomial distribution. If the lower bound of the CI of the response rate is ≥25%, the primary efficacy objective is achieved.

5.2 Secondary Endpoints

In order to preserve the study wise two-sided type I error rate of 0.05, rate of sustained response will be tested at the two-sided significance level of 0.05 if the primary endpoint, best overall cGVHD response rate, achieves statistical significance. Other secondary endpoints will be summarized with descriptive statistics. No formal statistical testing is planned for the other secondary endpoints.

5.2.1 Rate of Sustained Response

Sustained response is defined as NIH-defined response that sustain continuously for at least 5 months (140 days). Considering 3 days visit window allowed by protocol, the bound of sustained response is defined as 137 days. Intermittent SD assessment between response assessments is allowed. Of the total number of subjects who responded to study treatment, the proportion of subjects who meet the sustained response criterion will be summarized in the same manner as the primary endpoint. If the lower bound of the CI of the response rate is ≥25%, this secondary objective is achieved.

5.2.2 Duration of Response

Duration of Response (DOR) is defined as the interval between the date of initial documentation of a response, and the date of first documented evidence of progressive disease, death, or date of censoring if applicable, for responders only. The distribution (median and Kaplan-Meier curve) will be provided using Kaplan-Meier estimates to evaluate DOR. DOR will be right censored based on Table 1 for all responders:

Table 1: Date of Event or Censoring for Duration of Response

Situation	Date of DOR event or Censoring	Outcome
Death or disease progression occurred on or before the start date of subsequent cGVHD treatment documented at scheduled disease assessments or between two scheduled disease assessments.	Earliest date of adequate disease assessment documenting disease progression or date of death, whichever occurs first.	Progressed
New subsequent cGVHD treatment before disease progression	Date of last adequate disease assessment prior to or on start date of the new subsequent cGVHD treatment	Censored
Not known to have progressed or died at the data analysis cutoff date (this includes subjects who were known to have progressed or died after the data analysis cutoff date)	Date of last adequate disease assessment showing no evidence of disease progression.	Censored

For subjects who met more than one censoring condition, DOR will be censored according to the earliest censoring condition/date. For subjects who have incomplete date for initiation of subsequent cGVHD treatment, the partial date will be imputed as the earliest possible date that incorporates the available information from the partial date and does not contradict last dose date of study drug.

5.2.3 Corticosteroid Requirement Changes over Time

Systemic corticosteroid therapy for cGVHD will be monitored throughout the study. The corticosteroid dose level will be measured by the daily dose amount versus the weight of subject (mg/kg/day). For the days without weight measurement, the last observed weight measurement will be used. Considering the frequency of corticosteroid use might not be once daily, we use weekly average daily dose instead of the actual daily dose. The average corticosteroid dose level in each week is calculated by

Sum of total corticosteroid dose used in this week / 7

If a subject terminated the study drug in the middle of the week, the average corticosteroid dose level in that week will be calculated by

Sum of total corticosteroid dose used in the week before the study drug termination / actual days in the week up to the last dose of study drug.

Evaluation of systemic use of corticosteroid therapy will be performed for those subjects with SD or PD as their best overall response, and separately for subject with a best overall response of PR or CR.

5.2.4 Change in Lee cGVHD Symptom Scale

Subject-reported improvement in symptom burden will be evaluated. The symptom burden is measured according to the Lee cGVHD Symptom Scale (Lee 2002). There are 7 domains, and each has several items.

Subscale	Related Items	Maximum number of missing items to get a valid score
Skin	1, 2, 3, 4, 5	2
Energy	14, 21, 22, 23, 24, 25, 26	3
Lung	12, 13, 15, 16, 27	2
Eye	6, 7, 8	1
Nutrition	11, 17, 18, 19, 20	2
Mouth	9, 10	1
Psychological	28, 29, 30	1

A score is calculated for each subscale by taking the mean of all items completed if more than 50% were answered and normalizing to a 0 to 100 scale. A total summary score is calculated as the average of these 7 subscales if at least 4 subscales have valid scores. The SAS code copied from Lee's website for the calculation is in Appendix 8.2. A summary of total scores as well as each subscale scores for Lee cGVHD symptom scale will be performed throughout the study.

A change in >7 points on the Lee cGVHD Symptom Scale will be considered significant and relates to improvement in quality of life (Lee 2006). A summary of the proportion of subjects who have decreases of at least 7 points in Lee cGVHD symptom scale during the study will be performed.

Evaluation of Lee cGVHD Symptom Scale will be performed for those subjects with SD or PD as their best overall response, and separately for subject with a best overall response of PR or CR.

5.3 Exploratory Endpoints

The exploratory endpoint covered in this analysis plan is failure-free survival.

Failure free survival (FFS) is defined as no death, no relapse of underlying malignancy, and no new systemic immunosuppressive therapy for cGVHD. FFS will be right censored based on Table 2:

Table 2: Date of Event or Censoring for Failure Free Survival

Situation	Date of FFS event or Censoring	Outcome
Death.	Date of death	Event
New subsequent cGVHD treatment	Date of starting the new subsequent cGVHD treatment	Event
Recurrent of malignancy	Start date of recurrent of malignancy	Event
Not known to have event at the data analysis cutoff date (this includes subjects who were known to have event after the data analysis cutoff date)	Date of last known date showing no evidence of event.	Censored

The distribution (median and Kaplan-Meier curve) will be provided using Kaplan-Meier estimates to evaluate FFS.

6. Safety

DLT review to determine RP2D will be performed in the Dose Level Review Meeting by the Sponsor in conjunction with the investigators after careful consideration of all available safety and laboratory information. This analysis plan will not cover this procedure.

Safety data collected in both Phase 1b and Phase 2 will be summarized together. Unless specified otherwise, all safety analyses will be based on All Treated Population.

6.1 Adverse Events

The verbatim terms used in the CRF by investigators to identify adverse events (AEs) will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Adverse events will be graded by the investigator according the National Cancer Institute common terminology criteria for adverse events (CTCAE) Version 4.03.

Drug-related adverse events are those assessed by investigator as being possibly related or related to study drug.

Treatment-emergent AEs are defined as those events that 1) occur on or after the first day of study drug, and within 30 days following the last dose of study drug or initiation of subsequent cGVHD therapy; 2) any event with missing onset date and its resolution date is during the treatment phase unless the event was indicated in the CRF that was present

before the first day of study drug; 3) any event that is considered study drug-related regardless of the start date of the event; or 4) any event that is present at baseline but worsens in severity or is subsequently considered drug-related by the investigator.

For each adverse event, the percentage of subjects who experience at least 1 occurrence of the given event will be summarized. In the event a patient experiences repeat episodes of the same AE, then the event with the highest severity grade will be used for purposes of incidence tabulations.

Summaries of AEs include:

- Incidence of AEs and serious adverse events (SAEs) by System Organ Class (SOC) and preferred term
- Incidence of AEs and SAEs by preferred term
- Incidence of drug-related AEs and SAEs

AE leading to study treatment discontinuation for the subjects who discontinued study drug due to AE, AE leading to dose reduction, and AEs leading to death will be summarized.

6.1.1 Adverse Events of Special Interest – Major Bleeding

Hemorrhagic events will be identified by hemorrhage Standardized MedDRA Query [SMQ] excluding laboratory terms and be tabulated. Major hemorrhage is a subset of hemorrhagic events which are grade ≥ 3 or serious or belong to central nervous system (CNS) hemorrhage/hematoma.

6.1.2 Other Safety Observations

Other Malignancies

Other malignancies are defined as new malignant tumors including solid tumors, skin malignancies and hematologic malignancies and are to be reported. They will be summarized based on following categories: melanoma skin cancer, non-melanoma skin cancer and non-skin cancer. Relapse of the underlying malignancy that was the basis for transplantation will not be included in this analysis.

Hypersensitivity Reactions

Hypersensitivity Reactions include angioedema, anaphylactic reaction, anaphylactoid reaction, anaphylatic shock, anaphylactoid shock, urticaria, drug hypersensitivity, and hypersensitivity. All treatment emergent hypersensitivity reaction events will be evaluated based on preferred terms.

Hypertension

Hypertension includes hypertension, essential hypertension, hypertensive crisis, blood pressure increase, systolic hypertension, and retinopathy hypertensive. All treatment emergent hypertension events will be summarized by preferred terms.

Interstitial Lung Disease

Interstitial Lung Disease **(ILD)** will be determined based on ILD SMQ excluding radiation alveolitis, radiation fibrosis - lung, and radiation pneumonitis, pulmonary radiation injury and transfusion-related acute lung injury. All treatment emergent ILD events will be summarized by preferred terms.

Severe Cutaneous Adverse Reaction

Severe Cutaneous Adverse Reaction (SCAR) will be determined based on following prefer terms:

Skin and subcutaneous tissue disorders SOC	Acute generalised exanthematous pustulosis
	Cutaneous vasculitis
	Dermatitis bullous
	Dermatitis exfoliative
	Dermatitis exfoliative generalised
	Drug reaction with eosinophilia and systemic symptoms
	Epidermal necrosis
	Erythema multiforme
	Exfoliative rash
	Oculomucocutaneous syndrome
	Skin necrosis
	Stevens-Johnson syndrome
	Toxic epidermal necrolysis
	Toxic skin eruption

All treatment emergent SCAR events will be summarized by preferred terms.

6.2 Clinical Laboratory Tests

All laboratory values will be converted to SI units and classified as normal, low, or high based on normal ranges of University of California, San Francisco.

The gradable laboratory parameters will be graded using the NCI CTCAE v4.03. The worst postbaseline toxicity grade will be summarized for hematologic and chemistry parameters.

Shift table will also be used to evaluate creatinine clearance.

6.3 Vital Signs

Body temperature, heart rate, blood pressure, respiratory rate, and weight will be collected during the study. Descriptive statistics and change from baseline will be provided over time.

7. References

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8. Appendix

8.1 Visit Window for Analysis

Details for target date for each scheduled visit and time interval between scheduled visits are provided in the table below:

Visit	Start Day	Target Day	End Day
Baseline	Last measurement prior to or on the first dose date		
Cycle Visits			
Week 5	2	29	43
Week 13	44	85	127
Week 25	128	169	211
Week 37	212	253	295
Week 49	296	337	379
Week 61	380	421	463
Week 73	464	505	547
Week 85	548	589	631
Week 97	632	673	715
Week x (every 12 weeks, where x ≥ 97)	(x-1)*7-40	(x-1)*7+1	(x-1)*7+43

8.2 SAS code to calculate Lee cGVHD symptom scale

This code is copied from the website of Stephanie Lee Lab (http://research.fhcrc.org/lee/en/research-resources.html)

```
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,b3q,b3r,b3s,b3t) le 2 then
     sx_nutrition=mean(b3k,b3q,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;
```