STATISTICAL ANALYSIS PLAN

Study Title:	A Phase 2, Randomized, Double-blind, Placebo-controlled Study to Assess the Safety and Efficacy of Filgotinib and GS-9876 in Female Subjects with Moderately-to-Severely Active Cutaneous Lupus Erythematosus (CLE)
Name of Test Drug:	Filgotinib and Lanraplenib (GS-9876)
Study Number:	GS-US-436-4092
Protocol Version (Date):	Amendment 4 (15 October 2018)
Analysis Type:	Final
Analysis Plan Version:	Version 1.0
Analysis Plan Date:	13 May 2019
Analysis Plan Author(s):	PPD

CONFIDENTIAL AND PROPRIETARY INFORMATION

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LIST OF ABBREVIATIONS

AE	adverse event
ALT	alanine aminotransferase
ANCOVA	Analysis of covariance
AST	aspartate aminotransferase
BLQ	below the limit of quantitation
BMI	body mass index
CFR	Code of Federal Regulations
CI	confidence interval
CK	creatine kinase
CCLE	chronic cutaneous lupus erythematosus
CLASI	Cutaneous Lupus erythematosus disease Area and Severity Index
CLE	cutaneous lupus erythematosus
CMH	Cochran-Mantel-Haenszel
CRF	case report form
CSR	clinical study report
CTCAE	Common Toxicity Criteria for Adverse Events
DILI	drug-induced liver injury
DLQI	Dermatology Quality of Life Index
DMARD	Disease-modifying antirheumatic drug
DMC	data monitoring committee
ECG	electrocardiogram
EDC	electronic data capture
ET	early termination
FAS	Full Analysis Set
Hb	hemoglobin
HLT	high-level term
ICH	International Conference on Harmonization (of Technical Requirements for Registration of Pharmaceuticals for Human Use)
IXRS	interactive voice or web response system
LLT	lower-level term
LOQ	limit of quantitation
MACE	major adverse cardiovascular event
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed-effects model for repeated measures
MST	MedDRA search term
PK	pharmacokinetic
PT	preferred term
PTM	placebo to match
Q1, Q3	first quartile, third quartile

QRS	electrocardiographic deflection between the beginning of the Q wave and termination of the S wave representing time for ventricular depolarization
QT	electrocardiographic interval between the beginning of the Q wave and termination of the T wave representing the time for both ventricular depolarization and repolarization to occur
QTc	QT interval corrected for heart rate
QTcF	QT interval corrected for heart rate using Fridericia's formula
RA	rheumatoid arthritis
RR	electrocardiographic interval representing the time measurement between the R wave of one heartbeat and the R wave of the preceding heartbeat
SAE	serious adverse event
SCLE	subacute cutaneous lupus erythematosus
SAP	statistical analysis plan
SD	standard deviation
SI (units)	international system of units
SLE	systemic lupus erythematosus
SMQ	Standardized Medical Queries
SOC	system organ class
TEAE	treatment-emergent adverse event
TFLs	tables, figures, and listings
TSQM	Treatment Satisfaction Questionnaire for Medication
ULN	upper limit of normal
VAS	visual analog scale
VR	ventricular rate
WHO	World Health Organization

PHARMACOKINETIC ABBREVIATIONS

AUC_{last}	area under the concentration versus time curve from time zero to the last quantifiable concentration
AUC_{tau}	area under the concentration versus time curve over the dosing interval
C_{last}	last observed quantifiable concentration of the drug
C_{max}	maximum observed concentration of drug
C_{tau}	observed drug concentration at the end of the dosing interval
CLss/F	apparent oral clearance after administration of the drug: at steady state: CLss/F = Dose/AUC_{tau} , where "Dose" is the dose of the drug
$t_{1/2}$	estimate of the terminal elimination half-life of the drug, calculated by dividing the natural log of 2 by the terminal elimination rate constant (λ_z)
T_{last}	time (observed time point) of C_{last}
T_{max}	time (observed time point) of C_{max}
λz	terminal elimination rate constant, estimated by linear regression of the terminal elimination phase of the concentration of drug versus time curve

1. INTRODUCTION

This statistical analysis plan (SAP) describes the statistical analysis methods and data presentations to be used in tables, figures, and listings (TFLs) in the clinical study report (CSR) for Study GS-US-436-4092. This SAP is based on the study protocol amendment 4 dated 15 October 2018 and the electronic case report form (eCRF). The SAP will be finalized before the database freeze for the primary analysis. Any changes made after the finalization of the SAP will be documented in the CSR.

1.1. Study Objectives

The primary objective of this study is as follows:

- To evaluate the efficacy of filgotinib and lanraplenib in female subjects with moderately-to-severely active CLE

The secondary objectives of this study are as follows:

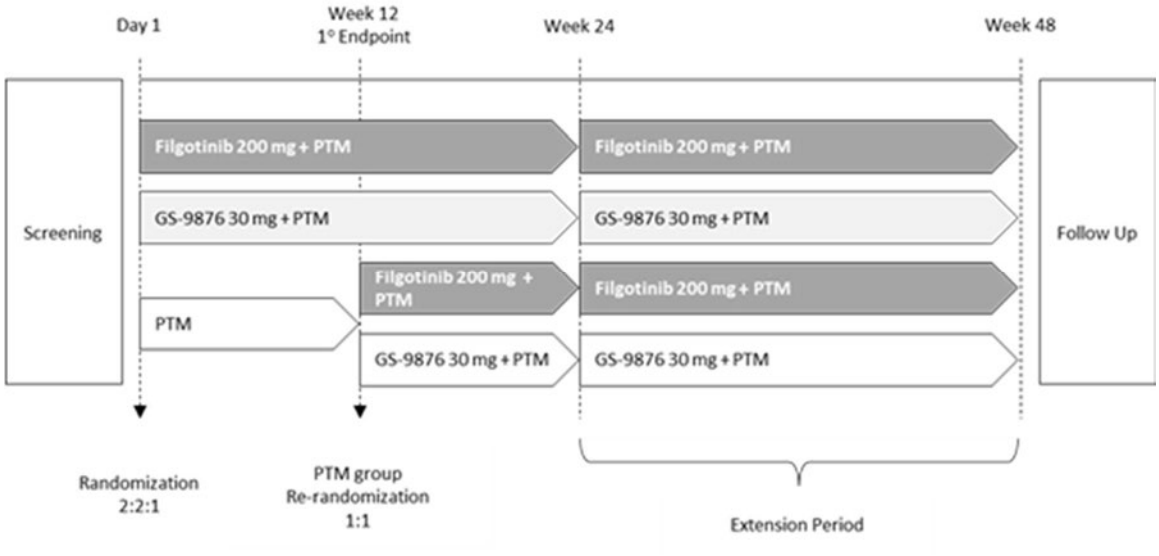
- To evaluate the safety and tolerability of filgotinib and lanraplenib in moderately-to-severely active CLE

The exploratory objectives of this study are as follows:

1.2. Study Design

This is a Phase 2, randomized, double-blind, placebo-controlled study to evaluate the safety and efficacy of filgotinib and lanraplenib in female subjects with moderately-to-severely active CLE.

A schematic of this study is as below:



Eligible subjects will be randomized 2:2:1 in a blinded fashion to 1 of 3 arms and receive daily oral doses of the following study drugs starting on Day 1 for 12 weeks:

Table 1. Study Treatments

Arm	Study Drugs
Filgotinib 200 mg (n=20)	filgotinib 200 mg + PTM lanraplenib 30 mg
Lanraplenib 30 mg (n=20)	lanraplenib 30 mg + PTM filgotinib 200 mg
Placebo (n=10)	PTM filgotinib 200 mg + PTM lanraplenib 30 mg

PTM = placebo to match

On Day 1, randomization will be stratified by two factors: (i) disease subtype (chronic cutaneous lupus erythematosus [CCLE] (eg, discoid lupus erythematosus [DLE]) vs. subacute cutaneous lupus erythematosus [SCLE]) and (ii) concurrent background disease-modifying antirheumatic drug [DMARD] use vs. no use.

At Week 12, upon completion of all scheduled assessments, subjects in placebo group will be re-randomized to receive filgotinib 200 mg + PTM lanraplenib 30 mg once daily or lanraplenib 30 mg + PTM filgotinib 200 mg once daily for the remainder of the study in a blinded fashion. Dosing and assessments for all subjects will continue through Week 24.

Subjects who have not permanently discontinued study drug dosing during the first 24-week period may enter the subsequent 24-week extension period where they will continue to receive their assigned dose of study drug, in a blinded fashion.

1.3. Sample Size and Power

With a sample size of 50 subjects (20 in each active treatment arm and 10 in the placebo arm), there is a 79% power to detect a 2 point difference between each active arm and the placebo arm in the primary endpoint, change from baseline in CLASI activity score at week 12, using a 2-sided 0.1 level test. This power calculation assumes a common standard deviation of 2 and a 10% drop-out rate per arm.

2. TYPE OF PLANNED ANALYSES

2.1. Interim Analyses

2.1.1. External Safety DMC

An external multidisciplinary Data Monitoring Committee (DMC) will review the progress of the study and perform interim reviews of the safety data in order to protect subject welfare and preserve study integrity. To ensure the best interests of the participants, the DMC will recommend to the sponsor if the nature, frequency, and severity of adverse effects associated with the study treatment warrant the early termination of the study, the continuation of the study, or the continuation of the study with modifications.

The initial review will be conducted after 50% of subjects have completed 12 week of treatment or have discontinued study early. Additional meetings may be scheduled as necessary.

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

2.1.2. Internal Data Monitoring

To assess the safety and efficacy of lanraplenib and filgotinib for further planning and development of these products, a Gilead internal unblinded team independent of the blinded study team will be assembled. This group will consist of at least one representative from Clinical Research, Biostatistics, and Pharmacovigilance/Epidemiology, and may include other personnel as necessary. The Gilead internal unblinded team will be granted access to unblinded clinical data including treatment assignments to closely monitor study progress and drug safety. The membership, responsibilities, conduct, specific activities and meeting schedule of the unblinded internal team will be documented in a Gilead Internal Unblinded Team Charter.

To mitigate the risks of inadvertently releasing the treatment information to the sites and subjects, the internal team will keep the unblinded information confidential and will not communicate the information to the blinded study team, site staff or subjects. Data unblinding due to medical emergency will follow standard Gilead procedures.

2.2. Primary (Week 12) Analysis

A planned Week 12 analysis will be conducted after all subjects have either completed the Week 12 visit or have prematurely discontinued from the study.

A pre-specified sponsor team (members are not actively involved in the conduct of the study) will review the Week 12 unblinded safety and efficacy analysis results. A memo and a list will be maintained which documents the individuals granted access to the Week 12 unblinded results along with the justification for unblinding in accordance with Gilead SOPs. The Interim Analysis Data Integrity and Communication Plan will be developed prior to unblinding. The Study Management Team members with direct involvement in the conduct of the study will remain

blinded to treatment assignments throughout the trial, until all subjects have completed all planned study visits and the database has been locked.

All planned analyses of the placebo-controlled period described in this SAP will be provided to the Designated Unblinded Study team (see the Data Integrity and Communication Plan) and will contain individual subject treatment assignments.

The following primary and secondary analysis reports and summaries may be provided to the project planning team (specified Gilead executives and the designated study team members):

- Demographics (Total column only)
- Baseline characteristics (Total column only)
- Disposition (Total column only)
- Primary Analysis – Change from Baseline in CLASI-A at Week 12
- Secondary Endpoints Analysis - Categorical changes in CLASI-A at Week 12
- Other analysis as deemed necessary for program planning purposes

These reports will contain unblinded treatment group level information (not the individual subject treatment assignments).

2.3. Final Analysis

After all subjects have completed the study or discontinue early, outstanding data queries have been resolved or adjudicated as unresolvable, and the data have been cleaned and finalized, the study blind will be broken and the final analysis of the data will be performed.

3. GENERAL CONSIDERATIONS FOR DATA ANALYSES

Analysis results will be presented using descriptive statistics. For categorical variables, the number and percentage of subjects in each category will be presented; for continuous variables, the number of subjects (n), mean, standard deviation (SD) or standard error (SE), median, first quartile (Q1), third quartile (Q3), minimum, and maximum will be presented.

All statistical tests will be 2-sided and performed at the 0.1 significance level unless otherwise specified.

By-subject listings will be presented for all subjects in the All Randomized Analysis Set and sorted by subject ID number, visit date, and time (if applicable). Data collected on log forms, such as adverse events, will be presented in chronological order within the subject. The treatment group to which subjects were randomized will be used in the listings. Age, sex at birth, race, and ethnicity will be included in the listings, as space permits.

3.1. Analysis Sets

Analysis sets define the subjects to be included in an analysis. Analysis sets and their definitions are provided in this section. Subjects included in each analysis set will be determined before the study blind is broken for analysis. The analysis set will be identified and included as a subtitle of each table, figure, and listing.

For each analysis set, the number and percentage of subjects eligible for inclusion, as well as the number and percentage of subjects who were excluded with the reasons for their exclusion, will be summarized by treatment group.

A listing of reasons for exclusion from analysis sets will be provided by subject.

3.1.1. All Randomized Analysis Set

All Randomized Analysis Set includes all subjects who were randomized in the study. This is the primary analysis set for by-subject listings.

3.1.2. Full Analysis Set

The Full Analysis Set (FAS) includes all subjects who were randomized and received at least one dose of study drug (filgotinib, lanraplenib or placebo). This is the primary analysis set for efficacy analyses.

3.1.3. Safety Analysis Set

The Safety Analysis Set includes all subjects who received at least 1 dose of study drug. This is the primary analysis set for safety analyses.

3.1.4. Per-Protocol Analysis Set

The per-protocol analysis will not be performed due to a limited number of subjects in the study.

3.1.5. Pharmacokinetic Analysis Set

The Pharmacokinetic (PK) Analysis Set will include all randomized subjects who took at least 1 dose of study drug and have at least 1 non-missing post-dose concentration value reported by the PK laboratory. This is the primary analysis set for all PK analyses. Within the PK Analysis Set, those subjects with PK exposure data successfully derived from the population PK modeling (if applicable) will be included in the analyses related to PK exposure.

3.1.6. Biomarker Analysis Set

The primary analysis set for biomarker analyses will be the Biomarker Analysis Set, which includes all randomized subjects who received at least one dose of study drug and have at least one baseline measurement available for the specific parameter of interest.

3.2. Subject Grouping

In the FAS and PP Analysis Set, subjects will be grouped according to the treatment to which they were initially randomized at Study Day 1. For the analyses based on the Safety Analysis Set, subjects will be grouped according to the actual treatment that they received. The actual treatment received will be considered to differ from the randomized treatment only when subject's actual treatment differs from randomized treatment for the entire treatment period.

For the analysis of the placebo-controlled period (up to week 12), subjects will be presented by three treatment groups:

- Filgotinib 200 mg
- Lanraplenib 30 mg
- Placebo

For the analyses for the entire study duration, subjects will be grouped into five treatment groups as specified in Table 2.

Table 2. Treatment Groups for the Entire Study Duration

Lanraplenib 30 mg	Lanraplenib 30 mg from Study Day 1
Filgotinib 200 mg	Filgotinib 200 mg from Study Day 1
Placebo/Lanraplenib 30 mg	Placebo up to Week 12 and lanraplenib 30 mg after Week 12
Placebo/Filgotinib 200 mg	Placebo up to Week 12 and filgotinib 200 mg after Week 12
Placebo	Placebo group with study drug withdrawn prior to or at Week 12 (did not receive drug assigned at Week 12)

For the PK analyses, subjects will be grouped according to the actual treatment they received.

3.3. Strata and Covariates

Subjects will be randomly assigned to treatment groups via the interactive voice or web response system (IXRS) in a 2:2:1 ratio to lanraplenib 30 mg, filgotinib 200 mg and placebo using a stratified randomization schedule. Stratification will be based on the following variables:

- Disease subtype (chronic cutaneous lupus erythematosus [CCLE] vs subacute cutaneous lupus erythematosus [SCLE])
- Concurrent background systemic disease-modifying antirheumatic drug [DMARD] use

For the stratification, systemic DMARDs administration will be considered. If there are discrepancies in stratification factor values between the IXRS and the clinical database, the values recorded in the clinical database will be used in the analyses. If it is impossible to derive the stratification factor from the clinical database due to missing values then the data from IXRS will be used.

Efficacy endpoints will be evaluated using stratification factors as covariates or stratification variables for analyses, as specified in Section 6.

For efficacy endpoints, the baseline value of the efficacy variable(s) will be included as a covariate in the efficacy analysis model.

3.4. Examination of Subject Subgroups

The primary and secondary efficacy endpoints will be examined using the following subgroups:

- Age (< 50 years and ≥ 50 years)
- Disease subtype (CCLE, SCLE)
- Concurrent background disease-modifying antirheumatic drug [DMARD] use at baseline (Yes, No)
- Concurrent use of systemic (oral) corticosteroids at baseline (Yes, No)
- Diagnosis of SLE (Yes, No)
- Duration of the disease (<10 years, >= 10 years)
- Baseline CLASI-A (<15, >=15)

The descriptive statistics for each treatment group within the corresponding subgroup will be provided.

3.5. Multiple Comparisons

All significance testing will be done at the significance level of 0.1 with no multiplicity adjustment in this proof-of-concept study, unless otherwise specified.

3.6. Missing Data and Outliers

3.6.1. Missing Data

In general, missing data will not be imputed unless methods for handling missing data are specified. Exceptions are presented in this document.

For missing last dosing date of study drug, imputation rules are described in Section 4.2.1. The handling of missing or incomplete dates for AE onset is described in Section 7.1.5.2, and for prior and concomitant medications in Section 7.4. Imputation rules adopted in the efficacy analyses are specified in Section 6.

3.6.2. Outliers

Outliers will be identified during the data management and data analysis process, but no sensitivity analyses will be conducted. All data will be included in the data analysis.

3.7. Data Handling Conventions and Transformations

In general, age (in years) on the date of the first dose of study drug will be used for analyses and presentation in listings. If an enrolled subject was not dosed with any study drug, the randomization date will be used instead of the first dosing date of study drug. For screen failures, the date the informed consent was signed will be used for age calculation. If only the birth year is collected on the CRF, "01 July" will be used for the unknown birth day and month for the purpose of age calculation. If only birth year and month are collected, "01" will be used for the unknown birth day.

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

- A value that is 1 unit less than the LOQ will be used to calculate descriptive statistics if the datum is reported in the form of "< x" (where x is considered the LOQ). For example, if the values are reported as < 50 and < 5.0, values of 49 and 4.9, respectively, will be used to calculate summary statistics. An exception to this rule is any value reported as < 1 or < 0.1, etc. For values reported as < 1 or < 0.1, a value of 0.9 or 0.09, respectively, will be used to calculate summary statistics.

- A value that is 1 unit above the LOQ will be used to calculate descriptive statistics if the datum is reported in the form of "> x" (where x is considered the LOQ). Values with decimal points will follow the same logic as above.

- The LOQ will be used to calculate descriptive statistics if the datum is reported in the form of "≤ x" or "≥ x" (where x is considered the LOQ).

Natural logarithm transformation will be used for plasma/blood concentrations and analysis of PK parameters. Plasma concentration values that are below the limit of quantitation (BLQ) will be presented as "BLQ" in the concentration data listing. Values that are BLQ will be treated as 0 at predose time points, and one-half the value of the LOQ at postbaseline time points.

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

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

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

3.8. Analysis Visit Windows

3.8.1. Definition of Study Day

Study day will be calculated from the first dosing date of study drug and derived as follows:

- For post dose study days: Assessment Date – First Dosing Date + 1
- For days prior to the first dose: Assessment Date – First Dosing Date

Therefore, Study Day 1 is the day of the first dose of any study drug.

For placebo subjects who were re-randomized to active treatment at Week 12, the On-Active-Treatment study day will be calculated as: Assessment Date – Date of the first dose of active treatment + 1. The date of the first dose of the study drug dispensed at Week 12 is recorded on CRF.

3.8.2. Analysis Visit Windows

The target study days for analysis visits are provided in the Table 3 below:

Table 3. Target Days for Analysis Visits

Nominal Visit	Nominal Study Day/ Study Day on Active Treatment
Screening	< 1
Baseline	<=1
Week 2	15
Week 4	29
Week 8	57
Week 12	85/1
Week 14	99/15
Week 16	113/29
Week 20	141/57
Week 24	169/85
Week 30	211/127
Week 36	253/169
Week 42	295/211
Week 48	337/253
Follow-up Visit	NA

The nominal visit as recorded on the CRF will be used when data are summarized by visit.

Any data recorded under unscheduled visits will not be assigned to a particular visit or time point. However, the following exceptions will be made:

- An unscheduled visit prior to the first dosing of study drug may be included in the calculation of the baseline value, if applicable
- Unscheduled visits after the first dose of study drug will be included in determining the maximum postbaseline toxicity grade in safety analyses.

For subjects who prematurely discontinue from the study, early termination (ET) data will be assigned to what would have been the next scheduled visit where the respective data were scheduled to be collected.

Data collected at a follow-up visit will be summarized as a separate visit, and labeled “Follow-up Visit.”

Data obtained after the follow-up visit or last dose date plus 30 days (whichever is later) will be excluded from the summaries, but will be included in the listings.

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

Depending on the statistical analysis method, single values may be required for each analysis window. For example, change from baseline by visit usually requires a single value.

If multiple valid, nonmissing, continuous measurements are recorded for the same visit, records will be chosen based on the following rules if a single value is needed:

- In general, the baseline value will be the last nonmissing value on or prior to the first dosing date of study drug (Study Day 1), except for the analyses of active treatment period where the first dosing date of the active drug will be used. If multiple measurements occur on the same day, the last nonmissing value on or prior to the date of first dosing of study drug will be considered as the baseline value. If time is available, then use date and time to select the records with the latest time for the date. When times of these multiple measurements are not available, the average of these measurements (for continuous data) will be considered as the baseline value.

- For postbaseline values:

  — The record closest to the target day for that visit will be selected.

  — If there are 2 records that are equidistant from the target day, the later record will be selected.

  — If there is more than 1 record on the selected day and time is not collected then the average will be taken, unless otherwise specified.

If multiple valid, nonmissing, categorical measurements exist for the same visit, records will be chosen based on the following rules if a single value is needed:

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

- For postbaseline visits

  — The record closest to the target day for that visit will be selected

  — If there are 2 records that are equidistant from the target day, the later record will be selected.

  — If there are multiple records with the same time or no time recorded on the same day, the value with the worst severity within the window will be selected (eg, abnormal will be selected over normal for safety ECG findings).

    All records will be listed by collection date.

3.9. Efficacy Estimands

Three efficacy estimands, a treatment-policy estimand and a hypothetical estimand are defined for the primary efficacy endpoint.

The **treatment-policy estimand** is the primary estimand for the primary endpoint.

1) Population: Subjects in the FAS

2) Variable: Primary and secondary endpoints

3) Intercurrent events: The occurrence of an intercurrent event is irrelevant. All observed values will be used regardless of occurrence of an intercurrent event

4) Population-level summary: The difference in adjusted means of change from baseline for the continuous primary endpoint, difference in proportions between each active treatment group and placebo group for the binary efficacy endpoints

The **hypothetical estimand** is defined as following. This is the supportive estimand for the primary efficacy endpoint.

1) Population: Subjects in FAS

2) Variable: Primary endpoint

3) Intercurrent events: The following intercurrent events are taken into account:

   — Subject takes prohibited medication

   — The dose of the medication required to be stable through Week 12 is changed at any time during the study

   — Subject discontinues from study treatment

4) Population-level summary: The difference in adjusted mean change from baseline.

The estimators associated with each of these estimands are described in Section 6.

4. SUBJECT DISPOSITION

4.1. Subject Enrollment and Disposition

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

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

The randomization schedule used for the study will be provided as an appendix to the CSR.

A summary of subject disposition will be provided by treatment group for both the entire study duration and by treatment phase. This summary will present the number of subjects in each of the categories listed below:

- Subjects screened
- Subjects randomized
- Safety Analysis Set
- Completed Study
- Prematurely discontinued study with reasons for discontinuation
- Completed study drug
- Prematurely discontinued study drug with reasons for discontinuation

The study and drug disposition will also be presented by study period with the following categories:

- Completed study up to Week 12, Week 24, and through the end of the study
- Completed study drug up to Week 12, Week 24, and through the end of study
- Did not complete the study/study drug up to Week 12, Week 24, and through the end of study with reasons for premature discontinuation of the study/study drug
- Re-randomized
- Continuing study drug (Week 12 analysis only)
- Continuing study (Week 12 analysis only)

For the status of study drug and study completion and reasons for premature discontinuation with the number and percentage of subjects in each category will be provided. The denominator for the percentage calculation will be the total number of subjects in the Safety Analysis Set corresponding to that column. In addition, a flowchart will be provided to depict the disposition.

For placebo subjects, completion of the study up to Week 12 will be based on the presence of the corresponding visit in EDC or presence of Early termination visit which is after Week 8 visit and the [date of ET visit – date of first dose + 1] >= 82 days (target date for Week 12 visit – protocol allowed visit window). Subjects are considered to complete 12 weeks of treatment if the start date of Week 12 treatment is provided or the [last dose date – first dose date +1] >= 82.

The by-subject listing of disposition will be provided by subject identification (ID) number in ascending order to support the above summary tables.

4.2. Extent of Study Drug Exposure and Adherence

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

4.2.1. Duration of Exposure to Study Drug

Total duration of exposure to study drug will be defined as last dosing date of any study drug minus first dosing date of any study drug plus 1, regardless of any temporary interruptions in study drug administration, and will be expressed in weeks using up to 1 decimal place (eg, 4.5 weeks). For Week 12 primary analysis, the data cut-off date can be used as the last dosing date for subjects continuing on study.

For subjects with a partial last dosing date (ie, month and year of last dose are known), the latest of the dispensing dates of study drug bottles, and the imputed last dose date [day imputed as last day of the month] will be used as the final imputed last dose date.

If only year is recorded (ie, month and day of last dose are missing) or the entire date is missing then the latest of the dispensing month of study drug bottles, study drug start month, and study drug bottle return month will be used to impute the unknown last dose month (and a year if the entire date is missing). With the month imputed, the aforementioned method will be used to impute the last dose date. If the imputed date is after the date of death, choose the death date.

In addition, the duration of active treatment will be provided. The calculation for the subjects originally randomized to placebo will include the period starting from the first day of active study drug (Week 12 treatment start date is recorded on CRF).

The total duration of exposure to study drug will be summarized using descriptive statistics (number of subjects [n], mean, SD, median, Q1, Q3, minimum, and maximum) and the percentage of subjects exposed through the following time periods: Day 1, Weeks 2, 4, 8, 12, 14, 16, 20, 24, 30, 36, 42, and 48. The subject is considered to be exposed up to Week X if the last dose of any study drug is at least visit target day (per Table 3) minus protocol-allowed window (protocol Appendix 2).

Summaries will be provided by treatment group for the Safety Analysis Set. No formal statistical testing is planned.

4.2.2. Adherence to Study Drug

The total number of doses administered will be summarized using descriptive statistics for each study drug.

The presumed total number of doses administered to a subject will be determined by the data collected on the drug accountability CRF using the following formula:

$$\text{Total Number of Doses Administered} = \left(\sum \text{No. of Doses Dispensed}\right) - \left(\sum \text{No. of Doses Returned}\right)$$

If a bottle is dispensed and returned empty, then the number of tablets returned will be entered as zero. If a bottle is dispensed but not returned (missing) then the number of tablets from that bottle will be counted as zero.

If calculated adherence is greater than 100%, the result will be set to 100%.

The adherence will be calculated separately for each treatment administered: filgotinib 200 mg/PTM or lanraplenib 30 mg/PTM. The overall adherence will be lowest of the two.

4.2.2.1. Prescribed Adherence

The level of prescribed adherence to the study drug regimen will be determined by the total amount of study drug administered relative to the total amount of study drug specified by the protocol for a subject who completes treatment in the study.

The level of prescribed adherence will be expressed as a percentage using the following formula:

$$\text{Prescribed Adherence (\%)} = \left(\frac{\text{Total Amount of Study Drug Administered}}{\text{Total Amount of Study Drug Specified by Protocol}}\right) \text{x } 100$$

Descriptive statistics for the level of prescribed adherence up to Week 12, up to Week 24 and the entire study duration with the number and percentage of subjects belonging to adherence categories: < 80, $\geq 80\%$ will be provided by treatment group for the Safety Analysis Set.

The expected amount of study drug to be administered is derived as:

- up to Week 12 is 84 (7 * 12) doses
- up to Week 24 is 168 (7 * 24) doses
- Entire study is 336 (7 * 48) doses

The total amount of study drug administered up to week 12/24 will be calculated based on the drug accountability reported on CRF: (total pills dispensed – total pills returned) up to Week 12/24 visit.

No formal statistical testing is planned.

By-subject listings of study drug administration and accountability will be provided separately by subject ID number in ascending order and in chronological order for each treatment separately.

4.3. Protocol Deviations

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

Protocol deviations occurring after subjects entered the study are documented during routine monitoring. The number and percentage of subjects with important protocol deviations by deviation reason (eg, violation of select inclusion/exclusion criteria) will be summarized by treatment group for the Safety Analysis Set. A by-subject listing will be provided for the subjects with important protocol deviations.

5. BASELINE CHARACTERISTICS

5.1. Demographics

Subject demographic variables will be summarized by treatment group and overall using descriptive statistics for continuous variables, and using number and percentage of subjects for categorical variables. The summary of demographic data will include the following:

- age (on the first dose date of any study drug) as a continuous variable
- age group (< 50, ≥ 50 years)
- race
- ethnicity (Hispanic or Latino, not Hispanic or Latino)

Subject demographic variables (i.e., age, sex, race, and ethnicity) will be summarized by treatment group and overall using descriptive statistics for age, and using number and percentage of subjects for sex, race, and ethnicity. The summary of demographic data will be provided for the Safety Analysis Set.

A by-subject demographic listing, including the informed consent date, will be provided by subject ID number in ascending order.

5.2. Baseline Characteristics

The baseline characteristics include:

- weight (kg)
- body mass index (BMI; in kg/m^2)
- CLE disease subtype (CCLE, SCLE)
- time from CLE diagnosis to enrollment (as continuous in years, < 10 and >= 10 years)
- diagnosis of SLE (Yes, No)
- diagnosis of RA (Yes, No)
- diagnosis of Sjogren's Syndrome (Yes, No)
- concurrent background systemic DMARD use at baseline (Yes, No)
- concurrent background use of systemic (oral) corticosteroids (Yes, No)
- concurrent background use of anti-malarial DMARD drugs (Yes, No)

- baseline CLASI Activity score (as continuous variable, categories <15 and >=15)
- baseline CLASI Damage score (as continuous variable, categories < 10 and >=10)
- baseline subject's global assessment of CLE activity (mm)
- baseline physician's global assessment of CLE activity (mm)

The time from CLE diagnosis will be calculated in years between the date of enrollment and the date of diagnosis. The missing month will be imputed with January, the missing day will be imputed with 1st day of the month.

The baseline characteristics will be summarized by treatment group and overall using descriptive statistics (n, mean, SD, median, Q1, Q3, minimum, and maximum) for continuous variables and using number and percentage for categorical variables.

The summary of baseline characteristics will be provided for the FAS. No formal statistical testing is planned.

A by-subject listing of other baseline characteristics will be provided by subject ID number in ascending order.

5.3. Medical History

Medical history will be collected at screening for CLE and other conditions.

The medical history data will be coded using the Medical Dictionary for Regulatory Activities (MedDRA).

Medical history data will be summarized by system organ class (SOC), preferred term (PT), treatment group, and overall. Subjects who report 2 or more medical history items that are coded to the same SOC and/or PT will be counted only once by the unique coded term in the summary. The summary will be provided for the Safety Analysis Set. No formal statistical testing is planned.

The CLE-related medical history will be summarized by treatment group and overall by the number and percentage of subjects with each CLE subtype.

6. EFFICACY ANALYSES

Efficacy endpoints will be evaluated for the following treatment periods: Placebo controlled period up to Week 12 and the entire study up to Week 48.

For the binary variables, non-responder imputation will be used. For continuous variables, imputation will not be performed prior to MMRM analysis.

The primary endpoint will be analyzed based on the estimands presented in Table 4.

Table 4.

Continuous Endpoint	Treatment Policy	Hypothetical
Population	FAS	FAS
Endpoint	Change from Baseline	Change from Baseline
Intercurrent Event	Ignore all intercurrent events	• Treatment discontinuation • Start of prohibited medication • The dose change of medication that required to be stable Treat data as missing after the event.
Estimator	MMRM with no imputation of missing data	MMRM with no imputation of missing data

6.1. Definition of the Primary Efficacy Endpoints

The primary efficacy endpoint for this study is the change in CLASI activity score from baseline to Week 12.

Activity score is the sum of the scores of the left side of the CLASI worksheet (i.e. for erythema, scale/hypertrophy, mucous membrane involvement and alopecia. See Appendix 2). The activity score ranges from 0 to 70 with higher score indicating more severe skin disease.

6.2. Analysis of the Primary Efficacy Endpoint

The primary analyses will be a test of superiority with the null hypotheses below:

- H01: There is no difference between filgotinib 200 mg and placebo in the change in CLASI activity score from baseline to Week 12

- H02: There is no difference between lanraplenib 30 mg and placebo in the change in CLASI activity score from baseline to Week 12

The primary endpoint will be analyzed using a mixed-effects repeated measures (MMRM) model. The model may include terms for baseline CLASI-A value, treatment, stratification factors (disease subtype, and concurrent background DMARD use), visit, and treatment-by-visit

interaction. Subject will be included as a random effect. The Kenward-Roger method will be used to estimate the degrees of freedom. The two treatment comparisons versus placebo will be done separately at the 2-sided 0.1 level. The unstructured (UN) variance-covariance matrix of repeated measures will be considered first. If model does not converge then ARH(1) structure will be applied.

The primary analysis will be based on the treatment policy estimand. The described analysis is the main estimator for the primary endpoint.

Descriptive statistics (n, mean, SD, median, Q1, Q3, minimum, and maximum) will be presented in the descriptive summaries. Adjusted means and 95% confidence intervals (CIs) will also be provided for each visit and treatment group.

Descriptive statistics of change from baseline in CLASI-A at Week 12 will be presented for the subgroups specified in Section 3.4.

The line plots for median (Q1, Q3) change (absolute and percent) in CLASI-A from baseline, mean (+/- 95% CI) change from baseline, and the adjusted estimates of mean change from baseline (+/- 95% CI) will be provided.

A plot of cumulative distribution of change from baseline in CLASI-A at Week 12 will be presented by treatment group on the observed data.

6.3. Sensitivity Analysis of Primary Endpoint

The following sensitivity analyses of the primary endpoint (Change in CLASI-A total score at Week 12) will be performed:

- primary analysis repeated on hypothetical estimand
- non-parametric ANCOVA analysis using rank transformed data

6.4. Secondary Efficacy Endpoints

6.4.1. Definition of Secondary Efficacy Endpoints

Secondary efficacy endpoints include:

- Proportion of subjects at Week 12 with a decrease of ≥ 5 points in CLASI activity score from baseline
- Proportion of subjects at Week 12 with no worsening in CLASI activity score from baseline (worsening defined as ≥ 3 point increase)
- Proportion of subjects at Week 24 with a decrease of ≥ 5 points in CLASI activity score from baseline
- Proportion of subjects at Week 24 with no worsening in CLASI activity score from baseline (worsening defined as ≥ 3 point increase)

6.4.2. Analysis Methods for Secondary Efficacy Endpoint

The proportion of subjects with a decrease of ≥ 5 points in CLASI activity score and the proportion of subjects with no worsening from baseline to Week 12 will be analyzed separately using Cochran-Mantel-Haenszel (CMH) test stratified by the randomization stratification factors. If stratification leads to small cell sizes, the strata will be pooled and the Fisher's Exact test will be used.

The proportion of subjects with a decrease of ≥ 5 points in CLASI activity score from baseline to Week 24 and no worsening in CLASI-A from baseline to Week 24 will be analyzed by one-sample exact binomial test for each active treatment group.

The number and percentage of subjects with a decrease of ≥ 5 points in CLASI activity score from baseline and no worsening at Week 12 and at Week 24 will be provided. 95% CIs for the percentage will be calculated using the Clopper-Pearson exact method.

The secondary endpoints analysis will be based on the FAS. The missing response data will be imputed as No Response. The sensitivity analysis without imputation of the missing values (observed cases) will also be performed.

6.5. Exploratory Efficacy Endpoints

6.5.1. Definition of Exploratory Efficacy Endpoints

Exploratory efficacy endpoints include:

[redacted]

6.5.2. Analysis Methods for Exploratory Efficacy Endpoints

[redacted]

CCI [redacted]

6.6. Changes From Protocol-Specified Efficacy Analyses

The treatment policy and hypothetical estimands have been added to the analyses of the primary endpoint.

7. SAFETY ANALYSES

The safety analyses will be performed for the placebo-controlled treatment period up to Week 12, up to Week 24, and for the entire study duration. Analyses for these treatment periods will be presented by the treatment groups specified in Section 3.

For the analyses of adverse events that include data after Week 12 the exposure-adjusted analyses will be presented.

For the AEs, laboratory abnormalities and concomitant medication data, the collection/start date will be used to determine which reporting period the record belongs to. For other parameters, the nominal visits will be used.

7.1. Adverse Events and Deaths

7.1.1. Adverse Event Dictionary

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

7.1.2. Adverse Event Severity

Adverse events are graded by the investigator as Grade 1, 2, 3, 4, or 5 according to toxicity criteria specified in the protocol (CTCAE 4.03). The severity grade of events for which the investigator did not record severity will be categorized as “missing” for tabular summaries and data listings. The missing category will be listed last in summary presentation.

7.1.3. Relationship of Adverse Events to Study Drug

Related AEs are those for which the investigator selected “Related” on the AE CRF to the question of “Related to filgotinib/placebo” or “Related to lanraplenib/placebo”. If AE is reported as “Related” to any of 2 study drugs then the AE is considered “Related to study treatment”. Relatedness will always default to the investigator’s choice, not that of the medical monitor. Events for which the investigator did not record relationship to study drug will be considered related to study drug for summary purposes. However, by-subject data listings will show the relationship as missing.

7.1.4. Serious Adverse Events

Serious adverse events (SAEs) will be identified and captured as SAEs if the AEs met the definitions of SAEs that were specified in the study protocol. SAEs captured and stored in the clinical database will be reconciled with the SAE database from the Pharmacovigilance & Epidemiology Department before data finalization.

7.1.5. Treatment-Emergent Adverse Events

7.1.5.1. Definition of Treatment-Emergent Adverse Events

Treatment-emergent adverse events (TEAEs) of the entire study duration are defined as 1 or both of the following:

- Any AEs with an onset date on or after any study drug start date and no later than 30 days after permanent discontinuation of any study drug
- Any AEs leading to premature discontinuation of study drug.

TEAEs up to Week12/24 are defined as 1 or both of the following:

- Any AEs with an onset date on or after Day 1, prior to start of Week 12/24 treatment and no later than the day before the Week 12/24 treatment start date. For subjects who discontinued treatment prior to Week 12/24 visit, any AEs with an onset date on or after the study drug start date and no later than 30 days after permanent discontinuation of study drug
- Any AEs leading to premature discontinuation of study drug prior to first Week 12/24 dosing

7.1.5.2. Incomplete Dates

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

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

An AE with completely missing onset and stop dates, or with the onset date missing and a stop date later than the first dosing date of study drug, will be considered to be treatment emergent. In addition, an AE with the onset date missing and incomplete stop date with the same or later month and year (or year alone if month is not recorded) as the first dosing date of study drug will be considered treatment emergent.

7.1.6. Summaries of Adverse Events and Deaths

Treatment-emergent AEs will be summarized based on the Safety Analysis Set. The tables will be presented by treatment period: placebo-controlled period (up to Week 12) and for weeks 12-48. The overall summary of TEAEs may also be provided for the entire study duration.

The number and percentage of subjects who experienced at least 1 TEAE will be provided and summarized by SOC, HLT, PT, and treatment group. For other AEs described below, summaries will be provided by SOC, PT, and treatment group:

- All TEAEs
- TEAEs of Grade 3 or higher (by maximum severity)
- All TE treatment-related AEs
- TE treatment-related AEs of Grade 3 or higher (by maximum severity)
- All TE SAEs
- All TE treatment-related SAEs
- All TEAEs leading to premature discontinuation of study drug
- All TEAEs leading to premature discontinuation of study
- All TEAEs leading to death (i.e. outcome of death)

A brief, high-level summary of AEs described above will be provided by treatment group and by the number and percentage of subjects who experienced the above AEs. All deaths observed in the study will also be included in this summary.

Multiple events will be counted only once per subject in each summary. Adverse events will be summarized and listed first in alphabetic order of SOC and HLT within each SOC (if applicable), and then by PT in descending order of total frequency within each SOC. For summaries by severity grade, the most severe grade will be used for those AEs that occurred more than once in an individual subject during the study.

In addition to the above summary tables, all TEAEs and TE treatment-related AEs will be summarized by PT only, in descending order of total frequency.

The data listings will be provided for the following:

- All AEs, indicating whether the event is treatment emergent
- All AEs of Grade 3 or higher
- SAEs
- Deaths
- AEs leading to premature discontinuation of study drug
- AEs leading to premature discontinuation of study

7.1.7. Adverse Events of Special Interest

Events of interest will be identified by the use of either SMQs or MSTs. However, should additional cases not detected by the predefined search term listings be identified during the clinical review process, these cases will also be reported by respective category. Serious major adverse cardiovascular events (MACE) will not be adjudicated.

Adverse events of special interest include:

- All infections (defined as all PTs within the Infections and Infestations SOC)
- Serious infections (defined as all PTs within the Infections and Infestations SOC that are SAEs)
- Infections of special interest as defined below
    A) Herpes zoster
    B) Active tuberculosis
    C) Opportunistic infections
    D) Hepatitis B or C (HBV and HCV) infections
- Venous thrombotic events and pulmonary embolism
- Malignancies
- Gastrointestinal (GI) perforations
- Liver transaminase elevation
- Serious potential major adverse cardiovascular events (MACE) defined by the following terms:
    A) Cardiovascular events
    B) Myocardial infarction
    C) Hospitalization for unstable angina
    D) Transient ischemic attack
    E) Stroke
    F) Hospitalization for cardiac failure
    G) Percutaneous coronary intervention

The number and percentage of patients with aforementioned events of special interest will be provided by the PT term.

A by-subject listing for all patients having AE of special interests at any time will be provided.

7.2. Laboratory Evaluations

Laboratory data collected during the study will be analyzed and summarized using both quantitative and qualitative methods. Summaries of laboratory data will be provided for the Safety Analysis Set and will include data collected up to the last dose of study drug plus 30 days for subjects who have permanently discontinued study drug, or all available data at the time of the database snapshot for subjects who were ongoing at the time of an interim analysis. The analysis will be based on values reported in conventional units. When values are below the LOQ, they will be listed as such, and the closest imputed value will be used for the purpose of calculating summary statistics as specified in Section 3.7. Hemolyzed test results will not be included in the analysis, but they will be listed in by-subject laboratory listings.

A baseline laboratory value for the placebo-controlled and entire study period will be defined as the last nonmissing measurement obtained on or prior to the date/time of first dose of any study drug. For the active treatment period, the baseline for the subjects originally randomized to placebo will be the measurement before or on the day when the first dose of active study treatment is administered.

A by-subject listing for laboratory test results will be provided by subject ID number and visit in chronological order for hematology, serum chemistry, and urinalysis separately. Values falling outside of the relevant reference range and/or having a severity grade of 1 or higher on the Common Terminology Criteria for Adverse Events (CTCAE severity grade) will be flagged in the data listings, as appropriate.

No formal statistical testing is planned.

7.2.1. Summaries of Numeric Laboratory Results

Descriptive statistics will be provided by treatment group for the following laboratory tests:

- Hematology
  - Hematocrit
  - Hemoglobin
  - Platelet count
  - Red blood cell count
  - White blood cell (WBC) count
  - Mean corpuscular volume

  - Lymphocytes
  - Monocytes
  - Neutrophils
  - Eosinophils
  - Basophils
- Chemistry
  - Alanine aminotransferase (ALT)
  - Aspartate aminotransferase (AST)
  - Alkaline phosphatase (ALP)
  - Total bilirubin
  - Serum creatinine
  - Creatinine clearance by Cockcroft-Gault formula
  - Creatine phosphokinase (CPK)
  - Glucose
- Lipid Panel
  - Triglycerides
  - Total cholesterol
  - HDL
  - LDL
  - LDL/HDL ratio

Fasting results for lipid profile and serum glucose will be presented separately from overall results.

Change from baseline to a postbaseline visit will be defined as the visit value minus the baseline value. The mean, median, Q1, Q3, minimum, and maximum values will be displayed to the reported number of digits; SD values will be displayed to the reported number of digits plus 1.

Median (Q1, Q3) of the observed values for the laboratory tests specified above will be plotted using a line plot by treatment group and visit.

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

7.2.2. Graded Laboratory Values

The CTCAE will be used to assign toxicity grades (0 to 4) to laboratory results for analysis. Grade 0 includes all values that do not meet the criteria for an abnormality of at least Grade 1. For laboratory tests with criteria for both increased and decreased levels, analyses for each direction (ie, increased, decreased) will be presented separately.

7.2.2.1. Treatment-Emergent Laboratory Abnormalities

Treatment-emergent laboratory abnormalities for the entire study period and in subjects discontinued treatment prematurely are defined as values that increase at least 1 toxicity grade from baseline at any postbaseline time point, up to and including the date of last dose of study drug plus 30 days for subjects who permanently discontinued study drug, or the last available date in the database snapshot for subjects who were still on treatment at the time of an interim analysis. If the relevant baseline laboratory value is missing, any abnormality of at least Grade 1 observed within the time frame specified above will be considered treatment emergent.

For the analyses of active treatment period, the baseline is the day of the first dose of active study drug administration.

For the analyses of placebo-controlled period, the lab abnormality occurring after (within 30 days) Week 12 visit is included only if subject did not continue treatment after Week 12.

The listing of all laboratory abnormalities will be provided.

7.2.2.2. Treatment-Emergent Marked Laboratory Abnormalities

Treatment-emergent marked laboratory abnormalities are defined as values that increase from baseline by at least 3 toxicity grades at any postbaseline time point, up to and including the date of the last dose of study drug plus 30 days for subjects who permanently discontinued study drug or the last available date in the database snapshot for subjects who were still on treatment at the time of an primary Week 12 analysis. If the relevant baseline laboratory value is missing, any Grade 3 or 4 values observed within the timeframe specified above will be considered treatment-emergent marked abnormalities.

Same rules as in the Section 7.2.2.1 apply for determination of TE abnormality in the placebo-controlled and entire study duration.

7.2.2.3. Summaries of Laboratory Abnormalities

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

- Treatment-emergent laboratory abnormalities
- Treatment-emergent grade 3 or 4 laboratory abnormalities
- Treatment-emergent marked laboratory abnormalities

The summaries of treatment-emergent laboratory abnormalities will be presented by treatment group and highest grade for the placebo-controlled and active treatment period. The listing of all laboratory abnormalities will be provided.

For all summaries of laboratory abnormalities, the denominator is the number of subjects with nonmissing postbaseline values, with the baseline determined per Section 7.2.

By-subject listings of treatment-emergent Grade 3 or 4 laboratory abnormalities and marked laboratory abnormalities will be provided by subject ID number and visit in chronological order. This listing will include all test results that were collected throughout the study for the lab test of interest, with all applicable severity grades displayed.

7.2.3. Liver-related Laboratory Evaluations

Liver-related abnormalities after initial study drug dosing will be examined and summarized using the number and percentage of subjects who were reported to have the following laboratory test values for postbaseline measurements:

- Aspartate aminotransferase (AST): (a) > 3 times of the upper limit of reference range (ULN); (b) > 5 x ULN; (c) > 10 x ULN; (d) > 20 x ULN
- Alanine aminotransferase (ALT): (a) > 3 x ULN; (b) > 5 x ULN; (c) > 10 x ULN; (d) > 20 x ULN
- AST or ALT: (a) > 3 x ULN; (b) > 5 x ULN; (c) > 10 x ULN; (d) > 20 x ULN
- Total bilirubin: > 2 x ULN
- Alkaline phosphatase (ALP) > 1.5 x ULN
- AST or ALT > 3 x ULN and total bilirubin: (a) > 1.5 x ULN; (b) > 2 x ULN

The summary will include data from all postbaseline visits on active treatment up to 30 days after the last dose of study drug. For individual laboratory tests, subjects will be counted once based on the most severe postbaseline values. For both the composite endpoint of AST or ALT and total bilirubin, subjects will be counted once when the criteria are met at the same

postbaseline visit date. The denominator is the number of subjects in the Safety Analysis Set who have nonmissing postbaseline values of all relevant tests at the same postbaseline visit date.

The analyses will be presented for the placebo-controlled period and entire study period.

A listing of subjects who met at least 1 of the above criteria will be provided.

7.3. Body Weight and Vital Signs

Descriptive statistics will be provided by treatment group for body weight, BMI and vital signs (pulse rate, systolic and diastolic blood pressure, body temperature, and respiratory rate) as follows:

- Baseline value
- Values at each postbaseline visit
- Change from baseline at each postbaseline visit

A baseline value will be defined as the last available value collected on or prior to the date of first dose of study drug. Change from baseline to a postbaseline visit will be defined as the postbaseline value minus the baseline value. Body weight and vital signs measured at unscheduled visits will be included for the baseline value selection.

In the case of multiple values at the visit, data will be selected for analysis as described in Section 3.8.3. No formal statistical testing is planned.

A by-subject listing of vital signs will be provided by subject ID number and visit in chronological order. Body weight and BMI will be included in the vital signs listing, if space permits. If not, they will be provided separately.

7.4. Prior and Concomitant Medications

Medications collected at screening and during the study will be coded using the current version of the Gilead-modified World Health Organization (WHO) Drug dictionary.

7.4.1. Prior Medications

Prior medications are defined as any medications taken and stopped prior to the day the subject took the first dose of study drug.

Prior medications will be summarized by each Anatomical Therapeutic Chemical (ATC) drug class level 2 and preferred name using the number and percentage of subjects for each treatment group and overall. A subject reporting the same medication more than once will be counted only once when calculating the number and percentage of subjects who received that medication. The summary will be ordered alphabetically by preferred term in order of descending overall frequency. For drugs with the same frequency, sorting will be done alphabetically.

For the purposes of analysis, any medication with a stop date prior to the first dosing date of study drug will be included in the prior medication. If a partial stop date is entered the medication will be considered prior unless the month and year (if day is missing) or year (if day and month are missing) of the stop date are after the first dosing date. The medications taken for CLE or SLE will be considered prior per designation on CRF.

Summaries will be based on the Safety Analysis Set. No formal statistical testing is planned.

7.4.2. Concomitant Medications

Concomitant medications are defined as medications taken on the date the subject first started study drug, or started after the date the subject first took study drug. Use of general and disease-specific (for CLE or SLE) concomitant medications will be summarized by preferred name using the number and percentage of subjects for each treatment group. A subject reporting the same medication more than once will be counted only once when calculating the number and percentage of subjects who received that medication. The summary will be ordered alphabetically by preferred term in descending overall frequency. For drugs with the same frequency, sorting will be done alphabetically.

For the purposes of analysis, any medication with a start date prior to or on the first dosing date of study drug and continued to be taken after the first dosing date, or started after the first dosing date but prior to or on the last dosing date of study drug will be considered concomitant medication. Medications started and stopped on the same day as the first dosing date or the last dosing date of study drug will also be considered concomitant. Medications with a stop date prior to the date of first dosing date of study drug or a start date after the last dosing date of study drug will be excluded from the concomitant medication summary.

If a partial stop date is entered, any medication with the month and year (if day is missing) or year (if day and month are missing) prior to the date of first study drug administration will be excluded from the concomitant medication summary. If a partial start date is entered, any medication with the month and year (if day is missing) or year (if day and month are missing) after the study drug stop date will be excluded from the concomitant medication summary. Medications with completely missing start and stop dates will be listed but not included in the concomitant medication summary, unless the medication is reported as ongoing. Summaries will be based on the Safety Analysis Set. No formal statistical testing is planned.

In addition, prior and concomitant medications for SLE and CLE will be presented in a separate summary table by medication category, and preferred term.

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

7.5. Electrocardiogram Results

A shift table of the investigators' assessment of ECG results at each visit compared with baseline values will be presented by treatment group using the following categories: normal; abnormal, not clinically significant; abnormal, clinically significant; or missing. The number and

percentage of subjects in each cross-classification group of the shift table will be presented. Subjects with a missing value at baseline or postbaseline will not be included in the denominator for percentage calculation. No formal statistical testing is planned.

A by-subject listing for ECG assessment results will be provided by subject ID number and visit in chronological order.

7.6. Other Safety Measures

A data listing will be provided for subjects who become pregnant during the study.

7.7. Changes From Protocol-Specified Safety Analyses

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

8. PHARMACOKINETIC (PK) ANALYSES

Blood samples for PK analysis will be collected at Week 2 (at least 30 minutes and up to 3 hours postdose), anytime at Week 4, and within 2 hours prior to study drug administration at Weeks 12 and 24.

Plasma concentrations of filgotinib, the active metabolite of filgotinib (GS-829845), and lanraplenib will be listed and summarized using descriptive statistics (eg, sample size, arithmetic mean, geometric mean, % coefficient of variation, standard deviation, median, minimum, and maximum).

8.1. PK Analysis Methods

Individual subject concentration data and individual subject PK parameters for filgotinib, GS-829845, and lanraplenib will be listed and summarized using descriptive statistics by treatment. Summary statistics (number [n], mean, SD, coefficient of variation [%CV], median, min, max, Q1, and Q3) will be presented for individual subject concentration data by time point (Week 2, Week 12 and Week 24) and by treatment. For Week 12 and 24 samples, only samples collected 20 to 28 hours after the prior dose will be included in the summary statistics.

Individual concentration data listings and summaries will include all subjects with concentration data. The sample size for each time point will be based on the number of subjects with nonmissing concentration data at that time point. The number of subjects with concentration BLQ will be presented for each time point. For summary statistics, BLQ values will be treated as 0 at predose and one-half of the lower limits of quantitation (LLOQ) for postdose time points.

9. REFERENCES

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Finlay AY and Khan GK. Dermatology Life Quality Index (DLQI): a simple practical measure for routine clinical use. Clin Exp Dermatol 1994; 19:210-216.

DLQI instructions for use and scoring. http://sites.cardiff.ac.uk/dermatology/quality-of-life/dermatology-quality-of-life-index-dlqi/dlqi-instructions-for-use-and-scoring/

10. SOFTWARE

SAS® Software Version 9.4. SAS Institute Inc., Cary, NC, USA.

nQuery Advisor(R) Version X.0. Statistical Solutions, Cork, Ireland.

11. SAP REVISION

Revision Date (DD MMM YYYY)	Section	Summary of Revision	Reason for Revision

Appendix 1. Schedule of Assessments

		Study Dosing Period									24-week Extension Period				ET[c]	F/U[d]
			Week 2	Week 4	Week 8	Week 12	Week 14	Week 16	Week 20	Week 24	Week 30	Week 36	Week 42	Week 48		
Study Procedures	**Screen[a]**	**Day 1[b]**	**± 2 days**	**± 3 days**	**± 3 days**	**± 3 days**	**± 5 days**	**± 5 days**	**± 5 days**	**± 5 days**	**± 7 days**	**± 7 days**	**± 7 days**	**± 7 days**	**± 5 days**	**± 5 days**
Written Informed Consent	X															
Review of Inclusion/ Exclusion Criteria	X															
Medical History[e]	X	X														
Height	X															
Weight	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Complete Physical Examination	X															
Symptom-driven Physical Examination[f]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Vital Signs[g]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physician's Global Assessment	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
CLASI	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Detailed Target Lesion Assessment[v]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Photography of Areas with Skin Involvement[w]		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Detailed Mucous Membrane Assessment[x]		X	X			X	X			X		X		X	
Subject's Global Assessment and other subject-reported measures[h]		X	X	X	X	X	X	X	X	X	X	X	X	X	X[i]
12-lead ECG	X									X		X		X	X[y]	
Hematology	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Chemistry	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Coagulation	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Fasting Lipids[j]		X				X				X			X			
CRP and ESR	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
HbA_{1c} and TSH	X															
Urinalysis and Urine protein to creatinine ratio	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Urine Drug and Alcohol Screen	X															
Serum Pregnancy Test[k]	X															
Urine Pregnancy Test[k, l]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
FSH Test[m]	X															
HIV-1, HIV-2, HBV, HCV Serology	X															

HCV Monitoring[n]						X				X		X		X	X[y]	
Quantiferon Test[o]	X															
Chest X-ray[o]	X															
Quantitative Serum Immunoglobulin Test		X			X				X				X			
Autoantibody Panel		X				X				X			X			
Complement Levels		X				X				X			X		X	X
Pharmacokinetics[p]			X	X		X				X						
CCI																
Whole Blood, Cytochex	X	X[s]	X	X		X				X					X	
Whole Blood, Heparin	X	X[s]	X	X		X				X					X	
Serum biomarker sample	X	X[s]	X	X		X				X				X	X	X
Plasma biomarker sample	X	X[s]	X	X		X				X				X	X	X
vfPBMC	X	X[s]	X	X		X				X					X	
PAXgene RNA sample	X	X[s]	X	X		X				X				X	X	X
Randomization		X				X[t]										
Study Drug Dispensing		X		X	X	X		X	X	X[u]	X	X	X			
Study Drug Accountability			X	X	X	X	X	X	X	X	X	X	X	X	X	

Review AEs & Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

a Prospective subjects should be screened no more than 28 days prior to randomization and administration of the first dose of study drugs.
b Day 1 procedures, including study drug administration, will be performed at the study center. All assessments will be performed prior to dosing unless otherwise indicated.
c Subjects who discontinue from the study prior to Week 24 (or prior to Week 48 for subjects entering the 24-week extension period), will return to the study center for ET assessments.
d Subjects will return to the study center for a FU visit 4 weeks (± 5 days) after their last dose of study drug. Subjects who discontinue study drug ≥ 4 weeks prior to their last visit will not be asked to return for the FU visit.
e At screening, medical history will include collection of demographics and a review of surgical history and CLE history (including documentation of prior skin biopsy results, if available). Medical history will be updated, as needed, on Day 1.
f Symptom-driven physical examinations will be performed, as needed, based on signs and symptoms.
g Vital signs include resting blood pressure, heart rate, respiratory rate, and temperature.
h Includes VAS (subject assessment of CLE on sexual activity; autoimmune disease-related dry eyes/mouth, body pain, joint pain/stiffness, and fatigue), SF-36, DLQI, and TSQM. Subject reported outcomes are recommended to be performed at the beginning of each visit prior to any other visit-related procedures (other than signing of informed consent).
i The TSQM will not be administered at the FU visit.
j An overnight fast (no food or drinks, except water) of at least 8 hours is required prior to collection of blood samples for lipid testing.
k Females of childbearing potential only (see Protocol Appendix 5).
l When visits are greater than 4 weeks apart, women should continue to have urine pregnancy tests every 4 weeks using at home pregnancy test kits that will be provided to them. The site will call the subject every 4 weeks to obtain results of these pregnancy tests and will record the information in the source documents and eCRF. If any urine pregnancy test is positive, study drug should be immediately interrupted and the subject should return to the study center for a serum pregnancy test.
m Females of non-childbearing potential only (see protocol Appendix 5).
n Viral monitoring for HCV every 12 weeks, as applicable (see exclusion criteria, protocol Section 4.3).
o Subjects previously treated for latent TB (see Inclusion # 9) do not need to have the QuantiFERON® TB-Gold In-Tube test (or equivalent assay), but a chest radiograph must be obtained if one is not available within 3 months prior to screening (with the report or films available for investigator review). All other subjects must have the QuantiFERON® TB-Gold In-Tube test (or equivalent assay) at screening and a chest radiograph (views as per local guidelines) at screening or within 3 months prior to screening (with the report or films available for investigator review).
p Pharmacokinetic samples will be collected on Week 2 (at least 30 minutes and up to 3 hours after dosing), Week 4 (anytime), Week 12 (within 2 hours prior to study drug administration), and Week 24 (within 2 hours prior to study drug administration).
q [redacted].
s On Day 1, biomarker samples will be collected prior to study drug administration.
t At the end of the Week 12 visit, subjects on placebo will be re-randomized 1:1 in a blinded fashion to receive filgotinib 200 mg + PTM GS-9876 30 mg once daily or GS-9876 30 mg + PTM filgotinib 200 mg once daily for the remainder of the study.
u For subjects who enter the 24-week extension period only.
v See protocol Section 6.9.2.3 for details.
w A separate manual will be provided for instructions on photography of areas with skin involvement.
x See protocol Section 6.9.2.4 for details.
y To be performed at ET visit if not completed within the prior 12 weeks

Appendix 2. Cutaneous Lupus Erythematosus Disease Area and Severity Index (CLASI)

Select the score in each anatomical location that describes the most severely affected cutaneous lupus-associated lesion

	activity		damage		
Anatomical Location	Erythema	Scale/ Hypertrophy	Dyspigmentation	Scarring / Atrophy/ Panniculitis	Anatomical Location
Extent	0-absent 1-pink; faint erythema 2- red; 3-dark red; purple /violaceous / crusted / hemorrhagic	0-absent; 1-scale 2-verrucous / hypertrophic	0-absent, 1-dyspigmentaton	0 … absent 1 … scarring 2 … severely atrophic scarring or panniculitis	
Scalp				See below	Scalp
Ears					Ears
Nose (incl. malar area)					Nose (incl. malar area)
Rest of the face					Rest of the face
V-area neck (frontal)					V-area neck (frontal)
Post. Neck &/or shoulders					Post. Neck &/or shoulders
Chest					Chest
Abdomen					Abdomen
Back, buttocks					Back, buttocks
Arms					Arms
Hands					Hands
Legs					Legs
Feet					Feet

Mucous membrane

Mucous membrane lesions (examine if patient confirms involvement)	
0-absent; 1-lesion or ulceration	

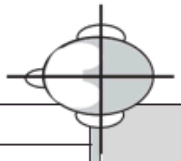
Dyspigmentation

Report duration of dyspigmentation after active lesions have resolved (verbal report by patient … tick appropriate box)

☐ Dyspigmentation usually lasts less than 12 months (dyspigmentation score above remains)

☐ Dyspigmentation usually lasts at least 12 months (dyspigmentation score is doubled)

Alopecia



Recent Hair loss (within the last 30 days /as reported by patient)	
1-Yes 0-No	

NB: if scarring and non-scarring aspects seem to coexist in one lesion, please score both

Divide the scalp into four quadrants as shown. The dividing line between right and left is the midline. The dividing line between frontal and occipital is the line connecting the highest points of the ear lobe. A quadrant is considered affected if there is a lesion within the quadrant.

Alopecia (clinically not obviously scarred)		Scarring of the scalp (judged clinically)	
0-absent 1-diffuse; non-inflammatory 2-focal or patchy in one quadrant; 3-focal or patchy in more than one quadrant		0- absent 3- in one quadrant 4- two quadrants 5- three quadrants 6- affects the whole skull	

Total Activity Score		Total Damage Score	
(For the activity score please add up the scores of the left side i.e. for Erythema, Scale / Hypertrophy, Mucous membrane involvement and Alopecia)		(For the damage score, please add up the scores of the right side, i.e. for Dyspigmentation, Scarring /Atrophy/ Panniculitis and Scarring of the Scalp)	