



## STATISTICAL ANALYSIS PLAN

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**Study Title:** A Phase 2, Randomized, Double-Blind, Multicenter Study Evaluating the Safety and Efficacy of Filgotinib and GS-9876 in Subjects with Lupus Membranous Nephropathy (LMN)

**Name of Test Drug:** Filgotinib and Lanraplenib (GS-9876)

**Study Number:** GS-US-437-4093

**Protocol Version (Date):** Amendment 2 (21 March 2018)

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**CONFIDENTIAL AND PROPRIETARY INFORMATION**

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## LIST OF ABBREVIATIONS

AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BLQ	below the limit of quantitation
BMI	body mass index
CI	confidence interval
CRF	case report form
CSR	clinical study report
CTCAE	Common Toxicity Criteria for Adverse Events
DMC	data monitoring committee
ECG	Electrocardiogram
eGFR	estimated glomerular filtration rate
ET	early termination
FAS	Full Analysis Set
HLT	high-level term
ICH	International Conference on Harmonization (of Technical Requirements for Registration of Pharmaceuticals for Human Use)
IWRS	interactive web response system
LLN	low limit of normal
LLT	lower-level term
LMN	Lupus Membranous Nephropathy
LOQ	limit of quantitation
MedDRA	Medical Dictionary for Regulatory Activities
PT	preferred term
PTM	placebo to match
Q1, Q3	first quartile, third quartile
SAP	statistical analysis plan
SD	standard deviation
SOC	system organ class
TEAE	treatment-emergent adverse event
TFLs	tables, figures, and listings
ULN	upper limit of normal
UPCR	urine protein creatinine ratio
WHO	World Health Organization

## 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-437-4093. This SAP is based on the study protocol amendment 2 dated 21 March 2018 and the electronic case report forms (eCRF). The SAP will be finalized before database finalization. Any changes made after the finalization of the SAP will be documented in the CSR.

The decision to discontinue the study due to enrollment challenges has been made on 18 December 2018. The screening has been stopped on 01 February 2019, with total 9 subjects enrolled in the study. Enrolled subjects were allowed to complete participation in the study up to Week 52.

This SAP describes the analyses to support the abbreviated CSR.

### 1.1. Study Objectives

The primary objective of this study is as follows:

- To evaluate the efficacy of filgotinib and lanraplenib in subjects with LMN

The secondary objectives of this study are as follows:

- To evaluate the safety and tolerability of filgotinib and lanraplenib in subjects with LMN
- To evaluate the PK of filgotinib and lanraplenib in subjects with LMN

The exploratory objectives are:

█ [REDACTED]

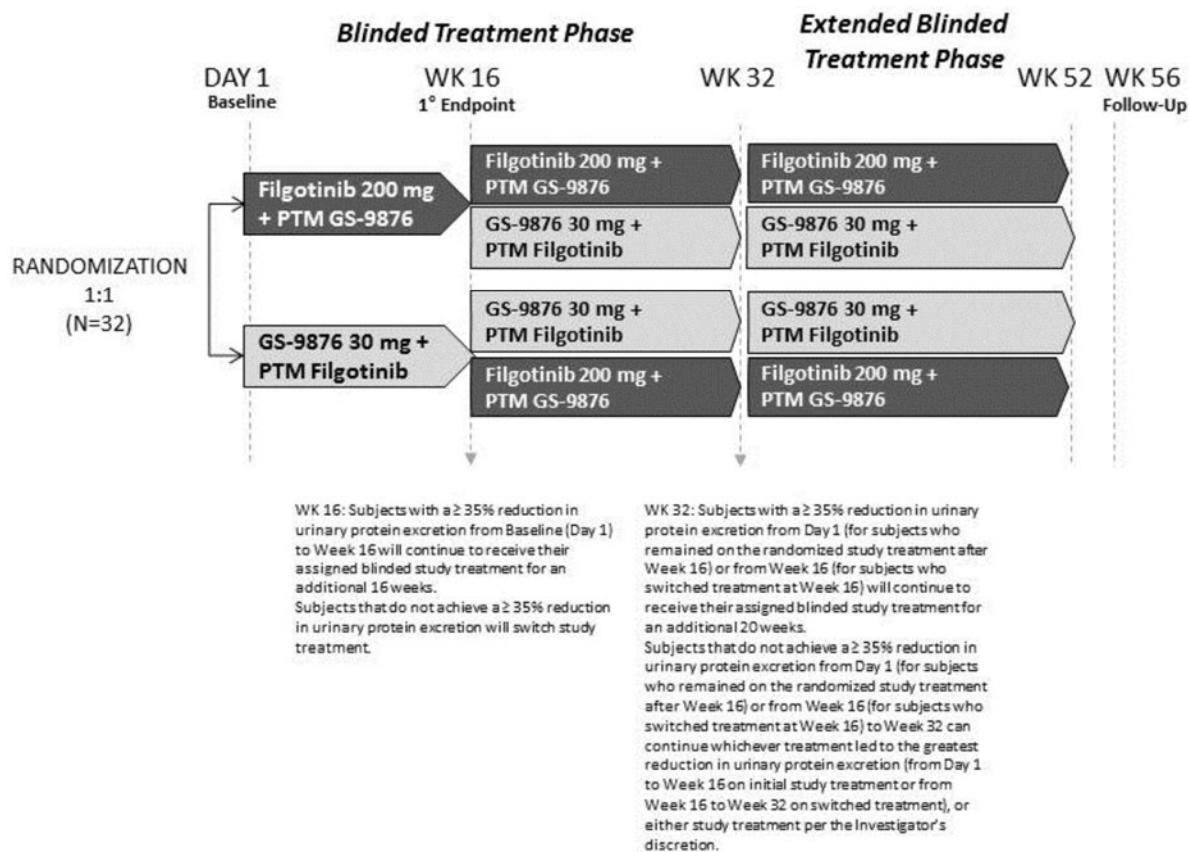
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### 1.2. Study Design

This is a Phase 2, randomized, double-blind, multicenter study to evaluate the safety and efficacy of filgotinib and lanraplenib in subjects with active LMN who are not in partial or complete remission in response to treatment with one or more anti-inflammatory or immunosuppressive agents.

A schematic of this study is provided in [Figure 1-1](#).

**Figure 1-1. Study Design Schematic**



Eligible subjects were randomized in a blinded fashion to 1 of 2 treatment arms in 1:1 ratio using a computerized IWRS system to receive once daily oral dose of the following study drugs starting on Day 1 for 16 weeks:

**Table 1-1. Study Treatments**

Treatment Arm	Study Drugs
Filgotinib (n=16)	filgotinib 200 mg + PTM lanraplenib 30 mg
Lanraplenib (n=16)	lanraplenib 30 mg + PTM filgotinib 200 mg
PTM = placebo to match	

Randomization will be stratified by prior treatment with cyclophosphamide.

Urinary protein excretion was determined using 2 methods – two consecutive morning voids as well as a 24-hour urine collection. For the Day 1 assessment, all 3 urine samples will be collected prior to Day 1, with the 24-hour urine collection as close to the Day 1 visit as possible.

At Week 16, the primary study endpoint will be assessed by urine protein excretion during a 24-hour urine collection. Two consecutive morning voids prior to the Week 16 visit will be used to determine response for subsequent study treatment. All subjects who achieve a  $\geq 35\%$  reduction in urinary protein excretion (using an average of the urine protein creatinine ratio (UPCR) from 2 morning voids) from Day 1 will continue to receive their assigned blinded study treatment (filgotinib 200 mg + PTM lanraplenib, or lanraplenib 30 mg + PTM filgotinib) for an additional 16 weeks. Additional details regarding urine collection procedures will be specified in the Laboratory Manual and Subject Procedures Manual.

Subjects who do not achieve a  $\geq 35\%$  reduction in urinary protein excretion from Day 1 to Week 16 will switch study treatment in a blinded fashion (ie, those on filgotinib will switch to lanraplenib + PTM filgotinib, while those on lanraplenib will switch to filgotinib + PTM lanraplenib).

After 32 weeks of blinded treatment, those who have a  $\geq 35\%$  reduction in urinary protein

excretion (using an average of the UPCR from 2 morning voids) from Day 1 (for subjects who remained on the randomized study treatment after Week 16) or from Week 16 (for subjects who switched treatment at Week 16) will continue their assigned blinded treatment for an additional 20 weeks in the Extended Blinded Treatment Phase. Subjects that do not achieve a  $\geq 35\%$  reduction in urinary protein excretion from Day 1 (for subjects who remained on the randomized study treatment after Week 16) or from Week 16 (for subjects who switched treatment at Week 16) to Week 32 will be allowed to continue whichever treatment led to the greatest reduction in urinary protein excretion (from Day 1 to Week 16 on initial study treatment or from Week 16 to Week 32 on switched treatment), or either study treatment per the Investigator's discretion (eg, differences in tolerability or other non-renal benefits that support overriding the treatment assignment according to reduction in urinary protein excretion) during the Extended Blinded Treatment Phase.

### **1.3. Sample Size and Power**

The sample size was chosen based on the practical considerations and to ensure that a clinically meaningful reduction in proteinuria from Baseline (Day 1) could be detected in any of the treatment groups, filgotinib or lanraplenib. With 16 subjects per treatment group (32 subjects total), there is a 80% power to detect a 35% reduction from Baseline (Day 1) in proteinuria at Week 16 with a standard deviation of 50% and a 2-sided 0.05 significance level.

The enrollment was stopped after 9 subjects were randomized.

## **2. TYPE OF PLANNED ANALYSIS**

### **2.1. Interim Analyses**

The first DMC data review meeting was planned to be conducted after approximately 50% of planned subjects enrolled and completed through 16 weeks of study treatment.

Due to early closure of the study enrollment, required number of subjects for the first planned DMC review was not reached. Therefore, no data reviews were performed by DMC.

### **2.2. Final Analysis**

After all subjects have completed the study, 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 provided; for continuous variables, the number of subjects (n), mean, standard deviation (SD), median, first quartile (Q1), third quartile (Q3), minimum, and maximum will be presented.

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 AEs, will be presented in chronological order within the subject. The treatment group to which subjects were randomized will be provided 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 and 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 randomized subjects who took at least 1 dose of study drug (filgotinib, lanraplenib). This is the primary analysis set for efficacy analyses.

##### **3.1.3. Safety Analysis Set**

The Safety Analysis Set includes all subjects who took at least 1 dose of study drug. This is the primary analysis set for safety analyses. All data collected during treatment plus 30 days after the last dose of any study drug will be included in the safety summaries.

#### **3.2. Subject Grouping**

For analyses based on the FAS, subjects will be grouped according to the treatment to which they were initially randomized at Study Day 1. For analyses based on the Safety Analysis Set,

subjects will be grouped according to the actual treatment 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.

### **3.3. Strata and Covariates**

Subjects were randomly assigned to treatment groups via the interactive voice or web response system (IXRS) in a 1:1 ratio using a stratified randomization schedule. Stratification was based on the prior treatment with cyclophosphamide.

The stratification factor values recorded in IXRS will be used for analyses.

### **3.4. Examination of Subject Subgroups**

There are no prespecified subject subgroups for efficacy and safety analyses.

### **3.5. Multiple Comparisons**

Adjustments for multiplicity will not be applied.

### **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](#).

#### **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**

The following conventions will be used for the imputation of date of birth when it is partially missing or not collected:

- If only month and year of birth is collected, then “01” will be imputed as the day of birth
- If only year of birth is collected, then “01 July” will be imputed as the day and month of birth
- If year of birth is missing, then date of birth will not be imputed

In general, age (in years) collected at Day 1 will be used for analyses and presented in listings. If age at Day 1 is not available for a subject, then age derived based on date of birth and the Day 1 visit date will be used instead. If an enrolled subject was not dosed with any study drug, the randomization date will be used instead of the Day 1 visit date. For screen failures, the date the first informed consent was signed will be used for the age derivation. 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.

The 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).

### **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 postdose 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 first dose of study drug administration.

The study day for treatment period 2 (From Week 16 to Week 32) / period 3 (from Week 32 to study end) will be calculated as: Assessment Date – Date of the first dose of the corresponding treatment period (Day 1 for treatment period 1; Week 16 for treatment period 2 and Week 32 for treatment period 3) + 1. The dates of the first dose of the study drug dispensed at Day 1/Week 16/Week 32 are recorded on CRF.

### 3.8.2. Analysis Visit Windows

The target study days for analysis visits are provided in the [Table 3-1](#)

**Table 3-1. Target Days for Analysis Visits**

Nominal Visit	Study Day from Day 1/ From Week 16/From Week 32
Screening	<1
Baseline	<=1
Week 1	8
Week 2	15
Week 4	29
Week 8	57
Week 12	85
Week 16	113/1
Week 18	127/15
Week 20	141/29
Week 24	169/57
Week 28	197/85
Week 32	225/113/1
Week 36	253/141/29
Week 40	281/169/57
Week 44	309/197/85
Week 48	337/225/113
Week 52	365/253/141
Follow-up Visit	NA

The nominal visit as recorded on the CRF will be used when data are summarized by visit. Any data relating to 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.
- The early termination (ET) data will be presented as a separate visit and labeled “ET Visit”.
- 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 Window**

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

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 nominal 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 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 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.

## **4. SUBJECT DISPOSITION**

### **4.1. Subject Enrollment and Disposition**

A summary of subject enrollment will be provided by treatment group 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.

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 treatment period with the following categories:

- Completed study up to Week 16, Week 32, and through the end of the study
- Completed study drug up to Week 16, Week 32, and through the end of study
- Did not complete the study/study drug up to Week 16, Week 32, and through the end of study with reasons for premature discontinuation of the study/study drug
- Treatment switched at Week 16/Week 32

For the status of study drug and study completion, and reasons for discontinuation, 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.

## **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 relative 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 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 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.

The total duration of exposure to study drug will be summarized using descriptive statistics and categorical summary (number and percentage of subjects exposed). 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**

An adherence to study drug will not be summarized.

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

## **4.3. Protocol Deviations**

A by-subject listing will be provided for those subjects who did not meet at least 1 eligibility (inclusion or exclusion) criterion. The listing will present the eligibility criterion (or criteria if more than 1 deviation) that subjects did not meet and related comments, if collected.

Protocol deviations occurring after subjects entered the study are documented during routine monitoring. A by-subject listing will be provided for the subjects with important protocol deviation.



## **5. BASELINE CHARACTERISTICS**

### **5.1. Demographics**

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. 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)
- Sex

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

### **5.2. Other Baseline Characteristics**

The baseline characteristics include:

- Prior treatment with cyclophosphamide (Yes, No)
- 24-hour urine protein (< 3g/d, > 3g/d)
- Baseline 24-hour urine protein
- Baseline eGFR
- Baseline UPCR (average of 2 morning voids)
- UPCR from a 24-hour urine collection
- Current treatment with systemic corticosteroids (Yes, No)

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 listed.

## **6. EFFICACY ANALYSES**

### **6.1. Primary Efficacy Endpoint**

The primary endpoint is the percent change in urine protein from Baseline (Day 1) to Week 16. Urine protein is assessed by urinary protein excretion during a 24-hour urine collection.

#### **6.1.1. Statistical Hypothesis for the Primary Efficacy Endpoint**

No statistical hypotheses will be tested.

#### **6.1.2. Analysis of the Primary Efficacy Endpoint**

The primary endpoint, the percent change from Baseline (Day 1) in 24-hour proteinuria at Week 16 will be presented in descriptive statistics for each treatment group.

### **6.2. Secondary Efficacy Endpoints**

#### **6.2.1. Definitions of Key Secondary Efficacy Endpoints**

The secondary efficacy endpoints include:

- Change from Baseline (Day 1) in urine protein (assessed by urine protein excretion during a 24-hour urine collection) at Week 16
- Change from Baseline (Day 1) in eGFR at Week 16
- Change from Baseline (Day 1) in UPCR (assessed by urine protein excretion during a 24-hour urine collection) at Week 16
- Proportion of subjects with partial remission (defined as urine protein excretion below  $< 3$  g/d and urine protein excretion decrease by  $\geq 50\%$  among subjects with Baseline (Day 1) nephrotic range proteinuria [urine protein excretion  $\geq 3$  g/d]; or urine protein excretion decrease by  $\geq 50\%$  among subjects with subnephrotic range proteinuria [urine protein excretion  $< 3$  g/d]) at Week 16
- Proportion of subjects with complete remission (defined as urine protein excretion below 0.5 g/day, with no hematuria) at Week 16

#### **6.2.2. Analysis Methods for Secondary Efficacy Endpoints**

The absolute changes and relative changes from baseline by visit will be provided in the descriptive summaries. Secondary endpoints and their components will be presented in listings.



### 6.3.2. Analysis Methods for Exploratory Efficacy Endpoints

CCI [REDACTED]

[REDACTED]

## **7. SAFETY ANALYSES**

### **7.1. Adverse Events and Deaths**

#### **7.1.1. Adverse Event Dictionary**

Clinical and laboratory adverse events (AEs) will be coded using the current version of MedDRA. 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 safety 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) are defined as 1 or both of the following:

- 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.

TEAEs of treatment period Up to Week 16 are defined as 1 or both of the following:

- Any AEs with an onset date on or after first dosing date of a treatment period, prior to the first dose of treatment at Week 16. For subjects who did not continue treatment past Week 16, 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 Week 16 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.

A brief, high-level summary of the number and percentage of subjects who experienced at least 1 TEAE in the categories described below will be provided by treatment group. All deaths observed in the study will also be included in this summary.

The number and percentage of subjects who experienced at least 1 TEAE will be provided and summarized by SOC, PT, severity and treatment group for the following:

- All TEAEs
- All TE treatment-related AEs
- All TE SAEs
- TEAEs of interest

For the AE categories described below, summaries will be provided by SOC, PT, and treatment group:

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

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 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, data listings will be provided for the following:

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

Adverse events of interest will be identified by the use of either Standardized MedDRA queries or MedDRA search terms.

The following adverse events of interest will be presented:

- 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)
- Herpes Zoster infection
- Opportunistic infections
- Active tuberculosis
- Hepatitis B and C



- Serious Major Adverse Cardiovascular Events (MACE)
  - Unstable angina
  - Cardiac failure
  - Stroke
  - Transient ischemic attack
  - Percutaneous coronary intervention
  - Myocardial Infarction
- Gastrointestinal perforation
- Venous thrombotic events and pulmonary embolism
- Malignancy including non-melanoma skin cancer
- Transaminases increased

## **7.2. Laboratory Evaluations**

The TE laboratory abnormalities will be reported by the treatment period.

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 for laboratory tests will not be provided. Hematology, chemistry and urinalysis results will be listed.

### **7.2.2. Graded Laboratory Values**

The CTCAE v4.03 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 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. 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.

The listing of all laboratory abnormalities will be provided.

#### 7.2.2.2. Summaries of Laboratory Abnormalities

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

For all summaries of laboratory abnormalities, the denominator is the number of subjects with nonmissing postbaseline values within study period.

A by-subject listing of treatment-emergent Grade 3 or 4 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 laboratory evaluations will be presented as part of chemistry results.

#### 7.3. Body Weight and Vital Signs

Body weight and vital signs will be listed.

#### 7.4. Prior and Concomitant Medications

Prior and concomitant medications will be listed.

#### 7.5. Electrocardiogram Results

Electrocardiogram results (overall assessment and 12-lead ECG) data will be listed.

#### 7.6. Changes From Protocol-Specified Safety Analyses

Only limited safety summaries are provided due to low number of subjects enrolled in the study prior to study termination.

## **8. SOFTWARE**

SAS<sup>®</sup> Software Version 9.4. SAS Institute Inc., Cary, NC, USA.

## 9. SAP REVISION

<b>Revision Date (DD MMM YYYY)</b>	<b>Section</b>	<b>Summary of Revision</b>	<b>Reason for Revision</b>

## 10. APPENDICES

### Appendix 1. Schedule of Assessments

#### Appendix 1. Schedule of Assessments

Visit Window (Days)	Blinded Treatment Phase						Extended Blinded Treatment Phase		End of Study		Unscheduled Visit (exacerbation of LMN) <sup>f</sup>
	Screen <sup>a</sup>	D1/ Baseline	Week 1	Weeks 2, 4, 8, 12, 18, 20, 24, 28	Week 16 <sup>b</sup>	Week 32 <sup>c</sup>	Weeks 36, 40, 44, 48	Week 52	F/U <sup>d</sup>	ET <sup>e</sup>	
	-35	0	±3	±3	±3	±3	±5	±5	±5	±5	
Written Informed Consent	X										
Medical History, including kidney biopsy report	X										
Review Inclusion/Exclusion Criteria	X	X									
Randomization		X									
Height	X										
Weight	X	X	X	X	X	X	X	X	X	X	
Complete Physical Examination	X								X	X	
Symptom driven Physical Examination <sup>g</sup>		X	X	X	X	X	X	X			X
2 Morning voids & 24 hour Urine Collection <sup>h</sup>	X <sup>h</sup>	X <sup>h</sup>			X <sup>h</sup>	X <sup>h</sup>		X <sup>h</sup>	X <sup>h</sup>		
Urinalysis <sup>i</sup>	X	X	X	X	X	X	X	X			X

Visit Window (Days)	Blinded Treatment Phase						Extended Blinded Treatment Phase		End of Study		Unscheduled Visit (exacerbation of LMN) <sup>f</sup>
	Screen <sup>a</sup>	D1/ Baseline	Week 1	Weeks 2, 4, 8, 12, 18, 20, 24, 28	Week 16 <sup>b</sup>	Week 32 <sup>c</sup>	Weeks 36, 40, 44, 48	Week 52	F/U <sup>d</sup>	ET <sup>e</sup>	
	-35	0	±3	±3	±3	±3	±5	±5	±5	±5	
SELENA SLEDAI <sup>j, bb</sup>		X		X	X	X	X	X	X		
BILAG <sup>k, bb</sup>		X			X	X		X	X		
Patient Global Assessment of disease activity <sup>l, bb</sup>		X			X	X		X	X		
Physician Global Assessment of disease activity <sup>m, bb</sup>		X			X	X		X	X		
36 Item Short Form Health Survey <sup>bb</sup>		X			X	X		X	X		
Vital Signs <sup>n</sup>	X	X	X	X	X	X	X	X	X	X	X
ECG	X	X			X	X		X		X	
Hematology	X	X	X	X	X	X	X	X	X	X	
Serum Chemistry	X	X	X	X	X	X	X	X	X	X	
Fasting Lipids		X			X	X			X		
Coagulation	X	X	X	X	X	X	X	X	X	X	
HbA <sub>1c</sub> and TSH	X										
CRP and ESR	X	X	X	X	X	X	X	X	X	X	
Quantitative Serum Immunoglobulin Test		X		X <sup>cc</sup>			X <sup>dd</sup>				
Autoantibody Panel & Complement Levels	X	X		X <sup>z</sup>	X	X		X	X	X	
Serum Pregnancy Test <sup>o</sup>	X										
Urine Pregnancy Test <sup>o, p</sup>		X	X	X	X	X	X	X	X	X	X
FSH Test <sup>q</sup>	X										

Visit Window (Days)	Blinded Treatment Phase						Extended Blinded Treatment Phase		End of Study		Unscheduled Visit (exacerbation of LMN) <sup>f</sup>
	Screen <sup>a</sup>	D1/ Baseline	Week 1	Weeks 2, 4, 8, 12, 18, 20, 24, 28	Week 16 <sup>b</sup>	Week 32 <sup>c</sup>	Weeks 36, 40, 44, 48	Week 52	F/U <sup>d</sup>	ET <sup>e</sup>	
	-35	0	±3	±3	±3	±3	±5	±5	±5	±5	
HIV 1/2, HBV, HCV Serology	X										
HCV RNA VL <sup>f</sup>	X	X	X	X	X	X	X	X	X	X	
QuantiFERON <sup>®</sup> TB Gold in Tube Test <sup>g</sup>	X										
Chest X Ray <sup>g</sup>	X										
Plasma PK Sample <sup>h</sup>				X	X	X					
Urine PK Samples <sup>h</sup>					X						
<b>CCI</b>											
Whole Blood TBNK Biomarker Sample	X	X		X <sup>x</sup>	X	X		X	X	X	
Serum Biomarker Sample	X	X		X <sup>x</sup>	X	X		X	X	X	
Plasma Biomarker Sample	X	X		X <sup>x</sup>	X	X		X	X	X	
vfPBMC Sample	X	X		X <sup>x</sup>	X	X		X	X	X	
PAXgene RNA Sample	X	X		X <sup>x</sup>	X	X		X	X	X	
Urine Biomarker Sample	X	X		X <sup>x</sup>	X	X		X	X	X	
In Clinic Study Drug Administration <sup>y</sup>		X		X	X	X					

Visit Window (Days)	Blinded Treatment Phase						Extended Blinded Treatment Phase		End of Study		Unscheduled Visit (exacerbation of LMN) <sup>f</sup>
	Screen <sup>a</sup>	D1/ Baseline	Week 1	Weeks 2, 4, 8, 12, 18, 20, 24, 28	Week 16 <sup>b</sup>	Week 32 <sup>c</sup>	Weeks 36, 40, 44, 48	Week 52	F/U <sup>d</sup>	ET <sup>e</sup>	
	-35	0	±3	±3	±3	±3	±5	±5	±5	±5	
Study Drug Accountability			X	X	X	X	X	X		X	
Study Drug Dispensing		X		X <sup>aa</sup>	X	X	X				
Review AEs & Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X

- a Prospective subjects should be screened no more than 35 days prior to the administration of the first dose of study treatment. The Screening visit will take two separate days to complete. In addition, Screening Day 2 cannot occur earlier than 3 days after Screening Day 1 due to the timing of the morning urine voids and the 24 hour urine collection.
- b Urinary protein excretion will be determined using 2 methods – 2 consecutive morning voids as well as a 24 hour urine collection. For the Baseline assessment, all 3 urine samples will be collected prior to Day 1, with the 24 hour urine collection as close to the Day 1 visit as possible. At Week 16, the primary study endpoint will be assessed by urine protein excretion during a 24 hour urine collection. Two consecutive morning voids prior to the Week 16 visit will be used to determine response for subsequent study treatment. All subjects who achieve a  $\geq 35\%$  reduction in urinary protein excretion (using an average of the UPCR from the morning voids) from Baseline (Day 1) will continue to receive their assigned blinded study treatment (filgotinib 200 mg + PTM lanraplenib, or lanraplenib 30 mg + PTM filgotinib) for an additional 16 weeks. Subjects who do not achieve a  $\geq 35\%$  reduction in urinary protein excretion from Baseline (Day 1) to Week 16 will switch study treatment for 16 weeks in a blinded fashion (ie, those on filgotinib will switch to lanraplenib + PTM filgotinib, while those on lanraplenib will switch to filgotinib + PTM lanraplenib)
- c After 32 weeks of blinded treatment, those who have a  $\geq 35\%$  reduction in urinary protein excretion (using an average of the UPCR from 2 morning voids) from Day 1 (for subjects who remained on the randomized study treatment after Week 16) or from Week 16 (for subjects who switched treatment at Week 16) will continue their assigned blinded treatment for an additional 20 weeks in the Extended Blinded Treatment Phase. Subjects that do not achieve a  $\geq 35\%$  reduction in urinary protein excretion from Day 1 (for subjects who remained on the randomized study treatment after Week 16) or from Week 16 (for subjects who switched treatment at Week 16) to Week 32 will be allowed to continue whichever treatment led to the greatest reduction in urinary protein excretion (from Day 1 to Week 16 on initial study treatment or from Week 16 to Week 32 on switched treatment), or either study treatment per the Investigator’s discretion during the Extended Blinded Treatment Phase.
- d The Follow up (FU) Visit as detailed in the End of Study section of the Study Procedures Table will be completed 4 weeks after the last dose of study treatment. For subjects that complete the entire study, the FU visit will be conducted at Week 56.
- e Subjects who discontinue from the study for any reason will complete the Early Termination (ET) Visit at the time of study discontinuation.
- f Subjects seen at an unscheduled visit for disease exacerbation (worsening of proteinuria, and/or decrease in eGFR) will complete the Unscheduled Visit assessments.
- g Symptom driven physical examinations will be performed, as needed, based on reported signs and symptoms.
- h Urinary protein excretion will be determined using 2 consecutive morning voids as well as a 24 hour urine collection.  
 For the Day 1 assessment, all 3 urine samples will be collected prior to Day 1, with the 24 hour urine collection as close to the Day 1 visit as possible.  
 For Week 16, subjects will submit 2 consecutive morning urine void samples to the study center approximately 7 days prior to the Week 16 visit to test their change in urinary protein excretion. Subjects will also submit a 24 hour urine collection that is collected immediately prior to the Week 16 visit, or as close to the Week 16 visit as possible. These results will inform their treatment assignment for the additional 16 weeks.



For Week 32, subjects will submit 2 consecutive morning urine void samples to the study center approximately 7 days prior to the Week 32 visit to test their change in urinary protein excretion. Subjects will also submit a 24 hour urine collection that is collected immediately prior to the Week 32 visit, or as close to the Week 32 visit as possible. These results will inform their treatment assignment for the additional 20 weeks in the Extended Blinded Treatment Phase.

- i The urinalysis will include urine microscopy and spot protein to creatinine ratio. As contamination by menstrual blood may interfere with the primary endpoint, whether or not the patient is menstruating will be recorded on the CRF; microscopic urine examination will evaluate for active urine sediment (any of: > 5 WBC/hpf [pyuria], > 5 RBC/hpf [hematuria], or red cell casts in the absence of infection or other causes). In such circumstances, investigators may ask patients to return for another screening visit.
- j Safety of Estrogens in Lupus Erythematosus National Assessment trial based SLE Disease Activity Index (SELENA SLEDAI)
- k British Isles Lupus Activity Group (BILAG)
- l Patient global assessment of disease activity
- m Physician global assessment of disease activity
- n Vital signs include resting blood pressure, respiratory rate, heart rate, and body temperature.
- o Females of childbearing potential only.
- p If a urine pregnancy test is positive, study drug should be immediately interrupted, and the subject should return to the site for a serum pregnancy test to confirm result.
- q Females of nonchildbearing potential only.
- r Subjects with positive HCV Ab, but negative HCV RNA VL at Screening are eligible per investigator judgment, but require ongoing monitoring during the study.
- s Subjects previously treated for latent TB or active TB described in Inclusion # 17 do not need to have the QuantiFERON<sup>®</sup> TB Gold In Tube test (or equivalent assay) obtained, but a chest radiograph must be obtained if not done so within 3 months prior to screening (with the report or films available for investigator review). All other subjects must have the QuantiFERON<sup>®</sup> TB Gold In Tube test (or equivalent assay) obtained at screening AND a chest radiograph (views as per local guidelines) taken at screening or within the 3 months prior to screening (with the report or films available for investigator review).
- t Blood samples will be collected for plasma PK analysis of filgotinib and its active metabolite GS 829845, and lanraplenib post dose at Weeks 2, 4 and 20 (at least 30 minutes and up to 3 hours after dosing), anytime at Weeks 8 and 24, and within 2 hours prior to dosing at Weeks 16 and 32.
- u Urine PK analyses will be collected for lanraplenib, filgotinib and its active metabolite, GS 829845, using the 24h urine collection at Week 16.  
[REDACTED]
- x Biomarker assessments will be collected at Week 2 only.
- y At Weeks 2, 4, and 20, subjects will be instructed to take their study drug in clinic as the first study procedure prior to any others scheduled for that visit. At Day 1, and Weeks 16 and 32, subjects will be instructed to take their study drug after predose assessments have been completed (eg, 2 hours after PK sample collection at Weeks 16 and 32).
- z Autoantibody panel and complement levels will be collected at Weeks 2, 4, and 8 only.
- aa Study drug will not be dispensed at Weeks 2 and 18.
- bb Questionnaires will be administered where available.
- cc Quantitative serum immunoglobulin testing will be performed at Week 8 and 24 only.
- dd Quantitative serum immunoglobulin testing will be performed at Week 48 only.