STATISTICAL ANALYSIS PLAN

Study Title:	A Randomized, Phase 2, Double-blind, Placebo-controlled Study to Assess the Safety and Efficacy of Filgotinib, GS-9876 and GS-4059 in Adult Subjects with Active Sjogren's Syndrome
Name of Test Drug:	Filgotinib, Lanraplenib (GS-9876) and Tirabrutinib (GS-4059)
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CONFIDENTIAL AND PROPRIETARY INFORMATION

TABLE OF CONTENTS

LIST OF ABBREVIATIONS 4
PHARMACOKINETIC ABBREVIATIONS 6
1. INTRODUCTION 7
1.1. Study Objectives 7
1.2. Study Design 7
1.3. Sample Size and Power 8
2. TYPE OF PLANNED ANALYSIS 9
2.1. Interim Analyses 9
2.2. Internal Data Monitoring 9
2.3. Primary (Week 24) Analysis 9
2.4. Final Analysis 10
3. GENERAL CONSIDERATIONS FOR DATA ANALYSES 11
3.1. Analysis Sets 11
3.1.1. All Randomized Analysis Set 11
3.1.2. Full Analysis Set 11
3.1.3. Safety Analysis Set 11
3.1.4. Per-Protocol Analysis Set 11
3.1.5. Pharmacokinetic Analysis Set 12
3.1.6. PK Substudy Analysis Set 12
3.1.7. Biomarker Analysis Set 12
3.2. Subject Grouping 12
3.3. Strata and Covariates 13
3.4. Examination of Subject Subgroups 13
3.5. Multiple Comparisons 14
3.6. Missing Data and Outliers 14
3.6.1. Missing Data 14
3.6.2. Outliers 14
3.7. Data Handling Conventions and Transformations 14
3.8. Analysis Visit Windows 15
3.8.1. Definition of Study Day 15
3.8.2. Analysis Visit Windows 15
3.8.3. Selection of Data in the Event of Multiple Records in an Analysis Visit Window 17
3.9. Efficacy Estimands 17
4. SUBJECT DISPOSITION 19
4.1. Subject Enrollment and Disposition 19
4.2. Extent of Study Drug Exposure and Adherence 20
4.2.1. Duration of Exposure to Study Drug 20
4.2.2. Adherence to Study Drug 21
4.2.2.1. Prescribed Adherence 21
4.3. Protocol Deviations 22
5. BASELINE CHARACTERISTICS 23
5.1. Demographics 23
5.2. Baseline Characteristics 23
5.3. Medical History 24
6. EFFICACY ANALYSES 25

6.1. Multiple Imputations of Missing Data 26
6.2. Definition of the Primary Efficacy Endpoint 26
6.3. Analysis for the Primary Efficacy Endpoint 27
6.3.1. Primary Analysis of Primary Endpoint 27
6.3.2. Sensitivity Analysis of Primary Endpoint 27
6.4. Secondary Efficacy Endpoints 27
6.4.1. Definition of Secondary Efficacy Endpoints 27
6.4.2. Analysis Methods for Secondary Efficacy Endpoints 28
6.5. Exploratory Efficacy Endpoints 28
6.5.1. Definition of Exploratory Efficacy Endpoints 28
6.5.2. Analysis Methods for Exploratory Efficacy Endpoints 31
6.6. Changes From Protocol-Specified Efficacy Analyses 32

7. SAFETY ANALYSES 33

7.1. Adverse Events and Deaths 33
7.1.1. Adverse Event Dictionary 33
7.1.2. Adverse Event Severity 33
7.1.3. Relationship of Adverse Events to Study Drug 33
7.1.4. Serious Adverse Events 33
7.1.5. Treatment-Emergent Adverse Events 34
7.1.5.1. Definition of Treatment-Emergent Adverse Events 34
7.1.5.2. Incomplete Dates 34
7.1.6. Summaries of Adverse Events and Deaths 35
7.1.7. Adverse Events of Special Interest 36
7.2. Laboratory Evaluations 38
7.2.1. Summaries of Numeric Laboratory Results 38
7.2.2. Graded Laboratory Values 39
7.2.2.1. Treatment-Emergent Laboratory Abnormalities 40
7.2.2.2. Treatment-Emergent Marked Laboratory Abnormalities 40
7.2.2.3. Summaries of Laboratory Abnormalities 40
7.2.3. Liver-related Laboratory Evaluations 41
7.2.4. Shifts Relative to the Baseline Value 41
7.3. Body Weight and Vital Signs 42
7.4. Prior and Concomitant Medications 42
7.4.1. Prior Medications 42
7.4.2. Concomitant Medications 43
7.5. Electrocardiogram Results 44
7.6. Other Safety Measures 44
7.7. Changes From Protocol-Specified Safety Analyses 44

8. PHARMACOKINETIC (PK) ANALYSES 45

8.1. Pharmacokinetic Sample Collection 45
8.2. PK Analyses Related to Intensive PK Sampling 45
8.3. Estimation of Pharmacokinetic Parameters 45
8.4. Pharmacokinetic Parameters 46
8.5. Statistical Analysis Methods 46

9. REFERENCES 48

10. SOFTWARE 49

11. SAP REVISION 50

12. APPENDIXES 51

LIST OF ABBREVIATIONS

AE	adverse event
ALT	alanine aminotransferase
ANCOVA	Analysis of covariance
AST	aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
AUC	area under the curve
BLQ	below the limit of quantitation
BMI	body mass index
CFR	Code of Federal Regulations
CI	confidence interval
CMH	Cochran Mantel Haenszel
CK	creatine kinase
csDMARD	Conventional synthetic disease-modifying antirheumatic drug
CRF	case report form
CSR	clinical study report
CTCAE	Common Toxicity Criteria for Adverse Events
DILI	drug-induced liver injury
DMC	data monitoring committee
DMARD	Disease-modifying antirheumatic drug
ECG	Electrocardiogram
EDC	Electronic Data Capture
ESSDAI	EULAR Sjogren's Syndrome Disease Activity Index
ESSPRI	EULAR Sjögren's Syndrome Patient Reported Index
ET	early termination
FAS	Full Analysis Set
Hb	hemoglobin
HLT	high-level term
hsCRP	high sensitivity C-Reactive Protein
ICH	International Conference on Harmonization (of Technical Requirements for Registration of Pharmaceuticals for Human Use)
LLOQ	lower limits of quantitation
IDEEL	Impact of Dry Eye on Everyday Life
IXRS	interactive voice or web response system
LOCF	last observation carry forward
LTT	lower-level term
LOQ	limit of quantitation
MACE	major adverse cardiovascular event
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	mixed effects repeated measures

MST	MedDRA Search Term
OHIP	Oral Health Impact Profile
PP	Per Protocol
PT	Preferred Term
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
SAP	statistical analysis plan
SAE	serious adverse event
SD	standard deviation
SI (units)	international system of units
SjS	Sjogren's Syndrome
SLE	systemic lupus erythematosus
SMQs	Standardized Medical Queries
SOC	system organ class
TEAE	treatment-emergent adverse event
TFLs	tables, figures, and listings
TMT	Trail Making Test
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-445-4189. This SAP is based on the study protocol amendment 1 dated 12 July 2018 and the electronic case report forms (eCRF). The SAP will be finalized before the primary analysis (Week 24) is performed. 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:

- To assess the efficacy of filgotinib, lanraplenib (GS-9876), and tirabrutinib (GS-4059) in adult subjects with active Sjogren's Syndrome (SjS)

The secondary objectives of this study are:

- To assess the safety and tolerability of filgotinib, lanraplenib, and tirabrutinib in active SjS
- To assess the effect of filgotinib, lanraplenib, and tirabrutinib on patient reported outcomes in active SjS

The exploratory objectives of this study are:

CCI

1.2. Study Design

This is a Phase 2, multicenter, randomized, double-blind, placebo-controlled study to evaluate the safety and efficacy of filgotinib, lanraplenib (GS-9876), and tirabrutinib (GS-4059) in adult male and female subjects with active SjS.

At Day 1, eligible subjects will be randomized 1:1:1:1 to daily oral filgotinib (200 mg), lanraplenib (30 mg), tirabrutinib (40 mg) or placebo to match (PTM). Randomization will be stratified by: use of concurrent immunomodulatory drugs at baseline (Y/N: conventional synthetic disease modifying antirheumatic drugs (csDMARD[s]) or corticosteroids), and the hematologic + biological component scores of the EULAR Sjogren's syndrome disease activity index (ESSDAI) obtained at screening (combined score of <2 or ≥ 2).

Stable medications at Day 1 should be continued during the study dosing period through Week 48. Dose adjustments for toxicities and dose adjustment of corticosteroids are allowed after Week 12. Subjects will return to the study site for scheduled study visits at Weeks 2, 4, 8, 12, 18, 24, 26, 28, 32, 36, 42, and 48 (Appendix 1).

At completion of the Week 24 visits, subjects on placebo will be re-randomized 1:1:1, in a blinded fashion, to daily oral filgotinib (200 mg), lanraplenib (30 mg), or tirabrutinib (40 mg) without further stratification. Dosing and assessments for all subjects will continue through Week 48.

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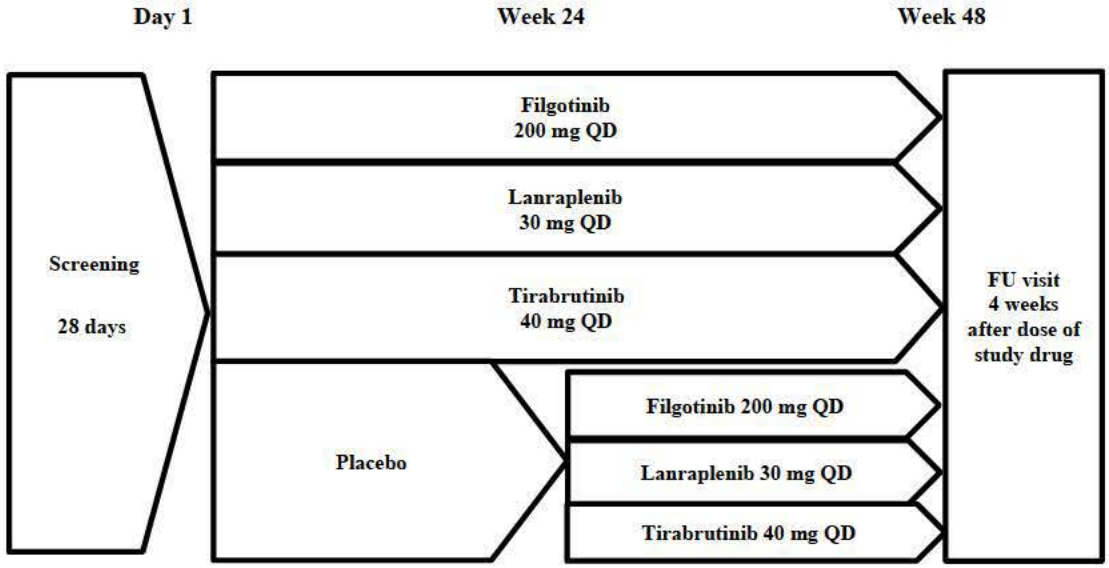
Subjects who discontinue study drug for any reason (other than noncompliance) may continue to participate in scheduled study visits and procedures, as long as deemed medically appropriate by the investigator. Subjects who discontinue all study participation will have an early termination (ET) visit; these subjects, and those who complete the study, should return to the study site for a follow-up visit, 4 weeks after the last dose of study drug (subjects who have discontinued study drug ≥ 4 weeks prior to the ET/Week 48 visit, do not need a follow up visit).

Figure 1. Study Design Schematic



1.3. Sample Size and Power

The sample size was estimated based on historical data. Assuming a response rate of 70% for an active arm and 30% for the placebo arm at Week 12, approximately 35 evaluable subjects will be needed in each arm to achieve 85% power to detect a significant difference at a 2-sided, 0.05-level. Enrollment of approximately 35 subjects per arm is planned to ensure that a sufficient number of subjects is available for the analysis of the primary endpoint.

2. TYPE OF PLANNED ANALYSIS

2.1. Interim Analyses

An external data monitoring committee (DMC) has not been established for this study. Therefore, no analyses will be conducted for the external DMC.

2.2. Internal Data Monitoring

To assess the safety and efficacy of filgotinib, lanraplenib and tirabrutinib, and 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 activities of the internal unblinded data monitoring team will be governed by the 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.

2.3. Primary (Week 24) Analysis

A planned Week 24 analysis will be conducted after all subjects have either completed their Week 24 visit or 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 24 unblinded safety and efficacy analysis results. A memo and a list will be maintained which documents the individuals granted access to the Week 24 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 Interim Analysis 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):

- Demographic characteristics (only Total column - all treatment groups combined)
- Baseline characteristics (only Total column)

- Disposition (only Total column)
- Primary Responder Analysis at Week 12
- Inferential analysis of ESSDAI Change from Baseline to Week 12 and Week 24
- Inferential analysis of EULAR Sjögren's Syndrome Patient Reported Index (ESSPRI) Change from Baseline to Week 12 and Week 24
- Other analyses as deemed necessary for program planning purposes

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

2.4. 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 presented; 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.

All statistical tests will be 2-sided and performed at the 0.05 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 AEs, will be presented in chronological order within the subject. The treatment group to which subjects were initially assigned 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 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 primary analysis set for efficacy analyses will be the Full Analysis Set (FAS), which includes all randomized subjects who received at least one dose of study drug.

3.1.3. Safety Analysis Set

The primary analysis set for safety analyses will be the Safety Analysis Set, which includes all subjects who received at least one dose of study drug.

3.1.4. Per-Protocol Analysis Set

No analyses will be performed using the Per-Protocol analysis set.

3.1.5. Pharmacokinetic Analysis Set

The Pharmacokinetic (PK) Analysis Set will include all subjects in the Safety Analysis Set who have at least 1 non-missing post-dose PK concentration data for filgotinib, lanraplenib, tirabrutinib, and/or their metabolite(s). This is the primary analysis set for all PK analyses.

3.1.6. PK Substudy Analysis Set

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3.1.7. 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 evaluable measurement available at any time point for a given biomarker of interest.

3.2. Subject Grouping

For the analysis of placebo-controlled period (up to week 24), subjects will be presented by four treatment groups:

- Filgotinib 200 mg
- Lanraplenib 30 mg
- Tirabrutinib 40 mg
- Placebo

For the analyses of the entire study period, subjects will be grouped into seven treatment groups as specified in Table 1. For the analyses based on the FAS Analysis Set, subjects will be grouped according to the treatment to which they were randomized at Study Day 1 and Week 24. 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 differ from the randomized treatment only when their actual treatment differs from randomized treatment for the entire treatment duration.

Table 1. Treatment Groups for the Entire Study Summaries

Filgotinib 200 mg	Filgotinib 200 mg from Study Day 1
Lanraplenib 30 mg	Lanraplenib 30 mg from Study Day 1
Tirabrutinib 40 mg	Tirabrutinib 40 mg from Study Day 1
Placebo/Filgotinib 200 mg	Placebo up to Week 24 and Filgotinib 200 mg after Week 24 first dose
Placebo/Lanraplenib 30 mg	Placebo up to Week 24 and Lanraplenib 30 mg after Week 24 first dose
Placebo/Tirabrutinib 40 mg	Placebo up to Week 24 and Tirabrutinib 40 mg after Week 24 first dose
Placebo	Placebo group with study drug withdrawn prior to or at Week 24 (not received drug assigned at Week 24)

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

3.3. Strata and Covariates

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

- Use of concurrent immunomodulatory drugs at baseline (Y/N: conventional synthetic disease modifying antirheumatic drugs (csDMARD[s]) or corticosteroids)
- Hematologic + biological component scores of the ESSDAI obtained at screening (combined score of <2 or ≥ 2)

Only systemic use of csDMARDs (route of administration oral, subcutaneous, intramuscular, or intravenous) is considered for the stratification. If there are discrepancies in stratification factor values between the IWRS and the clinical database, the values recorded in the clinical database will be used for analyses. If it is impossible to derive the stratification factor from the clinical database due to missing values, data from IWRS 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 baseline characteristics and randomization stratification variables:

- Age (< 50 years and ≥ 50 years)
- Diagnosis of autoimmune disease (Yes and No)
- Diagnosis of SLE (Yes, No)
- Diagnosis of RA (Yes, No)
- Duration of the disease (<5 years, >= 5 years)
- Use of concurrent immunomodulatory drugs (csDMARD or corticosteroids) at baseline (systemic use of these medications at Day1 – Yes and No)
- Hematological + biological component scores of the ESSDAI obtained at screening (combined score of <2 and ≥ 2).
- ESSDAI at Baseline (<14 and >=14)

3.5. Multiple Comparisons

All endpoint tests will be done at the significance level of 0.05 with no multiplicity adjustment in this proof-of-concept study.

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 determining treatment emergent AE status is described in Section 7.1.5.2. The handling of missing date for prior and concomitant medications is described 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 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.

For placebo subjects who were re-randomized to active treatment, 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 active treatment is recorded on CRF.

3.8.2. Analysis Visit Windows

The target study days for analysis visits are provided in the Table 2 below:

Table 2. 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
Week 18	127
Week 24	169/1
Week 26	183/15
Week 28	197/29
Week 32	225/57
Week 36	253/85
Week 42	295/127
Week 48	337/169
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 or screening 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. If this next scheduled visit for parameter falls on the visit after the latest performed scheduled visit as reported in the clinical database then the analysis visit is not assigned and the value is not included in the analyses.

Data collected at a follow-up visit will be summarized under a separate visit, and labeled "Follow-up Visit."

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.

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

- In general, the baseline value will be the last nonmissing value on or prior to the first dosing date of study drug, unless specified differently. If multiple measurements occur on the same day, the last nonmissing value prior to the time of first dosing of study drug will be considered as the baseline value. If these multiple measurements occur at the same time or the time is not available, the average of these measurements will be considered the baseline value.
- For postbaseline values:
  - The record closest to the nominal day for that visit will be selected.
  - If there are 2 records that are equidistant from the nominal day, the later record will be selected.
  - If there is more than 1 record on the selected day, the average will be taken, unless otherwise specified.

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

- For baseline, the last available record on or prior to the date of the first dose of study drug will be selected. If there are multiple records with the same time or no time recorded on the same day, the value with the lowest severity will be selected (e.g., normal will be selected over abnormal for safety electrocardiogram [ECG] findings).
- For postbaseline visits, 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 (e.g., 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, a hypothetical estimand and a composite estimand, are defined for the primary and secondary efficacy endpoints.

The **treatment-policy estimand** is the primary estimand for the primary and secondary efficacy endpoints.

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

The **hypothetical estimand** is defined as following. This is the supportive estimand for the primary and secondary efficacy endpoints.

1) Population: Subjects in the Full Analysis Set (FAS).

2) Variable: Primary and secondary endpoints

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

- Subject takes prohibited medication
- Subject changes the dose of the medication required to be stable per protocol
- Subject discontinues from study treatment

The **composite estimand** is defined as following. This is the supportive estimand for the primary and secondary efficacy endpoints.

1) Population: Subjects in the Full Analysis Set (FAS).

2) Variable: Primary and secondary endpoints

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

- Subject takes prohibited medication
- Subject changes the dose of the medication required to be stable per protocol
- Subject discontinues from study treatment

The estimators associated with each of these estimands are described in Table 3 of Section 6.

4. SUBJECT DISPOSITION

4.1. Subject Enrollment and Disposition

A summary of subject enrollment will be provided by 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 IWRS 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 IWRS 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 for the entire study duration and by treatment phase. This summary will present the number of subjects screened, the number of subjects randomized, and the number of subjects in each of the categories listed below:

- 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
- Re-randomized at Week 24
- Continuing study drug (Week 24 Analysis only)
- Continuing study (Week 24 Analysis only)

For the status of study drug and study completion and reasons for premature 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. In addition, a flowchart will be provided to depict the disposition.

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. Completion of treatment up to Week 12 is considered when the [date of last dose – date of first dose + 1] >= 82 days (target date for Week 12 visit minus protocol allowed visit window). Similar algorithm is applied to Week 24 completion. Subjects are considered to complete 24 weeks of treatment if the start date of Week 24 treatment is provided or the [last dose date – first dose date +1] >= 166. Subjects who complete Week 24 visit/treatment but did not continue beyond Week 24 are reported as "Discontinued at Week 24".

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 the last dosing date of any study drug minus the 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 (e.g. 4.5 weeks). For Week 24 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 (i.e., 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 (i.e., 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 24 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, 16,

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 2) minus protocol-allowed window (Appendix 1).

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

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

For each subject, the adherence will be calculated separately for each treatment administered: lanraplenib 30 mg/PTM, filgotinib 200 mg/PTM, or tirabrutinib 40 mg/PTM. The overall adherence to study drug will be defined as the lowest of the three.

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 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.

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 as well as the number and percentage of subjects in each of the two adherence categories, < 80% and ≥ 80%, will be presented by treatment group for the Safety Analysis Set.

The expected amount of study drug to be administered per protocol is defined as follows:

- Up to Week 12: 84 (7 * 12) doses
- Up to Week 24: 168 (7 * 24) doses
- Entire study duration: 336 (7 * 48) doses

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 (e.g., non-adherence to study drug, 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 those 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 be provided for the Safety Analysis Set for the following:

- age (on the first dose date of any study drug) as a continuous variable
- age group (< 50 years, ≥ 50 years)
- sex at birth (male, female)
- race
- ethnicity (Hispanic or Latino, not Hispanic or Latino)
- geographic region and country

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.

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

5.2. Baseline Characteristics

Baseline characteristics include:

- Weight (kg)
- Body mass index (BMI; in kg/m^2)
- Concurrent immunomodulatory drugs at baseline (Y/N: conventional synthetic disease modifying antirheumatic drugs (csDMARD[s]) or corticosteroids on Day 1)
- Concurrent background disease-modifying antirheumatic drug [DMARD] use (Yes, No)
- Concurrent use of systemic (oral) corticosteroids at baseline (Yes, No)
- Concurrent background use of anti-malarial DMARDs at baseline (Yes, No)
- hsCRP (descriptive statistics and categories above/below 1.5 ULN)

- ESSDAI (descriptive statistics and categories (<14 and >=14)
- ESSPRI (descriptive statistics)
- Diagnosis of autoimmune disease (Yes and No)
- Diagnosis of SLE (Yes, No)
- Diagnosis of RA (Yes, No)
- Diagnosis of SLE or RA (Yes, No)
- Duration of SjS disease (<5 years, >= 5 years)
- Hematological + biological component scores of the ESSDAI obtained at screening (combined score of <2 or ≥ 2)
- Baseline VAS: patient's global assessment of SjS, pain, fatigue, oral dryness, ocular dryness, vaginal dryness, sexual function, physician's global assessment of SjS
- Baseline Trail Making Test part A (TMT-A) and Trail Making Test part B (TMT-B)
- Baseline Schirmer's test result (average of eyes)
- Baseline unstimulated and stimulated salivary flow rate
- Baseline swollen and tender joint count (descriptive statistic and categorical: n> 0)
- SS-A and SS-B antibodies at baseline (positive and negative)

The time from SjS 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.

These 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 of subjects 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 SjS and other conditions.

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

Medical history 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 autoimmune comorbidities will be identified by Clinical Research based on MedDRA preferred terms.

6. EFFICACY ANALYSES

Efficacy endpoints will be evaluated for the following treatment periods: placebo-controlled period up to Week 24 and the entire study up to Week 48.

The primary and secondary endpoints analyses will be based on the estimands presented in the Table 3.

Table 3. Efficacy Estimands

Binary Endpoint	Treatment Policy (main)	Hypothetical	Composite
Population	FAS	FAS	FAS
Intercurrent Event	Ignore all intercurrent events	• Treatment discontinuation • Start of prohibited medication • The dose change of medication that is required to be stable Data after the event are treated as missing	• Treatment discontinuation • Start of prohibited medication • The dose change of medication that is required to be stable Data after the event are treated as no response
Main Estimator	Stratified CMH test with imputation of missing data using logistic regression	Stratified CMH test with imputation of missing data using logistic regression	Stratified CMH test with non-responder imputation of missing data

Continuous Endpoints	Treatment Policy (main)	Hypothetical	Composite
Intercurrent Event	Ignore all intercurrent events	• Treatment discontinuation • Start of prohibited medication • The dose change of medication that is required to be stable	• Treatment discontinuation • Start of prohibited medication • The dose change of medication that is required to be stable
Main Estimator	The treatment difference will be estimated using a mixed effects model for repeated measures. Missing data will be imputed using multiple imputation	The treatment difference will be estimated using a mixed effects model for repeated measures. Missing data will be imputed using multiple imputation	The treatment difference will be estimated using a mixed effects model for repeated measures. Missing data will be imputed using multiple imputation based on observed data from the placebo group

6.1. Multiple Imputations of Missing Data

Multiple imputation of binary variables: The MI procedure replaces each missing binary response value with a set of plausible values that represent the uncertainty about the right value to impute. Twenty imputed datasets will be generated based on logistic regression models. These multiple imputed data sets are then analyzed by using the same method for the primary analysis for complete data as specified in Section 6.3. The results from each set of imputed data sets will then be combined using Rubin's rule {Rubin 1987}. Stratification factors will be included in the imputation model.

Multiple imputation of continuous variables: All subjects with baseline measurement will be included. The MI procedure replaces each missing value with a set of plausible values that represent the uncertainty about the right value to impute. Twenty imputed datasets will be generated based on linear regression models on observed values. These multiple imputed data sets are then analyzed by using the analysis method specified in Section 6.4 for complete data. The result of each imputed data set will be combined using Rubin's rule {Rubin 1987}. Stratification factors and baseline values will be included in the imputation model as covariates.

6.2. Definition of the Primary Efficacy Endpoint

The primary endpoint is the proportion of subjects fulfilling protocol-specified response criteria at Week 12, as compared to baseline.

Response is defined as follows (also see Appendix 2):

- For subjects with elevated hsCRP (defined as hsCRP ≥1.5 upper limit of normal [ULN]) on Day 1, response is defined as achieving all of the following:
  - ≥ 20% improvement in hsCRP
  - ≥ 20% improvement in at least 3 out of 5 subject reported, SjS related visual analog scales (VAS; subject's assessment of global disease, pain, oral dryness, ocular dryness, and fatigue)
  - no worsening (i.e., no increase >30 mm from baseline) in any of the above VAS
- For subjects without elevated hsCRP (hsCRP <1.5 ULN) on Day 1, response is defined as achieving all of the following:
  - no increase in hsCRP to ≥ 1.5 ULN
  - ≥ 20% improvement in at least 3 out of 5 subject reported, SjS related VAS (subject's assessment of global disease, pain, oral dryness, ocular dryness, and fatigue)
  - no worsening (i.e., no increase >30 mm from baseline) in any of the above VAS

6.3. Analysis for the Primary Efficacy Endpoint

6.3.1. Primary Analysis of Primary Endpoint

In the primary analysis, the primary outcome in each active treatment group will be compared to the outcome in the placebo group using a superiority test at the 2-sided 0.05-level. The following null hypotheses will be tested (vs. the respective alternative hypotheses):

- H01: There is no difference in the responder rate between filgotinib 200 mg group and placebo group at Week 12
- H02: There is no difference in the responder rate between lanraplenib 30 mg group and placebo group at Week 12
- H03: There is no difference in the responder rate between tirabrutinib 40 mg group and placebo group at Week 12

The analyses will be performed using Cochran Mantel Haenszel (CMH) test adjusted for the randomization stratification factors. If CMH test stratified by both stratification factors is not appropriate due to small cell counts then the levels of the stratification by ESSDAI scores will be pooled, and the analysis will be stratified only by use of concurrent immunomodulatory drugs at baseline. Each of the three hypotheses will be tested separately at the 2-sided, 0.05-level.

The primary analysis will be based on the Treatment Policy Estimand, with missing values imputed by multiple imputation method described in Section 6.1.

The number and percentage of responders in each treatment group as well as 95% confidence intervals (CIs) will be presented for each visit.

6.3.2. Sensitivity Analysis of Primary Endpoint

The following sensitivity analyses of the primary endpoint will be performed:

- Using composite estimand
- Using hypothetical estimand

6.4. Secondary Efficacy Endpoints

6.4.1. Definition of Secondary Efficacy Endpoints

Secondary efficacy endpoints include:

- Change from baseline in ESSDAI total score at Week 12
- Change from baseline in ESSPRI total score at Week 12
- Change from baseline in ESSDAI total score at Week 24
- Change from baseline in ESSPRI total score at Week 24

6.4.2. Analysis Methods for Secondary Efficacy Endpoints

Each secondary endpoint will be analyzed using a mixed-effect repeated measures (MMRM) model with treatment, randomization stratification factors, visit, treatment-by-visit interaction as fixed effects, subjects as a random effect, and the respective baseline value (ESSDAI or ESSPRI) as a covariate. The Kenward-Roger method will be used to estimate the degrees of freedom. Each of the four endpoints will be tested separately at the 2-sided 0.05 level. The unstructured (UN) variance-covariance matrix of repeated measures will be considered first. If a model does not converge, then ARH(1) structure will be applied.

For each secondary endpoint, adjusted means (LS means) and 95% confidence intervals (CIs) obtained from the model will be presented for Weeks12 and Week 24 time points.

Missing data will be handled using the method described in Table 3.

The inferential analyses of the secondary endpoints will be based on the treatment policy estimand (main analysis of each secondary endpoint). Sensitivity non-parametric analyses of the secondary endpoints will be performed on rank-transformed data utilizing ANCOVA models with treatment group and stratification factors as effects and the rank-transformed baseline value as a covariate.

In addition, secondary efficacy analyses will be repeated for the hypothetical estimand and composite estimand.

Descriptive statistics (n, mean, SD, median, Q1, Q3, minimum, and maximum) will be presented by visit and treatment group, overall and for the subgroups listed in section 3.4.

Line plots for median (Q1, Q3) change from baseline, mean (+/- 95% CI) change from baseline, and adjusted mean (LS mean) change from baseline (+/- 95% CI) will be provided for ESSDAI total score, ESSPRI total score and its components.

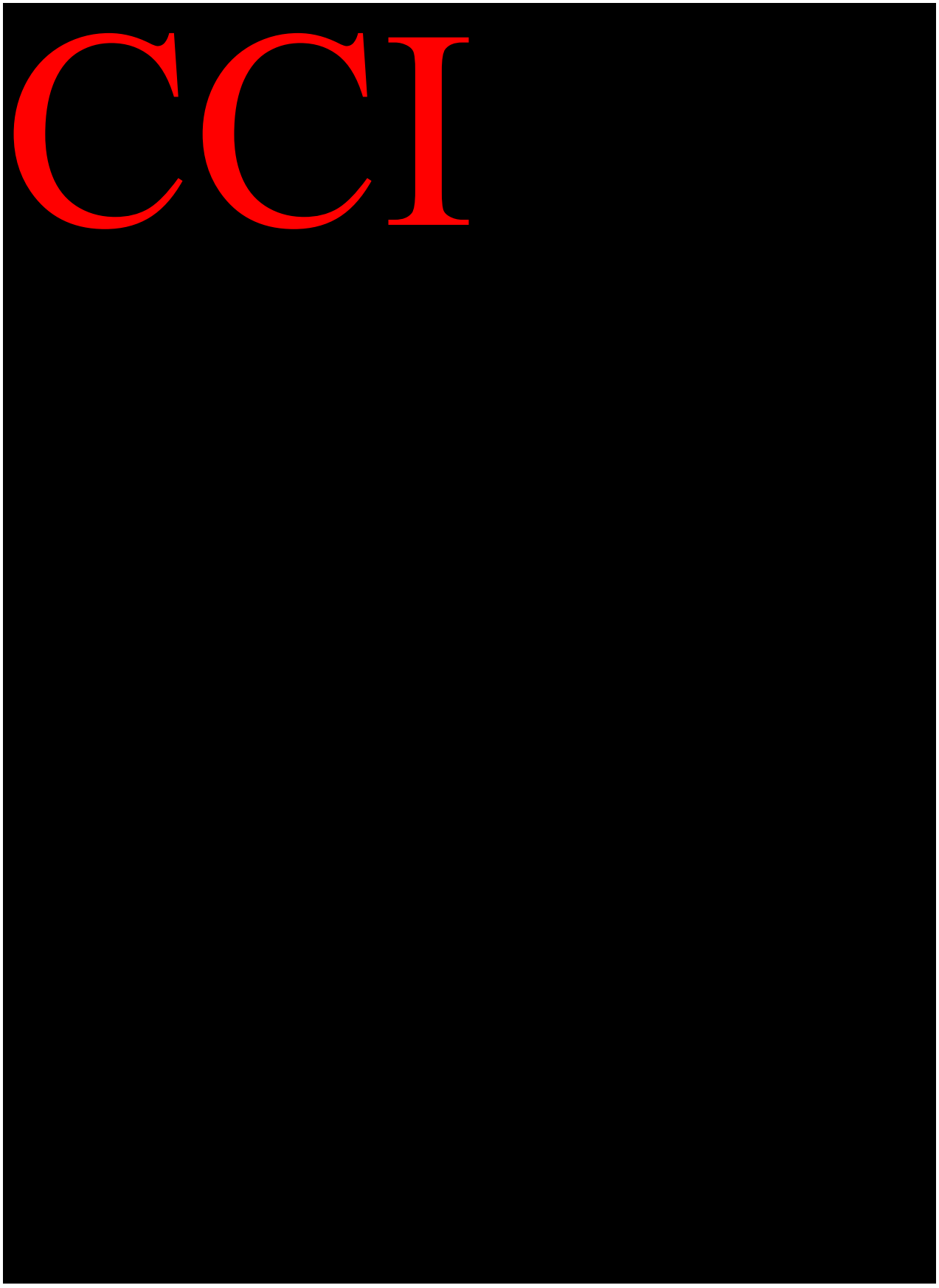
In addition, the box plots for ESSDAI total score and ESSPRI total score and change from baseline will be presented by visit and treatment group.

A cumulative plot of change from baseline in ESSDAI total score and in ESSPRI total score at Week 12 and Week 24 will be presented by treatment group.

6.5. Exploratory Efficacy Endpoints

CCI [redacted]


CCI


CCI

CCI

[redacted]

6.5.2. Analysis Methods for Exploratory Efficacy Endpoints

CCI

[redacted]

CCI [redacted]

[redacted]

6.6. Changes From Protocol-Specified Efficacy Analyses

The treatment policy, hypothetical and composite estimands have been added to the analyses of the primary and secondary endpoints.

7. SAFETY ANALYSES

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

For the analyses of adverse events (AEs) that include data after Week 24 the exposure-adjusted analyses will be presented.

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

7.1. Adverse Events and Deaths

7.1.1. Adverse Event Dictionary

Clinical and laboratory 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 lanraplenib/placebo", "Related to filgotinib/placebo" or "Related to tirabrutinib/placebo". If AE is reported as "Related" to any of 3 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 Gilead 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 Week 24 are defined as 1 or both of the following:

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

TEAEs of active treatment are defined similarly as the definition of the entire study duration, except that active study drug instead of any study drug will be used:

- Any AEs with an onset date on or after the first dose of active study drug and no later than 30 days after permanent discontinuation of active study drug.

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

TEAEs will be summarized based on the Safety Analysis Set.

The tables will be presented by treatment period: placebo-controlled period (up to Week 24) and active treatment period. The overall summary of TEAEs will 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

Adverse 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.

Adverse events of interest include:

- All infections (defined as all PTs within the Infections and Infestations SOC)
  - Infections of interest as defined below
    - Herpes zoster
    - Active tuberculosis
    - Opportunistic infections
    - Hepatitis B (HBV) or C (HCV) infections
- Serious infections (defined as all PTs within the Infections and Infestations SOC that are SAEs)
- Venous thrombotic events
- Malignancies
- Gastrointestinal (GI) perforations
- Liver transaminase elevation
- Bleeding or Haemorrhage (SMQ)
- Renal toxicity (MST)
- Cytopenia
  - HLT Anaemia deficiencies

- HLT Anaemias haemolytic immune
- HLT Anaemias haemolytic mechanical factor
- HLT Anaemias haemolytic NEC (not elsewhere classified)
- HLT Anaemias NEC
- HLT Leukopenias NEC
- HLT Marrow depression and hypoplastic anaemias
- HLT Neutropenias
- HLT Thrombocytopenias

  but excluding PTs in:

  - HLT Anaemias congenital (excluding haemoglobinopathies)
  - HLT Anaemias due to chronic disorders
  - HLT Anaemias haemolytic immune newborn

- Serious potential major adverse cardiovascular events (MACE) including the following:
  - Cardiovascular events
  - Myocardial infarction
  - Hospitalization for unstable angina
  - Transient ischemic attack
  - Stroke
  - Hospitalization for cardiac failure
  - Percutaneous coronary intervention
- Noninfectious Diarrhoea (SMQ)

Potential serious MACE events will not be adjudicated.

The number and percentage of patients with aforementioned events of special interest will be provided by the PT term for each category of AE of special interests.

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

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 latest 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 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 each laboratory test specified in the study protocol as follows:

- Baseline values
- Values at each postbaseline visit
- Change and percentage change from baseline at each postbaseline visit.

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
  - Creatinine phosphokinase (CPK)
  - Glucose
  - Triglycerides
  - Total cholesterol
  - High Density Lipoprotein (HDL)
  - LDL (Low Density Lipoprotein)
  - LDL/HDL ratio

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 Common Terminology Criteria for Adverse Events (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 (i.e., 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 laboratory abnormality occurring after Week 24 visit and no later than 30 days after the last dose of study drug is included only if subject does not continue treatment after Week 24.

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 24 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 period and entire study period.

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 entire study 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.

7.2.4. Shifts Relative to the Baseline Value

Shift tables will be presented for change in severity grade from baseline to Week 12 and Week 24.

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.

The presentations of prior and concomitant medications are described below. In addition, prior and concomitant medication for SjS, SLE and RA will be presented in a separate summary table by medication category (systemic corticosteroids, other corticosteroids, csDMARDs, anti-malarial DMARDs, biologic DMARDs, NSAIDs, other) and preferred term.

All prior and concomitant medications will be provided in a by-subject listing sorted by subject ID number and administration date in chronological order based on Safety Analysis Set.

7.4.1. Prior Medications

Prior medications are defined as any medications taken before a subject took the first study drug (stop date is prior to Day 1).

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.

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 while a subject is on study drug, regardless of when the medication was started. Use of general and disease-specific 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 medications 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 medications. 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.

In addition, prior and concomitant medications for SjS, SLE and RA will be presented in a separate summary table by medication category (csDMARD, systemic corticosteroids, other corticosteroids, NSAIDs, anti-malarial drugs and other), 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.

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

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

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

CCI [redacted]

8.1. Pharmacokinetic Sample Collection

PK samples will be collected prior to study drug administration (pre-dose) at Weeks 4, 8, 12, 24, 36, and 48/ET visit. At Week 18, PK samples will be collected approximately 2 hours post-dose. CCI [redacted].

8.2. PK Analyses Related to Intensive PK Sampling

CCI [redacted]

8.3. Estimation of Pharmacokinetic Parameters

PK parameters will be estimated using Phoenix WinNonlin® software using standard noncompartmental methods. The linear/log trapezoidal rule will be used in conjunction with the appropriate noncompartmental model, with input values for dose level, dosing time, plasma concentration, and corresponding real-time values, based on drug dosing times whenever possible.

For area under the curve (AUC), samples BLQ of the bioanalytical assays occurring prior to the achievement of the first quantifiable concentration will be assigned a concentration value of 0 to prevent overestimation of the initial AUC. Samples that are BLQ at all other time points will be treated as missing data in WinNonlin. The nominal time point for a key event or dosing interval (τ) may be used to permit direct calculation of AUC over specific time intervals. The appropriateness of this approach will be assessed by the PK scientist on a profile-by-profile basis.

Pharmacokinetic parameters such as AUC_{tau}, λ_z and $t_{1/2}$ are dependent on an accurate estimation of the terminal elimination phase of drug. The appropriateness of calculating these parameters will be evaluated upon inspection of PK data on a profile-by-profile basis by the PK scientist.

8.4. Pharmacokinetic Parameters

CCI [redacted]

Table 4. Study Treatments and Associated Analytes

Treatment	Analyte
Filgotinib 200 mg	Filgotinib, GS-829845
Lanraplenib 30 mg	Lanraplenib
Tirabrutinib 40 mg	Tirabrutinib

The analytes and parameters presented in Table 5 will be used to evaluate the PK objectives of the study. The primary PK parameters are AUC_{tau}, C_{tau}, and C_{max} of filgotinib, and active metabolite of filgotinib (GS-829845), lanraplenib and tirabrutinib. The PK parameters to be estimated in this study are listed and defined in the Pharmacokinetic Abbreviations section.

Table 5. Pharmacokinetic Parameters for Each Analyte

Analyte	Parameters
Filgotinib	AUC_{tau}, C_{tau}, C_{max}, T_{max}, λz, CL/F, Vz/F and $t_{1/2}$, if appropriate
GS-829845	AUC_{tau}, C_{tau}, C_{max}, T_{max}, λz, and $t_{1/2}$, if appropriate
Lanraplenib	AUC_{tau}, C_{tau}, C_{max}, T_{max},, λz, CL/F, Vz/F and $t_{1/2}$, if appropriate
Tirabrutinib	AUC_{tau}, C_{tau}, C_{max}, T_{max}, λz, CL/F, Vz/F and $t_{1/2}$, if appropriate

8.5. Statistical Analysis Methods

Individual subject concentration data and individual subject PK parameters for filgotinib, GS-829845, lanraplenib and tirabrutinib 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 both individual subject concentration data by time point and individual subject PK parameters by treatment. Moreover, the geometric mean, 95% CI, and the mean and SD of the natural log-transformed values will be presented for individual subject PK parameter data.

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.

For Weeks 4, 8, 12, 24, 36, and 48/ET visit data, only samples collected 20 to 28 hours after the prior dose will be included in the summary statistics. For Week 18 data, only samples collected 1 to 4 hours after the administration of study drug on the visit day will be included in the summary statistics.

Individual PK parameter data listings and summaries will include all subjects for whom PK parameter(s) can be derived. The sample size for each PK parameter will be based on the number of subjects with nonmissing data for that PK parameter.

The following tables will be provided for each analyte by treatment:

- Individual subject concentration data and summary statistics
- Individual subject plasma PK parameters and summary statistics

The following figures may be provided for each analyte by treatment:

- Individual subject concentration data versus time (on linear and semilogarithmic scales)
- Mean (± SD) concentration data versus time (on linear and semilogarithmic scales)
- Median (Q1, Q3) concentration data versus time (on linear and semilogarithmic scales)

Individual, mean, and median postdose concentration values that are ≤ LLOQ will not be displayed in the figures and remaining points connected.

The following listings will be provided:

- PK sampling details (and PK concentrations) by subject, including procedures, differences in scheduled and actual draw times, and sample age

9. REFERENCES

Rubin DB. Multiple Imputation for Nonresponse in Surveys. New York, NY: John Wiley & Sons, Inc; 1987.

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

12. APPENDIXES

Appendix 1. Schedule of Assessments

	Screening [a]	Day 1[b]	Week 2	Week 4	Week 8	Week 12	Week 18	Week 24	Week 26	Week 28	Week 32	Week 36	Week 42	Week 48/ET[c]	Follow Up visit 4 weeks after subject's last study visit [d]
Visit window	**None**	**None**	**+/- 3 days**	**+/- 3 days**	**+/- 3 days**	**+/- 3 days**	**+/- 3 days**	**+/- 3 days**	**+/- 3 days**	**+/- 3 days**	**+/- 3 days**	**+/- 7 days**	**+/- 7 days**	**+/- 7 days**	**+/- 7 days**
Fasting visit		x				X		x						x	
IP to be taken at the clinic		x	x	x	x	X	x	x	x	x	x	x	x	x	
Written Informed Consent	x														
Randomization		x[e]						x[f]							
Physical exam and provider assessments															
SjS medical/surgical history, including diagnosis and prior treatments,	x														
Medical /Surgical History (non-SjS)	x														
Vital Signs, including weight and height[g]	x	x	x	x	x	X	x	x	x	x	x	x	x	x	x
Complete Physical Examination	x							x						x	
Symptom-directed PE		x	x	x	x	X	x		x	x	x	x	x		x
ESSDAI	x	x[y]		x	x	X	x	x		x	x	x	x	x	
PE for domains of ESSDAI[h]	x	x		x	x	X	x	x		x	x	x	x	x	
28 Swollen and Tender Joint count	x	x	x	x	x	X	x	x	x	x	x	x	x	x	

Visit window	Screening [a] None	Day 1 [b] None	Week 2 +/- 3 days	Week 4 +/- 3 days	Week 8 +/- 3 days	Week 12 +/- 3 days	Week 18 +/- 3 days	Week 24 +/- 3 days	Week 26 +/- 3 days	Week 28 +/- 3 days	Week 32 +/- 3 days	Week 36 +/- 7 days	Week 42 +/- 7 days	Week 48/ET [c] +/- 7 days	Follow Up visit 4 weeks after subject's last study visit [d] +/- 7 days
Physician's Global Assessment of SjS activity	x	x	x	x	x	X	x	x	x	x	x	x	x	x	x
Physician's Global Assessment of concomitant RA or SLE disease activity as applicable	x	x	x	x	x	X	x	x	x	x	x	x	x	x	x
Laboratory assessments															
Urine drug screen[i]	x														
Urinalysis with spot protein/ microalbumin/creatinine	x	x	x	x	x	X	x	x	x	x	x	x	x	x	
Urine Pregnancy Test (female subjects of child bearing potential only)		x	x	x	x	X	x	x	x	x	x	x	x	x	x
Urine for biomarker (fasting)		x				X		x						x	
Serum Pregnancy Test (female subjects of child bearing potential) or FSH	x														
TB testing[j]	x														
CD19+ B cell count[k]	x														
HbA1c, TSH	x														
Hematology, ESR as applicable, chemistry and hsCRP	x	x	x	x	x	X	x	x	x	x	x	x	x	x	x
Viral Screening and Reflex PCR[l]	x														
Viral Monitoring[m]						X		x				x		x	

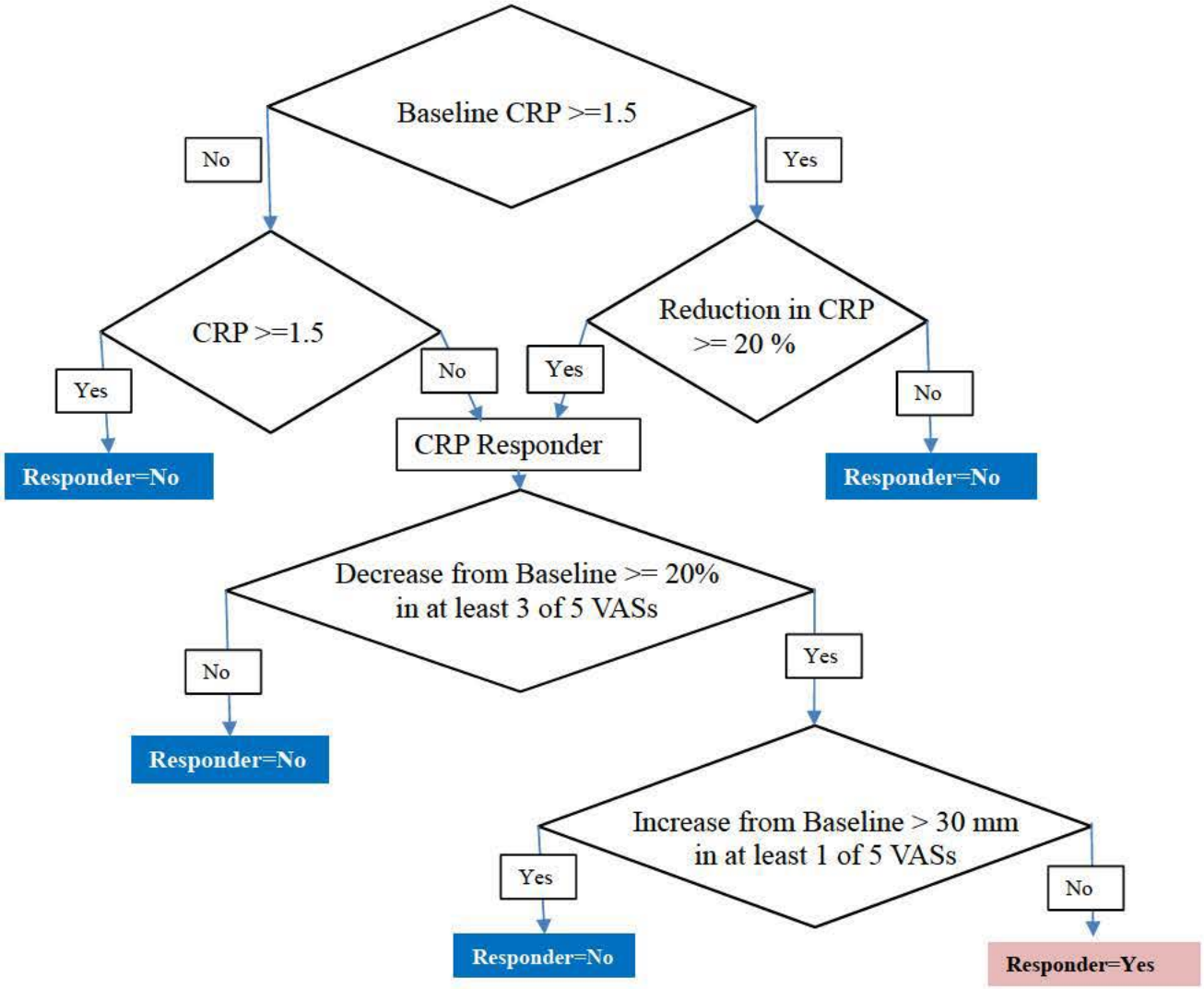
	Screening [a]	Day 1 [b]	Week 2	Week 4	Week 8	Week 12	Week 18	Week 24	Week 26	Week 28	Week 32	Week 36	Week 42	Week 48/ET [c]	Follow Up visit 4 weeks after subject's last study visit [d]
Visit window	**None**	**None**	**+/- 3 days**	**+/- 3 days**	**+/- 3 days**	**+/- 3 days**	**+/- 3 days**	**+/- 3 days**	**+/- 3 days**	**+/- 3 days**	**+/- 3 days**	**+/- 7 days**	**+/- 7 days**	**+/- 7 days**	**+/- 7 days**
Autoantibodies[n]	x	x				X		x						x	
Complement (C3, C4, CH50), and CK	x	x	x	x	x	X	x	x	x	x	x	x	x	x	
Cryoglobulins, total Ig, quant IgG, IgA, and IgM, serum and urine immunofixation	x			x		X		x		x		x		x	
Lipid profile (fasting)[o]		x				X		x						x	
PK samples[p]				x	x	X	x	x				x		x	
CCI															
Blood for Biomarker samples[r]	x	x	x	x	x	X	x	x	x	x	x	x	x	x	x
CCI															
PROs and questionnaires															
VAS[t]	x	x	x	x	x	X	x	x	x	x	x	x	x	x	x
ESSPRI	x	x	x	x	x	X	x	x	x	x	x	x	x	x	x
FACIT- Fatigue, OHIP-14, PROFAD-SSI-SF [u]		x		x	x	X	x	x		x	x	x	x	x	
SF-36, IDEEL [u]		x				X		x				x		x	
TSQM		x				X		x				x		x	
Cognitive testing		x		x	x	X	x	x		x	x	x	x	x	

Visit window	Screening [a] None	Day 1[b] None	Week 2 +/- 3 days	Week 4 +/- 3 days	Week 8 +/- 3 days	Week 12 +/- 3 days	Week 18 +/- 3 days	Week 24 +/- 3 days	Week 26 +/- 3 days	Week 28 +/- 3 days	Week 32 +/- 3 days	Week 36 +/- 7 days	Week 42 +/- 7 days	Week 48/ET[c] +/- 7 days	Follow Up visit 4 weeks after subject's last study visit [d] +/- 7 days
Procedures and Exams															
12-Lead ECG	x	x	x		x	x		x	x		x	x		x	x
Pulmonary function tests[v]	x					x		x						x	
CCI															
CCI															
Chest X-ray (as applicable)[z]	x														
CCI															
Drug dispensing		x		x	x	x	x	x		x	x	x	x		
Drug accountability			x	x	x	x	x	x	x	x	x	x	x	x	
Adverse Events	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Concomitant medications[x]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x

a Screening window is 28 days prior to Day 1
b Subject will begin study drug on Day 1, following baseline assessments and randomization.
c Early Termination Visit to be performed if subject discontinues before Week 48
d Follow up visit not needed if subject's last dose of study drug was >4 weeks prior to their last study visit
e Subjects will be randomized on Day 1 based on their use of concomitant medications (y/n: csDMARD and/or oral corticosteroid) and ESSDAI hematological plus biological domains score at Day 1, (Y/N: ESSDAI ≥ 2).
f Subjects on placebo will be re-randomized 1:1:1 to either filgotinib, or GS-9876 or GS-4059
g Height is only required at Visit 1 and subjects are to remove shoes during measurement
h Exam should include glandular exam, lymph nodes, general skin, neurologic exam for peripheral neuropathy, pulmonary exam

i Amphetamines Cocaine, Methadone Opiates
j Quantiferon gold
k As applicable
l Hepatitis B surface Ag and core Ab, Hepatitis C Ab, reflex HCV RNA, HIV 1 and 2 at Screening
m Viral monitoring for HCV as applicable (see study protocol.)
n At screening only: anti SSA and anti SSB
At Day 1: deamidated gliadin peptide antibodies (anti-DGP IgA or IgG); Anti-endomysial antibodies (EMA), RF, CCP, dsDNA, ANA, IgA anti-tTA (tissue transglutaminase antibodies),
At all subsequent time points: deamidated gliadin peptide antibodies (anti-DGP IgA or IgG); Anti-endomysial antibodies (EMA), RF, CCP, dsDNA, ANA, SSA, SSB, IgA anti-tTA (tissue transglutaminase antibodies),
o As outline in protocol Appendix 6
p PK samples will be collected prior to study drug administration (pre-dose) at Weeks 4, 8, 12, 24, 36, and 48/ET visit. At Week 18, PK samples will be collected approximately 2 hours post-dose
q CCI [redacted].
r Inflammation and Pathway Biomarkers, RNA Sample, Whole Blood Sample for MoA Studies. For biomarkers which require specific material for sampling and/or processing, to be done if and when the material is available at site.
s CCI [redacted]
t Visual analog scales include patient global assessment of SJS activity and concomitant RA, concomitant SLE disease activity as applicable, assessment of ocular, oral dryness, vaginal dryness (if applicable) assessment of pain, fatigue, CCI [redacted],
u If available in the primary language of the subject. Questionnaires addressing disease, activity and fatigue may be provided when and where available.
v PFT includes Spirometry. Subjects with the following contraindications to spirometry should not perform the exam: nausea, vomiting, recent stroke, eye surgery, thoracic/abdominal surgery and recent pneumothorax
w CCI [redacted]
x All non-SjS medication used within 30 days of consent (including any changes) is to be documented in the eCRF.
All prior medication(s) used in the treatment for SjS, are to be documented in the eCRF
y For ESSDAI at baseline, lab results and PFT from screening will be used
z For subject who had no previous chest X-ray available for review by the investigator within the last 3 months

Appendix 2. Primary Endpoint Derivation



Scenarios for VAS Values		Percent Change Calculated/ 20% Improvement derived?	30 mm Worsening Derived?	Effect on Primary Endpoint
Baseline	**Post-baseline**			
>0	>0	Calculated/derived	Derived	Not affected
0	>0	Assign % Change = blank/ 20% Improvement = NO	Derived	Not affected
0	0	Assign % Change = 0; 20% Improvement = NO	Worsening = NO	Not affected
> 0	0	Assign % Change = -100%	Worsening = NO	Not affected
Missing	Not Missing	Blank	Blank	Missing
Not Missing	Missing	Blank	Blank	Missing

Appendix 3. EULAR Sjögren's Syndrome Disease Activity Index (ESSDAI)

Promoted by European League Against Rheumatism (EULAR), the EULAR Sjögren's syndrome (SjS) disease activity index (ESSDAI) is a systemic disease physician-reported activity index that was designed to measure disease activity in patients with primary SjS. The ESSDAI is now used in multiple clinical trials as primary outcome measure.

In total, twelve organ-specific domains contributing to disease activity were identified. Each domain is divided into 3–4 levels of activity.

Domain	Activity Level	Description
Constitutional *Exclusion of fever of infectious origin and voluntary weight loss*	No = 0	Absence of the following symptoms
	Low = 3	Mild or intermittent fever (37.5°–38.5°C)/night sweats and/or involuntary weight loss of 5 to 10% of body weight
	Moderate = 6	Severe fever (>38.5°C)/night sweats and/or involuntary weight loss of >10% of body weight
Lymphadenopathy and lymphoma *Exclusion of infection*	No = 0	Absence of the following features
	Low = 4	Lymphadenopathy ≥ 1 cm in any nodal region or ≥ 2 cm in inguinal region
	Moderate = 8	Lymphadenopathy ≥ 2 cm in any nodal region or ≥ 3 cm in inguinal region, and/or splenomegaly (clinically palpable or assessed by imaging)
	High = 12	Current malignant B-cell proliferative disorder
Glandular *Exclusion of stone or infection*	No = 0	Absence of glandular swelling
	Low = 2	Small glandular swelling with enlarged parotid (≤ 3 cm), or limited submandibular (>2 cm) or lachrymal swelling (>1 cm)
	Moderate = 4	Major glandular swelling with enlarged parotid (> 3 cm), or important submandibular or lachrymal swelling
Articular *Exclusion of osteoarthritis*	No = 0	Absence of currently active articular involvement
	Low = 2	Arthralgias in hands, wrists, ankles and feet accompanied by morning stiffness (>30 min)
	Moderate = 4	1 to 5 (of 28 total count) synovitis
	High = 6	≥ 6 (of 28 total count) synovitis

Cutaneous *Rate as "No activity" stable long lasting features related to damage*	No = 0	Absence of currently active cutaneous involvement
	Low = 3	Erythema multiforma
	Moderate = 6	Limited cutaneous vasculitis, including urticarial vasculitis, or purpura limited to feet and ankle, or subacute cutaneous lupus
	High = 9	Diffuse cutaneous vasculitis, including urticarial vasculitis, or diffuse purpura, or ulcers related to vasculitis
Pulmonary *Rate as "No activity" stable long lasting features related to damage, or respiratory involvement not related to the disease (tobacco use etc.)*	No = 0	Absence of currently active pulmonary involvement
	Low = 5	Persistent cough or bronchial involvement with no radiographic abnormalities on radiography Or radiological or HRCT evidence of interstitial lung disease with: No breathlessness and normal lung function test.
	Moderate = 10	Moderately active pulmonary involvement, such as interstitial lung disease shown by HRCT with shortness of breath on exercise (NHYA II) or abnormal lung function tests restricted to: 70% >DL ≥ 40% or 80% >FVC≥60%
	High = 15	Highly active pulmonary involvement, such as interstitial lung disease shown by HRCT with shortness of breath at rest (NHYA III, IV) or with abnormal lung function tests: DL < 40% or FVC< 60%
Renal *Rate as "No activity" stable long lasting features related to damage, and renal involvement not related to the disease.* *If biopsy has been performed, please rate activity based on histological features first*	No = 0	Absence of currently active renal involvement with proteinuria< 0.5 g/d, no hematuria, no leucocyturia, no acidosis, or long-lasting stable proteinuria due to damage
	Low = 5	Evidence of mild active renal involvement, limited to tubular acidosis without renal failure or glomerular involvement with proteinuria (between 0.5 and 1 g/d) and without hematuria or renal failure (GFR ≥60 ml/min)
	Moderate = 10	Moderately active renal involvement, such as tubular acidosis with renal failure (GFR <60 ml/min) or glomerular involvement with proteinuria between 1 and 1.5 g/d and without hematuria or renal failure (GFR ≥60 ml/min) or histological evidence of extra-membranous glomerulonephritis or important interstitial lymphoid infiltrate
	High = 15	Highly active renal involvement, such as glomerular involvement with proteinuria >1.5 g/d or hematuria or renal failure (GFR <60 ml/min), or histological evidence of proliferative glomerulonephritis or cryoglobulinemia related renal involvement

Muscular *Exclusion of weakness due to corticosteroids*	No = 0	Absence of currently active muscular involvement
	Low = 6	Mild active myositis shown by abnormal EMG, MRI* or biopsy with no weakness and creatine kinase (N <CK ≤ 2N)
	Moderate = 12	Moderately active myositis proven by abnormal EMG , MRI* or biopsy with weakness (maximal deficit of 4/5), or elevated creatine kinase (2N<CK ≤4N),
	High = 18	Highly active myositis shown by abnormal EMG, MRI* or biopsy with weakness (deficit ≤ 3/5) or elevated creatine kinase (>4N)
PNS *Rate as "No activity" stable long lasting features related to damage or PNS involvement not related to the disease*	No = 0	Absence of currently active PNS involvement
	Low = 5	Mild active peripheral nervous system involvement, such as pure sensory axonal polyneuropathy shown by NCS or trigeminal (V) neuralgia
	Moderate = 10	Moderately active peripheral nervous system involvement shown by NCS, such as axonal sensory-motor neuropathy with maximal motor deficit of 4/5, pure sensory neuropathy with presence of cryoglobulinemic vasculitis, ganglionopathy with symptoms restricted to mild/moderate ataxia, inflammatory demyelinating polyneuropathy (CIDP) with mild functional impairment (maximal motor deficit of 4/5or mild ataxia), Or cranial nerve involvement of peripheral origin (except trigeminal (V) neralgia)
	High = 15	Highly active PNS involvement shown by NCS, such as axonal sensorymotor neuropathy with motor deficit ≤3/5, peripheral nerve involvement due to vasculitis (mononeuritis multiplex etc.), severe ataxia due to ganglionopathy, inflammatory demyelinating polyneuropathy (CIDP) with severe functional impairment: motor deficit ≤3/5 or severe ataxia
CNS *Rate as "No activity" stable long lasting features related to damage or CNS involvement not related to the disease*	No = 0	Absence of currently active CNS involvement
	Moderate = 10	Moderately active CNS features, such as cranial nerve involvement of central origin, optic neuritis or multiple sclerosis-like syndrome with symptoms restricted to pure sensory impairment or proven cognitive impairment
	High = 15	Highly active CNS features, such as cerebral vasculitis with cerebrovascular accident or transient ischemic attack, seizures, transverse myelitis, lymphocytic meningitis, multiple sclerosis-like syndrome with motor deficit.

Hematological *For anemia, neutropenia, and thrombopenia, only auto-immune cytopenia must be considered Exclusion of vitamin or iron deficiency, drug-induced cytopenia*	No = 0	Absence of auto-immune cytopenia
	Low = 2	Cytopenia of auto-immune origin with neutropenia (1000 < neutrophils < 1500/mm3), and/or anemia (10 < hemoglobin < 12 g/dl), and/or thrombocytopenia (100,000 < platelets < 150,000/mm3) Or lymphopenia (500 < lymphocytes < 1000/mm3)
	Moderate = 4	Cytopenia of auto-immune origin with neutropenia (500 ≤ neutrophils ≤ 1000/mm3), and/or anemia (8 ≤ hemoglobin ≤ 10 g/dl), and/or thrombocytopenia (50,000 ≤ platelets ≤ 100,000/mm3) Or lymphopenia (≤500/mm3)
	High = 6	3 Cytopenia of auto-immune origin with neutropenia (neutrophils < 500/mm3), and/or or anemia (hemoglobin < 8 g/dl) and/or thrombocytopenia (platelets <50,000/mm3)
Biological	No = 0	Absence of any of the following biological feature
	Low = 1	Clonal component and/or hypocomplementemia (low C4 or C3 or CH50) and/or hypergammaglobulinemia or high IgG level between 16 and 20 g/L
	Moderate = 2	Presence of cryoglobulinemia and/or hypergammaglobulinemia or high IgG level > 20 g/L, and/or recent onset hypogammaglobulinemia or recent decrease of IgG level (<5 g/L)

CIDP= chronic inflammatory demyelinating polyneuropathy; CK= creatine kinase; CNS= central nervous system; DLCO= diffusing CO capacity; EMG= electromyogram; FVC= forced vital capacity; GFR= glomerular filtration rate; Hb= hemoglobin; HRCT= high-resolution computed tomography; IgG= immunoglobulin G; NCS= nerve conduction studies; NHYA= New York heart association classification; Plt= platelet; PNS=peripheral nervous system

The ESSDAI overall score is obtained by addition of the twelve domain scores. The maximum theoretical ESSDAI score is 123. Usually, the score does not exceed 50.

Appendix 4. EULAR Sjögren's Syndrome Patients Reported Index (ESSPRI)

The ESSPRI is a patient-reported outcome assessment designed to evaluate the severity of patients' symptoms such as dryness, pain and fatigue in primary Sjögren's Syndrome. ESSPRI is being extensively used in SjS research. This index has shown a correlation with quality of life and functional status measures, and can be considered a useful predictor of health status of patients with SjS.

The ESSPRI questionnaire (see below) is completed by the patient and consists of three items to be given an activity level score between 0–10: pain (joint and/or muscle pain), fatigue and dryness (0 = no symptom at all and 10 = worst symptom imaginable). The patient must check one that best describes the severity of his/her symptoms in the worst stages.

Each domain represents the severity of the symptom independently. The total ESSPRI score is the mean of all three scores and therefore can range between 0–10.

Your doctor asked you to answer some questions related to your disease. To answer the questions, please consider the severity of your symptoms in the worst stages only during the last two weeks.

Please check the alternative that best describes your answer. Please answer all questions carefully.

Example:

No pain											Maximal imaginable pain
	☐	☐	☐	☐	☐	X	☐	☐	☐	☐	☐	
	0	1	2	3	4	5	6	7	8	9	10	

1) How severe has your dryness been during the last 2 weeks?

No dryness												Maximal imaginable dryness
	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	
	0	1	2	3	4	5	6	7	8	9	10	

2) How severe has your fatigue been during the last 2 weeks?

No fatigue												Maximum imaginable fatigue
	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	
	0	1	2	3	4	5	6	7	8	9	10	

3) How severe has your pain (joint or muscular pain, in your arms or legs) been during the last 2 weeks?

No pain												Maximal imaginable pain
	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	
	0	1	2	3	4	5	6	7	8	9	10	