Statistical Analysis Plan

Study M20-186

A Phase 2, Long-Term Extension (LTE) Study with Elsubrutinib and Upadacitinib Given Alone or in Combination (ABBV-599) in Subjects with Moderately to Severely Active Systemic Lupus Erythematosus Who Have Completed the M19-130 Phase 2 Randomized Controlled Trial (RCT)

Date: 02 January 2024

Version 2.0

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1.0 Introduction

This Statistical Analysis Plan (SAP) describes the statistical analyses for ABBV-599 Study M20-186.

Study M20-186 evaluates the long-term safety, tolerability, and efficacy of elsubrutinib and upadacitinib given alone or as the ABBV-599 (elsubrutinib/upadacitinib) combination in SLE subjects who have completed the Phase 2 Study M19-130.

The SAP will not be updated in case of administrative changes or amendments to the protocol unless the changes impact the analysis.

Unless noted otherwise, all analyses will be performed using SAS Version 9.4 (SAS Institute Inc., Cary, NC 27513) under the UNIX operating system.

2.0 Study Design and Objectives

2.1 Objectives and Hypotheses

Primary

The primary objective is to evaluate the longer-term safety and tolerability of elsubrutinib and upadacitinib given alone or as the ABBV-599 (elsubrutinib/upadacitinib) combination in SLE subjects who have completed the M19-130 Phase 2 study.

There is no planned hypothesis to be tested for this long-term extension (LTE) study.

Secondary

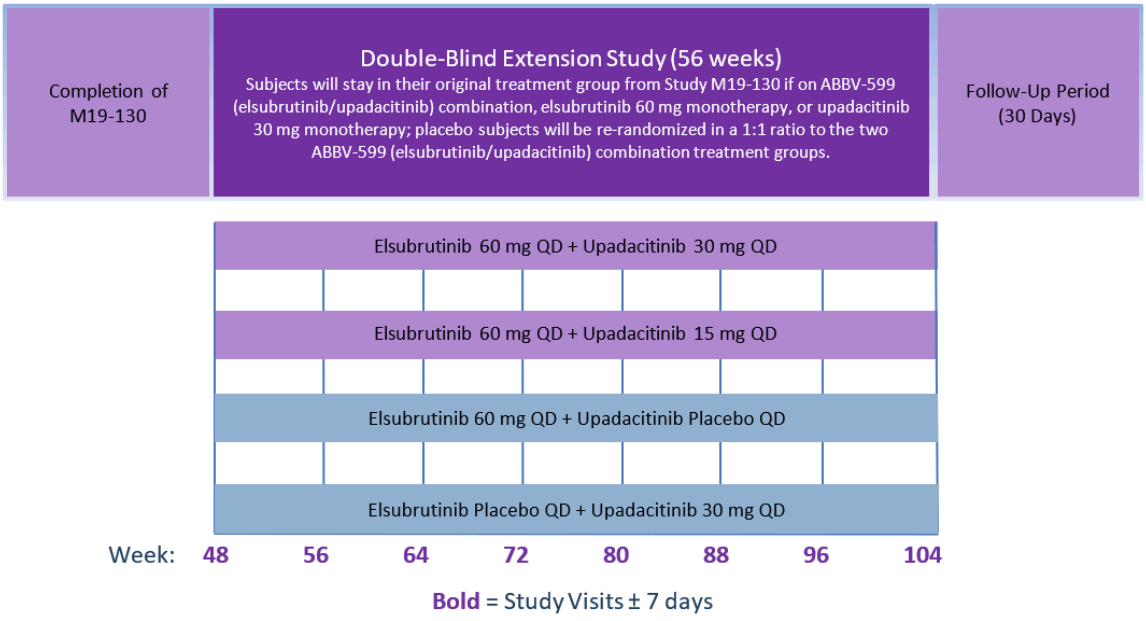
The secondary objective is to obtain longer-term efficacy data beyond Week 48 with the treatments studied in the RCT (monotherapies and combination) to more fully assess the risk/benefit of each treatment over time.

2.2 Study Design Overview

This is a double-blind LTE Phase 2 study to investigate the longer-term safety and efficacy of elsubrutinib and upadacitinib given alone or as the ABBV-599 (elsubrutinib/upadacitinib) combination in subjects with moderately to severely active SLE. The study population will consist of approximately 195 to 260 individuals who entered Study M19-130 with moderately to severely active SLE despite standard of care therapy and who have completed Study M19-130.

The schematic of the study is shown in Figure 1.

Figure 1. Study Schematic



QD = once daily

2.3 Treatment Assignment and Blinding

Prior to the planned Study M19-130 Interim Analysis, qualified subjects entering into LTE Study M20-186 stayed in their original treatment group from Study M19-130 if on

an ABBV-599 (elsubrutinib/upadacitinib) combination, elsubrutinib 60 mg monotherapy, or upadacitinib 30 mg monotherapy. Those originally assigned to the placebo group in Study M19-130 were randomized centrally in a 1:1 ratio to the 2 ABBV-599 (elsubrutinib/upadacitinib) combination treatment groups.

Prior to the planned Study M19-130 Interim Analysis, there were 4 treatment groups in this LTE study:

- Group 1: Elsubrutinib 60 mg QD and upadacitinib 30 mg QD
- Group 2: Elsubrutinib 60 mg QD and upadacitinib 15 mg QD
- Group 3: Elsubrutinib 60 mg QD and upadacitinib placebo QD
- Group 4: Elsubrutinib placebo QD and upadacitinib 30 mg QD

A planned unblinded interim analysis for Study M19-130 was performed when 50% of the planned subjects completed their Week 24 assessments. The objective of this analysis was to reassess the treatment regimens in Study M19-130 and the benefit/risk for rollover into Study M20-186.

Based on the benefit/risk assessment of the planned Study M19-130 Interim Analysis, subjects in 1 or more groups of LTE Study M20-186 may be discontinued. Subjects in any discontinued group(s) should return for a Premature Discontinuation (PD) visit and have a follow-up phone call 30 days after the last study drug dose.

This study includes a 56-week double-blind treatment period with study visits conducted at Weeks 48, 56, 64, 72, 80, 88, 96, and 104 (from the Baseline visit of Study M19-130), and a subsequent telephone follow-up call 30 days after the last visit to determine the status of any ongoing AEs/SAEs or the occurrence of any new AEs/SAEs. The plan is to extend the trial if data support the safety and efficacy endpoints during the 56-week LTE study duration.

The M19-130 Primary Analysis will be performed when all subjects have completed the Week 24 visit. The M20-186 study team will become unblinded after the M19-130

Week 24 Primary Analysis has been completed. Study sites and subjects will remain blinded to treatment assignment in Study M19-130 and Study M20-186 throughout the studies.

2.4 Sample Size Determination

This is the LTE study for Study M19-130. All eligible subjects who completed Study M19-130 will be enrolled in this study if the subject signs and dates the informed consent. Based on discontinuation criteria mandating efficacy in Study M19-130, it is anticipated that between 60% and 80% of subjects from Study M19-130 (195 to 260 subjects) will be enrolled in this LTE study.

3.0 Endpoints

3.1 Primary Efficacy Endpoint

There is no primary efficacy endpoint since this is the extension to the feeder Study M19-130. The primary objective is to investigate the longer-term safety of the ABBV-599 combination in patients with active SLE.

3.2 Secondary Efficacy Endpoints

- SLE Responder Index (SRI)-4
- British Isles Lupus Assessment Group (BILAG)-Based Combined Lupus Assessment (BICLA)
- Steroid burden, assessed as change from M19-130 baseline
- Number of mild/moderate, or severe flares per patient-year (respectively and overall) by Safety of Estrogens in Lupus Erythematosus National Assessment (SELENA) SLEDAI Flare Index (SFI), assessed by number and types of flare per subject compared across treatment groups

3.3 Other Efficacy Endpoints

The secondary efficacy endpoints are listed in Section 3.2. The additional efficacy endpoints are:

- Lupus Low Disease Activity State (LLDAS)
- ≥ 4-point decrease in SLEDAI-2K compared with M19-130 Baseline
- Achievement of 50% reduction of tender or swollen lupus joints (of those starting with total ≥ 6 affected joints) from M19-130 Baseline
- Achievement of 50% reduction in Cutaneous Lupus Erythematosus Disease Area and Severity Index (CLASI) activity score (of those starting with CLASI ≥ 10 at M19-130 Baseline)
- Change in SLEDAI-2K from M19-130 Baseline
- Change in BILAG from M19-130 Baseline
- Change in Functional Assessment of Chronic Illness Therapy - Fatigue (FACIT-F) from M19-130 Baseline
- Change in 36-Item Short Form Health Survey (SF-36) PCS and MCS from M19-130 Baseline
- Change in Lupus Quality of Life questionnaire (LupusQoL) from M19-130 Baseline
- Change in Pain Numerical Rating Scale (NRS) from M19-130 Baseline

3.4 Safety Endpoints

The following safety evaluations will be performed for the entire study duration as measures of safety and tolerability:

- AE monitoring
- Physical examinations
- Vital sign measurements
- ECGs
- Clinical laboratory testing (hematology, chemistry, and urinalysis)

3.5 Additional Endpoint(s)

No additional endpoints will be analyzed in the SAP.

4.0 Analysis Populations

The following population sets will be used for the analyses.

The Full Analysis Set (FAS) includes all subjects who completed Study M19-130 and received at least 1 dose of assigned study drug in Study M20-186. The FAS will be used for efficacy and baseline analyses. Subjects will be grouped according to treatment sequence as randomized for Study M19-130 and continued/reassigned to rollover into Study M20-186.

The Safety Analysis Set also includes all subjects who completed Study M19-130 and received at least 1 dose of assigned study drug in Study M20-186. Subjects will be grouped according to treatment sequence actually received. A subject's actual treatment will be determined by the most frequent dose regimen received. The Safety Analysis Set will be used for safety analyses.

5.0 Subject Disposition

The total number of subjects who were enrolled and treated will be summarized.

A summary of subject accountability will be provided where the number of subjects in each of the following categories will be summarized for each treatment group:

- Subjects enrolled in the study;
- Subjects who took at least one dose of study drug;
- Subjects who completed protocol-specified treatment;
- Subjects who prematurely discontinued study drug (all reasons and primary reason).

For end of study participation, the number and percentage of subjects who completed the protocol defined follow-up period (or did not with associated reasons) will be summarized overall and by treatment group.

The treatment groups will be described as follows indicating treatments from Study M19-130 to extension Study M20-186:

- Group 1: Elsubrutinib 60 mg/upadacitinib 30 mg to elsubrutinib 60 mg/upadacitinib 30 mg
- Group 2: Elsubrutinib 60 mg/upadacitinib 15 mg to elsubrutinib 60 mg/upadacitinib 15 mg
- Group 3: Elsubrutinib 60 mg to elsubrutinib 60 mg
- Group 4: Upadacitinib 30 mg to upadacitinib 30 mg
- Group 5a: Placebo to elsubrutinib 60 mg/upadacitinib 30 mg
- Group 5b: Placebo to elsubrutinib 60 mg/upadacitinib 15 mg

Treatment groups above are subject to change depending on potential M20-186 treatment re-assignments after M19-130 Interim Analysis.

6.0 Study Drug Duration and Compliance

Study Drug Duration

A summary of study drug duration (days) will be provided by each treatment arm for the Safety Analysis Set.

The duration of exposure to study drug will be summarized for each group as specified in Section 5.0, with the number of subjects, mean, standard deviation, median, minimum and maximum values. In addition, the number and percentage of subjects exposed to study drug will be summarized for Study M20-186 treatment period based on the following duration intervals:

- ≥ 1 day

- ≥ 57 days
- ≥ 113 days
- ≥ 169 days
- ≥ 225 days
- ≥ 281 days
- ≥ 337 days
- ≥ 393 days

The exposure to study drug in days for Study M20-186 period is calculated as:

Exposure = (date of last study medication in Study M20-186 – date of first study medication in Study M20-186 + 1)

Compliance

Study drug compliance will be summarized for each treatment group for FAS population. Descriptive statistics will be provided including sample size, mean, standard deviation, median, minimum and maximum.

Treatment compliance (TC) will be calculated using the following formula:

$$TC = \frac{Total\ number\ of\ tablets/\text{capsules}\ taken}{(last\ dose\ date - first\ dose\ date + 1) \times < number\ of\ tablets/\text{capsules}\ per\ day >} \times 100\%$$

- The total number of tablets/capsules taken will be calculated as the total number of tablets/capsules dispensed minus the total number of tablets/capsules returned.

  Note: If the bottle is not returned, total number of tablets/capsules returned is assumed to be 0.
- In M20-186: number of tablets per day is 1 and number of capsules per day is 3.

7.0 Demographics, Baseline Characteristics, Medical History, and Prior/Concomitant Medications

Demographics, baseline or disease characteristics, medical history, and prior and concomitant medications will be summarized for the FAS overall and by treatment group as described in Section 5.0. Categorical variables will be summarized with the number and percentage of subjects; percentages will be calculated based on the number of non-missing observations. Continuous variables will be summarized with descriptive statistics (number of non-missing observations, mean and standard deviation, median, minimum and maximum).

7.1 Demographics and Baseline Characteristics

The following demographic and baseline characteristics, as measured at baseline of the Study M19-130 study, will be summarized.

Demographic Characteristics

- Sex (male, female)
- Age (years)
- Age category [18 – < 40 years old, 40 – < 65 years old, ≥ 65 years old]
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino)
- Race (White, Black or African American, American Indian or Alaska Native, Native Hawaiian or Other Pacific Islander, Asian, Other)
- Geographic region (North America, South/Central America, Western Europe, Eastern Europe, Asia Japan, Asia Other, Other)
- Weight (kg)
- Weight Categories (< 60 kg, ≥ 60 kg)
- Height (cm)
- BMI (kg/m^2)
- Body Mass Index (BMI) Category (kg/m^2) (BMI < 25, BMI ≥ 25)

Other Baseline Characteristics

The following continuous variables will be summarized:

- SLEDAI-2K score
- Patient's Global Assessment of Disease Activity score
- Physician's Global Assessment of Disease Activity score
- LupusQoL score
- SF-36 score
- Time since onset of lupus (years), which will be calculated as follows:

  Time since onset of lupus (years) = year of first dose – year of initial diagnosis of SLE
- Number of tender joints (from 28-tender joint count)
- Number of swollen joints (from 28-swollen joint count)
- Daily dose of corticosteroid (mg/day)
- CLASI Total Activity Score
- CLASI Total Damage Score
- Complement C3 and C4 levels
- Anti-dsDNA level
- Urine protein to urine creatinine ratio
- Serum immunoglobulin (Ig)G and IgM concentrations
- Creatinine

The following categorical variables will be summarized:

- Anti-dsDNA status (positive defined as ≥ 30 IU/mL) (positive, negative)
- SLEDAI-2K status (< 10, ≥ 10)
- British Isles Lupus Assessment Group (BILAG) organ system involvement at baseline (yes or no for each organ system domain). Involvement requires a baseline BILAG disease activity score of A or B.

- BILAG A organ system involvement at baseline (yes or no for each organ system domain).
- SLEDAI-2K organ system involvement at baseline (yes or no for each organ system domain).
- C3 status (less than the lower limit of normal [LLN] (< 90.0 mg/dL)
- C4 status (less than LLN [< 10.0 mg/dL])
- Anti-Smith antibodies (≥ 30 AU/mL) (yes, no)
- Corticosteroid use (yes or no), and within those taking corticosteroids, < 10 mg/day or ≥ 10 mg/day.
- Corticosteroid use (yes or no), and within those taking corticosteroids, < 7.5 mg/day or ≥ 7.5 mg/day.
- Immunosuppressant use (yes or no):
  - Mycophenolate use (yes or no)
  - Azathioprine use (yes or no)
  - Methotrexate use (yes or no)
  - Tacrolimus use (yes or no)
  - Cyclosporine use (yes or no)
  - Leflunomide use (yes or no)
- Antimalarial use (yes or no):
  - Hydroxychloroquine (yes or no)
  - Chloroquine (yes or no)
  - Quinacrine (yes or no)

Clinical Tests at Screening

- Chest x-ray
- Tuberculin PPD skin test, QuantiFERON TB Gold test
- Serum pregnancy test

Immunization History

- Herpes Zoster immunization
- Hepatitis B immunization

Tobacco/Nicotine and Alcohol Use

- Tobacco/Nicotine Use (current, former, never, or unknown)
- Alcohol Use (current, former, never, or unknown)

7.2 Medical History

Medical history data will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). The actual version of the MedDRA coding dictionary will be noted in the statistical tables and clinical study report. Medical history data will be summarized and presented for the FAS population using body systems and conditions/diagnoses as captured on the CRF. The body systems will be presented in alphabetical order and the conditions/diagnoses will be presented in alphabetical order within each body system. The number and percentage of subjects with a condition/diagnosis will be summarized for each treatment group as well as overall. Subjects reporting more than one condition/diagnosis within a body system will be counted only once for that body system. No statistical comparison will be performed for medical history reporting.

7.3 Prior and Concomitant Medications

Prior and concomitant medications will be summarized by each treatment group as well as overall for the FAS.

Prior medications are those medications taken prior to the first dose of study drug in Study M19-130. This includes medications with a start date before the first study drug administration date, regardless of the end date of these medications. Medications taken on the day of the first dose of study drug are not counted as prior medications.

Concomitant medications are those medications, other than study drug, taken after the first dose of study drug in Study M20-186 and within 1 day of the last dose of study drug. This includes medications with a start date between first study drug administration in Study M20-186 and last study drug administration + 1 day, as well as, medications with a start date prior to first dose of study drug in Study M20-186 and which are ongoing after first dose of study drug. Medications taken on the day of the first dose of study drug in Study M20-186 are counted as concomitant medications.

The number and percentage of subjects who received a prior medication and the number and percentage of subjects who received a concomitant medication will be tabulated separately by the generic name assigned by the most current version of the World Health Organization (WHO) Drug Dictionary.

8.0 Efficacy Analyses

8.1 General Considerations

Analysis of efficacy endpoints will be conducted on the FAS based on treatment sequence as randomized for Study M19-130 and continued/reassigned to rollover into Study M20-186. For all efficacy endpoints, the descriptive statistics will be provided by treatment group. The statistics include number of observations, mean, standard deviation, minimum, median, and maximum for continuous variables; and number and percentage of subjects for categorical variables.

The analysis treatment groups will be described as follows indicating treatments from Study M19-130 to extension Study M20-186:

- Group 1: Elsubrutinib 60 mg/upadacitinib 30 mg to elsubrutinib 60 mg/upadacitinib 30 mg
- Group 2: Elsubrutinib 60 mg/upadacitinib 15 mg to elsubrutinib 60 mg/upadacitinib 15 mg
- Group 3: Elsubrutinib 60 mg to elsubrutinib 60 mg
- Group 4: Upadacitinib 30 mg to upadacitinib 30 mg

- Group 5a: Placebo to elsubrutinib 60 mg/upadacitinib 30 mg
- Group 5b: Placebo to elsubrutinib 60 mg/upadacitinib 15 mg

Analysis treatment groups above are subject to change depending on potential M20-186 treatment re-assignments after M19-130 Interim Analysis.

The Baseline for all efficacy analyses in this study will be the Baseline in Study M19-130, i.e., the last non-missing observation before the first administration of study drug in Study M19-130 or randomization in Study M19-130 if no study drug is given.

8.2 Handling of Missing Data

The analysis will be based on As Observed data, and no imputation will be conducted.

8.3 Primary Efficacy Endpoint and Analyses

There are no primary efficacy endpoints or analyses for this study.

8.4 Secondary Efficacy Analyses

Descriptive statistics will be provided for each treatment group for all visits. These include the number of observations, mean with 95% confidence interval, standard deviation, median, minimum and maximum for continuous endpoints and count endpoints; and frequencies and percentages with 95% confidence interval for binary endpoints.

No missing data imputation will be applied. All efficacy analyses will be based on As Observed (AO) analysis, and thus a subject who does not have an evaluation at the primary analysis time point will not be included.

8.5 Additional Efficacy Analyses

No additional efficacy analyses are planned.

8.6 Efficacy Subgroup Analyses

No subgroup analyses will be performed.

9.0 Safety Analyses

9.1 General Considerations

Safety analyses will include reporting of adverse events, laboratory, and vital signs measurements based on data in Study M20-186. Safety analyses will be carried out using the Safety Analysis Set.

The following summary statistics will be presented for subjects who have both baseline and post-baseline values for laboratory parameters and vital signs: the mean value at Baseline and at each respective protocol specified visit, and the mean, standard deviation and median for changes from Baseline. Categorical data will be summarized using frequencies and percentages. The number of non-missing values will be given. Missing safety data will not be imputed.

For safety analysis, Baseline is defined as the last available measurement before Study M19-130 study drug administration if the subjects took active treatment in Study M19-130, and the last available measurement before Study M20-186 study drug administration if the subjects took placebo in Study M19-130.

9.2 Adverse Events

Adverse events (AEs) will be summarized and presented using primary MedDRA System Organ Classes (SOCs) and preferred terms (PTs) according to the version of the MedDRA coding dictionary used for the study at the time of database lock. The actual version of the MedDRA coding dictionary used will be noted in the AE tables and in the clinical study report. Specific adverse events will be counted once for each subject for calculating percentages, unless stated otherwise. In addition, if the same adverse event occurs multiple times within a subject, the maximum toxicity grade and level of relationship to investigational product will be reported.

9.2.1 Treatment-Emergent Adverse Events

To summarize data from Study M20-186, a treatment-emergent Adverse Event (TEAE) is defined as an adverse event with an onset date that is on or after the first dose of study drug from Study M20-186, and no more than 30 days after the last dose of study drug from Study M20-186.

Events where the onset date is the same as Study M20-186 study drug start date are assumed to be treatment-emergent, unless the Study M20-186 study drug start time and the adverse event start time are collected and the adverse event start time is prior to the Study M20-186 study drug start time. If an incomplete onset date was collected for an adverse event, the event will be assumed to be treatment-emergent unless there is other evidence that confirms that the event was not treatment-emergent (e.g., the event end date was prior to the study drug start date). All treatment-emergent AEs will be summarized overall, as well as by primary MedDRA SOC and Preferred Term. The SOCs will be presented in alphabetical order, and the PTs will be presented in alphabetical order within each SOC.

The number and percentage of subjects experiencing TEAEs will be summarized.

9.2.2 Adverse Event Overview

The number and percentage of subjects experiencing TEAEs will be summarized by treatment group as specified in Section 6.0 and overall.

An overview of AEs will be presented consisting of the number and percentage of subjects experiencing at least one event for each of the following AE categories:

- Any treatment-emergent AE
- Any treatment-emergent AE related to study drug according to the investigator
- Any severe treatment-emergent AE
- Any serious treatment-emergent AE
- Any treatment-emergent AE leading to discontinuation of study drug

- Any treatment-emergent AE leading to death
- TEAE of special interest (AESIs) (as defined in Appendix B)
- Any COVID-19 related AE
- All deaths
- COVID-19 related deaths

Additional AEs may be considered for tabulation/summary based on recommendations from Clinical and Safety as deemed appropriate.

The number and percentage of subjects experiencing at least one event of treatment-emergent AEs will be summarized for each treatment group. In addition, an overview of AEs per 100 patient-years of study exposure will be presented for the AE categories defined above. The number of TEAEs reported, the total number of years of study drug exposure, and the TEAE rate per 100 patient-years will be presented.

9.2.3 Treatment-Emergent Adverse Events by SOC and/or PT

Treatment-emergent adverse events will be summarized by SOC and PT; by maximum relationship to study drug as assessed by the investigator (e.g., reasonable possibility or no reasonable possibility) and SOC and PT; by maximum toxicity grade and SOC and PT; and by subject number and SOC and PT. Specific adverse events will be counted once for each subject for calculating percentages, unless stated otherwise. In addition, if the same adverse event occurs multiple times within a subject, the maximum toxicity grade and level of relationship to investigational product will be reported.

In addition, treatment-emergent adverse events will be summarized by PT and sorted by decreasing frequency for the total active group.

9.2.4 Treatment-Emergent Adverse Events per Patient-Years of Exposure

TEAEs occurring during Study M20-186 will be summarized by event rate per 100 subject years, defined as

$$100 * (\text{Number of TEAEs})/(\text{Total Patient Years})$$

where total patient years is defined as the sum of the study drug exposure of all subjects normalized by 365.25 and rounded to 1 decimal place.

9.2.5 SAEs (Including Deaths) and Adverse Events Leading to Study Drug Discontinuation

SAEs (including deaths) and AEs leading to study drug discontinuation will be summarized by SOC and PT and in listing format.

9.2.6 Adverse Events of Special Interest

Adverse events of special interest (AESI) will be summarized by SOC and PT and will be based on standardized or company MedDRA queries (SMQs or CMQs). AESI are categorized in Appendix B. Tabular listings of AESIs will be provided.

9.2.7 Adverse Events by "Reasonably Possibly Related" Relationship

TEAEs and reasonably possibly related AEs occurring for more than 2% of the subjects in any of the treatment groups will also be summarized by MedDRA SOC and PT. If a subject has an AE with an unknown relationship, then the AE will be counted as 'related.'

9.2.8 Frequent (> 5%) Adverse Events and Reasonably Possibly Related Adverse Events by Preferred Term in Decreasing Frequency

TEAEs and reasonably possibly related AEs occurring for more than 5% of the subjects in any of the treatment arms will be summarized by MedDRA PT in decreasing frequency separately.

9.2.9 Listing of Adverse Events

The following additional summaries of AEs will be prepared.

- Listing of Subjects with Treatment-Emergent AESIs
- Listing of Subjects with Pretreatment SAEs
- Listing of Subjects with Treatment-Emergent SAEs
- Listing of Treatment-Emergent AEs that led to discontinuation of study drug
- Listing of all deaths.

9.3 Analysis of Laboratory Data

Data collected from central and local laboratories, including additional laboratory testing due to an SAE, will be used in all analyses, except for Baseline, where SAE-related laboratory assessments on or before the first dose of study drug will be excluded. The clinical laboratory tests defined in the protocol operations manual (e.g., hematology and clinical chemistry) will be summarized.

Each laboratory variable will be summarized for all time points (starting with Baseline) with the number of non-missing observations, mean and standard deviation, median, minimum and maximum.

Mean change from Baseline to each applicable post-Baseline visit will be summarized for selected laboratory variables, with the number of observations, Baseline mean, and visit mean, at each visit in Study M20-186 for each treatment group. The change from Baseline mean, standard error, and 95% confidence interval will be presented for the mean change from Baseline within each treatment group.

Shift tables will be provided for each hematology, clinical chemistry parameter. Shifts from Baseline to the following endpoints will be considered: post-Baseline value and final value. This analysis will be performed only for category of "low or normal" at Baseline which shift to 'high' and category of "high or normal" at Baseline which shift to category of 'low.'

For selected laboratory variables including hemoglobin, neutrophils, lymphocytes, platelets, creatinine, ALT, AST, CPK, LDL cholesterol, HDL cholesterol, total cholesterol, and triglycerides, a listing of all observations collected will be generated for subjects that had at least one post-Baseline observation meeting pre-defined criteria for potentially clinically important values. The number and percentage of subjects in each treatment group who have at least one post-Baseline observation meeting the pre-defined criteria for potentially clinically important values will be provided for each variable. The criteria for potentially clinically important laboratory values will be determined by NCI CTCAE version 4.03 of greater than Grade 3 or greater than Grade 4.

For the purpose of assessing for potential Hy's law cases, the frequencies and percentages of subjects with post baseline liver-specific function test values that meet the following criteria of potential clinical interest will be summarized by "as treated" treatment group:

- ALT ≥ 3 × ULN
- ALT ≥ 5 × ULN
- ALT ≥ 10 × ULN
- ALT ≥ 20 × ULN
- AST ≥ 3 × ULN
- AST ≥ 5 × ULN
- AST ≥ 10 × ULN
- AST ≥ 20 × ULN
- Total Bilirubin Level (TBL) ≥ 2 × ULN
- Alkaline phosphatase ≥ 1.5 × ULN
- ALT and/or AST ≥ 3 × ULN and concurrent TBL ≥ 1.5 × ULN
- ALT and/or AST ≥ 3 × ULN and concurrent TBL ≥ 2 × ULN

A listing of possible Hy's Law cases, defined as those who meet all of the following conditions simultaneously, will be provided: ALT > 3 × ULN or AST > 3 × ULN that is associated with an increase in bilirubin ≥ 2 × ULN and alkaline phosphatase < 2 × ULN.

9.4 Analysis of Vital Signs

Vital sign measurements of systolic and diastolic blood pressure, pulse rate, body temperature, and weight will be summarized.

Each vital sign variable will be summarized for all time points with the number of non-missing observations, mean and standard deviation, median, minimum and maximum. Mean change from Baseline to each applicable post-Baseline visit will be summarized for each vital sign variable, with the number of observations, Baseline mean, and visit mean. The change from Baseline mean, standard error, and 95% confidence interval will be presented for the mean change from Baseline within each treatment group.

Vital sign variables will be evaluated based on potentially clinically important (PCI) criteria (Appendix C). For each vital sign PCI criterion, the number and percentage of subjects who have a vital sign value meeting the criteria will be summarized. Listings will be provided to summarize subject-level vital sign data for subjects meeting PCI criteria.

9.5 Safety Subgroup Analyses

No planned safety subgroup analyses.

9.6 Other Safety Analyses

ECG is collected at Screening and Weeks 64, 80, and 96. The number and percentage of subjects with QTcF prolongation (QTcF > 500 msec) will be summarized by treatment groups using Safety Analysis Set population.

10.0 Other Analyses

No other analyses are planned.

11.0 Interim Analysis

11.1 Interim Analysis

No interim analysis is planned.

11.2 Data Monitoring Committee

An internal safety DMC composed of persons independent of the Study M19-130 and Study M20-186 protocols and with relevant expertise in their field will review unblinded safety data from the ongoing studies. The primary responsibility of the DMC will be to protect the safety of the subjects participating in Study M19-130 and in this study. When needed, high-level unblinded efficacy data may also be requested by the DMC and reviewed so that the DMC can assess benefit:risk of any emerging safety differences.

A separate DMC charter for Studies M19-130 and M20-186 was prepared outside of the protocols and described the roles and responsibilities of the DMC members, frequency of data reviews, planned interim analyses, relevant safety data to be assessed, and expectations for blinded communications for Studies M19-130 and M20-186.

12.0 Overall Type-I Error Control

No hypothesis tests will be conducted for the efficacy analysis.

13.0 Version History

Table 1. SAP Version History Summary

Version	Date	Summary
1.0	12 August 2020	Original version
2.0	02 January 2024	1. Updated to align with the updates in the protocol after M19-130 interim analysis. 2. Update analysis of study drug duration and analysis of safety to use M20-186 data only. Integrated data will be summarized later in the submission of SLE Phase 3 program.

14.0 References

1. Julious SA. Two-sided confidence intervals for the single proportion: comparison of seven methods by Robert G. Newcombe. Stat Med. 2005;24(21):3383-4.

Appendix A. Protocol Deviations

The number and percentage of subjects who reported at least one of the following protocol deviation categories will be provided.

- Subject entered into the study even though s/he did not satisfy entry criteria.
- Subject developed withdrawal criteria during the study and was not withdrawn.
- Subject received wrong treatment or incorrect dose of study.
- Subject took prohibited concomitant medication.

Appendix B. Definition of Adverse Events of Special Interest

Adverse Events of Special Interest (AESI) will be identified using the following search criteria:

AESI	Type of MedDRA Query	Broad or Narrow Search	SMQ/CMQ Search Criteria
Serious Infections	CMQ		"Infections" – Subset for SAEs
Opportunistic Infection excluding Tuberculosis and Herpes Zoster	CMQ		"Opportunistic Infection" excluding Tuberculosis and Herpes Zoster CMQ
Herpes Zoster	CMQ		"Herpes Zoster"
Active Tuberculosis	CMQ		"Active Tuberculosis"
Possible Malignancy	SMQ	Narrow	"Malignancies"
Malignancy	SMQ	Narrow	"Malignant Tumours"
Malignancies excluding NMSC	SMQ	Narrow	"Malignant Tumours" removing NMSC output
Non-Melanoma Skin Cancer (NMSC)	SMQ	Narrow	"Skin Malignant Tumours" removing Melanoma CMQ
Adjudicated GI perforations			Based on adjudicated results (the identification of events to be adjudicated are described in the GI Perforation charter)
Adjudicated cardiovascular events: MACE* Cardiovascular Death Non-fatal Myocardial Infarction Non-fatal Stroke Undetermined/Unknown Cause of Deaths Other Cardiovascular events	Output from CAC		
Anemia	CMQ		"Non-Hemolytic and Non-Aplastic Anemias"
Neutropenia	CMQ		"Hematological Toxicity – Neutropenia"
Lymphopenia	CMQ		"Hematological Toxicity - Lymphopenia"

AESI	Type of MedDRA Query	Broad or Narrow Search	SMQ/CMQ Search Criteria
Renal dysfunction	SMQ	Narrow	"Acute Renal Failure"
Hepatic disorders	SMQ	Narrow	"Drug Related Hepatic Disorders"
Adjudicated Thrombotic Events: VTE** Deep Vein Thrombosis Pulmonary Embolism Other Venous Thrombosis	Output from CAC		

* MACE: Major Adverse Cardiovascular Events, defined as cardiovascular death, non-fatal myocardial infarction and non-fatal stroke.

** VTE: Venous thromboembolic events, defined as deep vein thrombosis (DVT) and pulmonary embolism (PE) (fatal and non-fatal).

Appendix C. Potentially Clinically Important Criteria for Vital Sign Values

Vital Sign	Category	Criteria for Potential Clinically Important Vital Signs
Systolic blood pressure	Low	Value ≤ 90 mmHg and decrease ≥ 20 mmHg from Baseline
	High	Value ≥ 160 mmHg and increase ≥ 20 mmHg from Baseline
Diastolic blood pressure	Low	Value ≤ 50 mmHg and decrease ≥ 10 mmHg from Baseline
	High	Value ≥ 100 mmHg and increase ≥ 10 mmHg from Baseline
Weight	High	> 7% increase from baseline
	Low	> 7% decrease from baseline