IMSIDOLIMAB

A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of Imsidolimab (ANB019) in the Treatment of Adult Subjects with Generalized Pustular Psoriasis

Protocol Number: ANB019-301

Phase: III

Investigational New Drug (IND) Number: 136145

European Clinical Trials Database (EudraCT) Number: 2021-001447-27

NCT Number: NCT05352893

Sponsor Name: AnaptysBio, Inc.

Sponsor Address: 10770 Wateridge Circle, Suite 210 San Diego, CA 92121, United States

Statistical Analysis Plan

09 December 2022

9 STATISTICAL CONSIDERATIONS

9.1 STATISTICAL HYPOTHESES

The primary efficacy endpoint is the proportion of subjects achieving a GPPPGA score of 0 (clear) or 1 (almost clear) at Week 4.

There will be two marginal primary null hypotheses for the primary efficacy endpoint (ie, one for high dose [imsidolimab 750 mg] and the other for low dose [imsidolimab 300 mg]).

- The null hypothesis (H1) to be tested for high dose group is that the proportion of subjects achieving a GPPPGA score of 0 (clear) or 1 (almost clear) at Week 4 is the same for imsidolimab 750 mg and placebo.
- The null hypothesis (H2) to be tested for low dose group is that the proportion of subjects achieving a GPPPGA score of 0 (clear) or 1 (almost clear) at Week 4 is the same for imsidolimab 300 mg and placebo.

The key secondary efficacy endpoint is the proportion of subjects achieving a PRS score of 0 (clear) or 1 (almost clear) at Week 1.

There will be two marginal null hypotheses for the key secondary efficacy endpoint (ie, one for high dose [imsidolimab 750 mg] and the other for low dose [imsidolimab 300 mg]).

- The null hypothesis (H3) to be tested for high dose group is that the proportion of subjects achieving a PRS score of 0 (clear) or 1 (almost clear) at Week 1 is the same for imsidolimab 750 mg and placebo.
- The null hypothesis (H4) to be tested for low dose group is that the proportion of subjects achieving a PRS score of 0 (clear) or 1 (almost clear) at Week 1 is the same for imsidolimab 300 mg and placebo.

The global null hypothesis is that all the null hypotheses (H1, H2, H3 and H4) are true.

To address the issue of multiplicity in the testing of two doses of imsidolimab against placebo for two endpoints (ie, the primary endpoint and the key secondary endpoint), the fixed-sequence multiplicity testing method (Food and Drug Administration [FDA] Guidance for Industry: Multiple Endpoints in Clinical Trials, 2017) will be utilized. The fixed-sequence statistical strategy tests the two doses of the primary endpoint and the key secondary endpoint in a predefined order of H1→ H3→ H2→ H4, both at the same significance level alpha ($\alpha = 0.05$), moving to next testing only after a success on the previous testing. Based on this testing strategy, the familywise Type I error rate will be controlled at the same significance level alpha ($\alpha = 0.05$).

9.2 SAMPLE SIZE DETERMINATION

For each marginal null hypothesis testing, group sample sizes of 15 subjects in imsidolimab and 15 subjects in placebo achieve 82% power to detect a difference in the group proportions of 43.3%. The proportion in the imsidolimab group is assumed to be 10% under each of H_i, for i=1, 2, 3, and 4, and 53.3% under the alternative hypothesis. The proportion in the placebo group is assumed to be 10%. This is based on the two-sided Z-Test of two proportions, with unpooled variance and using a significance level, alpha, of 0.05.

Based on this 3-arm study design, 100,000 simulations were carried out using the statistical software EAST Version 6.5 module - Discrete Endpoint: Many-Sample Test - Multiple Comparisons Design - Pairwise Comparisons to Control - Differences of Proportions (Cytel, 2020). Using the fixed-sequence testing strategy, this study has 81% global power to detect at least one treatment dose which is truly different from the placebo arm for the primary endpoint given a total sample size 45 subjects randomized in a 1:1:1 ratio. This study has conjunctive power of 69% to detect both treatment dose arms which are truly different from the placebo arm for the primary endpoint. This study has conjunctive power of 44% to detect both treatment dose arms which are truly different from the placebo arm for the primary and the key secondary endpoints. This study provides disjunctive power of 81% to detect at least one treatment dose which is truly different from the placebo arm.

This study will include an interim analysis (IA), at which time a sample size re-estimation (SSRE) will be performed. To determine whether an increase in sample size is needed, a Promising Zone approach will be utilized. The sample size may be increased up to no more than 3 times the current sample size based on this assessment. Details of the SSRE procedures are described in the Statistical Analysis Plan (SAP) for the IA.

9.3 POPULATIONS FOR ANALYSES

The analysis sets are defined in Table 6.

Table 6: Analysis Sets

Analysis Set	Description
ITT Analysis Set	The ITT analysis set will include all randomized subjects. In this analysis set, treatment will be assigned based upon the treatment arm to which subjects were randomized regardless of which treatment they receive. ITT analysis set will be used for efficacy data analyses.
Safety Analysis Set	The safety analysis set will include all randomized subjects who receive 1 dose of imsidolimab or placebo. The safety analysis set will be used for all safety analyses. Subjects will be analyzed as treated.
Per Protocol Analysis Set	The per protocol analysis set will include all subjects in the ITT analysis set who do not have major protocol violations that would affect the evaluation of the primary efficacy endpoint. Per Protocol analysis set will be used for a sensitivity analysis of the primary endpoint.
PK Analysis Set	The PK analysis set will include all imsidolimab treated subjects in the safety analysis set who have at least 1 quantifiable postdose PK sample available and who do not have events or protocol deviations or events with the potential to affect PK concentrations. The PK analysis set will be used for all PK analyses.

Abbreviations: ITT, intent-to-treat; PK, pharmacokinetic.

9.4 STATISTICAL ANALYSES

9.4.1 GENERAL APPROACH

The statistical analysis will be performed using statistical analysis system (SAS®) Version 9.4 or higher. All details regarding the statistical analysis and the preparation of tables, listings, and figures will be described in the SAP and approved by AnaptysBio before database lock and any analysis is undertaken.

For categorical variables, the number and percentage (percentage of subjects in each category relative to the total number of subjects in the relevant analysis set or relative to the total number

of subjects in the relevant analysis set with assessments available [where appropriate]) in each category will be the default summary presentation.

The default summary statistics for continuous variables include number of contributing observations, mean, standard deviation (SD), median, minimum, and maximum. For PK parameters, coefficient of variation (CV) and geometric mean will also be presented, as appropriate.

Unless otherwise specified, "Baseline" is defined as the last observed value of the parameter of interest prior to the first intake of study treatment (this includes unscheduled visits). For numerical variables, change from Baseline will be calculated as the difference between the value of interest and the corresponding Baseline value.

Point estimates of treatment differences will be accompanied with 2-sided 95% confidence intervals (CIs), where applicable.

In the case of normality assumption violations, appropriate transformations or nonparametric methods may be used for analysis.

All data will be presented in by-subject listings.

9.4.2 SUBJECT DISPOSITION

A tabular presentation of the subject disposition will be provided. It will include the number of subjects consented, screened, randomized, treated, completed as well as the number of dropouts with reasons for discontinuation, and major protocol deviations or violations.

A listing will be presented to describe dates of Screening, assigned treatment, screen failed with reason, completion or early withdrawal, and the reason for early discontinuation, if applicable, for each subject. A list of protocol deviations/violations will be identified and discussed with the Investigator/AnaptysBio in dry run to categorize as major or minor with decisions of exclusion from analysis sets prior to unblinding.

During the COVID-19 pandemic, protocol deviations related to COVID-19 will be documented and information on how they will be handled in the analyses will be detailed in the SAP.

9.4.3 BASELINE DESCRIPTIVE STATISTICS

Subject characteristics obtained at Baseline will be summarized for all subjects taking imsidolimab or placebo.

Summaries will include descriptive statistics for categorical variables (n, frequency, and percentage) and for continuous variables (sample size [n], mean, SD, median, minimum, and maximum).

Medical history will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) latest version and listed for all subjects.

9.4.4 CONCOMITANT MEDICATION

All medications will be coded using the World Health Organization (WHO) Drug Dictionary and Anatomical Therapeutic Chemical (ATC) system. Each medication will be classified as prior medication if it is stopped prior to the first dose of study treatment, or as concomitant medication

if it is ongoing at the time of the first dose or is started after the first dose of study treatment. Prior and concomitant medications will be summarized descriptively with a by-subject listing.

9.4.5 ANALYSIS OF THE PRIMARY EFFICACY ENDPOINT

The primary efficacy endpoint is the proportion of subjects achieving a GPPPGA score of 0 (clear) or 1 (almost clear) at Week 4.

9.4.5.1 PRIMARY ESTIMAND

a) The target population is reflected by the patients that are eligible to be included in the clinical trial based on the inclusion/exclusion criteria in the protocol. The intent-to-treat (ITT) analysis set will include all randomized subjects. For the analysis, treatment will be assigned based upon the treatment arm to which subjects were randomized regardless of which treatment they receive.
b) The primary variable is the event occurrence (yes or no) of an individual subject to achieve a GPPPGA score of 0 (clear) or 1 (almost clear) at Week 4.
c) To handle intercurrent events (ICE) such as dropout and use of rescue medications, the composite strategy for estimand will be used, implemented by the worst score in GPPPGA score after rescue medication use. Therefore, subjects who take rescue medication will be treated as nonresponders on and after the visit when the rescue medication was taken. Subjects who drop out of the study before Week 4 or have a missing GPPPGA score at Week 4 will have missing data imputed by Multiple Imputations (MI) based on a hypothetical strategy (ie, assuming outcomes the subjects would have had, had they remained on their initially randomized treatment).
d) The population-level summary measure for the primary endpoint is the proportion of subjects achieving a GPPPGA score of 0 (clear) or 1 (almost clear) at Week 4. Estimator for between-group comparison of the primary endpoint will be the proportion difference in the primary endpoint between imsidolimab and placebo at Week 4.

9.4.5.2 PRIMARY STATISTICAL METHOD FOR ANALYSIS

The proportion of subjects who respond in each treatment group will be compared using a Cochran-Mantel-Haenszel (CMH) Chi-square test, stratified by Baseline GPPPGA score (ie, 3 [moderate] or 4 [severe]).

The CMH estimate, confidence limits, and test for the proportion difference will be done by using CMH stratum weights and the Sato variance estimator as implemented in SAS® 9.4.

For those subjects who did not receive rescue treatment, missing data at Week 4 will be imputed using a MI procedure, performed under the assumption that data is missing at random (MAR). The missing data imputation will be performed on the original score (GPPPGA) using normal Bayesian sequential regression for monotone data (intermittent missingness if present can be imputed using the MCMC procedure to complete data to monotone patterns) and then dichotomizing the imputed scores for the analysis. One-hundred imputation datasets will be created. Then CMH test will be performed on these imputed datasets. To pool estimates of the CMH statistics from analysis of the 100 multiply imputed data and obtain an overall p-value for the CMH test. A Wilson-Hilferty transformation to normalize the CMH chi-square distributed statistics will be applied prior to pooling the results to perform a combined CMH test (Ratitch 2013).

9.4.5.3 SENSITIVITY ANALYSIS

As a sensitivity analysis for assessing the robustness of the primary analysis method of the CMH Chi-squared test, the proportion of subjects who respond in each treatment group will be compared using the method of Mehrotra and Railkar (MR) Chi-square test, stratified by Baseline GPPPGA score (ie, 3 [moderate] or 4 [severe]). This method uses minimum risk weights, which minimize the mean square error of the estimate of the proportion difference.

As the nonresponse imputation relies on the strong assumption that patients who drop out have not responded, to assess the robustness of the primary imputation method for dropouts, placebo Multiple Imputation (pMI) method will be conducted as a sensitivity analysis for the analysis of the primary endpoint. pMI uses a different imputation assumption than the primary analysis. The pMI assumes that the statistical behavior of imsidolimab-treated patients and placebo-treated patients after the occurrence of intercurrent events will be the same as if patients were treated with placebo. In the context of efficacy data, pMI is a specific form of a Missing Not at Random (MNAR) analysis and expected to yield a conservative estimate for efficacy.

As an additional sensitivity analysis for the primary endpoint, tipping point multiple imputation analysis methodology will be conducted for the primary endpoint. Tipping point analysis methodology uses MNAR assumption. From a wide spectrum of conservative assumptions regarding the missingness mechanism, the tipping point can be identified while the result is no longer statistically significant.

In addition, as another sensitivity to assess the ITT population, per protocol analysis of the primary efficacy analysis will be also performed.

9.4.5.4 MULTIPLICITY ADJUSTMENT

The fixed-sequence statistical strategy tests the two doses of the primary endpoint and the key secondary endpoint in a predefined order from the primary endpoint and the key secondary endpoint of the high dose to the primary endpoint and the key secondary endpoint of the low dose, all at the same significance level alpha ($\alpha = 0.05$), moving to a second testing only after a success on the previous testing. That is, using the null hypotheses for the primary endpoint and the key secondary endpoint as defined in Section 9.1, the predefined order is H1→ H3→ H2→ H4.

Specifically, in the first step, the statistical hypothesis testing for the primary endpoint of the high dose group (imsidolimab 750 mg) against placebo will be performed; and the statistical hypothesis testing for the key secondary of the high dose group (imsidolimab 750 mg) against placebo will be performed only if the null hypothesis for the primary endpoint of imsidolimab 750 mg against placebo is rejected in the first step. Otherwise, the testing stops. Based on this testing strategy, the Type I error rate will be controlled at the same significance level alpha ($\alpha = 0.05$).

9.4.5.5 OTHER ANALYSES OF THE PRIMARY ENDPOINT

Possible effect of any covariates as well as investigation of sub-group analyses may also be performed. Details of such analyses will be described in the study SAP.

9.4.6 ANALYSIS OF THE KEY SECONDARY EFFICACY ENDPOINT

The key secondary efficacy endpoint is the proportion of subjects achieving a PRS score of 0 (clear) or 1 (almost clear) at Week 1.

9.4.6.1 SECONDARY ESTIMAND

a) The target population is reflected by the patients that are eligible to be included in the clinical trial based on the inclusion/exclusion criteria in the protocol. The ITT analysis set will include all randomized subjects. For the analysis, treatment will be assigned based upon the treatment arm to which subjects were randomized regardless of which treatment they receive.
b) The key secondary variable is the event occurrence (yes or no) of an individual subject to achieve a PRS score of 0 (clear) or 1 (almost clear) at Week 1.
c) To handle intercurrent events such as dropout and use of rescue medications, the composite strategy for estimand will be used implemented by the worst score in PRS score after rescue medication use. Therefore, subjects who take rescue medication will be treated as nonresponders on and after the visit when the rescue medication was taken. Subjects who drop out of the study before Week 1 or have a missing PRS score at Week 1 will have missing data imputed by MI based on a hypothetical strategy (ie, assuming outcomes the subjects would have had, had they remained on their initially randomized treatment).
d) The population-level summary measure for the key secondary endpoint is the proportion of subjects achieving a PRS score of 0 (clear) or 1 (almost clear) at Week 1. Estimator for between-group comparison of the key secondary endpoint will be the proportion difference in the key secondary endpoint between imsidolimab and placebo at Week 1.

9.4.6.2 THE KEY SECONDARY STATISTICAL METHOD FOR ANALYSIS

The similar statistical method for the primary endpoint will be applied to the key secondary endpoint. And similar missing data handling method for the primary endpoint will be used for the key secondary endpoint as well.

9.4.6.3 SENSITIVITY ANALYSIS

The similar sensitivity analyses of analysis of the primary endpoint will be applied for the analysis of the key secondary endpoint.

9.4.7 ANALYSIS OF THE ADDITIONAL SECONDARY EFFICACY ENDPOINTS

Following are the additional secondary efficacy endpoints:

- Proportion of subjects achieving at least a 2-grade decrease from Baseline in GPPPGA score at Week 4
- Proportion of subjects achieving clinical response on the CGI scale at Week 4. Clinical response is defined as “Very much improved,” “Much improved,” and “Minimally improved” on the CGI scale according to the mJDA severity index total score
- Change from Baseline in BSA affected with erythema with pustules as assessed by the mJDA severity index at Week 1

- Percent change from Baseline in BSA affected with erythema with pustules as assessed by the mJDA severity index at Week 1
- Change from Baseline in BSA affected with erythema with pustules as assessed by the mJDA severity index at Week 4
- Percent change from Baseline in BSA affected with erythema with pustules as assessed by the mJDA severity index at Week 4
- Change from Baseline in BSA affected with total erythema as assessed by the mJDA severity index at Week 4
- Percent change from Baseline in BSA affected with total erythema as assessed by the mJDA severity index at Week 4
- Change from Baseline in BSA affected with edema as assessed by the mJDA severity index at Week 4
- Percent change from Baseline in BSA affected with edema as assessed by the mJDA severity index at Week 4
- Proportion of subjects achieving GPPASI 50 at Week 4
- Proportion of subjects achieving GPPASI 75 at Week 4
- Change from Baseline in DLQI at Week 4
- Change from Baseline in EQ-5D-5L at Week 4
- Proportion of subjects with at least a 3-point decrease from Baseline in pain NRS at Week 4 for subjects with a Baseline pain NRS of at least 3

Subjects who receive prohibited systemic rescue medication prior to Week 4 will be considered nonresponders. For each endpoint, the proportion of subjects who respond in each treatment group will be compared using a CMH Chi-square test, stratified by Baseline GPPPGA score (ie, 3 [moderate] or 4 [severe]).

9.4.7.1 CATEGORICAL ENDPOINTS

The frequency and percentage of subjects for each categorical variable will be summarized. The difference in percentage between the imsidolimab and placebo groups will be tested by CMH Chi-square test, using the GPPPGA score at baseline (3 [moderate] or 4 [severe]) as stratification factor.

Frequency and percentages for each response Yes/No for categorical endpoints related to GPPPGA score, PRS score, clinical response on CGI, GPPASI, and pain NRS will be presented separately by visit for both treatment arms. Estimates of the difference between treatments (imsidolimab – placebo) will be presented along with 95% CIs.

9.4.7.2 CONTINUOUS ENDPOINTS

Summary statistics will be provided for absolute scores and change from Baseline to specified time points of DLQI and EQ-5D-5L; change and percent change from Baseline by visit and treatment arm will also be shown. A by-subject listing will be presented for each assessment, by visit.

The continuous data endpoints such as change from baseline will be analyzed using a linear mixed model for repeated measures (MMRM), including treatment, visit, and treatment by visit interaction as factors, and GPPPGA score at baseline (3 [moderate] or 4 [severe]) and baseline values as covariates. An unstructured correlation (UN) matrix will be used to model correlation

within a subject. The least-squares mean (LSM), least-squares mean estimate of group differences (LSMD), and the associated 95% CIs will be presented for each comparison. Summary statistics will also be provided for absolute scores and change from baseline.

9.4.8 ANALYSIS OF THE EXPLORATORY EFFICACY ENDPOINTS

Following are the exploratory efficacy endpoints:

- Proportion of subjects achieving a GPPPGA score of 0 (clear) or 1 (almost clear) at visits other than Week 4
- Proportion of subjects with at least a 2-point decrease from Baseline in GPPPGA score at visits other than Week 4
- Change from Baseline in GPPPGA at each visit
- Proportion of subjects achieving a PRS score of 0 (clear) or 1 (almost clear) at visits other than Week 1
- Proportion of subjects with at least a 2-point decrease from Baseline in PRS score at each visit
- Change from Baseline in PRS at each visit
- Proportion of subjects in each response category for the CGI-C at each visit
- Change from Baseline in mJDA severity index total score (sum of skin lesion total score and systemic manifestation and laboratory findings total score) at each visit
- Change from Baseline in skin lesion total score (sum of erythema with pustules, total erythema, and edema scores) of the mJDA severity index at each visit
- Change from Baseline in individual scores of erythema with pustules, erythema total, and edema of the mJDA severity index at each visit
- Change from Baseline in BSA affected with erythema with pustules as assessed by the mJDA severity index at visits other than Week 1 and Week 4
- Percent change from Baseline in BSA affected with erythema with pustules as assessed by the mJDA severity index at visits other than Week 1 and Week 4
- Change from Baseline in BSA affected with total erythema as assessed by the mJDA severity index at visits other than Week 4
- Percent change from Baseline in BSA affected with total erythema as assessed by the mJDA severity index at visits other than Week 4
- Change from Baseline in BSA affected with edema as assessed by the mJDA severity index at visits other than Week 4
- Percent change from Baseline in BSA affected with edema as assessed by the mJDA severity index at visits other than Week 4
- Change from Baseline in total score of systemic manifestations and laboratory findings (sum of fever, WBC count, CRP, serum albumin scores) of the mJDA severity index at each visit
- Change from Baseline in individual scores of systemic manifestations and laboratory findings (fever, WBC count, CRP, serum albumin) of the mJDA severity index at each visit
- Proportion of subjects that achieve normalization of mJDA systemic manifestations and laboratory findings (fever, WBC count, CRP, serum albumin)

- Change from Baseline in absolute values of systemic manifestations and laboratory findings as assessed by the mJDA severity index at each visit
- Percent change from Baseline in absolute values of systemic manifestations and laboratory findings as assessed by the mJDA severity index at each visit
- Proportion of subjects achieving clinical response on the CGI scale according to the mJDA severity index at visits other than Week 4
- Proportion of subjects achieving GPPASI 50 at visits other than Week 4
- Proportion of subjects achieving GPPASI 75 at visits other than Week 4
- Change from Baseline in GPPASI at each visit
- Percent change from Baseline in GPPASI at each visit
- Change from Baseline in total BSA affected with GPP at each visit
- Percent change from Baseline in total BSA affected with GPP at each visit
- Change from Baseline in BSA (excluding palms and soles) affected with pustules at each visit
- Percent change from Baseline in BSA (excluding palms and soles) affected with pustules at each visit
- Change from Baseline in DLQI at visits other than Week 4
- Change from Baseline in EQ-5D-5L at visits other than Week 4
- Change from Baseline in pain NRS at each visit
- Percent change from Baseline in pain NRS at each visit
- Proportion of subjects with at least a 3-point decrease from Baseline in pain NRS at visits other than Week 4 for subjects with a Baseline pain NRS of at least 3
- Proportion of subjects with at least 4-point decrease from Baseline in pain NRS at each visit for subjects with a Baseline pain NRS of at least 4
- Proportion of subjects in each response category for each question for the PGI-S at each visit
- Proportion of subjects in each response category for the PGI-B at each visit
- Proportion of subjects in each response category for the PGI-C at each visit
- Proportion of subjects achieving a “None” or “Mild” for each question in the PGI-S at each visit
- Proportion of subjects achieving “A little bothered” or “Not bothered at all” for the PGI-B at each visit
- Proportion of subjects achieving “A little better,” “Better” or “Much better” for the PGI-C at each visit
- Proportion of subjects in each response category for the SSQ at each visit
- Proportion of subjects achieving “slightly satisfied”, “somewhat satisfied” or “extremely satisfied” for the SSQ at each visit
- Proportion of subjects in each response category for the SSRS at Week 1, Week 4, and Week 12
- Proportion of subjects achieving “slightly satisfied”, “somewhat satisfied” or “extremely satisfied” for the SSRS at Week 1, Week 4, and Week 12
- Proportion of subjects requiring rescue medication
- Change from Baseline in PASI (for subjects with concurrent plaque psoriasis at Baseline) at each visit

Note: Reference to each visit in the exploratory endpoints excludes the visits covered by the primary and secondary endpoints.

Methods for analyzing the above categorical and continuous efficacy endpoints will mirror the methods described in Section 9.4.7.1 and 9.4.7.2, respectively. Treatment groups may be compared using appropriate statistical models to be described in the SAP. All testing will be exploratory in nature and assessed based on two-sided alpha = 0.05.

9.4.9 SAFETY ANALYSES

Following are the safety endpoints:

- Assessment of AEs, SAEs, and AEs leading to withdrawal
- Vital signs
- 12-Lead ECG
- Clinical safety laboratory tests (hematology, biochemistry, and urinalysis)

All safety analyses will be performed on the safety analysis set.

9.4.9.1 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

A TEAE is defined as:

- A new event that occurs during or after first dose of study treatment or,
- Any event present at Baseline that worsens in either intensity or frequency after first dose of study treatment.

Adverse events will be coded using the MedDRA and only TEAEs will be summarized. Number of events and percentage will be tabulated by preferred term (PT) and system organ class (SOC). Multiple occurrences of an AE for a subject will only be counted once per SOC and PT. Percentages will be determined relative to the subjects in the safety analysis set for the given treatment arm.

If the intensity or seriousness of the AE changes, the overall intensity or seriousness will be the maximum intensity or seriousness of the multiple occurrences. The TEAEs, SAEs, TEAEs leading to treatment discontinuation, and TEAEs leading to withdrawal of subject will be tabulated for each treatment arm.

All AE data will be listed for each subject.

Summaries over SOC and PT of TEAEs, TEAEs leading to death, SAEs, and TEAEs that led to discontinuation from the study or study treatment will be presented by treatment. Summaries will also be presented by relatedness to the study treatment and the severity of the TEAE.

9.4.9.2 12-LEAD ELECTROCARDIOGRAM, VITAL SIGNS, AND CLINICAL SAFETY LABORATORY TESTS

Summaries and listings of data for vital signs and safety laboratory tests result (hematology, biochemistry, and urinalysis) will be presented. Appropriate descriptive statistics will be summarized for the observed value at each scheduled assessment and for the corresponding change from Baseline.

For hematology and biochemistry tests, listings of subject data will also flag up any abnormal or out-of-range values. Clinically significant changes in the laboratory test parameters will be summarized and listed. Hematology and biochemistry data will be reported in System International units.

Descriptive statistics will be used to present the safety outcomes including, weight, 12-Lead ECG, vital signs, and clinical laboratory test results.

Change from Baseline will also be summarized for vital signs, and clinical laboratory tests results.

All ECG data results (normal/abnormal) will be summarized using frequency and percentage. Clinically significant abnormalities will be presented in by-subject listings.

9.4.10 PHARMACOKINETIC ANALYSES

Limited imsidolimab PK parameter analysis will be evaluated by assessment of drug concentrations in serum. These drug concentrations will be listed and summarized for each sampling time point using appropriate descriptive statistics. The PK parameters, where calculated, will be summarized using appropriate descriptive statistics and applied on the PK Analysis Set.

9.4.10.1 DERIVATION OF PHARMACOKINETIC PARAMETERS

Where possible, PK parameters will be derived using noncompartmental methods. The actual sampling times will be used in the PK parameter calculations. Further details of PK analysis, data handling, analysis procedures, and data reporting will be described separately in the SAP.

9.4.10.2 PHARMACOKINETIC CONCENTRATION DATA ANALYSIS

A subject listing of all concentration-time data following SC injections will be presented by subject and scheduled sample collection time.

Concentration data of imsidolimab will be summarized by day and nominal time point using the number of observations, arithmetic mean, SD, CV, minimum, median, maximum, and geometric mean.

Graphs for mean concentration-time data following IV administration will be presented. Individual subject concentration-time plots will also be presented.

Other presentations of data may be added at the discretion of the PK scientist, as appropriate, and will be described separately in the SAP.

9.4.10.3 PHARMACOKINETIC PARAMETER DATA ANALYSIS

Where possible, PK parameters will be summarized using number of observations, arithmetic mean, SD, CV, minimum, median, maximum, geometric mean, and geometric CV, with the exception of time to maximum observed concentration (T_{max}), which will be reported with n, minimum, median, and maximum only.

Graphs and PK parameters may be added at the discretion of the PK scientist, as appropriate, and will be described separately in the SAP.

9.4.10.4 POPULATION PHARMACOKINETICS ANALYSIS

Pharmacokinetic data from the study may also be used for population PK and/or PK/exposure-response analyses. If done, a separate analysis plan will be prepared and results will be reported separately from the Clinical Study Report (CSR).

9.4.11 IMMUNOGENICITY ANALYSES

Observed values for ADA levels/status will be listed by-subject and summarized with descriptive statistics based on the safety analysis set. If data permits, correlation will be analyzed between ADA levels/status and safety and efficacy endpoints.

Frequency and percentage of ADA response will be presented and listed. Further details of immunogenicity analyses will be described separately in the SAP.

9.4.12 BIOMARKER ANALYSIS

Tape strip and optional skin biopsy biomarker analysis will be performed by a third party designated by AnaptysBio. Further details of biomarker analysis will be described separately in the SAP, if analyzed. In this case, results of biomarker analyses will be listed by biomarker type, subject and day of collection. Statistical summary (mean, standard deviation, minimum, and maximum) across subjects will be provided by biomarker type and day of collection.

9.4.13 GENETIC ANALYSIS

Genetic analysis will be performed by a third party designated by AnaptysBio. DNA mutational status will be listed by gene variant, subject and day of collection. A separate analysis plan will be prepared for mRNA analyses, if performed, and results will be reported separately from the CSR.

9.4.14 PLANNED INTERIM ANALYSIS

An IA will be performed when approximately 30 subjects have primary efficacy data. That is, data for approximately 30 subjects will be available for the IA to occur. The expected number of subjects are 10 subjects in each of the two doses of imsidolimab and 10 subjects in placebo group. The IA will evaluate the treatment effect of the primary endpoint using the ITT Analysis Set.

Sample size re-estimation assessment will be based on the conditional power to detect the treatment difference in response rate. The study may continue to recruit to its target randomization of 45, or the sample size may be adjusted to a higher number. One of two possible recommendations will be provided by an independent data monitoring committee (IDMC):

- SSRE to allow for possible upwards adjustment in sample size
- Continue the study as planned, with no adjustments made to the sample size

The detailed statistical methodology is detailed in the SAP for the IA. The decision rules for the IA, the plan for maintaining blinding including safeguards of the unblinded analysis, and details on the IDMC are documented in the IA charter.