IMSIDOLIMAB

A Phase 3, Long-Term Extension Study to Evaluate the Safety and Efficacy of Imsidolimab (ANB019) in the Treatment of Adult Subjects with Generalized Pustular Psoriasis

Protocol Number: ANB019-302

Phase: III

Investigational New Drug (IND) Number: 136145

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Statistical Analysis Plan

19 August 2022

9 STATISTICAL CONSIDERATIONS

9.1 STATISTICAL HYPOTHESES

The primary study objective is to demonstrate long-term safety of imsidolimab in subjects with GPP flare. There is no formal statistical hypothesis. Descriptive statistics will be used to evaluate safety endpoints, including the incidence of TEAEs (SOC and PT) by randomized treatment arm in this study, and for imsidolimab treatment overall, including events during all imsidolimab exposure from both ANB019-301 and ANB019-302 studies.

9.2 SAMPLE SIZE DETERMINATION

No formal sample size or power calculations were performed for this extension study. The sample size is based on the number of subjects enrolled in the preceding Phase 3 study ANB019-301 and subjects consenting for the extension.

9.3 POPULATIONS FOR ANALYSES

The analysis sets are defined in Table 7.

Table 7: Analysis Sets

Analysis Set	Description
Safety Analysis Set – Extension (SAF-Ext)	The SAF-Ext population will be used for the analysis of safety data in this study. The SAF-Ext consists of all randomized subjects in ANB019-301 who are enrolled into the ANB019-302 extension study and received at least one dose of imsidolimab or placebo in this study. The SAF-Ext will be used for the safety analyses.
ITT Analysis Set	The ITT analysis set will include all enrolled subjects. In this analysis set, treatment will be assigned based upon the treatment arm to which subjects were assigned regardless of which treatment they receive.
mITT Analysis Set	The mITT analysis set is a subset of ITT subjects who had previously achieved a GPPPGA score of 0 [clear] or 1 [almost clear]). In this analysis set, treatment will be assigned based upon the treatment arm to which subjects were assigned regardless of which treatment they receive.
Per Protocol Analysis Set	The per protocol analysis set will include all subjects in the mITT analysis set who do not have major protocol violations that would affect the evaluation of the GPPPGA score.
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: GPPPGA, Generalized Pustular Psoriasis Physician's Global Assessment; ITT, intent-to-treat; mITT, modified intent-to-treat; PK, pharmacokinetic; SAF-Ext, safety analysis set – extension.

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 will be described in the Statistical Analysis Plan (SAP).

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.

Two baselines (ie, Study Baseline and Imsidolimab Baseline) are defined and will be used for the analysis as appropriate. The Study Baseline is defined as the last observed value of the parameter of interest prior to the first study treatment in the ANB019-302 study. The Imsidolimab Baseline is defined as the last observed value of the parameter of interest prior to the first imsidolimab administration in ANB019-301 or ANB019-302 studies, whichever imsidolimab administration was earlier. 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.

All data will be presented in by-subject listings. Imputation will be performed for missing GPPPGA and PRS score data using the similar approach as described in study protocol ANB019-301 (e.g., missing GPPPGA and PRS data imputation will be performed on the original score (GPPPGA/PRS) 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 responder analysis). Further inclusion of data from the ANB019-301 study in the reporting of this study will be described in the SAP.

9.4.2 SUBJECT DISPOSITION

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

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 Study Baseline will be summarized for all subjects taking imsidolimab, placebo, or rescue medication. For safety data summary of imsidolimab, the Imsidolimab Baseline will be used.

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).

For this extension study, no more medical history data will be collected as the medical history should have been collected and available from the ANB019-301 study.

9.4.4 CONCOMITANT MEDICATION

All medications will be coded using the World Health Organization (WHO) Drug Dictionary and Anatomical Therapeutic Chemical (ATC) system.

As this is an extension study from the preceding Phase 3 study ANB019-301, prior medication was only defined in the ANB019-301 study. Any medication that continues past Day 1 of this study or is started after the first dose of study treatment will be collected as concomitant medication. Prior and concomitant medications will be summarized descriptively with a by-subject listing.

9.4.5 ANALYSIS OF THE EFFICACY ENDPOINTS

9.4.5.1 CATEGORICAL ENDPOINTS

Frequency and percentages for each response Yes/No for categorical endpoints 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. The between-group difference in proportions will be tested using the Farrington-Manning score test. The 95% CIs will be estimated using the Farrington-Manning confidence limits as implemented in SAS® 9.4.

9.4.5.2 CONTINUOUS ENDPOINTS

Continuous variables will be analyzed using mixed-effects model for repeated measures (MMRM) method, with the treatment group as the main effect, with visit and interaction of treatment by visit as factors, and with Baseline values as a covariate. Summary statistics will be provided for absolute scores and change from Baseline to specified time points; 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. Mixed-effects model for repeated measures analysis will be used for statistical testing for longitudinal continuous endpoints as applicable.

9.4.5.3 TIME-TO-EVENT ENDPOINTS

Median and 95% CI for time-to-event endpoints will be estimated using Kaplan-Meier Method. The statistical comparison of the time-to-event endpoints between treatment groups will be performed using log-rank test.

9.4.5.4 ANALYSIS OF THE SECONDARY EFFICACY ENDPOINTS

Following are the secondary efficacy endpoints:

- Proportion of subjects with zero recurrence of GPP flare (defined by a GPPPGA ≥ 3 [moderate] in subjects who had previously achieved a GPPPGA score of 0 [clear] or 1 [almost clear]) through Week 24
- Proportion of subjects in remission (defined by a GPPPGA score of 0 [clear] or 1 [almost clear]) at Week 24, without intake of any rescue medications during the treatment period
- Time to first GPP flare recurrence
- Proportion of subjects with a GPPPGA score of 0 (clear) or 1 (almost clear) at Week 24
- Proportion of subjects with a PRS score of 0 (clear) or 1 (almost clear) at Week 24
- Time to first pustulation flare recurrence (defined by a PRS ≥ 3 [moderate] in subjects who had previously achieved a PRS score of 0 [clear] or 1 [almost clear])

- Proportion of subjects with a clinical response on the CGI scale at Week 24. Clinical response is defined as "Very much improved," "Much improved," and "Minimally improved" on CGI scale according to the mJDA severity index total score
- Proportion of subjects losing clinical response on the CGI scale (defined as subjects who had previously achieved clinical response defined as "minimally improved" or better on CGI scale according to the mJDA severity index total score and worsen to either "no change" or "worsened" on the CGI scale) at Week 24
- Change from Baseline in BSA affected with erythema with pustules as assessed by the mJDA severity index at Week 24
- Percent change from Baseline in BSA affected with erythema with pustules as assessed by the mJDA severity index at Week 24
- Change from Baseline in BSA affected with total erythema as assessed by the mJDA severity index at Week 24
- Percent change from Baseline in BSA affected with total erythema as assessed by the mJDA severity index at Week 24

In the analysis based on the Study Baseline (as define in Section 9.4.1), subjects who receive systemic rescue medication (other than imsidolimab) at any time during the studies ANB019-301 or ANB019-302 or topical rescue medication prior to Week 16 will be considered nonresponders. In the analyses based on the Imsidolimab Baseline (as define in Section 9.4.1), subjects who receive systemic rescue medication (other than imsidolimab) at any time or topical rescue medication prior to Week 16 will be considered nonresponders.

Time to first GPP flare recurrence and time to first pustulation flare recurrence will be analyzed using time-to-event analysis method described in Section 9.4.5.3. Response of binary outcome will be analyzed using the methods described in Section 9.4.5.1.

9.4.5.5 ANALYSIS OF THE EXPLORATORY EFFICACY ENDPOINTS

Following are the exploratory efficacy endpoints:

- Proportion of subjects with zero recurrence of GPP flare (defined by a GPPPGA ≥ 3 [moderate] in subjects who had previously achieved a GPPPGA score of 0 [clear] or 1 [almost clear]) through Week 52, Week 104, Week 148, and Week 156
- Proportion of subjects in remission (defined by a GPPPGA score of 0 [clear] or 1 [almost clear]) at Week 52, Week 104, Week 148, and Week 156, without intake of any rescue medications during the treatment period
- Proportion of subjects with a GPPPGA score of 0 (clear) or 1 (almost clear) at each visit except Week 24
- Proportion of subjects with a PRS score of 0 (clear) or 1 (almost clear) at each visit except Week 24
- Proportion of subjects with a clinical response on the CGI scale at each visit except Week 24. Clinical response is defined as "Very much improved," "Much improved," and "Minimally improved" on CGI scale according to the mJDA severity index total score
- Proportion of subjects losing clinical response on the CGI scale (defined as subjects who had previously achieved clinical response defined as "minimally improved" or better on CGI scale according to the mJDA severity index total score and worsen to either "no change" or "worsened" on the CGI scale) at each visit except Week 24

- Change from Baseline in BSA affected with erythema with pustules as assessed by the mJDA severity index at each visit except Week 24
- Percent change from Baseline in BSA affected with erythema with pustules as assessed by the mJDA severity index at each visit except Week 24
- Change from Baseline in BSA affected with total erythema as assessed by the mJDA severity index at each visit except Week 24
- Percent change from Baseline in BSA affected with total erythema as assessed by the mJDA severity index at each visit except Week 24
- Change from Baseline in BSA affected with edema as assessed by the mJDA severity index at each visit
- Percent change from Baseline in BSA affected with edema as assessed by the mJDA severity index at each visit
- Proportion of subjects with at least 3-point decrease from Baseline in pain NRS at each visit for subjects with a Baseline pain NRS of at least 3
- Change from Baseline in GPPPGA score at each visit
- Proportion of subjects with at least a 2-point decrease from Baseline in GPPPGA score at each visit
- Time to loss of response (defined by a GPPPGA score of ≥ 2 [mild] in subjects who had previously achieved a GPPPGA score of 0 [clear] or 1 [almost clear])
- Proportion of subjects with a maintenance of effect (defined by a GPPPGA score 0 [clear] or 1 [almost clear] at Week 24, Week 52, Week 104, and Week 148 in subjects who had previously achieved a GPPPGA score of 0 [clear] or 1 [almost clear])
- Change from Baseline in PRS score at each visit
- Proportion of subjects with at least a 2-point decrease from Baseline in PRS score at each visit
- Change from Baseline in mJDA severity index total score (sum of skin lesion total score and systemic manifestation 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, total erythema, and edema of the mJDA severity index at each visit
- Change from Baseline in total score of systemic manifestations and laboratory findings (sum of fever, WBC count, CRP, serum albumin) 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
- 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 in each response category for the CGI-C at each visit
- Proportion of subjects achieving GPPASI 50 at each visit
- Proportion of subjects achieving GPPASI 75 at each visit
- Time to loss of 50% of GPPASI improvement from Baseline in subjects who achieved GPPASI 75
- Change from Baseline in GPPPASI at each visit

- Percent change from Baseline in GPPPASI 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 pustule at each visit
- Percent change from Baseline in BSA (excluding palms and soles) affected with pustule at each visit
- Change from Baseline in EQ-5D-5L at Week 12, Week 24, Week 52, Week 104, Week 148, and Week 156
- Change from Baseline in DLQI at Week 12, Week 24, Week 52, Week 104, Week 148, and Week 156
- 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 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
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- 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 12, Week 24, Week 52, Week 104, Week 148 and Week 156
- Proportion of subjects achieving “slightly satisfied”, “somewhat satisfied” or “extremely satisfied” for the SSRS at Week 12, Week 24, Week 52, Week 104, Week 148 and Week 156
- Proportion of subjects receiving topical rescue medication from Week 16 to Week 24, Week 16 to Week 52, Week 16 to Week 104, Week 16 to Week 148, and Week 16 to Week 156
- Change from Baseline in PASI (for subjects with concurrent plaque psoriasis on Day 1 of the ANB019-301 study) at each visit
- Proportion of subjects achieving PASI 50 (for subjects with concurrent plaque psoriasis on Day 1 of the ANB019-301 study) at each visit
- Proportion of subjects achieving PASI 75 (for subjects with concurrent plaque psoriasis on Day 1 of the ANB019-301 study) at each visit

Methods for analyzing the exploratory categorical, continuous efficacy, and time-to-event endpoints will mirror the methods described in Section 9.4.5.1, 9.4.5.2, and 9.4.5.3, respectively.

9.4.6 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)

Safety analyses will be performed on the SAF-Ext. For the analysis of vital signs, 12-lead ECG, and clinical safety laboratory tests, Imsidolimab baseline will be used.

9.4.6.1 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 Medical Dictionary for Regulatory Activities (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 SAF-Ext 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.

9.4.6.2 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.

9.4.7 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.

9.4.7.1 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.

9.4.7.2 PHARMACOKINETIC CONCENTRATION DATA ANALYSIS

A subject listing of all concentration-time data following imsidolimab administration 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 imsidolimab 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.

9.4.7.3 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.

9.4.7.4 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).

9.4.8 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.

9.4.9 OPTIONAL GENETIC ANALYSIS

Genetic analysis will be performed by a third party designated by AnaptysBio. A separate analysis plan will be prepared for mRNA analyses, if performed, and results will be reported separately from the CSR.

9.4.10 PLANNED INTERIM ANALYSIS

Interim analyses for the long-term efficacy and safety assessment may be performed at the time a) when all subjects have completed the Week 24 visit, or have been discontinued from the study or have been lost to follow-up b) when all subjects have completed the Week 52 visit, or have been discontinued from the study or have been lost to follow-up c) when all subjects have completed the Week 104 visit, or have been discontinued from the study or have been lost to follow-up. Additional interim analysis may be performed to support submissions.