STATISTICAL ANALYSIS PLAN

ANB019-003

A Phase II, Randomized, Placebo-controlled, Double-blind, Multiple Dose Study to Evaluate the Efficacy and Safety of ANB019 in Subjects with Palmoplantar Pustulosis

AUTHORS: [redacted]

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1. INTRODUCTION

This document describes the rules and conventions to be used in the presentation and analysis of efficacy, safety and pharmacokinetic (PK) data for Protocol ANB019-003. It describes the data to be summarized and analyzed, including specifics of the statistical analyses to be performed. This statistical analysis plan (SAP) is based on final Protocol Amendment 5 and 5.1, dated 29 October 2020.
Changes to the protocol that impact the design, the data collected, or the statistical methods and that occur after the finalization of this SAP may require amendment of the approved SAP. Similarly, changes to the planned analysis variables and/or statistical methods described in the approved SAP may also require amendment of the protocol.

2. STUDY OBJECTIVES

2.1. PRIMARY OBJECTIVE

The primary objectives of the study are:

To determine the effect of ANB019 compared with placebo in subjects with PPP as measured by the Palmoplantar Pustulosis Psoriasis Area Severity Index (PPPASI).
To assess the safety and tolerability of ANB019 in subjects with PPP.

2.2. SECONDARY OBJECTIVES

The secondary objectives of the study are:

To determine the effect of ANB019 in subjects with PPP as measured by improvement in the PPPASI.
To determine the effect of ANB019 in subjects with PPP as measured by Palmoplantar Pustulosis Severity Index (PPSI).
To determine the proportion of subjects who achieved PPP disease clearance after administration of ANB019 as measured by the Palmoplantar Pustulosis (static) Investigator's Global Assessment (PPPIGA).
To determine the time to response with ANB019 in subjects with PPP.
To determine the relapse rate with ANB019 in subjects with PPP.

[redacted]

To evaluate the effect of ANB019 in subjects with plaque psoriasis at non acral sites (if present) as measured by the Psoriasis Area Severity Index (PASI) and affected body surface area (BSA).

- To evaluate the effect of ANB019 in subjects with pustular psoriasis at non acral sites (if present) as measured by BSA.
- To evaluate the effect of ANB019 on subject's quality of life.

To test for immunogenicity to ANB019.

To describe the PK of ANB019 in subjects with PPP.

2.3. EXPLORATORY OBJECTIVES

The exploratory objectives in this study are:

To explore the effect of ANB019 on skin biopsy biomarkers.

To provide photographic documentation of lesions.

3. ENDPOINTS

3.1. PRIMARY EFFICACY ENDPOINT

Mean change from Baseline in PPPASI at all study visits.

3.2. SAFETY AND TOLERABILITY ENDPOINTS

Assessment of adverse events (AEs).

Potentially significant and clinically important AEs, adverse events of special interest (AESIs), serious AEs (SAEs), and AEs leading to withdrawal.

Physical examinations.

Vital signs.

12-Lead electrocardiogram (ECG).

Clinical safety laboratory tests (hematology, biochemistry, and urinalysis).

3.3. SECONDARY ENDPOINTS

Proportion of subjects achieving PPPASI50 at all study center visits.

Proportion of subjects achieving PPPASI75 at all study center visits.

Change from Baseline in PPSI score at all study center visits.

Change in PPPIGA score at all study center visits.

Proportion of subjects with clear or almost clear assessment score on PPPIGA at all study center visits.

Change in fresh and total pustule count on palms and soles at all study center visits.

Time to response defined as time to achieve 75% reduction in fresh pustule count.

- Relapse rate defined as return to Baseline in fresh pustule count.

Change in PASI score and affected BSA at all study center visits, if plaque psoriasis is present at non- acral sites.

Improvement in pustular psoriasis at non- acral site BSA (if present) at all study center visits.

Change in clinical scores of Palmoplantar Pustulosis Quality of Life Instrument (PPPQLI), Dermatology Life Quality Index (DLQI), and Patient Assessment of Palmoplantar Pustulosis Disease Activity at all study center visits.

Presence of anti-drug- antibodies.

Pharmacokinetic endpoints

- Serum concentration following ANB019 administration.
- Maximum observed concentration (C_{max}).
- Time to maximum observed concentration (T_{max}).
- Area under the concentration-time curve (AUC).
- Terminal half-life ($t_{1/2}$).
- Other parameters as appropriate.

3.4. EXPLORATORY ENDPOINTS

- Skin biopsy biomarkers including but not limited to IL-36, IL-17, IL-23, and markers of neutrophils and dendritic cells infiltration.

Photographic documentation of lesions.

[redacted]

4. HYPOTHESIS

No formal hypothesis testing will be performed.

5. STUDY DESIGN

5.1. GENERAL DESCRIPTION

This is a randomized, multicenter, placebo-controlled, double-blind, multiple dose study designed to assess the efficacy as well as safety and tolerability of ANB019 compared with placebo in subjects with PPP. This study will also characterize the PK of ANB019 and explore the immune response to ANB019 in subjects with PPP.

Approximately 50 subjects will be enrolled from approximately 35 study centers (approximately 25 for non-German sites and approximately 10 for German sites) for study treatment. The expected duration of the study is approximately 28 weeks for non-German sites and 31 weeks for German sites. The screening period will be up to 48 days prior to administration of study treatment on Day 1. On Day 1, eligible subjects will be randomly allocated in a 1:1 ratio to receive either a 200 mg subcutaneous (SC) dose of ANB019 or placebo followed by 3 doses of 100 mg of ANB019 or placebo administered SC on Days 29, 57, and 85. The subjects will leave the study center when all postdose assessments have been completed and with the Investigator's approval.

Subjects will return to the study center for study assessments and follow-up visits on Days 3 and 8; weekly from Day 8 up to Day 29; every other week up to Day 85; and then monthly for 12 weeks to monitor changes in disease activity, safety, and tolerability. In addition, the subjects will be contacted via telephone by study staff to inquire about potential AEs and changes in concomitant medications on Days 36, 50, 64, and 78. The end of study (EOS) visit will be on Day 169 for subjects enrolled in non-German sites and Day 218 for subjects enrolled in German sites. All subjects will return to the study center for the EOS assessments.

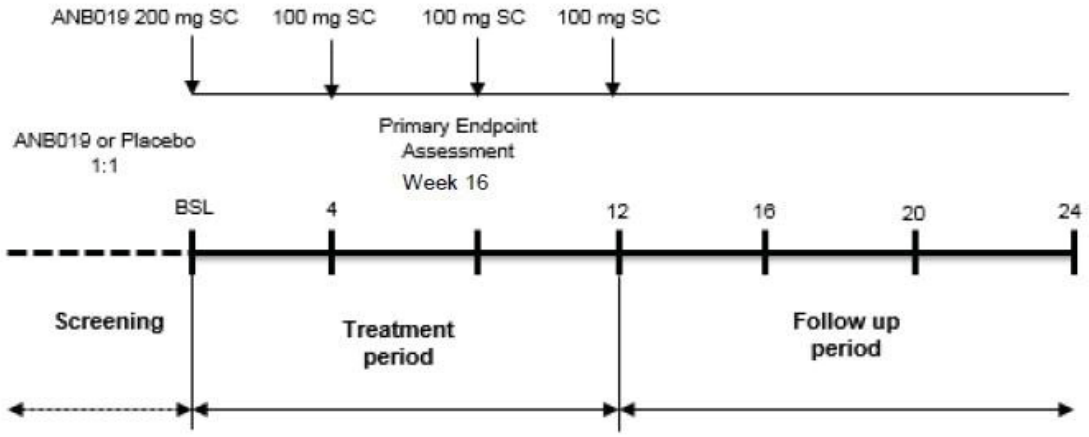
Disease activity (response to study treatment) will be evaluated for all subjects using the PPPASI, PPSI, PPPIGA, PASI (if plaque psoriasis at non-acral sites is present), and total affected BSA (if plaque psoriasis and/or pustular psoriasis is present at non-acral sites). In addition, relapse rate, time to response, and change in fresh and total number of pustule count on palms and soles will be recorded. The subject's quality of life

will be assessed using the PPPQLI, DLQI, and Patient Assessment of Palmoplantar Pustulosis Disease Activity.

Blood samples to determine PK and immunogenicity will be collected before the administration of ANB019 and at the other time points specified in the Schedule of Activities (SOA) in the Protocol. In addition, a punch biopsy (biomarker analysis) will be taken during the study (guidelines for optional punch skin biopsy will be located in Lab Manual). All subjects randomized in the study will be asked to participate in the skin biopsy; however, the subject's participation is optional.

Safety assessments including adverse event (AE)/serious adverse event (SAE) monitoring, vital signs, physical examination, ECGs, and laboratory measurements will be performed as specified in SOA.

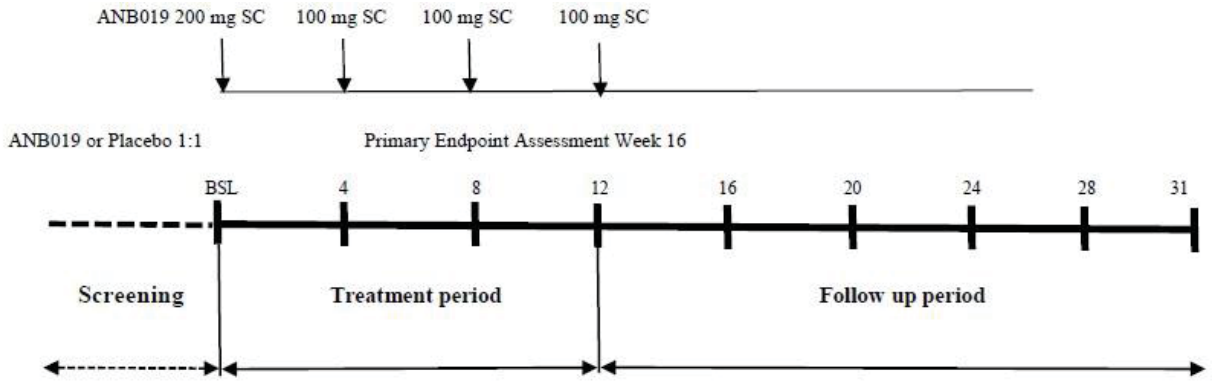
Study Schema for non-German sites



Abbreviations: BSL = baseline; SC = subcutaneous

[redacted]

Study Schema for German sites



Abbreviations: BSL = baseline; SC = subcutaneous

5.2. SAMPLE SIZE

The sample size is not based on statistical power considerations. Approximately 50 subjects will be enrolled from approximately 35 study centers (approximately 25 for non-German sites and approximately 10 for German sites) for study treatment.

5.3. SCHEDULE OF ACTIVITIES

Schedule of events can be found in Section 1.3 of the Protocol Ammendment 5 and 5.1.

5.4. TREATMENT ASSIGNMENT

This is a randomized, double-blind, placebo-controlled study with limited access to the randomization code. All subjects will be assigned a unique 'subject identification number' at the time of Screening. On Day 1, after verification that all inclusion and no exclusion criteria have been met, the subjects will be randomly allocated in a 1:1 ratio to receive ANB019 or placebo.

Randomization will be stratified based on the patient's history of plaque psoriasis, to ensure that the number of subjects enrolled with plaque psoriasis should not exceed 50%. As subjects become eligible, they will be assigned randomization numbers which will be used to assign the allocated treatment based on a randomization schedule. The Sponsor, Investigator, and subjects will be blinded to treatment assignment of ANB019 or placebo.

[redacted]

Please refer to the protocol Section 6.3 for more information.

5.5. CHANGES TO ANALYSIS FROM PROTOCOL

mITT set is included to analyze primary and some of the key secondary efficacy parameters.

6. PLANNED ANALYSES

6.1. DATA MONITORING COMMITTEE (DMC)

There will be no DMC for this study.

6.2. INTERIM ANALYSIS

An Interim Analysis (IA) will be performed when all active subjects complete their Week 16 visit. The scope of IA will be, to assess the primary and key secondary endpoints as well as key safety, PK and ADA endpoints.

6.3. FINAL ANALYSIS

All final, planned analyses identified in this SAP will be performed by [redacted] following AnaptysBio authorization of this SAP, Sponsor Authorization of the Safety, Per Protocol, Intention-to Treat, modified Intention-to Treat analysis sets, Database Lock (DBL), and Unblinding of Treatment. Final PK analyses will be performed by the [redacted] research pharmacokineticist. The PK summaries, data listings, and PK figures will be the responsibility of the PK biostatistician at [redacted].

7. ANALYSIS SETS

Agreement and authorization of subjects included/excluded from each analysis set, excluding the PK analysis set will be conducted prior to the final DBL of the study. In order to facilitate this, a Blind Data Review (BDR) process of non-PK data will be co-ordinated by the [redacted] Statistical Team Lead (STL), as described in the Blind Data Review Plan prior to the final DBL.

[redacted]

The analysis sets are defined in Table A.

Table A. 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 group to which subjects were randomized regardless of which treatment they receive.
mITT Analysis Set	The mITT analysis set will include all subjects in the ITT set with PPPASI score of at least 12 at Baseline.
Safety Analysis Set	The safety analysis set will include all randomized subjects who receive 1 dose of ANB019 or placebo. The safety analysis set will be used for all safety analyses. Subjects will be analyzed as treated.
Per Protocol Set	The Per Protocol set will include all subjects in the ITT set who do not have major protocol violations that would affect the evaluation of the primary efficacy endpoint.
PK Analysis Set	The PK analysis set will include all subjects in the safety 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; mITT = modified intent-to-treat; PK = pharmacokinetics

7.1. PER PROTOCOL ANALYSIS SET [PPAS]

The PPAS will include all subjects in the ITT who do not have major protocol deviations (PDs) that would affect the evaluation of the primary efficacy endpoint. From a statistical analysis perspective, the reason(s) for exclusion of subjects may be PD or other factors affecting the efficacy outcome or treatment of the subject. Protocol deviations identified during the clinical conduct of the study, as authorized in the final PD log, will also be taken into consideration in the final assignment of subjects to the analysis sets. All PDs will be reviewed during the Blind Data Review, as described in the Blind Data Review Plan.

The PPAS is further defined by the following criteria:

Sufficient essential efficacy data

[redacted]

Sufficient evidence of the study indication, i.e. palmoplantar pustulosis

- Eligibility in accordance with the protocol specified inclusion/exclusion criteria, including the use of only allowed concomitant medications, the use of rescue medications only a month after dosing and acceptable previous or current medical conditions

Adherence to the visit schedule

Overall compliance with the study treatment administration schedule

8. GENERAL CONSIDERATIONS

All data listings, summaries, and analyses will be performed under the guidance and approval of the Sponsor and in consistency with this SAP. Data for patients excluded from an analysis set will be included in the data listings, but not in the summaries. Coding of AEs and medical history will be done by Medical Dictionary for Regulatory Activities (MedDRA) directory Version 22 (or higher) and medications data by the World Health Organization (WHO)-drug dictionary dated Mar2019 (or higher) by [redacted]

The default summary statistics for continuous variables includes number of contributing observations (n), mean, standard deviation (SD), median, 95% confidence interval (CI) as applicable, minimum, and maximum or as described in the respective section. For categorical variables, the number, percentage, and exact 95% CI as applicable in each category will be the default summary presentation.

8.1. REFERENCE START DATE AND STUDY DAY

Study Day will be calculated from the reference start date, and will be used to show start/stop day of assessments and events. Reference start date, or reference date, is defined as the day of the first dose of study treatment (i.e. Day 1).

If the date of the event is on or after the reference date then:

Study Day = (date of event – reference date) + 1.

- If the date of the event is prior to the reference date then:

Study Day = (date of event – reference date).

In the situation where the event date is partial or missing, Study Day and any corresponding durations will appear partial or missing in the listings.

[redacted]

8.2. BASELINE

Unless otherwise specified, "Baseline" is defined as the last observed value of the parameter of interest prior to the Reference Start Date and time (including unscheduled visits). In the case where the last observed measurement and the reference start date coincide, that measurement other than Adverse Events (AEs) and concomitant medications (CMs) will be considered pre-treatment, but AEs and medications commencing on the reference start date will be considered post-treatment (therefore treatment-emergent). All assessments scheduled on the day of treatment administration, except postdose PK samples, should be performed before study treatment administration, unless otherwise noted.

8.3. RETESTS, UNSCHEDULED VISITS AND EARLY TERMINATION DATA

In general, for by-visit summaries, data recorded at the nominal visit will be presented. Unscheduled measurements will not be included in by-visit summaries, but will contribute to the Baseline or best/worst case value where required (e.g. shift table). In the case of a retest (same visit number assigned), the last available assessment will be used for by-visit summaries. Subjects terminating treatment or study early are required to attend the EOS visit at Day 169 for non-German subjects or at Day 218 for German subjects. Early termination data will be recorded at the nearest scheduled visit based on actual days from the reference date in by-visit summaries.

Listings will include scheduled, unscheduled, and early discontinuation data, with unscheduled visits sorted chronologically.

8.4. WINDOWING CONVENTIONS

Target study days are presented below:

	Study day		
Visit	Target	Lower limit	Upper limit
Screening	n/a	-48	n/a
Day 1 (Baseline)	1	n/a	n/a
Day 3	3	n/a	n/a
Day 8	8	n/a	n/a
Day 15	15	14	16

[redacted]

	Study day		
Visit	Target	Lower limit	Upper limit
Day 22	22	21	23
Day 29	29	28	30
Day 36 (telephone call)	36	34	38
Day 43	43	41	45
Day 50 (telephone call)	50	48	52
Day 57	57	55	59
Day 64 (telephone call)	64	62	66
Day 71	71	69	73
Day 78 (telephone call)	78	76	80
Day 85	85	83	87
Day 113: (follow-up)	113	111	115
Day 141 (follow-up)	141	139	143
Day 169 (follow-up)	169	167	171
Day 197 (follow-up) for German sites only	197	195	199
Day 218 (follow-up) for German sites only	218	216	220

8.5. STATISTICAL TESTS

There will be no hypothesis testing conducted in the study. Point estimates of treatment differences will be accompanied with two-sided 95% confidence intervals (CIs), where applicable. In the case of normality assumption violations, appropriate non-parametric methods, will be used for analysis. Statistical analyses of PK data are detailed under Section 19.

8.6. COMMON CALCULATIONS

For quantitative measurements, change from baseline will be calculated as:

Change from Baseline = Test Value at Visit X – Baseline Value

Percentage change from baseline will be calculated as:

[redacted]

Percent change from Baseline = [(Test Value at Visit X – Baseline Value) / Baseline Value] x 100

8.7. SOFTWARE VERSION

Non-compartmental PK parameter calculations will be performed using Phoenix® WinNonlin® 8.3 or higher (Certara, Princeton, New Jersey). All other derivations, statistical analyses, summaries, and listings will be generated using SAS® version 9.4 (SAS® Institute, Inc., Cary, North Carolina). Graphics will be prepared using the same versions of SAS®.

9. Statistical Considerations

9.1. ADJUSTMENTS FOR COVARIATES AND FACTORS TO BE INCLUDED IN ANALYSES

The following covariates and factors are used in the analyses. For details of their inclusion in the models, see the specific analysis section.

Covariates:

Baseline PPPASI score
Baseline Palmoplantar Pustulosis Quality of Life Instrument (PPPQLI)
Baseline Dermatological Life Quality Index (DLQI) and
Baseline Patient Assessment of Palmoplantar Pustulosis Disease Activity

Factors:

Treatment (ANB019/Placebo)
History of plaque psoriasis (Yes/No)

9.2. MULTICENTER STUDIES

This study will be conducted by multiple investigators at multiple centers internationally. Randomization to treatment groups is stratified by history of plaque psoriasis. Data from all sites will be pooled for analysis.

9.3. MISSING DATA

Missing safety data will not be imputed. Partial dates for safety data will be imputed as outlined in Appendix 2. Missing efficacy data will be handled as described in section 17.1.2 of this analysis plan. Missing PK data will be handled as described in Section 19.2.

9.4. MULTIPLE COMPARISONS

No formal hypothesis testing will be performed for this study, therefore no adjustment for multiple comparisons will be done. Planned statististical tests will be presented with their nominal p-value.

9.5. EXAMINATION OF SUBGROUPS

Descriptive analysis of the primary efficacy endpoint (PPPASI) will be performed for each category of history of plaque psoriasis (Yes/No) and will be performed based on ITT and mITT population.

10. OUTPUT PRESENTATIONS

Appendix 1 contains conventions for the presentation of data in outputs. The templates provided with this SAP describe the presentations for this study and therefore the format and content of the summary tables, figures, and listings to be provided by [redacted] Biostatistics. Minor modifications may be made to the tables, figures and listings to accommodate the data.

11. DISPOSITION AND WITHDRAWALS

All subjects who provide informed consent will be accounted for in this study.
Subject disposition will be listed and summarized, to include:

- Total subjects screened
- Number of screen failures (subjects who consent to participate in the clinical study but are not subsequently entered in the study), and by reason for screen failure
- Total number of subjects in the ITT
- Total number of subject in the mITT
- Total number of subjects in the SAF
- Total number of subjects in the PPAS

[redacted]

- Total number of subjects in the PK Analysis Set
  Total number of subjects who discontinue from study treatment, and by reason for discontinuation from study treatment
  Total number of subjects who discontinue from the study, and by reason for discontinuation from study treatment.

11.1. PROTOCOL DEVIATIONS

All protocol deviations observed during study conduct will be captured in the Clinical Trial Management System (CTMS). The Investigator and Sponsor will review the protocol deviation records from the CTMS and provide confirmation on the categorization of deviations.

Categorization definitions per the Protocol Deviation Plan are:

Important protocol deviations (IPD): Subset of protocol deviations that might significantly affect the completeness, accuracy, and/or reliability of the study data or that might significantly affect a subject's rights, safety, or wellbeing.

Non-important protocol deviations (N-IPD): Other deviation from the approved study protocol that have minimal impact on subject's rights, safety, or well-being, or integrity of data.

PDs will be grouped into standardized terms , e.g. "Informed Consent", "Eligibility", "Investigational Product" or equivalent terms in the PD log as per the Protocol Deviation Management Plan (PDMP) and will be used for reporting purpose in Statistical tables and listings.

PDs may include Covid-19 related deviations, if any, including but not limited to inability to travel to study site, travel restrictions interfering with administration of investigational product, illness interfering with administration of investigational product, and others. Covid-19 related PDs may be identified from the protocol deviation description if they are not classified seperately in the CTMS.

Protocol Deviations identified during the clinical conduct of the study, as authorized in the final PD log, will be summarized and presented in a listing that includes the type of deviation and whether it is Important or Non-Important based on PDMP.

12. DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Demographic data and other baseline characteristics will be listed and summarized by treatment group, overall and by history of psoriasis for the SAF analysis set. No statistical testing will be carried out for demographic or other baseline characteristics. The following demographic and other baseline characteristics will be reported for this study: age at IC (years), gender, race, ethnicity, weight (kg), height (cm), Body Mass Index (BMI) (kg/m^2), baseline PPPASI score, baseline PPSI score, baseline PPPIGA score, baseline PPPASI score of atleast 12, baseline total and fresh pustule count. Smoking history and current smoking status will also be summarized and listed. History of psoriasis will be included in the listing.

12.1. DERIVATIONS

BMI (kg/ m^2) = weight (kg)/ [height (m)]^2.
For current smokers:
If full Smoking start date and end date is available, then:
Smoking period duration (years) until informed consent = (Date of informed consent – Smoking start date + 1) / 365.25
If only month and year of Smoking start date and/or end date is available, then:
Smoking period duration (years) until informed consent = (Year/Month of informed consent – Year/Month of Smoking start date+1) / 12
If only year of Smoking start date and/or end date is available, then:
Smoking period duration (years) until informed consent = (Year of informed consent – Year of Smoking start date+1)

Baseline characteristics will include Baseline values of efficacy and safety variables.

13. MEDICAL HISTORY

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

14. MEDICATIONS

Medications will be presented for the SAF and coded using the latest version of the World Health Organization (WHO) Drug Dictionary and Anatomical Therapeutic Chemical (ATC) system. Prior, concomitant and rescue medications will be listed and summarized by treatment group, ATC level 2 categories and preferred name.

Prior and Concomitant medications will be identified as follows:

'Prior' medications are medications which started and stopped prior to the first dose of study medication.

'Concomitant' medications are medications which started prior to, on or after the first dose of study medication, but before the last dose of study medication, AND ended on or after the date of first dose of study medication or were ongoing at the end of the study.

See Appendix 2 for handling of partial dates for medications. In the case where it is not possible to define a medication as prior or concomitant, the medication will be classified as the worst case i.e. concomitant.

15. STUDY TREATMENT EXPOSURE

The prescribed dosage may not be changed. Study treatment can be interrupted temporarily or permanently per the Investigator's discretion. Exposure to study treatment will be listed and summarized for the SAF, and will be based on the number of dose administrations received by subjects.

Duration of treatment exposure (days) = (Date of last study medication administration – Date of first study medication administration) +1

Information on IP overdose will be presented in a listing.

16. STUDY MEDICATION COMPLIANCE

Compliance to study medication is defined as the administration of the study medications conforming to 100% of the dose specified in the protocol. Noncompliance is defined as taking less than 80% or more than 120% of IP during any evaluation period (during treatment period).

Compliance to study medication will be presented for safety population.

Overall Compliance to study medication will be summarized with respect to treatment groups. The formula used for calculation of Overall Compliance will be as follows :

Overall Compliance (%)= (Total number of doses received / total number of planed doses) * 100.

[redacted]

List of treatment noncompliance will be provided for safety population.

17. EFFICACY OUTCOMES

17.1. PRIMARY EFFICACY

17.1.1. PRIMARY EFFICACY ENDPOINT & DERIVATION

The primary efficacy endpoint is the change from Baseline in PPPASI at all study visits.

The PPPASI score is determined by assessing the glaborous skin of palms and soles, and adding scores for the characteristics of PPP viz. erythema (E), pustules (P) and desquamation (D). This total (E+P+D) is adjusted for the percentage area of palm and soles affected to obtain the total PPPASI score.

Total PPPASI Score = [(E+P+D) x Area x 0.2] (right palm) + [(E+P+D) x Area x 0.2] (left palm) + [(E+P+D) x Area x 0.3] (right sole) + [(E+P+D) x Area x 0.3] (left sole).

E, P and D scores: 0 = None, 1 = Slight, 2 = Moderate, 3 = Severe, 4 = Very severe.
Area affected (%): 0 = 0, 1 = >0 to <10, 2 = 10 to <30, 3 = 30 to <50, 4 = 50 to <70, 5 = 70 to <90, 6 = 90-100.

A lower PPPASI score indicates an improvement in a subject's condition.

17.1.2. MISSING DATA METHODS FOR PRIMARY EFFICACY ENDPOINT

Analysis of the primary endpoint will apply a general linear mixed model for repeated measures (MMRM) that uses all available data and assumes missing data due to dropouts to be missing at random. The Kenward Roger method will be used to calculate the denominator degrees of freedom and adjust standard errors for the test of fixed effects.

17.1.3. ANALYSIS OF PRIMARY EFFICACY ENDPOINT

This is an exploratory study and no hypothesis testing will be performed. The primary efficacy analysis

will be performed on the ITT and mITT at all study visits.
The change from Baseline in PPPASI at Week 4, 8, 12 and 16 will be analysed using a general linear MMRM. The model will include fixed effects for treatment, history of plaque psoriasis (Yes/No), visit, treatment by visit interaction, and baseline PPPASI score as covariate. Least-squares means (LSM) and associated standard errors for the change from baseline in PPPASI will be presented for each treatment group and the least-squares mean difference will be presented with the two-sided 95% confidence interval to assess the difference between the active and placebo group. In addition, descriptive statistics (n, mean, SD, median, minimum, and maximum) will be presented for PPPASI score and its change from baseline at all applicable visits.

SAS code to be used for this analysis can be found in Appendix 4.

17.1.4. Sensitivity Analysis of Primary Efficacy Endpoint(s)

For the primary efficacy analysis, an MMRM model will be fit. The robustness of that approach will be explored by duplicating the primary analysis using the PP set.

17.2. Secondary Efficacy

The secondary efficacy analyses will be performed on the analyzable ITT. PPPASI will also be analyzed using mITT.

17.2.1. Secondary Efficacy Endpoints, Derivations, and Analysis

17.2.1.1. Proportion of subjects achieving PPPASI50 and PPPASI75 at all study centers visits.

PPPASI50 is achieved when a subject experiences at least 50% reduction in PPPASI score from baseline. If a subject's percentage change from baseline in PPPASI score is less than or equal to -50, the subject will be counted as a responder and included in the count of subjects achieving PPPASI50. PPPASI75 is achieved when a subject achieves at least 75% reduction in PPPASI score from baseline PPPASI score. If a subject's percentage change in PPPASI score is less than or equal to -75, the subject will have achieved PPPASI75. This outcome will be measured for applicable every visit.
Missing PPPASI50 and PPPASI75 will occur due to missing data in actual PPPASI score and missing

[redacted]

PPPASI score will be handled by multiple imputation while deriving the PPPASI50 and PPPASI75 responses and will be used to analyze the efficacy data using logistic regression. The details of the imputation is provided in section 17.2.2.
Frequency and percentages of response for PPPASI50 and PPPASI75 will be presented by visit and treatment group.
The bar plots for proportion of subjects achieving PPPASI50 and PPPASI75 will be presented by visit and treatment group.
The binary response for each endpoint will be analyzed using a logistic regression model using a logit link. The model includes treatment as fixed effect, and history of plaque psoriasis (Yes/No) and Baseline PPPASI score as covariate. The results will be presented in terms of odds ratio together with its associated 2-sided 95% CIs for each visit.

17.2.1.2. Change in PPPASI Score at all study center visits

Summary statistics will be provided for absolute PPPASI scores and change and percentage change from Baseline by visit and treatment group.
The Mean ± Standard Deviation (SD) plot for change from baseline PPPASI will be presented by visit and treatment using ITT.

17.2.1.3. Change in PPSI Score at all study center visits

The PPSI score assesses the severity of PPP lesions and response to therapy, with scores ranging from 0 to 12. Erythema (E), Pustules (P) and Desquamation (D) will be assessed separately at the evaluation site (palms or soles) and scored as follows:
PPSI Score = E + P + D
where 0 = none, 1 = minimal, 2 = mild, 3 = moderate, 4 = severe
Change and percent change from Baseline in PPSI score will be determined for every visit. Change and percent change from Baseline is defined in Section 8.6.
Summary statistics will be provided for absolute PPSI scores as well as for change and percent change from Baseline by visit and treatment group.

17.2.1.4. Change in PPPIGA score at all study center visits

PPPIGA score ranges from from 0 (clear) to 4 (severe) and is assessed by the investigator at each visit. A detailed description of the PPPIGA score can be found in Appendix 9 of the protocol.

Frequency and percentage of each category will be summarized by visit and treatment group.
A shift table of change in PPPIGA scores from Baseline to Week 16 visit will be displayed by each PPPIGA category for both treatment groups.

17.2.1.5. Proportion of subjects with clear or almost clear assessment score on PPPIGA at all study center visits

The proportion of subjects with clear or almost clear assessment score on PPPIGA will be calculated for each visit as follows:
Proportion of subjects with clear or almost clear assessment score =
Number of subjects scoring 0 or 1 on the PPPIGA scale
Total number of subjects in treatment group
Subjects with missing data will be considered as not achieving 0 or 1 on the PPPIGA scale.
Frequency and percentages will be presented by visit and treatment group.
The binary response at Week 16 will be analyzed with a logistic regression model using a logit link. The model includes treatment as fixed effect, and history of psoriasis (Yes/No) and Baseline PPPIGA score as covariate. The results will be presented as odds ratio and 2-sided 95% CI.
The bar plot for proportion of subjects with clear or almost clear PPPIGA assessment will be presented by visit and treatment group.

17.2.1.6. Change in fresh and total pustule count on palms and soles at all study center visits

Change and percent change from Baseline in number of fresh and total pustule count on palms and soles will be determined for every applicable visit. Change and percent change from Baseline is defined in Section 8.6. Number and percentage of pustules will be reported by location, visit, and treatment for the following size categories: '<1 mm', '1-3 mm', '>3 to 10 mm', and 'confluent lakes of pus'.
Summary statistics for the fresh and total pustule count, as well as change from Baseline, will be provided by visit and treatment group. Frequency and percentages of the size of the majority of pustules will be presented for both the treatment groups for each visit.
The Mean ± Standard Deviation (SD) plots for change from baseline fresh and total pustule count for palms and soles will be presented by visit and treatment.

17.2.1.7. Time to response

Time to response is defined as the time in days to achieve 75% reduction in fresh pustule count from Baseline pustule count. If 75% reduction is not achieved, time to response will be censored at the time the subject discontinued the study, or 169 days (218 days for subjects in German sites) if the subject completed the study.
Time to response will be analyzed as a time-to-event endpoint. Response is defined as the achievement of 75% reduction in fresh pustule count from baseline pustule count. Subjects withdrawing from the study, lost to follow up or subjects without response at EOS will be censored. The Kaplan-Meier survival curves and 25th, 50th (median), and 75th percentiles will be provided by treatment group along with the 2-sided 95% CIs. Estimated survival distribution function along with the number of subjects at risk will be presented for each time point.

17.2.1.8. Relapse rate

Relapse rate is defined as a return to Baseline status in fresh pustule count, and is calculated as follows:
Relapse Rate =

$$\frac{\text{Number of Subjects with return to Baseline status in fresh pustule count}}{\text{Total Number of Subjects in Treatment Group with data available}} \text{ x } 100$$

Frequency and percentages will be summarized by visit and treatment group for subjects experiencing relapse.

17.2.1.9. Change in PASI score and affected BSA at all study center visits, if plaque psoriasis is present at non acral sites

Change and percentage change from Baseline in PASI score and affected BSA will be determined for all study visits for subjects with plaque psoriasis at non-acral sites. Change and percentage change from Baseline is defined in Section 8.6.

Summary statistics will be provided for absolute PASI scores of subjects with plaque psoriasis present at non-acral sites, as well as for percent change from Baseline in PASI score, by visit and treatment group (where reduction is improvement).

[redacted]

Summary statistics will also be provided for absolute affected BSA and percent reduction from Baseline in affected BSA by visit and treatment group.

The Mean ± Standard Deviation (SD) plot for change from baseline total PASI score will be presented by visit and treatment.

17.2.1.10. Improvement in Pustular Psoriasis at non acral site BSA (if present) at all study center visits

Improvement in Pustular Psoriasis at a non-acral site is defined as a reduction in the affected BSA. Percentage change from Baseline in affected BSA will be calculated by visit and treatment group for subjects with plaque psoriasis at non-acral sites. Percentage change from Baseline is defined in Section 8.6.

Summary statistics will be provided for percent change from Baseline in affected BSA at non acral site by visit and treatment group in subjects with pustular psoriasis (reduction is improvement).

17.2.1.11. Change in clinical scores of PPPQLI, DLQI and Patient Assessment of Palmoplantar Pustulosis Disease Activity at all study center visits.

Quality of Life (QoL) will be assessed using the Palmoplantar Pustulosis Quality of Life Instrument (PPPQLI), Dermatology Life Quality Index (DLQI) and Patient Assessment of Palmoplantar Pustulosis Disease Activity at all study center visits. See further details in Section 18.

Summary statistics, change and percent change from Baseline will be provided for absolute scores of PPPQLI, DLQI and Patient Assessment of Palmoplantar Pustulosis Disease Activity, by visit and treatment group. Additionally, DLQI will be summarized with counts and percentages for further different interpretable ranges: “0-1”, ”2-5”, ”6-10”, ”11-20”, ”21-30”.

By-subject listing will be presented for each questionnaire, by visit.

See Section 18 for a description of Quality of Life (QOL) Analyses.

17.2.1.12. Immunogenicity to ANB019-003 anti-drug antibodies

The Safety Analysis set will be used for immungenicity analysis.

[redacted]

A subject will be considered to be positive for ANB019-induced immunogenicity if the subject has one confirmed positive (in the confirmatory assay) immunogenicity response after dosing.

The frequency and percentage of positive immunogenicity response will be summarized by cohort and visit. Titer values will be summarized by cohort using appropriate descriptive statistics.

Observed values for ADA levels/status will be listed by-subject with descriptive statistics based on the safety analysis set. The ADA data will be summarized by visit as proportions with 95% CIs from a 2-sided exact test for the comparison of treatment groups, using the Clopper-Pearson method. If data permits, correlation will be analyzed between ADA levels and safety and efficacy endpoints.

17.2.1.13. PK parameters

Computation of PK parameters is described in Section 19.1

17.2.2. Missing Data Methods for Secondary Efficacy Endpoint(s)

Missing responses for categorical secondary response variables (PPPASI75 and PPPASI50) will be imputed using multiple imputation for the analysis of logistic regression. The method will first use non-responder imputation for missing values of PPPASI scores and then the imputed values along with the other available values will be used to derive the categorical responses variables PPPASI50 and PPPASI75 for applicable visits. Detailed multiple imputation steps are provided in the Appendix 3.

17.3. Exploratory Efficacy

17.3.1. Skin biopsy markers

Skin biopsy biomarker (including but not limited to IL-36, IL-17, IL-23, and markers of neutrophils and dendritic cells infiltration) analysis will be performed by a third party designated by the Sponsor. A listing of biomarker blood sample collection date and times will be provided. Biomarker data and change in serum cytokine concentrations from Baseline will be summarized.

17.3.2. Photographic documentation of lesions

No analyses or summaries will be provided for photographic documentations of lesions.

18. QUALITY OF LIFE (QOL) ANALYSIS

All QOL analyses will be performed on the ITT.

18.1.1. QOL VARIABLES & DERIVATIONS

18.1.1.1. Palmoplantar Pustulosis Quality of Life Instrument (PPPQLI)

The PPPQLI evaluates the impact of PPP on a subject's daily activities and ability to work by means of a 29 item questionnaire. Subjects rate their ability to perform daily activities with a response of No Difficulty, Mild Difficulty, Moderate Difficulty, Severe Difficulty or Totally Unable. The severity of PPP as experienced by the subject is assessed by means of a None, Mild, Moderate, Severe or Extreme response. The social impact of the disease, as well as the limitation of activity is also assessed.
Each of the responses is scored between 1 to 5, with a score of 5 representing the most severe level of limitation or pain. The total score for each subject will range from 29 to a maximum of 145, with a higher value indicating greater disease impact and poorer quality of life.

18.1.1.2. Dermatology Life Quality Index (DLQI)

The DLQI questionnaire will be used to assess treatment response on the subject's quality of life. The DLQI aims to measure how much a subject's skin problem affected their life in the preceding week. Subjects respond to 10 questions concerning daily activities with either Very much, A lot, A little, Not at all, Not relevant. Each question is scored as follows: (Finlay AY, 1994)

Response	Score
Very much	3
A lot	2
A little	1
Not at all / Not relevant	0
Question unanswered	0
Question 7: Yes (i.e. "prevented work or studying")	3

[redacted]

Response	Score
Question 7: No, but skin has been a problem at work or studying **a lot**	2
Question 7: No, but skin has been a problem at work or studying **a little**	1
Question 7: No, and skin has **not** been a problem at work or studying	0
Question 7: Not relevant	0

The score for each question is summed, resulting in a total DLQI score with a maximum of 30 and a minimum of 0. The higher the score, the more quality of life is impaired. The total DLQI score can be interpreted as follows:

0 -1	no effect at all on patient's life
2-5	small effect on patient's life
6-10	moderate effect on patient's life
11-20	very large effect on patient's life
21-30	extremely large effect on patient's life

Additional scoring notes:

- If one question is left unanswered this is scored 0 and the scores are summed and expressed out of a maximum of 30. If 2 or more questions are left unanswered the questionnaire is not scored.

18.1.1.3. Patient Assessment of Palmoplantar Pustulosis Disease Activity

The Patient Assessment of Palmoplantar Pustulosis Disease Activity will be an assessment of disease activity by subjects. All subjects will be asked to rate how active their disease condition on a 0 to100 mm standardized visual analog scale (VAS). Symptoms will be assessed utilizing the mean VAS score.

[redacted]

18.1.2. MISSING DATA METHODS

Refer Section 18.1.1.2 under "Additional scoring notes" for missing data handling for the DLQI. For the other QOL variables, there will be no imputation of missing data.

18.1.3. ANALYSIS OF QOL VARIABLES

Summary statistics will be provided for absolute PPPQLI, DLQI and Patient Assessment of Palmoplantar Pustulosis Disease Activity scores as well as for change from Baseline (see Section 8.6) by visit and treatment.

19. PHARMACOKINETICS

Derivation of serum PK parameters following ANB019 treatment will be the responsibility of the clinical pharmacokineticist at [redacted]. The PK summaries, summary figures, and data listings as well as the statistical analysis of the PK variables will be the responsibility of the study biostatistician at [redacted].

Some minor modifications may be necessary to the planned design of tables, figures, and listings to accommodate data collected during the actual study conduct.

19.1. VARIABLES & DERIVATIONS

19.1.1. SERUM CONCENTRATION DATA

The actual dates/time of PK sample collections and PK concentration of ANB019 will be listed. Concentration data of ANB019 will be summarized ($n \geq 3$) by day and nominal time point using N (sample size), n (available data), arithmetic mean, SD, coefficient of variation (CV), minimum, median, maximum, geometric mean, and geometric CV% using the PK analysis set. Concentrations that are below the limit of quantitation (BLQ) will be treated as zero for the computation of descriptive statistics. BLQ values set to zero for summary statistics, will be excluded from calculation of geometric mean.

Individual by-subject concentration-time data will be plotted by actual sampling times on linear and semi-logarithmic scales.

Graphs for ANB019 mean (±SD) concentration-time data following SC administration on Day 1 and Day 85 will be presented in linear and semi-logarithmic scale. Individual and mean trough concentrations for samples collected on Days 29, 57, 85 and 113 (4 weeks after last dose of 100 mg SC) will be graphically presented to visually assess time to attainment of steady state.

For ANB019 and where data are available, a statistical evaluation of the steady state will also be made using the trough (predose) plasma concentrations collected on Days 29, 57, 85, and 113 (4 weeks after last dose of 100 mg SC). All valid concentrations on the natural-log scale will be analyzed using mixed-effect analysis of variance (ANOVA) model with treatment day as a fixed repeated effect. From this model, orthogonal contrasts with 90% CI will be formed between the adjusted mean concentration at each study day and the mean concentrations for all the following study days using Helmert contrasts. Precisely, Day 29 will be compared to Days 57 through 113, Day 57 will be compared to Days 85 through 113 and so on. Prior to estimating the fixed effects and the contrasts, an appropriate treatment-specific covariance structure will be selected using corrected Akaike's information criterion (AICC).

Other presentations of data may be added at the discretion of the PK scientist, as appropriate. By-subject plots will be presented in linear and semi-logarithmic scale.

19.1.2. PHARMACOKINETIC PARAMETERS

Pharmacokinetic parameters will be calculated from the concentration-time data using noncompartmental techniques (Phoenix™ WinNonlin®, 8.3 or higher or later; Certara L.P., Princeton, New Jersey, USA). The actual (rather than nominal) sampling times will be used in the PK parameter calculations. If the collection time of a sample is not recorded, then the nominal time will be used to determine PK parameters.

The PK analysis set will be used for PK parameter analysis. The following PK parameters will be reported if data permits:

C_{max}	Maximum observed concentration, obtained directly from the observed concentration versus time data.
t_{max}	Time of maximum observed concentration, obtained directly from the observed concentration versus time data.
$AUC_{(0\text{-last})}$	Area under the concentration-time curve (AUC) from time zero (predose) to time of last quantifiable concentration, calculated by linear up/log down trapezoidal summation.
$AUC_{(0\text{-}672)}$	Area under the curve determined over the 28 day SC dosing interval following 1st SC dose [Note: this parameter will not be calculated if Day 29 predose data is missing. $AUC_{(0\text{-last})}$

[redacted]

	will be equal to $AUC_{(0-672)}$ if Day 29 data is available]
$AUC_{overall}$	Area under the curve across the 3 SC doses (Day 1 to Day 169) [Note: this parameter will not be calculated if Day 169 data is missing]
λz	terminal elimination phase rate constant
Cl/F	Apparent Clearance following SC dose
Vd/F	Apparent Volume of distribution following SC dose
$t_{1/2}$	Terminal half-life associated with λz
Note: The data from Day 1 to predose Day 29 will be used to calculate the above parameters except where noted.	

Additionally:

AUCs will be derived using the linear up/log down trapezoidal rule. Half life may also be estimated if appropriate and if sufficient data are available, following the last SC administration on Day 85 by utilizing ANB019 concentrations collected on Days 113, 141 and 169 (EOS). Only data points that describe the terminal elimination log-linear decline will be used in the regression equation for calculation of terminal elimination phase rate constant; C_{max} and any data point in the distribution phase are not included in the calculation. A general rule of adjusted $R^2 > 0.80$ will be considered as acceptable for calculation of the terminal elimination phase rate constant. If the adjusted R^2 falls below 0.80 and then the terminal elimination phase rate constant (λz), C_{max}, T_{max} $AUC_{(0-last)}$, $AUC_{(0-672)}$, $AUC_{overall}$ Vd/F, CL/F and $t_{1/2}$ will be reported as not determined (ND) from and that subject.

The extent of accumulation following monthly 100 mg SC administrations relative to the trough obtained after a single 200 mg SC injection dose will be calculated:

$RC_{min,D57}$: Predose Day 57/Predose Day 29
$RC_{min,D85}$: Predose Day 85/Predose Day 29

Subjects with partial data will be evaluated on a case-by-case basis to determine if sufficient data are available for reliable estimation of PK parameters.

For PK parameter calculations following Day 1 SC dose, the following conventions will be followed:

Concentrations that are BLQ or missing at predose or the beginning of the curve will be set to zero.
Any other BLQ concentrations will be assigned a value of zero if they precede quantifiable samples in the initial portion of the profile.

A BLQ value that occurs between quantifiable data points, especially prior to C_{max}, will be evaluated to determine if an assigned concentration of zero makes sense, or if exclusion of the data is warranted.

Following C_{max}, BLQ values embedded between two quantifiable data points will be treated as missing when calculating PK parameters.

- If a BLQ value occurs at the end of the collection interval (after the last quantifiable concentration), it will be set to zero.

  If consecutive BLQ concentrations are followed by quantifiable concentrations in the terminal portion of the concentration curve, these quantified values will be excluded from the PK analysis by setting them to missing, unless otherwise warranted by the concentration-time profile.

19.2. Missing Data Methods

Missing PK data will not be imputed.

19.3. Deviations Related to PK

Changes to the procedures or events which may impact the quality of the PK data, will be considered significant protocol deviations with respect to PK and will be described within the clinical study report body text.

These changes or events include any circumstances that could alter the evaluation of the PK. Examples include, but may not be limited to, sample processing errors that lead to inaccurate bioanalytical results, and/or inaccurate or missed dosing on or before the day of PK sampling.

In the case of a significant protocol deviation or event, PK data collected during the affected time period will be excluded from the study summaries.

Other changes to the procedures or events which do not impact the quality of the PK data will not be considered significant with respect to PK. Protocol deviations affecting PK will be determined post DBL and unblinding.

19.4. Analysis of PK Parameters

All PK parameters will be summarized for the PK analysis set using descriptive statistics, including N, n,

arithmetic mean, SD, CV%, median, minimum, maximum, geometric mean and geometric CV%, with the exception of t_{max}, which will be reported with n, minimum, median and maximum, only. Summary statistics will be determined ($n \geq 3$) from available data with no imputation of missing values.

A subject listing of individual PK parameters for ANB019 will be provided.

In addition to the graphical assessment of ANB019 and where data are available, a statistical evaluation of the steady state will also be made using the trough (predose) plasma concentrations collected on Days 29, 57, 85, and 113 (4 weeks after last dose of 100 mg SC; See Section 19.1.1).

19.5. PRECISION OF PK VARIABLES

All PK concentrations will be reported and analyzed with the same precision as the source data provided by the bioanalytical laboratory regardless of how many significant figures or decimals the data carry.

Derived PK parameters will be rounded for reporting purposes in by-subject listings.

The unrounded derived PK data will be considered the source data for the calculation of descriptive statistics.

For most derived PK parameters, three significant digits will be used as the standard rounding procedure for listings, with the following exceptions:

Parameters directly derived from source data (e.g., C_{max}) will be reported and analyzed with the same precision as the source data.

Parameters derived from actual elapsed sample collection times (e.g., t_{max}) will be reported to 2 decimal places with units of hours.

For the reporting of descriptive statistics for concentration and PK parameter variables:

The mean, SD, and geometric mean will be presented to one digit more precision than the source data.

The minimum, median, and maximum will be presented to the same precision as the source data.

CV% and geometric CV% will always be reported to one decimal place.

20. SAFETY OUTCOMES

All outputs for safety outcomes (AEs, SAEs, vital signs, ECGs, ADA, neutralizing antibodies, and clinical laboratory assessments at each specific time points) will be listed and summarized descriptively using the SAF. There will be no statistical comparisons between the treatment groups for safety data, unless otherwise specified within the relevant section.

Individual listings of SAEs and AEs will be summarized using the current MedDRA. Summaries and listings of data for vital signs, haematology, clinical chemistry and urinalysis laboratory tests, and ECGs will be presented. Appropriate descriptive statistics will be summarized for the observed value at each scheduled assessment and for the corresponding change from Baseline.

20.1. ADVERSE EVENTS

Adverse Events (AEs) will be coded using the most recent version of Medical Dictionary for Regulatory Activities (MedDRA) central coding dictionary.
Treatment emergent adverse events (TEAEs) are 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.

Only TEAEs will be summarized and number of subjects 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/PT. Percentages will be determined relative to all safety subjects exposed to ANB019 or placebo.
Adverse events with missing start dates will be considered treatment-emergent. AEs with missing stop dates or with stop dates after the end of the study date will be considered to have been ongoing at the end of the study.
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 group.
See Appendix 2 for handling of partial dates for AEs. In the case where it is not possible to define an AE as treatment emergent or not, the AE will be classified by the worst case; i.e. treatment emergent.
An overall summary (frequencies and percentages) of number of subjects within each of the sub-categories described below will be presented by treatment, SOC and PT, as specified in the templates.

[redacted]

Summaries over SOC and PT of TEAEs, TEAEs leading to death, SAEs, potentially significant TEAEs and clinically important TEAEs, AESIs, 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.

Listings will include TEAEs and Non-TEAEs, with TEAEs flagged. All AE data will be listed for each subject.

20.1.1. ALL TEAEs

Incidence of TEAEs will be summarized by SOC and PT and also broken down further by maximum severity and relationship to study treatment.

20.1.1.1. Severity

Severity is classed as mild, moderate or severe (increasing severity). TEAEs starting after the first dose of study treatment with a missing severity will be reported as the worst case (severe). If a subject reports a TEAE more than once within that SOC/ PT, the AE with the worst case severity will be used in the corresponding severity summaries.

20.1.1.2. Relationship to Study Medication

Relationship, as indicated by the Investigator, is classed as unrelated, possibly related or related (increasing severity of relationship). A ”related” TEAE is defined as a TEAE with a relationship to study treatment as “possibly related” or “related” to study treatment. TEAEs with a missing relationship to study treatment will be reported as “related”. If a subject reports the same AE more than once within that SOC/ PT, the AE with the worst case relationship to study treatment will be used in the corresponding relationship summaries.

20.1.2. TEAEs LEADING TO DISCONTINUATION OF TREATMENT

TEAEs leading to permanent discontinuation of study treatment will be identified by the “Drug permanently discontinued” option in the “Action taken with the study treatment” question on the AE eCRF page. A summary by SOC and PT will be prepared, as well as a subject listing.

20.1.3. TEAEs Leading to Withdrawal of Subjects

TEAEs leading to the withdrawal of subjects from the study will be identified by using the response to the question "Did the AE cause the subject to discontinue from the study?" on the AE eCRF page. A summary by SOC and PT will be prepared, as well as a subject listing.

20.1.4. Serious Adverse Events

Serious adverse events (SAEs) are those events recorded as "Serious" on the AE page of the eCRF. A summary of serious TEAEs by SOC and PT will be prepared, as well as a subject listing.

20.1.5. Adverse Events Leading to Death

TEAEs leading to Death are those events which are recorded as "Fatal" in the "Final Outcome" question on the Adverse Events page of the eCRF. A summary of TEAEs leading to death by SOC and PT will be prepared.

20.1.6. Adverse Events Related to Injection Site Reactions

Injection site reactions will be identified by the AE eCRF, using the question "Is this an injection site reaction?" A summary by SOC and PT will be prepared, as well as a subject listing.

20.1.7. Adverse Events Of Special Interest

Adverse events of special interest (AESI) will be identified by the AE eCRF, using the question "Is this Adverse Event of Special Interest (AESI)?". A summary of TEAEs of special interest by SOC and PT will be prepared, as well as a subject listing.

20.1.8. Disease Related Adverse Events

Disease related TEAEs will be identified by the AE eCRF, using the question "Is this a disease related event?", and will be listed and summarized.

20.2. LABORATORY EVALUATIONS

Results from the central laboratory will be included in the reporting of this study for Hematology, Biochemistry and Urinalysis. A list of laboratory assessments to be included in the outputs is included in Appendix 3 of the protocol.

Local laboratory tests will be allowed in the event that the central laboratory results will not be available immediately, and decisions regarding safety concerns need to be made. A central laboratory analysis will also be performed at the same time as the local laboratory test. Only the central laboratory test results will be summarized and reported.

Presentations will use Système International (SI) units.

Quantitative laboratory measurements reported as "< X", i.e. below the lower limit of quantification (BLQ), or "> X", i.e. above the upper limit of quantification (ULQ), will be converted to X for the purpose of quantitative summaries, but will be presented as recorded, i.e. as "< X" or "> X" in the listings.

The following summaries and listings will be provided for laboratory data:

Actual and change from baseline by visit (for quantitative measurements)

Frequency and percentages by visit (for categorical measurements)

A listing of all laboratory results, including follicle stimulating hormone (FSH) and pregnancy tests results, TB evaluations and serology and virology results.

Abnormal hematology and biochemistry values, according to normal range criteria, will be flagged in the listing.

20.2.1. LABORATORY REFERENCE RANGES

Quantitative laboratory measurements will be compared with the relevant laboratory reference ranges in SI units and categorized as:

Low: Below the lower limit of the laboratory reference range.

Normal: Within the laboratory reference range (upper and lower limit included).

High: Above the upper limit of the laboratory reference range.

Summaries and shift tables from baseline to EOS will be reported.

20.3. ECG EVALUATIONS

Results from the central electrocardiogram (ECG) Reading Centre will be included in the reporting of this

study.

The following ECG parameters will be reported for this study:

PR Interval (msec)

QRS Interval (msec)

QT Interval (msec)

QTcF Interval (msec) [derived]

HR (bpm)

- Overall assessment of ECG (Investigator's judgment) as:

Normal

- Abnormal, Not Clinically Significant (ANCS)
- Abnormal, Clinically Significant (ACS)

The following summaries will be provided for ECG data:

Actual and change from baseline by visit (for quantitative measurements)

Shift from baseline by visit and treatment group (for qualitative measurements)

Listing of clinically significant abnormalities

Electrocardiogram data will be listed using the actual and change from baseline values for the above parameters and will be summarized using descriptive statistics (n, mean, SD, median, and range) by treatment groups and all available visits.

The overall assessment of ECG data results (normal/abnormal) will be summarized using frequency and percentages.

Absolute values for QT and QTcF interval will be classified as:

≥450 msec

≥480 msec

≥500 msec

Since there are different ranges for QTcF between the males and females, we will summarize the QTcF by gender as defined below:

Absolute values of the QT interval as: Males: 431- 450 msec; Female: 451- 470 msec.

Abnormal values of the QT interval as: Males: > 450 msec Females: > 470 msec

Change from Baseline for QT and QTcF interval will be classified as:

>30 msec increase from Baseline

>60 msec increase from Baseline

A listing of ECG parameters and of the overall assessment will be provided.

20.4. VITAL SIGNS

The following Vital Signs measurements will be reported for this study:

Supine Systolic Blood Pressure (mmHg)
Supine Diastolic Blood Pressure (mmHg)
Supine Pulse Rate (bpm)
Respiratory Rate (breaths/min)
Body Temperature (^{0}C)
Weight (kg)
BMI (kg/m^2)

The following outputs will be provided for vital signs data:

Summary of actual and change from baseline by visit
A listing of vital signs observations will also be provided for each subject by visit.

20.4.1. VITAL SIGNS SPECIFIC DERIVATIONS

Body temperature will be presented in ^{0}C. All values in ^{0}F will be converted as follows:
°C = (°F – 32) / 1.8

20.5. PHYSICAL EXAMINATION

The following assessments will be taken at every physical examination: general appearance, skin, head/neck, pulmonary, cardiovascular, gastrointestinal, external genitourinary, lymphatic, and musculoskeletal system, extremities, eyes, nose, throat and neurologic status.
Results will be captured and summarized by the following categories:

Normal
Abnormal, not clinically significant (NCS)
Abnormal, clinically significant (CS)

Only abnormal findings will be presented in the listing.

21. DATA NOT SUMMARIZED OR PRESENTED

The other variables and/or domains not summarized or presented are:

[redacted]

Chest X-ray results

These domains and/or variables will not be summarized or presented, but will be available in the clinical study database, SDTM and/or ADaM datasets.

22. REFERENCES

Protocol: MYA11999-ANB019-003_Original Protocol_FINAL_27 Jul 2018-0001.pdf

Protocol: ANB019-003_AMD5_Final_29Oct2020_clean.pdf
Protocol: ANB019-003_AMD5.1_Final_29Oct2020_clean.pdf

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Finlay AY, Khan GK (1994). Cardiff University, Department of Dermatology. *Quality of Life Questionnaires – DLQI Instructions for use and scoring.* Retrieved November 8, 2018, from http://sites.cardiff.ac.uk/dermatology/quality-of-life/dermatology-quality-of-life-index-dlqi/dlqi-instructions-for-use-and-scoring/

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