TITLE PAGE

Protocol Title:	**A Phase 2, Randomized, Placebo-controlled, Double-blind, Multiple Dose Study to Evaluate the Efficacy and Safety of ANB019 in Subjects with Palmoplantar Pustulosis**
Protocol Number:	**ANB019-003**
Product:	**ANB019**
Study Phase:	**2**
Sponsor Name:	**AnaptysBio, Inc.**
Legal Registered Address:	**AnaptysBio, Inc.** **10421 Pacific Center Court, Suite 200,** **San Diego, CA 92121, United States**
Regulatory Agency Identifying Number(s):	
	National Clinical Trial (NCT) Number: 03633396 **Investigational New Drug (IND) Number: 136145** **European Clinical Trials Database (EudraCT) Number: 2017-004022-15**
Date of Protocol:	**29 October 2020, Amendment 5**

SPONSOR SIGNATURE PAGE

I confirm that I have read and approved this protocol in its entirety and will comply with the obligations as detailed in all applicable regulations and guidelines (eg, ICH GCP guidelines) and the protocol.

[redacted]

AnaptysBio Inc.

INVESTIGATOR'S AGREEMENT

Protocol Title: **A Phase 2, Randomized, Placebo-controlled, Double-blind, Multiple Dose Study to Evaluate the Efficacy and Safety of ANB019 in Subjects with Palmoplantar Pustulosis**

Protocol Number: **ANB019-003**

Protocol Version: **Amendment 5; 29 October 2020**

This protocol is a confidential communication of the Sponsor. I confirm that I have read this protocol; I understand it; and I will work according to this protocol. I will also work consistently with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with GCPs and the applicable laws and regulations. Acceptance of this document constitutes my agreement that no unpublished information contained herein will be published or disclosed without prior written approval from the Sponsor.

Instructions to the Investigator: Please SIGN and DATE this signature page. PRINT your name, title, and the name of the study center in which the study will be conducted. Return the signed copy to the Sponsor or designee.

I have read this protocol in its entirety and agree to conduct the study accordingly:

Signature of Investigator: _____ Date: _____

Printed Name: _____

Investigator Title: _____

Name/Address of Center: _____

_____

_____

_____

Protocol Amendment Summary of Changes Table

DOCUMENT HISTORY	
Document	**Date**
Amendment 5	29 October 2020
Amendment 4	11 Aug 2020
Amendment 3	23 June 2020
Amendment 2	19 December 2019
Amendment 1	17 October 2019
Original Protocol	27 July 2019

Amendment 5 (29 October 2020)

Overall Rationale for the Amendment:

This amendment was prepared to change the primary endpoint to PPASI mean change from Baseline, update Statistics, and apply minor edits.

Section # and Name	Description of Change	Brief Rationale
Document Header/Footer	Amendment number was updated in the header. The date was updated in the footer.	For accuracy and consistency with AnaptysBio style.
Title Page; Investigator's Agreement; Section 1.1 Synopsis	Updated date of protocol and amendment number.	Administrative for Amendment 5
Document History	Addition of Amendment 5	For accuracy and consistency with AnaptysBio style.
1.1 Synopsis	Removed text: Number of ~~Investigators and~~ Study Centers: Approximately 25 ~~Investigators and~~ study centers are expected to participate in this study.	Change was made because there may be sub-investigators.
1.1 Synopsis; 3.0 Objectives and Endpoints; 9.4.4 Efficacy Analysis	Changed the primary endpoint to mean change from Baseline in PPPASI at Week 16. Moved proportion of subjects achieving PPPASI50 at Week16 from primary to secondary objective.	A continuous measure such as change from Baseline may be more sensitive to change and is appropriate for a proof of concept study. A dichotomous measure such as PPASI50 may lose the granularity of patients who have improved but do not meet a 50% threshold.
1.1 Synopsis; 9.1 Statistical Hypotheses	The text "This is an exploratory study and no formal hypothesis testing will be performed" was replaced with "All hypothesis-based statistical testing will be considered exploratory in nature for this Phase 2 study."	Change was made to correct an error in description.
1.1 Synopsis; 9.4.4.1 Analysis of Primary Efficacy Endpoint	Changed description of statistical methods for analysis of primary efficacy endpoint.	Change was made due to change from a categorical primary endpoint of PPPASI50 to a

		continuous endpoint of change from Baseline in PPASI.
2.2 Background	Changed first-in-man to first-in-human	Change was made to be inclusive.
8.3 Adverse Events	Word "definitions" was added to sentence "The definitions of an AE and SAE can be found in Appendix 4."	Change was made for clarity.
Global	Minor editorial changes for accuracy and formatting.	Administrative

Amendment 4 (11 Aug 2020)

Overall Rationale for the Amendment:

This amendment was prepared to align the study protocol Risk/Benefit Assessment with the Risk/Benefit Assessment described in the ANB019 IB V. 6, 30 June 2020 and to apply minor edits.

Section # and Name	Description of Change	Brief Rationale
Document Header/Footer	Amendment number was updated in the header. The date was updated in the footer.	For accuracy and consistency with AnaptysBio style.
Title Page; Investigator's Agreement; Section 1.1 Synopsis	Updated date of protocol and amendment number.	Administrative for Amendment 4
Section 2.2 Background Clinical Studies; Section 2.3 Benefit/Risk Assessment	Provide context for clinical studies	For accuracy and clarification of clinical data
Section 2.3 Benefit/Risk Assessment	Updated Benefit/Risk Assessment to include ANB019-005 final TEAE results and 26-week toxicology study in cynomolgus monkeys	For accuracy and consistency with ANB019 IB V.6 , 30 June 2020
Document History	Addition of Amendment 3 and Amendment 4	For accuracy and consistency with AnaptysBio style.
Appendix 1 Abbreviations	Addition of AST and ALT to Abbreviations	For accuracy and consistency with AnaptysBio style.

Amendment 3 (23 June 2020)

Overall Rationale for the Amendment:

This amendment was prepared to make minor clarifications regarding protocol procedures and to apply minor edits.

Section # and Name	**Description of Change**	**Brief Rationale**
Global	Minor editorial changes for accuracy and formatting.	Administrative
Document Header/Footer	Amendment number was updated in the header. The date was updated in the footer.	For accuracy and consistency with AnaptysBio style.
Title Page; Investigator's Page; Section 1.1 Synopsis	Updated date of protocol and amendment number.	Administrative for Amendment 3.

Section # and Name	Description of Change	Brief Rationale
Section 1.1 Synopsis; Section 1.2 Schema, Figure 1; Section 3 Objectives and Endpoints; Section 9.4.4.1 Analysis of Primary Endpoint	Removed Week 4 from the primary analysis of PPASI50.	Adjusted the primary response endpoint to be assessed only at Week 16, though the PPASI50 will be collected at each study center visit through Week 16.
Section 1.1. Synopsis, Statistical Methods; and Section 9.4.4.1 Analysis of Primary Efficacy Endpoint	Revised text describing primary efficacy analysis with respect to analysis factors and use of 2-sided exact 95% test for the analysis of treatment differences.	To clarify text in Statistical Methods sections.
Section 5.2 Exclusion Criteria (#4 and #6)	Revised the wording of the exclusion criteria to permit enrollment of subjects with localized oral and genital herpes simplex that is well controlled.	To allow broader flexibility with subject screening and recruitment and to align with other similar studies.
Section 9.4.4.2 Analysis of Secondary Efficacy Endpoints	Revised description of logistic regression model to identify factors used for analysis of 2 secondary efficacy endpoints (proportion of subjects achieving PPPASI50 and PPPASI75 at all study centers and proportion of patients with clear or almost clear assessment score on PPPIGA at all study center visits).	To clarify description of logistic regression model used for analysis of the 2 endpoints described.

Amendment 2 (19 December 2019)

Overall Rationale for the Amendment:

This amendment was prepared to make minor clarifications regarding protocol procedures and to apply minor clarifications.

Section # and Name	Description of Change	Brief Rationale
Global	Minor editorial changes for accuracy and formatting.	Administrative
Document Header/Footer	Amendment number was updated in the header. A date was added to the footer.	For accuracy and consistency with AnaptysBio style.
Title Page; Synopsis	Changed “Phase II” to “Phase 2.” Updated Date of Protocol.	To comply with Style Guide, which recommends Arabic instead of Roman numerals for study phases. Administrative for Amendment 2.
Investigator Signature Page	Revised to “Investigator’s Agreement.” Added protocol title, number, and version, as well as additional language and instructions for the investigator prior to signing.	To maintain consistency with other AnaptysBio protocols.
Protocol Amendment Summary of Changes Table	New section: moved the summary of changes up from Appendix 14 to front	To comply with format for other protocols.

Section # and Name	Description of Change	Brief Rationale
	of the document after Investigator Signature page.	
Section 1.3; Section 5.2 Exclusion Criteria; Section 8.2.2 Chest X-ray	Revised the duration allowed for previous chest x-ray from 6 months to 12 months. In Section 8.2.2, removed the reference to other timepoints as noted in the Schedule of Activities.	To allow greater flexibility with subject screening procedures and ensure consistency throughout the protocol.
Section 2.1 Rationale	Added 2 sentences to the first and second paragraph that appear in the synopsis Rationale section but are missing in the body.	This edit was applied for consistency in the description of the rationale for this study.
Section 4.5.2 Criteria for Stopping the Study Section 6.3 Measures to Minimize Bias Appendix 2 Regulatory, Ethical, and Study Oversight Considerations	Removed reference to [redacted] and replaced with "CRO"	[redacted] will only be referenced for Lifecycle Safety.
Section 5.1. Inclusion Criteria; criterion 7 Section 8.2.6 Clinical Safety Laboratory Assessments	Removed the following sentence: "If any laboratory results are outside the upper or lower limits listed above, final determination of eligibility will be after Investigator assessment following consultation with the Medical Monitor and Sponsor.	This flexibility is not allowed.
Section 5.2 Exclusion Criteria; criterion 15 (4th bullet) Appendix 5 Excluded Medications	Removed "or twice the duration of the biological effect of the product prior to Baseline." Added "(whichever is longer)" after 3 months or 5 half-lives to clarify.	Team recommendation to support ex-US submissions.
Section 8.1.1 Palmoplantar Pustulosis Psoriasis Area Severity Index	Added missing reference to supporting appendix.	Administrative
Appendix 2 Regulatory, Ethical, and Study Oversight Considerations	Removed the phrase allowing for subject "or his/her legally authorized representative" from the text.	Not allowed; the subject must provide consent.
Appendix 14	Removed this appendix. Moved the amendment history information up to the front of the protocol. (This change is not tracked.)	Administrative to align with other protocol formats.

Amendment 1 (17 October 2019)

Overall Rationale for the Amendment:

This amendment was prepared to reorganize the immunogenicity endpoints, clarify the name of one of the assessment tools, increase the overall number of study centers, and make a few minor adjustments to study assessments.

Section # and Name	Description of Change	Brief Rationale
Global	Minor edits for formatting, spacing, spelling. References throughout the document were converted from numbers to author/year format to align with the AnaptysBio Style Guide.	Any necessary corrections were applied for clarity.
Title Page	Added NCT number.	Administrative
Sponsor Signature Page	Revised the language on the Sponsor signature page to include more detail regarding applicable guidelines.	Administrative
Investigator Signature Page	Moved up from Appendix 7 to the front of the document	Administrative; to align with other protocols.
Section 1.1 Synopsis; Section 3.0 Objectives and Endpoints	Moved immunogenicity endpoint to secondary objectives.	To clarify this objective and for reporting purposes to move this to a secondary objective instead of exploratory.
Section 1.1 Synopsis; Section 1.3 Schedule of Activities; Section 4.1 Study Design	Increased the screening period from 28 days (4 weeks) to 48 days.	To allow greater flexibility for scheduling and completion of screening activities and to align with other ANB019 protocols.
Section 1.1 Synopsis; Section 1.3 Schedule of Activities; Section 3 Objectives and Endpoints; Section 4.1 Study Design; Section 8.1.9 Patient Assessment of Palmoplantar Pustulosis Disease Activity, Section 9.4.4.2 Secondary Efficacy Endpoints; Appendix 13	Removed the reference to the Patient Global Assessment (PGA) of disease activity and replaced with Patient Assessment of Palmoplantar Pustulosis Disease Activity.	Clarified the name of the assessment scale.
Section 1.1 Synopsis; Section 6.1 Study Treatment Administered	Revised the language to describe the appearance of placebo.	To align with other protocols and currently approved language for drug product description.
Section 1.1 Synopsis; Section 9.2 Sample Size Determination	Increased the number of study centers from 10 to 25.	Administrative
Section 1.3 Schedule of Activities	Added an additional urine pregnancy text collection at the Week 20 study visit.	For added safety and to align with other ANB019 protocols.

Section # and Name	Description of Change	Brief Rationale
Section 1.3 Schedule of Activities; Appendix 3	For FSH collection, removed the criteria in the definition of postmenopausal that stated women must be 45 years of age.	To align with Appendix 6 on Contraceptive Guidance and with other protocols.
Section 1.3 Schedule of Activities	Added a row for telephone contact during the study and footnote *m* to clarify the days for the telephone contact and the information to be collected.	For safety follow-up and to align with other ANB019 studies.
Section 1.3 Schedule of Activities; Section 8.2.4 Vital Signs	For footnote *f* in the table as well as in section text, removed the term "axillary" from body temperature collection.	To allow greater flexibility in the collection of body temperature and to allow body temperature to be taken orally.
Section 1.3 Schedule of Activities	Revised footnote *l* to expand on the timing of the early termination visit for subjects who discontinue.	To provide clarity on follow-up visit required.
Section 2.2 Background	Added information on the 26-week nonclinical toxicity study that was conducted.	For completeness and consistency with other protocols.
Section 2.3 Benefit/Risk Assessment	Added a paragraph to characterize 1 event of sepsis experienced by a subject in an ANB019 study.	For clarity on safety reporting.
Section 5.1; Inclusion Criteria, criterion 1	Increased the upper age limit of subjects from 70 years to 75 years.	To increase the available pool of potential subjects and improve enrollment.
Section 5.1; Inclusion Criteria, criterion 3	Revised this criterion to remove reference to lack of response to prior topical or corticosteroid therapy.	To increase the available pool of potential subjects and improve enrollment.
Section 5.1; Inclusion Criteria, criterion 7	Added a caveat that out-of-range screening values may be assessed by the Investigator and subjects may be enrolled at the discretion of the Investigator following consultation with the Medical Monitor and Sponsor. Removed the clause allowing one repeat test for abnormal laboratory results.	To allow greater flexibility for Investigators to assess eligibility.
Section 5.1; Inclusion Criteria, criterion 10	Broadened the language on contraception to be inclusive of sites outside of North America. Added that hormonal contraception should be started 48 days prior to Day 1.	Administrative
Section 5.2; Exclusion Criteria, criterion 13	This was revised to allow squamous cell carcinoma as determined by the Investigator to be fully treatable.	To allow greater flexibility in enrollment.

Section # and Name	Description of Change	Brief Rationale
Section 5.2; Exclusion Criteria, criterion 17	Added a phrase that eligibility for subjects with a history of drug, alcohol, or substance abuse will be determined by the Investigator. Removed the example of excessive caffeine use.	To allow greater flexibility for the Investigator.
Section 5.2; Exclusion Criteria, criterion 26	Added a criterion to exclude subjects for inability to tolerate SC drug administration.	Administrative
Section 5.3 Lifestyle Considerations	Added this new section.	For consistency with other ANB019 protocols and to clarify the need to avoid exposure to sunlight.
Section 6.1 Treatments Administered, Text and Table 1	Clarified the appearance description of ANB019 and placebo. Table 1 - Added a row for study treatment description to include the appearance of the investigational product. Clarified the appearance of investigational product and placebo in running text in this section. Removed the rows for packaging and labeling and clarified dosing instructions.	To align with other protocols and for clarity in product description.
Section 6.3 Measures to Minimize Bias	Revised the last paragraph to indicate that the Sponsor will be notified for safety issues instead of the investigator	Administrative
Section 6.7 Treatment After End of Study	Revised the language to indicate that pregnancy through EOS or ET visit if applicable will be reported and followed.	To correct an error in the reporting language for pregnancy.
Section 7.2 Subject Discontinuation/Withdrawal from Study	Added a paragraph to describe the study procedures for early withdrawal.	For clarity with other protocols in the language describing early withdrawal.
Section 8.2.2 Chest X-ray	Move this up from Section 8.2.6 to 8.2.2	To align with other protocols.
Section 8.2.5 Electrocardiogram	Added one bullet to clarify that ECG information does not need to be entered into EDC.	Administrative to clarify documentation procedures.
Section 8.2.6 Clinical Safety Laboratory Assessments	Added a phrase to the second bullet to indicate that when local laboratory testing is required for the Investigator to make a decision to determine eligibility for study entry, the laboratory samples must be collected at the same time as the central laboratory	To clarify procedures for the Investigator.

Section # and Name	Description of Change	Brief Rationale
	sample. Added text to the third bullet regarding screening laboratory assessments to indicate that the Investigator will consult with the Medical Monitor and Sponsor to determine final eligibility of subjects who are outside clinical range for screening laboratory assessment.	
Section 8.2.7 Photography	Added text to explain that the collection of photographs will be standardized and described in a manual of procedures. Included a caveat that photographs may be transferred to central vendor or third party consultant for quality review or additional review.	For clarity around photograph distribution and analysis.
Section 8.2.8 Telephone Contact	Added a new section on Telephone Contact to clarify what will happen at these visits.	To provide clarity on these visits following the addition in Section 1.3 Schedule of Activities.
Section 8.3.5 Pregnancy	Revised the length of time pregnancy will be collected to align with text elsewhere in the protocol.	To provide clarity on the timing of collection of pregnancy information.
Section 8.5 Pharmacokinetics	Removed text describing sample volume and Vacutainer collection. Clarified that collection time will be documented based on a 24-hour clock. Text describing separation into aliquots was moved. Added Table 2 to outline PK and ADA collection procedures and timepoints.	To be less prescriptive and more transparent in protocol text and to provide clarity of documentation.
Section 8.7 Biomarkers	Added a statement that measurement of skin biopsy biomarkers may be performed by a third party.	To allow greater flexibility of study conduct.
Section 8.8 Immunogenicity Assessments	Added a statement that study samples will be divided into 2 aliquots (1 each for primary and a back-up): Removed text specifying the length of time that study samples will be stored.	For clarity of expectations.
Section 9.4.4.1 Analysis of Primary Efficacy Endpoints	Revised the statement on alternate statistical methods that are provided in the SAP.	To provide clarity and conciseness in the protocol.
Section 9.4.4.2 Analysis of Secondary Efficacy Endpoints	Added the endpoint for ADA assessment, which was missing. Clarified that no formal hypothesis testing will be performed.	Administrative

Section # and Name	Description of Change	Brief Rationale
Section 9.5 Interim Analyses	Replaced existing text stating no interim analysis was planned with text to indicate that interim analyses are planned and to briefly summarize these analyses.	Revised to reflect change in intent to perform interim analyses.
Section 10 References	Reordered references into alphabetical order. Added 3 additional references.	To align format and reference presentation with the current style guide.
Appendix 2 Regulatory, Ethical, and Study Oversight	Added additional text to outline informed consent process and genetic testing as it relates to data privacy.	To improve transparency on the informed consent process.
Appendix 6 Contraceptive Guidance	Added text to clarify premenarchal definition, as well as criteria for instances when fertility is unclear. Also added bullet to specify that WOCBP should refrain from donating oocytes for assisted reproduction during study conduct.	To improve the clarity and specificity of contraceptive guidelines.

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1.0 PROTOCOL SUMMARY

1.1 Synopsis

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

Protocol Number: ANB019-003

Rationale:

This study is designed to evaluate the efficacy and safety of multiple doses of ANB019 in subjects with palmoplantar pustulosis (PPP). Palmoplantar pustulosis is the most common localized form of pustular psoriasis confined to the skin of palms and/or soles (Navarini 2017). The interleukin-36 (IL-36) pathway, by promoting inflammatory responses, has been shown to play a key role in the disease pathology.

Recent studies of skin biopsies obtained from patients with clinically confirmed PPP indicated sustained activation of IL-36 pathway in PPP compared with normal and chronic plaque psoriasis skin biopsies suggesting that IL-36 inflammatory axis may be a main driver of the disease pathology (Johnston 2016). The study treatment, ANB019 is a high affinity humanized immunoglobulin G4 monoclonal antibody that specifically binds the interleukin-36 receptor (IL-36R) and antagonizes IL-36 signaling. Therefore, inhibition of IL-36 signaling by blocking IL-36R may provide a novel strategy to control the pathological inflammatory cascade driven by IL-36 in subjects with PPP. The information obtained from this study may provide important insights into potential new treatment options for pustular psoriasis including PPP.

Objectives and Endpoints

Objectives	Endpoints
Primary	
To determine the effect of ANB019 compared with placebo in subjects with PPP as measured by the Palmoplantar Pustulosis Psoriasis Area Severity Index (PPPASI).	Mean change from Baseline in PPPASI at Week 16.
To assess the safety and tolerability of ANB019 in subjects with PPP.	Assessment of adverse events (AEs). Potentially significant and clinically important AEs, adverse events of special interest (AESIs), serious adverse events (SAEs), and AEs leading to withdrawal. Physical examinations. Vital signs. 12-Lead electrocardiogram (ECG). Clinical safety laboratory tests (hematology, biochemistry, and urinalysis).

Objectives	Endpoints
Secondary	
To determine the effect of ANB019 in subjects with PPP as measured by improvement in the PPPASI.	Proportion of subjects achieving PPPASI50 at all study center visits. Proportion of subjects achieving PPPASI75 at all study center visits.
To determine the effect of ANB019 in subjects with PPP as measured by Palmoplantar Pustulosis Severity Index (PPSI).	Change from Baseline in PPSI score at all study center visits.
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).	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.
To determine the time to response with ANB019 in subjects with PPP.	Time to response defined as time to achieve 75% reduction in fresh pustule count.
To determine the relapse rate with ANB019 in subjects with PPP.	Relapse rate defined as return to Baseline in fresh pustule count.
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).	Change in PASI score and affected BSA at all study center visits, if plaque psoriasis is present at non-acral sites.
To evaluate the effect of ANB019 in subjects with pustular psoriasis at non-acral sites (if present) as measured by BSA.	Improvement in pustular psoriasis at non-acral site BSA (if present) at all study center visits.
To evaluate the effect of ANB019 on subject's quality of life.	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.
Immunogenicity: To test for immunogenicity to ANB019	Presence of anti-drug antibodies
Pharmacokinetics (PK): To describe the PK of ANB019 in subjects with PPP.	PK: Where possible, the following PK parameters will be determined for ANB019 after administration: 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.

Objectives	Endpoints
Exploratory	
To explore the effect of ANB019 on skin biopsy biomarkers.	Skin biopsy biomarkers including but not limited to IL-36, IL-17, IL-23, and markers of neutrophils and dendritic cells infiltration.
To provide photographic documentation of lesions.	Photographic documentation of lesions.

Overall Design:

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.

The study will have a screening period of 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 subcutaneously on Days 29, 57, and 85. The subjects will leave the study center following study treatment administration when all postdose assessments have been completed and with the Investigator's approval. Subjects with any ongoing AEs or SAEs while at the study center should remain at the study center until the Investigator has determined that these events have resolved or are deemed as not clinically significant. If any AE or SAE is reported at this visit, the study center staff will perform a telephone contact the next day to ensure that subject's condition is stable.

Subjects will return to the study center for study assessments and follow-up study 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 also be contacted via telephone by study staff to inquire about the potential AEs and changes in concomitant medications on Days 36, 50, 64, and 78.

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), total affected BSA (if plaque psoriasis and/or pustular psoriasis is present at non-acral sites), PPPQLI, DLQI, and Patient Assessment of Palmoplantar Pustulosis Disease Activity (Oji 2015). In addition, relapse rate, time to response, and change in fresh and total pustule count on palms and soles will be recorded.

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 (see Section 1.3). In addition, a punch biopsy (biomarker analysis) will be taken during the study. 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 AE/SAE monitoring, vital signs, physical examination, ECGs, hematology, biochemistry, and urinalysis will be performed during the study period.

The end of study (EOS) visit will be at Week 24 (Day 169) and all subjects will return to the study center for the EOS assessments (see Section 1.3).

Number of Study Centers:

Approximately 25 study centers are expected to participate in this study.

Number of Subjects:

The sample size is not based on statistical power considerations.

Approximately 50 subjects will be enrolled at 25 study centers.

Treatment Groups and Duration:

The study will have a screening period of up to 48 days, treatment period of 12 weeks, and follow-up period of 12 weeks.

Eligible subjects will be randomly allocated to receive either ANB019 or placebo in a 1:1 ratio. ANB019 will be provided in a glass vial as a sterile, colorless to yellowish and clear to slightly opalescent solution for injection. On Day 1, a dose of 200 mg ANB019 or placebo will be administered SC followed by 3 doses of 100 mg ANB019 or placebo SC on Days 29, 57, and 85.

The placebo contains no active drug ingredient and will be provided as a sterile, colorless to slightly yellowish and clear to very slightly opalescent solution for injection.

Statistical Methods:

This is an exploratory study and the number of subjects to be enrolled is not based on statistical power considerations. All hypothesis testing will be considered exploratory in nature. A total of approximately 50 subjects will be enrolled. All eligible subjects will be randomly allocated in a 1:1 ratio to receive multiple doses of ANB019 or placebo.

Analysis set includes Intent-to-Treat set, Safety analysis set, Per Protocol set, and PK analysis set.

The default summary statistics for continuous variables include number of contributing observations, mean, standard deviation (SD), median, minimum, and maximum.

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.

For primary and secondary continuous endpoints, change from Baseline will be evaluated, where possible. Actual and change in data from Baseline will be summarized descriptively for each treatment.

The primary efficacy endpoint is the change from Baseline in PPPASI at Week 16. This will be analyzed using a general linear mixed model for repeated measurements (MMRM) to include data collected at weeks 4, 8, 12 and 16. The model will include fixed effects for treatment, history of plaque psoriasis (Yes/No), categorical visit, the treatment by visit interaction, and Baseline PPPASI score as a covariate. Least-squares means (LSM) and associated standards 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 group and placebo.

Possible effect of any other covariates may also be investigated. Details of such analyses will be described in the Statistical Analysis Plan (SAP). Details of specific alternative statistical methods in the event model assumptions, if violated will be documented in the SAP. In addition, descriptive statistics (sample size, mean, SD, median, minimum, and maximum) will also be presented.

For safety and tolerability, treatment-emergent adverse events (TEAEs), SAEs, AESIs, vital signs, physical examinations, ECGs, and laboratory assessments at specific time points will be evaluated. All safety data will be summarized descriptively. Number and percentage of TEAEs will be presented for each treatment by Preferred Term and System Organ Class of the current Medical Dictionary for Regulatory Authorities. Individual listings 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 and listings of data for vital signs, 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. Baseline will be the last observed value of the parameter of interest prior to the first intake of study treatment.

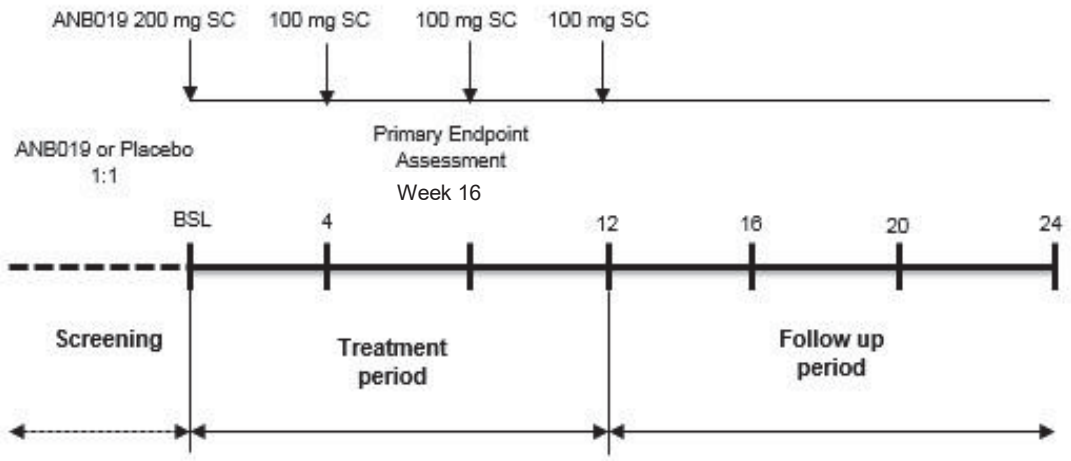
The exposure of ANB019 will be evaluated by assessment of drug concentrations in serum. ANB019 serum concentrations will be listed and summarized for each sampling time point using appropriate

descriptive statistics. The calculated PK parameters will be summarized using appropriate descriptive statistics. Pharmacokinetic data from the study may also be used for population PK and PK/response analyses. If done, a separate analysis plan will be prepared, and results will be reported separately from the Clinical Study Report.

Data Monitoring Committee: No

1.2 Schema

Figure 1 Study Schema



Abbreviations: BSL = baseline; SC = subcutaneous

1.3 Schedule of Activities

	Screening period	Treatment Period														Follow-up Period		
Procedure	**Screening (Up to 48 days prior to Day 1)**	**D1 W0**	**D3 W1**	**D8 W1**	**D15 W2** (±1 day)	**D22 W3** (±1 day)	**D29 W4** (±1 day)	**D36 W5** (±2 days)	**D43 W6** (±2 days)	**D50 W7** (±2 days)	**D57 W8** (±2 days)	**D64 W9** (±2 days)	**D71 W10** (±2 days)	**D78 W11** (±2 days)	**D85 W12** (±2 days)	**D113 W16** (±2 days)	**D141 W20** (±2 days)	**EOS/ D169 W24/ET[1]** (±2 days)
Informed consent	X																	
Inclusion and exclusion criteria	X	X																
Medical history	X																	
Height[a] and weight	X																	X
PPPASI, PPSI, PPPIGA[b]	X	X	X	X	X	X	X		X		X		X		X	X	X	X
PPPQLI, Patient Assessment of Palmoplantar Pustulosis Disease Activity, DLQI[b]	X	X	X	X	X	X	X		X		X		X		X	X	X	X
PASI (plaque psoriasis subjects only)[b]	X	X	X	X	X	X	X		X		X		X		X	X	X	X
Total affected BSA (for subjects with plaque psoriasis and/or pustular psoriasis at non-acral sites)[b]	X	X	X	X	X	X	X		X		X		X		X	X	X	X

	Screening period	**Treatment Period**														**Follow-up Period**		
Procedure	**Screening (Up to 48 days prior to Day 1)**	**D1 W0**	**D3 W1**	**D8 W1**	**D15 W2** (±1 day)	**D22 W3** (±1 day)	**D29 W4** (±1 day)	**D36 W5** (±2 days)	**D43 W6** (±2 days)	**D50 W7** (±2 days)	**D57 W8** (±2 days)	**D64 W9** (±2 days)	**D71 W10** (±2 days)	**D78 W11** (±2 days)	**D85 W12** (±2 days)	**D113 W16** (±2 days)	**D141 W20** (±2 days)	**EOS/ D169 W24/ET[l]** (±2 days)
Fresh and total pustule count on palms and soles	X	X	X	X	X	X	X		X		X		X		X	X	X	X
Complete physical examination[c]	X	X					X				X				X	X		X
12-Lead ECG[d]	X	X					X									X		X
Chest X-ray[e]	X																	
Vital signs[f]	X	X	X	X	X	X	X		X		X		X		X	X	X	X
Hematology and biochemistry[g]	X	X	X	X	X	X	X		X		X		X		X	X	X	X
Urinalysis[g]	X	X					X				X				X	X		X
TB screening (QuantiFERON®-TB Gold test)[g]	X																	
Virology[g]	X																	
Serum pregnancy test (WOCBP only)[g]	X																	X
Urine pregnancy test (WOCBP only)[g]		X					X				X				X	X	X	

	Screening period	**Treatment Period**														**Follow-up Period**		
Procedure	**Screening (Up to 48 days prior to Day 1)**	**D1 W0**	**D3 W1**	**D8 W1**	**D15 W2** (±1 day)	**D22 W3** (±1 day)	**D29 W4** (±1 day)	**D36 W5** (±2 days)	**D43 W6** (±2 days)	**D50 W7** (±2 days)	**D57 W8** (±2 days)	**D64 W9** (±2 days)	**D71 W10** (±2 days)	**D78 W11** (±2 days)	**D85 W12** (±2 days)	**D113 W16** (±2 days)	**D141 W20** (±2 days)	**EOS/ D169 W24/ET[l]** (±2 days)
FSH (Postmenopausal woman with at least 1 year of amenorrhea only)[g]	X																	
Samples for PK[h]		X[h]	X	X	X	X	X		X		X		X		X	X	X	X
Samples for ADA		X					X				X				X			X
Skin biopsies[i]		X		X														
Randomization		X																
Photography		X					X									X		
Telephone contact[m]								X		X		X		X				
ANB019/placebo administration		X[j]					X[j]				X[j]				X[j]			
AE/SAE review	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medication review	X[k]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Abbreviations: ADA = anti-drug antibody; AE = adverse event; BSA = body surface area; D = day; DLQI = Dermatology Life Quality Index; ECG = electrocardiogram; EOS = end of study; ET = early termination, FSH = follicle stimulating hormone; ICF = informed consent form; IL = interleukin; PASI = Psoriasis Area Severity Index; PK = pharmacokinetics; PPPASI = Palmoplantar Pustulosis Psoriasis Area Severity Index; PPSI = Palmoplantar Pustulosis Severity Index; PPPIGA = Palmoplantar Pustulosis (static) Investigator's Global Assessment; PPPQLI = Palmoplantar Pustulosis Quality of Life Instrument; SAE = serious adverse event; SC = subcutaneous; TB = tuberculosis; TC = telephone contact; W = week; WOCBP = woman of childbearing potential.

a Height to be measured at Screening only.

b Refer to Section 8.1 for details and instructions regarding PPPASI, PPSI, PPPIGA, PASI, total affected BSA, and quality of life questionnaires (PPPQLI, Patient Assessment of Palmoplantar Pustulosis Disease Activity, DLQI). The quality of life questionnaires should be the first assessments to be completed by the subject before all other assessments at the study center except at the screening visit. At the screening visit, the ICF should be signed before any study-related assessments are performed.

c Refer to Section 8.2.1 for details regarding the complete physical examination. A complete physical examination will include assessments of general appearance; skin; head/neck; pulmonary, cardiovascular, gastrointestinal, external genitourinary, lymphatic, and musculoskeletal systems; extremities; eyes; nose; throat; and neurologic status.

d Refer to Section 8.2.5 for details and instructions regarding the ECG. In addition to the time points specified in the Schedule of Activities, ECGs may be performed at any time during the study if in the opinion of the Investigator it is clinically warranted.

e Bidirectional posterior-anterior view and lateral view chest X-ray or as indicated by local treatment guidelines or practice will be performed at Screening. If a chest X-ray was performed within 12 months of Screening, it can be skipped at Screening.

f Vital signs assessment includes body temperature, pulse rate, blood pressure, and respiratory rate. Refer to Section 8.2.4 for details and instructions.

g Refer to Appendix 3 for details and instructions regarding clinical laboratory parameters and refer to Appendix 6 for the WOCBP definition.

h On Day 1, samples for PK will be collected at predose, 1 hour and 4 hours post SC administration. In addition, samples for PK will also be collected on Days 3, 8, 15, 22, 29, 43, 57, 71, 85, 113, 141, and 169. On Days 29, 57, and 85, the scheduled PK samples will be collected prior to SC administration (Refer to Table 2).

i In addition to the time points specified in the Schedule of Activities, skin biopsies (including but not limited to IL-36, IL-17, IL-23, and markers of neutrophils and dendritic cells infiltration) may be performed at other visits as appropriate to measure biomarkers. All randomized subjects will be asked to participate in the skin biopsy test; however, the subject's participation is optional. Subjects should provide their consent to participate in the skin biopsy. Punch biopsy will be collected on Day 1 (normal and psoriatic skin) and Day 8 (psoriatic skin only).

j On Days 1, 29, 57, and 85, all assessments should be performed prior to study treatment administration except postdose PK samples (on Day 1). **The specific order for performing the study assessments is as follows (applicable to all visits): First the quality of life questionnaires then the efficacy assessments, vital signs, physical examination, ECG, and then the blood sample collection.**

k At Screening, prior medications should be reviewed and documented. Refer to Section 6.5.

l The ET visit will include all procedures to be done at the ET/EOS visit. In case of early discontinuation, the subject will be encouraged to return to the study center for the follow-up period visits (week 16/Day113, and week 20/Day141 visits) followed by early termination/EOS visit (Week 24/Day169 visit).

m At Days 36, 50, 64, and 78, subjects will be contacted by phone for safety follow-up to assess for AEs and concomitant medications.

2.0 INTRODUCTION

ANB019 is a high affinity humanized immunoglobulin G4 (IgG4) monoclonal antibody (mAb) that specifically binds the interleukin-36 receptor (IL-36R) and antagonizes interleukin-36 (IL-36) signaling. The IL-36 cytokines (IL-36α, IL-36β, and IL-36γ) engage with IL-36R to initiate signaling events leading to proinflammatory responses. Interleukin-36 signaling is counter-balanced by the IL-36 receptor antagonist (IL-36Ra) that binds to IL-36R and competes with activity of IL-36 cytokines. The IL-36 pathway has been implicated in the pathogenesis of inflammatory skin diseases, including palmoplantar pustulosis (PPP). Recent studies of skin biopsies obtained from patients with clinically confirmed diagnosis of PPP indicated sustained activation of IL-36 pathway in PPP compared with normal and chronic plaque psoriasis skin biopsies suggesting a key role of IL-36 inflammatory axis as a main driver of the disease. Inhibition of IL-36 signaling, by targeting IL-36R with a specific mAb, may represent a novel strategy to control the pathological inflammatory cascade driven by activation of the IL-36. ANB019 is being developed as a potential first-in-class therapy for pustular psoriasis, including PPP and generalized pustular psoriasis, and other inflammatory diseases where the IL-36 pathway might have a pathogenic role.

2.1 Study Rationale

This study is designed to evaluate the efficacy as well as safety and tolerability of multiple doses of ANB019 in subjects with PPP. Palmoplantar pustulosis is the most common localized form of pustular psoriasis confined to the skin of palms and/or soles (Navarini 2017). The interleukin-36 (IL-36) pathway, by promoting inflammatory responses, has been shown to play a key role in the disease pathology.

Recent studies of skin biopsies obtained from patients with clinically confirmed PPP indicated sustained activation of the IL-36 pathway in PPP compared with normal and chronic plaque psoriasis skin biopsies suggesting that the IL-36 inflammatory axis may be a main driver of the disease pathology (Johnston 2016). The study treatment, ANB019 is a high affinity humanized immunoglobulin G4 monoclonal antibody that specifically binds the interleukin-36 receptor (IL-36R) and antagonizes IL-36 signaling. ANB019 is a mAb that specifically binds the IL-36R and antagonizes IL-36 signaling. Therefore, inhibition of IL-36 signaling by blocking IL-36R may provide a novel strategy to control the pathological inflammatory cascade driven by IL-36 in subjects with PPP. The information obtained from this study may provide important insights into potential new treatment options for pustular psoriasis including PPP.

2.2 Background

Palmoplantar pustulosis is the most common form of pustular psoriasis characterized by development of sterile pustules on palms and/or soles. The disease is strongly associated with smoking history and typically manifests between 40 and 50 years of age (Eriksson 1998).

Although PPP is often listed among pustular forms of psoriasis, recent genetic studies have provided evidence that PPP may not be related to psoriasis (Asumalathi 2003). The disease is persistent and painful, often resulting in significant functional impairment and diminished quality of life.

Treatment of PPP is challenging with more than two thirds of patients requiring systemic therapy (Adisen 2010). There is little evidence for the efficacy of any treatment, and commonly utilized therapies are often hampered by low efficacy and poor tolerability.

Several recent studies have demonstrated the involvement of IL-36 pathway in PPP suggesting that IL-36 may be an important contributor to the pathogenesis of PPP. Inhibition of the IL-36 signaling by blocking IL-36R potentially offers an additional and novel treatment approach for PPP patients who inadequately benefit from current therapies.

Nonclinical Studies

ANB019 has strong inhibitory activity of human as well as cynomolgus monkey IL-36R. Nonclinical data obtained from studies with ANB019 in primary human and cynomolgus monkey cells and from in vivo nonhuman primate studies demonstrated that:

- ANB019 shows reactivity with human and cynomolgus monkey IL-36R (dissociation constant [K_Ds] of [redacted], respectively), but not with mouse or rat IL-36R.
- In primary human and cynomolgus monkey cell populations, keratinocytes, peripheral blood mononuclear cells, and human whole blood, ANB019 inhibits IL-36R mediated release of IL-8.
- The observed serum half-life ($t_{1/2}$) of ANB019 in cynomolgus monkeys was [redacted] hours after a single intravenous (IV) dose administration, and [redacted] hours after a single subcutaneous (SC) dose administration at 10 mg/kg, with bioavailability approximately [redacted]% consistent with the anticipated pharmacokinetic (PK) characteristics for a human IgG4 scaffold mAb in the monkey.
- Repeat-dose, Good Laboratory Practice toxicity and toxicokinetic studies of 4,13, and 26 weeks in duration have been conducted with ANB019 administered by weekly SC and IV injection in cynomolgus monkeys. There were only minor treatment-related injection site findings in the 4-week repeat-dose study. Treatment-related effects in the 13-week toxicity study included increased observations of nonformed feces and prolapsed rectum, and protozoa in the stomachs of monkeys; the latter being consistent with the mechanism of action of an immune-modulator in cynomolgus monkeys (Dubey 2002). ANB019-related effects during the 26-week toxicity study were limited to a low incidence of nonadverse liquid feces for animals administered 60 mg/kg/dose IV. These studies established a no observed adverse effect level at the 60 mg/kg/dose when administered intravenously or subcutaneously after 26 weeks of dosing.

A detailed description of the physical, chemical, and pharmaceutical properties of ANB019 and nonclinical studies is provided in the current Investigator's Brochure (IB).

Clinical Studies

ANB019 was found to be safe and well tolerated in a first-in-human Phase 1 single ascending dose (SAD) and multiple ascending dose (MAD) study conducted in healthy subjects.

The SAD part of the study enrolled 48 healthy adults. Six dose levels were administered: 10 mg, 40 mg, 100 mg, 300 mg, and 750 mg by IV injection and 100 mg by SC injection. In each cohort, 6 of the 8 subjects received ANB019 and 2 received placebo. After single dose administration, ANB019 was generally well tolerated in male and female healthy adults 18 to 43 years old. Overall, 40 of 48 subjects (83%) experienced at least 1 treatment-emergent adverse event (TEAE). The percentage of subjects who experienced at least 1 TEAE was similar across treatment groups: 29 of 36 subjects, 81% in ANB019 group and 11 of 12 subjects, 92% in placebo. The most commonly reported TEAEs were upper respiratory tract infection (28% ANB019, 50% placebo), headache (28% ANB019, 25% placebo), viral upper respiratory tract infection (11% ANB019, 8% placebo), oropharyngeal pain (8% ANB019, 0% placebo), nausea (8% ANB019, 0% placebo), tension headache (6% ANB019, 8% placebo), gastroenteritis (6% ANB019, 0% placebo), herpes simplex (6% ANB019, 0% placebo), acne (6% ANB019, 0% placebo), catheter site pain (6% ANB019, 0% placebo), and muscle strain (6% ANB019, 0% placebo). The majority of TEAEs were mild (73%) and moderate (26%) in severity with exception of 1 severe AE of elevated creatine kinase (CK). The AE of elevated CK was reported on Day 15 following 100 mg IV administration. The spike in CK levels was caused by strenuous exercise and the AE was deemed unrelated to treatment. Creatine kinase levels normalized 1 week later.

No subject discontinued the study due to an AE. There were no serious adverse events (SAEs) reported in the SAD portion of the study. No clinically relevant abnormalities were noted in vital signs, physical examinations, electrocardiograms (ECGs), or laboratory parameters.

The MAD part of the study enrolled 24 healthy adults. Three dose levels were administered to 8 subjects in each cohort: 40 mg, 100 mg, and 300 mg by IV infusion once a week for 4 weeks. In each cohort, 6 of 8 subjects received ANB019 and 2 subjects received placebo. In the MAD part of the study, 19 of 24 subjects (79%) experienced at least 1 TEAE. Overall, ANB019 was generally well tolerated in healthy adults (20 to 37 years old). The TEAEs were reported by 16 of 18 subjects (89%) in the ANB019 treatment group and in 3 of 6 subjects (50%) in the placebo group following IV infusion once a week for 4 weeks. The most common TEAEs were headache (39% ANB019, 17% placebo) and upper respiratory tract infection (17% ANB019, 17% placebo). The majority of AEs were mild (83%) and moderate (17%) in severity with no severe events reported.

There was no AE leading to study treatment withdrawal reported. One subject developed AE of neutropenia 7 days after the last dose of ANB019 100 mg IV with absolute neutrophil count of 0.7×10^9/L (previously 2.3×10^9/L on Day 1, 2.1×10^9/L on Day 7, 2.0×10^9/L on Day 14, and 2.0×10^9/L on Day 21). The subject was completely well and asymptomatic with no recent illness reported. All other laboratory parameters were normal. The absolute neutrophil count returned to within the normal range 4 days later (3.1×10^9/L) and the subject completed the study. The AE was assessed by the Investigator as moderate and related to study treatment. There were no SAEs reported in the MAD part of the study. No meaningful trends were observed in vital signs, physical examinations, ECGs, or laboratory parameters.

The PK data generated after either a single or multiple IV dose administration indicated linear PK with area under the concentration-time curve (AUC) increasing in a generally dose proportionate manner. The mean maximum observed concentration (C_{max}) was [redacted] µg/mL following a single maximum dose of 750 mg IV and [redacted] µg/mL following a single 100 mg SC administration. The C_{max} increased with weekly IV dosing indicating accumulation during the 4-week dosing period. However, there was little change in serum concentration on Day 29 compared with predose Day 22, indicating that steady state had been achieved after 4 weekly doses. The terminal half-life of ANB019 was approximately [redacted] hours after SC injection and between [redacted] hours after IV injection.

ANB019-005 was a Phase 1 ethnobridging, SAD study in healthy Japanese and Caucasian subjects that evaluated the safety, tolerability, PK, and immunogenicity of ANB019 in 32 subjects. ANB019 was generally well tolerated. All reported TEAEs were mild in severity and there were no SAEs or SUSARs reported for this study. Transient elevations in liver enzymes were observed during the study in 9 subjects (8 in the ANB019 treatment group and 1 in the placebo group). However, only 5 subjects reported TEAEs consistent with elevated liver function test results. The elevations were generally mild, not clinically meaningful, and resolved. Two of the 5 subjects with TEAEs presented with elevated values at Screening that were considered not clinically meaningful by the investigator. No other clinically meaningful changes or trends were observed in hematology, clinical chemistry, vital signs, or ECGs.

2.3 Benefit/Risk Assessment

Participants with PPP may or may not receive direct benefit from participating in this study. Details about expected benefits and risks for participants in this study can be found in the IB and Informed Consent Form (ICF).

In ANB019-001 after single dose administration up to 750 mg either IV or SC, ANB019 was generally well tolerated in healthy adults with a similar proportion of subjects reporting TEAEs in the ANB019 and placebo groups, 81% and 92%, respectively. The most frequently reported TEAEs in the greatest proportion of subjects receiving ANB019 and placebo groups were upper respiratory tract infection (28% and 50%, respectively) and headache (28% and 25%,

respectively). In ANB019-005, single doses of ANB019 up to 750 mg administered by IV infusion or SC injection to 32 healthy Japanese and Caucasian adults were generally well tolerated. The most common TEAEs were alanine aminotransferase (ALT) increased (3 subjects [9.4%]) and aspartate aminotransferase (AST) increased (2 subjects [6.3%]).

There has been 1 SAE of sepsis reported in the ongoing ANB019-002 study in patients with generalized pustular psoriasis that was considered possibly related to the study drug. The subject had a medical history of sepsis and experienced the SAE after the 750 mg IV dose administration. Antibiotic treatment rapidly resolved the sepsis episode with complete patient recovery.

No major toxicities were observed in the 4-week repeat-dose toxicity study. The main finding consisted of minor, nonadverse, injection site reactions associated with the SC route of administration.

Administration of 60 mg/kg/dose of ANB019 via SC or IV bolus injection to male and female sexually mature cynomolgus monkeys once weekly for up to 26 weeks was well tolerated. No ANB019-related effects on the duration or number of menstrual cycles in females, or sperm density, total sperm count, percent motility, sperm morphology, or testicular measurements in males occurred during the dosing or recovery phase. ANB019-related effects were limited to a low incidence of nonadverse liquid feces for animals administered 60 mg/kg/dose IV. Thus the NOAEL was 60 mg/kg/dose administered by SC or IV injection.

Treatment-related effects observed in the 13-week repeat-dose toxicity study included protozoa in the stomach, an increase in nonformed feces and prolapsed rectum observations, the latter was not considered dose related. The increase in protozoa in the stomach has been observed in monkeys treated with immune-modulating drugs (Dubey 2002) and is consistent with the putative mechanism of action of ANB019. The increased incidence of protozoa, nonformed feces, and prolapsed rectum were not considered adverse as they responded to veterinarian intervention. Gastrointestinal infections can be clinically monitored and, in the case of most protozoa, are readily treatable even in the context of immunocompromised individuals (Farthing 2006). One female monkey receiving 60 mg/kg ANB019 IV was found moribund on Study Day 34. The cause of death was not determined and had an uncertain relationship to ANB019 but could be due to treatment-related immune-modulation. However, data published on IL-36R deficient humans shows no deleterious effect on general health and normal immune function is broadly preserved, indicating that inhibition of the IL-36R, apart from disease modification, does not generally compromise host defenses. Similar to other immune-modulating treatment paradigms, subjects should be closely monitored for any clinical gastrointestinal manifestations including infections and evaluated on an ongoing basis. If a gastrointestinal infection is suspected, the subject should be treated as clinically indicated.

As allergic or anaphylactic reactions may occur in subjects treated with mAbs, subjects should be observed during and after investigational product administration. Subjects with true allergic/anaphylactic reactions should not receive further doses of the product.

As ANB019 is a mAb, based on clinical studies with other mAbs, study participants may experience symptoms of an apparent allergic reaction to the drug, also known as ‘cytokine release syndrome.’ The symptoms of this vary dramatically but can include:

Mild to moderate fever, chills, headache, nausea, and vomiting.
Moderate to severe symptoms such as edema, hypotension, and pulmonary infiltrates (eg, blood and mucus in the lung).

Such reactions should be managed as clinically indicated and according to standard clinical practice.

3.0 OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	
To determine the effect of ANB019 compared with placebo in subjects with PPP as measured by the Palmoplantar Pustulosis Psoriasis Area Severity Index (PPPASI).	Mean change from Baseline in PPPASI at Week 16.
To assess the safety and tolerability of ANB019 in subjects with PPP.	Assessment of AEs. Potentially significant and clinically important AEs, adverse event of special interests (AESIs), SAEs, and AEs leading to withdrawal. Physical examinations. Vital signs. 12-Lead ECG. Clinical safety laboratory tests (hematology, biochemistry, and urinalysis).
Secondary	
To determine the effect of ANB019 in subjects with PPP as measured by improvement in the PPPASI.	Proportion of subjects achieving PPPASI50 at all study center visits. Proportion of subjects achieving PPPASI75 at all study center visits.
To determine the effect of ANB019 in subjects with PPP as measured by Palmoplantar Pustulosis Severity Index (PPSI).	Change from Baseline in PPSI score at all study center visits.
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).	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.
To determine the time to response with ANB019 in subjects with PPP.	Time to response defined as time to achieve 75% reduction in fresh pustule count.
To determine the relapse rate with ANB019 in subjects with PPP.	Relapse rate defined as return to Baseline in fresh pustule count.
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).	Change in PASI score and affected BSA at all study center visits, if plaque psoriasis is present at non-acral sites.
To evaluate the effect of ANB019 in subjects with pustular psoriasis at non-acral sites (if present) as measured by BSA.	Improvement in pustular psoriasis at non-acral site BSA (if present) at all study center visits.
To evaluate the effect of ANB019 on subject's quality of life.	Change in clinical scores of Palmoplantar Pustulosis Quality of Life Instrument (PPPQLI), Dermatology Life Quality Index (DLQI), and

Objectives	**Endpoints**
	Patient Assessment of Palmoplantar Pustulosis Disease Activity at all study center visits.
Immunogenicity: To test for immunogenicity to ANB019. PK: To describe the PK of ANB019 in subjects with PPP.	Presence of anti-drug antibodies PK: Where possible, the following PK parameters will be determined for ANB019 after administration: 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.
Exploratory	
To explore the effect of ANB019 on skin biopsy biomarkers. To provide photographic documentation of lesions.	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.

4.0 STUDY DESIGN

4.1 Overall Design

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.

The expected duration of the study is approximately 28 weeks. The screening period will be up to 48 days prior to administration of study treatment on Day 1. Written informed consent will be obtained from each subject prior to initiating any study-related procedures. Subjects will also provide consent for skin biopsies if they wish to participate in this test. All screening procedures will be conducted in accordance with the Schedule of Activities in Section 1.3.

On Day 1, subjects will present to the study center, and the eligible subjects will be randomly allocated in a 1:1 ratio to receive either a 200 mg 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. All procedures will be carried out in accordance with the Schedule of Activities in Section 1.3. The subjects will leave the study center when all postdose assessments have been completed and with the Investigator's approval. Subjects with any ongoing AEs or SAEs while at the study center should remain at the study center until the Investigator has determined that these events have resolved or are deemed as not clinically significant. If any AEs or SAEs reported at this visit, the study center staff will perform a telephone contact the next day to ensure that subject's condition is stable.

After completing Day 1 assessments, the 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 the potential AEs and changes in concomitant medications on Days 36, 50, 64, and 78. 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 (Oji 2015).

Blood samples to determine PK and immunogenicity will be collected before the administration of ANB019 and at the other time points specified (refer to Table 2). 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 AE/SAE monitoring, vital signs measurements, physical examinations, ECGs, and laboratory measurements will be performed during the study.

The end of study (EOS) visit will be at Week 24 (Day 169) and all subjects will return to the study center for the EOS assessments (see Section 1.3).

Concomitant medication use and AEs/SAEs will be recorded and reported throughout the study.

4.2 Scientific Rationale for Study Design

There is little evidence for the efficacy of any treatment of pustular psoriasis and no currently published guidelines for its management. The use of available treatments is limited by low efficacy and long-term adverse effects.

In this context, the development of agents with new mechanisms of action is considered important for future clinical practice. As ANB019 offers the potential for inhibition of IL-36 signaling by blocking IL-36R it may provide a novel strategy for treatment of patients with PPP.

4.3 Justification for Dose

ANB019 will be administered as a single SC dose of 200 mg followed by 3 doses of 100 mg SC administered on Days 29, 57, and 85.

The doses selected for the study demonstrated favorable safety and tolerability profile in a Phase 1 study conducted in healthy volunteers. In addition, ANB019 demonstrated linear PK with an estimated $t_{1/2}$ of [redacted] days at all doses tested with persistent pharmacodynamic activity. The loading dose of 200 mg SC administered on Day 1 was chosen to achieve C_{max} soon after dosing in order to provide optimal potential benefit to PPP patients and to reach steady state concentrations rapidly following 100 mg SC dosing. The 12-week treatment period is expected to provide better clinical outcome, thus potentially benefiting PPP patients and further assessing long-term safety and efficacy in patients with PPP.

4.4 End of Study Definition

A subject is considered to have completed the study if they have completed the last protocol specified visit, including the last visit on Day 169 (see Section 1.3).

The end of the study is defined as the date of the last visit of the last subject in the study.

4.5 Study Stopping Criteria

4.5.1 Stopping Criteria for Individual Subjects

Dosing for any individual subject will be stopped if the subject experiences a SAE or a clinically significant possibly drug-related AE, which in the opinion of the study physician, Investigator, or Sponsor's medical representative, warrants discontinuation of the study for that subject's wellbeing.

Details on subject withdrawal are presented in Section 7.0.

4.5.2 Criteria for Stopping the Study

Termination of a study may occur upon decision of the Sponsor, upon decision of the Investigator, by request of a regulatory authority, because of withdrawal of a positive vote by the responsible Independent Ethics Committee (IEC)/Institutional Review Board (IRB); or if new safety or efficacy information leads to an unfavorable risk-benefit judgment for any study medication. The Sponsor may discontinue the study if it becomes unjustifiable for medical or ethical reasons, for poor enrolment, or because of discontinuation of clinical development of ANB019 for safety reasons. Furthermore, the Investigator and/or Sponsor have the right to close a study center, at any time, after consultation between the involved parties.

The IEC/IRB, the competent authority and the local authority must be informed within 15 days of a decision being made. The Investigator is obliged to inform the local authority whereas information of the IEC/IRB and competent authority is to be performed by the Sponsor or contract research organization (CRO).

If the study center has to be closed prematurely, the Sponsor or CRO will provide all essential documents necessary for the Sponsor's Trial Master File as defined in the Note for Guidance on Good Clinical Practice (GCP) (CPMP/ICH/135/95).

The study will be terminated prematurely in the following cases:

If SAEs occur resulting in the risk-benefit ratio not being reasonable anymore.

If the pattern of AEs observed in the study interferes significantly with the risk-benefit evaluation provided to the Investigator prior to the start of the study.

If the number of discontinued subjects is so high or the number of included subjects is so low that proper completion of the study could not realistically be expected.

If the results of parallel studies show evidence for unacceptable risks.

If severe protocol violations and misconduct occur, which unacceptably affect the safety or rights of the subjects, or render questionable the validity of the study results.

5.0 STUDY POPULATION

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

It is imperative that subjects fully meet all the inclusion criteria and none of the exclusion criteria.

5.1 Inclusion Criteria

1. Male and female subjects must be 18 to 75 years of age (inclusive), at the time of signing the informed consent.
2. Clinically confirmed diagnosis of PPP with disease of sufficient impact and severity requiring systemic therapy.
3. Disease duration of at least 3 months prior to Screening.
4. Present with active pustules on palms or/and soles at Screening and Baseline.
5. At least moderate disease severity (score 3 = moderate) based on the PPPIGA (Appendix 9) at Screening.
6. Subjects with or without a history of plaque psoriasis can be enrolled (number of subjects enrolled with plaque psoriasis should not exceed 50%).
7. Meet the following laboratory criteria at Screening:
   Hemoglobin ≥ 90 g/L (≥ 9 g/dL).
   White blood cell count ≥ 3.0×10^9/L (≥ 3.0×10^3/μL).
   Platelets ≥ 100×10^9/L (≥ 100×10^3/μL).
   Serum creatinine <132.6 μmol/L (< 1.5 mg/dL).
   Alanine aminotransferase and aspartate aminotransferase ≤ 1.5 upper limit of normal (ULN).
   Total bilirubin ≤ 1.5 × (ULN) . Subjects with known Gilbert's disease who have serum bilirubin < 3 × (ULN) may be included.
8. Body mass index within the range of 18 to 36 kg/m^2, inclusive {body mass index = weight (kg)/[height (m)]^2} and total body weight > 50 kg (110 lb).
9. Subjects must be otherwise in a good health status as judged by the Investigator based on medical history, physical examination, ECG, hematology, chemistry, and urinalysis.
10. Contraceptive use by men or women should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.
    Contraception and pregnancy:
    a) A male subject must agree to use contraception as detailed in Appendix 6 of this protocol during the treatment period and for at least 220 days (which includes the duration of relevant exposure plus the duration of sperm cycle) after the study treatment and refrain from donating sperm during this period.
    b) Female subjects:

A female subject is eligible to participate if she has a negative serum pregnancy test (beta-human chorionic gonadotropin) at Screening and a negative urine pregnancy test at Baseline (see Appendix 6), is not breastfeeding, and at least 1 of the following conditions apply:

i) Not a woman of childbearing potential (WOCBP) as defined in Appendix 6.
OR

ii) A WOCBP who agrees to follow the contraceptive guidance in Appendix 6 during the treatment period and for at least 6 months after receiving the study treatment and refrain from donating oocytes for assisted reproduction during this period. The female subject's selected form of contraception must be effective by the time the female subject enters into the study (eg, hormonal contraception should be initiated at least 48 days before Day 1).

11. Capable of giving signed informed consent as described in Appendix 2, which includes compliance with the requirements and restrictions listed in the ICF and in this protocol.

5.2 Exclusion Criteria

Subjects are excluded from participating in the study if any of the following apply:

1. Have other forms of psoriasis (eg, erythrodermic, guttate) except plaque psoriasis.
2. Have concomitant dermatological (eg, subcorneal pustular dermatosis, impetigo herpetiformis, acute generalized exanthematous pustulosis) or medical conditions which may interfere with the Investigators' ability to evaluate the subject's response to therapy.
3. Have a history of clinically significant (as determined by the Investigator) cardiac, pulmonary, neurologic, gastrointestinal, endocrine, hematological, renal, hepatic, cerebral or psychiatric disease, or other major uncontrolled disease (a poorly controlled medical condition, such as but not limited to, poorly controlled diabetes, unstable ischemic heart disease, uncontrolled hypertension [systolic ≥160 mmHg and/or diastolic ≥95 mmHg based on the average of 2 blood pressure measurements], and moderate to severe heart failure [New York Heart Association Class III/IV]).
4. History of chronic or recurrent infectious disease, including but not limited to upper and lower respiratory infection (eg, sinusitis, bronchitis, and bronchiectasis), urinary tract infection (eg, recurrent pyelonephritis), and skin infection (eg, abscesses, infected skin wounds, or ulcers) within 24 months prior to Screening. Subjects with a history of localized oral or genital herpes simplex that, in the opinion of the Investigator, is well controlled will be eligible for study participation.
5. History of a serious infection (eg, hepatitis, pneumonia) that led to hospitalization or treatment with IV antibiotics or antiviral treatment for an infection within 3 months prior to Screening or any recent infection requiring systemic antibiotic or systemic antiviral treatment within 4 weeks of Baseline.

6. History or any evidence of active infection within 4 weeks of Baseline (eg, bronchopulmonary, urinary, or gastrointestinal), excluding localized oral or genital herpes simplex that, in the opinion of the Investigator, is well-controlled.
7. Presence of any factors that would predispose the subject to develop infection (eg, rectal fissures, poor dentition).
8. History of an opportunistic infection (eg, *Pneumocystis carinii*, aspergillosis, or mycobacteria other than tuberculosis [TB]), parasitic infections such as, but not exclusively, helminths, protozoa, *Trypanosoma cruzi* within 6 months prior to Screening.
9. History of a herpes zoster infection within 2 months prior to Screening.
10. Known or suspected autoimmune disorder, including but not limited to rheumatoid arthritis, systemic lupus erythematosus, polymyalgia rheumatica, giant cell arteritis, Behcet's disease, dermatomyositis, multiple sclerosis, moderate to severe asthma, or other severe forms of atopy, any autoimmune vasculitis, autoimmune hepatitis, or any other active autoimmune disease for which a subject requires medical follow-up or medical treatment.
11. Any history of known or suspected congenital or acquired immunodeficiency state, or condition that would compromise the subject's immune status (eg, history of splenectomy).
12. Any major surgery within 4 weeks of study treatment administration.
13. Malignancy or history of malignancy within 5 years prior to Screening, except for treated basal cell or squamous cell in situ carcinoma of the skin or squamous cell carcinomas deemed by the Principal Investigator to be fully treatable.
14. History of any significant drug allergy or reaction (such as anaphylaxis or hepatotoxicity) and reactivity to polysorbate 20, a component of ANB019 formulation, or the inactive ingredients (excipients).
15. Have taken the following drugs within the specified period prior to Screening or Baseline (Day 1):

    Topical medications for (including corticosteroids, retinoids or vitamin A or D analog preparations [tacrolimus, calcineurin inhibitor], topical H1 and H2 antihistamines, tar preparations, keratolytics, topical antimicrobials, other medicated topical agents) or herbal preparations within 2 weeks prior to Baseline.

    Systemic therapy including but not limited to cyclosporine, methotrexate, acitretin, alitretinoin, fumaric acid esters, corticosteroids, or any other immunosuppressant or immunomodulation drugs within 4 weeks prior to Baseline.

    Phototherapy (ie, ultraviolet light B [UVB]) or photochemotherapy (eg, psoralen and ultraviolet A [PUVA]) within 4 weeks prior to Baseline.

    Previous treatment with anti-tumor necrosis factor (TNF)/interleukin (IL-12/IL-23) and IL-17 or any other mAbs is not allowed within 3 months or 5 half-lives (whichever is longer).

    Antibiotic or antiviral medication within 4 weeks (topical 2 weeks and systemic 4 weeks) prior to Baseline.

Any investigational drug within 4 weeks or 5 half-lives, whichever is longer prior to Screening.

Live attenuated vaccine within 12 weeks prior to Screening and during the study.

Topical bland emollients (without pharmacological active ingredients) for pustular psoriasis are allowed during the study, except within 24 hours prior to the study visits. Rescue medication will be directed by the Investigator as needed (see Section 6.5.1).

16. History of active TB or latent TB infection as indicated by a positive QuantiFERON®-TB Gold test at Screening or within 6 months prior to Day 1 (If the test is indeterminate, it can be repeated only once), chest X-ray, and/or clinical examination or has had active TB disease at any time in the past.
17. History of drug, alcohol, or other substance abuse, or other factors limiting the ability to cooperate and to comply with the study protocol, as determined by the Investigator.
18. Pregnant or lactating females, or females who intend to become pregnant during the study period.
19. Donation of blood to a blood bank or in a clinical study (except a Screening visit) within 4 weeks of study treatment administration (within 2 weeks for plasma only).
20. Blood transfusion within 4 weeks of study treatment administration (Day 1).
21. Any other physical, mental, or medical conditions, which, in the opinion of the Investigator, make study participation inadvisable or could confound study assessments.
22. Clinically significant abnormality on chest X-ray at Screening or within 12 months prior to Screening.
23. Any clinically significant abnormalities on 12-Lead ECG at Screening.
24. Evidence of clinically significant abnormality in urinalysis as determined by the Investigator.
25. Positive blood screen for hepatitis C antibody, hepatitis B surface antigen, or human immunodeficiency virus 1 and 2 antibodies.
26. Inability to tolerate SC drug administration.

5.3 Lifestyle Considerations

Investigators should counsel subjects on avoidance of excessive exposure to sunlight during the study.

5.4 Screen Failures

Screen failures are defined as subjects who consent to participate in the clinical study but are not subsequently randomized in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure subjects to meet the Consolidated Standards of Reporting Trials publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAE.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened once after discussion with the Medical Monitor. Rescreened subjects should not be assigned the same subject number as for the initial screening.

6.0 STUDY TREATMENT

Study treatment is defined as any investigational treatment(s), marketed product(s), placebo, or medical device(s) intended to be administered to a clinical study participant according to the study protocol.

6.1 Study Treatment Administered

All eligible subjects in the study will be randomly allocated in a 1:1 ratio to receive 200 mg of ANB019 or placebo SC on Day 1 followed by 3 doses of 100 mg of ANB019 or placebo administered SC on Days 29, 57, and 85. Allocation of the subject to a study treatment will be performed using a central Interactive Voice/Web Response System (IVRS/IWRS) as defined in the User Requirements Specification and the Randomization Requirement Specification by the IWRS vendor.

ANB019 is a humanized [redacted] mAb that belongs in the class of anti-interleukin-36 receptor mAb.

ANB019 will be provided as a sterile, colorless to yellowish and clear to slightly opalescent solution for injection.

The placebo contains no active drug ingredient and will be provided as a sterile colorless to slightly yellowish and clear to very slightly opalescent solution for injection. Detailed administration instructions will be provided in the Pharmacy Manual.

Study treatment details are provided in Table 1.

Table 1 Study Treatment Details

Study Treatment Name:	ANB019 Anti-interleukin-36 receptor monoclonal antibody	Placebo
Study Treatment Description	ANB019 will be provided as a sterile, colorless to yellow and clear to slightly opalescent solution supplied in a single-use, 2R, Type I glass vial with a fill volume of [redacted] mL. Each vial contains [redacted] mg/mL.	The placebo contains no active ingredient and will be provided as a sterile, colorless to slightly yellowish, and clear to very slightly opalescent solution for injection supplied in a single-use, 2R, Type I glass vial with a fill volume of [redacted] mL.
Dosage Formulation:	The drug product is formulated as [redacted].	The Placebo is formulated: [redacted]
Unit Dose Strength(s)/Dosage Level(s):	A dose of 200 mg SC on Day 1 followed by100 mg SC on Days 29, 57, and 85.	An equivalent volume of placebo will be administered SC on Day 1 and on Days 29, 57, and 85

Route of Administration	SC injection (4 doses)	SC injection (4 doses)
Dosing Instructions:	For SC injections, ANB019 should be prepared by drawing up the required dosing volume into suitable sized syringe and attaching a dosing needle. No further dilution is required. Subjects receiving SC ANB019 will receive 1 mL × 2 injections for 200 mg dose on Day 1 and 1 mL × 1 injection for 100 mg dose on Days 29, 57, and 85. Subcutaneous injections should be rotated with each dose and should not be given into moles, scars, tattoos or areas where the skin is tender, bruised, red, hard, or not intact. Abdominal administration is the preferred site for SC doses. Detailed administration instructions will be provided in the Pharmacy Manual.	For SC injections, placebo should be prepared by drawing up the required dosing volume into suitable sized syringe and attaching a dosing needle. No further dilution is required. Subjects receiving SC placebo (on Day 1) will receive a 1 mL × 2 injections and on Days 29, 57, and 85, 1 mL × 1 injection. Subcutaneous injections should be rotated with each dose and should not be given into moles, scars, tattoos or areas where the skin is tender, bruised, red, hard, or not intact. Abdominal administration is the preferred site for SC doses.

Abbreviations: AE = adverse event; NaCl = sodium chloride; SC = subcutaneous

6.2 Preparation/Handling/Storage/Accountability

1. The Investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study treatment received and any discrepancies are reported and resolved before use of the study treatment.
2. Only subjects randomized in the study may receive study treatment and only authorized study center staff may supply or administer study treatment. Further guidance and information for the administration of the study treatment are provided in the Pharmacy Manual.
3. All study treatments must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the Investigator and authorized study center staff.
4. ANB019 vials must be refrigerated at 2°C to 8°C (36°F to 46°F) until the day of use. ANB019 should not be used beyond the re-test or expiration date provided by the manufacturer. Vial contents should not be frozen or shaken. ANB019 vials undiluted or diluted may be stored at room temperature (8°C to 25°C [46°F to 77°F]) for up to 8 hours. Vials are intended for single-use only; therefore, any remaining solution should be discarded.
5. The Investigator, institution, or the head of the medical institution (where applicable) is responsible for study treatment accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).
6. Further guidance and information for the final disposition of unused study treatment are provided in the Pharmacy Manual.

The Investigator, a member of the study center staff, or a hospital pharmacist must maintain an adequate record of the receipt and distribution of all study medication using the Drug Accountability Form. These forms must be available for inspection at any time.

6.3 Measures to Minimize Bias: Randomization and Blinding

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 sequential 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.

Once the subject meets all inclusion and no exclusion criteria and has provided an informed consent, the study center will request the treatment assignment using a central IVRS/IWRS.

All randomized subjects will be managed by IVRS/IWRS.

The process for breaking the blind will be handled through the IVRS/IWRS. Unblinding of treatment assignment during the study is discouraged and should occur only if it is absolutely necessary to know what treatment the subject received. If the Investigator deems identification of the study treatment is necessary for the purpose of providing urgent subject care, and knowledge of the subject's treatment assignment (ANB019 or placebo) will alter subsequent care, the treatment code for the specific subject will be obtained. Prior to unblinding, the Investigator or appropriate designee should attempt to contact the Medical Monitor to discuss the need to unblind a subject. In the event the Medical Monitor cannot be reached, the Investigator should ensure that the unblinding of the treatment code is performed in a discrete manner and the treatment is disclosed only to those persons involved with the direct medical care of the subject. The Investigator should contact the Sponsor's Medical Monitor immediately (within 24 hours to include weekends) following emergency unblinding.

The Sponsor and CRO must be notified immediately if a subject and/or Investigator is unblinded during the study. Interactive Web Response System can create the blinded and/or unblinded notification when the blind is broken, which can be sent via email as per the user role of IVRS/IWRS. Pertinent information regarding the circumstances of unblinding of a subject's treatment code must be documented in the subject's source documents.

6.4 Study Treatment Compliance

The prescribed dosage, timing, and mode of administration may not be changed. Any departures from the intended regimen must be recorded in the electronic case report forms (eCRFs).

For the study treatment administrations, date/time of administration, site of administration, and dose administered (entire dose/incomplete dose) will be documented in the eCRF.

6.5 Concomitant Therapy

Any medication or vaccine (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements) that the subject is receiving at the time of enrollment and receives during the study must be recorded on the eCRF along with:

Reason for use.
Dates of administration including start and end dates.
Dosage information including dose and frequency.

In addition, all prior medications used to treat PPP disease conditions and any other medications taken within 6 months prior to enrollment must be recorded in the eCRF. The concomitant treatments for other indications that are not listed in the prohibited medication section (see Appendix 5) must be on a stable dose for at least 4 weeks before study treatment administration (Day 1). Dose adjustments of these treatments should be avoided during the study.

The Medical Monitor should be contacted if there are any questions regarding concomitant or prior therapy.

Treatment with bland emollients (without pharmacological active ingredients) will be permitted throughout the study, except within 24 hours prior to the study visits. A list of excluded medications/therapy is provided in Appendix 5.

6.5.1 Rescue Medicine

Rescue medication will be directed by the Investigator as needed.

The study team will dispense rescue medication that will be obtained locally and will be reimbursed.

The use of rescue medications should be delayed, if possible, for at least 1 month following the administration of study treatment. Rescue medication may be used at the Investigator's discretion only if medically indicated for the wellbeing of the subject. The date and time of rescue medication administration as well as the name and dosage regimen of the rescue medication must be recorded.

6.6 Dose Modification

No dose modification is allowed in this study. Study treatment can be interrupted temporarily or permanently if deemed necessary as per the Investigator's discretion.

6.7 Treatment After the End of the Study

All subjects will return to the study center for the EOS (Day 169/Week 24) or Early Termination (ET) visit for final safety and EOS assessments. After this visit, subjects should be treated according to the Investigator's clinical judgment. Care after EOS/ET will not be provided by AnaptysBio Inc. Any significant AE which in the opinion of the Investigator is related to the study treatment, SAE, or pregnancy occurring through the EOS and/or ET visit should be reported to the [redacted] Safety team (see Appendix 4) and followed up until outcome.

7.0 DISCONTINUATION OF STUDY TREATMENT AND SUBJECT DISCONTINUATION/WITHDRAWAL

7.1 Discontinuation of Study Treatment

The subject's eligibility criteria will be checked prior to administration of the study treatment on Day 1. If a clinically significant finding or AE/SAE is identified, the Investigator will determine if the subject can receive the study treatment and continue in the study and if any change in subject management is needed.

In case of early withdrawal from the study treatment and study, the subject will be required to attend the ET visit and other follow-up period visits as soon as possible.

7.1.1 Temporary Interruption

Study treatment can be interrupted temporarily in case of an AE as per the Investigator's discretion. The Medical Monitor should be informed. Restarting of study treatment at the next scheduled administration study visits can be done after discussion with the Medical Monitor.

7.1.2 Rechallenge

The study treatment can be reintroduced at the next scheduled administration visit at the Investigator's discretion and after discussion with the Medical Monitor. In case of positive rechallenge the study treatment should be withdrawn permanently.

7.2 Subject Discontinuation/Withdrawal from the Study

A subject may withdraw from the study at any time at his/her own request or may be withdrawn at any time at the discretion of the Investigator for safety, behavioral, compliance, or administrative reasons.

In case of early withdrawal from the study drug and the study, the subject will be required to attend the ET visit (see the Schedule of Activities in Section 1.3). Subjects must be withdrawn from the study for any events described below, any SAE or significant AE which, in the opinion of the Investigator, is related to the study drug, or pregnancy occurring through the EOS should be followed until outcome.

The following events are considered sufficient reasons for discontinuing a subject from the study treatment and/or the study:

Any significant AE which in the opinion of the Investigator requires subject withdrawal.
Withdrawal of consent.
Significant deviation/lack of compliance with protocol.
Lost to follow-up.

Use of any excluded/prohibited medications treatment that in the opinion of the Investigator necessitates the subject being withdrawn (Refer to Appendix 5).

Termination of the study by the Investigator or Sponsor.

Pregnancy (Refer to Appendix 6 and Section 8.3.5).

New information suggests taking part in the study may not be in the participant's best interest.

Death.

Other.

If a subject withdraws consent for disclosure of future information, the Sponsor may retain and continue to use any data collected before such a withdrawal of consent.

If a subject withdraws from the study, he/she may request destruction of any samples taken and not tested, and the Investigator must document this in the study center study records.

See Schedule of Activities (see Section 1.3) for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.

Subjects withdrawing from the study prematurely for reasons other than a study treatment-related AE may be replaced at the discretion of the Investigator and Sponsor to ensure the required number of evaluable subjects.

7.3 Lost to Follow-up

A subject will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study center.

The following actions must be taken if a subject fails to return to the clinic for a required study visit:

The study center must attempt to contact the subject, reschedule the missed visit as soon as possible, counsel the subject on the importance of maintaining the assigned visit schedule, and ascertain whether or not the subject wishes to and/or should continue in the study.

Before a subject is deemed lost to follow-up, the Investigator or designee must make every effort to regain contact with the subject (where possible, 3 telephone calls and, if necessary, a certified letter to the subject's last known mailing address or local equivalent methods).

These contact attempts should be documented in the subject's medical record.

Should the subject continue to be unreachable, he/she will be considered to have withdrawn from the study.

8.0 STUDY ASSESSMENTS AND PROCEDURES

Study procedures and their timing are summarized in the Schedule of Activities (see Section 1.3).

Assessments scheduled on the day of study treatment administration must be performed prior to the study treatment administration unless otherwise noted (see Section 1.3).

There are visits where the protocol requires more than 1 procedure to be completed at the same time point. When indicated, the procedure must follow the specific order of events; refer to the Schedule of Activities (see Section 1.3) for instructions.

Protocol waivers or exemptions are not allowed.

Immediate safety concerns should be discussed with the Sponsor/designee immediately upon occurrence or awareness to determine if the subject should continue or discontinue in the study.

Adherence to the study design requirements, including those specified in the Schedule of Activities, is essential and required for study conduct.

All screening evaluations must be completed and reviewed to confirm that potential subjects meet all eligibility criteria. The Investigator will maintain a screening log to record details of all subjects screened and to confirm eligibility or record reasons for screening failure, as applicable.

Procedures conducted as part of the subject's routine clinical management (eg, blood count) and obtained before signing of the ICF may be utilized for Screening or Baseline purposes provided the procedures met the protocol specified criteria and were performed within the time frame defined in the Schedule of Activities (see Section 1.3).

The maximum amount of blood collected from each subject over the duration of the study, including any extra assessments that may be required, will be 184 mL.

Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

8.1 Efficacy Assessments

It is recommended that the same Investigator/Sub-Investigator completes the scales and questionnaires at all time points for a given subject.

Planned time points for all efficacy assessments are provided in the Schedule of Activities (see Section 1.3).

8.1.1 Palmoplantar Pustulosis Psoriasis Area Severity Index

The PPPASI score will be used in the study for an overall evaluation of response to treatment (to determine the efficacy of ANB019). It uses the key clinical aspects of the disease to enable accurate assessment namely: erythema; pustules; desquamation (scaling) and; area of palms and soles involved (Bhushan 2001). The PPPASI is presented in Appendix 7.

8.1.2 Palmoplantar Pustulosis Severity Index

The PPSI score is used for assessing and grading the severity of PPP lesions and their response to therapy. The PPSI produces a numeric score that ranges from 0 to 12. In the PPSI, either both palms or both soles, whichever has the most severe skin lesion at Screening will be identified as the evaluation sites and assessed at all subsequent visits. The evaluation sites will be assessed separately for erythema, pustules/vesicle, and desquamation/scaling, and each will be rated on a scale of 0 to 4. The PPSI is presented in Appendix 8.

8.1.3 Palmoplantar Pustulosis (Static) Investigator's Global Assessment

The PPPIGA score will be used in the study to determine the subject's response to treatment. The proportion of subjects who achieved "clear" or "almost clear" will be determined using this score. The Investigator will be asked to rate the severity of the subject's disease. A 5-point rating scale will be used as listed below:

0 = clear, 1 = almost clear, 2 = mild, 3 = moderate, 4 = severe. The PPPIGA is presented in Appendix 9.

8.1.4 Psoriasis Area Severity Index

The PASI scores will be used to determine the treatment response in subjects with plaque psoriasis (Fredriksson 1978). The PASI total score includes plaque characteristics (ie, erythema, induration, scaling), percentage of BSA affected and should be calculated by electronic data capture (EDC). The PASI is presented in Appendix 10.

8.1.5 Total Body Surface Area

The affected total BSA% of disease will be used to determine the treatment response in subjects with plaque psoriasis and/or pustular psoriasis at non-acral sites. This assessment will be performed if plaque psoriasis and/or pustular psoriasis at non-acral sites is presented.

8.1.6 Pustule Count on Palms and Soles

Fresh Pustule Count on Palms and Soles

To be included in the count, pustules must be macroscopically visible, white/yellow in color with no brown color, and present on the glabrous skin of the palms and/or soles. The size of the majority of pustules will be noted at each site (<1 mm, 1 to 3 mm, >3 to 10 mm, confluent lakes of pus).

Total Pustule Count on Palms and Soles

To be included in the count, pustules must be macroscopically visible, white/yellow/brown in color, with or without crust, and present on the glabrous skin of the palms and/or soles.

Time to response and relapse rate will be assessed and recorded. Time to response is defined as the time to achieve 75% reduction in fresh pustule count and relapse rate is defined as a return to Baseline status in fresh pustule count.

8.1.7 Dermatology Life Quality Index

The DLQI questionnaire will be used to assess treatment response on the subject's quality of life. The aim of this questionnaire is to measure how much the skin condition has affected the subject's life during the previous week.

Subjects will be asked to recall their experiences during the previous week by responding to 10 questions (Finlay 1994). The DLQI will be completed by the subject on a worksheet prior to any safety or efficacy evaluations. The questionnaire is self-explanatory and handed to the subject who is asked to fill it in without the need for a detailed explanation. The DLQI questionnaire is presented in Appendix 11.

8.1.8 Palmoplantar Pustulosis Quality of Life Instrument

The PPPQLI is a subject completed 32 item questionnaire capturing symptoms, impact on daily activities, and ability to work (Farley 2009). This questionnaire should be completed prior to any safety or efficacy assessments. The PPPQLI is presented in Appendix 12.

8.1.9 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) (Kane 2005). Symptoms will be assessed utilizing the mean VAS score (Schram 2011). It will be completed by the subject on a worksheet prior to any efficacy or safety evaluations. The subject will be asked to place a vertical stroke on a 100 mm VAS on which the left hand boundary represents very well, and the right hand boundary represents very poor. The distance from the mark to the left hand boundary will be reported. The Palmoplantar Pustulosis Disease Activity VAS is presented in Appendix 13.

8.2 Safety Assessments

Planned time points for all safety assessments are provided in the Schedule of Activities (see Section 1.3).

8.2.1 Physical Examinations

Complete physical examinations will be performed at the time points indicated in the Schedule of Activities (see Section 1.3).

A complete physical examination will include assessments of general appearance; skin; head/neck; pulmonary, cardiovascular, gastrointestinal, external genitourinary, lymphatic, and musculoskeletal system; extremities; eyes; nose; throat; and neurologic status.

A detailed examination of the skin should be performed at the time points indicated in the Schedule of Activities for the efficacy assessments (eg, PPPASI, PPPIGA, PASI, and BSA, pustule count).

Investigators should pay special attention to clinical signs related to previous serious illnesses.

8.2.2 Chest X-ray

Bidirectional posterior-anterior and lateral view chest X-ray or as indicated by local treatment guidelines or practice will be performed at Screening if not performed within 12 months prior to Screening (see Section 1.3).

8.2.3 Height and Weight

Height will be measured only at Screening and weight will be measured at Screening and the EOS visit.

8.2.4 Vital Signs

Body temperature, pulse rate, blood pressure, and respiratory rate will be assessed at the time points specified in Schedule of Activities (see Section 1.3).

Blood pressure and pulse will be assessed in the supine position with a completely automated device. Manual techniques will be used only if an automated device is not available.

Blood pressure and pulse measurements should be preceded by approximately 5 minutes of rest for the subject in a quiet setting without distractions (eg, television, cell phones).

Vital signs including body temperature, respiratory rate, and pulse rate (after 5 minutes rest) should be measured once. Arterial blood pressure should be measured twice (at intervals of approximately 5 minutes), using a validated device. The average of the 2 blood pressure readings will be entered in the eCRF.

8.2.5 Electrocardiograms

A single 12-lead ECG will be obtained at the time points specified in the Schedule of Activities (see Section 1.3) using a validated ECG machine that automatically calculates the pulse rate and measures PR, QRS, QT, and QTcF intervals.

The ECG will be reviewed by the central ECG laboratory team and the instructions and guidelines for collection (eg, equipment), transmission, and archiving of ECG data will be provided in the ECG Manual.

The ECG will be reviewed by the Investigator or an authorized representative who is experienced in the evaluation of ECGs and assessed for clinical significance.

The ECG individual data (with the exception of clinical significance) does not need to be entered into EDC.

8.2.6 Clinical Safety Laboratory Assessments

See Appendix 3 for the list of clinical laboratory tests to be performed and the Schedule of Activities (see Section 1.3) for the timing and frequency of the tests.

A central laboratory will be used to perform all laboratory tests except urine pregnancy dipstick which will be assessed by the study center staff. However, local laboratory tests will be allowed in the event that the central laboratory results will not be available immediately and the Investigator needs to make an immediate decision for any safety concerns based on laboratory results. If a local sample is required, it is important that the sample for central analysis is obtained at the same time.

The Investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the eCRF. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those that are not associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the subject's condition.

All laboratory tests with values considered clinically significantly abnormal during the study and including the subject's last study visit (EOS) should be repeated until the values return to normal or Baseline or are no longer considered clinically significant or judged medically stabilized by the Investigator or Medical Monitor.

> If such values do not return to normal/Baseline within a period of time judged reasonable by the Investigator, the etiology should be identified and the Sponsor notified.

All protocol-required laboratory assessments, as defined in Appendix 3, must be conducted in accordance with the Laboratory Manual and the Schedule of Activities.

> If laboratory values from non-protocol specified laboratory assessments performed at the institution's local laboratory require a change in subject management or are considered clinically significant by the Investigator (eg, SAE or AE or dose modification), then the results must be recorded in the eCRF.

8.2.7 Photography

Photography of the lesions will be performed at the time points mentioned in the Schedule of Activities (see Section 1.3) for documentation purposes only. A standardized approach to collection of photographs will be described in the manual provided to sites. Photographs will be transferred to a central vendor for quality review. Any further review of photographs may be conducted by a third party consultant.

8.2.8 Telephone Contact

At Days 36, 50, 64 and 78, subjects will be contacted by phone to assess for safety. Study staff will review for any new AEs or changes in concomitant medications. Any new/changed AEs and concomitant medications will be recorded on the eCRF.

8.3 Adverse Events

The definitions of an AE and SAE can be found in Appendix 4.

Adverse events will be reported by the subject (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

The Investigator and any designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following up all AEs including those are serious, considered related to the study treatment or study procedures, or that caused the subject to discontinue the study (see Section 7.0).

8.3.1 Time Period and Frequency for Collecting AE and SAE Information

All AEs as well as SAEs will be collected from the signing of the ICF until the EOS visit at the time points specified in the Schedule of Activities (see Section 1.3).

All SAEs will be recorded and reported to the Sponsor or designee within 24 hours, as indicated in Appendix 4. The Investigator will submit any updated SAE data to the [redacted] Safety within 24 hours of it being available.

Investigators are not obligated to actively seek AEs or SAEs after conclusion of the study participation. However, if the Investigator learns of any SAE, including a death, at any time after a subject has been discharged from the study, and he/she considers the event to be reasonably related to the study treatment or study participation, the Investigator must promptly notify the [redacted] Safety.

The method of recording, evaluating, and assessing causality of AE and SAE and the procedures for completing and transmitting SAE reports are provided in Appendix 4.

8.3.2 Method of Detecting AEs and SAEs

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the subject is the preferred method to inquire about AE occurrences.

8.3.3 Follow-up of AEs and SAEs

After the initial AE/SAE report, the Investigator is required to proactively follow each subject at subsequent visits/contacts. All AEs will be followed until resolution, stabilization, the event is

otherwise explained, or the subject is lost to follow-up (as defined in Section 7.3). Further information on follow-up procedures is given in Appendix 4.

8.3.4 Regulatory Reporting Requirements for SAEs

Prompt notification by the Investigator to the [redacted] Safety of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of subjects and the safety of a study treatment under clinical investigation are met.

[redacted] Safety has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study treatment under clinical investigation. The [redacted] Safety will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRB/IEC, and Investigators.

Investigator safety reports must be prepared for suspected unexpected serious adverse reactions according to local regulatory requirements and [redacted] Safety policy and forwarded to Investigators as necessary.

An Investigator who receives an Investigator safety report describing an SAE or other specific safety information (eg, summary or listing of SAEs) from the [redacted] Safety will review and then file it along with the IB and will notify the IRB/IEC, if appropriate according to local requirements.

8.3.5 Pregnancy

Details of all pregnancies in female subjects will be collected after the start of study treatment and until at least 28 days after the last dose.

Details of all pregnancies in female partners of male subjects will be collected while the male subject is in this study and through EOS (or ET visit if applicable).

If a pregnancy is reported, the Investigator should inform the [redacted] Safety within 24 hours of learning of the pregnancy and should follow the procedures outlined in Appendix 6.

If a pregnancy occurs, it will be followed up to determine the outcome, but no longer than 6 to 8 weeks after the estimated delivery date.

Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, and ectopic pregnancy) are considered SAEs.

8.3.6 Adverse Events of Special Interest

The following events are considered AESIs in this study.

Serious infection (requiring hospitalization; or with fatal outcome or sepsis; or requiring IV antibiotics/antimicrobials).

Serious allergic reaction.

Gastrointestinal clinical manifestations including infections.

All AESI, including follow-up, should be reported in an expedited manner. (Please follow procedures for AE/SAE recording and reporting outlined in Appendix 4).

8.3.7 Disease-related Events and/or Disease-related Outcomes Not Qualifying as AEs or SAEs

The following disease-related events (DREs) are common in subjects with PPP and can be serious/life-threatening:

Flare of PPP

Because these events are typically associated with the disease under study, they will not be reported according to the standard process for expedited reporting of SAEs even though the event may meet the definition of a SAE. These events will be recorded in the subject's eCRF.

***NOTE**: If either of the following conditions applies, then the event must be recorded and reported as an SAE (instead of a DRE):*

The event is, in the Investigator's opinion, of greater intensity, frequency, or duration than expected for the individual subject.

OR

The Investigator considers that there is a reasonable possibility that the event was related to study treatment.

8.4 Treatment of Overdose

For this study, any dose of ANB019 greater than 200 mg within a 24-hour time period on Day 1 and greater than 100 mg on Days 29, 57, and 85 will be considered an overdose.

In the improbable event of a suspected overdose, the following procedures should be executed:

Administration is to be discontinued.
The subject is to be monitored clinically.
Supportive measures are to be undertaken as clinically indicated.
Electrocardiography and clinical laboratory evaluations (ie, blood glucose, hepatic enzymes, creatinine, blood urea nitrogen, CK, and complete blood count) are to be performed and followed until all values return to baseline levels and AEs subside.

No information on overdose, maximum tolerated dose, or dose-limiting toxicities for ANB019 has been established at this time and since there are no known antidotes for ANB019, the treatment of overdose is at Investigator's discretion.

In the event of an overdose, the Investigator should:

1. Contact the Medical Monitor immediately.

2. Closely monitor the subject for any AE/SAE and laboratory abnormalities and follow-up until resolution.
3. Obtain a serum sample for PK analysis soon after the dose for SC administration and close to T_{max} (~164 hours) for SC injection.
4. Document the quantity of the excess dose as well as the duration of the overdose in the eCRF.

Decisions regarding dose interruptions or modifications will be made by the Investigator in consultation with the Medical Monitor based on the clinical evaluation of the subject.

8.5 Pharmacokinetics

Whole blood will be obtained for the determination of ANB019 in human serum. Samples will be collected according to the Schedule of Activities (see Section 1.3). Whole blood will be obtained from each subject for PK assessments during the study. Each serum sample will be divided into 2 aliquots (1 each for primary and a back-up). Samples collected for analyses of ANB019 serum concentration may also be used to correlate exposure to safety or efficacy aspects related to concerns arising during or after the study.

The actual date and time (24-hour clock) of the blood sample collection will be recorded in the subject's eCRF. The details of blood sample collection, sample tube labeling, sample preparation, storage, and shipping procedures will be described in a separate Laboratory Manual.

The measurement of the concentrations of ANB019 will be performed using a validated assay method. The analytical methods used to measure concentrations of ANB019 will be described in a separate bioanalytical report.

Only samples within the stability window of the assay will be analyzed.

Subject's confidentiality will be maintained. Drug concentration information that may unblind during the study will not be reported to study centers or blinded personnel until the study has been unblinded.

Table 2 PK/ADA Sample Collection and Timepoints

Study Visit	PK Sample Timepoint Plasma	ADA Sample Timepoint Serum
Day 1	Predose	Predose
	1 hr (10 min) postdose	
	4 hrs (10 min) post-dose	
Day 3	Anytime	
Day 8	Anytime	
Day 15	Anytime	
Day 22	Anytime	
Day 29	Predose	Predose
Day 43	Anytime	
Day 57	Predose	Predose
Day 71	Anytime	
Day 85	Predose	Predose
Day 113	Anytime	
Day 141	Anytime	
Day 169	Anytime	Anytime

ADA = anti-antibodies; hr(s) = hour(s); min = minutes; PK = pharmacokinetic.

8.6 Pharmacodynamics

Pharmacodynamic parameters are not evaluated in this study.

8.7 Biomarkers

Samples will be collected according to the Schedule of Activities (see Section 1.3) to measure skin biopsy biomarkers including but not limited to IL-36, IL-17, IL-23, and markers of neutrophils and dendritic cells infiltration.

The actual date and time of the sample collection will be recorded in the subject's eCRF. The details of skin biopsy collection, sample tube labeling, sample preparation, storage, and shipping procedures will be described in a separate Laboratory Manual.

The measurement of skin biopsy biomarkers may be performed by an additional third party (eg, a university Investigator) designated by the Sponsor. Samples may be stored for a maximum of 5 years (or according to local regulations) following the last subject's last visit for the study at a facility selected by the Sponsor to enable further analysis of biomarker responses to study treatment.

8.8 Immunogenicity Assessments

Antibodies to ANB019 will be evaluated in serum samples collected from all subjects according to the Schedule of Activities (see Section 1.3 and Table 2). Additionally, serum samples should

also be collected at the final visit from subjects who discontinued study treatment or were withdrawn from the study. These samples will be tested by the Sponsor or Sponsor's designee. Each serum sample will be divided into 2 aliquots (1 each for primary and a back-up).

Anti-drug antibody (ADA) analysis will be conducted using a screening assay against ANB019 to identify potential positive ADA samples. Samples testing positive for ADA in the screening assay will be further evaluated in a confirmatory assay against ANB019 to confirm the positive status of samples scored potentially positive by the screening assay. In confirmed positive samples, a third assay will be performed to determine the titer of confirmed positive samples. Confirmed positive ADA samples may be further evaluated for neutralizing activity.

The detection and characterization of antibodies to ANB019 will be performed using a validated assay method by or under the supervision of the Sponsor. All samples collected for detection of antibodies to study treatment will also be evaluated for ANB019 serum concentration to enable interpretation of the antibody data. Only samples within the stability window of the assay will be analyzed.

8.9 Health Economics or Medical Resource Utilization and Health Economics

Health Economics/Medical Resource Utilization and Health Economics parameters are not evaluated in this study.

9.0 STATISTICAL CONSIDERATIONS

9.1 Statistical Hypotheses

All hypothesis-based statistical testing will be considered exploratory in nature for this Phase 2 study.

9.2 Sample Size Determination

The sample size is not based on statistical power considerations.

Approximately 50 subjects will be enrolled from 25 study centers for study treatment. On Day 1, subjects who meet all the entry criteria will receive a 200 mg SC dose of ANB019 or placebo followed by 3 doses of 100 mg SC of ANB019 or placebo in a 1:1 ratio.

9.3 Analyses Sets

The analysis sets are defined in Table 3.

Table 3 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.
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; PK = pharmacokinetics

9.4 Statistical Analyses

The statistical analysis will be performed using statistical analysis system (SAS®) Version 9.4 or higher, if available. All details regarding the statistical analysis and the preparation of tables, listings, and figures will be described in the Statistical Analysis Plan (SAP) and approved by the Sponsor before database lock.

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.

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.

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.

Unless otherwise specified, all formal statistical tests will be 2-sided at the 5% significance level. 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 non-parametric methods may be used for analysis.

All data will be presented in by-subject listings.

9.4.1 Subject Disposition

A tabular presentation of the subject disposition will be provided. It will include the number of subjects 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/Sponsor in dry-run to categorize as major or minor and the same will be reported.

9.4.2 Subject Characteristics and Medical History

Subject characteristics obtained at Screening will be summarized for all subjects taking ANB019 or placebo. Subject characteristics may include, but are not limited to age, gender, height, weight, and BMI.

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

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

9.4.3 Concomitant Medication

All medications will be coded using the 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, concomitant, and rescue medications will be summarized by treatment group and by ATC level 2 categories and preferred name.

A listing of prior, concomitant, and rescue medications will be presented.

9.4.4 Efficacy Analyses

9.4.4.1 Analysis of Primary Efficacy Endpoint

The primary efficacy endpoint is the mean change from Baseline in PPPASI at Week 16.

The primary endpoint will be analyzed using a general linear mixed model for repeated measurements (MMRM) to include data collected at weeks 4, 8, 12 and 16. The model will include fixed effects for treatment, history of plaque psoriasis (Yes/No), categorical visit, the treatment by visit interaction, and Baseline PPPASI score as a covariate. Least-squares means (LSM) and associated standards 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 group and placebo.

Possible effect of any other covariates may also be investigated. Details of such analyses will be described in the SAP. Details of specific alternative statistical methods will be documented in the SAP.

In addition, descriptive statistics (n, mean, SD, median, minimum, and maximum) will be presented.

9.4.4.2 Analysis of Secondary Efficacy Endpoints

Following are the secondary efficacy endpoints:

Proportion of subjects achieving PPPASI50 at all study center visits.
Proportion of subjects achieving PPASI75 at all study center visits.
Change 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 status 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 PPPQLI, DLQI, and Patient Assessment of Palmoplantar Pustulosis Disease Activity at all study center visits.
Presence of anti-drug antibodies.

Proportion of Subjects Achieving PPPASI50 and PPPASI75 at All Study Center Visits:

Frequency and percentages for each response Yes/No for PPPASI50 and PPPASI75 will be presented separately by visit for both treatment arms.

The binary response for each endpoint will be analyzed using logistic regression model using a logit link. The model includes factors for treatment, history of plaque psoriasis (Yes/No), and Baseline PPPASI score. The results will be presented in terms of odds ratio together with its associated 2-sided 95% CIs.

Change in PPSI Score at All Study Center Visits:

Summary statistics will be provided for absolute PPSI scores as well as for change from Baseline by visit and treatment group.

Change in PPPIGA Score at All Study Center Visits:

Frequency and percentage will be summarized by each visit for both treatment arms.

A shift table of change in PPPIGA scores from Baseline to EOS visit will be displayed by each PPPIGA score for both treatment arms.

Proportion of Subjects with Clear or Almost Clear Assessment Score on PPPIGA at All Study Center Visits:

Frequency and percentages for each response Yes/No by visit will be presented for both treatment arms.

The binary response at EOS will be analyzed using logistic regression model using a logit link. The model includes factors for treatment and history of psoriasis (Yes/No), and Baseline PPPASI score as a covariate.

The results will be presented in terms of odds ratio together with its associated 2-sided 95% CIs.

Change in Fresh and Total Pustule Count on Palms and Soles at All Study Center Visits:

Summary statistics for the fresh and total pustule count, as well as change from Baseline, will be provided. Frequency and percentages of the size of the majority of pustules will be presented for

both the treatment arms. Change in fresh and total pustule count data throughout the study will also be analyzed. Further details of the analysis will be described in the SAP.

Time to Response defined as time to achieve 75% reduction in fresh pustule count:

Time to response will be analyzed as time-to-event endpoint. The Kaplan-Meier survival curves and 25th, 50th (median), and 75th percentiles will be provided along with the 2-sided 95% CIs. Subjects without response will be censored at the EOS.

Relapse Rate defined as return to Baseline in fresh pustule count:

Frequency and percentages will be summarized for subjects experiencing relapse.

Change in PASI Score and Affected BSA at All Study Center Visits, if Plaque Psoriasis is Present at Non-Acral Sites:

Summary statistics will be provided for absolute PASI scores as well as for percent change from Baseline by visit and treatment group.

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

Improvement in Pustular Psoriasis at Non-Acral Site BSA (if present) at All Study Center Visits:

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

Change in Clinical Scores of PPPQLI, DLQI, and Patient Assessment of Palmoplantar Pustulosis Disease Activity at All Study Center Visits:

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

The PPPQLI, DLQI, and Patient Assessment of Palmoplantar Pustulosis Disease Activity scores will be analyzed using a mixed model for repeated measures with treatment as fixed effect, history of plaque psoriasis (Yes/No) and Baseline scores as covariates.

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

9.4.5 Safety Analyses

Following are the primary safety and tolerability endpoints:

Assessment of AEs.

Potentially significant and clinically important AEs, AESIs, SAEs, and AEs leading to withdrawal.
Physical examinations.
Vital signs.
12-Lead ECG.
Clinical safety laboratory tests (hematology, biochemistry, and urinalysis).

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

9.4.5.1 Adverse Events and Serious Adverse Events

TEAE: 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 all safety subjects exposed to ANB019/placebo.

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, 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.

9.4.5.2 Physical Examinations, 12-Lead Electrocardiogram, Vital Signs, and Clinical Safety Laboratory Tests (Hematology, Biochemistry, and Urinalysis)

Summaries and listings of data for complete physical examination findings, 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, physical examination results, weight, BMI, 12-Lead ECG, vital, 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.

9.4.6 Pharmacokinetic Analyses

9.4.6.1 Derivation of Pharmacokinetic Parameters

The 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 detailed in the SAP.

Where possible, the following PK parameters will be determined for ANB019 after the first SC administration on Day 1:

Maximum observed concentration (C_{max}).

Time to maximum observed concentration (T_{max}).

Area under the curve (AUC) from zero (predose) to last quantifiable concentration [$AUC_{(0\text{-last})}$] and/or AUC determined over the 28-day SC dosing interval [$AUC_{(\tau)}$], if appropriate.

Half-life may be estimated, 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).

Furthermore, 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 determined or assessed graphically.

Additional PK parameters may be determined if deemed appropriate.

9.4.6.2 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 ANB019 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 SC administration on Day 1 and Day 85 will be presented. Individual subject concentration-time plots will also be presented.

Mean trough concentrations-time data will be graphically displayed for samples collected on Days 29, 57, 85, and 113 (4-weeks after last dose) to visually assess time to attainment of steady state. Time to steady state may also be explored by using inferential statistics, if deemed appropriate. Other presentations of data may be added at the discretion of the PK scientist, as appropriate, and will be described in detail in the SAP.

9.4.6.3 Pharmacokinetic Parameter Data Analysis

All 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 T_{max}, which will be reported with n, minimum, median, and maximum only.

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

9.4.6.4 Population Pharmacokinetics Analysis

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

9.4.7 Immunogenicity Analyses (Exploratory Endpoint Analysis)

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 as proportions with 95% CIs from a 2-sided exact test for the comparison of treatment arms, using the Clopper-Pearson method. If data permits, correlation will be analyzed between ADA levels and safety and efficacy endpoints.

Frequency and percentage of ADA response will be presented and listed.

9.4.8 Biomarker Analyses (Exploratory Endpoint Analysis)

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.

9.4.9 Missing Data

Missing data handling and possible sensitivity analysis will be described in the SAP.

9.5 Interim Analyses

An Interim Analysis (IA) might be performed when all active subjects complete their Week 16 visit for final assessment of all primary and secondary efficacy endpoints (for Week 16) and all safety data available (up to Week 24). Final database lock will include exploratory efficacy and safety analysis for all subjects for all visits.

9.6 Data Monitoring Committee

Not applicable.

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11.0 APPENDICES

Appendix 1 Abbreviations

Abbreviation	Definition
ADA	Anti-drug antibody
AE	Adverse event
AESI	Adverse event of special interest
ALT	Alanine aminotransferase
AST	Aspartate transaminase
ATC	Anatomical Therapeutic Chemical
AUC	Area under the concentration-time curve
BMI	Body mass index
BSA	Body Surface Area
CFR	Code of Federal Regulations
CI	Confidence interval
CK	Creatine kinase
C_{max}	Maximum observed concentration
CRF	Case Report Form CSR
Clinical Study Report CV	
Coefficient of variation	
DLQI	Dermatology Life Quality Index
DRE	Disease-related events
ECG	Electrocardiogram
EDC	Electronic data capture
eCRF	Electronic case report form
EOS	End of study
ET	Early termination
FSH	Follicle stimulating hormone
GCP	Good Clinical Practice
HRT	Hormonal replacement therapy
IB	Investigator’s Brochure
ICF	Informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IgG4	Immunoglobulin G4

Abbreviation	Definition
IL	Interleukin
IL-36R	Interleukin-36 receptor
IL-36Ra	Interleukin-36 receptor antagonist
IRB	Institutional Review Board
ITT	Intent-to-treat
IV	Intravenous
IVRS	Interactive Voice Response System
IWRS	Interactive Web Response System
mAb	Monoclonal antibody
MAD	Multiple ascending dose
MedDRA	Medical Dictionary for Regulatory Activities
n	Sample size
NaCl	Sodium chloride
PASI	Psoriasis Area Severity Index
PK	Pharmacokinetic(s)
PPP	Palmoplantar pustulosis
PPPASI	Palmoplantar Pustulosis Psoriasis Area Severity Index
PPSI	Palmoplantar Pustulosis Severity Index
PPPIGA	Palmoplantar Pustulosis (static) Investigator's Global Assessment
PPPQLI	Palmoplantar Pustulosis Quality of Life Instrument
PUVA	Psoralen and ultraviolet A
PT	Preferred Term
SAD	Single ascending dose
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SC	Subcutaneous
SD	Standard deviation
SOC	System Organ Class
SOP	Standard operating procedure
$t_{1/2}$	Terminal half-life
TB	Tuberculosis
TC	Telephone contact

Abbreviation	Definition
TEAE	Treatment-emergent adverse events
T_{max}	Time to maximum observed concentration
TNF	Tumor necrosis factor
ULN	Upper limit of normal
UVB	Ultraviolet light B
VAS	Visual analog scale
WOCBP	Woman of childbearing potential

Appendix 2 Regulatory, Ethical, and Study Oversight Considerations

Regulatory and Ethical Considerations

This study will be conducted in accordance with the protocol and with the following:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences International Ethical Guidelines.
- Applicable International Council for Harmonisation (ICH) GCP Guidelines.
- Applicable laws and regulations.

The protocol, protocol amendments, ICF, IB, and other relevant documents (eg, advertisements) must be submitted to an IRB/IEC by the Investigator and reviewed and approved by the IRB/IEC before the study is initiated.

Any amendments to the protocol will require IRB/IEC and regulatory authority approval, when applicable, before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to subjects.

The Investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC.
- Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures.
- Providing oversight of the conduct of the study at the study center and adherence to requirements of Code of Federal Regulations (21 CFR), ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations.

After reading the protocol, each Investigator will sign the protocol signature page and send a copy of the signed page to the Sponsor or representative. The study will not start at any study center at which the Investigator has not signed the protocol.

Insurance

Sponsor will provide insurance in accordance with local guidelines and requirements as a minimum for the subjects in this study. The terms of the insurance will be kept in the study files.

Informed Consent Process

The Investigator or his/her representative will explain the nature of the study to the subject and answer all questions regarding the study.

Subjects must be informed that their participation is voluntary. Subjects will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act requirements, where applicable, and the IRB/IEC or study center.

The medical record must include a statement that written informed consent was obtained before the subject was entered in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.

Subjects must be re-consented to the most current version of the ICF(s) during their participation in the study.

A copy of the ICF(s) must be provided to the subject.

Subjects who are rescreened are required to sign a new ICF.

The ICF will contain a separate section that addresses the use of remaining mandatory samples for optional exploratory research. The Investigator or authorized designee will explain to each subject the objectives of the exploratory research. Subjects will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the storage period. A separate signature will be required to document a subject's agreement to allow any remaining specimens to be used for exploratory research. Subjects who decline to participate in this optional research will not provide this separate signature

Data Protection

Subjects will be assigned a unique identifier by the Sponsor. Any subject records or datasets that are transferred to the Sponsor will contain the identifier only; subject names or any information which would make the subject identifiable will not be transferred.

The subject must be informed that his/her personal study-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure must also be explained to the subject.

The subject must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the Sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

The ICF will incorporate (or, in some cases, be accompanied by a separate document incorporating) wording that complies with relevant data protection and privacy legislation.

The Sponsor or its representative will not provide individual genotype results to subjects, any insurance company, any employer, their family members, general physician, or any other third party, unless required to do so by law.

Extra precautions are taken to preserve confidentiality and prevent genetic data being linked to the identity of the subject. In exceptional circumstances, however, certain individuals might see both the genetic data and the personal identifiers of a subject. For example, in the case of a medical emergency, the Sponsor or representative physician or

an Investigator might know a subject's identity and also have access to his or her genetic data. Also regulatory authorities may require access to the relevant files.

Administrative Structure

Table 4 Study Administrative Structure

Function	Responsible Organization
Study Operations Management Medical Monitoring	CRO
Study Master File	CRO
Randomization Code	CRO
Data Management	CRO
Clinical Supply Management	AnaptysBio, Inc./CRO
Quality Assurance Auditing	AnaptysBio, Inc./CRO
Biostatistics	AnaptysBio, Inc./CRO
Medical Writing	AnaptysBio, Inc.
Laboratory Assessments	CRO
Electrocardiogram Collection, Review, and Analysis	CRO
Pharmacokinetic Sample Testing	CRO

Medical Monitor

Further details can be found in the Medical Monitoring Plan. In case of any urgent medical issue contact: [redacted].

Dissemination of Clinical Study Data

The results of the study should be reported within 1 year from the end of the clinical study. Irrespective of the outcome, the Sponsor will submit to the European Union database a summary of the results of the clinical study within 1 year from the end of the clinical study. It shall be accompanied by a summary written in a manner that is understandable to laypersons.

Quality Control and Quality Assurance

According to the Guidelines of GCP (CPMP/ICH/135/95), the CRO is responsible for implementing and maintaining quality assurance and quality control systems with written Standard operating procedures (SOPs). Quality control will be applied to each stage of data handling.

The following steps will be taken to ensure the accuracy, consistency, completeness, and reliability of the data:

Central laboratories for clinical laboratory parameters.
Center Initiation visit.
Early center visits post-enrollment.
Routine center monitoring.
Ongoing center communication and training.
Data management quality control checks.
Continuous data acquisition and cleaning.
Internal review of data.
Quality control check of the final CSR.

In addition, Sponsor and/or the CRO may conduct periodic audits of the study processes, including, but not limited to study center, central laboratories, vendors, clinical database, and final CSR. When audits are conducted, access must be authorized for all study-related documents including medical history and concomitant medication documentation to authorized Sponsor's representatives and regulatory authorities.

Monitoring

The Sponsor has engaged the services of a CRO to perform all monitoring functions within this clinical study. The CRO's monitors will work in accordance with the CRO's SOPs. The monitor will establish and maintain regular contact between the Investigator and Sponsor. Monitoring will be carried out as determined by the risk assessment process conducted on the study.

The monitor will evaluate the competence of the study center, informing Sponsor about any problems relating to facilities, technical equipment, or medical staff. During the study, the monitor will check that written informed consent has been obtained from all subjects correctly and that data are recorded correctly and completely. The monitor is also entitled to compare entries in eCRFs with corresponding source data and to inform the Investigator of any errors or omissions. The monitor will also assess and control adherence to the protocol and ICH/GCP guidelines at the study center. The monitor will arrange for the supply of study treatment, ensure proper study treatment dispensing/accountability, and appropriate storage conditions are maintained.

Monitoring visits will be conducted according to all applicable regulatory requirements and standards. Regular monitoring visits will be made to each center while subjects are enrolled in the study.

During monitoring visits, all entries in the eCRFs will be compared with the original source documents (source data verification). For the following and all other items, this check will be 100%:

Subject identification number.
Subject consent obtained.
Subject eligibility criteria (inclusion and exclusion criteria).
Efficacy variables.
Safety variables.
Medical record of AE.

Data Management/Coding

Data generated within this clinical study will be handled according to the relevant SOPs of the Data Management and Biostatistics departments of the Sponsor and the CRO.

Electronic data capture will be used for this study, meaning that all eCRF data will be entered in electronic forms at the study center. Data collection will be completed by authorized study center staff designated by the Investigator. Appropriate training and security measures will be completed with the Investigator and all authorized study center staff prior to the study being initiated and any data being entered into the system for any study subjects.

All data must be entered in English. The eCRFs should always reflect the latest observations on the subjects participating in the study. Therefore, the eCRFs are to be completed as soon as possible during or after the subject's visit. To avoid inter-observer variability, every effort should be made to ensure that the same individual who made the initial Baseline determinations completes all efficacy and safety evaluations. The Investigator must verify that all data entries in the eCRFs are accurate and correct. If some assessments are not done, or if certain information is not available or not applicable or unknown, the Investigator should indicate this in the eCRF. The Investigator will be required to electronically sign off on the clinical data.

The monitor will review the eCRFs and evaluate them for completeness and consistency. The eCRF will be compared with the source documents to ensure that there are no discrepancies between critical data. All entries, corrections and alterations are to be made by the responsible Investigator or his/her designee. The monitor cannot enter data in the eCRFs. Once clinical data of the eCRF have been submitted to the central server, corrections to the data fields will be audit trailed, meaning that the reason for change, the name of the person who performed the change, together with time and date will be logged. Roles and rights of the center staff responsible for entering the clinical data into the eCRF will be determined in advance. If additional corrections are needed, the responsible monitor or Data Manager will raise a query in the EDC application. The appropriate study center staff will answer queries sent to the Investigator. This will be audit trailed by the EDC application meaning that the name of investigational staff, time and date stamp are captured.

The eCRF is essentially considered a data entry form and should not constitute the original (or source) medical records unless otherwise specified. Source documents are all documents used by the Investigator or hospital that relate to the subject's medical history, that verify the existence of

the subject, the inclusion and exclusion criteria and all records covering the subject's participation in the study. They include but are not limited to laboratory notes, ECG results, memoranda, pharmacy dispensing records, subject files, etc. Source data should be attributable, legible, contemporaneous, original, accurate, and complete. Changes to source data should be traceable, should not obscure the original entry, and should be explained if necessary (eg, via an audit trail).

The Investigator is responsible for maintaining source documents. These will be made available for inspection by the study monitor at each monitoring visit. The Investigator must submit a completed eCRF for each subject who receives study treatment, regardless of duration. All supportive documentation submitted with the eCRF, such as laboratory or hospital records, should be clearly identified with the study and subject number. Any personal information, including subject name, should be removed or rendered illegible to preserve individual confidentiality.

Electronic case report form records will be automatically appended with the identification of the creator, by means of their unique User ID. Specified records will be electronically signed by the Investigator to document his/her review of the data and acknowledgement that the data are accurate. This will be facilitated by means of the Investigator's unique User ID and password; date and time stamps will be added automatically at time of electronic signature. If an entry on an eCRF requires change, the correction should be made in accordance with the relevant software procedures. All changes will be fully recorded in a protected audit trail, and a reason for the change will be required.

Record Keeping

The Investigator must maintain essential study documents (protocol and protocol amendments, completed eCRFs, signed ICFs, relevant correspondence, and all other supporting documentation). The study center should plan on retaining such documents for approximately 15 years after study completion. The study center should retain such documents until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years after the formal discontinuation of clinical development of the study treatment (ANB019). These documents should be retained for a longer period if required by the applicable regulatory requirements or the hospital, institution, or private practice in which the study is being conducted. Subject identification codes (subject names and corresponding study numbers) will be retained for this same period of time. These documents may be transferred to another responsible party, acceptable to Sponsor, who agrees to abide by the retention policies. Written notification of transfer must be submitted to Sponsor. The Investigator must contact Sponsor prior to disposing of any study records.

Direct Access to Source Documents

The Investigator will prepare and maintain adequate and accurate source documents to record all observations and other pertinent data for each subject randomized into the study.

The Investigator will allow the Sponsor, CRO, and authorized regulatory authorities to have direct access to all documents pertaining to the study, including individual subject medical records, as appropriate. Such information must be kept confidential and must have locked facilities that allow for this. Subject identification number will be recorded on all documents related to the study.

Study and Study Center Closure

The Sponsor designee reserves the right to close the study center or terminate the study at any time for any reason at the sole discretion of the Sponsor. Study centers will be closed upon study completion. A study center is considered closed when all required documents and study supplies have been collected and a study center closure visit has been performed.

The Investigator may initiate study center closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study center by the Sponsor or Investigator may include but are not limited to:

- Failure of the Investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the Sponsor's procedures, or GCP guidelines.
- Inadequate recruitment of subjects by the Investigator.
- Discontinuation of further study treatment development.

Publication Policy

The data generated by this study are confidential information of the Sponsor. The Sponsor will make the results of the study publicly available. The publication policy with respect to the Investigator and study center will be set forth in the Clinical Trial Agreement.

Appendix 3 Clinical Laboratory Tests

The tests detailed in Table 5 will be performed by the central laboratory. The time points are specified in the Schedule of Activities (see Section 1.3).

Local laboratory tests will be allowed in the event that the central laboratory results will not be available immediately and the Investigator needs to take an immediate decision for any safety concerns. If a local sample is required, it is important that the sample for central analysis is obtained at the same time. Urine pregnancy dipstick will be performed at the study center prior to study treatment administration.

Protocol-specific requirements for inclusion or exclusion of subjects are detailed in Section 5.0 of the protocol.

Additional tests may be performed at any time during the study as determined necessary by the Investigator or required by local regulations.

Table 5 Protocol-required Safety Laboratory Assessments

Laboratory Assessments	Parameters	
Hematology	Hemoglobin	Red blood cell (RBC) count
	Hematocrit	White Blood Cell Count (WBC) with Differential:
	Packed cell volume (PCV)	Neutrophils
	Mean cell hemoglobin (MCH)	Lymphocytes
	Mean cell volume (MCV)	Monocytes
	Mean cell hemoglobin concentration (MCHC)	Eosinophils
		Basophils
	Platelet count	
Biochemistry	Alanine aminotransferase (ALT)	Creatinine
	Albumin	Gamma glutamyl transferase (GGT)
	Alkaline phosphatase (ALP)	Glucose
	Aspartate aminotransferase (AST)	Potassium
	Bicarbonate	Phosphate (Inorganic)
	Bilirubin (Total)	Protein (Total)
	Bilirubin (Direct-only if total is elevated)	Sodium
	Calcium	Blood urea nitrogen (urea)
	Chloride	Creatine kinase (CK)
	Uric acid	Triglycerides
	Lactate dehydrogenase	human C-reactive protein (hsCRP)
	Troponin	Total cholesterol (fractions)

Laboratory Assessments	**Parameters**	
Serum pregnancy	Human chorionic gonadotropin (hCG) pregnancy test (as needed for women of childbearing potential)	
Follicle stimulating hormone (FSH)	As needed in women of non-childbearing potential only (Postmenopausal woman with at least 1 year of amenorrhea)	
Urinalysis	Bilirubin	pH
	Blood	Protein
	Glucose	Specific gravity
	Ketones	Urobilinogen
	Leukocytes	Microbiology (At discretion of Investigator based on urinalysis results)
	Nitrites	Microscopy (At discretion of Investigator based on urinalysis results)
Viral serology	Hepatitis B surface antigen	
	Hepatitis C antibody	
	Human immunodeficiency virus antibodies	
Tuberculosis (TB) screening	QuantiFERON-TB Gold® In-Tube, the third-generation test (If the test indeterminate it can be retested only once)	
NOTES: Please see Schedule of Activities for laboratory tests time points. Pharmacokinetics and anti-drug antibody (ADA) samples will be collected as detailed in the Schedule of Activities. All blood samples must be drawn prior to administration of the study treatment, unless otherwise specified. The date and exact time of sample collection must be recorded.		

Investigators must document their review of each laboratory safety report.

Appendix 4 Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

Definition of AE

AE Definition
An AE is any untoward medical occurrence in a subject or subject, temporally associated with the use of study treatment, whether or not considered related to the study treatment. NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study treatment.

Events Meeting the AE Definition
Any abnormal laboratory test results (hematology, biochemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital signs measurements), including those that worsen from Baseline, considered clinically significant in the medical and scientific judgment of the Investigator (ie, not related to progression of underlying disease). Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. New conditions detected or diagnosed after study treatment administration even though it may have been present before the start of the study. Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction. Signs, symptoms, or the clinical sequelae of a suspected overdose of either study treatment or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae. “Lack of efficacy” or “failure of expected pharmacological action” per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfill the definition of an AE or SAE.

Events NOT Meeting the AE Definition
Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the subject’s condition. The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the subject’s condition. Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE. Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital). Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

Definition of SAE

An SAE is defined as any untoward medical occurrence that, at any dose:
a) Results in death
b) Is life-threatening The term 'life-threatening' in the definition of "serious" refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
c) Requires inpatient hospitalization or prolongation of existing hospitalization In general, hospitalization signifies that the subject has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious. Hospitalization for elective treatment of a pre-existing condition that did not worsen from Baseline is not considered an AE.
d) Results in persistent disability/incapacity The term disability means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
e) Is a congenital anomaly/birth defect
f) Other situations (Medically Significant Events): Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require medical or surgical intervention to prevent 1 of the other outcomes listed in the above definition. These events should usually be considered serious. Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

Recording and Follow-up of AE and/or SAE

AE and SAE Recording

When an AE/SAE occurs, it is the responsibility of the Investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostics reports) related to the event.

The Investigator will then record all relevant AE/SAE information (including event term, start and stop dates, severity, relationship to study treatment, outcome, if serious or non-serious) in the eCRF. Each event must be recorded separately.

It is **not** acceptable for the Investigator to send photocopies of the subject's medical records to [redacted] Safety in lieu of completion of the AE/SAE eCRF page.

There may be instances when copies of medical records for certain cases are requested by [redacted] Safety. In this case, all subject identifiers, with the exception of the subject number, will be redacted on the copies of the medical records before submission to [redacted] Safety.

The Investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity

The Investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to 1 of the following categories:

Mild: An event that is easily tolerated by the subject, causing minimal discomfort and not interfering with everyday activities.

Moderate: An event that causes sufficient discomfort and interferes with normal everyday activities.

Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with a SAE. Severe is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe.

An event is defined as 'serious' when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

Assessment of Causality

The Investigator is obligated to assess the relationship between study treatment and each occurrence of each AE/SAE. The AE must be characterized as unrelated, possibly related, and related.

- "Unrelated": clinical event with an incompatible time relationship to study treatment administration, and that could be explained by an underlying condition or other drugs or chemicals or is incontrovertibly not related to the study treatment.
- "Possibly related": clinical event with a reasonable time relationship to study treatment administration, and that is unlikely to be attributed to concurrent condition or other drugs or chemicals.
- "Related": clinical event with plausible time relationship to study treatment administration and that cannot be explained by concurrent condition or other drugs or chemicals.

The Investigator will use clinical judgment to determine the relationship.

Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study treatment administration will be considered and investigated.

The Investigator will also consult the IB in his/her assessment.

For each AE/SAE, the Investigator must document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.

There may be situations in which an SAE has occurred, and the Investigator has minimal information to include in the initial report to [redacted] Safety. However, it is very important that the Investigator always make an assessment of causality for every event before the initial transmission of the SAE data to [redacted] Safety.

The Investigator may change his/her opinion of causality in light of follow-up information and send a SAE follow-up report with the updated causality assessment.

The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AEs and SAEs

The Investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by [redacted] Safety to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.

If a subject dies during participation in the study, the Investigator will provide [redacted] Safety with a copy of any postmortem findings.

New or updated information will be recorded in the originally completed eCRF.

The Investigator will submit any updated SAE data to the [redacted] Safety within 24 hours of receipt of the information.

Reporting of SAEs

SAE Reporting to [redacted] Safety via an Electronic Data Collection Tool

The primary mechanism for reporting an SAE to [redacted] Safety will be the electronic data collection tool.

If the electronic system is unavailable for more than 24 hours, then the study center will use the paper SAE data collection tool (see next section).

The study center will enter the SAE data into the electronic system as soon as it becomes available.

After the study is completed at a given study center, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data.

If a study center receives a report of a new SAE from a subject or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the study center can report this information on a paper SAE form (see next section) and send the paper SAE form to [redacted] Safety team via facsimile transmission or email.

Contacts for SAE reporting can be found in SAE form.

SAE Reporting to [redacted] Safety via Paper Case Report Form (CRF)

Facsimile transmission of the SAE paper CRF is the preferred method to transmit this information to the [redacted] Safety team.

In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of the SAE data collection tool sent by overnight mail or courier service.

Initial notification via telephone does not replace the need for the Investigator to complete and sign the SAE CRF pages within the designated reporting time frames.

Contacts for SAE reporting can be found in SAE reporting form.

Appendix 5 Excluded Medications/Therapy

Excluded medications/therapy are listed below. The use of an excluded medication/therapy is a protocol violation and must be recorded in the eCRF.

Any therapy likely to have efficacy in PPP or psoriasis is prohibited. If treatment with any of these prohibited medications is essential, then the Investigator must notify the Medical Monitor in order to make a decision as to whether the subject will be withdrawn from the study.

All treatments likely to have efficacy in PPP need to be discontinued prior to treatment initiation (prior to Baseline [Day 1]) with washout periods as stipulated in the table below:

Table 6 List of Excluded Medications

Treatment	Washout period
Topical medication (including corticosteroid, retinoids or vitamin A or D analog preparations, tacrolimus, calcineurin inhibitor, topical H1 and H2 antihistamines, tar preparations, keratolytics, topical antimicrobials, other medicated topical agents) or herbal preparation	2 weeks prior to Baseline
Methotrexate, cyclosporin, acitretin, alitretinoin, fumaric acid esters, and corticosteroids or any other immunosuppressant or immunomodulation drugs	4 weeks prior to Baseline
Anti-TNF/IL-12/IL-23 and IL-17 or any other mAbs	3 month or 5 half-lives (whichever is longer)
Cyclophosphamide	6 months prior to Baseline
Phototherapy (ie, UVB) or photochemotherapy (PUVA)	4 weeks prior to Baseline
Other investigational drugs	30 days or 5 half-lives (whichever is longer) prior to Screening
Live attenuated vaccines	12 weeks prior to Screening
Antibiotic or antiviral	Topical: 2 weeks prior to Baseline Systemic: 4 weeks prior to Baseline

Abbreviations: IL = interleukin; mAb = monoclonal antibody; PUVA = psoralen and ultraviolet A; TNF = tumor necrosis factor; UVB = ultraviolet light B.

Note: Topical bland emollients (without pharmacological active ingredients) for pustular psoriasis are allowed during the study, except within 24 hours prior to the study visits.

All medications listed above are also restricted during the study period. If treatment with any of these prohibited treatments is essential, then the subject must notify the study team.

Appendix 6 Contraceptive Guidance and Collection of Pregnancy Information

Definitions:

Woman of childbearing potential (WOCBP)

A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile (see below).

If fertility is unclear (eg, amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before first dose of study intervention, additional evaluation should be considered.

Women in the following categories are not considered WOCBP

1. Premenarchal
2. Premenopausal female with 1 of the following:
   a) Documented hysterectomy.
   b) Documented bilateral salpingectomy.
   c) Documented bilateral oophorectomy.

   For individuals with permanent infertility due to an alternate medical cause other than the above, (eg, mullerian agenesis, androgen insensitivity), Investigator discretion should be applied to determining study entry.

   Note: Documentation can come from the study center personnel's review of the subject's medical records, medical examination, or medical history interview.
3. Postmenopausal female:
   a) A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.
   b) Females on HRT and whose menopausal status is in doubt will be required to use 1 of the non-estrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

Contraception Guidance

Male subjects

Male subjects with female partners of childbearing potential are eligible to participate if they agree to ONE of the following (during the protocol-defined time frame in Section 5.1):

Are abstinent from penile-vaginal intercourse as their usual and preferred lifestyle (abstinent on a long-term and persistent basis) and agree to remain abstinent.
Agree to use a male condom plus partner use of a contraceptive method with a failure rate of <1% per year when having penile-vaginal intercourse with a WOCBP who is not currently pregnant.

In addition, male subjects must refrain from donating sperm for the duration of the study and for 220 days (which includes the duration of relevant exposure plus the duration of sperm cycle) after the last dose of study treatment.

Male subjects with a pregnant or breastfeeding partner must agree to remain abstinent from penile-vaginal intercourse or use a male condom during each episode of penile penetration for the duration of the study and for 220 days (which includes the duration of relevant exposure plus the duration of sperm cycle) after the last dose of study treatment.

Female subjects

Female subjects of childbearing potential are eligible to participate if they agree to use highly effective methods of contraception consistently and correctly as described in the table below, and refrain from donating oocytes for assisted reproduction during this period.

Highly Effective Contraceptive Methods

Highly Effective Contraceptive Methods That Are User Dependent [a] *Failure rate of <1% per year when used consistently and correctly.*
Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation Oral. Intravaginal. Transdermal.
Progestogen only hormonal contraception associated with inhibition of ovulation Oral. Injectable.
Highly Effective Methods That Are User Independent [a]
Implantable progestogen only hormonal contraception associated with inhibition of ovulation Intrauterine device (IUD). Intrauterine hormone-releasing system (IUS). Bilateral tubal occlusion.
Vasectomized Partner *A vasectomized partner is a highly effective birth control method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.*
Sexual Abstinence *Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatment. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the subject.*
NOTES: [a] Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for subjects participating in clinical studies.

Pregnancy Testing:

Women of childbearing potential should only be included after a confirmed menstrual period and a negative highly sensitive serum pregnancy test at Screening and urine pregnancy test on Day 1 (prior to study treatment administration).

Women of childbearing potential should refrain from donating oocytes for assisted reproduction during this period.

Additional pregnancy testing should be performed as mentioned in the as mentioned in the Schedule of Activities (see Section 1.3).

Pregnancy testing will be performed whenever a menstrual cycle is missed or when pregnancy is otherwise suspected. Positive urine pregnancy test result should be confirmed with serum test.

Collection of Pregnancy Information

Male subjects with partners who become pregnant

The Investigator will attempt to collect pregnancy information on any male subject's female partner who becomes pregnant while the male subject is in this study. This applies only to male subjects who receive study treatment.

After obtaining the necessary signed informed consent from the pregnant female partner directly, the Investigator will record pregnancy information on the appropriate pregnancy form and submit it to the Sponsor within 24 hours of learning of the partner's pregnancy. The female partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to the Sponsor. Generally, the follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any termination of the pregnancy will be reported regardless of fetal status (presence or absence of anomalies) or indication for the procedure.

Female Subjects who become pregnant

The Investigator will collect pregnancy information on any female subject who becomes pregnant while participating in this study. Information will be recorded on the appropriate form and submitted to the Sponsor within 24 hours of learning of a subject's pregnancy. The subject will be followed to determine the outcome of the pregnancy. The Investigator will collect follow-up information on the subject and the neonate, and the information will be forwarded to the Sponsor. Generally, follow-up will not be required for longer than 6 to 8 weeks after the delivery date. Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for the procedure.

While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy will be reported as an AE or SAE. A spontaneous abortion is always considered to be an SAE and will be reported as such.

Any post-study pregnancy related SAE considered reasonably related to the study treatment by the Investigator will be reported to the Sponsor as described in Section 8.3.5. While the Investigator is not obligated to actively seek this information in former subjects, he or she may learn of an SAE through spontaneous reporting.

Any female subject who becomes pregnant while participating in the study will be withdrawn from the study.

Appendix 7 Palmoplantar Pustulosis Psoriasis Area Severity Index

Score	0	1	2	3	4	5	6
Erythema (E)	None	Slight	Moderate	Severe	Very severe		
Pustules (P) (total)	None	Slight	Moderate	Severe	Very severe		
Desquamation (D) (scaling)	None	Slight	Moderate	Severe	Very severe		
Area affected (%)[1]	0	>0<10	10<30	30<50	50<70	70<90	90-100

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

[1] where area assessed is glabrous skin on the palms/soles

Adapted from Psoriasis Area Severity Index (PASI) by Bhushan et al for a RCT evaluating lizarole in palmoplantar psoriasis.

Bhushan M, et al. Oral liarozole in the treatment of palmoplantar pustular psoriasis: a randomized, double-blind, placebo-controlled study. British Journal of Dermatology. 2001;145(4):546-53.

Appendix 8 Palmoplantar Pustulosis Severity Index

The PPSI assesses the severity of PPP lesions and their response to therapy with score that ranges from 0 to 12.

In the PPSI, the most severely affected location (palms or soles) will be identified as the evaluation sites at Screening.

The identified site will be assessed at all subsequent visits.

Evaluation sites will be assessed separately for erythema, pustules/vesicle, and desquamation/scale, and each will be rated for the more severely affected location (palms or soles) on a scale of 0 to 4.

The severity of the disease is calculated as follows:

The scoring for the signs of the disease (erythema, pustules/vesicle, and desquamation/scale) is:

0 = none, 1 = minimal, 2 = mild, 3 = moderate, and 4 = severe.

The PPSI formula is: PPSI total score= (E + P + D)

Where E = erythema, P = pustular/vesicle, and D = desquamation/scale.

Appendix 9 Palmoplantar Pustulosis (Static) Investigator's Global Assessment

Score	Wording	Detailed description
0	Clear	No signs of palmoplantar pustulosis; no scaling or crusts or pustules remain
1	Almost clear	Slight scaling and/or erythema and/or slight crusts; very few (yellow) and/or old (brown) pustules
2	Mild	Scaling and/or erythema and/or crusts; visible new (yellow) and/or old (brown) pustules of limited number and extent
3	Moderate	Prominent scaling and/or erythema and/or crusting; prominent new (yellow) and/or old (brown) pustules covering most of the area involved
4	Severe	Severe scaling and/or erythema and/or crusting; numerous new (yellow) and/or old (brown) pustules with / without major confluence, covering the entire area of at least 2 palmoplantar sites

Appendix 10 Psoriasis Area Severity Index Score

Plaque Characteristic	Lesion Score	Head	Upper Limbs	Trunk	Lower Limbs
Erythema	0 = None 1 = Slight 2 = Moderate 3 = Severe 4 = Very severe				
Induration/Thickness					
Scaling					
Add together each of the 3 scores for each body region to give 4 separate sums (A).					
Lesion Score Sum (A)					
Percentage Area	**Area Score**	**Head**	**Upper Limbs**	**Trunk**	**Lower Limbs**
Area Score (B) *Degree of involvement as a percentage for each body region affected (score each region with score between 0-6)*	0 = 0% 1 = 1% - 9% 2 = 10% - 29% 3 = 30% - 49% 4 = 50% - 69% 5 = 70% - 89% 6 = 90% - 100%				
Multiply Lesion Score Sum (A) by Area Score (B), for each body region, to give 4 individual subtotals (C).					
Subtotals (C)					
Multiply each of the Subtotals (C) by amount of body surface area represented by that region, i.e. x 0.1 for head, x 0.2 for upper body, x 0.3 for trunk, and x 0.4 for lower limbs.					
Body Surface Area		**x 0.1**	**x 0.2**	**x 0.3**	**x 0.4**
Totals (D)					
Add together each of the scores for each body region to give the final PASI Score.					

PASI Score = ☐

Fredriksson T, Pettersson U. Severe psoriasis-oral therapy with a new retinoid. 1978;157(4):238-44.

Appendix 11 Dermatology Life Quality Index

The aim of this questionnaire is to measure how much your skin problem has affected your life OVER THE LAST WEEK. Please tick one box for each question.

1. Over the last week, how **itchy**, **sore**, **painful** or **stinging** has your skin been?

   ❑ Very much ❑ A lot ❑ A little ❑ Not at all

2. Over the last week, how **embarrassed** or **self-conscious** have you been because of your skin?

   ❑ Very much ❑ A lot ❑ A little ❑ Not at all

3. Over the last week, how much has your skin interfered with you going **shopping** or looking after your **home** or **garden**?

   ❑ Very much ❑ A lot ❑ A little ❑ Not at all ❑ Not relevant

4. Over the last week, how much has your skin influenced the **clothes** you wear?

   ❑ Very much ❑ A lot ❑ A little ❑ Not at all ❑ Not relevant

5. Over the last week, how much has your skin affected any **social** or **leisure** activities?

   ❑ Very much ❑ A lot ❑ A little ❑ Not at all ❑ Not relevant

6. Over the last week, how much has your skin made it difficult to do any sport?

   ❑ Very much ❑ A lot ❑ A little ❑ Not at all ❑ Not relevant

7. Over the last week, has your skin prevented you from **working** or **studying**?

   ❑ Yes ❑ No ❑ Not relevant

   If "No", over the last week, how much has your skin been a problem at **work** or **studying**?

   ❑ A lot ❑ A little ❑ Not at all

8. Over the last week, how much has your skin created problems with your **partner** or any of your **close friends** or **relatives**?

   ❑ Very much ❑ A lot ❑ A little ❑ Not at all ❑ Not relevant

9. Over the last week, how much has your skin caused **sexual difficulties**?

   ❑ Very much ❑ A lot ❑ A little ❑ Not at all ❑ Not relevant

10. Over the last week, how much of a problem has the **treatment** for your skin been, for example by making your home messy, or by taking up time?

    ❑ Very much ❑ A lot ❑ A little ❑ Not at all ❑ Not relevant

Finlay AY, Kahn GK. Dermatology Life Quality Index (DLQI): A simple practical measure for routine clinical use. Clinical and Experimental Dermatology 1994;19: 210-216.

Appendix 12 Palmoplantar Pustulosis Quality of Life Instrument

Palmoplantar quality of life instrument

Hands*	**No difficulty**	**Mild difficulty**	**Moderate difficulty**	**Severe difficulty**	**Totally unable**
Open tight/new jar	1	2	3	4	5
Heavy household chores	1	2	3	4	5
Carry shopping bag/briefcase	1	2	3	4	5
Use knife to cut food	1	2	3	4	5
Make a bed	1	2	3	4	5
Write	1	2	3	4	5
Wash/blow-dry hair	1	2	3	4	5
Recreational activities (eg, golf, tennis, knitting)	1	2	3	4	5
During the past month, did your hands:	Not at all	Slightly	Moderately	Quite a bit	Extremely
Interfere with normal social activities?	1	2	3	4	5
Limit work/regular activities?	1	2	3	4	5
During the past month:	None	Mild	Moderate	Severe	Extreme
Hand pain	1	2	3	4	5
Hand burning/itching	1	2	3	4	5
Difficulty sleeping because of discomfort/pain in hands	1	2	3	4	5
I feel:	Strongly disagree	Disagree	Neither agree nor disagree	Agree	Strongly agree
Embarrassed about my hands/will avoid handshakes and/or caressing	1	2	3	4	5
Less capable/confident/useful because of my hand problem	1	2	3	4	5

Feet**	**No difficulty**	**Mild difficulty**	**Moderate difficulty**	**Severe difficulty**	**Totally unable**
Walking	1	2	3	4	5
Fast walking/running	1	2	3	4	5
Climbing stairs	1	2	3	4	5
Socks/stockings on/off	1	2	3	4	5
Pain level last month for:	None	Mild	Moderate	Severe	Could not do
Walking	1	2	3	4	5
Fast walking/running	1	2	3	4	5
Climbing stairs	1	2	3	4	5
Standing barefoot	1	2	3	4	5
Standing wearing shoes	1	2	3	4	5

Activity Limitation

How often have you avoided pedicures/other activities that expose your feet, due to embarrassment?
1: Not at all, 2: Rarely, 3: Sometimes, 4: Frequently, 5: All the time

How much did your feet interfere with normal work, including work outside the home and housework?
1: Not at all, 2: Rarely, 3: Sometimes, 4: Frequently, 5: All the time

How much did your feet interfere with your life and ability to do what you want?
1: Not at all, 2: Rarely, 3: Sometimes, 4: Frequently, 5: All the time

How much of the time did you use cane/crutches/walker to get around?
1: Not at all, 2: Rarely, 3: Sometimes, 4: Frequently, 5: All the time

How much of the time did you stay indoors most of the day due to foot problems?
1: Not at all, 2: Rarely, 3: Sometimes, 4: Frequently, 5: All the time

* Questions addressing hand functionality, pain, and social impact.
** Questions oriented at foot functionality, pain, and physical limitations secondary to foot disease.

Farley E, Masrour S, McKey J, Menter A. Palmoplantar psoriasis: a phenotypical and clinical review with introduction of a new quality-of-life assessment tool. *J Am Acad Dermatol*. 2009 Jun;60(6):1024-31.

Appendix 13 Patient Assessment of Palmoplantar Pustulosis Disease Activity

Considering all the ways your psoriasis affects you, on average, how have you been doing in the past week?