TITLE PAGE

Protocol Title: **A Single Arm Multiple Dose Study to Assess the Efficacy and Safety of ANB019 in Subjects with Generalized Pustular Psoriasis**

Protocol Number: **ANB019-002**

Product: **ANB019**

Study Phase: **2a**

Sponsor Name: **AnaptysBio Inc**.

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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.

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AnaptysBio

[redacted]

Date

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Name	**Date**
Title	

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1.0 PROTOCOL SUMMARY

1.1 Synopsis

Protocol Title: A Single Arm Multiple Dose Study to Assess the Efficacy and Safety of ANB019 in Subjects with Generalized Pustular Psoriasis

Rationale:

This study is designed to evaluate the efficacy and safety of multiple doses of ANB019 in subjects with generalized pustular psoriasis (GPP). Generalized pustular psoriasis is a severe, debilitating, and life-threatening systemic inflammatory disease (Marrakchi 2011, Benjegerdes 2016). The interleukin-36 (IL-36) pathway, by promoting inflammatory responses, has been shown to play a key role in pathogenesis of GPP.

In individuals with a normal IL-36/interleukin-36 receptor (IL-36R) axis, the action of the IL-36 cytokines is counter-balanced by IL-36Ra, an IL-36 receptor antagonist. This natural antagonist reduces excessive IL-36 response by blocking the binding of IL-36 agonist ligands to the IL-36R.

Several studies have identified IL-36RN mutations, the gene coding for IL-36Ra, in a subset of GPP patients (Marrakchi 2011; Onoufriadis 2011; Sugiura 2012; Capon 2013, Navarini 2017). These mutations disrupt the inhibitory function of IL-36Ra, leading to uncontrolled IL-36R activation. Other genetic defects have also been associated with GPP, including mutations in the *AP1S3* and *CARD14 genes* (Mahil 2016; Jordan 2012; Farooq 2013). Regardless of the presence of known mutations, activation of IL-36 pathway has been associated with sustained inflammatory response in GPP suggesting a key role of IL-36 in inflammatory skin diseases.

Currently, there is no approved and registered marketed therapy for GPP. Present treatment options are limited to existing plaque psoriasis and systemic immunomodulatory therapies, which have limited efficacy in GPP (Benjegerdes 2016). The investigational product, ANB019, is a monoclonal antibody (mAb) that specifically binds to 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 the IL-36 pathway in patients with GPP. The information obtained from this study may provide important insights into potential new treatment options for GPP.

Objectives and Endpoints:

Objectives	Endpoints
Primary	
• To evaluate the efficacy of ANB019 in subjects with active GPP as measured by the Clinical Global Impression (CGI) scale according to the modified Japanese Dermatology Association (JDA) severity index total score	• Proportion of subjects achieving clinical response at Week 4 and Week 16. Clinical response is defined as "Very much improved," "Much improved," and "Minimally improved" on CGI scale according to modified JDA severity index total score
• To assess the safety and tolerability of ANB019 in subjects with GPP	• Assessment of adverse events (AEs) • Potentially significant and clinically important AEs, adverse event of special interest (AESI), 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)
Secondary	
• To evaluate the effect of ANB019 on the total and individual skin lesion symptoms as measured by the modified JDA severity index score	• Change in modified JDA severity index total skin lesions score (sum of erythema, erythema with pustules, edema) at all study visits • Change in affected body surface area (BSA) of erythema with pustules, erythema, and edema as measured by modified JDA severity index at all study visits
• To evaluate the effect of ANB019 on total and individual components of systemic manifestations and laboratory findings as measured by modified JDA severity index score	• Change in total and individual scores in systemic manifestations and laboratory findings as measured by modified JDA severity index at all study visits
• To evaluate the effect of ANB019 on GPP using the Generalized Pustular Psoriasis Physician's Global Assessment (GPPPGA)	• Proportion of subjects achieving a GPPPGA score of 0 or 1 at all study visits • Change from Baseline in GPPPGA scores at all study visits
• To determine any treatment effect of ANB019 in plaque psoriasis (if present) as measured by Psoriasis Area Severity Index (PASI)	• Change in PASI score to evaluate a subject's overall plaque psoriasis disease state, if present, at all study visits
• To assess the effect of ANB019 on the subject's quality of life	• Change in Dermatology Life Quality Index (DLQI) total score at all study visits

• To determine the pharmacokinetics (PK) of ANB019 in GPP subjects	• Serum concentration following ANB019 administration. Following first dose administration of ANB019 these parameters will be determined: • Maximum observed concentration (C_{max}), time to maximum observed concentration (T_{max}), area under the concentration-time curve (AUC) and other parameters as appropriate
• To test for immunogenicity to ANB019	• Presence of anti-drug antibodies (ADA)
Exploratory	
• To explore the effects of ANB019 on skin biopsy biomarkers	• Skin biopsies biomarkers (including but not limited to IL-17, IL-23, IL-8, dendritic cells, epidermal thickness, and leukocytes infiltration)
• To assess the effect of ANB019 on inflammatory parameters such as serum cytokines including but not limited to IL-8	• Changes in serum cytokines as compared to baseline at Weeks 1, 4, 8, 12, 16, and 24
• Provide photographic documentation of lesions	• Photographic documentation of lesions
• To explore GPP-associated mutations and additional pharmacogenomic analysis	• Optional genetic testing (deoxyribonucleic acid [DNA] and messenger ribonucleic acid [mRNA])

Overall Design:

This is an open-label, single arm, multiple dose study aiming to assess the clinical efficacy, safety and tolerability, and PK of multiple doses of ANB019 in subjects with GPP.

The screening period will be up to 42 days (6 weeks) prior to administration of study drug on Day 1.

On Day 1, subjects who meet the entry criteria will receive a 750 mg intravenous (IV) dose of ANB019 in an open-label manner followed by 3 doses of 100 mg administered subcutaneously (SC) on Days 29, 57, and 85. The subjects will leave the study center after completing the 5 hours postdose assessments following IV administration and the 3 hours postdose assessments after the first and second SC injections and with the Investigator's approval. Subjects with any ongoing AEs or SAEs at the time of scheduled discharge from the study center should remain at the study center until the Investigator has determined that these events have been resolved or deemed as not clinically significant.

The subjects will return to the study center for follow-up visits on Day 3 and Day 8, weekly from Day 8 to Day 29, and then every other week up to Day 85, and monthly for 12 weeks to monitor changes in disease activity, safety, and tolerability. In addition, the subjects will be contacted via phone by study staff to assess for safety (eg, AEs and changes in concomitant medications) on Days 36, 50, 64, and 78.

Subjects who are nonresponders will be early terminated 4 weeks after the 750 mg IV dose administration. Refer to Section 4.1 for the definition of a nonresponder.

Subject's disease activity (response to study treatment) will be evaluated using the CGI, JDA, GPPPGA scale, total BSA, DLQI, and PASI (if plaque psoriasis is present) (Oji 2015; Navarini 2017).

Serum samples for PK and immunogenicity will be collected prior to administration of ANB019 and at the other time points specified in the Schedule of Activities (see Section 1.3). In addition, blood samples for genetic analysis and a punch biopsy will also be taken during the study. All subjects enrolled in the study will be asked to participate in the skin biopsy and/or genetic analysis; however, subject participation is optional.

Safety assessments including AE/SAE monitoring, vital signs, physical examination, ECGs, laboratory measurements, and urine assessments will be performed during the study period.

The End of Study (EOS) Visit will be on Day 169 and all subjects will return to the study center for the EOS procedures (see Section 1.3).

Number of Investigators and Study Centers:

Approximately 8-10 Investigators and 8-10 study centers are expected to participate in this study.

Number of Subjects:

The sample size is not based on statistical power considerations.

Approximately 10 subjects will be enrolled at 8-10 study centers.

Treatment Groups and Duration:

The study will have a screening period of up to 42 days (6 weeks), treatment period of 12 weeks, and follow-up period of 12 weeks.

Eligible subjects will receive 750 mg IV (1-hour duration) of ANB019 in an open-label manner in polyvinyl chloride or polyolefin bags following dilution to a total volume of 100 mL with 0.9% sodium chloride followed by 3 doses of 100 mg SC administered on Days 29, 57, and 85.

Statistical Methods:

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

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

Frequency and percentages for each response Yes/No will be presented separately by visit. A shift table of change from Baseline to EOS will be displayed for each score.

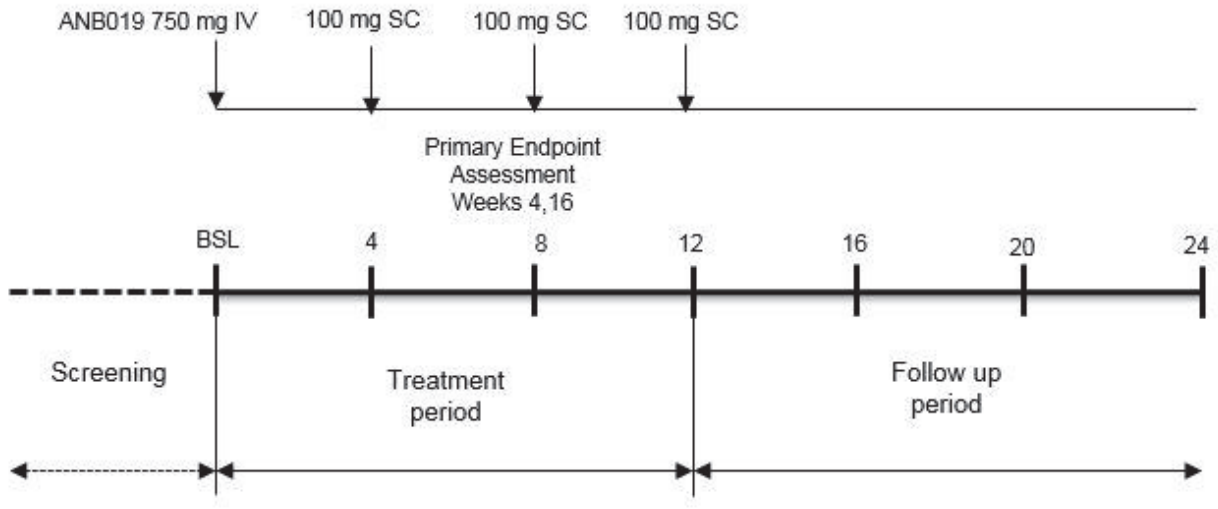
For safety and tolerability, AEs, SAEs, vital signs, physical examinations, and laboratory assessments at specific time points will be evaluated. All safety data will be summarized descriptively. Number and percentage of AEs will be presented for each treatment by preferred term and system organ class of the current Medical Dictionary for Regulatory Authorities (MedDRA) dictionary. Individual listings of all SAEs and AEs leading to discontinuation from the study drug will be summarized using the current MedDRA dictionary. Similar analyses will be performed for potential significance and clinical importance of AEs.

Summaries and listings of data for vital signs, hematology, biochemistry, and urinalysis laboratory tests 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 assessment before ANB019 dosing.

The PK of ANB019 will be evaluated by assessment of drug concentrations in serum. These drug concentrations will be listed and summarized for each sampling time point using appropriate descriptive statistics. The PK parameters will be summarized using appropriate descriptive statistics. Attainment of steady state will be graphically evaluated over the sampling period for the IV/SC treatment regimen.

An interim analysis will be performed when approximately 50% of subjects have completed their Week 4 visit or when at least 2 subjects have reached 16 weeks postdosing. The interim analysis will assess primary efficacy and all safety data.

1.2 Study Schema



Abbreviations: BSL = baseline; IV = intravenous, SC = subcutaneous.

1.3 Schedule of Activities

	Screening Period	Treatment Period														Follow-up Period		
Procedure	**(up to -42 days prior to D1/W-0)**	**D1 W0**	**D3 W1**	**D8 W1**	**D15** (±1) **W2**	**D22** (±1) **W3**	**D29** (±2) **W4**	**D36** (±2) **W5[a]**	**D43** (±2) **W6**	**D50** (±2) **W7[a]**	**D57** (±2) **W8**	**D64** (±2) **W9[a]**	**D71** (±2) **W10**	**D78** (±2) **W11[a]**	**D85** (±2) **W12**	**D113** (±2) **W16**	**D141** (±2) **W20**	**D169** (±2) **W24/EOS/ ET[b]**
Informed consent	X																	
Inclusion/exclusion criteria	X	X																
Medical history and prior medications	X																	
Height[c] and weight	X																	X
CGI[j]			X	X	X	X	X		X		X		X		X	X	X	X
Modified JDA, DLQI[d,n]	X	X	X	X	X	X	X		X		X		X		X	X	X	X
GPPPGA[d]	X	X	X	X	X	X	X		X		X		X		X	X	X	X
PASI if plaque psoriasis is present[d,n]	X	X	X	X	X	X	X		X		X		X		X	X	X	X
Serum cytokines[l]		X	X	X			X				X				X	X		X
Complete physical examination[e,l]	X	X					X				X				X	X		X
12-lead electrocardiogram[f]	X	X					X									X		X
Vital signs[g]	X	X	X	X	X	X	X		X		X		X		X	X	X	X
Safety laboratory testing[h,l]	X	X	X	X	X	X	X		X		X		X		X	X	X	X
Quantiferon®-TB Gold Test[h,l]	X																	
Virology[h,l]	X																	
Chest x-ray[n]	X																	
Urinalysis[h,l]	X	X					X				X				X	X		X

	Screening Period	Treatment Period														Follow-up Period		
Procedure	**(up to -42 days prior to D1/W-0)**	**D1 W0**	**D 3 W1**	**D8 W1**	**D15** (±1) **W2**	**D22** (±1) **W3**	**D29** (±2) **W4**	**D36** (±2) **W5[a]**	**D43** (±2) **W6**	**D50** (±2) **W7[a]**	**D57** (±2) **W8**	**D64** (±2) **W9[a]**	**D71** (±2) **W10**	**D78** (±2) **W11[a]**	**D85** (±2) **W12**	**D113** (±2) **W16**	**D141** (±2) **W20**	**D169** (±2) **W24/EOS /ET[b]**
Serum pregnancy test[h]	X																	X
Urine pregnancy test (WOCBP only)[h]		X					X				X				X	X	X	
FSH (postmenopausal woman aged over 45 years with at least 1 year of amenorrhea only)[h]	X																	
Samples for PK[j,l]		X	X	X	X	X	X		X		X		X		X	X	X	X
Skin biopsies[k]		X														X		
Photography		X					X									X		
Whole blood for DNA sampling[m]		X[j,k]																
Whole blood for mRNA sampling[m]		X[j,k]														X[k]		
Blood collection for ADA[n]		X					X				X				X			X
Telephone contact only								X		X		X		X				
ANB019 administration[o]		X					X				X				X			
AEs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medication	X[o]	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; CGI = Clinical Global Impression; D = day; DLQI = Dermatology Life Quality Index; ECG = electrocardiogram; EOS = end of study; ET = early termination, FSH = follicle stimulating hormone; ICF = Informed consent form; PASI = Psoriasis Area Severity Index; JDA = Japanese Dermatology Association; PK = pharmacokinetics; QoL = Quality of Life; SAE = serious adverse event; TB = tuberculosis; W = week; WOCBP = Woman of childbearing potential.

a. At Days 36, 50, 64, and 78, subjects will be contacted by phone for safety follow-up to assess for AEs and concomitant medications.
b. In case of early discontinuation, the subject will be encouraged to return to the study center for the ET/EOS visit (Week 24/Day 169).
c. Height to be measured at Screening only.
d. Refer to Section 8.1 for details and instructions regarding CGI, JDA, PASI, total BSA as measured by modified JDA, GPPPGA, and QoL questionnaire (DLQI). The QoL questionnaire should be the first assessment 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 prior to QoL questionnaire and other study related assessments.
e. Refer to Section 8.2.1 for details regarding complete physical examination. A complete physical examination will include assessments of general appearance; skin; head/neck; pulmonary, cardiovascular, gastrointestinal, external genitourinary, lymphatic, and musculoskeletal system; extremities; eyes (inspection and vision control); nose; throat; and neurologic status.
f. Refer to Section 8.2.5 for details and instructions regarding ECG. In addition to the time points specified in SoA, ECGs may be performed at any time during the study if in the opinion of the Investigator it is clinically warranted.
g. Vital signs assessment includes body temperature, pulse rate, blood pressure, and respiratory rate. Refer to Section 8.2.4 for details and instructions.
h. Refer to Appendix 3 for details and instructions regarding clinical laboratory parameters and refer to Appendix 6 for the WOCBP definition.
i. Bidirectional posterioanterior view and lateral view chest x-ray or as indicated by local treatment guidelines or practice will be performed at Screening, A chest x-ray is not required if performed within 6 months of Screening.
j. Refer to Section 8.5 and Table 2 for complete information on sample collection and time points.
k. Skin biopsies may be performed at other visits as appropriate. All subjects enrolled will be asked to participate in the skin biopsy test and/or genetic analysis; however, the subject's participation is optional. Subjects should provide their consent to participate in skin biopsy and genetic analysis. Punch biopsy will be collected on Day 1 (Normal and Psoriatic skin) and Week 16 (psoriatic skin only).
l. Samples must be collected before study drug administration on Day 1.
m. Optional whole blood collection for DNA and mRNA requires separate pharmacogenetic informed consent form (ICF).
n. On Days 1, 29, 57, and 85, all assessments should be performed prior to study treatment administration except for the postdose PK samples on Day 1 (Table 2). The specific order for performing the study procedures is as follows (applicable to all visits): First QoL questionnaires then the efficacy assessments, vital signs, physical examination, ECG, and blood sample collection.
o. Subjects will remain in the study center for approximately 5 hours for the postdose assessments after IV administration and the 3 hours postdose assessments after the first and second SC injections and will be discharged as per the Investigator's judgment.

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2.0 INTRODUCTION

ANB019 is a high affinity humanized IgG4 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 pro-inflammatory responses. IL-36 signaling is counter balanced by IL-36Ra, an IL-36 receptor antagonist that binds to IL-36R and competes with activity of IL-36 cytokines. Mutations in the gene encoding the IL-36Ra (*IL-36RN*) result in uncontrolled activation of the IL-36 pathway leading to the development of generalized pustular psoriasis (GPP), a severe and life-threatening disease (Marrakchi 2011, Benjegerdes 2016). As such, 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 the IL-36 pathway activation. ANB019 is being developed as a potential first-in-class therapy for GPP, palmoplantar pustular psoriasis (PPP), and other inflammatory diseases where the IL-36 pathway might play a pathogenic role.

2.1 Study Rationale

This study is designed to evaluate the efficacy and safety of multiple doses of ANB019 in subjects with GPP. Generalized pustular psoriasis is a severe, debilitating, and life-threatening systemic inflammatory disease (Marrakchi 2011, Benjegerdes 2016). Skin lesions manifest with widespread sterile pustules on erythematous skin over large BSAs. Skin rash is accompanied by high fever, general malaise, leukocytosis, elevated C-reactive protein (CRP), and frequently includes functional extracutaneous organ involvement that might lead to mortality (Marrakchi 2011). The IL-36 is associated with acute and chronic inflammation and has been shown to play a key role in pathogenesis of GPP. Several studies have identified GPP-associated *IL-36RN* in a subset of GPP patients (Marrakchi 2011; Onoufriadis 2011; Sugiura 2012; Capon 2013, Navarini 2017). These mutations disrupt the inhibitory function of IL-36Ra, leading to uncontrolled IL-36R activation. Other genetic defects have also been associated with GPP, including mutations in the *AP1S3* and *CARD14* genes (Mahil 2016; Jordan 2012; Farooq 2013). Regardless of mutations, activation of the IL-36 pathway has been associated with a sustained inflammatory response in pustular psoriasis suggesting a key role of IL-36 in inflammatory skin diseases. Currently there is no approved therapy for GPP. Treatment options are limited to existing plaque psoriasis (PP) and systemic immunomodulatory therapies, which have limited and inconsistent efficacy (Benjegerdes 2016). ANB019 is an 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 pathway in patients with pustular psoriasis. The information obtained from this study is considered important for future clinical practice as it may provide important insights into potential new treatment options for GPP.

2.2 Background

Generalized pustular psoriasis is a severe inflammatory skin disease characterized by the presence of widespread pustules covering almost the entire body along with systemic inflammatory manifestations, such as fever, leukocytosis, and elevated CRP.

Generalized pustular psoriasis is a rare disease in the US, and although the exact prevalence has not been fully estimated, it is considered to affect only a few thousand individuals. The prevalence of GPP has been studied in Japan and France and reported as approximately 7.46 and 1.76 cases per million of the population, respectively (Ohkawara 1996; Augey 2006). Although GPP has been associated with psoriasis, it is considered as a distinct disease entity based on different pathological pathways. Several studies have identified GPP-associated *IL-36RN* mutations in a subset of GPP patients (Marrakchi 2011; Onoufriadis 2011; Sugiura 2012; Capon 2013, Navarini 2017). These mutations disrupt the inhibitory function of IL-36Ra, leading to uncontrolled IL-36R activation. While a significant proportion of GPP cases are associated with deficiency of IL-36Ra, also known as DITRA, approximately 51% to 84% of patients reported no mutation of the *IL-36RN*. Other genetic defects have also been associated with GPP, including mutations in the *AP1S3* and *CARD14* genes (Mahil 2016; Jordan 2012; Ohkawara 1996). Regardless of the presence of known mutations, activation of IL-36 pathway has been associated with sustained inflammatory response in GPP suggesting a key role of IL-36 in inflammatory skin diseases.

There is no effective and approved treatment for GPP. Recurrent flares are common, even years after diagnosis (Benjegerdes 2016, Oji 2015, Navarini 2017). Patients often require continued systemic immunomodulatory therapy causing significant and severe AEs. Therefore, inhibition of IL-36 by targeting the IL-36R with ANB019 will control excessive activation of the IL-36 pathway and potentially offer a novel and effective treatment for patients with GPP.

2.2.1 Nonclinical Studies

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

- ANB019 shows reactivity with human and cynomolgus monkey IL-36R (dissociation constant [redacted]), 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 interleukin-8 (IL-8).
- The observed serum half-life of ANB019 in cynomolgus monkeys was 304 hours after single IV dose administration, and 310 hours after single SC dose administration at 10 mg/kg, with

bioavailability approximately 76% consistent with the anticipated PK characteristics for a human IgG4 scaffold mAb in the monkey.

- Repeat-dose, Good Laboratory Practice toxicity and toxicokinetic studies of 4 and 13 weeks in duration have been conducted with ANB019 administered by weekly SC and IV injection to 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 (Augey 2006). These studies established a no observed adverse effect level for males at 60 mg/kg/dose administered IV and for females at 60 mg/kg/dose administered SC after 13 weeks of dosing.

2.2.2 Clinical Studies

ANB019-001, a first in human Phase I study in healthy subjects and subjects with psoriasis has been conducted (ANB019-001 2018).

The Single Ascending Dose (SAD) part of the study enrolled 48 healthy adults and has been completed. Six dose levels were administered to 8 subjects in each cohort: 10 mg, 40 mg, 100 mg, 300 mg, and 750 mg by IV injection and 100 mg by SC injection. After single dose administration, ANB019 was generally well tolerated in male and female healthy adults 18-43 years old. Overall, 40 subjects (83%) experienced at least one treatment-emergent adverse event (TEAE). The percentage of subjects who experienced at least 1 TEAE was similar across treatment groups: 29 subjects, 81% in ANB019 group and 11 subjects, 92% in placebo. The most commonly reported AEs were upper respiratory tract infection (URTI) (28% ANB019, 50% placebo), headache (28% ANB019, 25% placebo), viral URTI (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), and catheter site pain (6% ANB019, 0% placebo). All other SAEs occurred as single events. The majority of TEAEs were mild (73%) and moderate (26%) in severity with exception of 1 severe AE of elevated creatine kinase deemed unrelated to study treatment. No subject discontinued the study due to AE. There were no 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.

One subject with PP was enrolled and completed the study as per protocol. This subject received a single dose of 750 mg by IV injection. The PP cohort was removed from the study and no further subjects were enrolled. No TEAEs were reported for the subject with PP in the SAD part of the study.

The Multiple Ascending Dose (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 Day1, 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] following a single maximum dose of [redacted] following a single [redacted] 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 597 hours after SC injection and between [redacted] after IV injection.

2.3 Benefit/Risk Assessment

Subjects with GPP may or may not receive direct benefit from participating in this study. Details about specific benefits and risks for participants in this clinical trial can be found in the Investigator's Brochure (IB) and ICF.

The safety profile of ANB019 in humans is limited.

ANB019 was well tolerated in healthy male and female adults, and in 1 subject with PP, in first in human Phase I study (Australian Study ANB019-001) when administered as single or multiple doses, up to 100 mg by SC and 750 mg by IV injection. Overall summaries of TEAEs by severity and relationship showed no marked differences between treatments (ANB019 versus

placebo) and no apparent dose-related trends in subjects following ANB019 administration. Commonly occurring TEAEs of headache and upper respiratory tract infection occurred in both the SAD and MAD parts of the study. There were no death or serious adverse events (SAEs) and no subjects withdrawn due to TEAEs.

There has been 1 SAE of sepsis reported in the ongoing ANB019-002 study 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, non-adverse, injection site reactions associated with the SC route of administration.

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 dose-related. The increase in protozoa in the stomach has been observed in monkeys treated with immune-modulating drugs (Augey 2006) 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 are clinically monitorable 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 the moribund nature was not determined and had an uncertain relationship to ANB019 but could be due to treatment-related immune-modulation. However, data published on IL-36 R deficient humans shows no deleterious effect on general health and normal immune function broadly preserved, indicating that inhibition of IL-36 R, apart from disease modification, does not compromise host defenses. Similar to other immune-modulating treatment paradigms, subjects should be closely monitored for any gastrointestinal clinical manifestations including infections and evaluated on 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 study drug administration. Subjects with true allergic/anaphylactic reactions should not receive further doses of the product.

As ANB019 is an 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 signs and 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 evaluate the efficacy of ANB019 in subjects with active GPP as measured by the Clinical Global Impression (CGI) scale according to the modified Japanese Dermatology Association (JDA) severity index total score	• Proportion of subjects achieving clinical response at Week 4 and Week 16. Clinical response is defined as "Very much improved," "Much improved," and "Minimally improved" on CGI scale according to modified JDA severity index total score
• To assess the safety and tolerability of ANB019 in subjects with GPP	• 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)
Secondary	
• To evaluate the effect of ANB019 on the total and individual skin lesion symptoms as measured by the modified JDA severity index score	• Change in modified JDA severity index total skin lesions score (sum of erythema, erythema with pustules, edema) at all study visits • Change in affected BSA of erythema with pustules, erythema, and edema as measured by modified JDA severity index at all study visits
• To evaluate the effect of ANB019 on total and individual components of systemic manifestations and laboratory findings as measured by modified JDA severity index score	• Change in total and individual scores in systemic manifestations and laboratory findings as measured by modified JDA severity index at all study visits
• To evaluate the effect of ANB019 on GPP using the GPPPGA	• Proportion of subjects achieving a GPPPGA score of 0 or 1 at all study visits • Change from Baseline in GPPPGA scores at all study visits

• To determine any treatment effect of ANB019 in PP (if present) as measured Psoriasis Area Severity Index (PASI)	• Change in PASI score to evaluate a subject's overall PP disease state if present at all study visits
• To assess the effect of ANB019 on the subject's quality of life	• Change in Dermatology Life Quality Index (DLQI) total score at all study visits
• To determine the PK of ANB019 in GPP subjects	• Serum concentration following ANB019 administration Following first dose administration of ANB019 these parameters will be determined: • C_{max}, T_{max}, AUC, and other parameters as appropriate
• To test for immunogenicity to ANB019	• Presence of ADA
Exploratory	
• To explore the effects of ANB019 on skin biopsy biomarkers	• Skin biopsies biomarkers (including but not limited to IL-17, IL-22, IL-8, dendritic cells, epidermal thickness, and leukocytes infiltration)
• To assess the effect of ANB019 on inflammatory parameters such as serum cytokines including but not limited to IL-8	• Change in serum cytokines as compared to baseline at Weeks 1, 4, 8, 12, 16, and 24
• Provide photographic documentation of lesions	• Photographic documentation of lesions
• To explore GPP-associated mutations and additional pharmacogenomic analysis	• Optional genetic testing (DNA and mRNA)

4.0 STUDY DESIGN

4.1 Overall Design

This is an open-label, single arm, multiple dose study to assess the clinical efficacy, as well as the safety, tolerability, and PK of multiple doses of ANB019 in subjects with GPP.

The screening period will be up to 42 days (6 weeks) prior to administration of study drug on Day 1. Written informed consent will be obtained from each subject prior to initiating any study related procedures. All screening procedures will be conducted in accordance with the Schedule of Activities (see Section 1.3).

On Day 1, subjects who meet the entry criteria will receive a 750 mg IV dose of ANB019 in an open-label manner followed by 3 doses of 100 mg SC administered on Days 29, 57, and 85. Subjects will leave the study center after completion of the 5 hours postdose assessments following IV administration and the 3 hours postdose assessments after the first and second SC injections and with the Investigator's approval. Subjects with any ongoing AEs or SAEs at the time of scheduled discharge from 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.

After completing Day 1 assessments, the subjects will return to the study center for follow-up visits on Days 3, 8, weekly from Day 8 to Day 29, and every other week up to Day 85, and monthly for 12 weeks to monitor changes in disease activity, safety, and tolerability. In addition, subjects will be contacted via phone by study staff to assess for safety (eg, AEs and changes in concomitant medications) on Days 36, 50, 64, and 78.

Subjects who are nonresponders will be early terminated 4 weeks after the 750 mg IV dose administration. A nonresponder is defined as:

- "No change" on CGI: 0 points change in JDA total score and not meeting "other criteria" for minimally improved.
- "Worsened" based on CGI: ≥1-point increase in JDA total score.

Disease activity (response to study treatment) will be evaluated using the CGI scale according to the modified JDA severity index, change in total BSA as measured by modified JDA index affected by GPP, systemic manifestations and laboratory findings as per modified JDA severity index, GPPPGA scale, and PASI score (if PP is present). In addition, change in serum cytokines (including but not limited to IL-8) will be recorded. Quality of life (QoL) will be assessed using the DLQI.

Serum samples for 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). Refer to Table 2 for additional information on sample collection and time points. All subjects

enrolled in the study will be asked to participate in the skin biopsy and/or genetic analysis; however, participation is optional and subjects will be asked to give specific consent for these assessments.

Safety assessments including AE/SAE monitoring, vital signs measurements, physical examination, ECGs, laboratory measurements, and urine assessments will be performed during the study.

The EOS visit will be on Day 169 and all subjects will return to the study center for the EOS procedures (see Section 1.3).

4.2 Scientific Rationale for Study Design

Currently there are no approved treatment modalities for use in subjects with GPP, and there is little evidence-based information to guide the management of this severe, life-threatening type of psoriasis.

In this context, the development of agents with new mechanisms of action is considered important for future clinical practice. This open-label single arm multiple dose study may provide evidence-based information about the clinical effect of this novel treatment.

4.3 Justification for Dose

ANB019 will be administered as a single IV dose of 750 mg followed by 3 doses of 100 mg SC administered on Days 29, 57, and 85.

The doses selected for this study have demonstrated favorable safety profile and prolonged pharmacodynamic activity in a Phase I study (ANB019-001). A loading dose of 750 mg IV will be administered on Day 1 to enable steady state concentration to be reached faster at initiation of the ANB019 l00 mg SC dose. The 12-week treatment duration is expected to provide adequate time to assess the safety and efficacy of ANB019 in subjects with GPP.

4.4 End of Study Definition

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

The EOS 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 an 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 trial medication. The Sponsor may discontinue the trial if it becomes unjustifiable for medical or ethical reasons, for poor enrollment, or because of discontinuation of clinical development of ANB0019 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 [redacted].

If the study center has to be closed prematurely, [redacted] 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 of the inclusion criteria and none of the exclusion criteria.

5.1 Inclusion Criteria

Subjects are eligible to be included in the study only if all of the following criteria apply:

1. Male and female subjects must be 18 to 75 years of age inclusive, at the time of signing the informed consent.
2. Have clinically confirmed diagnosis of active GPP.
3. Have a Japanese Dermatology Association severity index total score of >6 **and** must be present with active pustules and erythema accounting for at least 10% of BSA **or** have a GPPPGA score of at least moderate severity.
4. Must be candidates for systemic therapy or phototherapy as assessed by the Investigator.
5. Meet the following laboratory screening criteria:
   a) Hemoglobin ≥90 g/L (≥9 g/dL)
   b) White blood cell count ≥3.0 × 10^9/L (≥3.0 × 10^3/μL)
   c) Platelets ≥100 × 10^9/L (≥100 × 10^3/μL)
   d) Serum creatinine <132.6 μmol/L (<1.5 mg/dL)
   e) Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels ≤1.5× upper limit of normal (ULN)
   f) Total bilirubin ≤1.5 × ULN. Subjects with known Gilbert's disease who have a serum bilirubin <3 × ULN may be enrolled
6. Body mass index (BMI) of 18 to 36 kg/m^2, inclusive, {BMI = weight (kg)/ [height (m)]^2}, and total body weight >50 kg (110 lb).
7. Subjects must be otherwise in a good health as judged by the Investigator based on medical history, physical examination, ECG, hematology, and chemistry laboratory parameters, and urinalysis.
8. 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 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.
   - 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 28 days before Day 1).

9. 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, guttate) except PP.
2. Have concomitant dermatological (eg, subcorneal pustular dermatosis, impetigo herpetiformis, acute generalized exanthematous pustulosis) or medical conditions which may interfere with the Investigator's 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 tension 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 chest 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.
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).

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, including, but not limited to,, helminths, protozoa, *Trypanosoma cruzi* within 6 months of 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, fibromyalgia, systemic lupus erythematosus, polymyalgia rheumatica, giant cell arteritis, Bechet'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 drug administration.
13. Malignancy or history of malignancy within 5 years, except for treated basal cell or squamous cell in situ carcinomas of the skin or squamous cell carcinomas deemed by the Principle Investigator to be fully treated.
14. History of any significant drug allergy or reaction (such as anaphylaxis or hepatotoxicity) and reactivity to [redacted], a component of ANB019 formulation, or the inactive ingredients (excipients).

    a) Have taken the following drugs within the specified period prior to Screening or Baseline:Topical medication (including corticosteroid, retinoids or vitamin A or D analog preparations, tacrolimus, calcineurin inhibitor, topical H1 and H2 antihistamines, tar preparations, topical antimicrobials, other medicated topical agents) or herbal preparation within 2 weeks prior to baseline.

    b) 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. A tapering washout of systemic therapies (eg, cyclosporine, methotrexate, and retinoids) can be used and the study drug can be introduced before the end of the washout period.

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

    d) Previous treatment with anti-tumor necrosis factor/interleukin (IL-12/IL-23) and IL-17 or any other mAbs is not allowed within 3 months or 5 half-lives or twice the duration of the biological effect of the product prior to baseline.

    e) Live attenuated vaccine within 12 weeks of screening and during the study.

    f) Any investigational drug within 4 weeks or 5 half-lives, whichever is longer, of screening.

g) Antibiotic or antiviral medication within 4 weeks of baseline.

15. 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. (Refer 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 (eg, excessive caffeine use) 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 at the Screening Visit) within 4 weeks of study drug administration (within 2 weeks for plasma only).
20. Blood transfusion within 4 weeks of study drug administration.
21. Inability to tolerate IV drug administration.
22. Any other physical, mental, or medical conditions, which, in the opinion of the Investigator, make study participation inadvisable or could confound study assessments.
23. Clinically significant abnormality on chest x-ray at Screening or within 6 months prior to Screening.
24. Clinically significant abnormalities on 12-lead ECG at Screening.
25. Evidence of clinically significant abnormality in urinalysis as determined by the Investigator.
26. Positive blood screen for hepatitis C antibody, hepatitis B surface antigen, or HIV-1 or HIV-2 antibodies.

5.3 Lifestyle Considerations

Exposure to sunlight should be avoided 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 enrolled 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 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 subject according to the study protocol.

6.1 Study Treatment Administered

Eligible subjects will receive 750 mg of ANB019 IV in an open-label manner followed by 3 doses of 100 mg SC administered on Days 29, 57, and 85.

Due to the potential for infusion reactions with protein drugs, ANB019 should be administered in an environment under close supervision of a physician and where full resuscitation facilities are immediately available. Allergic/anaphylactic reactions and infusion-related reactions typically begin during, or within several hours of dose administration. The onset of symptoms may be rapid, and some reactions may be life-threatening. The study treatment should be immediately stopped and permanently withdrawn in case of severe allergic/anaphylactic reactions. For treatment of allergic reactions, current local standard of care guidelines should be followed.

Study treatment details are provided in Table 1.

Table 1 Study Treatment Details

Study Treatment Name:	ANB019 (anti-interleukin-36 receptor [IL-36R] monoclonal antibody)
Dosage Formulation:	The drug product is formulated as [redacted]
Study Treatment Description	ANB019 drug product is a sterile, clear to slightly opalescent and colorless to yellow solution supplied in a single-use, 2R, Type I glass vial with a [redacted]
Unit Dose Strength(s)/Dosage Level(s):	A dose of 750 mg/[redacted] intravenously (IV) followed by 3 doses of 100 mg/mL subcutaneously (SC) administered on Days 29, 57, and 85.
Route of Administration	IV infusion (1 dose) and SC injections (3 doses).
Dosing Instructions:	ANB019 will be administered to subjects by IV infusion in polyvinyl chloride or polyolefin bags following dilution to a total volume of [redacted] with sterile normal saline (0.9% NaCl). Infusions will be administered over [redacted]. The infusion may be slowed or interrupted for subjects experiencing infusion-related AEs. 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 ANB019 will receive [redacted] (100 mg) SC injection. The 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.

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 enrolled in the study may receive study treatment and only authorized study center staff may supply or administer study treatment. 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.
3. 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 may be stored at room temperature (8°C to 25°C [46°F to 77°F]) in a diluted or undiluted state for up to a maximum of [redacted]. Once ANB019 has been diluted with sterile 0.9% NaCl, the solution may be stored at room temperature (8°C to 25°C [46°F to 77°F]) for

up to [redacted]. Vials are intended for single-use only; therefore, any remaining solution should be discarded.

4. 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).
5. 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 drug 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 section is not applicable as this is an open-label study.

6.4 Study Treatment Compliance

The prescribed dosage, timing, and mode of administration may not be changed except in cases of infusion-related AEs, the study drug administration may be slowed or interrupted. Any departures from the intended regimen must be recorded in the electronic case report forms (eCRFs). Infusion start date/time and infusion end date/time will be documented in the subject's eCRF. Any infusion interruptions (stop date/time and restart date/time), changes in infusion rate, and/or incomplete dose administration will also be documented in the subject's 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 GPP 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 must be on a stable dose for at least 4 weeks before study treatment administration. 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 trial, 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. Rescue medication in the form of topical corticosteroids (eg, betamethasone valerate ointment and cream, mometasone furoate ointment and cream) can be used during the study for a period of up to 1 week on a daily basis on affected areas to provide symptomatic relief. The introduction of any rescue medication must be communicated and discussed with the Medical Monitor. Rescue medication will be provided by the site and reimbursed by the Sponsor.

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.

The addition of any systemic psoriasis medication that is likely to impact psoriasis signs and symptoms (eg, cyclosporine, methotrexate, and retinoid) will require the subject to be withdrawn from the study.

6.6 Dose Modification

No dose modification is allowed in this study. Study treatment can be interrupted temporarily only once or permanently if deemed necessary as per the Investigator's discretion. Refer to Section 7.1.

6.7 Treatment After the End of the Study

All subjects will return to the study center for the EOS (Day 169) or 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 drug, SAE, or pregnancy occurring through the EOS visit and 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

Discontinuation from study treatment will require subjects to discontinue from the study. Study treatment may be interrupted only once during the study for an AE at the Investigator's discretion.

7.1.1 Temporary Interruption

Only one dose of study treatment may be interrupted temporarily in the case of an AE per the Investigator's discretion. The Medical Monitor and the Sponsor should be informed of all details pertaining to the decision. Study drug may be resumed at the next scheduled dosing visit after discussion with the Medical Monitor. In the case of a recurring or new AE after study treatment has resumed, the subject will be early terminated. If a clinically significant finding is identified (including, but not limited to changes from baseline) after enrollment, the Investigator or qualified designee will determine if any change in subject management is needed. Any new clinically relevant finding will be reported as an AE.

7.1.2 Re-challenge

Not applicable for this study.

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 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 under the following circumstances, any significant AE which in the opinion of the Investigator is related to the study drug or SAE, or pregnancy occurring through the EOS visit and should be followed-up until outcome:

- Prior to study treatment administration, the Investigator decides that the subject should be withdrawn or is at risk. If this decision is made because of an AE or a clinically significant laboratory value, the study drug should not be administered and appropriate measures are to be taken. AnaptysBio Inc. and/or [redacted] is to be notified immediately.
- Significant deviation/lack of compliance with protocol other than the use of excluded/prohibited medications.
- Use of any excluded/prohibited medications that in the opinion of the Investigator necessitates the subject being withdrawn (Appendix 5).
- Termination of the study by the Investigator or Sponsor.
- Pregnancy (Appendix 6 and Section 8.3.5 Pregnancy).

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

If the 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 (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 drug 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 and reschedule the missed visit as soon as possible and 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 Section 1.3.
- Protocol waivers or exemptions are not allowed.
- Immediate safety concerns should be discussed with the Medical Monitor and the Sponsor or 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 (see Section 1.3), 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 not exceed 204 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 complete the scales and questionnaires at all time points for a given subject.

8.1.1 Clinical Global Impression

The CGI scale will be used to assess the clinical response to study treatment. The change will be categorized as "Very much improved," "Much improved," "Minimally improved," "No change," and "Worsened" according to the modified JDA severity index total score (see Appendix 8).

8.1.2 Modified Japanese Dermatology Association (JDA) Severity Index

The modified JDA severity index score will be used for the assessment of the skin lesions, assessment of systemic manifestations and laboratory findings, and change in affected BSA of erythema, pustules, and edema (see Appendix 9).

The total severity score is categorized as Mild (total score: 1 to 6), Moderate (total score: 7 to 10), or Severe (total score: 11 to 17).

8.1.3 Psoriasis Area Severity Index (Only in Subjects With PP)

Psoriasis Area Severity Index scores will be used to determine the treatment response in subjects with PP. The PASI total score includes plaque characteristics (ie, erythema, induration, scaling), percentage of BSA affected and should be calculated by electronic data capture (EDC) (see Appendix 10).

8.1.4 Generalized Pustular Psoriasis Physician's Global Assessment Scale

The GPPPGA is a physician-based assessment of the severity of GPP (specifically pustules, erythema, and scaling or crusting of pustular psoriasis lesions). Each component is scored on a 5-point scale, ranging from 0 (least severe) to 4 (most severe) to assess the severity of GPP (Bachelez 2019; Marrakchi 2019). The average is calculated for scoring.

Subjects will be assessed using the GPPPGA at each study visit (excluding those visits that are phone calls). Refer to Appendix 11 for additional information.

8.1.5 Dermatology Life Quality Index

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

Subjects will be asked to recall their experiences during the previous week by responding to 10 questions. 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 (see Appendix 12).

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 (inspection and vision control); 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, CGI, modified JDA severity index, PASI [if PP is present]).

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 6 months prior to screening and other time points specified in the Schedule of Activities (see Section 1.3).

8.2.3 Height and Weight

Height will be measured only at the Screening Visit. Weight will be measured at the Screening and EOS Visits.

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 measurements 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 of rest) should be measured once. Arterial blood pressure should be measured twice (at intervals of approximately 5 minutes), using a validated device. Average of both the readings will be entered in eCRF.

8.2.5 Electrocardiograms

- A single 12-lead ECG will be obtained at the time points specified in 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 laboratory team for quality and interpretation. Instructions and guidelines for collection (e.g, 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 which will be documented in the EDC.
- The ECG individual data (with the exception of clinical significance) does not need to be entered into EDC.

8.2.6 Photography

Photography of the lesions will be performed at the time points mentioned in Schedule of Activities (see Section 1.3) for documentation purpose 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.

8.2.7 Clinical Safety Laboratory Assessments

- See Appendix 3 for the list of clinical laboratory tests to be performed and to 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 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 take an immediate decision for any safety concerns based on laboratory results.
- 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 case report form. 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 participation in the study including the subject's last EOS visit 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 (see Section 1.3).
    - 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.

8.2.8 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 AEs, including that 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 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 AE or SAE 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.

8.3.2 Method of Detecting AEs and SAEs

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.

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 SAEs, and non-serious AEs of special interest (as defined in Section 8.3.6), 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.

- The [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 until at least 28 days after the last dose.
- 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 AESI 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 Infusion-related Adverse Events

The ANB019 infusion may be slowed or interrupted for subjects experiencing infusion-related AEs. Following the infusion, all subjects will be observed for fever, chills, rigors, hypotension, nausea, or other infusion-related AEs. The subjects will leave the study center after completing

the 5 hours postdose assessments after IV administration and the 3 hours postdose assessments after the first and second SC injections and with the Investigator's approval.

8.3.8 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 GPP and can be serious/life-threatening:

- Flare of GPP.

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 on the corresponding eCRF page 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 >750 mg/[redacted] within a 24-hour time period on Day 1 and >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, creatine kinase, and complete blood count) are to be performed and followed until all values return to baseline levels and AEs subside.

Sponsor does not recommend specific treatment for an overdose.

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 within 24 hours from the date of the last dose of study treatment if requested by the Medical Monitor (determined on a case-by-case basis).
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 presented in Section 1.3. Approximately 65 mL total of 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 which are within the stability window of the bioanalytical assay will be analyzed.

Table 2 PK/ADA Sample Collection and Timepoints

Study Visit	PK Sample Timepoint Plasma	ADA Sample Timepoint Serum
Day 1[a]	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-drug antibodies; hr(s) = hour(s); min = minutes; PK = pharmacokinetic.
[a] Infusion of study treatment will take approximately 1 hour. Therefore, the 1-hour PK sample collection on Day 1 must start immediately at the end of the infusion. The 4-hour collection must occur exactly 3 hours after the 1-hour collection is completed.

8.6 Pharmacodynamics

Pharmacodynamic parameters will not be evaluated in this study.

8.7 Genetics

Pharmacogenomic testing is optional and voluntary. For those patients who signed the original pharmacogenomics ICF, a whole blood sample will be collected at the study visit as specified in the study flow chart and this sample will be stored for future analysis. Specific procedures for storage and shipping of pharmacogenomic samples will be provided in a lab manual.

DNA testing will be performed **only** at Day 1. Ribonucleic acid (RNA) testing will be performed on Day 1 and Week 16. The DNA and RNA samples may be used to determine a possible relationship between genes and response to treatment with ANB019 and possible side effects to ANB019. Genes that may be studied will be identified later as these are for exploratory purposes. These prepared samples will be transferred to the pre-identified lab that will, on behalf of AnaptysBio, extract DNA and RNA from the samples (See Appendix 7 for information regarding genetic research). Details on processes for collection and shipment and destruction of these samples can be found in a separate Laboratory Manual.

8.8 Biomarkers

Samples will be collected according to the schedule presented in Section 1.3 to measure skin biopsy biomarkers. Measurements may include but are not limited to immunohistochemistry and Reverse Transcription Polymerase Chain Reaction to assess psoriasis associated markers of

inflammation (eg, IL-17, IL-23, IL-8, dendritic cells, epidermal thickness, and leukocytes infiltration).

The actual date and time of the 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 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.

A 5 mL blood sample will be collected in a serum separator tube to measure change in serum cytokine (including but not limited to IL-8) concentration at each time point mentioned in the Schedule of Activities (see Section 1.3). A qualified fit for purpose assay will performed by or under the supervision of the Sponsor.

8.9 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 EOS visit from subjects who discontinued study treatment or were withdrawn from the study. Each serum sample will be divided into 2 aliquots (1 each for primary and a back-up).

The 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.

8.10 Health Economics or Medical Resource Utilization and Health Economics

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

9.0 STATISTICAL CONSIDERATIONS

9.1 Statistical Hypotheses

This is an exploratory study and no formal hypothesis testing will be performed.

9.2 Sample Size Determination

The sample size is not based on statistical power considerations.

Approximately 10 subjects will be enrolled at 8 study centers for study treatment. On Day 1, subjects who meet all of the entry criteria will receive a 750 mg IV dose of ANB019 in an open-label manner followed by 3 doses of 100 mg SC administered on Days 29, 57, and 85.

9.3 Populations for Analyses

For purposes of analysis, the analysis sets in Table 3 are defined.

Table 3 Analysis Sets

Full Analysis Set (FAS)	The FAS analysis set will include all subjects, regardless of whether or not the treatment was received. Subjects will be analyzed according to treatment received.
Safety Analysis Set	The Safety Analysis Set will include all enrolled subjects who receive at least 1 dose of ANB019. The Safety Analysis Set will be used for all safety analyses. Subjects will be analyzed according to treatment received.
Per Protocol Analysis Set (PPS)	The Per Protocol analysis set will include all subjects in the FAS analysis 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 Analysis Set who have at least 1 quantifiable PK sample available and who do not have events or deviations with the potential to affect PK concentrations. The PK analysis set will be used for all PK analyses.

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). The SAP will be developed and finalized before database lock and will describe the subject analysis sets to be included in the analyses, and procedures for accounting for missing, unused, and spurious data. This section is a summary of the planned statistical analyses of the primary and secondary endpoints.

The default summary statistics for continuous variables includes number of contributing observations (n), mean, standard deviation (SD), median, minimum, and maximum. (See Section 9.4.7 for PK).

For categorical variables, the number and percentage (the 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 drug (this includes unscheduled visits). For numerical variables, change from Baseline will be calculated as the difference between the value of interest and the corresponding baseline value.

Point estimates will be accompanied with 2-sided 95% confidence interval (CIs), where applicable.

In the case of normality assumption violations, appropriate non-parametric methods will 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, enrolled, treated, completed as well as the number of dropouts, with reasons for discontinuation, and major protocol deviations or violations.

A listing will be presented to describe dates of screening, assigned treatment, screen failed with reason, completion or early withdrawal, and the reason for early discontinuation, if applicable, for each subject. A list of protocol deviations/violations will be identified and discussed with the Investigator/AnaptysBio Inc. 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. 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 (sample size, frequency, and percent).

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

9.4.3 Concomitant Medication

All medications will be coded using the World Health Organization 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 drug, or as concomitant medication if it is ongoing at the time of the first dose or is started after the first dose of study drug. Prior, concomitant and rescue medications will be summarized 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 Endpoints

The primary efficacy endpoint is the proportion of subjects achieving clinical response at Weeks 4 and 16. Clinical response is defined as “Very much improved”, “Much improved”, and “Minimally improved” on CGI scale according to modified JDA severity index total score. The number and percentage of subjects achieving clinical response will be summarized in tabular form at Weeks 4 and 16. Each subjects CGI score will be plotted at all study visits.

9.4.4.2 Analysis of Secondary Efficacy Endpoints

Following are the secondary efficacy endpoints:

- Change in modified JDA severity index total skin lesions score (sum of erythema, erythema with pustules, edema) at all study visits.

Descriptive statistics will be presented at all study visits. Each subject’s modified JDA severity index total skin lesion score will be plotted at all study visits.

- Change in affected BSA of erythema with pustules, erythema, and edema as measured by modified JDA severity index score at all study visits:

Descriptive statistics will be generated at all study visits. An overlay plot of each subject’s value over all study visits will be generated for each component score.

- Change in total and individual scores in systemic manifestations and laboratory findings as measured by modified JDA severity index at all study visits.

Descriptive statistics will be generated at each measurement time for each numeric systemic manifestation and laboratory finding. An overlay plot of each subject's value over all study visits will be generated for each measurement time.

- GPPPGA change from Baseline scores for all study visits.
- GPPPGA score at all study visits.

The GPPPGA will be summarized at each postbaseline visit for change from Baseline scores and for the proportion of subjects achieving a GPPPGA score of 0 or 1. A separate overlay plot will display each subject's GPPPGA score for all study visits.

- Change in PASI score to evaluate a subject's overall PP disease state if present for all study visits:

Summary statistics will be provided for absolute PASI scores as well as for percent change from Baseline for all study visits.

- Change in DLQI total score at all study visits:

Summary statistics will be provided for average DLQI scores, as well as for percent change from Baseline for all study visits.

9.4.5 Safety Analyses

- Assessment of AEs/SAEs (potentially significant and clinically important AEs, SAEs, and AEs leading to withdrawal)
- Physical examinations
- 12-lead ECG
- Vital signs
- 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

Treatment-emergent adverse event: 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.

Only TEAEs will be summarized.

Adverse events will be coded using the MedDRA. Number of events and percentage will be tabulated by preferred term and system organ class. An event that occurred one or more times on treatment period for a subject will contribute 1 observation to the numerator and denominator

comprising all safety subjects exposed to ANB019. 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, AESIs, SAEs, TEAEs leading to treatment discontinuation, and TEAEs leading to withdrawal of subject will be tabulated for each treatment period.

Adverse events, AESIs, and SAEs will be listed for each subject.

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

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

Summaries and listings of data for both limited and complete physical examination findings, vital signs, hematology, biochemistry, and urinalysis laboratory tests 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 clinical laboratory 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 signs measurements, and clinical laboratory test results.

Change from Baseline will also be summarized for vital signs measurements, clinical laboratory test results.

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

9.4.6 Immunogenicity Analyses

Observed values for ADA status/titers will be listed by subject and summarized with descriptive statistics based on the Safety Analysis Set. If data permits, any correlation between ADA status and safety and efficacy endpoints will be evaluated.

9.4.7 Pharmacokinetic/Pharmacodynamic Analyses

9.4.7.1 Derivation of Pharmacokinetic Parameters

The PK parameters will be derived using non-compartmental methods using the PK analysis set. 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.

The following PK parameters will be determined for ANB019:

- Maximum observed concentration (C_{max}).
- Time to maximum observed concentration (T_{max}).
- Area under the curve (AUC).

Additional PK parameters may be determined if deemed appropriate.

9.4.7.2 Pharmacokinetic Concentration Data Analysis

A subject listing of all concentration-time data following study drug administration will be presented by subject and scheduled sample collection time.

Concentration data of ANB019 will be summarized by route/day and nominal time point using the number of observations (n), arithmetic mean, SD, coefficient of variation (CV), minimum, median, maximum, and geometric mean.

Graphs for mean concentration-time data following IV administration will be presented. Individual subject plots will also be presented. Other presentations of data may be added at the discretion of the PK scientist, as appropriate, and will be described in detail in the SAP.

9.4.7.3 Pharmacokinetic Parameter Data Analysis

All PK parameters will be summarized using n, 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.

9.4.8 Exploratory Biomarker Analyses

Observed and change from Baseline for circulating biomarkers will be listed and summarized descriptively by nominal time point and treatment using the Safety Analysis Set. Baseline will be the last assessment before study treatment administration.

The relationship between ANB019 concentrations and biomarker endpoints will be explored graphically.

Skin biomarker analysis may be performed by additional third party (eg, a university Investigator) 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 and Final Analyses

An interim analysis will be performed when approximately 50% of subjects have completed their Week 4 visit or when at least 2 subjects have reached 16 weeks postdosing. The interim analysis will assess primary efficacy and all safety data. Data from interim analyses might be used as a guideline for possible protocol modifications and planning of future clinical studies.

10.0 REFERENCES

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11.0 APPENDICES

Appendix 1 Abbreviations

Abbreviation	Definition
ADA	Anti-drug antibodies
AE	Adverse event
AESI	Adverse event of special interest
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
AUC	Area under the concentration-time curve
BMI	Body mass index
BSA	Body surface area
CGI	Clinical Global Impression
CI	Confidence interval
C_{max}	Maximum observed concentration
CRF	Case report form
CRP	C-reactive protein
CSR	Clinical Study report
CV	Coefficient of variation
DLQI	Dermatology Life Quality Index
DNA	Deoxyribonucleic acid
DRE	Disease-related events
ECG	Electrocardiogram
eCRF	Electronic case report form
EOS	End of study
ET	Early termination
FAS	Full Analysis Set
FSH	Follicle stimulating hormone
GLP	Good Laboratory Practices.
GPP	Generalized pustular psoriasis
GPPPGA	Generalized Pustular Psoriasis Physician's Global Assessment
IB	Investigator's Brochure
ICF	Informed consent form
ICH	International Council for Harmonisation

Abbreviation	Definition
IEC	Independent Ethics Committee
IL-36	Interleukin-36
IL-36R	Interleukin-36 receptor
IRB	Institutional Review Board
IV	Intravenous
JDA	Japanese Dermatology Association
mAb	Monoclonal antibody
MAD	Multiple Ascending Dose
MedDRA	Medical Dictionary for Regulatory Activities
mRNA	Messenger ribonucleic acid
NaCl	Sodium chloride
PASI	Psoriasis Area Severity Index
PK	Pharmacokinetic
PP	Plaque psoriasis
PPP	Palmoplantar pustular psoriasis
PT	Preferred term
PUVA	Psoralen and Ultraviolet A
QoL	Quality of life
RNA	Ribonucleic acid
SAD	Single Ascending Dose
SAE	Serious adverse event
SAP	Statistical analysis plan
SC	Subcutaneous
SD	Standard deviation
SOC	System Organ Class
SOP	Standard operating procedures
TB	Tuberculosis
TEAE	Treatment-emergent adverse event
T_{max}	Time to maximum observed concentration
ULN	Upper limit of normal
URTI	Upper respiratory tract infection
WBC	White blood cell
WOCBP	Women 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 (CIOMS) International Ethical Guidelines.
  - Applicable International Council for Harmonisation (ICH) GCP Guidelines.
  - Applicable laws and regulations.
- The protocol, protocol amendments, ICF, Investigator Brochure, 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 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 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 or his/her legally authorized representative and answer all questions regarding the study.
- Subjects must be informed that their participation is voluntary. Subjects or their legally authorized representative 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 or the subject's legally authorized representative.
- 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	[redacted]
Study Master File	[redacted]
Data Management	[redacted]
Clinical Supply Management	[redacted]
Quality Assurance Auditing	[redacted]
Biostatistics	[redacted]
Medical Writing	[redacted]
Laboratory Assessments	[redacted]
Electrocardiogram Collection, Review, and Analysis	[redacted]
Pharmacokinetic Sample Testing	[redacted]

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 EU 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), [redacted] 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 clinical study report (CSR).

In addition, Sponsor and/or [redacted] 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

Sponsor has engaged the services of a contract research organization, [redacted] to perform all monitoring functions within this clinical study. [redacted]' monitors will work in accordance with [redacted] SOPs. The monitor will establish and maintain regular contact between the Investigator and Sponsor.

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 [redacted].

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.

Data Handling and 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 enrolled into the study.

The Investigator will allow Sponsor, [redacted], 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 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 need 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 Count
	Hematocrit	White Blood Cell Count (WBC) with Differential:
		Neutrophils
	Mean cell hemoglobin (MCH)	Lymphocytes
	Mean cell volume (MCV)	Monocytes
	Mean cell hemoglobin concentration (MCHC)	Eosinophils
	Platelet count	Basophils
Clinical Chemistry	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 (hCRP)

Laboratory Assessments	**Parameters**	
	Troponin	Total Cholesterol
Serum pregnancy	Human chorionic gonadotropin (hCG) pregnancy test (as needed for women of childbearing potential)	
FSH	As needed in women of non-childbearing potential only (Postmenopausal woman aged over 45 years 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 (Section 1.3) for laboratory tests time points. PK and ADA samples will be collected as detailed in the Schedule of Activities All blood samples must be drawn prior to administration of the study drug on Day 1. 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, clinical chemistry, 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 fulfil 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 fulfils 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: • 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 in the CRF. 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 CRF 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 drug administration, and that could be explained by an underlying condition or other drugs or chemicals or is incontrovertibly not related to the IP
  - "Possibly related" Clinical event with a reasonable time relationship to study drug 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 drug 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 and/or Product Information, for marketed products, 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 CRF.
- 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 team 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) or (see next section) and send the paper SAE form to [redacted] Safety team via facsimile transmission.
- Contacts for SAE reporting can be found in SAE form.

SAE Reporting to [redacted] Safety via Paper 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 is 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 GPP or psoriasis is prohibited. If treatment with any of these prohibited treatments is essential then the subject must notify the study team and they will be withdrawn from the trial.

All treatments likely to have efficacy in GPP need to be discontinued prior to treatment initiation (prior to Day 1) with washout periods as stipulated in Table 6.

A tapering washout of systemic therapies (eg, cyclosporine, methotrexate, and retinoids) can be used and the study drug can be introduced before the end of the washout period. Systemic conventional medications (eg, cyclosporine, methotrexate, and retinoids) must be stopped at the day the study drug has been administered.

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
Methotrexate, cyclosporin, acitretin, alitretinoin, Fumaric acid esters, and corticosteroids or any other immunosuppressant or immunomodulating drugs	4 weeks
Anti-tumor necrosis factor/interleukin (IL-12/IL-23) and IL-17 or any other mAbs	3 months or 5 half -lives
Cyclophosphamide	6 months
Phototherapy or PUVA	4 weeks
Antibiotics and antivirals	Topical: 2 weeks Systemic: 4 weeks
Other investigational drugs	30 days or 5 half-lives (whichever is longer)
Live attenuated vaccines	3 months

Abbreviations: mAbs = monoclonal antibodies; PUVA = psoralen and ultraviolet A.

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:
   - Documented hysterectomy.
   - Documented bilateral salpingectomy.
   - 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 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.
   - 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.

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 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 Genetics

Use/Analysis of DNA/mRNA

- Genetic variation may impact a subject's response to study treatment, susceptibility to, and severity and progression of disease. Variable response to study treatment may be due to genetic determinants that impact drug absorption, distribution, metabolism, and excretion; mechanism of action of the drug; disease etiology; and/or molecular subtype of the disease being treated. Therefore, where local regulations and IRB/IEC allow, a blood sample will be collected for DNA analysis from consenting subjects.
- DNA/mRNA samples will be used to study disease pathogenesis and to determine potential genetic biomarkers of response to treatment. Genetic research may consist of the analysis of 1 or more candidate genes or the analysis of genetic markers throughout the genome or analysis of the entire genome.
- DNA samples will be analyzed for genetic analysis.
- The samples may be analyzed as part of a multi-study assessment of genetic factors involved in the response to study treatment or study treatments of this class to understand study disease or related conditions.
- Samples will be sent to the designated laboratory where they will be stored according to ICH GCP and GLP requirements with adequate measures to protect confidentiality. Genetic analysis using DNA/mRNA samples may be performed by additional third party (eg, a university Investigator) designated by the Sponsor. The results of genetic analyses may be reported in the CSR or in a separate study summary.
- The samples may be retained while research on study treatment or study treatments of this class or indication continues as described in the ICF.

Appendix 8 Clinical Global Impression

Category	Change in modified JDA severity index total score for GPP	and/or	Category description
Very much improved	Reduction by 3 or >points	or	Clear or almost clear of signs of GPP
Much improved	Reduction by 1 or 2 points	or	At least one of the following: • Area of erythema with pustules (%) reduced by ≤30% or • Clinically meaningful improvement in at least 2 other components of the modified JDA severity index for GPP (area of erythema, area of edema, fever, WBC, CRP, Alb)
Minimally improved	0 points (no change)	and	At least one of the following: • Area of erythema with pustules (%) reduced by ≤20% or • Clinically meaningful improvement in at least 1 other components of the modified JDA severity index for GPP (area of erythema, area of edema, fever, white blood cell [WBC], C-reactive protein [CRP], Alb)
No change	0 points (no change)	and	Not meeting the other criteria of "minimally improved"
Worsened	≥ + 1 point	-	Not applicable

Appendix 9 Modified Japanese Dermatological Association (JDA) Severity Index

	Score			
	0	1	2	3
Assessment of skin lesions				
Area of erythema with pustules	0%	> 0%, < 10%	≥ 10%, < 50%	≥ 50%
Area of erythema (total)	0%	> 0%, < 25%	≥ 25%, < 75%	≥ 75%
Area of edema	0%	> 0%, < 10%	≥ 10%, < 50%	≥ 50%
Assessment of systemic manifestations and laboratory findings				
Fever	<37°C (<98.6 F)	≥ 37°C, < 38.5°C ≥98.6 F, <101.3 F	≥ 38.5°C (≥101.3 F)	–
WBC count	<10,000/µL (<10 × 10^9/L)	≥10,000/µL, <15,000 µL (≥10 × 10^9/L, <15 × 10^9/L)	≥15,000/µL (≥15 × 10^9/L)	–
CRP	< 0.3 mg/dL (<3 mg/L)	≥ 0.3 mg/dL, < 7 mg/dL (≥3 mg/L, < 70 mg/dL)	≥7 mg/dL (≥ 70 mg/dL)	–
Serum albumin	≥ 3.8 mg/dL (≥ 38 g/L)	< 3.8 g/dL, ≥3 mg/dL (< 38 g/L, ≥ 30 g/L)	< 3 mg/dL (< 30 g/L)	–
Severity index (total score): 1-6=mild; 7-10=moderate; 11-17=severe				

The table is adapted from Imafuku S, Honma M, Okubo Y, Komine M, Ohtsuki M, Morita A, et al. Efficacy and safety of secukinumab in patients with generalized pustular psoriasis: A 52 week analysis from phase 3 open-label multicenter Japanese study. The Journal of Dermatology. 2016;43:1011-1017.

Appendix 10 Psoriasis Area Severity Index Score (PASI)

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 BSA represented by that region, i.e. × 0.1 for head, × 0.2 for upper body, × 0.3 for trunk, and × 0.4 for lower limbs.					
Body Surface Area		× 0.1	× 0.2	× 0.3	× 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 Generalized Pustular Psoriasis Physician Global Assessment Scale

The GPPPGA scale will be used to assess the impact and severity of GPP. The Investigator will rate the impact and severity of disease at each study visit (excluding those that are phone calls) using the following scale.

Score	Wording	Detailed description
0	Clear	Normal skin or post - inflammatory hyperpigmentation, no visible pustules, no scaling or crusting
1	Almost clear	Faint, diffuse pink or slight red erythema, low density occasional small discrete pustules (noncoalescent), superficial focal scaling or crusting restricted to periphery of lesions
2	Mild	Light red erythema, moderate density grouped discrete small pustules (noncoalescent), predominantly fine scaling or crusting
3	Moderate	Bright red erythema, high density pustules with some coalescence, moderate scaling or crusting covering most or all lesions
4	Severe	Deep fiery red erythema, very high density pustules with pustular lakes, severe scaling or crusting covering most or all lesions

The table is adapted from Bachelez H, Choon SE, Marrakchi S, et al. Inhibition of the IL-36 Pathway for the Treatment of Generalized Pustular Psoriasis. N Engl J Med 2019; 380:(10).

Appendix 12 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

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

Appendix 13 Summary of Changes

Protocol ANB019-002: Amendment 1, 15 January 2018
Replaces: Original Protocol, 12 December 2017

Section 1.1 Synopsis, Section 4.1 Overall Design and Table 1 Schedule of Activities (footnote)

- Description of Change: Added text to indicate that a minimum 3 hour observation period is required after the first and second subcutaneous injections and deleted from the following text 'no such limit for study center observation after SC administration'.
- Purpose of Change: Medicines and Healthcare Products Regulatory Agency (MHRA) request.

Section 5.1 Inclusion Criteria and Appendix 6 Contraceptive Guidance and Collection of Pregnancy Information:

- Description of Change: Text revised to specify that in addition to prohibition on sperm donation for the specified duration, ova donation for assisted reproduction is also prohibited. The duration for males was revised to 220 days (from 6 months).
- Purpose of Change: MHRA request.

Protocol ANB019-002: Amendment 2, 27 July 2018
Replaces: Amendment 1, 15 January 2018

Section 1.1 Synopsis and Section 4.1 Overall Design:

- Description of Change: Text revised to remove a minimum of 7 days screening period requirement and updated 'up to 28 days'.
- Purpose of Change: To simplify enrollment of newly diagnosed subjects.
- Description of change: Updated the number of Investigators and number of study centers from 3 to 5.
- Purpose of change: To reflect the updated number of Investigators and study centers (administrative change).

Section 2.2 Background (Clinical studies).

- Description of Change: Added the percentage for mild and moderate TEAEs and details about 1 severe AE.
- Purpose of Change: To reflect the updated Phase I Study results (ANB019-001, SAD part).

Section 2.2 Background and Section 2.3 Benefit/Risk Assessment:

- Description of Change: Text revised to include SAD (PP) safety and MAD (healthy volunteers) safety and PK data from the Phase I study (ANB019-001) in healthy volunteers and PP subjects.
- Purpose of Change: To reflect New safety and PK data from the Phase I study (ANB019-001).

Section 5.1 Inclusion Criteria:

- Description of Change: Added SI and conventional units for hemoglobin, white blood cell count, platelets, and serum creatinine.
- Purpose of Change: To reflect both SI and conventional units for hemoglobin, white blood cell count, platelets, and serum creatinine.

Section 5.2 Exclusion Criteria:

- Description of Change: Text revised to clarify the requirement to stop all systemic conventional therapies (eg. cyclosporine, methotrexate, and retinoid) the day the study drug is administered.
- Purpose of Change: To clarify the use of systemic therapies in case of tapering washout at study start.
- Description of Change: Revised to remove definition of regular alcohol consumption and excessive smoking
- Purpose of Change: Text removed as definition is not applicable in United Kingdom.

Section 5.3 1 Meals and Dietary Restrictions:

- Description of Change: Removed Meals and Dietary Restrictions.
- Purpose of Change: Section removed as study centers are not going to provide meal and subjects are allowed to bring meal for themselves.

Section 6.2 Preparation /Handling/Storage/Accountability

- Description of Change: Text regarding ANB019 storage reworded slightly and deleted the repetitive text
- Purpose of Change: Sentence combined to avoid repetition.

Section 6.5.1 Rescue Medicine:

- Description of Change: Section revised to include guidance for using rescue medication in the form of topical corticosteroids (eg. betamethasone valerate ointment and cream, mometasone furoate ointment and cream) and guidance for adding any systemic psoriasis medication that is likely to impact psoriasis signs and symptoms (eg. cyclosporine, methotrexate, retinoid).
- Purpose of Change: To provide clarity on rescue medication usage.
- Description of Change: Added text to indicate ‘introduction of any rescue medication must be communicated and discussed with the Sponsor’.
- Purpose of Change: To ensure that use of rescue medication must be communicated and discussed with the Sponsor.

Section 8.0 Study Assessments and Procedures.

Section 8.1.4 Total Body Surface Area (Study Assessments and Procedures).

- Description of Change: Revised to remove the section 8.1.4 describing assessment of body surface area affected by GPP.

- Purpose of Change: Text removed as BSA involvement is measured as part of modified JDA scale.

Section 8.2.5 Chest X-ray and Table 1 Schedule of Assessment (footnote).

- Description of Change: Bidirectional posterior-anterior and lateral view chest X-ray or as indicated by local treatment guidelines or practice is updated to include that it will be performed at Screening if not performed within 6 months prior to screening and other time points specified in the Schedule of Activities.
- Purpose of Change: To provide clarity on the time point of X-ray.
- Description of Change: Added text to indicate that 'In case of early discontinuation, the subject will be encouraged to return to the study center for the follow-up period visits (Week 16/Day 113 and Week 20/Day 141) and ET/EOS visit (Week 24/Day 169). The follow-up period visits are not actual calendar weeks and have to occur 4/8/12 Weeks post-discontinuation.'
- Purpose of Change: To provide clarity in case of early discontinuation and follow-up period (ET/EOS visit).

Section 8.3.7 Infusion-related adverse events:

- Description of Change: Added text to indicate that a minimum 3 hour observation period is required after the first and second SC injections and deleted the following text: "no such limit for study center observation after SC administration". In addition, text regarding IV administration modified to improve clarity.
- Purpose of Change: To provide details regarding duration of assessment period after SC administration and text reworded for clarity.

Section 8.8 Biomarkers:

- Description of Change: Storage duration of biomarkers sample were updated to 5 years from 1 year.
- Purpose of Change: To reflect the country specific storage requirement.

Section 8.9 Immunogenicity assessment:

- Description of Change: Immunogenicity Sample storage time period updated from 1 to 5 years.
- Purpose of Change: To reflect the country specific storage requirement.
- Description of Change: Added text to indicate that "only samples within the stability window of the assay will be analyzed".
- Purpose of Change: Updated to clarify that only the samples within the stability window of assay will be analyzed.

Appendix 2 Regulatory, Ethical, and Study Oversight Considerations (Administrative Structure), Medical Monitor.

- Description of Change: [redacted] emergency contact number updated.
- Purpose of Change: Administrative change.

Appendix 8 Signature of Investigator.

- Description of Change: Protocol version updated to ‘Amendment 2’.
- Purpose of Change: Administrative change.

Additional changes in Table 1 Schedule of Activities:

- Description of Change: Screening period updated to include “up to 28 days.
- Purpose of Change: To simplify the enrollment of newly diagnosed subjects.
- Description of Change: Removed “total BSA”.
- Purpose of Change: Text removed as BSA involvement is measured as part of modified JDA scale.

In addition, minor spelling, grammar, abbreviations, and formatting corrections have been made

Protocol ANB019-002: Amendment 3, 20 March 2019
Replaces: Amendment 2, 27 July 2018

Title Page:

- Description of the change: Title page updated to reflect ‘Amendment 3.’
- Purpose of the change: Administrative change.

Sponsor Signature Page:

- Description of the change: Updated wording added to indicate Sponsor’s responsibilities in signing the signature page; revised Sponsor signatory information
- Purpose of the change: To better align with the format in other clinical program protocols.

Investigator Signature Page:

- Description of the change: Moved the Investigator Signature Page from Appendix 2 to just after the Table of Contents and updated wording to indicate Investigator’s responsibilities in signing the signature page.
- Purpose of the change: As requested by the clinical development team to align with other similar protocols.

Synopsis and Global

- Description of the change: Formatted references from superscript to author/year format to align with regulatory publication guidelines.
- Purpose of the change: To align with revised Anaptys Style Guide.
- Description of change: Updated the number of Investigators and number of study centers from 5 to 8-10.
- Purpose of change: To reflect the updated number of Investigators and study centers (administrative change).

Synopsis and Section 3:

- Description of the change: Additional wording added to the secondary endpoints for PK analysis; moved immunogenicity objective (to assess ADA) from exploratory to secondary endpoint; retitled *tertiary/exploratory* endpoints section to *exploratory* endpoints.
- Purpose of the change: To capture an additional endpoint and to better clarify the PK and pharmacogenomic testing; to place greater emphasis on immunogenicity testing.
- Description of the change: Added an additional secondary endpoint to assess the proportion of subjects achieving a score of 0 or 1 on the Generalized Pustular Psoriasis Physician's Global Assessment scale.
- Purpose of the change: To further characterize efficacy assessments for GPP.

Synopsis, Section 1.3 Schedule of Activities, and Section 4 Study Design

- Description of the change: Revised the screening period from "up to 28 days" to "up to 42 days (Week -0)."
- Purpose of the change: To allow for more flexibility during the screening period.

1.3 Schedule of Activities

- Description of the change: Added a row for whole blood collection for mRNA; added a footnote to clarify those study visits that were phone contact only; rearranged order of footnotes
- Purpose of the change: To align with the additional PK endpoint added in the synopsis and Section 3; to improve clarity on phone visits versus site visits.

2.2 Background

- Description of the change: Added a reference in the text to a previously published CSR.
- Purpose of the change: To cite data that had been described in this section.

4 Study Design, 8.2.4 Pharmacokinetics

- Description of the change: Added Table to detail the sample collection and time points for PK and ADA testing
- Purpose of the change: To easily identify collection times and visit requirements for PK and ADA testing.

5.1 Inclusion Criteria

- Description of the change:
    - Revised criterion #1 to increase the upper age limit from 65 to 75.
    - Revised criterion #3 regarding disease criteria for study entry during the screening period;
    - Revised criterion #6 to omit repeat confirmation for ALT or AST that was above the ULN

- Purpose of the change:
    - To clarify requirements for subjects entering the study with regards to JDA score and percentage of affected BSA;
    - To streamline and clarify procedures.

5.2 Exclusion criteria

- Description of the change:
    - Criterion #1: Removed 2 examples of other forms of psoriasis that were excluded from participation
    - Criterion #17: Added a phrase that history of drug and alcohol abuse and any potential impact on the ability to participate would be "determined by the Investigator."
- Purpose of the change: To allow greater flexibility for eligibility.

6.5.1 Rescue Medication

- Description of the change: Minor wording edits to this section regarding use of rescue medication and withdrawal of subjects.
- Purpose of the change: To improve text clarity and streamline details.

6.6 Dose Modification

- Description of the change: Added wording to clarify that study treatment may be interrupted only once before being permanently discontinued.
- Purpose of the change: To clarify dose modification versus when subjects should be withdrawn.

7.1 Discontinuation of Study Treatment

- Description of the change: Revised the wording of this section to clarify discontinuation from treatment versus study and to better characterize subjects who are considered early termination.
- Purpose of the change: To align with common protocol template language.

7.1.1 Temporary Interruption

- Description of the change: Revised the heading title. Added some additional text about recurring or new AEs related study treatment interruption.
- Purpose of the change: To clarify guidelines for interruption of study treatment and to specify that interruption would be allowed only once per subject.

7.1.2 Re-challenge

- Description of the change: Added a statement that this was not applicable.
- Purpose of the change: Details about restarting treatment that has been interrupted is covered in the previous section and this section is not needed; however, a placeholder sentence was added to cover this section.

8.1.4 Generalized Pustular Psoriasis Physician's Global Assessment Scale

- Description of the change: New section added to describe the GPPPGA scale.
- Purpose of the change: This assessment scale was added as a secondary endpoint to assess the impact of GPP at each study visit. Appendix 12 was also added to include the scale.

8.2.4 Electrocardiograms

- Description of the change: Clarified that ECGs will be reviewed by the central laboratory "for quality and interpretation" and that ECG data would not be entered into EDC with the exception of clinical significance.
- Purpose of the change: To reduce confusion over procedures and clarify the central lab's role in ECG processing.

8.2.6 Photography

- Description of the change: Language was revised to describe a standardized approach for collection of photographs and the process for transfer and quality review.
- Purpose of the change: To provide further guidance and clarity.

8.2.8 Telephone Contact

- Description of the change: Added this section to clarify the visits that are phone contact only versus site visits.
- Purpose of the change: To clarify visit purpose and procedures for phone contact.

8.5 Pharmacokinetics

- Description of the change: Added Table 2 to outline the collection schedule for pharmacokinetic assessments during the study.
- Purpose of the change: To clarify PK collection time points.

8.7 Genetics

- Description of the change: Revised language to characterize additional DNA/RNA testing and optional pharmacogenomic testing
- Purpose of the change: To align with revisions made to exploratory endpoints for PK and pharmacogenomics

9.3 Populations for Analyses

- Description of the change: Updated Table 3 to describe analysis populations.
- Purpose of the change: To better align with the statistical analysis plan for this study.

9.4.4 Efficacy Analyses

- Description of the change: Added additional text to support the added efficacy endpoint for the GPPPGA at Weeks 1 through 16.
- Purpose of the change: To describe the analysis associated with this endpoint.

9.4.6 Immunogenicity Analyses

- Description of the change: added description of how statistical data will be presented
- Purpose of the change: Text added to better characterize the presentation of statistical data for ADA status and efficacy and safety endpoints

9.4.8 Biomarker Analyses

- Description of the change: Removed the following sentences – Results will be presented in terms of 95% CIs. In addition, the n, mean, SD, median, minimum and maximum will also be prevented.
- Purpose of the change: To clarify language in this section, as well as presentation of data.

10 References

- Description of the change:
    - Added the following reference: A Double-Blind, Randomized, Placebo-Controlled, Single Ascending Dose (SAD) and Multiple Ascending Dose (MAD) Study to Evaluate the Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of ANB019 in Healthy Subjects and Psoriasis Patients. Protocol No.: ANB019-001. Clinical Study Report. 22 June 2018
    - Added the following reference: Bachelez H, Choon SE, Marrakchi S, et al. Inhibition of the IL-36 Pathway for the Treatment of Generalized Pustular Psoriasis. N Engl J Med 2019; 380:(10).
    - Added the following reference: Marrakchi S, Burden A, Tsai T, et al. Inhibition of the Interleukin-36 Pathway for the Treatment of Generalized Pustular Psoriasis [To the Editor]. N. Engl. J. Med. 2019; 380:10.
- Purpose of the change:
    - To provide a citation for clinical trial data and information provided in Section 2.
    - To provide a citation for the GPPPGA scale in the objectives and endpoints, as well as Appendix 11.
    - To provide a citation for the description of the GPPPGA scale in Section 8.1.4.

Appendix 8 Signature of Investigator

- Description of the change: Removed this appendix and renumbered remaining appendices.
- Purpose of the change: Moved the Investigator's signature up to immediately follow the Sponsor's signature at the beginning of the document to better align with AnaptysBio preferences for protocol organization.

Appendix 11 Generalized Pustular Psoriasis Physician's Global Assessment

- Description of the change: New appendix was added.

- Purpose of the change: To support the added secondary endpoint of the GPPPGA assessment at each study visit.

In addition, minor spelling, grammar, abbreviations, editing, and formatting corrections have been made throughout, as needed.

Protocol ANB019-002: Amendment 4, 30 August 2019
Replaces: Amendment 3, 20 March 2019

Overall Rationale for the Amendment:

This amendment was prepared to incorporate significant changes to the statistical methods section to characterize how the study endpoints would be analyzed, as well as to modify the eligibility criteria and correct other inconsistencies within the text.

Global Changes

- Description of the change: Minor edits applied for spelling and grammar, formatting, consistency, and spacing as needed.
- Purpose of the change: To clean-up for consistency, style, and formatting

Section 1.1 Protocol Synopsis, Section 3 Study Objectives

- Description of the change: Revised the secondary objectives to remove change from Baseline in GPPPGA score at all study visits and to assess change in Dermatology Life Quality Index (DLQI) total score instead of improvement in DLQI total score at all visits. Exploratory endpoint was revised for skin biopsies to assess IL-8 dendritic cells, not IL-6 dendritic cells. Removed references to logistic regression model using logit link.
- Purpose of the change: Statistical methods were revised to better characterize the proposed endpoints and goals of the study. The IL-8 change was necessary to correct inconsistencies in the protocol.

Section 1.1. Synopsis

- Description of the change: In the statistical methods section, a paragraph regarding the primary endpoint analysis was deleted.
- Purpose of the change: The discussion in the protocol is designed to be more brief and concise, with full details provided in the SAP.

Section 1.3 Schedule of Activities

- Description of the change: Footnote p was removed. Additional footnotes were moved and adjusted as needed on the schedule.
- Purpose of the change: To provide clarity and consistency in the table.

Section 2.3 Benefit/Risk Assessment

- Description of the change: Added one paragraph about an SAE of sepsis that has been reported during the study for 1 subject.

- Purpose of the change: To better characterize known safety issues to date. This event was considered possibly related; the subject had a medical history of sepsis.

Section 5.1 Inclusion Criteria

- Description of the change:
    - Criterion 5 was removed which specified the enrollment of subjects with or without a history of PP and PsA.
    - Criterion 5 (formerly 6): a statement was added that any laboratory values that are out-of-range at Screening will be left to the Investigator's discretion as to whether or not a subject is eligible.
- Purpose of the change: To clarify permitted disease characteristics of the study population. Subjects must have active diagnosis of generalized pustular psoriasis (GPP) and to allow greater flexibility for Investigator assessment after consultation with [redacted] Medical Monitor and the Sponsor for determination of eligibility for out or range laboratory assessments

Section 5.2 Exclusion Criteria

- Description of the change: Criterion 13 was modified to include squamous cell carcinoma deemed fully treatable by the Investigator as permissible.
- Purpose of the change: To clarify permitted disease characteristics of the study population. Subjects must have active diagnosis of generalized pustular psoriasis (GPP) and to allow greater flexibility for Investigator assessment

Section 6.1 Study Treatments Administered, Table 1

- Description of the change: Revised the table to clarify the language around dose administration and to state that infusions may be slowed for subjects experiencing infusion-related reactions. Removed rows for packaging and manufacturing.
- Purpose of the change: To clarify the study treatment language and make the table more concise.

Section 6.7 Treatment After End of Study

- Description of the change: Revised the statement on collection of AEs to include any occurring through End of Study (rather than 30 days after End of Study
- Purpose of the change: To clarify collection and timing of adverse events.

Section 8.2.7 Clinical Safety Laboratory Assessments

- Description of the change: Added a bullet to indicate that screening laboratory assessments that were out-of-range would be reviewed by the Investigator to determine eligibility.
- Purpose of the change: To allow greater flexibility for Investigator assessment and determination of eligibility for out or range laboratory assessments.

Section 8.5 Pharmacokinetics

- Description of the change:
    - Added a paragraph to the text to indicate how samples will be collected and divided for primary and back-up analysis.

  - Removed collection specification for 5 mL Vaccutainer X tube.
  - Clarified that sample collection time will be documented using a 24-hour clock. Included a statement on procedures is a subject refuses PK blood sample collection.
  - Revised Table 2 to add a footnote to the Day 1 PK collection timepoint to clarify that the PK collection must begin immediately at the end of the infusion.
- Purpose of the change: For clarity on sample collection and documentation.

Section 8.8 Biomarkers

- Description of the change: Revised the sentence on measurement of skin biopsy markers to clarify that analyses may be performed by a third party. Revised the language on blood sample collection to clarify the assay to be used. IL-6 was deleted from the list of biomarkers.
- Purpose of the change: To allow greater flexibility on sample analysis.

Section 8.9 Immunogenicity Assessments

- Description of the change: Added a statement to clarify how aliquot samples will be divided. Removed a statement that clarified the length of time for sample storage.
- Purpose of the change: To provide clarity on sample collection procedures.

Section 9.3 Population for Analyses, Table 3

- Description of the change: Removed the ITT Analysis Set and replaced with Full Analysis Set (FAS) in the table. Removed any references to randomization. The PPS will now be based on the FAS instead of the ITT set.Additional text was added to clarify use of the PK analysis set.
- Purpose of the change: This is an open-label study. All enrolled subjects will be analyzed according to treatment received.

Section 9.4.4.1 Primary Efficacy Endpoint Analyses

- Description of the change: Added a clarification on the analysis of clinical response and Clinical Global Impression (CGI) score. Deleted detailed text on statistical analysis as it will be moved to the SAP.
- Purpose of the change: For clarity on statistical analysis presentation.

Section 9.4.4.2 Secondary Efficacy Endpoint Analyses

- Description of the change:
  - Clarified that secondary endpoints will be analyzed at all study visits through Week 16 for modified JDA severity index score, descriptive statistics, GPPPGA score, and PASI score. Deleted detailed text on statistical analysis as it will be moved to the SAP.
  - Included a statement that summary statistics will be provided for average DLQI scores instead of absolute scores, in addition to the percent change from Baseline through Week 16 instead of by study visit.
- Purpose of the change: For greater clarity on secondary endpoint analysis.

Section 9.4.7.1 Derivation of PK Parameters

- Description of the change: Clarified that PK parameters will be analyzed using the PK analysis set.
- Purpose of the change: For clarity of analysis description.

Section 9.4.7.2 Pharmacokinetic Concentrations

- Description of the change: Removed the trough concentrations from plots.
- Purpose of the change: For clarity of PK analysis.

Section 9.4.8 Exploratory Biomarker Analyses

- Description of the change: Added additional text to clarify the analysis of exploratory biomarkers and how their relationship to ANB019 concentrations will be characterized.
- Purpose of the change: For greater clarity on exploratory analyses objectives and goals.

Section 9.5 Interim and Final Analyses

- Description of the change: Added a paragraph to clarify the timing of interim analysis for this study.
- Purpose of the change: Administrative change to clarify interim and final analyses for this study.

Appendix 1 Abbreviations

- Description of the change: Abbreviations added or removed to align with usage following edits for amendment 4.
- Purpose of the change: Administrative

Appendix 2 Regulatory, Ethical, and Study Oversight

- Description of the change: Revised Table 4 to clarify study roles between [redacted] and Anaptys
- Purpose of the change: For clarity on study administrative structure.

Appendix 7 Genetics

- Description of the change: Clarified when mRNA will be analyzed. Deleted text regarding the duration of retention of samples.
- Purpose of the change: to align with analysis of DNA samples. The duration of sample retention is specified in the ICF.

Protocol ANB019-002: Amendment 5, 29 October 2019

Replaces: Amendment 4, 30 August 2019

Overall Rationale for the Amendment:

This amendment was prepared to comply with a request from the Medicines and Healthcare Products Regulatory Agency to remove the flexibility for Investigators to discuss eligibility for those patients who do not meet screening laboratory eligibility criteria.

Global Changes

- Description of the change: Minor edits applied for formatting and consistency.
- Purpose of the change: Administrative

Section 5.1 (Inclusion Criterion #5) and Section 8.2.7 Clinical Safety Laboratory Assessments

- Description of the change: The sentence permitting the Investigator to assess eligibility in consultation with the Medical Monitor and the Sponsor, for those subject who fail to meet laboratory screening criteria, has been removed.
- Purpose of the change: To remove this flexibility for subject enrollment and to comply with the Medicines and Healthcare Products Regulatory Agency request.