A Phase 2, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of Imsidolimab (ANB019) in the Treatment of Subjects with Acne Vulgaris

Protocol Number: ANB019-209

Investigational New Drug (IND) Number: 136145

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Sponsor Medical Expert and Signatory: [redacted] MD, PhD

[redacted]

Original Protocol (Version 1.0)

11 February 2021

SPONSOR SIGNATURE PAGE

I confirm that I have read and approved this protocol in its entirety and will comply with the obligations as detailed in all applicable regulations and guidelines (eg, International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use [ICH] Good Clinical Practice [GCP] guidelines) and the protocol.

[redacted]

11-Feb-2021

Date (DD-MMM-YYYY)

AnaptysBio, Inc.

INVESTIGATOR'S AGREEMENT

PROTOCOL TITLE: A Phase 2, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of Imsidolimab (ANB019) in the Treatment of Subjects with Acne Vulgaris

PROTOCOL NO: ANB019-209

VERSION: Original Protocol (Version 1.0)

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 Acceptance of this document constitutes my agreement that no unpublished information contained herein will be published or disclosed without prior written approval from AnaptysBio.

Instructions to the Investigator: Please SIGN and DATE (DD-MMM-YYYY) this signature page. PRINT your name, title, and the name of the study site in which the study will be conducted. Return the signed copy to AnaptysBio or designee.

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

Signature of Investigator: _____ Date: _____

Printed Name: _____

Investigator Title: _____

Name/Address of Site: _____

_____

_____

_____

DOCUMENT HISTORY

DOCUMENT HISTORY	
Document	**Date**
Original Protocol (Version 1.0)	11 February 2021

TABLE OF ABBREVIATIONS

ADA	anti-drug antibody
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
AV	acne vulgaris
BMI	body mass index
CFR	Code of Federal Regulations
CI	confidence interval
CK	creatine kinase
CDLQI	Children's Dermatology Life Quality Index
C_{max}	maximum observed concentration
CONSORT	Consolidated Standards of Reporting Trials
COVID-19	Coronavirus Disease 2019
CRO	contract research organization
CSR	Clinical Study Report
CV	coefficient of variation
D	day
DLQI	Dermatology Life Quality Index
EC	Ethics Committee
ECG	electrocardiograms
eCRF	electronic case report form
EDC	electronic data capture
EGFRi	epidermal growth factor receptor inhibitor
EOS	end of study
ET	early termination
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GGT	gamma glutamyl transferase
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
GPP	generalized pustular psoriasis
H_0	null hypothesis
hCG	human chorionic gonadotropin
HHS	Health and Human Services
HIPAA	Health Information Portability and Accountability Act
hr	hour(s)
HRT	hormonal replacement therapy
hsCRP	human C-reactive protein
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IGA	Investigator's Global Assessment
IgG4	immunoglobulin G4

IL	interleukin
IL-36R	interleukin 36 receptor
IL-36Ra	IL-36 receptor antagonist
IND	Investigational New Drug
IRB	Institutional Review Board
ITT	intent-to-treat
IUD	intrauterine device
IUS	intrauterine hormone-releasing system
IV	intravenous
IWRS	Interactive Web Response System
K_D	dissociation constant
LSM	least-squares means
mAb	monoclonal antibody
MAD	multiple ascending dose
MedDRA	Medical Dictionary for Regulatory Activities
min	minute
MMRM	mixed effects model for repeated measures
mRNA	messenger RNA
NaCl	sodium chloride
NOAEL	no observed adverse effect level
OTC	over-the-counter
PBMC	peripheral blood mononuclear cell
PDT	photodynamic therapy
PGA	Physician's Global Assessment
PGIC	Patient Global Impression of Change
PGIS	Patient Global Impression of Severity
PK	Pharmacokinetic
PPP	palmoplantar pustulosis
PRIDE	papulopustules and/or paronychia, regulatory abnormalities of hair growth, itching, and dryness due to EGFRi
PRN	as needed (*pro re nata)*
PT	preferred term
QC	quality control
RNA	ribonucleic acid
SAD	single ascending dose
SAE	serious adverse event
SAP	Statistical Analysis Plan
SC	subcutaneous
SD	standard deviation
SoA	Schedule of Activities
SOC	system organ class
SOP	standard operating procedure
SSQ	Subject Satisfaction Questionnaire
SSRS	Subject Satisfaction Rating Scale
$t_{1/2}$	terminal half-life
TB	tuberculosis
TEAE	treatment-emergent adverse event
Th-17	T-helper 17
TK	toxicokinetic

T_{max}	time to maximum observed concentration
TNF	tumor necrosis factor
ULN	upper limit of normal
URTI	upper respiratory tract infection
W	week
WHO	World Health Organization
WOCBP	woman of childbearing potential

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STATEMENT OF COMPLIANCE

The study will be conducted in accordance with the protocol, applicable ICH GCP guidelines, and applicable local laws and regulations. The Investigator will assure that no planned deviation from, or changes to the protocol will take place without prior agreement from the IND Sponsor and documented approval from the Institutional Review Board (IRB)/Ethics Committee (EC), except where necessary to eliminate an immediate hazard(s) to the study subjects. All personnel involved in the conduct of this study have completed ICH GCP Training.

The protocol, informed consent form(s) (ICFs) and assent form(s), recruitment materials, and all subject materials will be submitted to the IRB/EC for review and approval. Approval of the protocol and the consent forms must be obtained before any subject is enrolled. Any amendment to the protocol will require review and approval by the IRB/EC before the changes are implemented to the study. In addition, all changes to the consent/assent forms will be IRB/EC-approved; a determination will be made regarding whether a new consent/assent needs to be obtained from subjects who provided consent/assent using previously approved forms.

1 PROTOCOL SUMMARY

1.1 SYNOPSIS

Title: A Phase 2, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of Imsidolimab (ANB019) in the Treatment of Subjects with Acne Vulgaris

Short Title: Efficacy and Safety of Imsidolimab in Subjects with Acne Vulgaris

Study Description: This is a Phase 2, multicenter, randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of imsidolimab in adolescent and adult subjects with acne vulgaris (AV). This study also will characterize the pharmacokinetic (PK) profile of imsidolimab and explore the immune response to imsidolimab in subjects with AV.

To be eligible for this study, subjects must be aged 12 to 45 years and have moderate to severe facial acne vulgaris at Screening and Day 1, defined as follows:

1. Facial IGA score of 3 (moderate) or 4 (severe).
2. At least 20 and no more than 100 inflammatory lesions on the face.
3. No more than 100 noninflammatory lesions on the face.
4. No more than 5 nodules (≥ 5 mm) on the face.

The maximum study duration per subject is approximately 24 weeks, which includes a screening period of up to 30 days followed by a 12-week treatment period and an 8-week safety follow-up period.

Eligible subjects will be randomized (1:1:1) to receive either imsidolimab (at 1 of 2 different regimens) or placebo, subcutaneously (SC) administered on 3 occasions: Day 1, Day 29 (Week 4), and Day 57 (Week 8). The randomization will be stratified based on facial IGA score at baseline (3 [moderate] versus 4 [severe]).

The treatment arms will be as follows:

1. Imsidolimab 400 mg on Day 1, followed by 200 mg on Days 29 and 57
2. Imsidolimab 200 mg on Day 1, followed by 100 mg on Days 29 and 57
3. Placebo on Days 1, 29, and 57

For scheduled on-site study visits, subjects will come to the study site on 7 occasions: Screening and Days 1, 15, 29, 57, 85, and 141 (end of study [EOS])/early termination [ET]). All procedures will be conducted in accordance with the Schedule of Activities (SoA) in Section 1.3.

Disease activity will be evaluated for all subjects using facial inflammatory and noninflammatory lesion count, Facial Investigator's Global Assessment (IGA), Truncal (chest, neck, and back) Physician's Global Assessment [PGA]), Dermatology Life Quality Index (DLQI) for subjects ≥16 years of age and Children's Dermatology Life Quality Index (CDLQI) for subjects < 16 years of age, Patient Global Impression of Severity (PGIS), Patient Global Impression of Change (PGIC), Subject Satisfaction Questionnaire (SSQ), and Subject Satisfaction Rating Scale (SSRS).

Safety assessments will include adverse event (AE)/serious adverse event (SAE) monitoring, vital signs, physical examination, electrocardiograms (ECGs), and clinical laboratory tests (hematology, biochemistry, and urinalysis).

Facial photography will be conducted at each study visit. Optional truncal photography will be performed at selected sites.

Blood samples will be collected during the study to determine PK and immunogenicity (presence of anti-drug antibodies [ADA] to imsidolimab) on Day 1 before the administration of the study treatment and at the other time points specified in the SoA (Section 1.3). Any remaining serum/plasma from samples collected for PK/PD immunogenicity endpoints may be retained for assay method development, troubleshooting, or validation. The samples will not be used for any type of genetic analyses.

Tape strips will be collected at Day 1, Week 4, and Week 12 to study key biomarkers.

Interim analyses (IA) may be performed for assessment of all primary and secondary efficacy endpoints and evaluation of all safety data available.

Objectives:

Primary Objective:

- To evaluate the efficacy of imsidolimab in subjects with AV

Secondary Objective:

- To evaluate the safety of imsidolimab in subjects with AV
- To evaluate the effect of imsidolimab on AV signs and symptoms and quality of life in subjects with AV

Exploratory Objectives:

- To further evaluate the effect of imsidolimab on AV signs and symptoms and quality of life in subjects with AV
- To explore the effect of imsidolimab on cutaneous biomarkers
- To test for immunogenicity to imsidolimab
- To describe the PK profile of imsidolimab in subjects with AV

Endpoints:

Primary Endpoint:

- Change from Baseline in facial inflammatory lesion counts at Week 12

Secondary Efficacy Endpoints:

- Change from Baseline in facial inflammatory lesion counts at visits other than Week 12
- Percent change from Baseline in facial inflammatory lesion counts at each visit
- Change from Baseline in facial noninflammatory lesion counts at each visit
- Percent change from Baseline in facial noninflammatory lesion counts at each visit
- Change from Baseline in total facial lesion (inflammatory and noninflammatory lesions) counts at each visit
- Percent change from Baseline in total facial lesion (inflammatory and noninflammatory lesions) counts at each visit
- Change from Baseline in Facial IGA at each visit
- Proportion of subjects achieving a Facial IGA of clear (0) or almost clear (1) with at least a 2-grade decrease from Baseline at each visit
- Proportion of subjects in each response category for the PGIS at each visit
- Proportion of subjects in each response category for the PGIC at each post-Baseline visit
- Change from Baseline in DLQI/CDLQI at each visit

Safety Endpoint:

- Incidence of AEs, SAEs, and AEs leading to withdrawals, as well as changes in vital signs, clinical laboratory parameters (hematology, biochemistry, and urinalysis), and 12-lead ECGs

Exploratory Endpoints:

- Two-point decrease from Baseline in Facial IGA at each visit
- Change from Baseline in Truncal PGA for chest at each visit
- Change from Baseline in Truncal PGA for neck at each visit
- Change from Baseline in Truncal PGA for back at each visit

- Proportion of subjects achieving a Truncal PGA for chest of clear (0) or almost clear (1) with at least a 2-grade decrease from Baseline at each visit
  Proportion of subjects achieving a Truncal PGA for neck of clear (0) or almost clear (1) with at least a 2-grade decrease from Baseline at each visit
- Proportion of subjects achieving a Truncal PGA for back of clear (0) or almost clear (1) with at least a 2-grade decrease from Baseline at each visit
- Proportion of subjects in each response category for the SSQ at each visit
- Proportion of subjects in each response category for the SSRS at Week 12 and Week 20
- Change from Baseline in lesion counts based on blinded photographic assessment at each visit
- Assessment of biomarkers in tape strips
- Assessment of PK of imsidolimab in AV subjects
- Assessment of ADA concentrations following administration of imsidolimab

Study Population: Approximately 120 male and female subjects aged 12 to 45 years with clinically confirmed diagnosis of AV

Inclusion Criteria:

1. Male and female aged 12 to 45 years (inclusive) at the time of signing the informed consent/assent.
2. Moderate to severe facial AV at Screening and Day 1, defined as follows:
   a. Facial IGA score of 3 (moderate) or 4 (severe)
   b. At least 20 and no more than 100 inflammatory lesions on the face
   c. No more than 100 noninflammatory lesions on the face.
   d. No more than 5 nodules (≥5 mm) on the face
3. Subject agrees to use Cetaphil Skin Cleanser on a regular basis (ideally once or twice daily) for at least 1 week prior to Day 1 and agrees to continue using Cetaphil Skin Cleanser at the same frequency throughout the study.
4. Subject must meet the following laboratory criteria at screening:
   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) ≤ 2 upper limit of normal (ULN)
   f. Total bilirubin ≤ 1.5 × ULN. Subjects with known Gilbert's disease who have serum bilirubin < 3 × ULN may be included
5. Body weight ≥ 40 kg and body mass index (BMI) within the range of 18 to 40 kg/m^2 for adults and 16 to 40 kg/m^2 for adolescents, inclusive {BMI = weight (kg)/[height (m)]^2}).

6. Contraceptive use by men and women should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.

   Contraception and pregnancy:

   a. A male subject must agree to use contraception as detailed in Appendix 1 of this protocol during the treatment period and for at least 200 days (which includes the duration of relevant exposure plus the duration of sperm cycle) after the last study treatment administration and refrain from donating sperm during this period.
   b. Female subjects:
      i. A woman of childbearing potential (WOCBP) is eligible to participate if she has a negative serum pregnancy test (β-human chorionic gonadotropin) at screening and a negative urine pregnancy test at Day 1 (see Appendix 1), is not breastfeeding, and agrees to follow the contraceptive guidance in Appendix 1 during the treatment period and for at least 6 months after receiving the study treatment, and refrains 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 at Day 1 (eg, hormonal contraception should be initiated at least 12 Weeks before Day 1. For WOCBP, hormonal contraceptives must be used without schedule changes and in steady doses during the study treatment. Starting hormonal contraceptives during the study is not permitted. Use of any hormonal contraceptives containing drospirenone, chlormadinone acetate, or cyproterone acetate is prohibited unless part of a stable contraceptive regimen as described in Section 6.5.1.
      ii. A woman not of childbearing potential as defined in Appendix 1, must have a follicle-stimulating hormone (FSH) test confirming nonchildbearing potential.
      iii. An adolescent subject who experiences menarche during the trial will be considered a WOCBP and will be required to follow the contraceptive guidance for WOCBP in Appendix 1 and undergo pregnancy testing as detailed in the SoA (Section 1.3).
7. Willing to participate and capable of giving written informed consent, which must be personally signed and dated by the subject and obtained prior to any trial-related activities. Subjects who need to provide assent, as per local requirement, need to have their parent(s) or legal representative read and sign the informed consent form prior to any study-related procedures. Adolescent

subjects who reach 18 years of age during the study must be reconsented as adults.

8. Willing to comply with all study procedures and lifestyle considerations, and must be available for the duration of the study.

Exclusion Criteria:

1. Has acne fulminans or conglobate or secondary acne, including drug induced acne (steroids, cloracne, lithium, epidermal growth factor receptor inhibitors [EGFRi, eg, cetuximab, erlotinib, panitumumab, gefitinib], associated with acneiform eruptions, including PRIDE [papulopustules and/or paronychia, regulatory abnormalities of hair growth, itching, and dryness due to EGFRi]) syndrome).
2. Acne associated with known hormonal imbalances such as polycystic ovaries, Cushing syndrome, congenital adrenal hyperplasia (CAH), androgen-secreting tumors, and acromegaly. Patients with signs/symptoms of hyperandrogenism such as hirsutism should undergo hormonal status assessment at the discretion of the Investigator.
3. Acne as part of a known genetic syndrome, such as SAPHO, PAPA, PASH or other variants possibly associated with PSTPIP1 gene.
4. Extensive (acne) keloids and hypertrophic scarring making clinical evaluation difficult.
5. Hidradenitis suppurativa also called acne inversa.
6. Other forms of acne rosacea, peri-oral dermatitis and gram-negative folliculitis.
7. Concomitant dermatological condition (skin burn, sun burn, extensive scarring), or excessive facial hair or beard that may interfere with the Investigator's ability to evaluate the subject's response to therapy.
8. Clinically significant medical condition or physical/laboratory/ECG/vital signs abnormality that would, in the opinion of the Investigator, put the subject at undue risk or interfere with interpretation of study results.
9. Any evidence of active infection that required systemic treatment within 4 weeks of Day 1 (eg, bronchopulmonary, urinary, or gastrointestinal).
   Note: Subjects with localized oral or genital herpes simplex that, in the opinion of the Investigator, is well-controlled may participate in the study.
10. Opportunistic infection (eg, Pneumocystis carinii, aspergillosis, or mycobacteria other than tuberculosis [TB]) or parasitic infections (eg, helminths, protozoa, Trypanosoma cruzi) within 6 months prior to screening.
11. Herpes zoster infection within 8 weeks prior to screening.
12. Known or suspected congenital or acquired immunodeficiency state, or condition that would compromise the subject's immune status (eg, history of splenectomy).

13. History of cancer or lymphoproliferative disease within 5 years prior to Day 1. Subjects with successfully treated nonmetastatic cutaneous squamous cell or basal cell carcinoma and/or localized carcinoma in situ of the cervix are not to be excluded.
14. Any major surgery within 4 weeks prior to Day 1 or has a major surgery planned during the study.
15. Any significant drug allergy or reaction (such as anaphylaxis or hepatotoxicity) and reactivity to polysorbate-20, a component of imsidolimab formulation, or the inactive ingredients (excipients).
16. Has taken the following drugs or had the following procedures within the specified period prior to Day 1:
    a. Over-the-counter (OTC) topical medication for the treatment of AV, including benzoyl peroxide, topical anti-inflammatory medications, corticosteroids, salicylic acid, α-hydroxy/glycolic, or antibacterial/antiseptic soap or wash within 2 weeks prior to Day 1.
    b. Prescription topical retinoids (eg, tretinoin, tazarotene, adapalene, dapsone) or antimicrobials (eg, clindamycin, erythromycin), or other prescription topical medications for the treatment of AV within 4 weeks prior to Day 1. Topical antibiotics may be used to treat non-acne skin lesions not on the face.
    c. Systemic anti-acne drugs not mentioned in other exclusion criteria within 4 weeks prior to Day 1.
    d. Oral or injectable corticosteroids within 4 weeks prior to Day 1 or require them during the study.
    Note: Intranasal corticosteroids and inhaled corticosteroids are allowed. Eye and ear drops containing corticosteroids are also allowed.
    e. Use of any systemic hormonal treatment (in particular anti-androgens, such as spironolactone, finasteride, flutamide) within 4 weeks before Day 1. Oral contraceptives can be continued if stable for the last 12 weeks before Day 1 and if stable in dose and dosing regimen and type (brand), and if the subject plans to continue throughout the study period.
    f. Drospirenone, chlormadinone acetate, or cyproterone acetate within 12 weeks prior to Day 1, unless part of a stable contraceptive regimen as described in Section 6.5.1.
    g. Previous surgical, physical (such as ThermaClear™), light (including blue or UV light, photodynamic therapy [PDT]) or laser therapy within 12 weeks prior to Day 1.
    h. Cryodestruction, chemodestruction, dermabrasion, acne surgery, intralesional steroids, X-ray therapy procedures performed on the face within 12 weeks prior to Day 1.
    i. Systemic antibiotics (including tetracyclines) within 4 weeks prior to Day 1.
    j. Systemic antiviral medication (except for prevention of localized oral or genital herpes simplex) within 4 weeks prior to Day 1.

k. Any nonbiologic investigational drug within 4 weeks or 5 half-lives, whichever is longer prior to Day 1.
l. Marketed or investigational biological agent within 12 weeks or 5 half-lives (whichever is longer) prior to Day 1.
m. Live attenuated vaccine within 12 weeks prior to Day 1 , including any approved for COVID-19. Live attenuated vaccines may be utilized after the subjects complete the 8-week standard safety follow-up period of the study. Note: Non-live-attenuated vaccines for COVID-19 (eg, RNA-based vaccines, protein-based vaccines) are allowed during the study.
n. Previous treatment with anti-IL-36R, anti-IL-36, anti-tumor necrosis factor (TNF)/ IL-12/IL-23/ IL-17, or any other mAbs within 12 weeks or 5 half-lives (whichever is longer) prior to Day 1.
o. Oral retinoid (eg, isotretinoin) or vitamin A supplements > 10,000 U/d within 26 weeks prior to Day 1.
p. Previous treatment with imsidolimab.

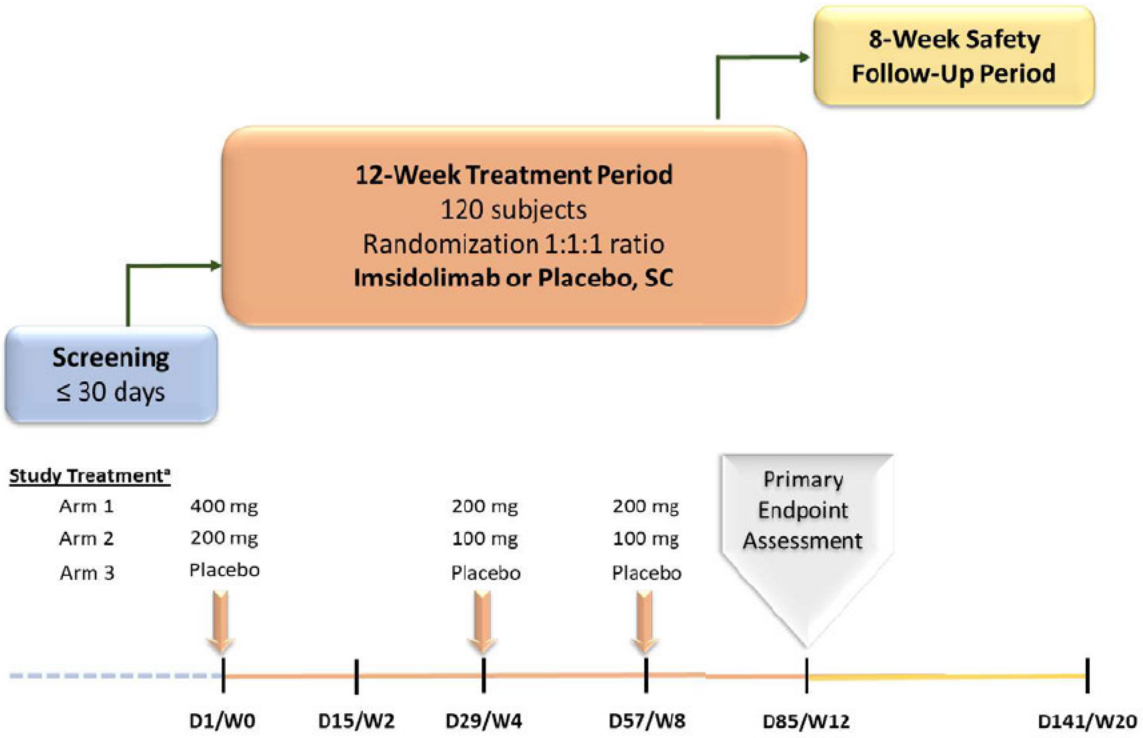
17. Has had excessive sun exposure, is planning a trip to a sunny climate, or has used tanning booths within 4 weeks prior to Day 1 or is not willing to minimize natural and artificial sunlight exposure during the study. Use of sunscreen products and protective apparel are recommended when sun exposure cannot be avoided.
18. Active TB or latent TB infection as indicated by a positive QuantiFERON®-TB Gold test at screening or within 6 months prior to screening (if the test is indeterminate, it can be repeated only once; chest X-ray will be administered per local standards, as required), and/or clinical examination, or has had active TB disease at any time in the past.
19. Clinically significant drug or alcohol abuse in the last year prior to Day 1, or other factors limiting the ability to cooperate and to comply with the study protocol, as determined by the Investigator.
20. Subject is a pregnant or lactating woman, or a woman who intends to become pregnant during the study period.
21. Any other physical, mental, or medical conditions, which, in the opinion of the Investigator, make study participation inadvisable or could confound study assessments.
22. Positive blood screen for hepatitis C antibody and hepatitis C RNA, antibodies to hepatitis B core antigens, hepatitis B surface antigen, or human immunodeficiency virus 1 and 2 antibodies.
23. Is not able to tolerate SC drug administration.

Phase:	2
Study Centers	Approximately 12 study centers are expected to participate in this study.

Enrolling Subjects:	
Description of Study Treatments:	Imsidolimab (ANB019) will be provided in a glass vial as a sterile, colorless to yellow, and clear to slightly opalescent solution for injection. The placebo contains no active ingredient and will be provided as a sterile, colorless to slightly yellowish, and clear to very slightly opalescent solution for injection. Imsidolimab will be administered as SC injection. Placebo will also be administered as SC injection in the same volumes as imsidolimab.
Rescue Medication:	Not applicable
Subject Duration:	The maximum study duration per subject included in this study is approximately 24 weeks from first visit to last visit.

1.2 SCHEMA

Figure 1: ANB019-209 Study Schema



Abbreviations: D, day; SC, subcutaneously; W, week.

[a] Study treatment will be administered according to the following schedule:

Arm 1: Imsidolimab 400 mg on Day 1, 200 mg on Days 29 and 57

Arm 2: Imsidolimab 200 mg on Day 1, 100 mg on Days 29 and 57

Arm 3: Placebo on Days 1, 29, and 57

Study treatment will be administered as 2 x 2 mL injections on Day 1 and 1 x 2 mL injection on Days 29 and 57, according to Table 3.

1.3 SCHEDULE OF ACTIVITIES

The screening evaluation will only be performed after the subject has agreed to participate and has signed and dated the ICF or assent. No treatment or study-related procedures will be initiated before informed consent/assent (when applicable) is signed. The Day 1 visit must be performed, at the latest, 30 days after the screening visit.

The screening evaluation will be performed according to the inclusion and exclusion criteria. If the subject fulfills all inclusion criteria and no exclusion criteria, he or she may be included in the study.

Table 1 provides a description of the procedures to be performed at each visit during the study. Of note, the primary endpoint will be evaluated on Day 85 (Week 12).

Unless specified otherwise, the study assessments scheduled on Day 1 must be performed before study treatment administration. The specific order for performing the study assessments is as follows (applicable to all visits):

- Subject-reported questionnaires
- Efficacy assessments (global assessments [Facial IGA] **must** be performed before more quantitative assessments [lesion count])
- Physical examination
- ECG
- Vital signs
- Blood samples collection (for safety, PK, ADA)
- Photography (may be performed anytime predose provided it is before skin sample collection)
- Tape stripping

The Coronavirus Disease 2019 (COVID-19) pandemic may impact the ability to adhere to the study procedures described in Table 1 due to challenges that include, but are not limited to, subject preferences, site closures, travel restrictions, and quarantines. Please refer to Section 4.5 for more details on allowable, as necessary, modifications to the protocol due to COVID-19 restrictions, including conducting optional home visits when on-site study visits are considered not feasible. Such modifications in study conduct always must be in accordance with local regulations/mandates.

Table 1: Schedule of Activities

	Screening Period	Treatment Period					Follow-Up Period
Study visit Window (days)	**(-30 to -1)**	**D1**	**D15 (W2)** (±2)	**D29 (W4)** (±4)	**D57 (W8)** (±4)	**D85 (W12)** (±4)	**D141 (W20) (EOS/ET)[a]** (±5)
Informed consent/assent[b]	X						
Demographics	X						
Inclusion and exclusion criteria	X	X					
Medical and surgical history	X	X					
Height and weight[c]	X	X				X	X
Complete physical examination[d]	X	X		X	X	X	X
Vital signs[e]	X	X	X	X	X	X	X
12-Lead ECG[f]	X	X		X		X	X
Hematology and biochemistry[g]	X	X	X	X	X	X	X
Urinalysis[g]	X	X		X	X	X	X
TB screening (QuantiFERON®-TB Gold test)/chest x-ray per local standard[g]	X						
Viral serology[g]	X						
FSH[g]	X						
Serum pregnancy test (WOCBP only)[g]	X						X
Urine pregnancy test (WOCBP only)[g]		X	X	X	X	X	
Facial IGA[h]	X	X	X	X	X	X	X
Facial inflammatory/noninflammatory lesion count[h]	X	X	X	X	X	X	X
Truncal (chest, neck, and back) PGA[h]	X	X	X	X	X	X	X
PGIS[h]	X	X	X	X	X	X	X
PGIC[h]			X	X	X	X	X
DLQI/CDLQI[h]		X	X	X	X	X	X
SSQ[h]		X	X	X	X	X	X
SSRS[h]						X	X
Photography	X	X	X	X	X	X	X
Blood samples for PK[i]		X	X	X	X	X	X
Blood samples for ADA		X	X	X	X	X	X
Tape strip collection[j]		X		X		X	
Randomization		X					
Study treatment administration[k]		X		X	X		
AE/SAE review	X	Continuously					
Concomitant medication review[l]	X	Continuously					

Table 1: Schedule of Activities (continued)

Abbreviations: ADA, anti-drug antibody; AE, adverse event; CDLQI, Children's Dermatology Life Quality Index; D, day; DLQI, Dermatology Life Quality Index; ECG, electrocardiogram; EOS, end of study; ET, early termination, FSH, follicle-stimulating hormone; IGA, Investigator's Global Assessment; PGA, Physician's Global Assessment PGIC, Patient Global Impression of Change; PGIS, Patient Global Impression of Severity; PK, pharmacokinetic; SAE, serious adverse event; SC, subcutaneous; SoA, Schedule of Activities; SSRS, Subject Satisfaction Rating Scale; SSQ, Subject Satisfaction Questionnaire; TB, tuberculosis; W, week; WOCBP, woman of childbearing potential.

[a] The ET visit will include all procedures to be done at the EOS visit (Day 141 [Week 20]).
[b] Adolescent subjects who reach 18 years of age during the study must be reconsented as adults.
[c] Height will be measured at screening only. Subjects below the age of 18 at the start of the study will have height measured at Week 12.
[d] Refer to Section 8.2.3 for details regarding the complete physical examination.
[e] Refer to Section 8.2.4 for details and instructions regarding vital signs.
[f] Refer to Section 8.2.5 for details and instructions regarding the ECG. In addition to the time points specified in the SoA, ECGs may be performed at any time during the study if, in the opinion of the Investigator, it is clinically warranted.
[g] If a negative QuantiFERON®-TB Gold test result was obtained within 6 months of screening, it can be skipped at screening. A chest X-ray will be administered per local standards, as required. The FSH testing is performed for women not of childbearing potential (postmenopausal women with at least 12 months of amenorrhea without an alternative medical cause). An adolescent subject who experiences menarche during the trial will be considered a WOCBP (refer to Appendix 1 for definition of WOCBP) and will be required to follow the contraceptive guidance in Appendix 1 and undergo scheduled pregnancy testing. Additional pregnancy testing may be performed whenever a menstrual cycle is missed or when pregnancy is otherwise suspected. Refer to Appendix 10 for instructions regarding clinical laboratory parameters.
[h] Refer to Section 8.1 for details and instructions regarding facial lesion count, facial IGA, truncal (chest, neck, and back) IGA, PGI-S, PGI-C, DLQI (subjects ≥ 16 years of age)/CDLQI (subjects < 16 years of age), SSQ, and SSRS. Facial IGA must be performed before facial lesion count.
[i] On Day 1, samples for PK will be collected at predose and 2 hr (± 10 min) post SC administration. See Table 5.
[j] Tape stripping will be performed for all randomized subjects as part of this study (not optional). Tape strips will be collected from non-lesional and lesional skin at Day 1 and Week 12 and from lesional skin at Week 4.
[k] During the treatment period, subjects will receive either imsidolimab or placebo SC administered as follows: 400 mg imsidolimab, 200 mg imsidolimab, or placebo on Day 1; followed by 200 mg imsidolimab, 100 mg imsidolimab, or placebo on Days 29 and 57.
[l] At screening, prior medications should be reviewed and documented. Refer to Section 6.5.

2 INTRODUCTION

2.1 STUDY RATIONALE

Acne vulgaris is a chronic dermatological condition that can result from a multitude of triggers including genetics, hormones, infections, and lifestyle, and is one of the most commonly occurring conditions in the world (Bhate 2013). Ongoing and severe acne can reduce quality of life, result in scarring, and have significant psychological impacts. The various triggers frequently result in proliferation of *Propionibacterium acnes* (*P. acnes*), which further elicits an inflammatory response in and around the pilosebaceous unit resulting in lesions (comedones, papules, pustules, nodules) (Dreno 2017; Suh 2015).

The inflammatory response in patients with acne has been shown to involve a variety of cytokines/receptors including TNFα, various interleukins, and MMPs. Di Caprio et al. (2017) conducted a biopsy-based assessment of IL-36Ra and IL-36 cytokine expression in lesional samples from subjects with AV and found that subjects with AV had significantly elevated expression of IL-36 cytokines, but not IL-36Ra, relative to controls. IL-36Ra is known to inhibit the effects of Interleukin-36 cytokines (IL-36α, IL-36β and IL-36γ) via competing with their receptor IL-36R and thereby inhibiting their proinflammatory effects. Additionally, it was shown that IL-36Ra expression was negatively correlated with IL-8 expression. This is consistent with previous investigations demonstrating IL-36–mediated induction of IL-8 expression (Carrier 2011). Abd El All et al. (2007) assessed IL-8 expression in skin biopsies from lesional and nonlesional skin in 29 subjects and found that lesional skin had significantly increased IL-8 expression compared to nonlesional skin. Furthermore, IL-8 expression was shown to be associated with increased inflammatory infiltrates in the dermis. In vitro, Nagy et al. (2005) co cultured human keratinocytes with four different strains of *P. acnes* and found that all four strains resulted in significantly elevated IL-8 mRNA expression, indicative of a potential inflammatory response. In sum, AV is associated with multifactorial triggers which result in an inflammatory response leading to various lesions.

Imsidolimab is a high affinity, humanized immunoglobulin G4 (IgG4) monoclonal antibody (mAb) that specifically binds IL-36 receptor (IL-36R) and antagonizes IL-36 signaling. The IL-36 cytokines (IL-36α, IL-36β, and IL-36γ) engage with IL-36R to initiate signaling events leading to proinflammatory responses. IL-36 signaling is counterbalanced by IL36Ra. Because the IL-36 pathway has been implicated in amplifying inflammatory skin diseases, inhibition of IL-36 signaling, by targeting IL36R with a specific mAb, may represent a novel strategy to control the pathological inflammatory cascade driven by IL-36 pathway activation. Imsidolimab is currently being studied as a potential first-in-class therapy for several cutaneous indications, including generalized pustular psoriasis (GPP), palmoplantar pustulosis (PPP), ichthyosis, hidradenitis suppurativa, and other inflammatory diseases in which the IL-36 pathway may play

a significant role in augmenting the disease. Imsidolimab may be beneficial in suppressing the inflammation in patients with AV.

2.2 BACKGROUND

2.2.1 NONCLINICAL STUDIES

Imsidolimab exhibits strong inhibitory activity for human as well as cynomolgus monkey IL36R (cyIL-36R) cell populations. Nonclinical data obtained from studies with imsidolimab in primary human and cynomolgus monkey cells and from in vivo nonhuman primate studies demonstrated that imsidolimab shows reactivity with human and cynomolgus monkey IL36R (dissociation constant [K_D] of 67.9 ± 31.4 pM and 80.0 ± 49.6 pM, respectively), but not with mouse or rat IL-36R.

In primary human and cynomolgus monkey cell populations, keratinocytes, peripheral blood mononuclear cells (PBMCs), and human whole blood, imsidolimab inhibited IL-36R mediated release of IL-8.

The terminal half-life ($t_{1/2}$) of imsidolimab in cynomolgus monkeys was 304 hr after single intravenous (IV) dose administration, and 310 hr after a 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 cynomolgus monkey.

Repeat-dose, Good Laboratory Practice (GLP) toxicity and toxicokinetic (TK) studies of 4, 13, and 26 weeks in duration have been conducted with imsidolimab administered by weekly SC and IV injection in cynomolgus monkeys. There were only minor treatment-related injection site findings in the 4-week repeat-dose study. Treatment-related effects in the 13-week toxicity study included increased observations of nonformed feces and prolapsed rectum, and protozoa in the stomachs of cynomolgus monkeys; the latter being consistent with the mechanism of action of an immune-modulator in cynomolgus monkeys (Dubey 2002). Weekly administrations of vehicle control article, 30 mg/kg/dose imsidolimab via SC injection, or 60 mg/kg/dose imsidolimab via SC or IV bolus injection, to male and female sexually mature cynomolgus monkeys during the 26-week toxicity and TK study was well tolerated. Imsidolimab-related effects were limited to a low incidence of liquid feces not considered AEs for animals administered 60 mg/kg/dose IV. Thus, the no observed adverse effect level (NOAEL) is 60 mg/kg/dose administered by SC or IV injection. These data provide a strong scientific rationale for advancing imsidolimab through clinical development.

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

2.2.2 CLINICAL STUDIES

Currently, two Phase 1 clinical studies (ANB019-001 and ANB019-005) have been completed. Study ANB019-001 was a Phase 1, first-in-human, single ascending dose (SAD) and multiple ascending dose (MAD) study in healthy volunteers and in subjects with psoriasis. Study ANB019-005 was a Phase 1, ethno-bridging study, a single-dose safety, tolerability, PK, and immunogenicity study of imsidolimab in healthy Japanese and Caucasian subjects. A detailed description of the safety and tolerability, and PK/pharmacodynamic (PD) results of these two Phase 1 clinical studies is provided in the IB.

In addition, four Phase 2 studies (ANB019-002, ANB019-003, ANB019-206 and ANB019-207) to evaluate clinical activity and safety of imsidolimab in GPP, PPP, ichthyosis, and EGFRi/MEKi related acneiform rash, respectively, are ongoing. Study ANB019-002 is a single-arm, multiple-dose study to be conducted in subjects with active GPP. Study ANB019-003 is a randomized, placebo-controlled, multiple dose study to be conducted in subjects with PPP. Study ANB019-206 is a randomized, placebo-controlled, multiple dose study to be conducted in adolescent and adult subjects with ichthyosis. Study ANB019-207 is a randomized, placebo-controlled, multiple dose study to be conducted in subjects with acneiform rash resulting from treatment with EGFRi/MEKi therapy.

2.3 RISK/BENEFIT ASSESSMENT

2.3.1 KNOWN POTENTIAL RISKS

No major toxicities were observed in the 4-week repeat-dose toxicity study in cynomolgus monkeys. The main finding consisted of minor, injection site reactions associated with the SC route of administration and not considered AEs.

In cynomolgus monkeys, 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 observation was not considered dose related. The increase in protozoa in the stomach has been observed in monkeys treated with immune-modulating drugs (Dubey 2002) and is consistent with the putative mechanism of action of imsidolimab. During the 26-week repeat-dose toxicity study, imsidolimab-related effects were limited to a low incidence of liquid feces. In the monkeys, the increased incidence of protozoa, nonformed feces, and prolapsed rectum were not considered AEs as they responded to veterinarian intervention. In humans, gastrointestinal infections can be clinically monitored and, in the case of most protozoa, are readily treatable even in the context of immunocompromised individuals (Farthing 2006).

One female monkey receiving 60 mg/kg imsidolimab IV was found moribund on Study Day 34. The cause of death was not determined and had an uncertain relationship to imsidolimab but

could be due to treatment-related immune modulation. However, data published on IL-36R deficient humans shows no deleterious effect on general health, and normal immune function is broadly preserved, indicating that inhibition of IL-36R, does not generally compromise host defenses. Similar to other immune-modulating treatment paradigms, subjects should be closely monitored for any clinical gastrointestinal manifestations including infections and evaluated on an ongoing basis. If a gastrointestinal infection is suspected, the subject should be treated as clinically indicated.

In the ANB019-001 study in healthy adults, single doses of imsidolimab up to 750 mg administered by IV infusion or SC injection to 32 healthy adults in the SAD part of the Phase 1 study were generally well tolerated with a similar number of treatment-emergent adverse event (TEAEs) reported in subjects receiving imsidolimab or placebo, 29 subjects (81%) and 11 subjects (92%), respectively. The most frequently reported AEs were upper respiratory tract infection (URTI; 10 [28%] imsidolimab; 6 [50%] placebo), headache (10 [28%] imsidolimab; 3 [25%] placebo), and viral URTI (4 [11%] imsidolimab; 1 [8%] placebo). Additionally, multiple doses of imsidolimab up to 300 mg administered by IV infusion once weekly for 4 weeks to 18 healthy adults were also well tolerated. Overall, TEAEs occurred in 16 subjects (89%) receiving imsidolimab and in 3 subjects (50%) receiving the placebo. The most common AEs were headache (7 [39%] imsidolimab; 1 [17%] placebo) and URTI (3 [17%] imsidolimab; 1 [17%] placebo).

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

One SAE of sepsis was reported in the ongoing ANB019-002 study in subjects with GPP; the SAE 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 subject recovery. Further details of imsidolimab clinical studies are in the IB.

As allergic or anaphylactic reactions may occur in any subjects treated with mAbs, subjects should be observed during study drug administration and for a period of 2 hr after study drug administration. Subjects with true allergic/anaphylactic reactions should not receive further doses of the monoclonal antibody. Symptoms of an apparent allergic reaction to the drug, also known as ‘cytokine release syndrome’, vary dramatically but can include:

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

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

2.3.2 KNOWN POTENTIAL BENEFITS

Subjects with AV may or may not receive direct benefit from participating in this study. Participation in this study also may help generate future benefit for larger groups of patients with AV if imsidolimab proves to be successful in treating this disease.

2.3.3 ASSESSMENT OF POTENTIAL RISKS AND BENEFITS

All quality, pharmacology and toxicology data, and satisfactory safety and tolerability data demonstrated in nonclinical and clinical studies are considered sufficient to expect a positive benefit/risk ratio for the treatment of AV with imsidolimab, and therefore to initiate this study.

The risk to subjects in this trial will be minimized by compliance with the eligibility criteria, proper study design, and close monitoring.

3 OBJECTIVES AND ENDPOINTS

3.1 PRIMARY OBJECTIVE AND ENDPOINT

Primary Objective	Primary Endpoint
To evaluate the efficacy of imsidolimab in subjects with AV	Change from Baseline in facial inflammatory lesion counts at Week 12

3.2 SECONDARY OBJECTIVES AND ENDPOINTS

Secondary Objectives	Secondary Endpoints
To evaluate the safety of imsidolimab in subjects with AV	Incidence of AEs, SAEs, and AEs leading to treatment discontinuation, as well as changes in vital signs, clinical laboratory parameters (hematology, biochemistry, and urinalysis), and 12-lead ECGs
To evaluate the effect of imsidolimab on AV signs and symptoms and quality of life in subjects with AV	• Change from Baseline in facial inflammatory lesion counts at visits other than Week 12 • Percent change from Baseline in facial inflammatory lesion counts at each visit • Change from Baseline in facial noninflammatory lesion counts at each visit • Percent change from Baseline in facial noninflammatory lesion counts at each visit • Change from Baseline in total facial lesion (inflammatory and noninflammatory lesions) counts at each visit • Percent change from Baseline in total facial lesion (inflammatory and noninflammatory lesions) counts at each visit • Change from Baseline in Facial IGA at each visit • Proportion of subjects achieving a Facial IGA of clear (0) or almost clear (1) with at least a 2-grade decrease from Baseline at each visit • Proportion of subjects in each response category for the PGIS at each visit • Proportion of subjects in each response category for the PGIC at each post-Baseline visit • Change from Baseline in DLQI/CDLQI at each visit

3.3 EXPLORATORY OBJECTIVES AND ENDPOINTS

Exploratory Objectives	Exploratory Endpoints
To further evaluate the effect of imsidolimab on AV signs and symptoms and quality of life in subjects with AV	• Two-point decrease from Baseline in Facial IGA at each visit • Change from Baseline in Truncal PGA for chest at each visit • Change from Baseline in Truncal PGA for neck at each visit

Exploratory Objectives	Exploratory Endpoints
	• Change from Baseline in Truncal PGA for back at each visit • Proportion of subjects achieving a Truncal PGA for chest of clear (0) or almost clear (1) with at least a 2-grade decrease from Baseline at each visit Proportion of subjects achieving a Truncal PGA for neck of clear (0) or almost clear (1) with at least a 2-grade decrease from Baseline at each visit • Proportion of subjects achieving a Truncal PGA for back of clear (0) or almost clear (1) with at least a 2-grade decrease from Baseline at each visit • Proportion of subjects in each response category for the SSQ at each visit • Proportion of subjects in each response category for the SSRS at Week 12 and Week 20 • Change from Baseline in lesion counts based on blinded photographic assessment at each visit
To explore the effect of imsidolimab on cutaneous biomarkers	Assessment of biomarkers in tape strips
To test for immunogenicity to imsidolimab	Presence of anti-drug antibodies to imsidolimab
To describe the PK profile of imsidolimab in subjects with AV	Serum concentration following imsidolimab administration and other parameters as appropriate will be determined to describe the PK profile of imsidolimab

4 STUDY DESIGN

4.1 OVERALL DESIGN

his is a Phase 2, multicenter, randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of imsidolimab in adolescent and adult subjects with AV. This study will also characterize the PK profile of imsidolimab and explore the immune response to imsidolimab in subjects with AV.

To be eligible for this study, subjects must be aged 12 to 45 and have moderate to severe facial acne vulgaris at Screening and Day 1, defined as follows:

1. Facial IGA score of 3 (moderate) or 4 (severe).
2. At least 20 and no more than 100 inflammatory lesions on the face.
3. No more than 100 noninflammatory lesions on the face.
4. No more than 5 nodules (≥ 5 mm) on the face.

The maximum study duration per subject is approximately 24 weeks, which includes a screening period of up to 30 days followed by a 12-week treatment period and an 8-week safety follow-up period.

Eligible subjects will be randomized (1:1:1) to receive either imsidolimab (at 1 of 2 different regimens) or placebo, SC administered on 3 occasions: Day 1, Day 29 (Week 4), and Day 57 (Week 8). The randomization will be stratified based on facial IGA score at baseline (3 [moderate] versus 4 [severe]).

The treatment arms will be as follows:

1. Imsidolimab 400 mg on Day 1, followed by 200 mg on Days 29 and 57
2. Imsidolimab 200 mg on Day 1, followed by 100 mg on Days 29 and 57
3. Placebo on Days 1, 29, and 57

For scheduled on-site study visits, subjects will come to the study site on 7 occasions: Screening and Days 1, 15, 29, 57, 85, and 141 (EOS)/ET. All procedures will be conducted in accordance with the SoA in Section 1.3.

Disease activity will be evaluated for all subjects using facial inflammatory and noninflammatory lesion count, Facial IGA, Truncal (chest, neck, and back) PGA, DLQI for subjects ≥16 years of age and CDLQI for subjects < 16 years of age, PGIS, PGIC, SSQ, and SSRS.

Safety assessments will include AE/ SAE monitoring, vital signs, physical examination, ECGs, and clinical laboratory tests (hematology, biochemistry, and urinalysis).

Facial photography will be conducted at each study visit. Optional truncal photography will be performed at selected sites.

Blood samples will be collected during the study to determine PK and immunogenicity (presence of ADA to imsidolimab) on Day 1 before the administration of the study treatment and at the

other time points specified in the SoA (Section 1.3). Any remaining serum/plasma from samples collected for PK/PD immunogenicity endpoints may be retained for assay method development, troubleshooting, or validation. The samples will not be used for any type of genetic analyses.

Tape strips will be collected at Day 1, Week 4, and Week 12 to study key biomarkers.

Interim analyses (IA) may be performed for assessment of all primary and secondary efficacy endpoints and evaluation of all safety data available.

4.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

Acne vulgaris remains one of the most commonly occurring chronic diseases in the world and can result in scarring and have significant impact on quality of life. The multiple pathophysiological triggers for AV have resulted in many different treatment options/targets (eg, antibiotics, hormonal agents, retinoids). In this context, the development of agents with new mechanisms of action and improved safety profiles is considered important for future clinical practice and may provide additional options to patients who do not respond to or cannot tolerate existing therapies. As imsidolimab offers the potential for inhibition of IL-36 signaling by blocking IL-36R, it may provide a novel strategy for treatment of patients with AV.

The proposed design is considered appropriate for assessing the safety and tolerability of imsidolimab in subjects with AV, and the efficacy of imsidolimab compared with placebo in subjects with AV.

Randomization will ensure random allocation of subjects to treatment arms to reduce bias. Because efficacy assessments of AV have a high degree of subjectivity, the study will be double-blinded. The highest degree of subject and assessor (Investigator or designee) blinding should be sought to achieve credible inference. It is also important to have a placebo in this Phase 2 study to control for confounding factors, such as potential Investigator bias, and to ensure that the statistical procedures can be appropriately applied.

4.3 JUSTIFICATION FOR DOSE

During the treatment period, imsidolimab will be SC administered as a 400-mg dose on Day 1, followed by 200-mg doses on Days 29 and 57; or as a 200 mg dose on Day 1, followed by 100-mg doses on Days 29 and 57.

The doses selected for the study demonstrated a favorable safety and tolerability profile in a Phase 1 study conducted in healthy volunteers. In addition, imsidolimab demonstrated linear PK with an estimated $t_{1/2}$ of approximately 28 days at all doses tested with persistent pharmacodynamic activity. The loading dose of 400 mg SC administered on Day 1 was chosen to quickly achieve the initial PK exposure needed for response soon after dosing in order to

provide optimal potential benefit to AV subjects and to reach steady state concentrations rapidly following 200 mg SC dosing. The loading dose of 200 mg SC administered on Day 1 followed by 100 mg doses every four weeks is expected to be lower than the exposure-response curve, allowing for the assessment of dose-dependent effects and to inform dosing in future studies.

4.4 END OF STUDY DEFINITION

A subject is considered to have completed the study if he or she has completed all periods of the study including the last specified visit (Day 141 [Week 20]/) shown in the SoA (Section 1.3).

The end of the study is defined as completion of the last visit or procedure shown in the SoA by the last subject included the study.

4.5 MODIFICATIONS TO STUDY CONDUCT DUE TO THE CORONAVIRUS DISEASE 2019 (COVID-19) PANDEMIC

As a consequence of the COVID-19 pandemic that has had a worldwide impact, including cases in North America and Europe, control measures in place in different regions may impact the ability to adhere to some of the study procedures described in this protocol. Due to challenges that include, but are not limited to, subject preferences, study site closures, travel restrictions, and quarantines, some modifications to study conduct during the COVID-19 pandemic may be necessary to ensure study continuity, including conducting optional home visits when on-site study visits are considered not feasible. Such modifications in study conduct always must be in accordance with local regulations/mandates. The following are allowable, as necessary, modifications to study conduct during the COVID-19 pandemic:

- Prior to a visit at the study site, the subject may be contacted and screened for potential exposure to or infection with COVID-19 per site, local or federal requirements. If the subject is suspected of having been or is currently infected with COVID-19, the on-site visit should either be re-scheduled or a virtual visit may be performed, as applicable.
- In the event that a subject cannot attend their regularly scheduled study visits in person due to COVID-19 necessitating a limit on in-person contact, the Investigator may perform safety and efficacy assessments by phone or video, with home nursing visit support for procedures that cannot be done virtually. The Investigator may use the technology platform that is currently available to them. Suggested platforms include Apple FaceTime, Zoom for Healthcare, Facebook Messenger video chat, Microsoft Team, Google Hangouts video, and Skype. Home nursing visit support may be used in addition to phone or video at visits that require procedures that cannot be done via phone or video alone, such as but not limited to, ECG, PK draws, clinical laboratory draws, study drug administration. The home nurse will collect the lab samples and perform all applicable study assessments that are possible during a home visit, including collection of adverse events and concomitant medications.

During the COVID period, if any data is collected at a home visit, it will be recorded by the home nurse in the source documents and the originals will be sent back to the site for data entry into the electronic data capture system for storage/archiving.

- Clinical laboratory tests (chemistry and hematology) and pregnancy tests may be performed by local laboratory if home nursing visits are not possible and sample collection cannot be performed at the study site due to COVID 19-related limitations, including but not limited to site closure. Abnormal laboratory results should be promptly communicated to the Medical Monitor. Subjects' anonymity must be maintained when communicating results to the Medical Monitor.
- At home study drug administration by home health nurses may be done.
- Source documentation should note that the visit was performed virtually (not face-to-face), and note the name of the local laboratory where laboratory tests were done.
- If certain study procedures or assessments cannot be completed per the schedule of events, the reason for the missed assessment (ie, laboratory, vital signs, physical exams, etc.) must be noted in the source documentation (eg, COVID-19), captured in the protocol deviations documentation, and reported to the IRB/Ethics Committee, as applicable.

A detailed assessment of COVID-19 related risk and mitigation measures will be documented in the appropriate study plans.

5 STUDY POPULATION

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

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

5.1 INCLUSION CRITERIA

To be eligible to participate in this study, a subject must meet all of the following criteria, either at the screening and Day 1 visits or only at one of the specified visits (screening or Day 1) as noted in the criterion:

1. Male and female aged 12 to 45 years (inclusive) at the time of signing the informed consent/assent.
2. Moderate to severe facial AV at Screening and Day 1, defined as follows:
    a. Facial IGA score of 3 (moderate) or 4 (severe)
    b. At least 20 and no more than 100 inflammatory lesions on the face
    c. No more than 100 noninflammatory lesions on the face.
    d. No more than 5 nodules (≥5 mm) on the face
3. Subject agrees to use Cetaphil Skin Cleanser on a regular basis (ideally once or twice daily) for at least 1 week prior to Day 1 and agrees to continue using Cetaphil Skin Cleanser at the same frequency throughout the study.
4. Subject must meet the following laboratory criteria at screening:
    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 × 109/L (≥ 100×10^3/µL)
    d. Serum creatinine <132.6 µmol/L (< 1.5 mg/dL)
    e. Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤ 2 upper limit of normal (ULN)
    f. Total bilirubin ≤ 1.5 × ULN. Subjects with known Gilbert's disease who have serum bilirubin < 3 × ULN may be included
5. Body weight ≥ 40 kg and BMI within the range of 18 to 40 kg/m^2 for adults and 16 to 40 kg/m^2 for adolescents, inclusive {BMI = weight (kg)/[height (m)]^2}).
6. Contraceptive use by men and women should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.

    Contraception and pregnancy:

    a. A male subject must agree to use contraception as detailed in Appendix 1 of this protocol during the treatment period and for at least 200 days (which includes the duration of relevant exposure plus the duration of sperm cycle) after the last study treatment administration and refrain from donating sperm during this period.

b. Female subjects:
    i. A woman of childbearing potential (WOCBP) is eligible to participate if she has a negative serum pregnancy test (β-human chorionic gonadotropin) at screening and a negative urine pregnancy test at Day 1 (see Appendix 1), is not breastfeeding, and agrees to follow the contraceptive guidance in Appendix 1 during the treatment period and for at least 6 months after receiving the study treatment, and refrains 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 at Day 1 (eg, hormonal contraception should be initiated at least 12 Weeks before Day 1. For WOCBP, hormonal contraceptives must be used without schedule changes and in steady doses during the study treatment. Starting hormonal contraceptives during the study is not permitted. Use of any hormonal contraceptives containing drospirenone, chlormadinone acetate, or cyproterone acetate is prohibited unless part of a stable contraceptive regimen as described in Section 6.5.1.
    ii. A woman not of childbearing potential as defined in Appendix 1, must have a follicle-stimulating hormone (FSH) test confirming nonchildbearing potential.
    iii. An adolescent subject who experiences menarche during the trial will be considered a WOCBP and will be required to follow the contraceptive guidance for WOCBP in Appendix 1 and undergo pregnancy testing as detailed in the SoA (Section 1.3).
7. Willing to participate and capable of giving written informed consent, which must be personally signed and dated by the subject and obtained prior to any trial-related activities. Subjects who need to provide assent, as per local requirement, need to have their parent(s) or legal representative read and sign the informed consent form prior to any study-related procedures. Adolescent subjects who reach 18 years of age during the study must be reconsented as adults.
8. Willing to comply with all study procedures and lifestyle considerations, and must be available for the duration of the study.

5.2 EXCLUSION CRITERIA

A subject who meets any of the following criteria at the screening and/or Day 1 visits, as applicable, will be excluded from participation in this study:

1. Has acne fulminans or conglobate or secondary acne, including drug induced acne (steroids, cloracne, lithium, EGFRi [eg, cetuximab, erlotinib, panitumumab, gefitinib], associated with acneiform eruptions, including PRIDE [papulopustules and/or paronychia, regulatory abnormalities of hair growth, itching, and dryness due to EGFRi]) syndrome).
2. Acne associated with known hormonal imbalances such as polycystic ovaries, Cushing syndrome, congenital adrenal hyperplasia (CAH), androgen-secreting tumors, and

acromegaly. Patients with signs/symptoms of hyperandrogenism such as hirsutism should undergo hormonal status assessment at the discretion of the Investigator.

3. Acne as part of a known genetic syndrome, such as SAPHO, PAPA, PASH or other variants possibly associated with PSTPIP1 gene.
4. Extensive (acne) keloids and hypertrophic scarring making clinical evaluation difficult.
5. Hidradenitis suppurativa also called acne inversa.
6. Other forms of acne rosacea, peri-oral dermatitis and gram-negative folliculitis.
7. Concomitant dermatological condition (skin burn, sun burn, extensive scarring), or excessive facial hair or beard that may interfere with the Investigator's ability to evaluate the subject's response to therapy.
8. Clinically significant medical condition or physical/laboratory/ECG/vital signs abnormality that would, in the opinion of the Investigator, put the subject at undue risk or interfere with interpretation of study results.
9. Any evidence of active infection that required systemic treatment within 4 weeks of Day 1 (eg, bronchopulmonary, urinary, or gastrointestinal).
   Note: Subjects with localized oral or genital herpes simplex that, in the opinion of the Investigator, is well-controlled may participate in the study.
10. Opportunistic infection (eg, Pneumocystis carinii, aspergillosis, or mycobacteria other than tuberculosis [TB]) or parasitic infections (eg, helminths, protozoa, Trypanosoma cruzi) within 6 months prior to screening.
11. Herpes zoster infection within 8 weeks prior to screening.
12. Known or suspected congenital or acquired immunodeficiency state, or condition that would compromise the subject's immune status (eg, history of splenectomy).
13. History of cancer or lymphoproliferative disease within 5 years prior to Day 1. Subjects with successfully treated nonmetastatic cutaneous squamous cell or basal cell carcinoma and/or localized carcinoma in situ of the cervix are not to be excluded.
14. Any major surgery within 4 weeks prior to Day 1 or has a major surgery planned during the study.
15. Any significant drug allergy or reaction (such as anaphylaxis or hepatotoxicity) and reactivity to polysorbate-20, a component of imsidolimab formulation, or the inactive ingredients (excipients).
16. Has taken the following drugs or had the following procedures within the specified period prior to Day 1:
    a. Over-the-counter (OTC) topical medication for the treatment of AV, including benzoyl peroxide, topical anti-inflammatory medications, corticosteroids, salicylic acid, α-hydroxy/glycolic, or antibacterial/antiseptic soap or wash within 2 weeks prior to Day 1.
    b. Prescription topical retinoids (eg, tretinoin, tazarotene, adapalene, dapsone) or antimicrobials (eg, clindamycin, erythromycin), or other prescription topical

medications for the treatment of AV within 4 weeks prior to Day 1. Topical antibiotics may be used to treat non-acne skin lesions not on the face.

c. Systemic anti-acne drugs not mentioned in other exclusion criteria within 4 weeks prior to Day 1.
d. Oral or injectable corticosteroids within 4 weeks prior to Day 1 or require them during the study.
   Note: Intranasal corticosteroids and inhaled corticosteroids are allowed. Eye and ear drops containing corticosteroids are also allowed.
e. Use of any systemic hormonal treatment (in particular anti-androgens, such as spironolactone, finasteride, flutamide) within 4 weeks before Day 1. Oral contraceptives can be continued if stable for the last 12 weeks before Day 1 and if stable in dose and dosing regimen and type (brand), and if the subject plans to continue throughout the study period.
f. Drospirenone, chlormadinone acetate, or cyproterone acetate within 12 weeks prior to Day 1, unless part of a stable contraceptive regimen as described in Section 6.5.1.
g. Previous surgical, physical (such as ThermaClear™), light (including blue or UV light, photodynamic therapy [PDT]) or laser therapy within 12 weeks prior to Day 1.
h. Cryodestruction, chemodestruction, dermabrasion, acne surgery, intralesional steroids, X-ray therapy procedures performed on the face within 12 weeks prior to Day 1.
i. Systemic antibiotics (including tetracyclines) within 4 weeks prior to Day 1.
j. Systemic antiviral medication (except for prevention of localized oral or genital herpes simplex) within 4 weeks prior to Day 1.
k. Any nonbiologic investigational drug within 4 weeks or 5 half-lives, whichever is longer prior to Day 1.
l. Marketed or investigational biological agent within 12 weeks or 5 half-lives (whichever is longer) prior to Day 1.
m. Live attenuated vaccine within 12 weeks prior to Day 1 , including any approved for COVID-19. Live attenuated vaccines may be utilized after the subjects complete the 8-week standard safety follow-up period of the study. Note: Non-live-attenuated vaccines for COVID-19 (eg, RNA-based vaccines, protein-based vaccines) are allowed during the study.
n. Previous treatment with anti-IL-36R, anti-IL-36, anti-tumor necrosis factor (TNF)/ IL-12/IL-23/ IL-17, or any other mAbs within 12 weeks or 5 half-lives (whichever is longer) prior to Day 1.
o. Oral retinoid (eg, isotretinoin) or vitamin A supplements > 10,000 U/d within 26 weeks prior to Day 1.
p. Previous treatment with imsidolimab.

17. Has had excessive sun exposure, is planning a trip to a sunny climate, or has used tanning booths within 4 weeks prior to Day 1 or is not willing to minimize natural and artificial

sunlight exposure during the study. Use of sunscreen products and protective apparel are recommended when sun exposure cannot be avoided.

18. Active TB or latent TB infection as indicated by a positive QuantiFERON®-TB Gold test at screening or within 6 months prior to screening (if the test is indeterminate, it can be repeated only once; chest X-ray will be administered per local standards, as required), and/or clinical examination, or has had active TB disease at any time in the past.
19. Clinically significant drug or alcohol abuse in the last year prior to Day 1, or other factors limiting the ability to cooperate and to comply with the study protocol, as determined by the Investigator.
20. Subject is a pregnant or lactating woman, or a woman who intends to become pregnant during the study period.
21. Any other physical, mental, or medical conditions, which, in the opinion of the Investigator, make study participation inadvisable or could confound study assessments.
22. Positive blood screen for hepatitis C antibody and hepatitis C RNA, antibodies to hepatitis B core antigens, hepatitis B surface antigen, or human immunodeficiency virus 1 and 2 antibodies.
23. Is not able to tolerate SC drug administration.

5.3 LIFESTYLE CONSIDERATIONS

Subjects will be provided with Cetaphil Skin Cleanser, which is the only cleanser permitted during the conduct of the study and should be used as described in Section 6.5.1.

Topical bland emollients (without pharmacological active ingredients) are allowed during the study, except within 3 hr prior to the study visit. Make-up, facial moisturizers, creams, lotions, and/or sunscreens are also allowed during the study, except within 3 hr prior to the study visit. Use of sunscreen products and protective apparel are recommended when sun exposure cannot be avoided.

For subjects who use emollients, make-up, facial moisturizers, creams, lotions, and/or sunscreens, the same product brands/types should be used at the same frequency throughout the study. Every effort should be made to keep the same products throughout the study. In case a subject applied these products on the face on a visit day, they will be instructed to wash their face with Cetaphil Skin Cleanser at least 3 hr before the visit and not reapply these products on the face before the visit.

Subjects should continue with their regular shaving habits (if applicable) during the study, but must not shave their face within 3 hr prior to study the visit.

5.4 SCREEN FAILURES

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

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened once after discussion with the Medical Monitor. Rescreened subjects should not be assigned the same subject number as for the initial screening. All procedures planned at the screening visit, including signature of a new consent/assent form, will be performed.

5.5 STRATEGIES FOR RECRUITMENT AND RETENTION

The recruitment and retention strategies for the study will be covered in other study plans.

6 STUDY TREATMENT

Study treatment is defined as any investigational treatment or placebo intended to be administered to a clinical study subject according to the study protocol.

6.1 STUDY TREATMENT ADMINISTRATION

6.1.1 STUDY TREATMENT DESCRIPTION

Imsidolimab is a humanized IgG4 (S228P)/kappa mAb that belongs in the class of anti-IL-36R mAb. Details regarding imsidolimab and placebo study treatment are described in Table 2 and further information will be provided in the Pharmacy Manual.

6.1.2 DOSING AND ADMINISTRATION

Study treatment dosing and administration details are provided in Table 2. Further information will be provided in the Pharmacy Manual.

Table 2: Study Treatment Details

Study Treatment Name:	**Imsidolimab (ANB019) Anti-interleukin 36 receptor monoclonal antibody**	**Placebo**
Dosage Form:	Solution for injection	
Source of procurement:	AnaptysBio, Inc.	
Study Treatment Description	Imsidolimab will be provided as a sterile, colorless to yellow, and clear to slightly opalescent solution supplied in a single use, 2R, Type I glass vial with a fill volume of 1.2 mL. Each vial contains 120 mg of imsidolimab at a concentration of 100 mg/mL.	The placebo contains no active ingredient and will be provided as a sterile, colorless to slightly yellowish, and clear to very slightly opalescent solution supplied in a single use, 2R, Type I glass vial with a fill volume of 1.2 mL.
Dosage Formulation:	100 mg/mL imsidolimab in 25 mM-histidine, 60 mM-NaCl, 145 mM sorbitol, and 0.02% v/v polysorbate-20 at pH 6.0.	Placebo (25 mM-histidine, 60 mM-NaCl, 145 mM sorbitol, and 0.02% v/v polysorbate-20, at pH 6.0).
Unit Dose Strength(s)/ Dosage Level(s):	Study treatment will be administered as 400/200/100 mg of imsidolimab or placebo. 1 mL vials of active and placebo doses will be provided to sites and prepared by an unblinded pharmacist according to Table 3.	
Route of Administration:	SC injection (3 doses during the treatment period)	
Dosing Instructions:	Imsidolimab and placebo should be administered by clinic staff trained in best practices for SC administration of study treatments.	

Study Treatment Name:	**Imsidolimab (ANB019) Anti-interleukin 36 receptor monoclonal antibody**	**Placebo**
	For SC injections, imsidolimab and placebo should be prepared by drawing up the required dosing volume into suitable sized syringe and attaching a dosing needle. No further dilution is required. Syringes should be covered in tape by an unblinded pharmacist to obscure color and volume. The preferred anatomical site of SC administration is the abdomen; however, the injection may be made in the upper arm, if needed. A 30-minute observation period should be included after the first dose administered. The same anatomical site should be used throughout the entire study for a given subject (ie, do not administer one dose into the upper arm and at a subsequent visit or dose, administer the next dose into the abdomen). Subsequent doses should be rotated within an anatomical site (ie, if the upper left abdominal quadrant is used as the initial site of administration, then the next administration at a subsequent visit should be rotated to the upper right quadrant). Subcutaneous injections should not be given into moles, scars, tattoos, or areas where the skin is tender, bruised, red, hard, or not intact. Prior to SC needle insertion, the skin will be pinched between the thumb and index finger to separate the subcutaneous layer from the muscle. The needle is to be injected at a 90-degree angle to the fat pad. The plunger will be pressed gently until the entire dose is delivered to the SC space and the needle will be held in place (fully depressed) for 10 seconds after the injection is administered. The needle will be removed and then the skin pinch released; any leakage or backflow of fluid from the administration site onto the surface of the skin will be noted and documented in the eCRF. The site of administration is NOT to be massaged by either the clinic staff or by the subject for at least 60 minutes after drug administration.	

Abbreviations: eCRF, electronic case report form; NaCl, sodium chloride; SC, subcutaneous.

The contents of the label will be in accordance with all applicable regulatory requirements.

Table 3: Treatment Administration Schedule

Arm	Day 1 2 x 2 mL[a]	Weeks 4 and 8 1 x 2 mL[a]
1 (400mg/200mg)	2 x 2 mL imsidolimab	1 x 2 mL imsidolimab
2 (200mg/100mg)	1 x 2 mL imsidolimab 1 x 2 mL placebo	1 x 2 mL [imsidolimab (1 mL): placebo (1 mL)]
3 (Placebo)	2 x 2 mL placebo	1 x 2 mL placebo

a Study treatment will be provided as 1 mL vials of imsidolimab 100 mg/mL or placebo, and 2 mL will be prepared from two individual vials in a covered syringe by an unblinded pharmacist according to the schedule above. The contents of the syringe and the injection procedure will not be visible to subjects.

6.2 PREPARATION/HANDLING/STORAGE/ACCOUNTABILITY

The Investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study treatments received, and any discrepancies are to be reported and resolved before use of the study treatment.

Only subjects randomized in the study may receive study treatment and only authorized study site staff may supply or administer study treatment. Further guidance and information for the administration of the study treatment are provided in the Pharmacy Manual.

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 site staff.

Imsidolimab vials must be refrigerated at 2°C to 8°C (36°F to 46°F) until the day of use. Imsidolimab must not be used beyond the re-test or expiration date provided by the manufacturer. Vial contents should not be frozen or shaken. Imsidolimab vials undiluted may be stored at room temperature (8°C to 25°C [46°F to 77°F]) for up to 8 hr. Vials are intended for single use only; therefore, any remaining solution should not be used and should be discarded after study treatment accountability and reconciliation.

The Investigator is responsible for study treatment accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).

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

Further guidance and information for the final disposition of unused study treatment are provided in the Pharmacy Manual.

6.3 MEASURES TO MINIMIZE BIAS: RANDOMIZATION AND BLINDING

This study includes a randomized, double-blind treatment period and safety follow-up period. The blind will be maintained throughout the study with limited and controlled access to the randomization code.

All subjects will be assigned a unique 'subject identification number' at the time of screening. On Day 1, after verification that all inclusion and no exclusion criteria have been met, the subjects will be stratified by facial IGA score at baseline (3 [moderate] versus 4 [severe]) and randomized in a 1:1:1 ratio to receive imsidolimab at one of two doses or placebo. As subjects become eligible, they will be assigned unique randomization numbers, which will be used to assign the allocated treatment based on a randomization schedule.

The 400 mg loading dose of imsidolimab will be delivered to subjects in Arm 1 as two 2-mL injections. To maintain the blind, subjects in Arm 2 receiving the 200 mg loading dose will receive one 2-mL injection of imsidolimab and one 2-mL injection of placebo, and subjects assigned to placebo will receive two 2-ml injections of placebo (see Table 3). At Weeks 4 and 8, subjects will receive 1 x 2 mL injection of either imsidolimab, 1:1 imsidolimab:placebo, or placebo. AnaptysBio, Investigator, and subjects will be blinded to treatment assignment of imsidolimab or placebo. An unblinded Pharmacist will be responsible for study treatment dispensing. Because active study treatment is slightly different in appearance from placebo, syringes will be covered in tape.

Once the subject has provided informed consent/assent and meets all inclusion and no exclusion criteria, the study site will request the treatment assignment using a central Interactive Web Response System (IWRS).

The process for breaking the blind will be handled through the IWRS. Unblinding is undertaken by a predetermined process to ensure that participating subject and study team are not unblinded unnecessarily and the study results are not compromised. Unblinding of treatment assignment during the study should occur only if it is necessary to know what treatment the subject received during the placebo-controlled period. Unblinding should occur if the Investigator deems identification of the study treatment is necessary for the purpose of providing urgent subject care, and knowledge of the subject's treatment assignment (imsidolimab or placebo) will alter subsequent care (emergency unblinding).

In the event that emergency unblinding is necessary, the Investigator must ensure that the unblinding of the treatment code is performed in a discrete manner and the treatment is disclosed only to those persons involved with the direct medical care of the subject. The Investigator must provide the reason for unblinding to the AnaptysBio Medical Monitor according to AnaptysBio instructions following emergency unblinding.

AnaptysBio and the contract research organization (CRO) must be notified when a subject and/or Investigator is unblinded during the study. The IWRS will create the blinded and/or unblinded notification when the blind is broken, which can be sent via email as per the user role of IWRS. The unblinding will be captured in the IWRS audit trail. Pertinent information regarding the circumstances of unblinding of a subject's treatment code must be documented in the subject's source documents.

6.4 STUDY TREATMENT COMPLIANCE

Study treatment compliance in this study will be under the direct control of the Investigator; the study treatments will be administered on site.

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

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

6.5 CONCOMITANT THERAPY

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

- Reason for use
- Dates of administration including start and end dates
- Dosage information including dose, route, and frequency

In addition, all prior medications used to treat AV disease conditions taken within 6 months prior to enrollment and any other medications taken within 4 weeks prior to enrollment must be recorded in the eCRF. The concomitant treatments for other indications that are not listed in the prohibited therapies or procedures (Section 6.5.2) must be on a stable dose for at least 4 weeks before study treatment administration (Day 1). Dose adjustments of these treatments should be avoided during the study. Live attenuated vaccines may be utilized after the subjects complete the safety follow-up period of the study. During the follow-up period, no study drug will be administered and 12 weeks (at least three half-lives of study drug) is estimated to be a sufficient period after the last dose administration when a live attenuated vaccine can be safety administered.

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

6.5.1 PERMITTED THERAPIES

Cetaphil Skin Cleanser is the only permitted skin cleanser during the conduct of the study. Subject should use Cetaphil Skin Cleanser on a regular basis (ideally once or twice daily) for at least 1 week prior to Day 1 and at the same frequency throughout the study.

Topical bland emollients (without pharmacological active ingredients) are allowed during the study, except within 3 hr prior to study visits. Make-up, facial moisturizers, creams, lotions, and/or sunscreens are also allowed during the study, except within 3 hr prior to the study visit.

Oral contraceptives should be continued if stable for the last 12 weeks before Day 1 and if stable in dose and dosing regimen and type (brand) and if the subject plans to continue throughout the study period.

Intranasal corticosteroids and inhaled corticosteroids are allowed. Eye and eardrops containing corticosteroids are also allowed.

Non-live-attenuated vaccines for COVID-19 (eg, RNA-based vaccines, protein-based vaccines) are allowed during the study. The Medical Monitor should be consulted to confirm that the vaccine received is allowed and that subject participation in the study should be continued. Of note, COVID-19 vaccines should be captured as a concomitant medication and any related symptoms documented as AEs.

6.5.2 PROHIBITED MEDICATIONS OR PROCEDURES

Prohibited medications/therapy are listed in Table 4. The use of a prohibited medication/therapy is a protocol violation and must be recorded in the eCRF. Subjects who start prohibited medications or therapies that have been demonstrated to be effective for treatment of AV during the study will be withdrawn from study treatment. Subjects who start any other prohibited medications or therapies during the study may be withdrawn from study treatment if an impact on efficacy assessment or safety of the subjects is expected. If in any doubt, Investigator is advised to discuss medications with the Medical Monitor. In addition, the Investigator must notify the Medical Monitor in order to make a decision as to whether the subject will be withdrawn from the study.

All treatments likely to have efficacy in AV need to be discontinued prior to treatment initiation (prior to Day 1). All medications listed below are also restricted during the study period. If treatment with any of these prohibited treatments is essential, then the subject must notify the study team.

Table 4: List of Prohibited Medications and Procedures

Prohibited Medication/Procedure	Washout Period
Over-the-counter (OTC) topical medication for the treatment of acne vulgaris, including benzoyl peroxide, topical anti-inflammatory medications, corticosteroids, salicylic acid, α-hydroxy/glycolic, or antibacterial/antiseptic soap or wash.	2 weeks of Day 1
Prescription topical retinoids (eg, tretinoin, tazarotene, adapalene, dapsone) or antimicrobials (eg, clindamycin, erythromycin), or other prescription topical medications for the treatment of AV. Topical antibiotics may be used to treat non-acne skin lesions not on the face.	4 weeks of Day 1
Systemic anti-acne drugs not mentioned in other exclusion criteria within 4 weeks prior to Day 1.	4 weeks of Day 1
Oral or injectable corticosteroids within 4 weeks prior to Day 1 or require them during the study. Note: Intranasal corticosteroids and inhaled corticosteroids are allowed. Eye and ear drops containing corticosteroids are also allowed.	4 weeks of Day 1
Use of any systemic hormonal treatment (in particular anti-androgens, such as spironolactone, finasteride, flutamide). Oral contraceptives can be continued if stable for the last 12 weeks before Day 1 and if stable in dose and dosing regimen and type (brand), and if the subject plans to continue throughout the study period.	4 weeks of Day 1
Systemic antibiotics (including tetracyclines).	4 weeks of Day 1
Systemic antiviral medication (except for prevention of localized oral or genital herpes simplex).	4 weeks of Day 1
Any nonbiologic investigational drug.	4 weeks or 5 half-lives of Day 1, whichever is longer
Previous surgical, physical (such as ThermaClear™), light (including blue or UV light, PDT) or laser therapy.	12 weeks of Day 1
Cryodestruction, chemodestruction, dermabrasion, acne surgery, intralesional steroids, X-ray therapy procedures performed on the face.	12 weeks of Day 1
Marketed or investigational biological agent.	12 weeks or 5 half-lives of Day 1, whichever is longer
Live-attenuated vaccine. Note: Non-live attenuated vaccines for COVID-19 (eg, RNA-based vaccines, protein-based vaccines) are allowed during the study.	12 weeks of Day 1
Previous treatment with anti-IL-36R, anti-IL-36, anti-tumor necrosis factor (TNF)/IL-12/IL-23/ IL-17 mAbs	12 weeks or 5 half-lives of Day 1, whichever is longer
Drospirenone, chlormadinone acetate, or cyproterone acetate, unless part of a stable contraceptive regimen as described in Section 6.5.1	12 weeks of Day 1
Oral retinoid (eg, isotretinoin) or vitamin A supplements > 10,000 U/d	26 weeks of Day 1

Abbreviations: AV, acne vulgaris; COVID-19, Coronavirus Disease 2019; OTC, over-the-counter; PDT, photodynamic therapy

6.6 RESCUE TREATMENT

No rescue treatments are permitted in this study.

6.7 DOSE MODIFICATION

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

6.8 TREATMENT AFTER THE END OF THE STUDY

All subjects will return to the study site for the EOS (Day 141/Week 20) or ET visit for final safety and EOS assessments. After this visit, subjects should be treated according to the clinical judgment of the subject's physician. Care after EOS/ET will not be provided by AnaptysBio, Inc. Any SAE or pregnancy occurring through the EOS visit should be reported to the pharmacovigilance unit (Section 8.2.1) and followed up until an outcome is determined.

7 STUDY TREATMENT DISCONTINUATION AND SUBJECT DISCONTINUATION/WITHDRAWAL

7.1 DISCONTINUATION OF STUDY TREATMENT

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

Discontinuation from study treatment does not mean discontinuation from the study, and remaining study procedures should be completed as indicated by the study protocol. In case of early withdrawal from the study treatment and study, the subject will be required to attend the ET visit.

7.1.1 TEMPORARY INTERRUPTION

Study treatment can be interrupted temporarily for any individual subject in case of an AE as per the Investigator's discretion. The Medical Monitor should be informed. Re-starting of study treatment can be done after discussion with the Medical Monitor.

7.1.2 RE-CHALLENGE

The study treatment can be reintroduced at the next scheduled administration visit at the Investigator's discretion and after discussion with the Medical Monitor. Study treatment will be reintroduced at the maintenance dose (200 mg imsidolimab, 100 mg imsidolimab, or placebo). In case of positive re-challenge, the study treatment should be withdrawn permanently.

7.2 SUBJECT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

A subject may withdraw from the study at any time at his or 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 treatment and the study, the subject will be required to attend the ET visit (see the SoA in Section 1.3). After the ET visit, additional follow-up visits may be scheduled to follow any ongoing AE. Subjects must be withdrawn from the study under the following circumstances, any SAE or AE which, in the opinion of the Investigator, warrant study discontinuation for safety reasons, or pregnancy occurring through the EOS, which should be followed up until outcome.

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

- Pregnancy (refer to Appendix 1 and Section 8.2.1.8)
- Significant deviation/lack of compliance with protocol
- Any significant AE, laboratory abnormality, or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the subject in the opinion of the Investigator
- Disease progression which requires discontinuation of the study treatment
- Withdrawal of consent
- Lost to follow-up
- Use of any prohibited medication or treatment that in the opinion of the Investigator necessitates the subject being withdrawn (refer to Section 6.5.2)
- Termination of the subject participation by the Investigator or AnaptysBio

The reason for subject discontinuation or withdrawal from the study will be recorded on the eCRF.

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

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

Subjects withdrawing from the study prematurely for reasons other than a study treatment-related AE may be replaced at the discretion of AnaptysBio.

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 site.

The following actions must be taken if a subject fails to return to the clinic for a required study visit (unless this is required by the COVID-19 situation and virtual visits are scheduled instead):

- The study site 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. If the re-scheduled visit falls within the next visit's window, then the visit should be considered a missed visit and the subject should come in for the next scheduled visit as planned. Missed visits must be captured in the eCRFs and will be recorded as a protocol deviation.

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

8 STUDY ASSESSMENTS AND PROCEDURES

Study procedures and their timing are summarized in the SoA (Section 1.3). Assessments scheduled on the day of study treatment administration must be performed prior to the study treatment administration unless otherwise noted. There are visits where the protocol requires more than 1 procedure to be completed at the same time point. When indicated, the procedures must follow the specific order of events; see Section 1.3 for instructions.

Protocol waivers or exemptions are not allowed.

Immediate safety concerns should be discussed with the Medical Monitor 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 SoA, 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 purposes provided the procedures met the protocol specified criteria and were performed within the time frame defined in the SoA (Section 1.3).

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

8.1 EFFICACY ASSESSMENTS

Clinical evaluations of AV will be performed by an experienced and qualified dermatologist (board certified or equivalent) or other suitably qualified and experienced designee. To assure consistency and reduce variability, the same assessor should perform all assessments on a given subject, whenever possible (especially at Day 1 and Week 12). Facial IGA must be done before facial lesion counts.

8.1.1 PATIENT GLOBAL IMPRESSION OF SEVERITY

The PGIS will be assessed at the visits specified in the SoA (Section 1.3). It is a single-item question, which asks the subject to rate the current severity of AV. The response options are "Clear skin", "Mild", "Moderate", "Severe".

The PGIS will be completed by the subject on a worksheet prior to any safety and efficacy evaluations. The questionnaire is self-explanatory and handed to the subject who is asked to fill it in without the need for a detailed explanation. The PGIS (modified from Yalcin 2003) is presented in Appendix 2.

8.1.2 PATIENT GLOBAL IMPRESSION OF CHANGE

The PGIC will be assessed at the visits specified in the SoA (Section 1.3). The PGIC is a single-item, self-administered questionnaire, which asks the subject to rate the change in their symptom severity ("Very much better" to "Very much worse").

The PGIC will be completed by the subject on a worksheet prior to any safety and efficacy evaluations. The questionnaire is self-explanatory and handed to the subject who is asked to fill it in without the need for a detailed explanation. The PGIC (modified from Yalcin 2003) is presented in Appendix 3.

8.1.3 DERMATOLOGY LIFE QUALITY INDEX QUESTIONNAIRE/CHILDREN'S DERMATOLGY LIFE QUALITY INDEX QUESTIONNAIRE

The DLQI/CDLQI questionnaires will be assessed at the visits specified in the SoA (Section 1.3). They are simple 10-question validated questionnaires (Finlay 1994; Lewis-Jones 1995). The DLQI/CDLQI score ranges from 0 (no effect on the subject's life) to 30 (extremely large effect on the subject's life). The aim of these subject-reported questionnaires is to measure how much the skin condition has affected the subject's quality of life during the previous week.

The CDLQI will be administered to subjects < 16 years old and the DLQI will be administered to subjects ≥ 16 years old. Subjects will be administered the same questionnaire during the entire study based on their age at Day 1.

The DLQI/CDLQI will be completed by the subject on a worksheet prior to any safety and efficacy evaluations. The questionnaires are self-explanatory and will be filled in by the subjects without the need for a detailed explanation. The DLQI and CDLQI are presented in Appendix 4 and Appendix 5, respectively.

8.1.4 SUBJECT SATISFACTION QUESTIONNAIRE

The SSQ asks subjects to rate their satisfaction with their acne condition on a 7-point scale from 0 (extremely dissatisfied) to 6 (extremely satisfied) (Appendix 6). It will be administered at Week 1 and all subsequent study visits.

8.1.5 SUBJECT SATISFACTION RATING SCALE

The SSRS asks subjects to rate their satisfaction with their study treatment on a 7-point scale from 0 (extremely dissatisfied) to 6 (extremely satisfied) (Appendix 7). It will be administered at Week 12 and Week 20 (EOS).

8.1.6 FACIAL INVESTIGATOR'S GLOBAL ASSESSMENT

The Facial IGA is a global assessment that will be used to assess the current state of AV on the face at each visit. It is a 5-point morphological assessment ranging from 0 (clear) to 4 (severe). The Facial IGA is an overall global evaluation of acne that should be performed at arm's length distance from the subject and must be performed before the acne lesion count. The Facial IGA is presented in Appendix 8.

8.1.7 TRUNCAL PHYSICIAN'S GLOBAL ASSESSMENT

The truncal PGA is a global assessment that will be used to assess the current state of AV on the chest, neck, and back at each visit. Each area will be evaluated and scored separately on a scale ranging from 0 (clear) to 4 (severe). The Truncal PGA is an overall global evaluation of acne that should be performed at arm's length distance from the subject. The Truncal PGA scale is presented in Appendix 9.

8.1.8 FACIAL INFLAMMATORY/NONINFLAMMATORY LESION COUNT

The number of acne inflammatory lesions (pustules, papules, and nodular lesions) and noninflammatory lesions (open and closed comedones) will be counted at Baseline, and at each visit and recorded separately. At Baseline, the total of both inflammatory and noninflammatory lesions will also be calculated.

Subjects will be examined in a well-lit room and without the aid of magnifying instruments. Facial inflammatory lesion counts will be made at the forehead, left and right cheeks, nose, and chin. Noninflammatory lesion counts will be made at the forehead, left and right cheeks, and chin.

Lesion counts will be based on the following definitions:

Inflammatory Lesions	
Papule	A small, solid elevation 5 mm or less in diameter.
Pustule	A small, circumscribed elevation of the skin that contains yellow-white exudate.
Nodule	A circumscribed, elevated, lesion generally more than 5 mm in diameter.
Noninflammatory Lesions	
Open comedone	A mass of sebaceous material that is impacted behind an open follicular orifice (blackhead)
Closed comedone	A mass of sebaceous material that is impacted behind a closed follicular orifice (whitehead)

8.2 SAFETY ASSESSMENTS

8.2.1 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

8.2.1.1 DEFINITION OF ADVERSE EVENTS

An AE is any untoward medical occurrence in a subject temporally associated with the use of a study treatment, whether or not considered related to the study treatment.

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 a study treatment that does not necessarily have a causal relationship with this treatment.

8.2.1.1.1 EVENTS MEETING THE ADVERSE EVENT DEFINITION

Events meeting the AE definition include:

- Any abnormal laboratory test results (hematology, biochemistry, or urinalysis) or other safety assessments (eg, ECG, vital signs measurements), including those that worsen from Day 1, considered clinically significant in the medical and scientific judgment of the Investigator (ie, not related to progression of underlying disease).
- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after study treatment administration even though it may have been present before the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.

- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study treatment or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.

"Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfill the definition of an AE or SAE.

8.2.1.1.2 EVENTS NOT MEETING THE ADVERSE EVENT DEFINITION

Events not meeting the AE definition include:

- 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.

8.2.1.2 DEFINITION OF SERIOUS ADVERSE EVENTS

An AE or suspected adverse reaction is considered "serious" if, in the view of either the Investigator or AnaptysBio, it results, at any dose, in any of the following outcomes:

- Death
- **Life-threatening adverse event –** 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.

- **Inpatient hospitalization or prolongation of existing hospitalization –** In general, hospitalization signifies that the subject has been admitted (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious. Hospitalization for elective treatment of a pre-existing condition that did not worsen from Baseline is not considered an AE.

- **Persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions –** 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.

- Congenital anomaly/birth defect

- **Other important medical events –** Events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include invasive or malignant cancers, allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

8.2.1.3 CLASSIFICATION OF AN ADVERSE EVENT

8.2.1.3.1 SEVERITY OF EVENT

The intensity of an AE is an estimate of the relative severity of the event. The Investigator will make an assessment of intensity for each AE and SAE reported during the study based on his or her clinical experience and familiarity with the literature. The following definitions are to be used to rate the severity of an AE:

- **Mild –** Events require minimal or no treatment, is easily tolerated by the subject, causing minimal discomfort, and do not interfere with the subject's daily activities.

- **Moderate –** Events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning and sufficient discomfort to the subject.

- **Severe –** Events interrupt a subject's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually potentially life-threatening or incapacitating. Of note, the term "severe" does not necessarily equate to "serious". 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.

8.2.1.3.2 RELATIONSHIP TO STUDY TREATMENT

All AEs must have their relationship to study treatment assessed by the Investigator who examines and evaluates the subject based on temporal relationship and his or her clinical judgment. Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study treatment administration will be considered and investigated. The Investigator will also consult the IB in his or her assessment. The degree of certainty about causality will be graded using the categories below. In a clinical study, the study treatment must always be suspect.

- **Unrelated –** Clinical event incontrovertibly not related to the study treatment.

- **Unlikely to be related –** Clinical event with an incompatible time relationship to study treatment administration which makes a causal relationship improbable, and in which an underlying condition or other drugs or chemicals provides plausible explanations.

- **Possibly related –** Clinical event with a reasonable time relationship to study treatment administration, and that is unlikely to be attributed to concurrent condition or other drugs or chemicals.

- **Related –** Clinical event with plausible time relationship to study treatment administration and that cannot be explained by concurrent condition or other drugs or chemicals.

For each AE/SAE, the Investigator must document in the medical notes that he or 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 the pharmacovigilance unit. 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 the pharmacovigilance unit within 24 hr of awareness of the event.

The Investigator may change his or 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.

8.2.1.3.3 EXPECTEDNESS

The pharmacovigilance unit will be responsible for determining whether an AE is expected or unexpected as interpreted through the IB. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the study treatment.

8.2.1.4 TIME PERIOD AND FREQUENCY FOR EVENT ASSESSMENT AND FOLLOW-UP

The occurrence of an AE or SAE may come to the attention of study personnel during study visits and interviews of a study subject presenting for medical care, or upon review by a study monitor.

All AEs including local and systemic reactions will be captured on the appropriate eCRF. Information to be collected includes event description, date of onset, clinician's assessment of severity, seriousness, relationship to study treatment (assessed only by those with the training and authority to make a diagnosis), action taken, and outcome of the event. All AEs occurring while on study must be documented appropriately regardless of relationship (see Section 8.2.1.3.2). All AEs will be followed to adequate resolution.

Study site personnel will note the occurrence and nature of each subject's medical condition(s) present prior to the informed consent signature in the appropriate section of the source document and eCRF. During the study, site personnel will note any change in the condition(s) and the occurrence and nature of any AE. Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and nonleading verbal questioning of the subject is the preferred method to inquire about AE occurrences.

Should a subject experience an AE at any time after the screening visit informed consent signature until the end of participation in the study, the event will be recorded as an AE in the source document and eCRF. Any SAE related to the study participation (eg, screening procedure) will be recorded in the source document and eCRF from the time consent is given to participate in the study until the end of participation in the study (EOS/ET visit).

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

Any medical condition that is present at the time that the subject is screened will be considered as medical history and not reported as an AE. However, if the study subject's condition deteriorates at any time during the study, it will be recorded as an AE.

Changes in the severity of an AE/SAE will be documented to allow an assessment of the duration of the event at each level of severity to be performed. AEs characterized as intermittent require documentation of onset and duration of each episode.

The Investigator is responsible for appropriate medical care of subjects during the study. After the initial AE/SAE report, the Investigator is required to proactively follow each subject at subsequent visits/contacts. The Investigator also remains responsible for following through with an appropriate health care option for all AEs that are ongoing at the end of the study. The subject should be followed until the event is resolved or stable. If an AE is ongoing at the end of study, the follow-up duration is left to the discretion of the Investigator. Follow-up frequency will be performed at the discretion of the Investigator.

Whenever possible, clinically significant abnormal laboratory results are to be reported using the diagnostic that resulted in the clinically significant abnormal laboratory results and not the actual abnormal test.

8.2.1.5 ADVERSE EVENT REPORTING

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

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

It is not acceptable for the Investigator to send photocopies of the subject's medical records to the pharmacovigilance unit in lieu of completion of the AE/SAE eCRF page.

There may be instances when copies of medical records for certain cases are requested by the pharmacovigilance unit. 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 the pharmacovigilance unit.

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.

The Investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the pharmacovigilance unit 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.

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

8.2.1.6 SERIOUS ADVERSE EVENT REPORTING

Prompt notification by the Investigator to the pharmacovigilance unit 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. All SAEs will be recorded and reported to the pharmacovigilance unit within 24 hr of awareness. The Investigator will submit any updated SAE data to the pharmacovigilance unit within 24 hr of receipt of the information as outlined in the Safety Reporting Instructions that will be provided to the sites and in the study Safety Management Plan.

The pharmacovigilance unit will inform the Medical Monitor, AnaptysBio, and Innovaderm within 1 business day of awareness of a new SAE. The pharmacovigilance unit will process and evaluate all SAEs as soon as the reports are received. For each SAE received, the pharmacovigilance unit, in consultation with AnaptysBio if needed, will make a determination as to whether the criteria for expedited reporting to relevant regulatory authorities have been met.

AnaptysBio or designee 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. AnaptysBio or designee will comply with country specific regulatory requirements relating to safety reporting to the regulatory authority, IRB/EC, and Investigators.

Investigator safety reports must be prepared for suspected unexpected SAEs according to local regulatory requirements and pharmacovigilance unit 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 pharmacovigilance unit will review and then file it along with the IB and will notify the IRB/EC, if appropriate according to local requirements.

If a subject dies while participating in the study, the Investigator will provide the pharmacovigilance unit with a copy of any postmortem findings.

8.2.1.6.1 REPORTING VIA AN ELECTRONIC DATA COLLECTION TOOL

The primary mechanism for reporting an SAE to the pharmacovigilance unit will be the EDC clinical database.

If the electronic system is unavailable, then the study site will use the back-up paper SAE Report Form. The study site will then enter the SAE data into the EDC system as soon as it becomes available.

After the study is completed and the database is locked, the tooled system will be taken off-line to prevent the entry of new data or changes to existing data.

If a study site receives a report of a new SAE from a subject or receives updated data on a previously reported SAE after the EDC system is locked, then the study site can report this information on a paper SAE form and email the form to the pharmacovigilance unit.

Contacts for SAE reporting can be found in SAE form and Safety Reporting Instructions that will be provided to the sites.

8.2.1.6.2 REPORTING VIA PAPER CASE REPORT FORM

In rare circumstances, and in the absence of EDC or email, notification by telephone is acceptable for notifying the pharmacovigilance unit of an SAE. Once the EDC is available, the SAE must be reported in the system within 24 hr of it becoming available.

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 Safety Reporting Instructions that will be provided to the sites.

8.2.1.7 REPORTING EVENTS TO SUBJECTS

Not applicable.

8.2.1.8 REPORTING OF PREGNANCY

If a female subject or a female partner of a male subject becomes pregnant during the study and up to 28 days after the end of the study, the subject should inform the study site as soon as possible.

If a pregnancy is reported, the Investigator should inform the pharmacovigilance unit within 24 hours of learning of the pregnancy and should follow the procedures outlined in Appendix 1.

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, where consent has been obtained to do so.

Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, and ectopic pregnancy) are considered SAEs and must be reported within 24 hours of awareness as described in Section 8.2.1.6.

8.2.1.9 TREATMENT OF OVERDOSE

For this study, any dose of imsidolimab or placebo administered in a volume exceeding the planned dosing detailed in Table 3 (Dose Strength[s]/Dosage Level[s]) 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 (CK), and complete blood count) are to be performed and followed until all values return to Baseline levels and AEs subside, if applicable.

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

In the event of an overdose, the Investigator should:

1. Contact the Medical Monitor immediately.
2. Closely monitor the subject for any AE/SAE and laboratory abnormalities and follow-up until resolution.
3. Obtain a serum sample for PK analysis soon after the dose for SC administration.
4. Document the quantity of the excess dose as well as the duration of the overdose in the eCRF.

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

8.2.2 HEIGHT AND WEIGHT

Height (cm) and weight (kg) will be collected to calculate the BMI. Height and weight will be measured at the time points specified in the SoA (Section 1.3).

8.2.3 PHYSICAL EXAMINATIONS

Complete physical examinations will be performed at the time points indicated in the SoA (Section 1.3).

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

A detailed examination of the skin should be performed at the time points indicated in the SoA for the efficacy assessments (eg, lesion count).

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

8.2.4 VITAL SIGNS

Body temperature (°C), pulse rate (bpm), blood pressure (mmHg), and respiratory rate (breath/min) will be assessed at the time points specified in SoA (Section 1.3).

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

Blood pressure and pulse rate measurements should be preceded by at least 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 at least 5 minutes rest) should be measured once. Arterial blood pressure should be measured twice (at intervals of at least 5 minutes), using a validated device.

8.2.5 ELECTROCARDIOGRAMS

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

Additional information will be provided in a separate manual.

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

The ECG individual data (including clinical significance that will be reported as AE) will be entered into the electronic data capture (EDC).

8.2.6 CLINICAL SAFETY LABORATORY ASSESSMENTS

See Appendix 10 for the list of clinical laboratory tests to be performed and the SoA (Section 1.3) for the timing and frequency of the tests.

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

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

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

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

All protocol-required laboratory assessments, as defined in Appendix 10, must be conducted in accordance with the Laboratory Manual and the SoA.

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), then the results must be recorded in the eCRF.

8.3 OTHER ASSESSMENTS

8.3.1 PHOTOGRAPHY

Photography of face will be performed at the time points mentioned in the SoA (Section 1.3) for documentation and exploratory facial lesion count analyses. Additional analyses may be defined in a separate manual.

Additional information on photography will be described in the manual provided to sites.

Optional truncal photography will be performed at selected sites.

8.3.2 PHARMACOKINETICS

Whole blood will be obtained for the determination of imsidolimab concentration in human serum. Samples will be collected according to the SoA (Section 1.3) and Table 5. 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 imsidolimab serum concentration also may be used to correlate exposure to safety or efficacy as well as supportive analysis for dose justification.

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 imsidolimab will be performed using a validated assay method under the supervision of AnaptysBio. The analytical methods used to measure concentrations of imsidolimab will be described in a separate bioanalytical report.

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

While PK samples must be collected from subjects randomized to the placebo arm to maintain the blinding of treatment assignment, PK assay results for these subjects are not needed for the safe conduct or proper interpretation of this study. These samples may not be analyzed unless needed to investigate if a dosing error has occurred. Personnel at the bioanalytical laboratory performing PK assays will be unblinded, the clinical study team members, and study site staff (with the exception of the unblinded Pharmacist) will remain blinded to treatment for the duration of the study. Data may be de-identified for quality review. Additional details on de-identification or unblinding of the PK data, if applicable, will be described in a separate plan.

Drug concentration information that may unblind the study will not be reported to study sites or blinded personnel until the study has been unblinded.

Table 5: Pharmacokinetic and Anti-drug Antibody Collection Schedule

Study Visit	PK Sample Time Point	ADA Sample Time Point
Day 1	Predose	Predose
	2 hr (± 10 min) postdose	
Day 15	Anytime	Anytime
Day 29	Predose	Predose
Day 57	Predose	Predose
Day 85	Anytime	Anytime
Day 141	Anytime	Anytime

Abbreviations: ADA, anti-drug antibody; hr, hours; min, minutes; PK, pharmacokinetic

8.3.3 IMMUNOGENICITY ASSESSMENTS

Anti-drug antibodies to imsidolimab will be evaluated in serum samples collected from all subjects according to the SoA (Section 1.3) and Table 5. Additionally, serum samples also should be collected at the final visit from subjects who discontinued study treatment or were withdrawn from the study. These samples will be tested by AnaptysBio or its designee. Each serum sample will be divided into 2 aliquots (1 each for primary and a back-up).

The detection and characterization of antibodies to imsidolimab will be performed using a validated assay method by or under the supervision of AnaptysBio.

Serum samples will be tested in a multi-tiered approach. A validated screening assay for antibodies binding to imsidolimab initially will be used to assess serum samples. Samples that are determined putative positive in the screening assay then will be subjected to a confirmatory assay to demonstrate that antibodies are specific to imsidolimab. Samples that are identified as positive in the confirmatory assay will be further characterized in a validated titer assay and the titer of confirmed positive samples will be reported. Other analyses may be performed to verify the stability of antibodies to study treatment and/or to further characterize the immunogenicity of study treatment.

Samples that are confirmed positive for antibodies binding to imsidolimab may be further characterized for their ability to neutralize the activity of the study treatment using a validated neutralizing antibody assay method and the presence and/or titer of ADA may be correlated to safety and PK data.

8.3.4 BIOMARKER ANALYSIS

8.3.4.1 TAPE STRIPPING

Tape strip samples will be collected from non-lesional and lesional skin according to the SoA (Section 1.3) to measure cutaneous biomarkers including but not limited to IL-36R, Th-17 cytokines such as IL-17A, and markers of neutrophils and dendritic cell infiltration.

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

The measurement of tape strip biomarkers may be performed by an additional third party (eg, a university Investigator) designated by AnaptysBio.

9 STATISTICAL CONSIDERATIONS

9.1 STATISTICAL HYPOTHESES

The primary analysis for this study is to compare the mean facial inflammatory lesion count for imsidolimab with placebo during the treatment period, at a two-sided alpha = 0.10 level. Any testing being performed for secondary or exploratory endpoints will be considered exploratory in nature based on a 2-sided alpha = 0.10

H_0: $\mu_{imsidolimab} - \mu_{Placebo} = 0$ vs. H_A: $\mu_{imsidolimab} - \mu_{Placebo} \neq 0$

9.2 SAMPLE SIZE DETERMINATION

Approximately 120 subjects will be stratified based on facial IGA score at baseline (3 [moderate] versus 4 [severe]) and randomized in a 1:1:1 ratio to receive one of the following study treatments:

- Imsidolimab 400 mg on Day 1, 200 mg on Days 29 and 57
- Imsidolimab 200 mg on Day 1, 100 mg on Days 29 and 57
- Placebo on Days 1, 29, and 57

For this Phase 2 study, the sample size was chosen empirically. Assuming a total of 10% of subjects will discontinue prior to Week 12, there will be approximately 108 evaluable subjects (36 subjects in each arm) at the end of Week 12.

The study has 80% power to detect a between-group treatment difference of 6.1 lesions in the primary endpoint of mean change from baseline in the AN count at Week 12, using a 2-sided, equal-variance two-sample t-test at the $\alpha = 0.10$ level, with the assumption of a common standard deviation (SD) of 10.4 lesions. The assumption was based on Arazlo (tazarotene) acne Phase 3 Study Trial-301 results (Arazlo 2019). Table 6 shows more information on power from a set of scenarios of variability and between-group mean differences.

Table 6: Power Exploration for Different Scenarios of Variability and Between-group Mean Differences

Common Standard Deviation (SD)	Between-group mean difference	Power (%)	
		1-sided test	2-sided test
8	3	62	48
	4	80	68
	5	92	84
	6	97	94
10	3	50	36

Common Standard Deviation (SD)	Between-group mean difference	Power (%)	
		1-sided test	2-sided test
	4	66	52
	5	80	68
	6	90	82
12	3	41	28
	4	55	41
	5	69	55
	6	80	68

Note: An equal variance two-sample t-test at alpha=0.10 is used for the power calculations.

9.3 POPULATIONS FOR ANALYSES

The analysis sets are defined in Table 7.

Table 7: Analysis Sets

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

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

9.4 STATISTICAL ANALYSES

9.4.1 GENERAL APPROACH

The statistical analysis will be performed using SAS® Version 9.4 or higher. All details regarding the statistical analysis and the preparation of tables, listings, and figures will be described in the Statistical Analysis Plan (SAP).

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

For categorical variables, the number and percentage (percentage of subjects in each category relative to the total number of subjects in the relevant analysis set or relative to the total number of subjects in the relevant analysis set with assessments available [where appropriate]) in each category will be the default summary presentation.

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

Unless otherwise specified, all formal statistical tests will be 2-sided at the 10% significance level. Point estimates of treatment differences will be accompanied with 2-sided 90% confidence intervals (CIs), where applicable.

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

All data will be presented in by-subject listings.

9.4.2 SUBJECT DISPOSITION

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

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

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

9.4.3 BASELINE DESCRIPTIVE STATISTICS

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

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

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

9.4.4 CONCOMITANT MEDICATION

All medications will be coded using the World Health Organization (WHO) Drug Dictionary and Anatomical Therapeutic Chemical (ATC) system. Each medication will be classified as prior medication if it is stopped prior to the first dose of study treatment, or as concomitant medication if it is ongoing at the time of the first dose or is started after the first dose of study treatment. Prior, concomitant, and rescue medications will be summarized descriptively with a by-subject listing.

To handle the issue of rescue medication use, the efficacy data on and after the use rescue medication will be set to missing in the efficacy analysis.

9.4.5 ANALYSIS OF THE PRIMARY EFFICACY ENDPOINT

The primary efficacy endpoint is the change from Baseline in facial inflammatory lesion count at Week 12.

A general linear mixed model repeated measures (MMRM) analysis will be used to estimate the least-squares means (LSM) and associated standard errors for the change from Baseline in facial inflammatory lesion count to Week 12. The model will include change from Baseline in facial inflammatory lesion count at Week 12 as the dependent variable, fixed effects for treatment arm, categorical time point, and the treatment by time point interaction, and the Baseline facial inflammatory lesion count and the stratification factor (ie, facial IGA score at baseline) as covariates. An unstructured covariance structure will be used. The difference between LSMs (imsidolimab – placebo) at Week 12 will be presented along with the associated 90% CI and p-value.

Possible effect of any other covariates as well as investigation of variables through sub-group analysis may also be investigated.

9.4.6 ANALYSIS OF THE SECONDARY EFFICACY ENDPOINTS

Following are the secondary efficacy endpoints:

- Change from Baseline in facial inflammatory lesion counts at visits other than Week 12
- Percent change from Baseline in facial inflammatory lesion counts at each visit

- Change from Baseline in facial noninflammatory lesion counts at each visit
- Percent change from Baseline in facial noninflammatory lesion counts at each visit
- Change from Baseline in total facial lesion (inflammatory and noninflammatory lesions) counts at each visit
- Percent change from Baseline in total facial lesion (inflammatory and noninflammatory lesions) counts at each visit
- Change from Baseline in Facial IGA at each visit
- Proportion of subjects achieving a Facial IGA of clear (0) or almost clear (1) with at least a 2-grade decrease from Baseline at each visit
- Proportion of subjects in each response category for the PGIS at each visit
- Proportion of subjects in each response category for the PGIC at each post-Baseline visit
- Change from Baseline in DLQI/CDLQI at each visit

9.4.6.1 CATEGORICAL ENDPOINTS

Frequency and percentages for each response Yes/No for categorical endpoints will be presented separately by visit for each treatment arm. Estimates of the difference between treatments (imsidolimab – placebo) will be presented along with exact 90% CIs. Treatment arms will be compared using an exact test.

9.4.6.2 CONTINUOUS ENDPOINTS

Summary statistics will be provided by visit and treatment arm. A by-subject listing will be presented for each assessment, by visit.

9.4.7 ANALYSIS OF THE EXPLORATORY EFFICACY ENDPOINTS

Following are the exploratory efficacy endpoints:

- Two-point decrease from Baseline in Facial IGA at each visit
- Change from Baseline in Truncal PGA for chest at each visit
- Change from Baseline in Truncal PGA for neck at each visit
- Change from Baseline in Truncal PGA for back at each visit
- Proportion of subjects achieving a Truncal PGA for chest of clear (0) or almost clear (1) with at least a 2-grade decrease from Baseline at each visit Proportion of subjects achieving a Truncal PGA for neck of clear (0) or almost clear (1) with at least a 2-grade decrease from Baseline at each visit
- Proportion of subjects achieving a Truncal PGA for back of clear (0) or almost clear (1) with at least a 2-grade decrease from Baseline at each visit
- Proportion of subjects in each response category for the SSQ at each visit
- Proportion of subjects in each response category for the SSRS at Week 12 and Week 20
- Change from Baseline in lesion counts based on blinded photographic assessment at each visit

Methods for analyzing the above categorical and continuous efficacy endpoints will mirror the methods described in Section 9.4.6.1 and 9.4.6.2, respectively.

9.4.8 SAFETY ANALYSES

Following are the primary safety and tolerability endpoints:

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

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

9.4.8.1 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

A TEAE is defined as:

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

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

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

All AE data will be listed for each subject.

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

9.4.8.2 12-LEAD ELECTROCARDIOGRAM, VITAL SIGNS, AND CLINICAL SAFETY LABORATORY TESTS

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

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

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

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

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

9.4.9 PHARMACOKINETIC ANALYSES

Limited imsidolimab PK parameter analysis will be evaluated by assessment of drug concentrations in serum. These drug concentrations will be listed and summarized for each sampling time point using appropriate descriptive statistics. The PK parameters will be summarized using appropriate descriptive statistics.

9.4.9.1 DERIVATION OF PHARMACOKINETIC PARAMETERS

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

9.4.9.2 PHARMACOKINETIC CONCENTRATION DATA ANALYSIS

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

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

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

Mean trough concentrations-time data will be graphically displayed for samples collected at the visits specified in the SoA (Section 1.3) to visually assess time to attainment of steady state. Time to steady state may also be explored by using inferential statistics, if deemed appropriate. Other presentations of data may be added at the discretion of the PK scientist, as appropriate, and will be described in detail in a separate analysis plan.

9.4.9.3 PHARMACOKINETIC PARAMETER DATA ANALYSIS

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

9.4.9.4 POPULATION PHARMACOKINETICS ANALYSIS

Pharmacokinetic data from the study may also be used for population PK and PK/response analyses. The data may be combined with PK data from other imsidolimab studies, if needed, to conduct the population PK analysis. If done, a separate analysis plan will be prepared, and results will be reported separately from the Clinical Study Report (CSR).

9.4.9.5 IMMUNOGENICITY ANALYSES

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

Frequency and percentage of ADA response will be presented and listed and correlated to safety and PK endpoints.

9.4.10 BIOMARKER ANALYSES

Tape strip samples will be collected from nonlesional and lesional skin according to the SoA (Section 1.3) to measure cutaneous biomarkers including but not limited to IL-36R, Th-17 cytokines such as IL-17A, and markers of neutrophils and dendritic cell infiltration.

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

The measurement of tape strips biomarkers may be performed by an additional third party (eg, a university Investigator) designated by AnaptysBio.

9.4.11 PLANNED INTERIM ANALYSIS

Interim analyses (IA) may be performed for assessment of all primary and secondary efficacy endpoints, and evaluation of all safety data available.

The rationale for these analyses is to assist in making decisions for potential future development of this treatment. No adjustments to the current protocol are planned as a result of the interim analyses; therefore, overall alpha in the analyses of the primary analysis is expected to be maintained at 0.10, two-sided.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

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

10.1.1 INFORMED CONSENT PROCESS

10.1.1.1 CONSENT AND OTHER INFORMATIONAL DOCUMENTS PROVIDED TO SUBJECTS

An ICF, and assent when required, describing in detail the study treatments, study procedures, and risks will be given to the subjects, and written documentation of informed consent is required prior to starting any study-related procedures. The following materials will be submitted to the IRB/EC with this protocol: subject self-reported questionnaires, ICF/assent, IB, and other relevant documents (eg, advertisements).

10.1.1.2 CONSENT PROCEDURES AND DOCUMENTATION

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continues throughout the individual's study participation. Each informed consent document must adhere to the ethical principles stated in the Declaration of Helsinki and will include the elements required by FDA regulations in 21 CFR Part 50, as well as the elements required by the ICH GCP guideline, and applicable federal and local regulatory requirements. The consent form will be IRB/EC -approved, and the subject will be asked to read and review the document. An assent is to be obtained from subjects who need to provide assent, as per local requirements, and their parent(s) or legal representative has to sign and date the ICF.

The Investigator or his/her representative will explain the research study to the subject and answer any questions that may arise. A verbal explanation will be provided in terms suited to the subject's comprehension of the purposes, procedures, and potential risks of the study and of their rights as research subjects. Subjects will have the opportunity to carefully review the written consent form and ask questions prior to signing. The subjects should have the opportunity to discuss the study with their family or surrogates or think about it prior to agreeing to participate. The subject will sign the informed consent/assent document prior to any procedures being done specifically for the study.

Subjects must be informed that participation is voluntary and that they may withdraw from the study at any time, without prejudice. A copy of the informed consent/assent document will be given to the subjects for their records. The informed consent process will be conducted and documented in the source document (including the date), and the form signed, before the subject undergoes any study-specific procedures. The rights and welfare of the subjects will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

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/assent.

Subjects must be re-consented to the most current version of the ICF(s)/assent(s) during their participation in the study. Subjects who are rescreened are required to sign a new ICF/assent.

10.1.2 STUDY DISCONTINUATION AND CLOSURE

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to study subjects, Investigator, the IND sponsor, and regulatory authorities, as applicable. If the study is prematurely terminated or suspended, the Investigator will promptly inform study subjects and the IRB/EC and will provide the reason(s) for the termination or suspension. Study subjects will be contacted, as applicable, and be informed of changes to study visit schedule.

Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to subjects
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable
- Scientific or corporate reasons

Study may resume once concerns about safety, protocol compliance, and data quality are addressed, and satisfy AnaptysBio, IRB/EC and/or regulatory authorities.

10.1.3 CONFIDENTIALITY AND PRIVACY

Subject confidentiality and privacy are strictly held in trust by the participating Investigators, their staff, and AnaptysBio and their interventions. This confidentiality is extended to cover testing of biological samples and genetic tests in addition to the clinical information relating to subjects. Therefore, the study protocol, documentation, data, and all other information generated

will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of AnaptysBio.

All research activities will be conducted in a setting as private as possible. The Investigator must assure that the subjects' anonymity will be maintained and that subjects' identities are protected from unauthorized parties. On CRFs or other documents submitted to AnaptysBio, subjects should not be identified by their names, but by an identification code. The Investigator should keep a subject log relating codes with the names of subjects. The Investigator should maintain in strict confidence documents not for submission to AnaptysBio (eg, subjects' written consent forms).

The study monitor, other authorized representatives of AnaptysBio, and representatives of the IRB/EC, regulatory agencies, or pharmaceutical company supplying study treatment may inspect all documents and records required to be maintained by the Investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the subjects in this study. The clinical study site will permit access to such records.

The study subject's contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by the applicable legal or regulatory requirements, the reviewing IRB/EC, Institutional policies, or AnaptysBio requirements.

Study subject research data, which are for purposes of statistical analysis and scientific reporting, will be transmitted to and stored at the data management company responsible for data management, analysis, and reporting. This will not include the subject's contact or identifying information. Rather, individual subjects and their research data will be identified by a unique study identification number. The study data entry and study management systems used by clinical study sites and by data management research staff will be secured and password protected. At the end of the study, all study databases will be de-identified and archived by AnaptysBio.

All information generated in this study must be considered highly confidential and must not be disclosed to any persons not directly concerned with the study without written prior permission from AnaptysBio. Authorized regulatory officials and AnaptysBio personnel (or their representatives) will be allowed full access to inspect and copy the records. All study investigational product, subject bodily fluids, and/or other materials collected shall be used solely in accordance with this protocol, unless otherwise agreed to in writing by AnaptysBio. Subjects will only be identified by unique subject numbers on eCRFs. Every subject will be given a copy of each version of the ICF that he or she signs before and during the study. Each ICF may also include authorization allowing the institution, Investigator, and AnaptysBio to use and disclose personal health information in compliance with the Health Information Portability and Accountability Act (HIPAA).

10.1.4 FUTURE USE OF STORED SPECIMENS AND DATA

With the subject's approval and approval by IRB/EC, de-identified biological samples will be stored at a certified, licensed central laboratory. During the conduct of the study, a subject may choose to withdraw consent to have biological specimens stored for future research. Once samples have been analyzed specimens will be destroyed. If no analyses have been completed within 5 years following EOS, samples will be destroyed.

Any remaining serum/plasma from samples collected for PK/PD immunogenicity endpoints may be retained for assay method development, troubleshooting, or validation. These samples may also be used for research purposes, but will not be used for any type of genetic analyses.

10.1.5 MEDICAL MONITOR

Medical monitoring will be conducted to ensure the early recognition, identification and reporting of issues impacting on subjects' health and well-being throughout the trial. Details of medical monitoring with contact information of the Medical Monitors will be documented in a Medical Monitoring Plan.

10.1.6 SAFETY OVERSIGHT

No data and safety monitoring board is required as part of this study.

10.1.7 CLINICAL MONITORING

All aspects of the study will be monitored by AnaptysBio or authorized representatives of AnaptysBio according to GCP and Standard Operating Procedures (SOPs) for compliance with applicable government regulations, (ie, Informed Consent Regulations [US 21CFR, Part 50] and Institutional Review Board regulations [US 21CFR, Part 56.103]).

Access to all records, both during the study and after study completion, should be made available to AnaptysBio at any time for review and audit to ensure the integrity of the data. The Investigator must notify AnaptysBio immediately if the responsible IRB/EC has been disqualified or if proceedings leading to disqualification have begun.

The Investigator must conduct the protocol in accordance with applicable GCP regulations and guidelines; applicable informed consent regulations (US 21CFR, Part 50); and in compliance with the Declaration of Helsinki. Every attempt must be made to follow the protocol and to obtain and record all data requested for each subject at the specified times. If data are not recorded per protocol, the reasons must be clearly documented on the eCRF/records.

Before study initiation, at a study site initiation visit or at a meeting with the Investigator(s), a representative from AnaptysBio will review the protocol and study eCRFs with the

Investigator(s) and their staff. During the study, the study monitor will visit the study site regularly to check the completeness of subject records, the accuracy of entries on the eCRFs, the adherence to the protocol and to GCP, the progress of enrollment, and to ensure that consent is being sought and obtained in compliance with applicable regulations, and that the study drug is being stored, dispensed and accounted for according to specifications.

The Investigator and key study personnel must be available to assist the monitor during these visits. The Investigator must give the monitor access to relevant hospital or clinical records, to confirm their consistency with the eCRF entries. No information in these records about the identity of the subjects will leave the study site.

Monitoring standards require full verification for the presence of informed consent, adherence to the inclusion/exclusion criteria, documentation of SAEs, and the recording of primary efficacy and safety variables. Additional checks of the consistency of the source data with the eCRFs will be performed according to the study-specific Monitoring Plan.

The Investigator must promptly complete the eCRFs after the subject's visit. The monitor is responsible for reviewing them and clarifying and resolving any data queries. A copy of the eCRFs will be retained by the Investigator who must ensure that it is stored in a secure place with other study documents, such as the protocol, the IB, and any protocol amendments.

The Investigator must provide AnaptysBio and the responsible IRB/EC with a study summary shortly after study completion, or as designated by AnaptysBio.

10.1.8 QUALITY ASSURANCE AND QUALITY CONTROL

Each clinical site will perform internal quality management of study conduct, data and biological specimen collection, documentation and completion.

Quality control (QC) procedures will be implemented beginning with the data entry system, and data QC checks, which will be run on the database, will be generated. Any missing data or data anomalies will be communicated to the site(s) for clarification/resolution.

Following written SOPs, the monitors will verify that the clinical trial is conducted and data are generated and biological specimens are collected, documented (recorded), and reported in compliance with the protocol, ICH GCP, and applicable regulatory requirements (eg, GLP, Good Manufacturing Practices [GMP]).

The investigational site will provide direct access to all trial related sites, source data/documents, and reports for the purpose of monitoring and auditing by AnaptysBio, and inspection by IRB/EC and local and regulatory authorities.

10.1.9 DATA HANDLING AND RECORD KEEPING

10.1.9.1 DATA COLLECTION AND MANAGEMENT RESPONSIBILITIES

All protocol-specified data will be recorded in site source documents. Study data will be entered within the clinical database eCRFs from the original source documents. Upon each subject's completion of the study, the Investigator is required to sign and affirm the data entered in the subject CRF along with a statement attesting that all pages of the subject's case report have been reviewed. All Investigator data attestation signatures will be made through the 21 CFR Part11 compliant EDC system. Signature stamps and "per signatures" are not acceptable.

It is AnaptysBio's policy that study data be verifiable with the source data which necessitates access to all original recordings, laboratory reports, and other records for each subject. The Investigator must therefore agree to allow access to subjects' records, and source data must be made available for all study data. Subjects (or their legal representatives) must also allow access to their medical records. Subjects will be informed of the importance of increased record access and permission granted by signature on the informed consent document prior to screening.

Checks will be performed to ensure quality, consistency, and completeness of the data. Instances of missing or uninterpretable data will be resolved with the Investigator or study coordinator. Data queries, documented within the clinical database, will be accessible to the research facility through the EDC system. Study site personnel will be responsible for providing resolutions to the data queries and for correcting the eCRFs, as appropriate.

The Investigator must keep written or electronic source documents for every subject participating in the clinical study. for the appropriate document retention period. The subject file that identifies the study in which the subject is participating must include the subject's available demographic and medical information including:

- Name
- Contact information
- Year of birth
- Sex
- Medical history
- Concomitant therapies/medication
- Study visit dates
- Performed examinations, evaluations, and clinical findings
- Investigational product administration
- AEs, SAEs, or pregnancy (as applicable)

Additionally, any other documents with source data, especially original printouts of data that were generated by technical equipment must be included in the subject's source document (eg, laboratory value listings). All these documents must have at least the subject's study number, and the date of the evaluation.

The data recorded during the course of the study will be documented in the eCRF and/or the study-specific forms. Before or at study termination, all data must be forwarded to AnaptysBio. The data will then be recorded, evaluated, and stored in anonymous or coded form in accordance with data-protection regulations.

Subjects will authorize the use of their protected health information during the informed consent process in accordance with the applicable privacy requirements. Subjects who deny permission to use and disclose protected health information will not be eligible to participate in the study.

The Investigator will ensure that the study documents forwarded to AnaptysBio, and any other documents, contain no mention of subject names. Any amendments and corrections necessary will be undertaken in both the source documents and eCRFs (as appropriate), and countersigned by the Investigator, or documented designee, stating the date of the amendment/correction. Errors must remain legible and may not be deleted with correction aids. The Investigator must state his/her reason for the correction of any data. In the case of missing data/remarks, the entry spaces provided in the eCRF should be cancelled out so as to avoid unnecessary follow-up inquiries.

Electronic CRFs will be kept by AnaptysBio or an authorized designee in a secured area. Clinical data will be recorded in a computer format for subsequent statistical analyses. Data files will be stored on electronic media with a final master data file kept by AnaptysBio after descriptive and statistical analyses and reports have been generated and are complete.

It is the responsibility of the Investigator to ensure that the study site file is maintained in accordance with the ICH Guidance for Industry E6(R2) GCP: Consolidated Guidance, Section 8 – Essential Documents for the Conduct of a Clinical Trial.

10.1.9.2 STUDY RECORDS RETENTION

Study documents should be retained for a minimum of 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 until at least 2 years have elapsed since the formal discontinuation of clinical development of the study treatment. These documents should be retained for a longer period, however, if required by local regulations or as specified in the study agreement, whichever retention period is longer.

If the Investigator withdraws from the study (eg, relocation, retirement) all study-related records should be transferred to a mutually agreed upon designee. Notice of such transfer will be provided to AnaptysBio in writing. No records will be destroyed without the written consent of AnaptysBio, if applicable. It is the responsibility of AnaptysBio to inform the Investigator when these documents no longer need to be retained.

10.1.10 PROTOCOL DEVIATIONS

A protocol deviation is any noncompliance with the clinical trial protocol or ICH GCP requirements. The noncompliance may be either on the part of the subject, the Investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly. Protocol deviations related to COVID-19 pandemic will be identified and documented accordingly.

These practices are consistent with ICH GCP:

- 4.5 Compliance with Protocol, Sections 4.5.1, 4.5.2, and 4.5.3
- 5.1 Quality Assurance and Quality Control, Section 5.1.1
- 5.20 Noncompliance, Sections 5.20.1, and 5.20.2.

It is the responsibility of the Investigator to use continuous vigilance to identify and report deviations as soon as possible. All deviations must be addressed in study source documents, and applicable deviations must be sent to the reviewing IRB/EC per their policies. The Investigator is responsible for knowing and adhering to the reviewing IRB/EC requirements. Further details about the handling of protocol deviations will be included in the Protocol Deviation Management Plan, Data Management Plan, Medical Monitoring Plan, blind data review documentation, and SAP.

This study will be conducted as described in this protocol, except for an emergency situation in which the protection, safety, and well-being of the subject requires immediate intervention, based on the judgment of the Investigator (or a designee, appropriately trained professional designated by the Investigator). In the event of a significant deviation from the protocol due to an emergency, accident, or mistake, the Investigator or designee must contact the Medical Monitor and AnaptysBio at the earliest possible time by telephone. This will allow an early joint decision regarding the subject's continuation in the study. This decision will be documented by the Investigator and the Medical Monitor. Please refer to Section 4.5 for allowable, as necessary, modifications to the protocol due to COVID-19 restrictions.

The monitor must ensure that a prompt action is taken to secure compliance. If a noncompliance that significantly affects or has the potential to significantly affect human subject protection or

reliability of trial results is discovered, the CRO and AnaptysBio should perform a root cause analysis and implement appropriate corrective and preventive actions.

10.1.11 PUBLICATION AND DATA SHARING POLICY

This study will be conducted in accordance with the following publication and data sharing policies and regulations: It is understood by the Investigator that the information generated in this study will be used by AnaptysBio in connection with the development of the product. To allow for the use of information derived from the study, it is understood that the Investigator is obliged to provide the AnaptysBio with complete test results, all study data, and access to all study records.

Any results of medical investigations with AnaptysBio's products and/or publication/lecture/manuscripts based thereon, shall be exchanged and discussed by the Investigator and AnaptysBio representative(s), 30 days before submission for publication or presentation. Due regard shall be given to AnaptysBio's legitimate interests for example, manuscript authorship, obtaining optimal patent protection, coordinating and maintaining the proprietary nature of submissions to health authorities, coordinating with other ongoing studies in the same field, and protecting confidential data and information. AnaptysBio shall be furnished with a copy of any proposed publication. Comments shall be rendered without undue delay.

In cases of publications or presentations of material arising from multicenter clinical investigations, the AnaptysBio is to serve as coordinator and referee. Individual Investigators who are part of a multicenter investigation may not publish or present data that are considered common to a multicenter investigation without the consent of the other participating Investigators and the prior review of AnaptysBio.

Results from investigations shall not be made available to any third party by the investigating team outside the publication procedure as outlined previously. AnaptysBio will not quote from publications by Investigators in its scientific information and/or promotional material without full acknowledgment of the source (ie, author and reference).

10.1.12 CONFLICT OF INTEREST POLICY

The independence of this study from any actual or perceived influence is critical. Therefore, any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, financial interest, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the design and conduct of this study. AnaptysBio has established policies and procedures for all study group members to disclose all conflicts of interest and will establish a mechanism for the management of all reported dualities of interest.

10.2 ADDITIONAL CONSIDERATIONS

10.2.1 ETHICS AND RESPONSIBILITY

This study must be conducted in compliance with the protocol, the ICH Guidance for Industry E6(R2) GCP: Consolidated Guidance, the Declaration of Helsinki, IRB/EC requirements, and all applicable national and local regulatory requirements. Investigators must submit all essential regulatory documentation, as required by local and national regulations (including approval of the protocol and ICF by a Health and Human Services [HHS]-registered IRB/EC) to AnaptysBio before investigational product will be shipped to the respective study sites.

10.2.2 AMENDMENT POLICY

Only AnaptysBio (or designee) may modify the protocol. Amendments must be approved by all applicable national and local committees including, but not limited to, the government regulatory authorities and/or regional IRB/EC before implementation. The only exception is when an Investigator considers that a subject may be harmed, and immediate action is necessary. Under these circumstances, approval of the chairman of the IRB/EC, or an authorized designee, must be sought immediately. The Investigator should inform AnaptysBio, and the full IRB/EC, no later than 5 working days after the emergency occurs. Protocol-specified safety reporting requirements must be adhered to, independent of any other variables.

10.2.3 INSURANCE

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

11 REFERENCES

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12 APPENDICES

APPENDIX 1: 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 treatment, additional evaluation should be considered.

Women in the following categories are not considered WOCBP

1. Premenarchal
2. Premenopausal female with 1 of the following:
   a) Documented hysterectomy.
   b) Documented bilateral salpingectomy.
   c) Documented bilateral oophorectomy.
   Note: 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 site personnel's review of the subject's medical records, medical examination, or medical history interview.
3. Postmenopausal female:
   a) A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high FSH level in the postmenopausal range will be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.
   b) Females on HRT and whose menopausal status is in doubt will be required to use 1 of the nonestrogen 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 for the duration of the study and for 200 days (which includes the duration of relevant exposure plus the duration of sperm cycle) after the last dose of study treatment:

- 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 200 days 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 200 days after the last dose of study treatment.

Female subjects

Female subjects of childbearing potential are eligible to participate if they agree to use highly effective methods of contraception consistently and correctly as described in the table below and during the protocol-defined time frame in Section 5.1, and refrain from donating oocytes for assisted reproduction during this period. For WOCBP, hormonal contraceptives must be used without schedule changes and in steady doses during the study treatment. Starting hormonal contraceptives during the study is not permitted. Use of any hormonal contraceptives containing drospirenone, chlormadinone acetate and cyproterone acetate is prohibited unless part of a stable contraceptive regimen as described in Section 6.5.1.

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)
  - Implants inserted beneath the skin
- 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.

[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).

Additional pregnancy testing should be performed as mentioned in the SoA (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 pharmacovigilance unit within 24 hr 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 AnaptysBio. 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.

Any SAEs associated with the pregnancy in the male subject's partner should also be reported to the pharmacovigilance unit within 24 hr of the event using the back-up Paper Report Form.

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 pharmacovigilance unit within 24 hr 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 AnaptysBio. 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 poststudy pregnancy related SAE considered reasonably related to the study treatment by the Investigator will be reported to the AnaptysBio as described in Section 8.2.1.8. 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 2: PATIENT GLOBAL IMPRESSION OF SEVERITY

Overall, how would you rate the **severity** of your acne now?

1. ☐ Clear Skin
2. ☐ Mild
3. ☐ Moderate
4. ☐ Severe

APPENDIX 3: PATIENT GLOBAL IMPRESSION OF CHANGE

Overall, how would you rate the change in severity of your acne compared with how it was before you started taking the medication in this study?

1. ☐ Very much better
2. ☐ Much better
3. ☐ A little better
4. ☐ No change
5. ☐ A little worse
6. ☐ Much worse
7. ☐ Very much worse

APPENDIX 4: 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 **yard?**	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 for you 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 any **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 ☐

Please check you have answered EVERY question. Thank you.

If two or more questions are left unanswered the questionnaire is not scored. If two or more response options are ticked, the response option with the highest score should be recorded. If there is a response between two tick boxes, the lower of the two score options should be recorded.

Scoring:

Very much	3 points
A lot	2 points
A little	1 point
Not at all	0 points
Not relevant	0 points

Question 7, 'prevented work or studying' 3 points

The DLQI is calculated by summing the score of each question resulting in a maximum of 30 and a minimum of 0. The higher the score, the more quality of life is impaired.

APPENDIX 5: CHILDREN'S DERMATOLOGY LIFE QUALITY INDEX

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

1.	Over the last week, how **itchy**, **"scratchy"**, **sore** or **painful** has your skin been?	Very much Quite a lot Only a little Not at all	☐ ☐ ☐ ☐
2.	Over the last week, how **embarrassed** or **self conscious**, **upset** or **sad** have you been because of your skin?	Very much Quite a lot Only a little Not at all	☐ ☐ ☐ ☐
3.	Over the last week, how much has your skin affected your **friendships**?	Very much Quite a lot Only a little Not at all	☐ ☐ ☐ ☐
4.	Over the last week, how much have you changed or worn **different** or **special clothes/shoes** because of your skin?	Very much Quite a lot Only a little Not at all	☐ ☐ ☐ ☐
5.	Over the last week, how much has your skin trouble affected **going out**, **playing**, or **doing hobbies**?	Very much Quite a lot Only a little Not at all	☐ ☐ ☐ ☐
6.	Over the last week, how much have you avoided **swimming** or **other sports** because of your skin trouble?	Very much Quite a lot Only a little Not at all	☐ ☐ ☐ ☐
7.	Last week, was it **school time?** ⇒ **If school time**: Over the last week, how much did your skin affect your **school work**?	Prevented school Very much Quite a lot Only a little Not at all	☐ ☐ ☐ ☐ ☐
	OR		
	was it **vacation time?** ⇒ **If vacation time**: How much over the last week, has your skin problem interfered with your enjoyment of the **vacation**?	Very much Quite a lot Only a little Not at all	☐ ☐ ☐ ☐
8.	Over the last week, how much trouble have you had because of your skin with	Very much Quite a lot	☐ ☐

	other people **calling you names**, **teasing**, **bullying**, **asking questions** or **avoiding you**?	Only a little Not at all	☐ ☐
9.	Over the last week, how much has your **sleep** been affected by your skin problem?	Very much Quite a lot Only a little Not at all	☐ ☐ ☐ ☐
10.	Over the last week, how much of a problem has the **treatment** for your skin been?	Very much Quite a lot Only a little Not at all	☐ ☐ ☐ ☐

Please check that you have answered EVERY question. Thank you.

APPENDIX 6: SUBJECT SATISFACTION QUESTIONNAIRE

Questions:

Day 1:

At the present time, how satisfied are you with your acne condition?

All visits after Day 1:

At the present time, how satisfied are you with your acne condition, whether or not in your judgement it is entirely due to treatment in this study?

Answer Scale:

(6) extremely satisfied
(5) somewhat satisfied
(4) slightly satisfied
(3) neither satisfied nor dissatisfied
(2) slightly dissatisfied
(1) somewhat dissatisfied
(0) extremely dissatisfied

APPENDIX 7: SUBJECT SATISFACTION RATING SCALE

Question:

How satisfied are you with the treatment you have received in this study?

Answer Scale:

(6) extremely satisfied
(5) somewhat satisfied
(4) slightly satisfied
(3) neither satisfied nor dissatisfied
(2) slightly dissatisfied
(1) somewhat dissatisfied
(0) extremely dissatisfied

APPENDIX 8: FACIAL INVESTIGATOR'S GLOBAL ASSESSMENT

The IGA tool will be used to assess face (Section 8.1.6).

Investigator's Global Assessment (IGA) Face		
0	Clear	Clear skin with no inflammatory or non-inflammatory lesions
1	Almost Clear	A few scattered comedones and a few small papules.
2	Mild	Easily recognizable; less than half the surface is involved. Some comedones and some papules and pustules.
3	Moderate	More than half of the surface is involved. Many comedones, papules, and pustules. One nodule may be present.
4	Severe	Entire surface is involved. Covered with comedones, numerous papules and pustules. Few nodules may be present.

APPENDIX 9: PHYSICIAN'S GLOBAL ASSESSMENT

The PGA tool will be used to assess the following areas of the trunk: chest, back, and neck (Section 8.1.7). Individual PGA assessments will be made of each region.

Physician's Global Assessment (PGA) Trunk		
0	Clear	Clear skin with no inflammatory or non-inflammatory lesions
1	Almost Clear	A few scattered comedones and a few small papules.
2	Mild	Easily recognizable; less than half the surface is involved. Some comedones and some papules and pustules.
3	Moderate	More than half of the surface is involved. Many comedones, papules, and pustules. One nodule may be present.
4	Severe	Entire surface is involved. Covered with comedones, numerous papules and pustules. Few nodules may be present.

APPENDIX 10: CLINICAL LABORATORY TESTS

The tests detailed in Table 8 will be performed by the central laboratory. The time points are specified in the SoA (Section 1.3).

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

Protocol-specific requirements for inclusion or exclusion of subjects are detailed in Section 5 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.

Investigators must document their review of each laboratory safety report.

Table 8: Protocol-required Safety Laboratory Assessments by Central Laboratory

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

Laboratory Assessments	**Parameters**
Follicle stimulating hormone (FSH)	In women of nonchildbearing potential only (postmenopausal woman with at least 12 months of amenorrhea without an alternative medical cause)
Urinalysis	Bilirubin Blood Glucose Ketones Leukocytes Nitrites pH Protein Specific gravity Urobilinogen Microscopy (At discretion of Investigator based on urinalysis results)
Viral serology and testing	Antibodies to hepatitis B core antigens Hepatitis B surface antigen Hepatitis C antibody and reflex RNA 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 SoA for laboratory tests time points. All blood samples must be drawn prior to administration of the study treatment, unless otherwise specified. The date and exact time of sample collection must be recorded.	