AnaptysBio

Clinical Study Report

Protocol Number: ANB019-209

Sponsor: AnaptysBio, Inc.

16.1.9 Documentation of Statistical Methods

16.1.9.1 Statistical Analysis Plan for Study ANB019-209 – Version 1.0 (28 Feb 2022)

STATISTICAL ANALYSIS PLAN
FOR STUDY ANB019-209

Trial Sponsor:	AnaptysBio, Inc.
Protocol Number:	ANB019-209
IND Number:	136145
Investigational Drug:	Anti-interleukin 36 receptor monoclonal antibody
Indication:	Subjects with Acne Vulgaris
Drug Number:	ANB019 (Imsidolimab)
Dosage Form/Strength/Dose:	Solution for Injection/100 mg/400, 200 or 100 mg • Imsidolimab 400 mg on Day 1, followed by 200 mg on Days 29 and 57. • Imsidolimab 200 mg on Day 1, followed by 100 mg on Days 29 and 57. • Placebo on Days 1, 29, and 57

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

Version:	v1.0
Sign-off Date:	
Archive Date:	

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CHANGE LOG FOR CHANGES MADE AFTER THE INITIAL APPROVAL

Revision Date*	Section(s) Modified	Brief Description of Revision(s) or Reason(s) for Revision	Modifications Reviewed and Approved by**
			AnaptysBio, Everest

* Update the Last Revision Dates on the cover page and the document header.
** Provide person's initial and last name.

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GLOSSARY OF ABBREVIATIONS

Abbreviation	Term
ADA	Anti-drug antibody
AE	Adverse event
ATC	Anatomical Therapeutic Chemical
AV	Acne Vulgaris
BDRM	Blinded data review meeting
BMI	Body mass index
BLQ	Below the limit of quantitation
CDLQI	Children's Dermatology Life Quality Index
CI	Confidence interval
CMH	Cochran-Mantel-Haenszel
COVID-19	Coronavirus Disease 2019
CRF	Case report form
CV	Coefficient of variation
DLQI	Dermatology Life Quality Index
ECG	Electrocardiograms
eCRF	Electronic case report forms
Everest	Everest Clinical Research
FCS	Fully Conditional Specification
FSH	Follicle-stimulating hormone
IGA	Investigator Global Assessment
GEE	Generalized estimating equations
IND	Investigational new drug
ITT	Intention-to-treat
LS	Least squares
MCMC	Monte Carlo Markov Chain
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed model for repeated measures

GLOSSARY OF ABBREVIATIONS

Abbreviation	Term
NCA	Non-compartmental analysis
PAS	Parametric Acne Severity
PGA	Physician's Global Assessment
PGI-C	Patient Global Impression of Change
PGI-S	Patient Global Impression of Severity
PK	Pharmacokinetic
PP	Per Protocol
Prob	Probability
SAE	Serious adverse event
SAP	Statistical analysis plan
SAS	Statistical analysis system
SC	Subcutaneous/subcutaneously
SD	Standard deviation
SoA	Schedule of Activities
SOC	System organ class
SOP	Standard operating procedure
SSQ	Subject Satisfaction Questionnaire
SSRS	Subject Satisfaction Rating Scale
TB	Tuberculosis
TEAE	Treatment-emergent adverse event
WHO Global	World Health Organization Drug Dictionary
WOCBP	Woman of childbearing potential

1. INTRODUCTION

This Statistical Analysis Plan (SAP) describes the pre-specified statistical methods for the display, summary, and analysis of data collected within the scope of the latest version of the ANB019-209 Protocol (Version 1.0 dated 12 February 2021). As with any SAP, the proposed methods and approaches to the data analysis should be deemed as flexible. The analysis of the data should allow changes in the plan to the extent that deviations from the original plan would provide a more reliable and valid analysis of the data. As such, the statistical analysis to a certain degree is iterative since much of the planning is based on assumptions that require verification. The purpose of this plan is to provide general guidelines from which the analysis will proceed. Nevertheless, deviations from these guidelines must be substantiated by a sound statistical rationale.

The SAP should be read in conjunction with the study protocol and the Case Report Forms (CRFs). This version of the SAP has been developed using the final version of the protocol mentioned above.

This study is designed to evaluate the efficacy and safety of imsidolimab in the treatment of subjects with acne vulgaris (AV). (See Protocol **Sections 2.1** to **2.3** for details.)

2. STUDY OBJECTIVES

2.1 Primary Objective

- To evaluate the efficacy of imsidolimab in subjects with AV

2.2 Secondary Objectives

- 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

2.3 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

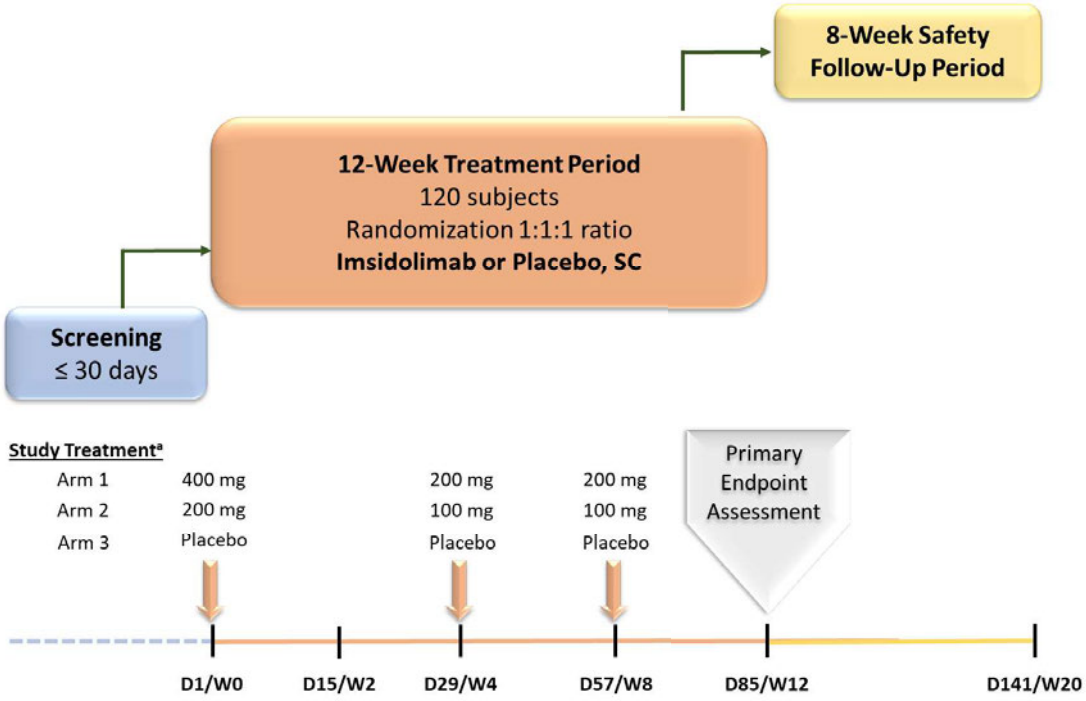
3. STUDY DESIGN

3.1 Study Design

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 AV. This study also will characterize the pharmacokinetic (PK) profile of imsidolimab and explore the immune response to imsidolimab in subjects with AV. This study will be conducted at approximately 15 sites, contributing approximately 8-12 subjects per site. Approximately 120 adult male and female subjects, aged 12 to 45 years with clinically confirmed diagnosis of AV will be enrolled in this study. At the screening and Day 1 visits, the subjects will need to have a facial Investigator Global Assessment (IGA) score of 3 (moderate) or 4 (severe), at least 20 and no more than 100 inflammatory lesions on the face, no more than 100 noninflammatory lesions on the face, and no more than 5 nodules (≥5 mm) on the face. 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] vs. 4 [severe]). 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.

The overall study design is summarized and illustrated in **Figure 1**.



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 × 2 mL injections on Day 1 and 1 x 2 mL injection on Days 29 and 57, according to Protocol **Table 3**.

Figure 1 Study Schema

3.2 Randomization

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] vs. 4 [severe]) and randomized in a 1:1:1 ratio to receive imsidolimab at one of two doses or placebo.

3.3 Hypothesis Testing

The primary analysis for this study is to compare the mean facial inflammatory lesion count for imsidolimab at each dose 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.

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

3.4 Interim Analysis

A primary analysis, considered as the interim analysis of this study, will be performed when all randomized subjects have reached Week 12 or discontinued. The purpose of the primary analysis is to assist AnaptysBio executive management in making decisions for potential future development of this compound. No adjustments to the protocol are planned as a result of the primary analysis; as such, the type I error will not be adjusted in the primary analysis and is expected to be maintained at 0.10, two-sided.

Only data collected on or prior to the data cut-off date will be included in the primary analyses.

Generation of Blinded Reports

In the primary analysis, blinded tables, listings, and graphs will be produced by the Everest Clinical Research Corporation (Everest) study statistician and study programmer based upon dummy randomization codes. Blinded reports may be shared with the study team for review of ongoing data, production of dry run results, or other reasons as Everest standard operating procedures (SOPs) and AnaptysBio SOPs allow.

Generation of Unblinded Reports

The subject, clinical site personnel, and AnaptysBio will be unaware of the randomized treatment assigned to a subject. However, the primary analysis itself will be unblinded. At Everest, only the Unblinded Statistician and the Unblinded Programmer(s) responsible for the primary analysis will be aware of the treatment assigned to a subject. The Unblinded Statistician and Unblinded Programmer(s) will both be appointed by Everest, a company external to AnaptysBio. The Unblinded Statistician and Unblinded Programmer(s) will not be involved in writing the SAP, or in decisions about how the statistical analyses will be conducted, or in daily activities of this study other than those involved in preparing and performing unblinded primary analysis; however, these individuals may be involved in the generation of the randomization list for this study. The Unblinded Statistician and Unblinded Programmer(s) will function independently of the investigators and AnaptysBio/Innovaderm clinical study team members. All unblinded roles and responsibilities of these individuals, the sources of the unblinded information, and the processes to maintain the blind are detailed in the Unblinded Data Management Plan.

The Unblinded Statistician and Unblinded Programmer(s) will be in possession of unblinding treatment codes produced for the Interactive Web-based Response System (IWRS) which is used to randomize subjects to treatment, and managed by a separate team at Everest. Upon successful generation of the blinded versions of the datasets and analyses, the Unblinded Statistician and Unblinded Programmer(s) will be responsible for generating unblinded datasets and analyses according to this SAP. The unblinded primary analysis results will be provided to a designated member of AnaptysBio executive management by the Unblinded Statistician.

3.5 Sample Size

Approximately 120 subjects will be stratified based on facial IGA score at baseline (3 [moderate] vs. 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

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 facial inflammatory lesion 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.[1] **Table 1** shows more information on power from a set of scenarios of variability and between-group mean differences.

Table 1 Power Exploration for Different Scenarios of Variability and Between-group Mean Differences

Common Standard Deviation	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
	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.

3.6 Study Procedures and Schedule of Activities

Study procedures and their timing are summarized in the Schedule of Activities (**Table 2**).

Table 2 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
PGI-S[h]	X	X	X	X	X	X	X
PGI-C[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					

Table 2 Schedule of Activities

	Screening Period	Treatment Period	Follow-Up Period
Concomitant medication review[l]	X	Continuously	

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; PGI-C, Patient Global Impression of Change; PGI-S, 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 Protocol **Section 8.2.3** for details regarding the complete physical examination.

[e] Refer to Protocol **Section 8.2.4** for details and instructions regarding vital signs.

[f] Refer to Protocol **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 Protocol **Appendix 1** for definition of WOCBP) and will be required to follow the contraceptive guidance in Protocol **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 Protocol **Appendix 10** for instructions regarding clinical laboratory parameters.

[h] Refer to Protocol **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 7**.

[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 Protocol **Section 6.5**.

4. DATA AND ANALYTICAL QUALITY ASSURANCE

The overall quality assurance procedures for the study data, statistical programming, and analyses are described in Everest's SOPs. Detailed data management procedures are documented in the Data Management Plan, Data Validation Check Specifications, and Data Review Plan. Detailed statistical and programming quality control and quality assurance procedures are documented in the Statistical Analysis and Programming Quality Control/Quality Assurance Plan.

The study endpoints and analytic approaches are both prospectively defined and documented in the protocol and in this SAP. The SAP will be finalized prior to the primary analysis data snapshot, and protocol deviations will be identified and decisions for inclusion and exclusion of subjects from the Per Protocol Analysis Set (**Section 5.3**) will be made prior to the final database lock and data analysis.

5. ANALYSIS SETS

5.1 Intent-to-Treat Analysis Set

The Intent-to-Treat (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.

5.2 Safety Analysis Set

The Safety Analysis Set will include all randomized subjects who receive at least 1 dose of imsidolimab or placebo. The Safety Analysis Set will be used for all safety analyses. Subjects will be analyzed as treated. If a subject receives both treatments, they will be analyzed in the imsidolimab group.

5.3 Per Protocol Analysis Set

The Per Protocol (PP) Analysis Set will include all subjects in the ITT Analysis Set who do not have important protocol violations that would affect the evaluation of the primary efficacy endpoint. Further details on the determination of protocol deviations are described in **Section 7.3**.

5.4 Pharmacokinetic Analysis Set

The PK Analysis Set will include all imsidolimab-treated subjects in the Safety Analysis Set who have at least 1 quantifiable post-dose PK sample available and who do not have events or protocol deviations with the potential to affect PK concentrations. The PK Analysis Set will be used for all PK analyses.

The PK Analysis Set will be determined after review of the clinical study data (e.g., concomitant medications, study drug dosing information, and adverse events [AEs]). Prior to the final PK analysis, subject data as well as protocol deviations will be reviewed in a blinded manner by Everest, AnaptysBio, and Innovaderm at the blinded data review meeting (BDRM) for inclusion/exclusion into the PK Analysis Set.

5.5 Populations for Primary Analyses

Demographics will be summarized on the ITT Analysis Set; PP, PK, and Safety Analysis Sets will be tabulated only if they are different from ITT Analysis Set for demographics. Extent of exposure, safety, biomarker, and anti-drug antibody (ADA) data will be summarized on the Safety Analysis Set. PK

parameters will be summarized on the PK Analysis Set. Efficacy analyses will be performed on the ITT and (where indicated) PP Analysis Sets.

6. SPECIFICATION OF ENDPOINTS AND VARIABLES

Unless specified otherwise, baseline will be the last available measurement taken prior to the first dose of study treatment.

Change from baseline will be calculated as the difference between the observed value at a specified visit and the corresponding baseline value.

The percentage change from baseline at Week X is defined as:

$$100\% \times \{(\text{Observed value at Week X} - \text{baseline value}) / \text{baseline value}\}$$

6.1 Demographic and Baseline Characteristics

6.1.1 Demography and Physical Characteristics

Subject demographics will be summarized overall as well as by treatment arm. Additionally, baseline values of the efficacy measures for facial IGA, facial inflammatory/noninflammatory lesion counts, truncal physician's global assessment (PGA), patient-global impression of severity (PGI-S), dermatology life quality index (DLQI) total score, children's dermatology life quality index (CDLQI) total score, and subject satisfaction questionnaire (SSQ) will be summarized overall as well as by treatment arm in the baseline disease characteristics output.

Demographic and baseline characteristic variables summarized will include the following:

- Age
- Age group ([12, 18) years, [18, 30) years, ≥30 years)
- Age group ([12, 16) years, ≥16 years)
- Age group ([12, 25) years, ≥25 years)
- Sex
- Sex and Age group (Male and [12, 25) years, Male and ≥25 years, Female and [12, 25) years, Female and ≥25 years)
- Race
- Ethnicity (Hispanic or Non-Hispanic)
- Country
- Woman of childbearing potential (Yes or No)
- Smoking history
- Weight (kg)
- Height (cm)
- Body mass index (BMI; kg/m^2)
- Facial IGA at Baseline (Grade 3, Grade 4)
- Facial papule lesion counts at Baseline
- Facial pustule lesion counts at Baseline
- Facial nodule lesion counts at Baseline
- Facial papule and pustule lesion counts at Baseline
- Facial inflammatory lesion counts at Baseline
- Facial noninflammatory lesion counts at Baseline
- Total facial lesion counts at Baseline

- Truncal PGA (chest, back, neck, and overall) at Baseline (Grade 0 to Grade 4)
- PGI-S at Baseline (Grade 1 to Grade 4)
- DLQI total score at Baseline
- CDLQI total score at Baseline
- SSQ at Baseline (Grade 0 to Grade 6)

6.1.2 Medical and Surgical History

Medical and surgical history will be collected at the Screening visit and will be coded using the version of the Medical Dictionary for Regulatory Activities (MedDRA) specified in the approved Data Management Plan.

6.1.3 Prior and Concomitant Medications

Any medication that the subject is receiving at the time of enrollment and receives during the study will be recorded on the Prior and Concomitant Medications CRF page. Prior medication is any medication stopped prior to the first dose of study treatment.

Concomitant medication is any medication continued to be taken at the time of the first dose or started after the first dose of study treatment.

Coding: Verbatim medication or treatment terms will be coded by Everest Clinical Research and will be assigned a preferred name and an Anatomical Therapeutic Chemical Class (ATC) Level 2 term (when available) using the version of the World Health Organization Drug Dictionary (WHODrug Global) specified in the approved Data Management Plan.

Multiple ATC assignments: If there are multiple ATC codes assigned to the same concomitant medication, the "primary" one based on a medical evaluation will be used.

Uncoded Medication: Before the database lock, uncoded medications/treatments may be assigned the string "UNCODED" as the ATC code, and the verbatim term will be used as the preferred name, so they can be included in the summary tables. In final datasets, all the terms will be coded.

6.2 Efficacy

6.2.1 Study Day and Visit Window Definitions

Efficacy data obtained from unscheduled visits will be allocated to the scheduled visit corresponding to the visit window they fall in as specified in **Table 3**. For summary tables and figures, efficacy data will be analyzed based on the visit window specified in **Table 3**. Only if the data from the nominal visit or time point is missing will data from unscheduled visits for the same nominal visit or time point be used. If more than one unscheduled visit exists in a given window, the earlier (closer to nominal visit) measurement will be used. Efficacy from scheduled and unscheduled visits will be listed.

Table 3 Analysis Visit Windows

Nominal Visit	Nominal Day	Visit Window (day)
Screening	-30 to -1	-30 to -1
Day 1	1	1 (Pre-dose)
Week 2	15	1 (Post-dose) to 22

Table 3 Analysis Visit Windows

Nominal Visit	Nominal Day	Visit Window (day)
Week 4	29	23 to 42
Week 8	57	43 to 71
Week 12	85	72 to 99
Week 20	141	≥100

Study Day and Day of Assessment or Event definitions are provided in **Appendix 1, Data Handling Rules**.

6.2.2 Primary Efficacy Variable

The primary endpoint for this study is the change from baseline in facial inflammatory lesion counts at Week 12. The number of facial inflammatory lesions (pustules, papules, and nodular lesions) will be counted at the visits specified in the Schedule of Activities in **Table 2**, according to the definitions presented in **Table 4**. Facial inflammatory lesion counts will be made at the forehead, left and right cheeks, nose, and chin. The number of pustules, papules, and nodular lesions as well as the summed total for each visit will be documented in the electronic case report form (eCRF). Change from baseline at Week 12 will be calculated as the difference between the observed value at Week 12 and the corresponding baseline value.

Table 4 Definitions of Inflammatory Lesions

Type of Lesion	Definition
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.

6.2.3 Secondary Efficacy Variables

The secondary efficacy endpoints are as follows.

- **Percent change from Baseline in facial inflammatory lesion counts at each visit**

  The percentage change from baseline in facial inflammatory lesion counts at each visit (Weeks 2, 4, 8, 12, and 20) will be calculated.
- **Change from Baseline in facial inflammatory lesion counts at visits other than Week 12**

  Change from baseline in facial inflammatory lesion counts at visits other than Week 12 (Weeks 2, 4, 8, and 20) will be calculated.
- **Percent change from Baseline in facial noninflammatory lesion counts at each visit**

  The number of facial noninflammatory lesions (open and closed comedones) will be counted at the visits specified in the Schedule of Activities in **Table 2**, according to the definitions presented in **Table 5**. Noninflammatory lesion counts will be made at the forehead, left and right cheeks,

and chin. The percentage change from baseline in facial noninflammatory lesion counts at each visit (Weeks 2, 4, 8, 12, and 20) will be calculated.

Table 5 Definitions of Noninflammatory Lesions

Type of Lesion	Definition
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)

- **Change from Baseline in facial noninflammatory lesion counts at each visit**

  Change from baseline in facial noninflammatory lesion counts at each visit (Weeks 2, 4, 8, 12, and 20) will be calculated.

- **Percent change from Baseline in total facial lesion (inflammatory and noninflammatory lesions) counts at each visit**

  The percentage change from baseline in total facial lesion (inflammatory and noninflammatory lesions) counts at each visit (Weeks 2, 4, 8, 12, and 20) will be calculated.

- **Change from Baseline in total facial lesion (inflammatory and noninflammatory lesions) counts at each visit**

  Change from baseline in total facial lesion (inflammatory and noninflammatory lesions) counts at each visit (Weeks 2, 4, 8, 12, and 20) will be calculated.

- **Change from Baseline in facial IGA at each visit**

  The facial IGA is a 5-point morphological assessment of facial acneiform rash, ranged from 0 (Clear) to 4 (Severe). The facial IGA is a global evaluation that will be performed at arm's length distance from the subject and must be performed before the facial inflammatory lesion count.

  Change from baseline in facial IGA at each visit (Weeks 2, 4, 8, 12, and 20) will be calculated.

  The number and percentage of subjects who have facial IGA Grade 0, 1, 2, 3, 4 at baseline and the shifts from baseline grades to each visit (Weeks 2, 4, 8, 12, and 20) will be calculated based on these values.

- **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**

  For each treatment group, the number of subjects achieving a facial IGA of clear (0) or almost clear (1) with at least a 2-grade decrease from baseline will be calculated at each visit (Weeks 2, 4, 8, 12, and 20). The proportion of such subjects will be calculated for each treatment group at each visit as:

$$\frac{\begin{array}{c}Number\ of\ subjects\ achieving\ aa\ facial\ IGA\ of\ clear\ (0)\ or\ almost\ clear\ (1)\ with\ baseline \\ facial\ IGA\ score\ \geq\ 2\ at\ Week\ x\end{array}}{\begin{array}{c}Number\ of\ subjects\ in\ treatment\ group\ with\ with\ baseline\ facial\ IGA\ score\ \geq\ 2 \\ and\ facial\ IGA\ at\ Week\ x\end{array}}$$

- **Proportion of subjects in each response category for the PGI-S at each visit**

  The PGI-S is a single-item question, which asks the subject to rate the current severity of AV ("Clear skin", "Mild", "Moderate", and "Severe").

For each treatment group, the number of subjects in each response category for the PGI-S will be calculated at each visit specified in the Schedule of Activities in **Table 2**. The proportion of such subjects will be calculated for each treatment group at each visit (Weeks 0, 2, 4, 8, 12, and 20) as:

$$\frac{Number\ of\ subjects\ with\ PGI\text{-}S\ of\ "Clear\ skin"\ at\ Week\ x}{Number\ of\ subjects\ in\ treatment\ group\ with\ PGI\text{-}S\ at\ Week\ x}$$

$$\frac{Number\ of\ subjects\ with\ PGI\text{-}S\ of\ "Mild"\ at\ Week\ x}{Number\ of\ subjects\ in\ treatment\ group\ with\ PGI\text{-}S\ at\ Week\ x}$$

$$\frac{Number\ of\ subjects\ with\ PGI\text{-}S\ of\ "Moderate"\ at\ Week\ x}{Number\ of\ subjects\ in\ treatment\ group\ with\ PGI\text{-}S\ at\ Week\ x}$$

$$\frac{Number\ of\ subjects\ with\ PGI\text{-}S\ of\ "Severe"\ at\ Week\ x}{Number\ of\ subjects\ in\ treatment\ group\ with\ PGI\text{-}S\ at\ Week\ x}$$

- **Proportion of subjects in each response category for the PGI-C at each post-Baseline visit**

  The Patient Global Impression of change (PGI-C) 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").

  For each treatment group, the number of subjects in each response category for the PGI-C will be calculated at each post-baseline visit specified in the Schedule of Activities in **Table 2**. The proportion of such subjects will be calculated for each treatment group at each post-baseline visit (Weeks 2, 4, 8, 12, and 20) as:

$$\frac{Number\ of\ subjects\ with\ PGI\text{-}C\ of\ "Not\ at\ all\ bothered"\ at\ Week\ x}{Number\ of\ subjects\ in\ treatment\ group\ with\ PGI\text{-}C\ at\ Week\ x}$$

$$\frac{Number\ of\ subjects\ with\ PGI\text{-}C\ of\ "Very\ much\ better"\ at\ Week\ x}{Number\ of\ subjects\ in\ treatment\ group\ with\ PGI\text{-}C\ at\ Week\ x}$$

$$\frac{Number\ of\ subjects\ with\ PGI\text{-}C\ of\ "Much\ better"\ at\ Week\ x}{Number\ of\ subjects\ in\ treatment\ group\ with\ PGI\text{-}C\ at\ Week\ x}$$

$$\frac{Number\ of\ subjects\ with\ PGI\text{-}C\ of\ "A\ little\ better"\ at\ Week\ x}{Number\ of\ subjects\ in\ treatment\ group\ with\ PGI\text{-}C\ at\ Week\ x}$$

$$\frac{Number\ of\ subjects\ with\ PGI\text{-}C\ of\ "No\ change"\ at\ Week\ x}{Number\ of\ subjects\ in\ treatment\ group\ with\ PGI\text{-}C\ at\ Week\ x}$$

$$\frac{Number\ of\ subjects\ with\ PGI\text{-}C\ of\ "A\ little\ worse"\ at\ Week\ x}{Number\ of\ subjects\ in\ treatment\ group\ with\ PGI\text{-}C\ at\ Week\ x}$$

$$\frac{Number\ of\ subjects\ with\ PGI\text{-}C\ of\ "Much\ worse"\ at\ Week\ x}{Number\ of\ subjects\ in\ treatment\ group\ with\ PGI\text{-}C\ at\ Week\ x}$$

$$\frac{Number\ of\ subjects\ with\ PGI\text{-}C\ of\ "Very\ much\ worse"\ at\ Week\ x}{Number\ of\ subjects\ in\ treatment\ group\ with\ PGI\text{-}C\ at\ Week\ x}$$

- **Change from Baseline in DLQI at each visit**

  The DLQI is a simple 10-question validated questionnaire.[2] These will be assessed at the visits specified in the Schedule of Activities in **Table 2**. Each item is assigned a value from 0 = not at all to 3 = very much and the score is the sum of the individual items (range from 0 to 30). Subjects will be administered the same questionnaire during the entire study based on their age at Day 1, so no subjects who begin the study with the CDLQI will take the DLQI. Additional scoring details are below:[3]

  - If one question is unanswered, this score is allocated to 0.
  - If two or more questions are left unanswered the questionnaire is not scored.
  - For question 7:
    - An answer of "Yes" is scored as 3;
    - An answer of "Not Relevant" is scored as 0;
    - An answer of "No" is scored depending on the follow up question: *If "No", over the last week how much has your skin been a problem at work or studying?* "A Lot" is scored as 2 and "A Little" is scored as 1.

  Change from baseline in DLQI at each visit (Weeks 2, 4, 8, 12, and 20) will be calculated.

- **Change from Baseline in CDLQI at each visit**

  The CDLQI is a simple 10-question validated questionnaire.[4] These will be assessed at the visits specified in the Schedule of Activities in **Table 2**. Each item is assigned a value from 0 = not at all to 3 = very much (3 = prevented school for question 7) and the score is the sum of the individual items (range from 0 to 30). The CDLQI 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. Additional scoring details are below:

  - If one question is unanswered, this score is allocated to 0.
  - If two or more questions are left unanswered the questionnaire is not scored.

  Change from baseline in CDLQI at each visit (Weeks 2, 4, 8, 12, and 20) will be calculated.

6.2.4 Exploratory Efficacy Variables

- **Percent change from Baseline in facial papule lesion counts at each visit**

  The percentage change from baseline in facial papule lesion counts at each visit (Weeks 2, 4, 8, 12, and 20) will be calculated.

- **Change from Baseline in facial papule lesion counts at each visit**

  Change from baseline in facial papule lesion counts at each visit (Weeks 2, 4, 8, 12, and 20) will be calculated.

- **Percent change from Baseline in facial pustule lesion counts at each visit**

  The percentage change from baseline in facial pustule lesion counts at each visit (Weeks 2, 4, 8, 12, and 20) will be calculated.

- **Change from Baseline in facial pustule lesion counts at each visit**

  Change from baseline in facial pustule lesion counts at each visit (Weeks 2, 4, 8, 12, and 20) will be calculated.

- **Percent change from Baseline in facial nodule lesion counts at each visit**

  The percentage change from baseline in facial nodule lesion counts at each visit (Weeks 2, 4, 8, 12, and 20) will be calculated.

- **Change from Baseline in facial nodule lesion counts at each visit**

  Change from baseline in facial nodule lesion counts at each visit (Weeks 2, 4, 8, 12, and 20) will be calculated.

- **Change from Baseline in Truncal PGA for chest at each visit**

  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).

  Change from baseline in Truncal PGA for chest at each visit (Weeks 2, 4, 8, 12, and 20) will be calculated.

  The number and percentage of subjects who have Truncal PGA Grade 0, 1, 2, 3, 4 for chest at baseline and the shifts from baseline grades to each visit (Weeks 2, 4, 8, 12, and 20) will be calculated based on these values.

- **Change from Baseline in Truncal PGA for neck at each visit**

  Change from baseline in Truncal PGA for neck at each visit (Weeks 2, 4, 8, 12, and 20) will be calculated.

  The number and percentage of subjects who have Truncal PGA Grade 0, 1, 2, 3, 4 for neck at baseline and the shifts from baseline grades to each visit (Weeks 2, 4, 8, 12, and 20) will be calculated based on these values.

- **Change from Baseline in Truncal PGA for back at each visit**

  Change from baseline in Truncal PGA for back at each visit (Weeks 2, 4, 8, 12, and 20) will be calculated.

  The number and percentage of subjects who have Truncal PGA Grade 0, 1, 2, 3, 4 for back at baseline and the shifts from baseline grades to each visit (Weeks 2, 4, 8, 12, and 20) will be calculated based on these values.

- **Change from Baseline in overall Truncal PGA at each visit**

  The overall Truncal PGA is determined from the average of Truncal PGA scores for 3 body areas in the form of a whole number, according to the definitions presented in **Table 6**.

  Change from baseline in overall Truncal PGA at each visit (Weeks 2, 4, 8, 12, and 20) will be calculated.

Table 6 Overall Truncal PGA

Overall Truncal PGA	Average Score
0	0 (all component=0)
1	0 to <1.5
2	≥ 1.5 to <2.5
3	≥ 2.5 to <3.5
4	≥ 3.5

- **Proportion of subjects with at least 1-point decrease from Baseline in facial IGA at each visit**

  For each treatment group, the number of subjects with at least 1-point decrease from baseline in facial IGA will be calculated at each visit (Weeks 2, 4, 8, 12, and 20). The proportion of such subjects will be calculated for each treatment group at each visit as:

$$\frac{Number\ of\ subjects\ with\ (facial\ IGA\ at\ Week\ x\ -\ facial\ IGA\ at\ baseline)\ \leq\ -1}{Number\ of\ subjects\ in\ treatment\ group\ with\ baseline\ facial\ IGA\ score\ \geq\ 1\ and\ facial\ IGA\ at\ Week\ x}$$

- **Proportion of subjects with at least 2-point decrease from Baseline in facial IGA at each visit**

  For each treatment group, the number of subjects with at least 2-point decrease from baseline in facial IGA will be calculated at each visit (Weeks 2, 4, 8, 12, and 20). The proportion of such subjects will be calculated for each treatment group at each visit as:

$$\frac{Number\ of\ subjects\ with\ (facial\ IGA\ at\ Week\ x\ -\ facial\ IGA\ at\ baseline)\ \leq\ -2}{Number\ of\ subjects\ in\ treatment\ group\ with\ baseline\ facial\ IGA\ score\ \geq\ 2\ and\ facial\ IGA\ at\ Week\ x}$$

- **Proportion of subjects with at least 1-point decrease from Baseline in overall Truncal PGA at each visit for subjects with Baseline overall Truncal PGA score of at least 1**

  For each treatment group, the number of subjects with at least 1-point decrease from baseline in overall Truncal PGA will be calculated at each visit (Weeks 2, 4, 8, 12, and 20). The proportion of such subjects will be calculated for each treatment group at each visit as:

$$\frac{Number\ of\ subjects\ with\ (overall\ Truncal\ PGA\ at\ Week\ x\ -\ overall\ Truncal\ PGA\ at\ baseline)\ \leq\ -1}{Number\ of\ subjects\ in\ treatment\ group\ with\ baseline\ overall\ Truncal\ PGA\ \geq\ 1\ and\ overall\ Truncal\ PGA\ at\ Week\ x}$$

- **Proportion of subjects with at least 2-point decrease from Baseline in overall Truncal PGA at each visit for subjects with Baseline overall Truncal PGA score of at least 2**

  For each treatment group, the number of subjects with at least 2-point decrease from baseline in overall Truncal PGA will be calculated at each visit (Weeks 2, 4, 8, 12, and 20). The proportion of such subjects will be calculated for each treatment group at each visit as:

$$\frac{Number\ of\ subjects\ with\ (overall\ Truncal\ PGA\ at\ Week\ x\ -\ overall\ Truncal\ PGA\ at\ baseline)\ \leq\ -2}{Number\ of\ subjects\ in\ treatment\ group\ with\ baseline\ overall\ Truncal\ PGA\ \geq\ 2\ and\ overall\ Truncal\ PGA\ at\ Week\ x}$$

- **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**

  For each treatment group, the number of subjects achieving a Truncal PGA for chest of clear (0) or almost clear (1) with at least a 2-grade decrease from baseline will be calculated at each visit (Weeks 2, 4, 8, 12, and 20). The proportion of such subjects will be calculated for each treatment group at each visit as:

$$\frac{Number\ of\ subjects\ achieving\ a\ Truncal\ PGA\ for\ chest\ of\ clear\ (0)\ or\ almost\ clear\ (1)\ with\ baseline\ Truncal\ PGA\ for\ chest\ \geq\ 2\ at\ Week\ x}{Number\ of\ subjects\ in\ treatment\ group\ with\ baseline\ Truncal\ PGA\ for\ chest\ \geq\ 2\ and\ Truncal\ PGA\ for\ chest\ at\ Week\ x}$$

- **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**

  For each treatment group, the number of subjects achieving a Truncal PGA for neck of clear (0) or almost clear (1) with at least a 2-grade decrease from baseline will be calculated at each visit (Weeks 2, 4, 8, 12, and 20). The proportion of such subjects will be calculated for each treatment group at each visit as:

$$\frac{\begin{array}{c}Number\ of\ subjects\ achieving\ a\ Truncal\ PGA\ for\ neck\ of\ clear\ (0)\ or\ almost\ clear\ (1)\ with\ baseline\\ Truncal\ PGA\ for\ neck\ \geq\ 2\ at\ Week\ x\end{array}}{\begin{array}{c}Number\ of\ subjects\ in\ treatment\ group\ with\ baseline\ Truncal\ PGA\ for\ neck\ \geq\ 2\\ and\ Truncal\ PGA\ for\ neck\ at\ Week\ x\end{array}}$$

- **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**

  For each treatment group, the number of subjects achieving a Truncal PGA for back of clear (0) or almost clear (1) with at least a 2-grade decrease from baseline will be calculated at each visit (Weeks 2, 4, 8, 12, and 20). The proportion of such subjects will be calculated for each treatment group at each visit as:

$$\frac{\begin{array}{c}Number\ of\ subjects\ achieving\ a\ Truncal\ PGA\ for\ back\ of\ clear\ (0)\ or\ almost\ clear\ (1)\ with\ baseline\\ Truncal\ PGA\ for\ back\ \geq\ 2\ at\ Week\ x\end{array}}{\begin{array}{c}Number\ of\ subjects\ in\ treatment\ group\ with\ baseline\ Truncal\ PGA\ for\ back\ \geq\ 2\\ and\ Truncal\ PGA\ for\ back\ at\ Week\ x\end{array}}$$

- **Proportion of subjects achieving an overall Truncal PGA of clear (0) or almost clear (1) with at least a 2-grade decrease from Baseline at each visit for subjects with Baseline overall Truncal PGA score of at least 2**

  For each treatment group, the number of subjects achieving an overall Truncal PGA of clear (0) or almost clear (1) with at least a 2-grade decrease from baseline will be calculated at each visit (Weeks 2, 4, 8, 12, and 20). The proportion of such subjects will be calculated for each treatment group at each visit as:

$$\frac{\begin{array}{c}Number\ of\ subjects\ achieving\ an\ overall\ Truncal\ PGA\ \ of\ clear\ (0)\ or\ almost\ clear\ (1)\ with\ baseline\\ overall\ Truncal\ PGA\ \geq\ 2\ at\ Week\ x\end{array}}{\begin{array}{c}Number\ of\ subjects\ in\ treatment\ group\ with\ baseline\ Truncal\ PGA\ for\ back\ \geq\ 2\\ and\ Truncal\ PGA\ for\ back\ at\ Week\ x\end{array}}$$

- **Proportion of subjects achieving improvement ("Much better" or "Very much better") according to the PGI-C at each post-Baseline visit**

  For each treatment group, the number of subjects achieving improvement ("Much better" or "Very much better") according to the PGI-C will be calculated at each post-baseline visit specified in the Schedule of Activities in **Table 2**. The proportion of such subjects will be calculated for each treatment group at each post-baseline visit (Weeks 2, 4, 8, 12, and 20) as:

$$\frac{Number\ of\ subjects\ with\ PGI\text{-}C\ of\ "Much\ better"\ or\ "Very\ much\ better"\ at\ Week\ x}{Number\ of\ subjects\ in\ treatment\ group\ with\ PGI\text{-}C\ at\ Week\ x}$$

- **Proportion of subjects achieving improvement ("A little better", "Much better" or "Very much better") according to the PGI-C at each post-Baseline visit**

  For each treatment group, the number of subjects achieving improvement ("A little better", "Much better" or "Very much better") according to the PGI-C will be calculated at each post-baseline visit specified in the Schedule of Activities in **Table 2**. The proportion of such subjects will be calculated for each treatment group at each post-baseline visit (Weeks 2, 4, 8, 12, and 20) as:

$$\frac{Number\ of\ subjects\ with\ PGI\text{-}C\ of\ "A\ little\ better","Much\ better"\ or\ "Very\ much\ better"\ at\ Week\ x}{Number\ of\ subjects\ in\ treatment\ group\ with\ PGI\text{-}C\ at\ Week\ x}$$

- **Proportion of subjects achieving "Mild" or "Clear skin" according to the PGI-S at each visit**

  For each treatment group, the number of subjects achieving "Mild" or "Clear skin" according to the PGI-S will be calculated at each visit specified in the Schedule of Activities in **Table 2**. The proportion of such subjects will be calculated for each treatment group at each visit (Weeks 0, 2, 4, 8, 12, and 20) as:

$$\frac{Number\ of\ subjects\ with\ PGI\text{-}S\ of\ "Mild"\ or\ "Clear\ skin"at\ Week\ x}{Number\ of\ subjects\ in\ treatment\ group\ with\ PGI\text{-}S\ at\ Week\ x}$$

- **Change from Baseline in PGI-S at each visit**

  Change from baseline in PGI-S at each visit (Weeks 2, 4, 8, 12, and 20) will be calculated.

  The number and percentage of subjects who have PGI-S Grade 1, 2, 3, 4 at baseline and the shifts from baseline grades to each visit (Weeks 2, 4, 8, 12, and 20) will be calculated based on these values.

- **Proportion of subjects in each response category for the SSQ at each visit**

  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). It will be assessed at the visits specified in the Schedule of Activities in **Table 2**.

  For each treatment group, the number of subjects in each response category for the SSQ will be calculated at each visit (Weeks 0, 2, 4, 8, 12 and 20). The proportion of such subjects will be calculated for each treatment group at each visit as:

$$\frac{Number\ of\ subjects\ with\ SSQ\ of\ "extremely\ satisfied"\ at\ Week\ x}{Number\ of\ subjects\ in\ treatment\ group\ with\ SSQ\ at\ Week\ x}$$

$$\frac{Number\ of\ subjects\ with\ SSQ\ of\ "somewhat\ satisfied"\ at\ Week\ x}{Number\ of\ subjects\ in\ treatment\ group\ with\ SSQ\ at\ Week\ x}$$

$$\frac{Number\ of\ subjects\ with\ SSQ\ of\ "slightly\ satisfied"\ at\ Week\ x}{Number\ of\ subjects\ in\ treatment\ group\ with\ SSQ\ at\ Week\ x}$$

$$\frac{Number\ of\ subjects\ with\ SSQ\ of\ "neither\ satisfied\ nor\ dissatisfied"\ at\ Week\ x}{Number\ of\ subjects\ in\ treatment\ group\ with\ SSQ\ at\ Week\ x}$$

$$\frac{Number\ of\ subjects\ with\ SSQ\ of\ "slightly\ dissatisfied"\ at\ Week\ x}{Number\ of\ subjects\ in\ treatment\ group\ with\ SSQ\ at\ Week\ x}$$

$$\frac{Number\ of\ subjects\ with\ SSQ\ of\ \text{“somewhat dissatisfied”}\ at\ Week\ x}{Number\ of\ subjects\ in\ treatment\ group\ with\ SSQ\ at\ Week\ x}$$

$$\frac{Number\ of\ subjects\ with\ SSQ\ of\ \text{“extremely dissatisfied”}\ at\ Week\ x}{Number\ of\ subjects\ in\ treatment\ group\ with\ SSQ\ at\ Week\ x}$$

- **Proportion of subjects achieving “slightly satisfied”, “somewhat satisfied,” or “extremely satisfied” according to the SSQ at each visit**

  For each treatment group, the number of subjects achieving “slightly satisfied”, “somewhat satisfied”, or “extremely satisfied” according to the SSQ will be calculated at each visit (Weeks 0, 2, 4, 8, 12 and 20). The proportion of such subjects will be calculated for each treatment group at each visit as:

$$\frac{Number\ of\ subjects\ with\ SSQ\ of\ \text{“slightly satisfied”, “somewhat satisfied”, or “extremely satisfied”}\ at\ Week\ x}{Number\ of\ subjects\ in\ treatment\ group\ with\ SSQ\ at\ Week\ x}$$

- **Proportion of subjects in each response category for the SSRS at Week 12 and Week 20**

  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). It will be assessed at Weeks 12 and 20.

  For each treatment group, the number of subjects in each response category for the SSRS will be calculated at Weeks 12 and 20. The proportion of such subjects will be calculated for each treatment group at Weeks 12 and 20 as:

$$\frac{Number\ of\ subjects\ with\ SSRS\ of\ \text{“extremely satisfied”}\ at\ Week\ x}{Number\ of\ subjects\ in\ treatment\ group\ with\ SSRS\ at\ Week\ x}$$

$$\frac{Number\ of\ subjects\ with\ SSRS\ of\ \text{“somewhat satisfied”}\ at\ Week\ x}{Number\ of\ subjects\ in\ treatment\ group\ with\ SSRS\ at\ Week\ x}$$

$$\frac{Number\ of\ subjects\ with\ SSRS\ of\ \text{“slightly satisfied”}\ at\ Week\ x}{Number\ of\ subjects\ in\ treatment\ group\ with\ SSRS\ at\ Week\ x}$$

$$\frac{Number\ of\ subjects\ with\ SSRS\ of\ \text{“neither satisfied nor dissatisfied”}\ at\ Week\ x}{Number\ of\ subjects\ in\ treatment\ group\ with\ SSRS\ at\ Week\ x}$$

$$\frac{Number\ of\ subjects\ with\ SSRS\ of\ \text{“slightly dissatisfied”}\ at\ Week\ x}{Number\ of\ subjects\ in\ treatment\ group\ with\ SSRS\ at\ Week\ x}$$

$$\frac{Number\ of\ subjects\ with\ SSRS\ of\ \text{“somewhat dissatisfied”}\ at\ Week\ x}{Number\ of\ subjects\ in\ treatment\ group\ with\ SSRS\ at\ Week\ x}$$

$$\frac{Number\ of\ subjects\ with\ SSRS\ of\ \text{“extremely dissatisfied”}\ at\ Week\ x}{Number\ of\ subjects\ in\ treatment\ group\ with\ SSRS\ at\ Week\ x}$$

- **Proportion of subjects achieving “slightly satisfied”, “somewhat satisfied”, or “extremely satisfied” according to the SSRS at Week 12 and Week 20**

  For each treatment group, the number of subjects achieving “slightly satisfied”, “somewhat satisfied”, or “extremely satisfied” according to the SSRS will be calculated Week 12 and

Week 20. The proportion of such subjects will be calculated for each treatment group at each visit as:

$$\frac{\begin{array}{c}Number\ of\ subjects\ with\ SSRS\ of\ "slightly\ satisfied", "somewhat\ satisfied", or\ "extremely\ satisfied"\\ at\ Week\ x\end{array}}{Number\ of\ subjects\ in\ treatment\ group\ with\ SSRS\ at\ Week\ x}$$

- **Proportion of subjects achieving a DLQI of 0 or 1 at each visit for subjects with Baseline DLQI of at least 2**

  For each treatment group, the number of subjects achieving a DLQI of 0 or 1 with baseline DLQI of at least 2 will be calculated at each visit (Weeks 2, 4, 8, 12, and 20). The proportion of such subjects will be calculated for each treatment group at each visit as:

$$\frac{Number\ of\ subjects\ achieving\ a\ DLQI\ of\ 0\ or\ 1\ with\ baseline\ DLQI\ \geq\ 2\ at\ Week\ x}{\begin{array}{c}Number\ of\ subjects\ in\ treatment\ group\ with\ baseline\ DLQI\ \geq\ 2\\ and\ DLQI\ at\ Week\ x\end{array}}$$

- **Proportion of subjects with less than 5 facial inflammatory lesion count (papules and pustules) at each visit**

  For each treatment group, the number of subjects with less than 5 facial inflammatory lesion count (papules and pustules) will be calculated at each visit (Weeks 2, 4, 8, 12, and 20). The proportion of such subjects will be calculated for each treatment group at each visit as:

$$\frac{\begin{array}{c}Number\ of\ subjects\ with\ less\ than\ 5\ facial\ inflammatory\ lesion\ count\\ (papules\ and\ pustules)\ at\ Week\ x\end{array}}{\begin{array}{c}Number\ of\ subjects\ in\ treatment\ group\ with\ facial\ inflammatory\ lesion\ count\\ (papules\ and\ pustules)\ at\ Week\ x\end{array}}$$

6.2.4.1 Photography

The exploratory endpoints based on photography of face include the following:

- **Change from Baseline in lesion counts based on blinded photographic assessment at each visit**

  The number of facial lesion counts (inflammatory and noninflammatory) will be counted by a standardized review of photographs at the visits specified in the Schedule of Activities in **Table 2**.

  The change from baseline in total lesion counts based on blinded photographic assessment at each visit (Weeks 2, 4, 8, 12 and 20) will be calculated.

- **Change from Baseline in inflammatory lesion counts based on blinded photographic assessment at each visit**

  The change from baseline in inflammatory lesion counts based on blinded photographic assessment at each visit (Weeks 2, 4, 8, 12 and 20) will be calculated.

- **Change from Baseline in noninflammatory lesion counts based on blinded photographic assessment at each visit**

  The change from baseline in noninflammatory lesion counts based on blinded photographic assessment at each visit (Weeks 2, 4, 8, 12 and 20) will be calculated.

- **Change from Baseline in Parametric Acne Severity (PAS) score based on blinded photographic assessment at each visit**

  The change from baseline in PAS score based on blinded photographic assessment at each visit (Weeks 2, 4, 8, 12 and 20) will be calculated.
- **Change from Baseline in erythema score based on blinded photographic assessment at each visit**

  The change from baseline in erythema score based on blinded photographic assessment at each visit (Weeks 2, 4, 8, 12 and 20) will be calculated.

6.3 Pharmacokinetic Variables

Concentration time data will be collected following imsidolimab administration to evaluate the PK profile of imsidolimab. Samples from subjects having received imsidolimab only will be analyzed for PK; no placebo samples will be analyzed. Pharmacokinetic samples will be collected at the time points indicated in **Table 7** below.

Table 7 Pharmacokinetic Sample Collection and Time Points

Study Visit	Pharmacokinetic Sample Time Point
Day 1	Pre-dose
Day 1	2 hours ±10 minutes post-dose
Day 15	Anytime
Day 29	Pre-dose
Day 57	Pre-dose
Day 85	Anytime
Day 141	Anytime

Non-compartmental analysis (NCA) will not be conducted due to minimal PK sampling. However, other presentations of PK information may be added at the discretion of the PK scientist.

Population PK modelling may be performed by the Sponsor or another designated vendor, and if done, will be described in a separate PK analysis plan and report.

6.4 Immunogenicity Variables

- **Presence of ADA to imsidolimab**

  Anti-drug antibodies samples will be collected at the time points indicated in **Table 8** below:

Table 8 ADA Sample Collection and Time Points

Study Visit	ADA Sample Time Point
Day 1	Pre-dose
Day 15	Anytime
Day 29	Pre-dose

Day 57	Pre-dose
Day 85	Anytime
Day 141	Anytime

Abbreviations: ADA = anti-drug antibody

ADA assessments will be conducted utilizing a tiered approach that includes:

1. A screening assay that identifies potential binding ADA in serum samples.
2. A confirmatory assay that confirms the binding specificity of the drug.
3. A titer assay that measures the titer of confirmed ADA. A sample that has been found negative in the screening or confirmatory assay will not have a titer value.

A subject will be considered to be positive for imsidolimab-induced immunogenicity if the subject has one confirmed positive ADA response after dosing. Confirmed positive ADA samples may also be tested for neutralizing ADA.

Antidrug antibody variables include status (positive or negative) and titers as follows:

- Total subjects with negative ADA response at all times
- Total subjects with confirmed positive ADA response at any time
- Pre-existing immune-reactivity, defined as either
  - A positive ADA at baseline with all post-treatment ADA results negative, or
  - A positive ADA at baseline with all post-treatment ADA responses less than 4-fold over baseline titer levels.
- Treatment-emergent: any post-treatment positive ADA when the baseline ADA result is negative
- Treatment-boosted: any post-treatment positive ADA that is greater than or equal to 4-fold over baseline titer level when baseline is ADA positive
- Overall ADA incidence: the proportion (%) of subjects with positive ADA, either treatment-emergent or treatment-boosted, relative to all imsidolimab treated subjects
- Titer values

6.5 Biomarker Variables

- **Assessment of biomarkers in tape strips**

  The analysis of tape strips biomarkers will be performed by an additional third party designated by the Sponsor.

6.6 Safety

Adverse events, serious adverse events (SAEs), AEs leading to discontinuation of study treatment, and AEs leading to withdrawal from study, as well as changes in vital signs, clinical laboratory parameters (hematology, biochemistry, and urinalysis), and 12-lead electrocardiograms (ECGs) will be evaluated to meet the safety objectives of the study.

6.6.1 Study Day and Visit Window Definitions

Adverse events will be closely monitored on each subject throughout their participation in the study.

Safety assessments for other safety variables will occur as detailed in the Schedule of Activities in **Table 2**.

6.6.2 Extent of Exposure to Study Medication and Compliance

The number of doses received by the subject for a study treatment will be calculated.

The number of days of exposure to a study treatment will be defined as (Date of last treatment – Date of first dose of treatment) + 1.

Total dose received will be the total amount (in mg) of study treatment taken during the treatment period.

Dose intensity for a specified period is defined as (total dose received by a subject during that period/total expected dose during the same period) x 100%.

The expected number of doses for imsidolimab treatment arms is as follows:

- Imsidolimab 400 mg/200 mg: 400 mg on Day 1, 200 mg on Days 29 and 57.
- Imsidolimab 200 mg/100 mg: 200 mg on Day 1, 100 mg on Days 29 and 57.

6.6.3 Adverse Events

Adverse events experienced by the subjects will be collected throughout the entire study and will be coded using the version of the MedDRA specified in the approved Data Management Plan. Analysis of AEs will be carried out on the Safety Analysis Set.

An AE is considered treatment-emergent if the date of onset is during or after first dose of study treatment, or if the AE present at Baseline that worsens in either intensity or frequency after first dose of study treatment. An AE that begins on the same date as the first dose of study treatment is treatment-emergent if the AE begins on or after the time of first dose or if the time of AE onset is unknown.

The severity of AEs will be evaluated as “Mild”, “Moderate”, and “Severe” using the criteria specified in **Section 8.2.1.3.1** of the study protocol.

Adverse events will be classified as related, possibly related, unlikely to be related, or unrelated to study treatment using the criteria specified in **Section 8.2.1.3.2** of the study protocol. If the relationship to study treatment is missing, then the relationship will be set to “related” in the summaries of AEs.

Adverse events will be categorized as serious or non-serious using the definition specified in **Section 8.2.1** of the study protocol.

Events with Partial Onset Dates

All treatment-emergent adverse events (TEAEs) will be included in the tabulations regardless of the completeness of the onset dates. Partial dates will be imputed in order to determine if an AE is treatment-emergent using the rules in **Appendix 1**; however, imputed dates will not be provided in the data listings.

Uncoded Events: Before the database lock, uncoded events will be assigned the string “UNCODED” as the body system, and the verbatim term will be used as the preferred term, so they can be included in the summary tables. In the final dataset, all the adverse events will have been coded.

6.6.3.1 Deaths

All deaths (if any) which occur during the study will be listed.

6.6.4 Laboratory Data

Clinical laboratory tests that will be performed in this study are summarized in **Appendix 10** of the study Protocol. Local laboratory samples will be collected in the eCRF when the central laboratory results are not available immediately, and the Investigator needs to take an immediate decision for any safety concerns, however, local laboratory results will be not used in the summary tables. All laboratory data will be listed, but only hematology, biochemistry, and urinalysis will be summarized.

Conversion to the International System of Units

All laboratory data will be stored in the database with the units in which they are originally reported. Laboratory data in summary tables and subject data listings will be presented in the International System of Units (SI units). Laboratory data not reported in SI units will be converted to SI units before further processing or data analysis.

Abnormal Values

Based upon laboratory normal ranges, laboratory test results will be categorized according to the normal range as low, normal, and high. Subjects with laboratory data outside the normal range will be listed with abnormal values flagged.

6.6.5 Vital Signs

Vital signs including body temperature (°C), pulse rate (bpm), systolic and diastolic blood pressure (mmHg), respiratory rate (breath/min), weight (kg), and height (cm) will be obtained in accordance with the Schedule of Activities in **Table 2**. Changes from baseline in vital signs variables will be evaluated.

6.6.6 Electrocardiogram (ECG)

ECG parameters, including heart rate as well as RR, PR, QRS, QT, and QTcF intervals will be collected according to the Schedule of Activities in **Table 2**. Changes in ECG parameters between baseline and each subsequent scheduled assessment will be calculated.

The outcome of the overall evaluation is to be recorded as normal/abnormal in the eCRF, with any abnormalities being recorded as not clinically significant or clinically significant.

6.6.7 Other Safety Assessments

The following assessments will be performed, but will not be used to define additional safety parameters for the study: chest X-ray, physical examination, tuberculosis (TB) screening, pregnancy tests (serum or urine), viral serology, and follicle-stimulating hormone (FSH). Data from these assessments will be available in datasets and will be listed.

7. STATISTICAL ANALYSIS

7.1 Data Handling Rules and Definitions, Including Handling of Missing Data

Except where specified all continuous variables will be summarized with descriptive statistics (the number of non-missing values, mean, SD, median, first and third quartiles, minimum, and maximum). Where data have been logarithmically transformed for analysis, the summary statistics on the back-transformed data will include the geometric mean (calculated as [exp (m)], where m is the mean of the data on the log scale) and the coefficient of variation (CV; calculated as $100\sqrt{}$ [exp (s^2)-1], where s is the SD of the data on the log scale). All categorical variables will be summarized with frequency counts and

percentages. Tabulations will be provided based on all subjects combined, as well as separately by treatment group.

Missing data will be maintained as missing in the analysis datasets, unless specified otherwise. For variables where missing data are imputed, the analysis dataset will contain a new variable with the imputed value and the original variable value will be maintained as missing.

Data Imputation for Primary and Secondary Efficacy Analyses

1. Multiple Imputation with Fully Conditional Specification (FCS) Method

The FCS method will be used as a sensitivity analysis for the analyses of facial IGA and facial inflammatory/noninflammatory lesion counts. FCS methods can be used to impute missing values for variables with an arbitrary missing data pattern, assuming the existence of a joint distribution for these variables. Both intermittent and monotone missing values will be imputed in the same way with regression-based predictive mean matching method. The missing values will be imputed sequentially, with all previous visits included as additional covariates.

The steps of performing a sequential regression imputation are as follows:

a) If there is any missing value at Week 2, it will be imputed using a regression-based predictive mean matching method. For facial inflammatory/noninflammatory lesion counts, randomization seeds of 20220118 and 20220119 will be used respectively, the regression will include the covariates of age, sex, treatment group, facial IGA score at baseline (Grade 3 vs. 4), and the baseline measurement of corresponding lesion counts. For facial IGA, a randomization seed of 20220121 will be used, and the covariates included in the regression will be age, sex, treatment group, and baseline facial IGA score as a continuous variable.
b) All remaining missing visits will be imputed sequentially by the same regression, with covariates specified above in Step (a) and the lag values (including the imputed values) from earlier visits.
c) The imputed values will be rounded to the nearest integer for facial IGA and facial inflammatory/noninflammatory lesion counts.
d) The linear mixed model for repeated measures (MMRM) for continuous endpoints as described in **Section 7.5.1** and **Section 7.5.2**, respectively, will be applied to each imputed dataset. For categorical endpoints, the binary outcomes will be derived from the imputed data for each patient. The Cochran-Mantel-Haenszel (CMH) test as described in **Section 7.5.2** will be used for each imputed dataset, and the effect will be measured as Prob (concordance) - Prob (discordance) by Somers' d (interpretable also as a generalized risk difference) pooled across the facial IGA strata.[5]

One hundred independent data replications will be done with SAS PROC MI. Results across the replicated datasets will then be combined into the final estimate using SAS PROC MIANALYZE.

2. Tipping Point Analyses

As the primary analysis (MMRM) relies on the missing at random assumption, to evaluate the robustness of the primary analysis approach, a sensitivity analysis using the tipping-point approach will be conducted.

The following steps will be used to determine the tipping point:

a) Intermittent missing values will be imputed using the Monte Carlo Markov Chain (MCMC) approach to create a monotone missing pattern. The imputation will be implemented separately for each treatment and each facial IGA stratum (Grade 3 or 4), under the assumption that different treatments and facial IGA strata may have distinct posterior distributions. The imputation will

include all the post-baseline values, with age, and baseline value of the corresponding endpoint as covariates.

b) If there is any missing value at timepoint 1 (Week 2), it will be imputed using a regression based MI method for monotone missingness. Covariates included in the modelling are age, sex, treatment group, facial IGA score at baseline (Grade 3 vs. 4), and baseline value of the corresponding endpoint.
c) A delta score will be added to the imputed value at timepoint 1 for subjects missing data at timepoint 1 in the imsidolimab treatment groups, thus worsening the imputed value. The delta value will start at 0 and will be increased in a repeated process until the comparison of imsidolimab to placebo is no longer significant at 0.10 level in Step (f).
d) All remaining timepoints will be imputed sequentially by repeating Steps (b) and (c) for each timepoint, including lag values from earlier timepoints in the imputation model (lag values will include imputed values from the previous step), in addition to the covariates specified above in Step (b). Data from subjects who have already had their responses increased by delta in the previous step(s) will not be further increased by delta again since the regression on the previous value carries this increase forward. This principle also extends to the preliminary step of imputing intermittently missing visits. Thus, if an intermittent missing value is encountered for a subject in the imsidolimab treatment groups, delta adjustment will not apply for the subsequent imputations of the monotone part of the missing visits, for that subject.
e) For each imputed dataset, perform the same primary analysis (MMRM) as described in **Section 7.5.1** to estimate treatment differences between each dose of imsidolimab and placebo. Results across the imputed datasets will then be combined using SAS PROC MIANALYZE.
f) Step (c) to (e) will be repeated with gradually increased delta values until the tipping point is reached.

One hundred independent dataset replications will be done with SAS PROC MI. The resulting one hundred estimates of the treatment differences and standard errors will then be combined into the final estimate using SAS PROC MIANALYZE.

Data Imputation for Adverse Events Summaries by Relationship to Study Drug

For the AE summaries by relationship to study drug, an AE with a missing relationship to study drug will be deemed as definitely related. Imputed values will not be listed in data listings.

Use of Data from Unscheduled Assessments for Laboratory, ECG, and Vital Sign Summaries (Continuous Parameters)

Data from unscheduled visits will be listed; duplicate unscheduled measurements will not be shown twice. If the data from the scheduled visit is missing, data from unscheduled visits that fall in the visit window of the same scheduled visit will be used. In cases where there are multiple unscheduled visits, the most recent unscheduled visit will be used.

Data Imputation (All Laboratory, Immunogenicity, and Biomarker Summaries)

Laboratory values of '>=x' or '<=x' will be taken as the value of x in the analyses. If a laboratory value is prefixed with '>', the available original value +0.001 will be used for table summaries; if a laboratory value is prefixed with '<', then the original value –0.001 will be used in table summaries.

Study Dates and Day of Assessment or Event

Study Day and Day of Assessment or Event definitions are provided in **Appendix 1**, **Data Handling Rules**.

Incorrect Stratification

If there is any discrepancy between the IWRS-based and clinical-data-based stratification factor, the clinical-data-based value will be used for efficacy analyses.

7.2 Subject Disposition

Disposition for all subjects will be tabulated and listed. The tabulation will include the number of subjects screened, randomized, and treated, randomized but not treated, the number of subjects completing the treatment period, and the number of subjects who complete the study (including follow-up) as well as who discontinue study early will also be presented; for subjects who discontinue, the reason for discontinuation will also be included. The number and percentage of randomized subjects included in the ITT, PP, Safety, and PK Analysis Sets will also be tabulated.

The randomization stratification factor and treatment assignment will be listed together. If there are any subjects who took study treatment other than what was randomized during the study, both the treatment assigned at randomization and actual treatment(s) received during the Treatment Period will be listed. The duration of actual treatment will also be listed.

The reason for exclusion of a subject from the PP, Safety, and PK Analysis Sets will be listed for all randomized subjects; the Coronavirus Disease 2019 (COVID-19) related reasons for exclusion from the PP Analysis Set may be considered. In addition, randomized subjects who violate the important protocol deviations will be listed.

7.3 Deviations

All protocol deviations will be identified and discussed with the Sponsor during the BDRM prior to final database lock. Important protocol deviations for exclusion from the PP Analysis Set will be determined and appropriately categorized in this meeting. These are defined as potential protocol deviations that may significantly affect the reliability of efficacy study data.

All important protocol deviations will be summarized by treatment group and overall subjects for the ITT Analysis Set. All protocol deviations will be listed.

7.4 Demographic and Baseline Characteristics

7.4.1 Demography and Physical Characteristics

Demographics and baseline characteristics variables that are listed in **Section 6.1** will be summarized by treatment and all data will be provided in listings. Continuous baseline parameters (such as age, height, weight, BMI, facial inflammatory lesion counts, facial noninflammatory lesion counts, and DLQI/CDLQI total score), facial IGA, Truncal PGA, PGI-S, and SSQ will be summarized descriptively using mean, median, SD, minimum, maximum, first quartile, and third quartile. For categorical baseline and demographic parameters (such as age group, country, reproductive status, sex, ethnicity, race, smoking history, facial IGA, Truncal PGA, PGI-S, and SSQ), frequencies and percentages of subjects will be provided; baseline facial IGA will be reported by individual Grade 3 or 4.

7.4.2 Medical and Surgical History

Medical and surgical history at screening will be summarized for the Safety Analysis Set and listed for the ITT Analysis Set.

7.4.3 Prior and Concomitant Medications

Refer to **Appendix 1** for definitions of prior and concomitant medications. Prior and concomitant medications will be summarized by ATC class, preferred term, and actual treatment received for the Safety Analysis Set. In summary tables, subjects will only be reported once for the medication or for the class of drug s/he has taken. Prior and concomitant medications will be displayed in separate listings.

7.5 Efficacy Analyses

The ITT Analysis Set will be used as the primary analysis set for all efficacy analyses. Per protocol analyses will be performed on the primary as well as the following secondary endpoints:

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

No adjustment for multiplicity will be made.

All statistical tests will be performed at the 10% level of significance unless otherwise stated. All confidence intervals (CIs) will be reported as 2-sided 90% CIs unless otherwise stated. Descriptive statistics will be provided for the continuous variables as number of subjects, mean, SD, standard error of the mean, first and third quartiles, minimum, and maximum. Descriptive summaries of continuous variables will be shown for baseline, change from baseline to endpoint, and percent change from baseline to endpoint. All data will be listed in data listings.

7.5.1 Primary Efficacy Analysis

The primary estimand, comprising four components, is defined as follows:

a) The target population consists of patients with acne vulgaris that are eligible to be included in the clinical trial based on the inclusion/exclusion criteria in the protocol. The ITT Analysis Set will include all randomized subjects. For the analysis, treatment will be assigned based upon the treatment arm to which subjects were randomized regardless of which treatment they receive.
b) The primary variable is the change from baseline in facial inflammatory lesion count of an individual subject at Week 12.
c) To handle intercurrent events such as use of rescue medications, the hypothetical strategy for estimand will be used. Data collected following receipt of rescue medication (if any) will be considered missing in the analysis.
d) The population-level summary measures will be the population mean differences in the primary variable between each dose of imsidolimab and placebo at Week 12.

A MMRM model will be used with treatment, visit (Weeks 2, 4, 8, and 12), treatment by visit interaction, and facial IGA score at baseline (Grade 3 vs. 4) as categorical covariates and the baseline value of response as the only continuous covariate; only the visits up to and including week 12 are used. An unstructured correlation (UN) matrix will be used to model correlation within a subject; if convergence is an issue, a Toeplitz structure may be considered. Subjects with missing data at Week 12 due to early discontinuation will be included in the model.

The least squares (LS) mean and the standard error of this mean with the corresponding two-sided 90% CI will be provided for each treatment based on the model. The LS mean difference between treatments (imsidolimab – placebo), as well as the corresponding two-sided 90% CI will be provided based on the model. Summary statistics and the results of statistical testing in facial inflammatory lesion count at Week 12 will be tabulated. The LS mean change from baseline as well as differences between treatments in facial inflammatory lesion count will be plotted across post-baseline visits by treatment in separate plots.

7.5.2 Secondary Efficacy Analyses

7.5.2.1 Percent Change from Baseline in Facial Inflammatory Lesion Counts at Each Visit

Percent change from baseline in facial inflammatory lesion counts will be presented together with the primary endpoint. This endpoint will be analyzed using a similar MMRM model as specified for the primary endpoint. The percent change from baseline in facial inflammatory lesion counts will be the response variable in the model.

7.5.2.2 Change from Baseline in Facial Inflammatory Lesion Counts at Visits Other Than Week 12

This secondary endpoint will be presented together with the primary endpoint. Summary statistics and the results of statistical testing in facial inflammatory lesion counts at visits other than Week 12 will be tabulated. The change from baseline in facial inflammatory lesion counts will be analyzed using the same MMRM model as for the primary endpoint.

7.5.2.3 Percent Change from Baseline in Facial Noninflammatory Lesion Counts at Each Visit

Percent change from baseline in facial noninflammatory lesion counts at each visit will be analyzed using a similar MMRM model as specified for the primary endpoint. The percent change from baseline in facial noninflammatory lesion counts will be the response variable in the model.

7.5.2.4 Change from Baseline in Facial Noninflammatory Lesion Counts at Each Visit

Change from baseline in facial noninflammatory lesion counts at each visit will be analyzed using a similar MMRM model as specified for the primary endpoint. The change from baseline in facial noninflammatory lesion counts will be the response variable in the model.

7.5.2.5 Percent 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 will be analyzed using the MMRM approach defined for the primary endpoint. The percent change from baseline in total facial lesion (inflammatory and noninflammatory lesions) counts will be the response variable in the model.

7.5.2.6 Change from Baseline in Total Facial Lesion (Inflammatory and Noninflammatory Lesions) Counts at Each Visit

Change from baseline in total facial lesion (inflammatory and noninflammatory lesions) counts at each visit will be analyzed using a similar MMRM model as specified for the primary endpoint. The change

from baseline in total facial lesion (inflammatory and noninflammatory lesions) counts will be the response variable in the model.

7.5.2.7 Change from Baseline in Facial IGA at Each Visit

Change from baseline in facial IGA at each visit will be analyzed using a similar MMRM model as specified for the primary endpoint. The MMRM model will include treatment, visit, and treatment by visit interaction as categorical covariates and baseline facial IGA score as the only continuous variable. An unstructured correlation (UN) matrix will be used to model correlation within a subject; if convergence is an issue, a Toeplitz structure may be considered.

In addition, the following exploratory analyses will be performed:

- Change from baseline in facial IGA will be summarized in shift tables. In the shift table, for each treatment, the counts and percentages will be shown for baseline values crossed with each post-baseline timepoint. Agreement between the baseline score and each post-baseline score will be estimated with a weighted Kappa coefficient and corresponding 90% CI[7]. A test of treatment difference for agreement will consist of a CMH test (ANOVA of row means) applied to a 2×3×5 Table (Baseline IGA facial strata × treatment × agreement score), where the agreement score is the Cicchetti-Allison weight[8] used for the weighted Kappa coefficient, which is 1-|difference|/4 for a 5 point score such as the facial IGA, so the value is =1 if there is perfect agreement, ¾ if the scores are one category apart (in either direction), ½ if 2 apart, ¼ if 3 apart and 0 if 4 apart. The latter score can happen only if baseline score is 4 and post-baseline score is 0.
- Change from baseline in facial IGA at Week 12 will be analyzed using an ordinal logistic regression model with treatment, facial IGA score at baseline (Grade 3 vs. 4) as categorical covariates. Odds ratios resulting from this model along with 90% CI will be reported.

7.5.2.8 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

The frequency and percentage of subjects achieving a facial IGA of clear (0) or almost clear (1) with at least a 2-grade decrease from baseline will be summarized at each visit. The difference in percentage between each dose of imsidolimab and placebo will be estimated by an unadjusted risk difference in proportions with 90% exact unconditional CIs. This will be performed overall and within each facial IGA stratum (Grade 3 or 4). The common risk difference will also be tested using a generalized CMH test (ANOVA for row means), adjusting for facial IGA at baseline (Grade 3 vs. 4).

An additional exploratory analysis will be performed by visit for the proportion of subjects achieving a facial IGA of clear (0) or almost clear (1) with at least a 2-grade decrease from baseline. A repeated measures generalized estimating equations (GEE) model with a logit link will be used. The model will include treatment, visit, treatment by visit interaction, and baseline facial IGA score as categorical covariates. Data from protocol-specified visits up to Week 20 will be included in the analysis. An unstructured correlation matrix will be used to model correlation within a subject; if convergence is an issue, a Toeplitz structure may be considered. An odds ratio resulting from this model along with 90% CI will be reported.

7.5.2.9 Proportion of Subjects in Each Response Category for the PGI-S at Each Visit

The frequency and percentage of subjects in each response category for the PGI-S will be summarized at each visit. The difference in distribution between each dose of imsidolimab and placebo will be compared using a Wilcoxon rank-sum test and Somers' D statistic which may be interpreted as a generalized risk

difference.[5] This will be performed over all subjects and within each stratum for facial IGA (Grade 3 or 4). The common risk difference will also be tested using a generalized CMH test (ANOVA for row means), adjusting for facial IGA at baseline (Grade 3 vs. 4).

7.5.2.10 Proportion of Subjects in Each Response Category for the PGI-C at Each Post-Baseline visit

Proportion of subjects in each response category for the PGI-C at each post-Baseline visit will be summarized and analyzed using the approach defined for the proportion of subjects in each response category for the PGI-C, as described in **Section 7.5.2.9**.

7.5.2.11 Change from Baseline in DLQI/CDLQI at each visit

Change from baseline in DLQI/CDLQI total score at each visit will be analyzed separately as well as together using a similar MMRM model as specified for the primary endpoint in **Section 7.5.1**.

7.5.3 Exploratory Efficacy Analyses

The continuous data endpoints of change and percent change from baseline will be analyzed using the MMRM approach as described for the primary efficacy analysis in **Section 7.5.1**. Summary statistics and the results of statistical testing at each visit will be provided for each continuous exploratory variable. In addition, the change from baseline in PGI-S and Truncal PGA (by body region as well as the overall and the worst score across three regions) will be summarized and analyzed by shift tables and ordinal logistic regressions as described in **Section 7.5.2.7**. Baseline of the response variable will be added to the ordinal logistic regression model as a categorical variable. The overall Truncal PGA will be presented separately for all subjects, adolescents, and adults.

The frequency and percentage of subjects for subjects for categorical exploratory endpoints related to Truncal PGA (by body region as well as the overall and the worst score across three regions), facial IGA, PGI-C, PGI-S, SSQ, and SSRS will be summarized at each protocol-specified visit. For proportion of subjects in each response category for the SSQ and SSRS, the difference in distribution between each dose of imsidolimab and placebo will be analyzed using the approach described for the proportion of subjects in each response category for the PGI-C in **Section 7.5.2.9**. For other categorical exploratory endpoints, an unadjusted risk difference and 90% exact unconditional CIs will be estimated between each dose of imsidolimab and placebo for all subjects and within each stratum for facial IGA at baseline (Grade 3 vs. 4); the common risk difference will also be tested using a generalized CMH test as described in **Section 7.5.2.8**.

7.5.4 Sensitivity Analyses

A number of sensitivity analyses are planned to evaluate the robustness of the primary and secondary efficacy results.

For the primary efficacy endpoint, the following sensitivity analyses will be performed:

- Analysis of primary efficacy endpoint using the PP Analysis Set.
- Analysis of primary efficacy endpoint for adolescent subjects (age <16 years).
- Analysis of primary efficacy endpoint by age group ([12, 25) years, ≥25 years).
- Analysis of primary efficacy endpoint by age and sex (male and [12, 25) years, male and ≥25 years, female and [12, 25) years, female and ≥25 years)
- Sex (male, female) will be added to the MMRM as a categorical variable if this model can converge.

- Site will be added to the MMRM as a fixed categorical effect if this model can converge. Small sites (enrollment less than 5 subjects) will be pooled together.
- Smoking history (current smoker vs non-current smoker) will be added to the MMRM as a fixed categorical effect if this model can converge.
- The papule and pustule count will be summed and analyzed using a similar MMRM model as specified for the primary analysis for ITT Analysis Set.
- Multiple imputation with FCS method (**Section 7.1**).
- Tipping point analysis (**Section 7.1**).
- Prior to database lock and unblinding, the assumption of normality in the change from baseline in facial inflammatory lesion count will be checked by visually inspecting the distribution of the residuals. If the normality assumption is not met, a repeated measures model using a GEE approach with an alternative distribution or any transformation will be considered. An unstructured correlation matrix will be used in the model if GEE is decided to be used; a Toeplitz structure may be considered if convergence is an issue. However, the results from the primary efficacy analysis will be considered the primary efficacy results.

For the secondary efficacy endpoints listed in **Section 7.5**, the following sensitivity analyses will be performed:

- Analyses of secondary efficacy endpoints using the PP Analysis Set.
- Multiple imputation with FCS method (**Section 7.1**).

7.5.5 Subgroup Analyses

Subgroup analyses will be carried out but only for the primary efficacy endpoint. Each subgroup will be analyzed separately using descriptive statistics. No hypothesis tests will be performed. Subgroup variables that will be examined include:

- Baseline Facial Inflammatory Lesion Count:
  - ≥ Median value
  - < Median value
- Age groups:
  - [12, 18) years
  - [18, 30) years
  - ≥30 years
- Sex groups:
  - Male
  - Female
- Baseline facial IGA:
  - Grade 3
  - Grade 4
- Race:
  - White
  - Non-white
- Prior systemic oral antibiotics:
  - No
  - Yes

- Prior systemic oral retinoid:
  - No
  - Yes

7.6 Pharmacokinetic Analyses

The PK analysis will be performed for subjects in the PK Analysis Set.

Mean trough serum concentration-time data for samples collected on Days 29, 57, and 85 will be tabulated as well as graphically presented as scatter plots. Nominal collection times will be used for graphs.

A subject listing of all concentration-time data following SC injections will be presented by subject and scheduled sample collection time. All 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, geometric mean, and CV of geometric mean. Concentration time data values reported as below the limit of quantification (BLQ) that occur at pre-dose or prior to the first observed non-BLQ positive concentration will be set to zero or will be set to missing for records that occur after the last quantifiable concentration.

7.7 Immunogenicity Analyses

ADA status and titer values will be listed by subject and time point. ADA incidences (overall, treatment-emergent, and treatment-boosted) will be tabulated as absolute occurrence (n) and proportion (%) of subjects by treatment group and visit. Descriptive statistics including number of subjects, mean, median, SD, minimum, and maximum of the titer values by treatment group and visit, where possible, will be provided. Neutralizing antibodies, if assayed and present, will also be summarized. The relationship between changes in PK profile and treatment-emergent positive responses will be evaluated to identify a potential impact ADA on imsidolimab exposure. Box plots of ADA status relative to trough concentrations will be plotted. Where possible, evaluation of ADA impact on efficacy and safety may be performed and summarized separately.

All immunogenicity results will be listed.

7.8 Biomarker Analyses

Biomarker analyses will be performed by a third party designated by the Sponsor. A separate analysis plan will be created for the biomarker analyses.

7.9 Safety Analyses

Safety analyses will be performed using the Safety Analysis Set. Safety parameters include AEs, exposure, clinical laboratory parameters (hematology, biochemistry, and urinalysis), vital signs, and ECGs. Summaries of safety parameters will be presented overall as well as by treatment group.

7.9.1 Extent of Exposure to Study Medication and Compliance

Descriptive statistics (n, mean, SD, median, minimum, and maximum) will be presented for the number of doses received, the number of days of exposure to study treatment, total dose received, total dose

expected, and dose intensity by treatment group. In addition to summary statistics on the dose intensity as a continuous variable, this will also be categorized into bins: 0-33%, >33-66%, >66-100%, and >100%. Dose intensity and dosing information will be listed.

7.9.2 Adverse Events

Adverse events will be summarized by the number and percentage of subjects experiencing an event. Tables will show the overall incidence of AEs and the incidence for each treatment group. All reported AEs will be listed, but only TEAEs will be summarized.

Adverse Events Counting Rules:

1. A subject with more than one different AE in a particular system organ class (SOC) will be counted only once in the total of subjects experiencing adverse events in that particular SOC.
2. A subject having experienced the same event (AE preferred term) more than once during the study will be counted only once in the number of subjects with that event for counts of subjects or incidence measures.
3. If an event changes in intensity or in seriousness during the study, it will be counted only once with the worst grade and seriousness respectively.
4. If the causal relationship to the study drug is assessed differently, it will be counted only once by considering the "Worst" documented degree of relationship.

A TEAE overview summary table will be provided with the incidences of subjects with at least one TEAE, at least one serious TEAE, at least one TEAE related to study treatment, at least one serious TEAE related to study treatment, at least one TEAE leading to treatment discontinuation, at least one serious TEAE leading to treatment discontinuation, at least one TEAE leading to withdrawal from study, at least one serious TEAE leading to withdrawal from study, at least one severe TEAE, at least one severe study treatment-related TEAE, and number of deaths.

Summary tabulations of the following will be prepared for all subjects, for each treatment, for each primary system organ class, and for each preferred term within a system organ class. These will report counts and incidences of these categories:

- All TEAEs
- Study treatment-related TEAEs
- TEAEs leading to discontinuation of study treatment
- TEAEs leading to withdrawal from study
- Non-serious TEAEs with >5% incidence rate in any treatment group
- Serious TEAEs
- Study treatment-related serious TEAEs
- TEAEs by relationship to study treatment
- TEAEs by highest severity and treatment
- Severe TEAEs
- Severe study treatment-related TEAEs

Supporting data listings will be provided by treatment group, including:

- All AEs (including any AEs reported in the study)
- SAEs
- AEs resulting in study treatment discontinuation
- AEs leading to withdrawal from study

7.9.3 Laboratory Data

Summary statistics (n, mean, median, SD, minimum, and maximum) for the baseline assessment and for the observed value and change from baseline at each nominal post-baseline visit for scheduled laboratory assessments of continuous laboratory variables will be tabulated. Shift tables (e.g., tables that show the number of subjects who are low, normal, or high at baseline vs. each post-baseline scheduled assessment) will be produced.

If there are multiple laboratory values for the same parameter at a given visit, the last value will be chosen for analysis.

All data will be displayed in subject data listings for Safety Analysis Set.

7.9.4 Vital Signs

Summary statistics (n, mean, median, SD, minimum, and maximum) of the raw values and change from baseline for pulse rate, systolic blood pressure, diastolic blood pressure, body temperature, respiratory rate, weight, and height will be tabulated by treatment and visit separately for adolescents and adults, as well as together.

Vital sign measurements (pulse rate, systolic blood pressure, diastolic blood pressure, body temperature, respiratory rate, weight, and height) during the study will be displayed in a vital signs listing.

7.9.5 Electrocardiogram (ECG)

ECG data (heart rate, PR interval, RR interval, QRS interval, QT interval, and QTcF interval) will be tabulated with summary statistics (n, mean, median, SD, minimum, and maximum) by visit for both the raw values as well as the changes from baseline. If there are multiple ECG values for the same parameter at a given visit, the last value will be chosen for analysis.

The overall ECG results will be classified by the investigator as “normal,” “abnormal, not clinically significant,” or “abnormal, clinically significant.” Three-by-three contingency tables will be presented to summarize the shift from the baseline category to the worst post-baseline value. Summary results will include the count and percentage of subjects within each shift category and treatment group.

All ECG data as well as clinically significant abnormalities will be presented in a by-subject listing.

7.9.6 Other Safety Assessments

Chest X-ray, physical examination, TB test results, pregnancy test, viral serology, and FSH will be presented in listings for the Safety Analysis Set. The overall evaluation of physical examination results at each visit will be listed for subjects with any abnormal physical examination findings. No AEs of special interest will be defined.

8. CHANGES FROM METHODS PLANNED IN THE PROTOCOL

The following exploratory analyses have been added:

- Change and percent change from Baseline in facial papule lesion counts at each visit
- Change and percent change from Baseline in facial pustule lesion counts at each visit
- Change and percent change from Baseline in facial nodule lesion counts at each visit
- Change from Baseline in overall Truncal PGA at each visit
- Proportion of subjects with at least 1-point decrease from Baseline in facial IGA at each visit

- Proportion of subjects with at least 1-point decrease from Baseline in overall Truncal PGA at each visit for subjects with Baseline overall Truncal PGA score of at least 1
- Proportion of subjects with at least 2-point decrease from Baseline in overall Truncal PGA at each visit for subjects with Baseline overall Truncal PGA score of at least 2
- Proportion of subjects achieving an overall Truncal PGA of clear (0) or almost clear (1) with at least a 2-grade decrease from Baseline at each visit for subjects with Baseline overall Truncal PGA score of at least 2
- Proportion of subjects achieving improvement ("Much better" or "Very much better") according to the PGI-C at each visit
- Proportion of subjects achieving improvement ("A little better", "Much better" or "Very much better") according to the PGI-C at each visit
- Proportion of subjects achieving "Mild" or "Clear skin" according to the PGI-S at each visit
- Change from Baseline in PGI-S at each visit
- Proportion of subjects achieving "slightly satisfied", "somewhat satisfied", or "extremely satisfied" according to the SSQ at each visit
- Proportion of subjects achieving "slightly satisfied", "somewhat satisfied", or "extremely satisfied" according to the SSRS at Week 12 and Week 20
- Proportion of subjects achieving a DLQI of 0 or 1 at each visit for subjects with Baseline DLQI of at least 2
- Change from Baseline in PAS score based on blinded photographic assessment at each visit
- Change from Baseline in erythema score based on blinded photographic assessment at each visit

9. STATISTICAL SOFTWARE

The statistical software to be used for generation of the tables, listings, and figures is Statistical Analysis System® (SAS) version 9.4 or higher.

10. REFERENCES

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11. APPENDIX 1 DATA HANDLING RULES

The following table presents the algorithms to be used in SAS to calculate the derived variables, including rules for handling other missing data or partial dates, or irregular/unexpected data issues.

Category	Description	Data Handling Rules
1. Medical and Surgical History	Medical and Surgical History Beginning Date of Condition	• Missing day of begin date of condition will be imputed as the 1st of the month for the purpose of computing the onset day. • Missing month of begin date of condition will be imputed as June for the purpose of computing the onset day
	Medical and Surgical History End Date of Condition	• Missing day of end date of condition will be imputed as the 30th of the month for the purpose of computing the onset day. • Missing month of end date of condition will be imputed as June for the purpose of computing the onset day
2. First and Last Treatment Dates	Date/time of first and last dose of a study treatment	• The date and time (24 hr. clock) of the first dose of study treatment will be taken from the Dosing eCRF. The date of the last dose of study treatment will be the last date of dosing from the Dosing eCRF for the treatment.
3. Last Visit Date	Date of Last Visit	Date of last visit according to the Visit eCRF.
4. Last Study Participation Date (SDTM variable, typically named RFPENDTC)	Last Study Participation Date (SDTM variable, RFPENDTC), where SDTM denotes Study Data Tabulation Model	Last study participation date is defined as last known date of contact which is the later of the following dates: last visit date, date of the last dose, date of study completion or discontinuation, or death date.
5. Study Day Definitions	**Study Day** for assessment/event which occurs on or after the start of study treatment	Study Day = Date of assessment/event – date of the first dose of study treatment + 1.
	Study Day for assessments/events on days prior to the first dose of study treatment in the study	Study Day = Date of assessment/event – first dose date of treatment in the study.
	Study Day of Randomization	Study Day of Randomization = Date of randomization – date of the first dose of study treatment in the study + 1. Study Day is 1 if baseline day is on the day of randomization.
	First Dose Day	**First Dose Day** in the study is defined as the study day of the first dose of study treatment in the study (Study Day 1).
	Last Dose Day	**Last Dose Day** in the study is defined as the study day of the last dose of study treatment in the study (defined as the last date of dosing from the Dosing CRF pages).
	Last Study Day	**For subjects who did not receive study treatment in the study (e.g., Non-Randomized subjects)**, Last Study Day is defined as

Category	Description	Data Handling Rules
		(the later of the last visit date and the date of study completion or discontinuation from the End of Study CRF) – Date of Screening Visit + 1. **For subjects who received study treatment in the study,** Last Study Day is defined as (the later of the last visit date and the date of study completion or discontinuation from the End of Study CRF) – first dose date in the study + 1.
	Days Since Last Dose for event (e.g., Death)	**Days Since Last Dose** is defined as date of event – date of last dose of study treatment.
6. Duration of event	The duration of any event	The duration of any event is defined as (stop date – start date + 1).
7. Prior and concomitant medication/ treatment	Prior and concomitant medication/treatment	1. Prior medication/treatment is any medication/treatment stopped prior to the first dose of study treatment (or the date of the randomization visit, Day 1, if the date of the start of study medication is missing). Medication/treatment continued into the treatment period will not be considered prior. 2. A medication/treatment will be identified as a concomitant medication/treatment if any of the following are true: • The start date or the end date is on or after the date of the start of study treatment (or the date of randomization, Day 1, if missing). • The medication/treatment is checked as 'Ongoing', and the start date of the medication/treatment is prior to the first dose of study treatment (or the date of the randomization visit, Day 1, if the date of the start of study medication is missing). • The start date and the end date are both missing
8. Adverse event	Treatment-emergent adverse event	If the AE start date is partial/missing, then • If AE start date is completely missing, then the AE is considered as treatment-emergent. • If both AE start month and day are missing and AE start year is the same or after the first dose year, then the AE is considered as treatment-emergent. • If AE start day is missing and AE start year and month are the same or after the first dose year and month, then the AE is considered as treatment-emergent. Missing/incomplete (partial) AE start and end dates will not be imputed for data listings.
	Missing relationship to study drug	For TEAE summary by relationship, a TEAE with a missing relationship to study drug will be considered as related.
9. Vital Signs	Multiple assessments for the same visit	If there are multiple vital sign values for the same parameter at a given visit, the last value will be chosen for analysis.

12. APPENDIX 2 SAS CODE FOR STATISTICAL ANALYSES

This section will be completed after examining the existing data and prior to the final signoff of this SAP.

Test	Template SAS Code for Modeling (SAS Version 9.4)
Linear Repeated Measures Analysis of Covariance for the primary endpoint	PROC MIXED METHOD=REML; CLASS SUBJECT TRT VISIT BASEFIGA; MODEL Y = BASE BASEFIGA TRT|VISIT / DDFM=KR SOLUTION OUTP=OUT; REPEATED VISIT / TYPE = UN SUBJECT=SUBJECT; LSMEANS TRT|VISIT / PDIFF CL ALPHA=0.1; ODS OUTPUT LSMEANS=MEANS; ODS OUTPUT DIFFS=DIFF; RUN; Where TRT is treatment, VISIT is the study visit number, BASEFIGA is the facial IGA score at baseline, and BASE is the baseline of outcome variable.
Negative Binomial with GEE using PROC GENMOD	PROC GENMOD; CLASS SUBJECT TRT VISIT BASEFIGA; MODEL Y= BASE BASEFIGA TRT|VISIT / LINK=LOG DIST=NEGBIN; REPEATED SUBJECT=SUBJECT / TYPE=UN; LSMEANS TRT|VISIT / DIFF CL ALPHA=0.1; ODS OUTPUT LSMEANDIFFS = LSDIFS ESTIMATES=EST LSMEANS=LSMEANS PARAMETERESTIMATES=PE; RUN; Where TRT is treatment, VISIT is the study visit number, BASEFIGA is the facial IGA score at baseline, and BASE is the baseline of outcome variable.
Impute Intermittent Missing using the Monte Carlo Markov Chain (MCMC) approach	PROC MI DATA=data_in SEED=20210710 NIMPUTE=100 OUT=LESION_MONO; BY BASEFIGA TRT; /*Assuming different treatment, baseline facial IGA has different distribution*/ MCMC CHAIN=MULTIPLE IMPUTE=MONOTONE; /*Only impute intermittent missing values*/ VAR AGE BASE LESION1 – LESION5; /*Impute lesion count from Week 2 to Week 20, with age and baseline as covariates*/ RUN;

Test	Template SAS Code for Modeling (SAS Version 9.4)
Multiple Imputation with FCS Method	PROC MI MIN=0 ROUND=1 SEED=20220118; CLASS BASEFIGA TRT SEX; FCS REGPMM(LESION2 = LESION1 AGE SEX TRT BASE BASEFIGA); FCS REGPMM(LESION3 = LESION1 LESION2 AGE SEX TRT BASE BASEFIGA); FCS REGPMM(LESION4 = LESION1-LESION3 AGE SEX TRT BASE BASEFIGA); FCS REGPMM(LESION5 = LESION1 LESION4 AGE SEX TRT BASE BASEFIGA); VAR LESION1 – LESION5 AGE SEX TRT BASE BASEFIGA; RUN; Add 'MAX=4' in the PROC MI statement if response variable is facial IGA score.
Combine Parameter Estimates for LSmeans	PROC MIANALYZE DATA=OUTREG; BY VISIT; MODELEFFECTS TRT; /* TRT IS THE VARIABLE FOR LS TREATMENT DIFFERENCES */ STDERR TRTERR; /* TRTERR IS THE STANDARD ERROR FOR TREATMENT DIFFERENCES */ RUN;
Logistic Regression with GEE using PROC GENMOD	PROC GENMOD DESCENDING; CLASS SUBJECT TRT VISIT BASE; MODEL Y= BASE TRT|VISIT / LINK=LOGIT DIST=BIN; REPEATED SUBJECT=SUBJECT / TYPE=UN; LSMEANS TRT|VISIT / DIFF CL ALPHA=0.1; ODS OUTPUT LSMEANDIFFS = LSDIFS ESTIMATES=EST LSMEANS=LSMEANS PARAMETERESTIMATES=PE; RUN; Where TRT is treatment, VISIT is the study visit number, and BASE is the baseline of outcome variable.
Ordinal Logistic Regression using PROC LOGISTIC	PROC LOGISTIC; CLASS TRT BASE BASEFIGA; MODEL Y = TRT BASE BASEFIGA; RUN; Where Y is the ordinal outcome variable, TRT is treatment, BASEFIGA is the facial IGA score at baseline, BASE the baseline of outcome variable. Remove BASEFIGA from the model if outcome variable is facial IGA.

Test	Template SAS Code for Modeling (SAS Version 9.4)
Cochran-Mantel-Haenszel ANOVA statistics (row means score)	PROC FREQ; TABLES BASEFIGA*TRT*X/CMH2 ALPHA=0.1; RUN; Where BASEFIGA is facial IGA at baseline, TRT is treatment, and X is the outcome variable.
Exact unconditional CI	PROC FREQ; TABLES TRT*X/ RISKDIFF(CL=EXACT) ALPHA=0.1; EXACT RISKDIFF; RUN; Where TRT is treatment, and X is the outcome variable.
Obtaining generalized risk difference	PROC FREQ; TABLES TRT*X / ALL LIST MISSING ALPHA=0.1; TEST SMDCR; RUN; Where TRT is treatment, and X is the outcome variable.
Weighted Kappa and confidence interval	PROC FREQ; WEIGHT COUNT; TABLES BASEFIGA*TRT*X/AGREE ALPHA=0.1; RUN; Where BASEFIGA is facial IGA at baseline, TRT is treatment, and X is the outcome variable.
Test of treatment difference for agreement	PROC FREQ; TABLES BASEFIGA*TRT*X/CMH2; RUN; Where BASEFIGA is facial IGA at baseline, TRT is treatment, and X is the Cicchetti-Allison weight of outcome variable. Cicchetti-Allison weight = 1-abs(CHG)/(k-1), where k = number of categories of the outcome variable.

13. APPENDIX 3 MOCKUP TABLES, LISTINGS, AND GRAPHS (TLGs)

Mockup tables, listings, and graphs are presented in a separate document.