STATISTICAL ANALYSIS PLAN
FOR STUDY ANB019-207

Trial Sponsor:	AnaptysBio, Inc.
Protocol Number:	ANB019-207
IND Number:	136145
EUDRACT Number:	2020-003494-22
Investigational Drug:	Anti-interleukin 36 receptor monoclonal antibody
Indication:	Acneiform Rash in Subjects with EGFRi or MEKi Therapy
Drug Number:	ANB019 (Imsidolimab)
Dosage Form/Strength/Dose:	Solution for Injection/200 mg/400 mg or 200 mg • 400-mg dose, administered as 2 mL × 2 SC injections at 200 mg each on Day 1. • 200-mg dose, administered as 2 mL × 1 SC injection at 200 mg on Day 29, 57, and 85.

Protocol Title: A Phase 2a, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of ANB019 in the Treatment of Acneiform Rash in Subjects with Neoplasm Receiving EGFRi or MEKi Therapy

Version:	v1.0
Sign-off Date:	11-Jan-2022
Archive Date:	

SIGNATURES

Study Biostatistician: [redacted]

Everest Clinical Research Corporation

[redacted] 06 Jan 2022 16:47:04 (-05 00)

REASON: I approve this document.

fe2784cd-a0dc-4257-9164-a2e1cb0a07fc

06-Jan-2022

Signature **Date**

Peer Review Biostatistician: [redacted]

Everest Clinical Research Corporation

[redacted] 06 Jan 2022 18:24:39 (-05 00)

REASON: I approve this document.

f143fb23-9c7c-42b6-b1b5-0a1f5414b92c

06-Jan-2022

Signature **Date**

Approved by: [redacted]

Everest Clinical Research Corporation

[redacted] 06 Jan 2022 16:48:02 (-05 00)

REASON: I approve this document.

effda0b6-2b58-43c6-bf93-c4f487523739

6-Jan-2022

Signature **Date**

Approved by: [redacted]

AnaptysBio, Inc.

[redacted] 06 Jan 2022 18:40:25 (-05 00)

REASON: I approve this document.

0ba82a8c-7f33-4b1f-95d0-4a561b278e5d

06-Jan-2022

Signature **Date**

Approved by: [redacted]

AnaptysBio

[redacted] [redacted]

07 Jan 2022 13:42:55 (-05 00)

REASON: I approve this document.

90fac5a3-d720-4bb0-a1f2-5d76848f4558

07Jan2022

Signature **Date**

Approved by: [redacted]

AnaptysBio

[redacted] [redacted]

11 Jan 2022 16:24:02 (-05 00)

REASON: I approve this document.

b913c35d-fe61-4f7a-ba1b-f5ce1ea0b672

11-Jan-2022

Signature **Date**

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.

DocUUID : 93a3edcd-2870-4a57-89a7-e204316f6e07

TABLE OF CONTENTS

GLOSSARY OF ABBREVIATIONS

Abbreviation	Term
ADA	Anti-drug antibody
ADL	Activities of daily living
AE	Adverse event
ATC	Anatomical therapeutic chemical
BDRM	Blinded data review meeting
BLQ	Below the limit of quantitation
BMI	Body mass index
CI	Confidence interval
CMH	Cochran-Mantel-Haenszel
CRF	Case report form
COVID-19	Coronavirus Disease 2019
CTCAE	Common Terminology Criteria for Adverse Events
CV	Coefficient of variation
ECG	Electrocardiograms
ECOG	Eastern cooperative oncology group
eCRF	Electronic case report forms
EGFRi	Epidermal growth factor receptor inhibitor
Everest	Everest Clinical Research
FACT-EGFRi-18	Functional Assessment of Cancer Therapy - Epidermal Growth Factor Receptor Inhibitor 18
FSH	Follicle-stimulating hormone
GEE	Generalized estimating equations
IGA	Investigator Global Assessment
IND	Investigational new drug
ITT	Intention-to-treat
IV	Intravenous
IWRS	Interactive Web-based Response System

DocUUID : 93a3edcd-2870-4a57-89a7-e204316f6e07

GLOSSARY OF ABBREVIATIONS

LS	Least squares
MASCC	Multinational Association for Supportive Care in Cancer
MCMC	Monte Carlo Markov Chain
MedDRA	Medical Dictionary for Regulatory Activities
MEKi	Mitogen-activated protein/extracellular signal-regulated kinase inhibitor
MESTT	MASCC EGFRi Skin Toxicity Tool
MMRM	Mixed model for repeated measures
NRS	Numeric rating scale
PGI-C	Patient Global Impression of Change
PGI-S	Patient Global Impression of Severity
pMI	Placebo multiple imputation
PK	Pharmacokinetic
PP	Per Protocol
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
STIDAT	Systemic Therapy Induced Diarrhea Assessment Tool
TB	Tuberculosis
TEAE	Treatment-emergent adverse event
WHODrug 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 ANB019-207 Protocol (Version Amendment 2 dated 05 August 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 acneiform rash in subjects with neoplasm who are currently receiving an epidermal growth factor receptor inhibitor (EGFRi) or mitogen-activated protein/extracellular signal-regulated kinase inhibitor (MEKi) therapy. (See Protocol **Sections 2.1** to **2.3** for details).

2. STUDY OBJECTIVES

2.1 Primary Objective

- To assess the efficacy of imsidolimab compared with placebo in reduction of acneiform rash in subjects receiving EGFRi or MEKi therapy as measured by facial inflammatory lesion count

2.2 Secondary Objectives

- To determine the effect of imsidolimab compared with placebo on acneiform rash signs and symptoms, and quality of life in subjects receiving EGFRi or MEKi therapy
- To assess the safety and tolerability of imsidolimab in subjects with acneiform rash receiving EGFRi or MEKi therapy

2.3 Exploratory Objectives

- To further evaluate the effect of imsidolimab compared with placebo on acneiform rash signs and symptoms, and quality of life in subjects receiving EGFRi or MEKi therapy
- To explore the effect of imsidolimab on other EGFRi/MEKi adverse drug reactions (paronychia, dry skin, alopecia, and pruritus)
- To assess the effect of imsidolimab on gastrointestinal inflammation in subjects with acneiform rash receiving EGFRi or MEKi therapy
- To explore the effect of imsidolimab on cutaneous biomarkers
- To explore the effect of imsidolimab on acneiform rash as measured by facial inflammatory lesion count using standardized photographs
- To describe the pharmacokinetic (PK) profile of imsidolimab in subjects with acneiform rash receiving EGFRi or MEKi therapy

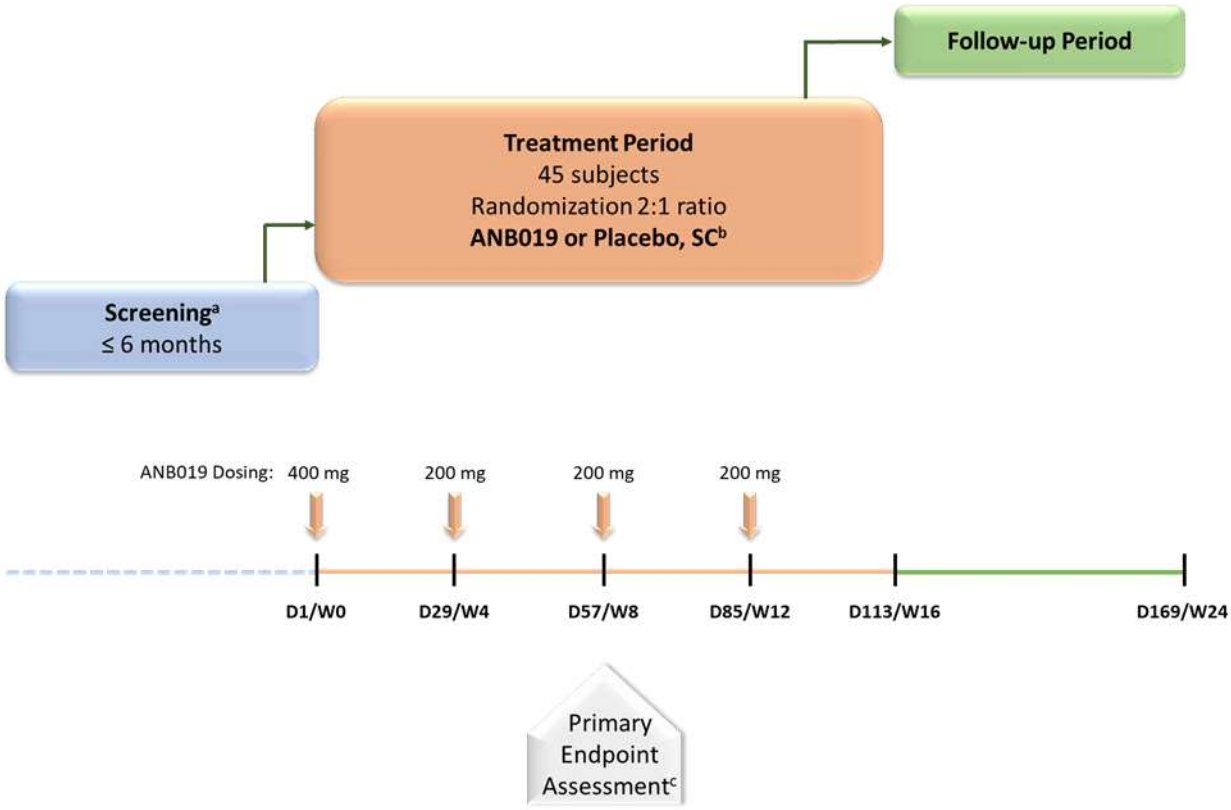
- To test for immunogenicity to imsidolimab

3. STUDY DESIGN

3.1 Study Design

This study is a Phase 2a, multicenter, randomized, double-blind, placebo-controlled study designed to evaluate the efficacy, safety, and tolerability of multiple doses of imsidolimab in the treatment of acneiform rash in subjects with neoplasm receiving EGFRi/MEKi. This study will also characterize the PK profile of imsidolimab and explore the immune response to imsidolimab in subjects with EGFRi/MEKi-associated acneiform rash. Approximately 45 adult male and female subjects, aged 18 to 75 years, will be randomized in this study. To be eligible for the study, subjects must be receiving oral or injectable commercially available EGFRi or MEKi therapy at the Screening and Day 1 visits. Subjects can enter the initial screening regardless of their current acneiform rash status and severity (as described in Protocol **Section 5.1**). However, at the Screening Part 2 and at Day 1, subjects must have an acneiform rash of Grade ≥ 2 as per CTCAE Version 5.0, and ≥ 20 inflammatory lesions on the face. Randomization will be stratified based on acneiform rash CTCAE grade at baseline and therapy the subject is receiving (EGFRi vs MEKi). The expected study duration per subject is up to approximately 12 months from the screening to last visit. Subjects who enter the screening period without an acneiform rash or with an acneiform rash severity that does not meet the requirements of Inclusion Criterion 3 (refer to Protocol **Section 5.1**) may remain in Screening for up to 6 months and be reevaluated if/when an acneiform rash develops or worsens as long as they remain on EGFRi or MEKi therapy. Once the acneiform rash severity meets the requirements of Inclusion Criterion 3, a last screening visit (Screening Part 2; refer to Protocol **Section 1.3**) must be performed, within 15 days prior to Day 1, ideally within 1 week. The screening period will be followed by a 16-week treatment period and an 8-week follow-up period.

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



Abbreviations: D = Day; SC = subcutaneous; W = week.
[a] Depending on subject acneiform rash status, the screening visit may be planned either as 1 visit (for subjects who already have an acneiform rash) or as 2 separate visits (for subjects not having an acneiform rash at the initial screening visit): Screening Part 1 and Screening Part 2. Screening Part 2 will only be performed once subject is having an acneiform rash. Screening Part 2 assessments must be performed within 15 days prior to Day 1 (ideally within 1 week) and safety evaluation results required to confirm eligibility must be obtained before randomization.
[b] During the treatment period, subjects will receive either ANB019 or placebo, SC administered at 4 time points: 400-mg dose of ANB019 or placebo on Day 1; 200-mg dose of ANB019 or placebo on Days 29, 57, and 85.
[c] The primary endpoint will be evaluated on Day 57 (Week 8).

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 randomized in a 2:1 ratio to receive imsidolimab or placebo. Randomization will be stratified based on acneiform rash CTCAE grade at baseline (Grade 2 vs. Grade 3 or 4) and therapy the subject is receiving (EGFRi vs MEKi).

3.3 Hypothesis Testing

The primary analysis for this study is to compare the mean change from baseline in facial inflammatory lesion count for imsidolimab with placebo at Week 8 of the double-blind treatment period, at a two-sided

alpha = 0.05 level. Any testing being performed for the secondary or exploratory endpoints will be considered exploratory in nature based on a two-sided alpha = 0.05.

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

3.4 Interim Analyses

One interim analysis will be performed when approximately 50% of the randomized subjects have reached Week 8. A second interim analysis will be performed using a separate data cut-off when all randomized subjects have reached Week 12 or discontinued. The purpose of the interim analyses 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 interim analyses; as such, the type I error will not be adjusted in the primary analysis and is expected to be maintained at 0.05, two-sided. The primary efficacy endpoint as well as the following secondary and exploratory efficacy endpoints will be evaluated:

- Percent change from Baseline in facial inflammatory lesion count (papules and pustules) at Week 8
- Proportion of subjects with an improvement of at least 1 grade from Baseline in acneiform rash CTCAE grading scale at Week 8
- Proportion of subjects with an improvement of at least 1 grade from Baseline in acneiform rash modified MESTT grading scale (total score) at Week 8
- Time to first response of 1 grade improvement from Baseline on the acneiform rash modified MESTT grading scale (facial assessment)
- Change from Baseline in pruritus numeric rating scare (NRS) at Week 8
- Percent change from Baseline in pruritus NRS at Week 8
- Proportion of subjects with an improvement of at least 1 grade from Baseline in acneiform rash CTCAE grading at each visit other than Week 8
- Change from Baseline in pain NRS at each visit other than Week 8
- Percent change from Baseline in pain NRS at each visit other than Week 8
- Proportion of subjects achieving an improvement of 50% from Baseline in facial inflammatory lesion count (papules and pustules) at each visit
- Proportion of subjects achieving an improvement of 75% from Baseline in facial inflammatory lesion count (papules and pustules) at each visit
- Change from Baseline in acneiform rash CTCAE grading scale at each visit
- Change from Baseline in acneiform rash modified MESTT grading scale (total score) at each visit
- Percent change from Baseline in acneiform rash modified MESTT grading scale (total score) at each visit
- Change from Baseline in Investigator Global Assessment (IGA) at each visit
- Proportion of subjects achieving an IGA of clear (0) or almost clear (1) at each visit
- Change from Baseline in facial IGA at each visit
- Proportion of subjects with at least a 3-point decrease in pruritus NRS at each visit for subjects with a Baseline pruritus NRS of at least 3
- Proportion of subjects with at least a 3-point decrease in pain NRS at each visit for subjects with a Baseline pain NRS of at least 3
- Proportion of subjects in each response category for the Patient Global Impression of Severity (PGI-S) at each visit
- Proportion of subjects in each response category for the Patient Global Impression of Change (PGI-C) at each post-baseline visit

- Proportion of subjects receiving rescue medication from Week 4 through Week 24
- Proportion of subjects that do not require a dose reduction of EGFRi or MEKi therapy due to acneiform rash at each visit
- Proportion of subjects that do not require cessation of EGFRi or MEKi therapy due to acneiform rash at each visit
- Change from Baseline in Systemic Therapy-Induced Diarrhea Assessment Tool (STIDAT) at each visit
- Percent change from Baseline in STIDAT at each visit

The sensitivity analysis using the while on treatment strategy defined in **Section 7.5.1** will also be evaluated Listings of facial inflammatory lesion count (papules and pustules), acneiform rash CTCAE grade, acneiform rash Modified MESTT grade, and STIDAT will be provided.

Subject disposition, analysis sets, demographics, baseline characteristics, and prior, concomitant, and rescue medications will be tabulated and listed as detailed in **Sections 7.2** and **7.4**. Serum concentrations of imsidolimab and anti-drug antibody levels will be tabulated. Safety data including adverse events (AEs), exposure, clinical laboratory measures (hematology, biochemistry, and urinalysis), vital signs, and electrocardiograms (ECGs) will be tabulated and listed as detailed in **Section 7.9**.

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

Generation of Blinded Reports

In the interim analyses, 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

The primary efficacy endpoint is the change from baseline in facial inflammatory lesion count at Week 8. The null hypothesis (H_0) to be tested is that the mean change from baseline to Week 8 in lesion count is the same for imsidolimab and placebo. Treatment arm sample sizes of 30 (imsidolimab) and 15 (placebo) achieve 80% power to reject H_0 of equal means if the population mean difference is -10.6 (imsidolimab – placebo), with a common standard deviation (SD) within both groups of 11.7, and significance level (alpha) of 0.05 using a two-sided two-sample equal-variance t-test.

3.6 Study Procedures and Schedule of Activities

Study procedures and their timing are summarized in the Schedule of Activities (**Table 1**)

Table 1 Schedule of Activities

Study visit Window (days)	Screening Period (-6 months to -1 day)		Treatment Period						Follow-up Period
	Screening[a]		D1 W0	D15 W2 (±2)	D29 W4 (±2)	D57 W8 (±4)	D85 W12 (±4)	D113 W16 (EOT/ET)[b] (±4)	D169 W24 (EOS) (±5)
	Part 1 Initial visit	Part 2 (-15 to -1)							
Informed consent	X								
Demographics	X	X							
Fitzpatrick skin type classification	X[c]								
Inclusion and exclusion criteria	X	X[d]	X[d]						
Medical and surgical history	X	X	X						
Height and weight[e]	X	X	X					X	X
Chest X-ray[f]		X							
Physical examination[g]		X	X	X	X	X	X	X	X
Vital signs[h]		X	X	X	X	X	X	X	X
12-lead ECG[i]		X						X	
Clinical laboratory assessments[j]		X	X	X	X	X	X	X	X
TB screening (QuantiFERON®-TB Gold test)[j]		X							
Viral serology[j]		X							
FSH[j]		X							
Serum pregnancy test (WOCBP only)[j]		X							X
Urine pregnancy test (WOCBP only)[j]			X	X	X	X	X	X	
Blood samples for PK[k]				X	X	X	X	X	X
Blood samples for ADA			X		X	X		X	X
ECOG[l]			X						
IGA, facial IGA[l]			X	X	X	X	X	X	X
Facial inflammatory lesion count[l]		X	X	X	X	X	X	X	X
Acneiform rash CTCAE grading[l]		X	X	X	X	X	X	X	X
Acneiform rash modified MESTT[l]			X	X	X	X	X	X	X
Pruritus and pain NRS[l]			X	X	X	X	X	X	X
FACT-EGFRi-18, PGI-S, PGI-C[l]			X	X	X	X	X	X	X
Number of nail folds with paronychia[l]			X	X	X	X	X	X	X
Paronychia, dry skin, alopecia, pruritus CTCAE grading[l]			X	X	X	X	X	X	X
STIDAT[l]			X	X	X	X	X	X	X
Tape strips collection[m]			X			X		X	
Photography			X		X	X		X	X
Randomization			X						
Imsidolimab/placebo administration[n]			X		X	X	X		

Study visit Window (days)	Screening Period (-6 months to -1 day)		Treatment Period						Follow-up Period
	Screening[a]		D1 W0	D15 W2 (±2)	D29 W4 (±2)	D57 W8 (±4)	D85 W12 (±4)	D113 W16 (EOT/ET)[b] (±4)	D169 W24 (EOS) (±5)
	Part 1 Initial visit	Part 1 Initial visit							
AE/SAE review	X	X	Continuously						
Concomitant medication review	X[o]	X[o]	Continuously						

Abbreviations: ADA = anti-drug antibody; AE = adverse event; CTCAE = Common Terminology Criteria for Adverse Events; D = day; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; EGFRi = epidermal growth factor receptor inhibitor; EOT = end of treatment; ET = early termination; EOS = end of study; FACT-EGFRi-18 = Functional Assessment of Cancer Therapy EGFRi 18; FSH = follicle-stimulating hormone; IGA = Investigator Global Assessment; MASCC = Multinational Association for Supportive Care in Cancer; modified MESTT, MASCC EGFRi Skin Toxicity Tool; NRS = Numeric Rating Scale; PGI-C = Patient Global Impression of Change; PGI-S = Patient Global Impression of Severity; PK = pharmacokinetics; SAE = serious adverse event; SC = subcutaneous; SoA = Schedule of Activities; STIDAT = Systemic Therapy Induced Diarrhea Assessment Tool; TB = tuberculosis; W = week; WOCBP = woman of childbearing potential.

[a] Depending on subject acneiform rash status, the screening visit may be planned either as 1 visit (for subjects who already have an acneiform rash) or as 2 separate visits (for subjects not having an acneiform rash at the initial screening visit): Screening Part 1 and Screening Part 2. Screening Part 2 will only be performed once subject is having an acneiform rash. Screening Part 2 assessments must be performed within 15 days prior to Day 1 (ideally within 1 week) and safety evaluation results required to confirm eligibility must be obtained before randomization.

[b] The ET visit will include all procedures to be done at the EOT/ET visit (Day 113/Week 16 visit).

[c] If not collected at Screening, may be collected at any visit thereafter.

[d] At the Screening (Screening Part 2 for subjects not having an acneiform rash at the initial Screening) and Day 1 visits, the subjects will need to have an active acneiform rash of Grade ≥ 2 as per CTCAE Version 5.0, and ≥ 20 inflammatory lesions on the face.

[e] Height will be measured at Screening only (Screening Part 1 for subjects not having an acneiform rash).

[f] Refer to Protocol **Section 8.2.3** for details regarding the chest X-ray. A chest X-ray (both posterior-anterior and lateral views) must be done during the screening prior to Day 1 unless the report from a chest X ray or a chest CT scan, done within 6 months before the first administration of study drug, and read by a qualified radiologist is already available.

[g] Refer to Protocol **Section 8.2.4** for details regarding the complete physical examination.

[h] Refer to Protocol **Section 8.2.5** for details and instructions regarding vital signs.

[i] Refer to Protocol **Section 8.2.6** 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.

[j] The FSH testing is performed for postmenopausal women with at least 12 months of amenorrhea without an alternative medical cause to confirm they meet not of childbearing potential criteria. Additional pregnancy testing may be performed whenever a menstrual cycle is missed or when pregnancy is otherwise suspected. Local laboratory tests will also be allowed at Screening for TB and viral serology testing. Refer to Protocol **Appendix 7** for details and instructions regarding clinical laboratory parameters and refer to **Appendix 1** for the WOCBP definition.

[k] Blood sample for PK will be collected prior to SC administration. In addition, samples for PK will also be collected on Days 15, 29, 57, 85, 113, and 169 (refer to Protocol **Table 15**).

[l] Refer to the Protocol **Section 8.1** for details and instructions regarding ECOG, facial inflammatory lesion count, acneiform rash CTCAE, acneiform rash modified MESTT, IGA, facial IGA, pain and pruritus NRSs, FACT-EGFRi-18, PGI-S, PGI-C, nail folds with paronychia, paronychia, dry skin, alopecia, and pruritus CTCAE grading, and STIDAT. The IGA/facial IGA assessment must be performed prior to the facial lesion count assessment. PGI-C is not to be performed at Day 1.

[m] Tape strips will be collected on Day 1, Day 57, and Day 113 from nonlesional and lesional skin.

[n] During the treatment period, subjects will receive either imsidolimab or placebo, SC administered at 4 time points: 400-mg dose of imsidolimab or placebo on Day 1; 200 mg dose of imsidolimab or placebo on Days 29, 57, and 85.

[o] 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 first interim analysis data snapshot, and protocol violations will be identified and decisions for inclusion and exclusion of subjects from the Per Protocol Analysis Set will be made prior to the final database lock and data analysis.

5. ANALYSIS SETS

5.1 Intent-to-Treat Analysis Set

The ITT Analysis Set will include all randomized subjects. In this analysis set, treatment will be assigned based upon the treatment arm to which subjects were randomized regardless of which treatment they received. ITT Analysis Set will be used for efficacy data 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 violations are described in **Section 7.3**. Per Protocol analysis set will be used for a sensitivity analysis of the primary endpoint and for some secondary endpoints.

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 except that the Safety Analysis Set will be used for all PK analyses during the interim 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). 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 for the ITT Analysis Set; demographics for the PP, PK, and Safety Analysis Sets will be tabulated only if they are different from ITT Analysis Set. Extent of exposure, safety, biomarker, and anti-drug antibody (ADA) data will be summarized for the Safety Analysis Set. PK parameters will be summarized for 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% × {(Observed value at Week X - baseline value) / 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 acneiform rash CTCAE grade, duration of acneiform rash, Eastern Cooperative Oncology Group (ECOG) score, facial inflammatory lesion counts, facial IGA, IGA, acneiform rash modified MESTT, pruritus NRS, pain NRS, functional assessment of cancer therapy EGFRi 18 (FACT-EGFRi-18) total score, PGI-S, STIDAT total score, number of nail folds with paronychia, and paronychia, dry skin, alopecia, and pruritus CTCAE grade 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 ([18, 45) years, [45, 65) years, ≥65 years)
- Sex
- Race
- Ethnicity (Hispanic or Non-Hispanic)
- Country
- Woman of childbearing potential (Yes or No)
- Weight (kg)
- Height (cm)
- Body mass index (BMI; kg/m^2)
- Acneiform rash CTCAE grade at Baseline (Grade 2 vs Grade 3 or 4)
- Duration of acneiform rash (weeks)
- Neoplasm therapy at Baseline (EGFRi or MEKi)
- Facial Papule Lesion Count at Baseline

- Facial Pustule Lesion Count at Baseline
- Facial inflammatory lesion counts at Baseline
- ECOG at Baseline (Grade 0 to Grade 2)
- Facial IGA at Baseline (Grade 0 to Grade 4)
- IGA at Baseline (Grade 0 to Grade 4)
- Acneiform rash modified MESTT grade (face, scalp, chest, back, and total score) at Baseline (Grade 1 to Grade 3 for individual body regions; Grade 4 to Grade 12 for total score)
- Pruritus NRS at Baseline (Grade 0 to Grade 10)
- Pain NRS at Baseline (Grade 0 to Grade 10)
- FACT-EGFRi-18 total score at Baseline
- PGI-S at Baseline (Grade 1 to Grade 4)
- STIDAT total score at Baseline
- Paronychia, dry skin, alopecia, and pruritus CTCAE grade at Baseline (Grade 0 to Grade 3)

6.1.2 Medical History

Medical 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, Concomitant, and Rescue Medications/Treatments

All medications taken within 6 months prior to Day 1 and all concomitant therapy taken by the subject while on study will be recorded on the Concomitant Medications CRF page. Prior medication/treatment is any medication/treatment stopped prior to the first dose of study treatment.

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

Rescue medications taken by the subject to control intolerable symptoms of EGFRi/MEKi-associated acneiform rash during the study will be recorded on the Rescue Medication CRF page.

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 term 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 2**. For summary tables and figures, efficacy data will be analyzed based on the visit window specified in **Table 2**. 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 2 Analysis Visit Windows

Nominal Visit	Nominal Day	Visit Window (day)
Screening Part 1[a]	-183 to -1	-183 to -1
Screening/Screening Part 2[a]	-15 to -1	-15 to -1
Day 1	1	1 (Pre-dose)
Week 2	15	1 (Post-dose) to 22
Week 4	29	23 to 42
Week 8	57	43 to 71
Week 12	85	72 to 99
Week 16	113	100 to 141
Week 24	169	≥142

[a] Depending on subject acneiform rash status, the screening visit may be planned either as 1 visit (for subjects who already have an acneiform rash) or as 2 separate visits (for subjects not having an acneiform rash at the initial screening visit): Screening Part 1 and Screening Part 2.

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 count (papules and pustules) at Week 8. The number of facial inflammatory lesions (papules and pustules) on the face (excluding the neck and scalp area) will be counted at the visits specified in the Schedule of Activities in **Table 1**, according to the definitions presented in **Table 3**. Total number of facial inflammatory lesions for each visit will be documented in the electronic case report form (eCRF). Change from baseline at Week 8 will be calculated as the difference between the observed value at Week 8 and the corresponding baseline value.

Table 3 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

6.2.3 Secondary Efficacy Variables

The secondary efficacy endpoints are as follows.

- **Percent change from Baseline in facial inflammatory lesion count (papules and pustules) at Week 8**

  The percentage change from baseline in facial inflammatory lesion count at Week 8 will be calculated.

- **Proportion of subjects with an improvement of at least 1 grade from Baseline in acneiform rash CTCAE grading scale at Week 8**

  The acneiform rash CTCAE grading scale of the acneiform rash severity is a 6-point scale ranging from 0 to 5, with 0 indicating no evidence of rash and 5 indicating death. A description of each scale is provided in **Table 4**.

Table 4 Grading of Acneiform Rash According to the CTCAE

Grade	Definition
0	No evidence of rash
1	Papules and/or pustules covering < 10% BSA, which may or may not be associated with symptoms of pruritus or tenderness
2	Papules and/or pustules covering 10-30% BSA, which may or may not be associated with symptoms of pruritus or tenderness; associated with psychosocial impact; limiting instrumental ADL; papules and/or pustules covering > 30% BSA with or without mild symptoms
3	Papules and/or pustules covering > 30% BSA with moderate or severe symptoms; limiting self‑care ADL; associated with local superinfection with oral antibiotics indicated
4	Life-threatening consequences; papules and/or pustules covering any % BSA, which may or may not be associated with symptoms of pruritus or tenderness and are associated with extensive superinfection with IV antibiotics indicated
5	Death

Abbreviations: ADL = activities of daily living; BSA = body surface area; CTCAE = Common Terminology Criteria for Adverse Events; IV = intravenous.

For each treatment group, the number of subjects with at least 1 grade improvement from baseline in acneiform rash CTCAE grading scale will be calculated at Week 8. The proportion of such subjects will be calculated for each treatment group as:

$$\frac{\begin{array}{c}Number\ of\ subjects\ with\\(acneiform\ rash\ CTCAE\ grade\ at\ Week\ 8\ -\ acneiform\ rash\ CTCAE\ grade\ at\ baseline)\ \leq\ -1\end{array}}{\begin{array}{c}Number\ of\ subjects\ in\ treatment\ group\ with\ baseline\ acneiform\ rash\ CTCAE\ grade\ \geq\ 1\ and\\acneiform\ rash\ CTCAE\ grade\ at\ Week\ 8\end{array}}$$

- **Time to first response of 1 grade improvement from Baseline on the acneiform rash CTCAE grading scale**

  Time to first response of 1 grade improvement from baseline on the acneiform rash CTCAE grading scale is defined as follows:

  Date of the first response of 1 grade improvement from baseline on the acneiform rash CTCAE grading scale – Date of the first dose of study treatment (or from randomization for any subjects randomized but not treated) + 1.

- **Proportion of subjects with an improvement of at least 1 grade from Baseline in acneiform rash modified MESTT grading scale (total score) at Week 8**

  The modified Multinational Association for Supportive Care in Cancer (MASCC) EGFRi Skin Toxicity Tool (MESTT) grading scale of the acneiform rash severity is a 3-point scale ranging from 1 to 3. A description of each scale is provided in **Table 5**. Grading is performed individually for the face, scalp, chest, and back.[1, 6] The sum of all body region scores yields the total score that may therefore vary between 4 and 12. If a subject has incomplete items less than 50%, missing items will be imputed as the average of reported items for that subject. Otherwise, the total score is set to missing.

Table 5 Grading of Acneiform Rash According to the MESTT

Grade	Definition
1	1A: papules or pustules ≤5; OR 1 area of erythema or edema <1cm in size
	1B: papules or pustules ≤5; OR 1 area of erythema or edema <1cm in size; AND pain or pruritus
2	2A: papules or pustules 6-20; OR 2-5 areas of erythema or edema <1cm in size
	2B: Papules or pustules 6-20; OR 2-5 areas of erythema or edema <1cm in size; AND pain, pruritus, or effect on emotions or functioning
3	3A: papules or pustules > 20; OR more than 5 areas of erythema or edema <1cm in size
	3B: papules or pustules > 20; OR more than 5 areas of erythema or edema <1cm in size; AND pain, pruritus, or effect on emotions or functioning

Abbreviations: MEST = Multinational Association for Supportive Care in Cancer EGFRi Skin Toxicity Tool

For each treatment group, the number of subjects with at least 1 grade improvement from baseline in acneiform rash modified MESTT grading scale (total score) will be calculated at Week 8. The proportion of such subjects will be calculated for each treatment group as:

$$\frac{Number\ of\ subjects\ with\ \{acneiform\ rash\ modified\ MESTT\ grade\ (total\ score)\ at\ Week\ 8\ -\ acneiform\ rash\ modified\ MESTT\ grade\ (total\ score)\ at\ baseline\}\ \leq\ -1}{Number\ of\ subjects\ in\ treatment\ group\ with\ baseline\ acneiform\ rash\ modified\ MESTT\ grade\ (total\ score)\ \geq\ 1\ and\ acneiform\ rash\ modified\ MESTT\ grade\ (total\ score)\ at\ Week\ 8}$$

- **Time to first response of 1 grade improvement from Baseline on the acneiform rash modified MESTT grading scale (total score)**

  Time to first response of 1 grade improvement from baseline on the acneiform rash modified MESTT grading scale (total score) is defined as follows:

  Date of onset of the first response of 1 grade improvement from baseline on the acneiform rash modified MESTT grading scale (total score) – Date of the first dose of study treatment (or from randomization for any subjects randomized but not treated) + 1.

- **Proportion of subjects with an improvement of at least 1 grade from Baseline in acneiform rash modified MESTT grading scale (facial assessment) at Week 8**

  For each treatment group, the number of subjects with an improvement of at least 1 grade from baseline in acneiform rash modified MESTT grading scale (facial assessment) will be calculated at Week 8. The proportion of such subjects will be calculated for each treatment group at Week 8 as:

$$\frac{Number\ of\ subjects\ with\ \{acneiform\ rash\ modified\ MESTT\ grade\ (facial\ assessment)\ at\ Week\ 8\ -\ acneiform\ rash\ modified\ MESTT\ grade\ (facial\ assessment)\ at\ baseline\}\ \leq\ -1}{Number\ of\ subjects\ in\ treatment\ group\ with\ baseline\ acneiform\ rash\ modified\ MESTT\ grade\ (facial\ assessment)\ \geq\ 1\ and\ acneiform\ rash\ modified\ MESTT\ grade\ (facial\ assessment)\ at\ Week\ 8}$$

- **Time to first response of 1 grade improvement from Baseline on the acneiform rash modified MESTT grading scale (facial assessment)**

  Time to first response of 1 grade improvement from baseline on the acneiform rash modified MESTT grading scale (facial assessment) is defined as follows:

  Date of onset of the first response of 1 grade improvement from baseline on the acneiform rash modified MESTT grading scale (facial assessment) – Date of the first dose of study treatment (or from randomization for any subjects randomized but not treated) + 1.

- **Change from Baseline in pruritus NRS at Week 8**

  The intensity of pruritus will be evaluated by asking subjects to assign a numerical score representing of the worst intensity over the last 24 hours of their symptoms on a scale from 0 to 10, with 0 indicating no itch and 10 indicating the worst imaginable itch.

  Change from baseline in pruritus NRS at Week 8 will be calculated.

- **Percent change from Baseline in pruritus NRS at Week 8**

  The percentage change from baseline in pruritus NRS will be calculated.

- **Change from Baseline in pain NRS at Week 8**

  The intensity of pain will be evaluated by asking subjects to assign a numerical score representing of the worst intensity over the last 24 hours of their symptoms on a scale from 0 to 10, with 0 indicating no pain and 10 indicating the worst imaginable pain.

  Change from baseline in pain NRS at Week 8 will be calculated.

- **Percent change from Baseline in pain NRS at Week 8**

  The percentage change from baseline in pain NRS at Week 8 will be calculated.

- **Change from Baseline in FACT-EGFRi-18 at Week 8**

  The FACT-EGFRi-18 is an 18-item Likert-scaled questionnaire, arranged in three dimensions: physical (seven items), social/emotional (six items), and functional well-being (five items).[11] The response scores ranged from 0 (not at all) to 4 (very much).

  The total score (the endpoint of interest) will be obtained by multiplying the sum of the subscale by the number of items in the scale (18), and then dividing by the number of items actually answered. More than 50% of the items (e.g., a minimum of 10 of 18 items) must be answered to calculate the total score. Otherwise, the total score is set to missing.

  Change from baseline in FACT-EGFRi-18 at Week 8 will be calculated.

6.2.4 Exploratory Efficacy Variables

- **Change from Baseline in facial inflammatory lesion count (papules and pustules) at each visit other than Week 8**

  Change from baseline in facial inflammatory lesion count (papules and pustules) at visits other than Week 8 (Weeks 2, 4, 12, 16, and 24) will be calculated.

- **Percent change from Baseline in facial inflammatory lesion count (papules and pustules) at each visit other than Week 8**

  The percentage change from baseline in facial inflammatory lesion count (papules and pustules) at visits other than Week 8 (Weeks 2, 4, 12, 16, and 24) will be calculated.

- **Change from Baseline in facial papule count at each visit**

  Change from baseline in facial papule counts at each visit (Weeks 2, 4, 8, 12, 16, and 24) will be calculated.

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

  The percentage change from baseline in facial papule counts at each visit (Weeks 2, 4, 8, 12, 16, and 24) will be calculated.

- **Change from Baseline in facial pustule count at each visit**

  Change from baseline in facial pustule counts at each visit (Weeks 2, 4, 8, 12, 16, and 24) will be calculated.

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

  The percentage change from baseline in facial pustule counts at each visit (Weeks 2, 4, 8, 12, 16, and 24) will be calculated.

- **Proportion of subjects with an improvement of at least 1 grade from Baseline in acneiform rash CTCAE grading at each visit other than Week 8**

  The proportion of subjects with at least 1 grade improvement from baseline in acneiform rash CTCAE grading scale will be calculated at visits other than Week 8 (Weeks 2, 4, 12, 16, and 24). The proportion of such subjects will be calculated for each treatment group at each visit as:

$$\frac{\begin{array}{c}Number\ of\ subjects\ with\\ (acneiform\ rash\ CTCAE\ grade\ at\ Week\ x\ -\ acneiform\ rash\ CTCAE\ grade\ at\ baseline)\ \leq -1\end{array}}{\begin{array}{c}Number\ of\ subjects\ in\ treatment\ group\ with\ baseline\ acneiform\ rash\ CTCAE\ grade\ \geq\ 1\ and\\ acneiform\ rash\ CTCAE\ grade\ at\ Week\ x\end{array}}$$

- **Proportion of subjects with an improvement of at least 1 grade from Baseline in acneiform rash modified MESTT grading scale (total score) at each visit other than Week 8**

  The proportion of subjects with at least 1 grade improvement from baseline in acneiform rash modified MESTT grading scale (total score) will be calculated at visits other than Week 8 (Weeks 2, 4, 12, 16, and 24). The proportion of such subjects will be calculated for each treatment group at each visit as:

$$\frac{\begin{array}{c}Number\ of\ subjects\ with\ \{acneiform\ rash\ modified\ MESTT\ grade\ (total\ score)\ at\ Week\ x\ -\\ acneiform\ rash\ modified\ MESTT\ grade\ (total\ score)\ at\ baseline\}\ \leq -1\end{array}}{\begin{array}{c}Number\ of\ subjects\ in\ treatment\ group\ with\ baseline\ acneiform\ rash\ modified\\ MESTT\ grade\ (total\ score)\ \geq\ 1\ and\ acneiform\ rash\ modified\ MESTT\ grade\ (total\ score)\ at\ Week\ x.\end{array}}$$

- **Change from Baseline in pruritus NRS at each visit other than Week 8**

  Change from baseline in pruritus NRS at visits other than Week 8 (Weeks 2, 4, 12, 16, and 24) will be calculated.

- **Percent change from Baseline in pruritus NRS at each visit other than Week 8**

  The percentage change from baseline in pruritus NRS at visits other than Week 8 (Weeks 2, 4, 12, 16, and 24) will be calculated.

- **Change from Baseline in pain NRS at each visit other than Week 8**

  Change from baseline in pain NRS at visits other than Week 8 (Weeks 2, 4, 12, 16, and 24) will be calculated.

- **Percent change from Baseline in pain NRS at each visit other than Week 8**

  The percentage change from baseline in pain NRS at visits other than Week 8 (Weeks 2, 4, 12, 16, and 24) will be calculated.

- **Change from Baseline in FACT-EGFRi-18 at each visit other than Week 8**

  Change from baseline in FACT-EGFRi-18 at visits other than Week 8 (Weeks 2, 4, 12, 16, and 24) will be calculated.

- **Proportion of subjects achieving an improvement of 50% from Baseline in facial inflammatory lesion count (papules and pustules) at each visit**

  For each treatment group, the number of subjects achieving an improvement of 50% from baseline in facial inflammatory lesion count (papules and pustules) at each visit (Weeks 2, 4, 8, 12, 16, and 24) will be calculated. The proportion of such subjects will be calculated for each treatment group at each visit as:

$$\frac{\begin{array}{c}Number\ of\ subjects\ with\ \%\ change\ from\ baseline\ in\ facial\ inflammatory\\ lesion\ count\ (papules\ and\ pustules)\ at\ Week\ x\ \geq 50\%\end{array}}{\begin{array}{c}Number\ of\ subjects\ in\ treatment\ group\ with\ facial\ inflammatory\\ lesion\ count\ (papules\ and\ pustules)\ at\ Week\ x\end{array}}$$

- **Proportion of subjects achieving an improvement of 75% from Baseline in facial inflammatory lesion count (papules and pustules) at each visit**

  For each treatment group, the number of subjects achieving an improvement of 75% from baseline in facial inflammatory lesion count (papules and pustules) will be calculated at each visit (Weeks 2, 4, 8, 12, 16, and 24). The proportion of such subjects will be calculated for each treatment group at each visit as:

$$\frac{\begin{array}{c}Number\ of\ subjects\ with\ \%\ change\ from\ baseline\ in\ facial\ inflammatory\\ lesion\ count\ (papules\ and\ pustules)\ at\ Week\ x\ \geq 75\%\end{array}}{\begin{array}{c}Number\ of\ subjects\ in\ treatment\ group\ with\ facial\ inflammatory\\ lesion\ count\ (papules\ and\ pustules)\ at\ Week\ x\end{array}}$$

- **Change from Baseline in acneiform rash CTCAE grading scale at each visit**

  Change from baseline in acneiform rash CTCAE grading scale at each visit (Weeks 2, 4, 8, 12, 16, and 24) will be calculated.

  The number and percentage of subjects who have acneiform rash CTCAE Grade 2, 3, or 4 at baseline and the shifts from baseline grades to each visit (Weeks 2, 4, 8, 12, 16, and 24) will be calculated based on these values.

- **Change from Baseline in acneiform rash modified MESTT grading scale (total score) at each visit**

  Change from baseline in acneiform rash modified MESTT grading scale (total score) at each visit (Weeks 2, 4, 8, 12, 16, and 24) will be calculated.

- **Percent change from Baseline in acneiform rash modified MESTT grading scale (total score) at each visit**

  The percentage change from baseline in acneiform rash modified MESTT grading scale (total score) at each visit (Weeks 2, 4, 8, 12, 16, and 24) will be calculated.

- **Change from Baseline in acneiform rash modified MESTT grading scale (facial assessment) at each visit**

  Change from baseline in acneiform rash modified MESTT grading scale (facial assessment) at each visit (Weeks 2, 4, 8, 12, 16, and 24) will be calculated.

  The number and percentage of subjects who have MESTT Grade 1, 2 or 3 at baseline and the shifts from baseline grades to each visit (Weeks 2, 4, 8, 12, 16, and 24) will be calculated for the face based on these values.

- **Change from Baseline in acneiform rash modified MESTT grading scale (back assessment) at each visit**

  Change from baseline in acneiform rash modified MESTT grading scale (back assessment) at each visit (Weeks 2, 4, 8, 12, 16, and 24) will be calculated.

  The number and percentage of subjects who have MESTT Grade 1, 2 or 3 at baseline and the shifts from baseline grades to each visit (Weeks 2, 4, 8, 12, 16, and 24) will be calculated for the face based on these values.

- **Change from Baseline in acneiform rash modified MESTT grading scale (scalp assessment) at each visit**

  Change from baseline in acneiform rash modified MESTT grading scale (scalp assessment) at each visit (Weeks 2, 4, 8, 12, 16, and 24) will be calculated.

  The number and percentage of subjects who have MESTT Grade 1, 2 or 3 at baseline and the shifts from baseline grades to each visit (Weeks 2, 4, 8, 12, 16, and 24) will be calculated for the face based on these values.

- **Change from Baseline in acneiform rash modified MESTT grading scale (chest assessment) at each visit**

  Change from baseline in acneiform rash modified MESTT grading scale (chest assessment) at each visit (Weeks 2, 4, 8, 12, 16, and 24) will be calculated.

  The number and percentage of subjects who have MESTT Grade 1, 2 or 3 at baseline and the shifts from baseline grades to each visit (Weeks 2, 4, 8, 12, 16, and 24) will be calculated for the face based on these values.

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

  The IGA is a 5-point morphological assessment of acneiform rash severity on the entire body, ranged from 0 (Clear) to 4 (Severe). The 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 IGA at each visit (Weeks 2, 4, 8, 12, 16, and 24) will be calculated.

  The number and percentage of subjects who have IGA Grade 0, 1, 2, 3, 4 at baseline and the shifts from baseline grades to each visit (Weeks 2, 4, 8, 12, 16, and 24) will be calculated based on these values.

- **Proportion of subjects achieving an IGA of clear (0) or almost clear (1) at each visit**

  For each treatment group, the number of subjects achieving an IGA of clear (0) or almost clear (1) will be calculated at each visit (Weeks 0, 2, 4, 8, 12, 16, and 24). The proportion of such subjects will be calculated for each treatment group at each visit as:

$$\frac{Number\ of\ subjects\ achieving\ an\ IGA\ of\ clear\ (0)\ or\ almost\ clear\ (1)\ at\ Week\ x}{Number\ of\ subjects\ in\ treatment\ group\ with\ IGA\ at\ Week\ x}$$

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

  For each treatment group, the number of subjects with at least 2-point decrease in IGA will be calculated at each visit (Weeks 2, 4, 8, 12, 16, and 24). The proportion of such subjects will be calculated for each treatment group at each visit as:

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

- **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 (None) 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, 16, and 24) 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, 16, and 24) will be calculated based on these values.

- **Proportion of subjects achieving a facial IGA of none (0) or minimal (1) at each visit**

  For each treatment group, the number of subjects achieving a facial IGA of none (0) or minimal (1) will be calculated at each visit (Weeks 0, 2, 4, 8, 12, 16, and 24). The proportion of such subjects will be calculated for each treatment group at each visit as:

$$\frac{Number\ of\ subjects\ achieving\ a\ facial\ IGA\ of\ none\ (0)\ or\ minimal\ (1)\ at\ Week\ x}{Number\ of\ subjects\ in\ treatment\ group\ with\ facial\ IGA\ at\ Week\ x}$$

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

  For each treatment group, the number of subjects with at least 2-point decrease in facial IGA will be calculated at each visit (Weeks 2, 4, 8, 12, 16, and 24). 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 3-point decrease in pruritus NRS at each visit for subjects with a Baseline pruritus NRS of at least 3**

  For each treatment group, the number of subjects with at least 3-point decrease in pruritus NRS for subjects with a baseline pruritus NRS of at least 3 will be calculated at each visit (Weeks 2, 4, 8, 12, 16, and 24). The proportion of such subjects will be calculated for each treatment group at each visit as:

$$\frac{Number\ of\ subjects\ with\ (pruritus\ NRS\ at\ Week\ x\ -\ pruritus\ NRS\ at\ baseline)\ \leq\ -3}{Number\ of\ subjects\ in\ treatment\ group\ with\ baseline\ pruritus\ NRS\ \geq\ 3\ and\ pruritus\ NRS\ at\ Week\ x}$$

- **Proportion of subjects with at least 4-point decrease in pruritus NRS at each visit for subjects with a Baseline pruritus NRS of at least 4**

  For each treatment group, the number of subjects with at least 4-point decrease in pruritus NRS for subjects with a baseline pruritus NRS of at least 4 will be calculated at each visit (Weeks 2, 4, 8, 12, 16, and 24). The proportion of such subjects will be calculated for each treatment group at each visit as:

$$\frac{Number\ of\ subjects\ with\ (pruritus\ NRS\ at\ Week\ x\ -\ pruritus\ NRS\ at\ baseline)\ \leq\ -4}{Number\ of\ subjects\ in\ treatment\ group\ with\ baseline\ pruritus\ NRS\ \geq\ 4\ and\ pruritus\ NRS\ at\ Week\ x}$$

- **Proportion of subjects with at least 3-point decrease in pain NRS at each visit for subjects with a Baseline pain NRS of at least 3**

  For each treatment group, the number of subjects with at least 3-point decrease in pain NRS for subjects with a baseline pain NRS of at least 3 will be calculated at each visit (Weeks 2, 4, 8, 12, 16, and 24). The proportion of such subjects will be calculated for each treatment group at each visit as:

$$\frac{Number\ of\ subjects\ with\ (pain\ NRS\ at\ Week\ x\ -\ pain\ NRS\ at\ baseline)\ \leq\ -3}{Number\ of\ subjects\ in\ treatment\ group\ with\ baseline\ pain\ NRS\ \geq\ 3\ and\ pain\ NRS\ at\ Week\ x}$$

- **Proportion of subjects with at least 4-point decrease in pain NRS at each visit for subjects with a Baseline pain NRS of at least 4**

  For each treatment group, the number of subjects with at least 4-point decrease in pain NRS for subjects with a baseline pain NRS of at least 4 will be calculated at each visit (Weeks 2, 4, 8, 12, 16, and 24). The proportion of such subjects will be calculated for each treatment group at each visit as:

$$\frac{Number\ of\ subjects\ with\ (pain\ NRS\ at\ Week\ x\ -\ pain\ NRS\ at\ baseline)\ \leq\ -4}{Number\ of\ subjects\ in\ treatment\ group\ with\ baseline\ pain\ NRS\ \geq\ 4\ and\ pain\ NRS\ at\ Week\ x}$$

- **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 the acneiform rash ("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 1**. The proportion of such subjects will be calculated for each treatment group at each visit (Weeks 0, 2, 4, 8, 12, 16, and 24) 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 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 1**. The proportion of such subjects will be calculated for each treatment group at each post-baseline visit (Weeks 2, 4, 8, 12, 16, and 24) as:

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

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

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

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

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

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

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

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

- **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 (Weeks 0, 2, 4, 8, 12, 16, and 24). The proportion of such subjects will be calculated for each treatment group at each visit as:

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

- **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 (Weeks 2, 4, 8, 12, 16, and 24). The proportion of such subjects will be calculated for each treatment group at each post-baseline visit 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 receiving rescue medication from Week 4 through Week 24**

  For each treatment group, the number of subjects receiving rescue medication from Week 4 through Week 24 will be calculated. The proportion of such subjects will be calculated for each treatment group as:

$$\frac{Number\ of\ subjects\ receiving\ rescue\ medication\ from\ Week\ 4\ through\ Week\ 24}{Number\ of\ subjects\ in\ treatment\ group}$$

  Rescue medication is as defined in **Section 6.1.3**.

- **Proportion of subjects that do not require a dose reduction of EGFRi or MEKi therapy due to acneiform rash at each visit**

  For each treatment group, the number of subjects that do not require a dose reduction of EGFRi or MEKi therapy due to acneiform rash will be calculated at each visit (Weeks 0, 2, 4, 8, 12, 16, and 24). The proportion of such subjects will be calculated for each treatment group at each visit as:

$$\frac{Number\ of\ subjects\ that\ do\ not\ require\ a\ dose\ reduction\ of\ EGFRi\ or\ MEKi\ therapy\ due\ to\ acneiform\ rash\ at\ Week\ x}{Number\ of\ subjects\ in\ treatment\ group}$$

- **Proportion of subjects that do not require cessation of EGFRi or MEKi therapy due to acneiform rash at each visit**

  For each treatment group, the number of subjects that do not require cessation of EGFRi or MEKi therapy due to acneiform rash will be calculated at each visit (Weeks 0, 2, 4, 8, 12, 16, and 24). The proportion of such subjects will be calculated for each treatment group at each visit as:

$$\frac{Number\ of\ subjects\ that\ do\ not\ require\ cessation\ of\ EGFRi\ or\ MEKi\ therapy\ due\ to\ acneiform\ rash\ at\ Week\ x}{Number\ of\ subjects\ in\ treatment\ group}$$

- **Change from Baseline in number of nail folds with paronychia at each visit**

  The number of nail folds with paronychia will be counted by investigator and recorded in the eCRF, where paronychia is defined as disorder characterized by an infectious process (i.e., edema, erythema, disruption of the cuticle) involving the soft tissues around the nail.[3]

  Change from baseline in number of nail folds with paronychia at each visit (Weeks 2, 4, 8, 12, 16, and 24) will be calculated.

- **Proportion of subjects with paronychia, dry skin, alopecia, and pruritus of Grade 0 or 1 as per CTCAE grading scale at each visit**

  The CTCAE grading scale and their description are provided in **Table 6** for paronychia, **Table 7** for dry skin, **Table 8** for alopecia, and **Table 9** for pruritus.

Table 6 Grading of Paronychia According to CTCAE

Grade	Definition
0	No evidence of paronychia
1	Nail fold edema or erythema; disruption of the cuticle
2	Local intervention indicated; oral intervention indicated (e.g., antibiotic, antifungal, antiviral); nail fold edema or erythema with pain; associated with discharge or nail plate separation; limiting instrumental ADL.
3	Operative intervention indicated; IV antibiotics indicated; limiting self-care ADL

Abbreviations: ADL = activities of daily living; CTCAE = Common Terminology Criteria for Adverse Events; IV = intravenous.

Table 7 Grading of Dry Skin According to CTCAE

Grade	Definition
0	No evidence of dry skin
1	Covering <10% BSA and no associated erythema or pruritus
2	Covering 10–30% BSA and associated with erythema or pruritus; limiting instrumental ADL
3	Covering >30% BSA and associated with pruritus; limiting self-care ADL

Abbreviations: ADL = activities of daily living; BSA = body surface area; CTCAE = Common Terminology Criteria for Adverse Events.

Table 8 Grading of Alopecia According to CTCAE

Grade	Definition
0	No evidence of alopecia
1	Hair loss of <50% of normal for that individual that is not obvious from a distance but only on close inspection; a different hair style may be required to cover the hair loss but it does not require a wig or hair piece to camouflage
2	Hair loss of ≥50% normal for that individual that is readily apparent to others; a wig or hair piece is necessary if the patient desires to completely camouflage the hair loss; associated with psychosocial impact

Abbreviations: CTCAE = Common Terminology Criteria for Adverse Events.

Table 9 Grading of Pruritus According to CTCAE

Grade	Definition
0	No evidence of pruritus
1	Mild or localized; topical intervention indicated
2	Widespread and intermittent; skin changes from scratching (e.g., edema, papulation, excoriations, lichenification, oozing/crusts); oral intervention indicated; limiting instrumental ADL
3	Widespread and constant; limiting self-care ADL or sleep; systemic corticosteroid or immunosuppressive therapy indicated

Abbreviations: ADL = activities of daily living; CTCAE = Common Terminology Criteria for Adverse Events.

For each treatment group, the number of subjects with paronychia, dry skin, alopecia, and pruritus of Grade 0 or 1 as per CTCAE grading scale will be calculated at each visit (Weeks 0, 2, 4, 8, 12, 16, and 24). The proportion of such subjects will be calculated for each treatment group at each visit as:

$$\frac{\begin{array}{c}Number\ of\ subjects\ with\ paronychia, dry\ skin, alopecia, and\ pruritus\ of\ Grade\ 0\ or\ 1\\ as\ per\ CTCAE\ grading\ scale\ at\ Week\ x\end{array}}{\begin{array}{c}Number\ of\ subjects\ in\ treatment\ group\ with\ paronychia, dry\ skin, alopecia, and\ pruritus\\ CTCAE\ grading\ scale\end{array}}$$

- **Proportion of subjects with an improvement of at least 1 grade from Baseline in acneiform rash modified MESTT grading scale (facial assessment) at each visit other than Week 8**

  For each treatment group, the number of subjects with an improvement of at least 1 grade from baseline in acneiform rash modified MESTT grading scale (facial assessment) will be calculated at visits other than Week 8 (Weeks 2, 4, 12, 16, and 24). The proportion of such subjects will be calculated for each treatment group at each visit as:

$$\frac{\begin{array}{c}Number\ of\ subjects\ with\ \{acneiform\ rash\ modified\ MESTT\ grade\ (facial\ assessment)\ at\ Week\ x\ -\\ acneiform\ rash\ modified\ MESTT\ grade\ (facial\ assessment)\ at\ baseline\}\ \leq\ -1\end{array}}{\begin{array}{c}Number\ of\ subjects\ in\ treatment\ group\ with\ baseline\ acneiform\ rash\ modified\ MESTT\ grade\\ (facial\ assessment)\ \geq\ 1\ and\ acneiform\ rash\ modified\ MESTT\ grade\ (facial\ assessment)\ at\ Week\ x\end{array}}$$

- **Proportion of subjects with an improvement of at least 1 grade from Baseline in acneiform rash modified MESTT grading scale (back assessment) at each visit**

  For each treatment group, the number of subjects with an improvement of at least 1 grade from baseline in acneiform rash modified MESTT grading scale (back assessment) will be calculated at each visit (Weeks 2, 4, 8, 12, 16, and 24). The proportion of such subjects will be calculated for each treatment group at each visit as:

$$\frac{Number\ of\ subjects\ with\ \{acneiform\ rash\ modified\ MESTT\ grade\ (back\ assessment)\ at\ Week\ x\ -\ acneiform\ rash\ modified\ MESTT\ grade\ (back\ assessment)\ at\ baseline\} \leq -1}{Number\ of\ subjects\ in\ treatment\ group\ with\ baseline\ acneiform\ rash\ modified\ MESTT\ grade\ (back\ assessment) \geq 1\ and\ acneiform\ rash\ modified\ MESTT\ grade\ (back\ assessment)\ at\ Week\ x}$$

- **Proportion of subjects with an improvement of at least 1 grade from Baseline in acneiform rash modified MESTT grading scale (scalp assessment) at each visit**

  For each treatment group, the number of subjects with an improvement of at least 1 grade from baseline in acneiform rash modified MESTT grading scale (scalp assessment) will be calculated at each visit (Weeks 2, 4, 8, 12, 16, and 24). The proportion of such subjects will be calculated for each treatment group at each visit as:

$$\frac{Number\ of\ subjects\ with\ \{acneiform\ rash\ modified\ MESTT\ grade\ (scalp\ assessment)\ at\ Week\ x\ -\ acneiform\ rash\ modified\ MESTT\ grade\ (scalp\ assessment)\ at\ baseline\} \leq -1}{Number\ of\ subjects\ in\ treatment\ group\ with\ baseline\ acneiform\ rash\ modified\ MESTT\ grade\ (scalp\ assessment) \geq 1\ and\ acneiform\ rash\ modified\ MESTT\ grade\ (scalp\ assessment)\ at\ Week\ x}$$

- **Proportion of subjects with an improvement of at least 1 grade from Baseline in acneiform rash modified MESTT grading scale (chest assessment) at each visit**

  For each treatment group, the number of subjects with an improvement of at least 1 grade from baseline in acneiform rash modified MESTT grading scale (chest assessment) will be calculated at each visit (Weeks 2, 4, 8, 12, 16, and 24). The proportion of such subjects will be calculated for each treatment group at each visit as:

$$\frac{Number\ of\ subjects\ with\ \{acneiform\ rash\ modified\ MESTT\ grade\ (chest\ assessment)\ at\ Week\ x\ -\ acneiform\ rash\ modified\ MESTT\ grade\ (chest\ assessment)\ at\ baseline\} \leq -1}{Number\ of\ subjects\ in\ treatment\ group\ with\ baseline\ acneiform\ rash\ modified\ MESTT\ grade\ (chest\ assessment) \geq 1\ and\ acneiform\ rash\ modified\ MESTT\ grade\ (chest\ assessment)\ at\ Week\ x}$$

- **Time to first response of 1 grade improvement from Baseline on the acneiform rash modified MESTT grading scale (back assessment)**

  Time to first response of 1 grade improvement from baseline on the acneiform rash modified MESTT grading scale (back assessment) is defined as follows:

  Date of onset of the first response of 1 grade improvement from baseline on the acneiform rash modified MESTT grading scale (back assessment) – Date of the first dose of study treatment (or from randomization for any subjects randomized but not treated) + 1.

- **Time to first response of 1 grade improvement from Baseline on the acneiform rash modified MESTT grading scale (scalp assessment)**

  Time to first response of 1 grade improvement from baseline on the acneiform rash modified MESTT grading scale (scalp assessment) is defined as follows:

  Date of onset of the first response of 1 grade improvement from baseline on the acneiform rash modified MESTT grading scale (scalp assessment) – Date of the first dose of study treatment (or from randomization for any subjects randomized but not treated) + 1.

- **Time to first response of 1 grade improvement from Baseline on the acneiform rash modified MESTT grading scale (chest assessment)**

  Time to first response of 1 grade improvement from baseline on the acneiform rash modified MESTT grading scale (chest assessment) is defined as follows:

  Date of onset of the first response of 1 grade improvement from baseline on the acneiform rash modified MESTT grading scale (chest assessment) – Date of the first dose of study treatment (or from randomization for any subjects randomized but not treated) + 1.

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

  The STIDAT assesses patient's perception of having diarrhea, daily number of bowel movements, daily number of diarrhea episodes, antidiarrheal medication use, the presence of urgency, abdominal discomfort, fecal incontinence, patient's perception of diarrhea severity, and quality of life.

  The score calculation for each of 9 components and the summed total (the endpoint of interest) is defined in **Table 10**[4]:

Table 10 Scoring System of STIDAT

Component	Score Calculation
Patient's perception of having diarrhea	N1 × 0.193
Daily number of bowel movements	N3 × 0.050
Daily number of diarrhea episodes	N3 × 0.161
Antidiarrheal medication use	N1 × 0.060
Presence of urgency	N1 × 0.048
Presence of abdominal discomfort	N1 × 0.031
Presence of fecal incontinence	N1 × 0.016
Patient's perception of diarrhea severity	N2 × 0.529
Quality of life	Average of the five quality of life dimensions x (−0.048)
Total	Sum of component scores + 0.48

N1: Yes = 1, No = 0; N2: Minimal diarrhea = 1, Moderate diarrhea = 2, Severe diarrhea = 3; N3: an integer value ≥0.

  Change from baseline in STIDAT at each visit (Weeks 2, 4, 8, 12, 16, and 24) will be calculated.

- **Percent change from Baseline in STIDAT at each visit**

  The percentage change from baseline in STIDAT at each visit (Weeks 2, 4, 8, 12, 16, and 24) will be calculated.

- **Change from baseline in inflammatory lesion counts as determined by standardized photographs at each visit**

  The number of facial inflammatory lesions will be counted by a standardized review of photographs at the visits specified in the Schedule of Activities in **Table 1**.

Change from baseline in inflammatory lesion counts as determined by standardized photographs at each visit (Weeks 2, 4, 8, 12, 16, and 24) will be calculated.

- **Percent change from baseline in inflammatory lesion counts as determined by standardized photographs at each visit**

  The percentage change from baseline in inflammatory lesion counts as determined by standardized photographs at each visit (Weeks 2, 4, 8, 12, 16, and 24) 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 11**.

Table 11 Pharmacokinetic Sample Collection and Time Points

Study Visit	Pharmacokinetic Sample Time Point
Day 15	Anytime
Day 29	Pre-dose
Day 57	Pre-dose
Day 85	Pre-dose
Day 113	Anytime
Day 169	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 12**.

Table 12 ADA Sample Collection and Time Points

Study Visit	ADA Sample Time Point
Day 1	Pre-dose
Day 29	Pre-dose
Day 57	Pre-dose
Day 113	Anytime
Day 169	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

- **Skin tape strip biomarkers analysis including, but not limited to, IL-36 and Th-17**

  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 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 for 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 1**.

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 amount of doses for imsidolimab study treatment is:

- 400 mg on Day 1, 200 mg on Days 29, 57, and 85.

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 imputation 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 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 7** of the study Protocol. Local laboratory samples will be collected on 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), and weight (kg) will be obtained in accordance with the Schedule of Activities in **Table 1.** Changes from baseline in vital signs variables will be evaluated.

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

6.6.6 Electrocardiogram (ECG)

ECG parameters, including RR, PR, QRS, QT, QTcB, and QTcF intervals will be collected according to the Schedule of Activities in **Table 1.** 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 captured in the eCRF 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 Efficacy Analysis

1. Placebo Multiple Imputation

As a sensitivity analysis of the primary analysis under Missing Not at Random (MNAR), placebo Multiple Imputation (pMI) method will be conducted. The pMI assumes that the statistical behavior of imsidolimab-treated patients and placebo-treated patients after the occurrence of intercurrent events such as use of rescue medications will be the same as if patients were treated with placebo. In the context of efficacy data, pMI is a specific form of a MNAR analysis and expected to yield a conservative estimate for efficacy. The efficacy data on and after the use of rescue medication will be set to missing prior to the pMI analysis.

The steps of performing a pMI are as follows:

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, under the assumption that different treatments may have distinct posterior distributions. The imputation will include all the post-baseline values, and the corresponding baseline value as covariates.
b) All the monotone missing values will be multiply-imputed using the imputation model built from the placebo group. Covariates included in the modelling are age, sex, treatment group, acneiform rash CTCAE grade at baseline (Grade 2 vs. 3 or 4), neoplasm therapy (EGFRi/MEKi), all the post-baseline values, and the corresponding baseline value.

c) The linear mixed model for repeated measures (MMRM) for primary endpoint as described in **Section 7.5.1**., will be applied to each imputed dataset.

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 MCMC approach to create a monotone missing pattern. The imputation will be implemented separately for each treatment, under the assumption that different treatments may have distinct posterior distributions. The imputation will include all the post-baseline values, and the corresponding baseline value 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, acneiform rash CTCAE grade at baseline (Grade 2 vs. 3 or 4), neoplasm therapy (EGFRi/MEKi), and the corresponding baseline value.

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 0.05 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 group, 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 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.

<u>Data Imputation for Adverse Events Summaries by Relationship to Study Drug</u>

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 consented, 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 the number who discontinue study early will also be presented; for subjects who discontinue, the reason for discontinuation will 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 or exclusion of partial data (at some but not all time points) for a subject 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 inclusion/exclusion criteria and 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 primary 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 which 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 count, duration of acneiform rash, FACT-EGFRi-18 total score, STIDAT total score, and number of nail folds with paronychia), acneiform rash CTCAE grade, ECOG, IGA, facial IGA, acneiform rash modified MESTT grade, pruritus NRS, pain NRS, PGI-S, and paronychia, dry skin, alopecia, and pruritus CTCAE grade 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, acneiform rash CTCAE grade, ECOG, IGA, facial IGA, acneiform rash modified MESTT grade, pruritus NRS, pain NRS, PGI-S, and paronychia, dry skin, alopecia, and pruritus CTCAE grade), frequencies and percentages of subjects will be provided; baseline acneiform rash grading will be reported by individual Grade 2, 3 or 4.

7.4.2 Medical History

Medical history at screening will be summarized for the Safety Analysis Set and listed for the ITT Analysis Set. Type of neoplasm at baseline will be provided in a separate listing for the ITT Analysis Set.

7.4.3 Prior, Concomitant, and Rescue Medications/Treatments

Refer to **Appendix 1** for definitions of prior and concomitant treatments. Prior, concomitant, and rescue medications/treatments will be summarized by ATC class, preferred name, 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, concomitant, and rescue 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 endpoint as well as the following secondary endpoints:

- Percent change from Baseline in facial inflammatory lesion count (papules and pustules) at Week 8
- Proportion of subjects with an improvement of at least 1 grade from Baseline in acneiform rash CTCAE grading scale at Week 8
- Proportion of subjects with an improvement of at least 1 grade from Baseline in acneiform rash modified MESTT grading scale (total score) at Week 8
- Change from Baseline in pruritus NRS at Week 8
- Percent change from Baseline in pruritus NRS at Week 8

All statistical tests will be performed at the 5% level of significance unless otherwise stated. All confidence intervals (CIs) will be reported as 2-sided 95% 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. For categorical

variables, the number and percentage in each category will be presented. Subjects with missing scores, dose reduction data, or rescue medication data at a given visit will be considered to have not met the criteria of interest (i.e., nonresponse). 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 is reflected by the patients 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 facial inflammatory lesion count (papules and pustules) of an individual subject at Week 8.
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 measure for the primary endpoint is mean change from Baseline in facial inflammatory lesion count (papules and pustules) at Week 8. The estimator for between-group comparison of the primary endpoint will be the difference in the primary endpoint between imsidolimab and placebo at Week 8.

A MMRM model will be used with treatment, visit, treatment by visit interaction, acneiform rash CTCAE grade at baseline (Grade 2 vs. 3 or 4), and neoplasm therapy (EGFRi/MEKi) as categorical covariates and the baseline value of response as the only continuous covariate. 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 8 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 95% 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 95% CI will be provided based on the model. Summary statistics and the results of statistical testing in facial inflammatory lesion count (papules and pustules) at Week 8 will be tabulated. The LS mean change from baseline as well as differences between treatments in facial inflammatory lesion count (papules and pustules) 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 Count (Papules and Pustules) at Week 8

The percent change from baseline in facial inflammatory lesion count (papules and pustules) will be presented together with the primary endpoint. This endpoint will be analyzed using a similar MMRM model as for the primary endpoint. The percent change from baseline in facial inflammatory lesion count (papules and pustules) will be the response variable in the model.

7.5.2.2 Proportion of Subjects with an Improvement of at Least 1 Grade from Baseline in Acneiform Rash CTCAE Grading Scale at Week 8

The frequency and percentage of subjects with an improvement of at least 1 grade from baseline in acneiform rash CTCAE grading scale will be summarized at Week 8. The difference in percentage between the imsidolimab and placebo will be estimated by an unadjusted risk difference in proportions with 95% exact unconditional CIs. This will be performed overall and within each neoplasm therapy stratum (EGFRi/MEKi). The common risk difference will also be tested using a generalized Cochran-Mantel-Haenszel (CMH) test (ANOVA for row means), adjusting for neoplasm therapy (EGFRi/MEKi).

An additional exploratory analysis will be performed by visit, for the proportion of subjects with an improvement of at least 1 grade from baseline in acneiform rash CTCAE grading scale. A repeated measures GEE model with a logit link will be used. The model will include treatment, visit (Weeks 2, 4, 8), treatment by visit interaction, and neoplasm therapy (EGFRi/MEKi) as categorical covariates. 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 95% CI will be reported.

7.5.2.3 Time to First Response of 1 Grade Improvement from Baseline On the Acneiform Rash CTCAE Grading Scale

The Kaplan-Meier method will be used to estimate the quartiles of the survival distribution;[6] 95% Brookmeyer-Crowley CIs will also be calculated.[7]

To compare treatments, the time to first response of 1 grade improvement from baseline on the acneiform rash CTCAE grading scale will be analyzed up through Week 24 using a Cox regression model. Treatment comparisons will be performed using the model, adjusting for neoplasm therapy (EGFRi/MEKi) as the categorical covariate. Estimated adjusted hazard ratios relative to the comparator for each treatment comparison will be displayed along with the associated Wald two-sided 95% CIs and p-values.

Time to first response of 1 grade improvement from baseline on the acneiform rash CTCAE grading scale will be displayed graphically for each treatment using a Kaplan-Meier curve. Subjects who do not experience one grade improvement from baseline on the acneiform rash CTCAE grading scale during the study will be censored at the Week 24 visit. Subjects who withdraw from the study early without experiencing one grade improvement from baseline on the acneiform rash CTCAE grading scale will be censored at the date of withdrawal or the last date of treatment, whichever is later.

Prior to database lock and unblinding, reasons for early discontinuation will be reviewed to assess if the adjustment for competing risks is needed in the Cox regression model.

7.5.2.4 Proportion of Subjects with an Improvement of at Least 1 Grade from Baseline in Acneiform Rash Modified MESTT Grading Scale (Total Score) at Week 8

The frequency and percentage of subjects with at least 1 grade improvement from baseline in acneiform rash modified MESTT grading scale (total score) will be summarized at Week 8. The difference in percentage between the imsidolimab and placebo will be estimated by an unadjusted risk difference in proportions with 95% exact unconditional CIs. This will be performed overall and within each stratum for neoplasm therapy (EGFRi/MEKi) and baseline acneiform rash grade (Grade 2 vs. 3 or 4). The common risk difference will also be tested using a generalized CMH test (ANOVA for row means), adjusting for neoplasm therapy (EGFRi/MEKi) and baseline acneiform rash CTCAE grade (Grade 2 vs. 3 or 4).

An additional exploratory analysis will be performed by visit, for the proportion of subjects with at least 1 grade improvement from baseline in acneiform rash modified MESTT grading scale (total score) using a similar repeated measures GEE model as described in **Section 7.5.2.2**, but adding baseline acneiform rash CTCAE grade (Grade 2 vs. 3 or 4) as a fixed categorical covariate in the model.

7.5.2.5 Time to First Response of 1 Grade Improvement from Baseline on the Acneiform Rash Modified MESTT Grading Scale (Total Score)

Time to first response of 1 grade improvement from baseline on the acneiform rash modified MESTT grading scale (total score) will be analyzed and displayed similarly to the time-to-event analysis on the 1 grade improvement of acneiform rash CTCAE grading scale as described in **Section 7.5.2.3**, but adding baseline acneiform rash CTCAE grade (Grade 2 vs. 3 or 4) as a fixed categorical covariate in the Cox regression model.

7.5.2.6 Proportion of Subjects with an Improvement of at Least 1 Grade from Baseline in Acneiform Rash Modified MESTT Grading Scale (Facial Assessment) at Week 8

The frequency and percentage of subjects with at least 1 grade improvement from baseline in acneiform rash modified MESTT grading scale (facial assessment) will be summarized and analyzed similarly to proportion of subjects with at least 1 grade improvement from baseline in acneiform rash modified MESTT grading scale (total score), as described in **Section 7.5.2.4**. The additional exploratory analysis as described in **Section 7.5.2.4** will also be performed.

7.5.2.7 Time to First Response of 1 Grade Improvement from Baseline on the Acneiform Rash Modified MESTT Grading Scale (Facial Assessment)

Time to first response of 1 grade improvement from baseline on the acneiform rash modified MESTT grading scale (facial assessment) will be analyzed and displayed similarly to the time-to-event analysis on the 1 grade improvement of acneiform rash CTCAE grading scale as described in **Section 7.5.2.3**, but adding baseline acneiform rash CTCAE grade (Grade 2 vs. 3 or 4) as a fixed categorical covariate in the Cox regression model.

7.5.2.8 Change from Baseline in Pruritus NRS at Week 8

Change from baseline in pruritus NRS at Week 8 will be analyzed using a similar MMRM model as specified for the primary endpoint.

7.5.2.9 Percent change from Baseline in Pruritus NRS at Week 8

Percent change from baseline in pruritus NRS at Week 8 will be analyzed using the MMRM approach defined for percent change from baseline in facial inflammatory lesion count at Week 8.

7.5.2.10 Change from Baseline in Pain NRS at Week 8

Change from baseline in pain NRS at Week 8 will be analyzed using a similar MMRM model as specified for the primary endpoint.

7.5.2.11 Percent change from Baseline in Pain NRS at Week 8

Percent change from baseline in pain NRS at Week 8 will be analyzed using the MMRM approach defined for percent change from baseline in facial inflammatory lesion count at Week 8.

7.5.2.12 Change from Baseline in FACT-EGFRi-18 at Week 8

Change from baseline in in FACT-EGFRi-18 at Week 8 will analyzed be using a similar MMRM model as for the primary endpoint.

7.5.3 Exploratory Efficacy Analyses

The change and percent change from baseline in each continuous exploratory variable (change from baseline in facial inflammatory lesion count, facial papule count, facial pustule count, pruritus NRS, pain NRS, IGA, facial IGA, FACT-EGFRi-18, acneiform rash CTCAE grading scale, acneiform rash modified MESTT grading scale for face, scalp, chest, back, and total score, number of nail folds with paronychia, and STIDAT; percent change from baseline in facial inflammatory lesion count, facial papule count, facial pustule count, pruritus NRS, pain NRS, acneiform rash modified MESTT grading scale for total score, and STIDAT) will be analyzed using a similar MMRM model 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 acneiform rash CTCAE grading scale, IGA, facial IGA, and acneiform rash modified MESTT grading scale (face, scalp, chest, and back regions individually) 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. Concordance between the tables will be estimated with a weighted Kappa coefficient and corresponding 95% CI;[8] between-treatment tests for agreement adjusting the strata will be evaluated using a Cochran Q test.[9] An additional exploratory analysis will be performed for the change from baseline in acneiform rash CTCAE grading scale and modified MESTT grading scale (face, scalp, chest, and back) at Week 8 using an ordinal logistic regression model with treatment, acneiform rash CTCAE grade at baseline (Grade 2 vs. 3 or 4), neoplasm therapy (EGFRi/MEKi), and the baseline value of response as categorical covariates. An odds ratio resulting from this model along with 95% CI will be reported.

The time-to-event analysis for 1 grade improvement from baseline on the acneiform rash modified MESTT grading scale for the back, scalp, and chest will be analyzed and displayed similarly the time-to-event analysis on the acneiform rash modified MESTT grading scale (total score), as described in **Section 7.5.2.5**.

The frequency and percentage of subjects for categorical exploratory endpoints related to inflammatory lesion count, acneiform rash CTCAE, acneiform rash modified MESTT (by body region and total score), IGA, facial IGA, pruritus and pain NRS, PGI-S, PGI-C, subjects that do not require dose reduction of EGFRi or MEKi therapy, and rescue medication will be summarized separately by visit. An unadjusted risk difference and its 95% exact unconditional CIs will be estimated between the imsidolimab and placebo groups overall and within each stratum for neoplasm therapy (EGFRi/MEKi) and baseline acneiform rash grade (2 vs. 3 or 4); the common risk difference will also be tested using a generalized CMH test as described in **Section 7.5.2.4**. For PGI-S and PGI-C, the difference in distribution between the imsidolimab and placebo groups will be compared by using a Wilcoxon rank-sum test and Somers'd statistic, which may be interpreted as a generalized risk difference.[2] This will be performed overall and within each stratum for neoplasm therapy (EGFRi/MEKi) and baseline acneiform rash grade (2 vs. 3 or 4).

The effect of rescue medication use on or after Week 4 may also be performed as ad hoc analyses through appropriate methods depending on the pattern of rescue medication use.

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 using the While on Treatment strategy for both ITT and PP Analysis Sets. Data collected following receipt of rescue medication (if any) will be excluded in the analysis.
- Region (US, Europe) and sex (male, female) will be added to the MMRM as fixed categorical effects if this model can converge.
- Site will be added to the MMRM as a fixed categorical effect if this model can converge.
- Placebo multiple imputation 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 (papules and pustules) will be checked by visually inspecting the distribution of the residuals. If the normality assumption is not met, a repeated measures model using generalized estimating equations (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.

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:

- Age groups:
  - [18, 45) years
  - [45, 65) years
  - ≥65 years
- Sex groups:
  - Male
  - Female
- Acneiform rash CTCAE grade at Baseline:
  - Grade 2

  - Grade 3-4
- Duration of acneiform rash at Baseline:
  - < 4 weeks
  - ≥4 weeks
- Neoplasm therapy:
  - EGFRi
  - MEKi
- Route of administration for EGFRi/MEKi related medications
  - Biologic
  - Oral
- Rescue medication used during the treatment period:
  - Yes
  - No

7.6 Pharmacokinetic Analyses

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

Mean trough serum concentrations-time data for samples collected on Days 29, 57, 85 and 113 (4 weeks after the last dose) will be tabulated as well as presented graphically to visually assess time to attainment of steady state. 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. 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. 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 by treatment group for the number of doses received, the number of days of exposure to study treatment, total dose received, total dose expected, and dose intensity. In addition to summary statistics on the dose intensity as a continuous variable, dose intensity will also be categorized into bins: 0-25%, >25-50%, >50-75%, >75-100%, 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 adverse event 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 adverse events (including any AEs reported in the study)
- Serious adverse events
- Adverse events resulting in study treatment discontinuation
- Adverse events leading to withdrawal from study
- Adverse events leading to death

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 versus 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, and weight, will be tabulated by treatment, visit, and time point.

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, QTcB 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. The overall ECG result classified as “normal”, “abnormal, not clinically significant”, or “abnormal, clinically significant” will be summarized by treatment group.

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

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

There is no change from the planned methods in the protocol.

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

1. Chan A, Tan EH. How well does the MESTT correlate with CTCAE scale for the grading of dermatological toxicities associated with oral tyrosine kinase inhibitors? Support Care Cancer. 2011; 19:1667–1674.
2. Edwardes MD, M Baltzan. The generalization of the odds ratio, risk ratio and risk difference to r x k tables. Stat Med. 2000 Jul 30; 19(14):1901-14.
3. Lacouture ME, Maitland ML, Segaert S, et al. A proposed EGFR inhibitor dermatologic adverse event-specific grading scale from the MASCC skin toxicity study group. Support Care Cancer. 2010; 18:509–522.
4. Lui M, Gallo-Hershberg D, DeAngelis C. Development and validation of a patient-reported questionnaire assessing systemic therapy induced diarrhea in oncology patients. Health and Quality of Life Outcomes. 2017; 15:249.
5. Richter C, Trojahn C, Hillmann K, Dobos G, Stroux A, Kottner J, Blume-Peytavi U. Reduction of Inflammatory and Noninflammatory Lesions with Topical Tyrothricin 0.1% in the Treatment of Mild to Severe Acne Papulopustulosa: A Randomized Clinical Trial. Skin Pharmacol Physiol. 2016; 29:1-8.
6. Kaplan, EL, Meier, P. Nonparametric estimation from incomplete observations. J. Amer. Statist. Assoc. 1958; 53(282):457–481.
7. Brookmeyer R, and Crowley J. A Confidence Interval for the Median Survival Time. Biometrics. 1982; 38:29–41.
8. Cohen J. Weighed kappa: Nominal scale agreement with provision for scaled disagreement or partial credit. Psychological Bulletin. 1968; 70(4):213–220.
9. Cochran WG. The Comparison of Percentages in Matched Samples. Biometrika. 1950; 37(3/4):256–266.
10. Shmueli ES, Geva R, Yarom N, et al. Topical doxycycline foam 4% for prophylactic management of epidermal growth factor receptor inhibitor skin toxicity: an exploratory phase 2, randomized, double-blind clinical study. Supportive Care in Cancer. 2019; 27:3027–3033.
11. Wagner LI, Rosenbaum SE, Gandhi M, et al. The development of a Functional Assessment of Cancer Therapy (FACT) questionnaire to assess dermatologic symptoms associated with epidermal growth factor receptor inhibitors (FACT-EGFRI-18). Support Care Cancer. 2013; 21(4):1033-41.

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 History	Medical History Begin 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 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).

Category	Description	Data Handling Rules
	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 (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: o 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). o 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). o 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.

Category	Description	Data Handling Rules
	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 BASEACGR THERAPY; MODEL Y = BASE BASEACGR THERAPY TRT|VISIT /DDFM=KR SOLUTION OUTP=OUT; REPEATED VISIT / TYPE = UN SUBJECT=SUBJECT; LSMEANS TRT|VISIT / PDIFF CL; ODS OUTPUT LSMEANS=MEANS; ODS OUTPUT DIFFS=DIFF; RUN; Where TRT is treatment, VISIT is the study visit number, BASEACGR is acneiform rash CTCAE grade at baseline (Grade 2 vs. 3 or 4), THERAPY is the neoplasm therapy received (EGFRi/MEKi), and BASE is the baseline of outcome variable.
Impute Intermittent Missing using the Monte Carlo Markov Chain (MCMC) approach	PROC MI DATA=ANC_ORIG SEED=20210903 NIMPUTE=100 OUT=LESION_MONO; BY TRT; /*Assuming different treatment has different distribution*/ MCMC CHAIN=MULTIPLE IMPUTE=MONOTONE; /*Only impute intermittent missing values*/ VAR BASE LESION1 – LESION6; /*Impute lesion count from Week 2 to Week 24, with baseline as covariates*/ RUN;
Control-based multiple imputation	PROC MI DATA=LESION_MONO SEED=20210904 NIMPUTE=1 OUT=OUTM1; CLASS TRT01PN SEX BASEACGR THERAPY; BY _IMPUTATION_; VAR AGE TRT01PN SEX BASEACGR THERAPY BASE LESION1 – LESION6; MONOTONE REG (LESION2 – LESION6); MNAR MODEL (LESION1 – LESION6/ MODELOBS = (TRT01PN = '0')); /*Control=Placebo*/ RUN;
Negative binomial with GEE using PROC GENMOD	PROC GENMOD; CLASS SUBJECT TRT VISIT BASEACGR THERAPY;

Test	Template SAS Code for Modeling (SAS Version 9.4)
	MODEL Y= BASE BASEACGR THERAPY TRT|VISIT / LINK=LOG DIST=NEGBIN; REPEATED SUBJECT=SUBJECT / TYPE=UN; LSMEANS TRT|VISIT / DIFF CL; ODS OUTPUT LSMEANDIFFS = LSDIFS ESTIMATES=EST LSMEANS=LSMEANS PARAMETERESTIMATES=PE; Where TRT is treatment, VISIT is the study visit number, BASEACGR is acneiform rash CTCAE grade at baseline (Grade 2 vs. 3 or 4), THERAPY is the neoplasm therapy received (EGFRi/MEKi), and BASE is the baseline of outcome variable.
Logistic Regression with GEE using PROC GENMOD	PROC GENMOD DESCENDING; CLASS SUBJECT TRT VISIT BASEACGR THERAPY; MODEL Y= BASEACGR THERAPY TRT|VISIT / LINK=LOGIT DIST=BIN; REPEATED SUBJECT=SUBJECT / TYPE=UN; LSMEANS TRT|VISIT / DIFF CL; ODS OUTPUT LSMEANDIFFS = LSDIFS ESTIMATES=EST LSMEANS=LSMEANS PARAMETERESTIMATES=PE; Where TRT is treatment, VISIT is the study visit number, BASEACGR is acneiform rash CTCAE grade at baseline (Grade 2 vs. 3 or 4), and THERAPY is the neoplasm therapy received (EGFRi/MEKi).
Ordinal Logistic Regression using PROC LOGISTIC	PROC LOGISTIC; CLASS TRT BASEACGR THERAPY; MODEL Y = TRT BASEACGR THERAPY; RUN; Where Y is the ordinal outcome variable, TRT is treatment, BASEACGR is acneiform rash CTCAE grade at baseline (Grade 2 vs. 3 or 4), THERAPY is the neoplasm therapy received (EGFRi/MEKi).
Cox regression model e.g. for first response of 1 grade improvement from baseline on the acneiform rash CTCAE grading scale	ODS GRAPHICS ON; PROC PHREG PLOTS (OVERLAY)=(SURVIVAL CUMHAZ LOGLOGS); CLASS THERAPY TRT / PARAM=GLM; MODEL TIME*CENSOR(0)=TRT THERAPY; OUT=PRED1 SURVIVAL=_ALL_ / ROWID=SUBJECT; RUN; ODS GRAPHICS OFF; Hazard ratios with Wald two-sided 95% confidence limits for these ratios will also be provided for all treatment comparisons.

Test	Template SAS Code for Modeling (SAS Version 9.4)
	Where TIME is the survival time, TRT is treatment, THERAPY is the neoplasm therapy received (EGFRi/MEKi). See the SAP text regarding censoring rules and survival time.
Kaplan-Meier Survival method model e.g. for first response of 1 grade improvement from baseline on the acneiform rash CTCAE grading scale	PROC LIFETEST METHOD=KM PLOTS = (S) OUTSURV=OUT; TIME TIME*CENSOR(0); STRATA TRT/DIFF=ALL; RUN; Get 95% CI from dataset 'out'. ** event=1; censored=0; See the SAP text regarding censoring rules.
Cochran-Mantel-Haenszel ANOVA statistics (row means score)	PROC FREQ; TABLES STRATA1* STRATA2*TRT*X/CMH2; RUN; Where STRATA1 and STRATA2 are the randomization stratification factors, TRT is treatment, and X is the outcome variable.
Exact unconditional CI	PROC FREQ; TABLES TRT*X/ RISKDIFF(CL=EXACT); 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; TEST SMDCR; RUN; Where TRT is treatment, and X is the outcome variable.
Weighted Kappa and Cochran's Q test	PROC FREQ; WEIGHT COUNT; TABLES STRATA1* STRATA2*TRT*X/AGREE ALPHA=0.1; RUN; Where STRATA1 and STRATA2 are the randomization stratification factors, TRT is treatment, and X is the outcome variable.

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

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

DocUUID : 93a3edcd-2870-4a57-89a7-e204316f6e07