STATISTICAL ANALYSIS PLAN
FOR STUDY ANB019-208

Trial Sponsor:	AnaptysBio, Inc.
Protocol Number:	ANB019-208
IND Number:	136145
EUDRACT Number:	TBD
Investigational Drug:	Anti-interleukin 36 receptor monoclonal antibody
Indication:	Hidradenitis Suppurativa
Drug Number:	ANB019 (imsidolimab)
Dosage Form/Strength/Dose:	2 mL Solution for Injection/200 mg/400 mg, 2 mL Solution for Injection/200 mg/200 mg, 2 mL Solution for Injection/100 mg/200 mg, or 2 mL Solution for Injection/100 mg/100 mg. • Arm 1: Imsidolimab 400 mg on Day 1; 200 mg on Day 29, 57 and 85; 200 mg on Day 113; followed by 200 mg on Days 141, 169 and 197. • Arm 2: Imsidolimab 200 mg on Day 1; 100 mg on Days 29, 57 and 85; 100 mg dose on Day 113; followed by 100 mg on Days 141, 169 and 197. • Arm 3A: Placebo on Days 1, 29, 57, and 85; imsidolimab 400 mg on Day 113; followed by 200 mg on Days 141, 169, and 197. • Arm 3B: Placebo on Days 1, 29, 57, and 85; imsidolimab 200 mg on Day 113; followed by 100 mg on Days 141, 169 and 197.

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

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CHANGE LOG FOR CHANGES MADE AFTER THE INITIAL APPROVAL

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

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

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GLOSSARY OF ABBREVIATIONS

Abbreviation	Term
ADA	Anti-drug antibody
AE	Adverse event
AN	Abscess and inflammatory nodule
AN50	At least 50% reduction in abscess and inflammatory nodule count from baseline
AN75	At least 75% reduction in abscess and inflammatory nodule count from baseline
ATC	Anatomical therapeutic chemical
BDRM	Blinded data review meeting
BMI	Body mass index
CI	Confidence interval
CRF	Case report form
CV	Coefficient of variation
D	Day
DLQI	Dermatology Life Quality Index
ECG	Electrocardiograms
eCRF	Electronic case report form
EOS	End of Study
ET	Early Termination
[redacted]	[redacted]
FCS	Fully Conditional Specification
FSH	Follicle-stimulating hormone
GEE	Generalized estimating equations
H_0	Null hypothesis
H_A	Alternative hypothesis
HiSCR50	Hidradenitis Suppurativa Clinical Response 50
HiSCR75	Hidradenitis Suppurativa Clinical Response 75
HiSQoL	Hidradenitis Suppurativa Quality of Life
Hrs	Hours

GLOSSARY OF ABBREVIATIONS

HS	Hidradenitis Suppurativa
HS-PGA	Hidradenitis Suppurativa Physician Global Assessment
HS-PtGA	Hidradenitis Suppurativa Patient Global Assessment
IHS4	International Hidradenitis Suppurativa Severity Score System
IL	Interleukin
IL-36R	Interleukin 36 receptor
IND	Investigational New Drug
ITT	Intention-to-treat
IWRS	Interactive Web-based Response System
LSM	Least squares mean
MedDRA	Medical Dictionary for Regulatory Activities
Min	Minute
MMRM	Mixed effects model for repeated measures
MAR	Missing at random
NCA	Non-compartmental Analysis
NRS	Numeric rating scale
PGI-B	Patient Global Impression of Bother
PGI-C	Patient Global Impression of Change
PGI-S	Patient Global Impression of Severity
PK	Pharmacokinetic
PP	Per Protocol
PT	Preferred Term
QTcF	Corrected QT interval by Fredericia
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SAS	Statistical analysis system
SC	Subcutaneous/subcutaneously
SD	Standard deviation

GLOSSARY OF ABBREVIATIONS

SoA	Schedule of Activities
SOC	System organ class
SOP	Standard operating procedure
TB	Tuberculosis
TEAE	Treatment-emergent adverse event
Th-17	T-helper 17
TNF	Tumor necrosis factor
W	Week
WHO-DD	World Health Organization Drug Dictionary
WOCBP	Woman of childbearing potential

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1. INTRODUCTION

This Statistical Analysis Plan (SAP) outlines the statistical methods for the display, summary and analysis of data collected within the scope of the latest version of the ANB019-208 Protocol (Amendment 1, dated 24 September 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 and the version of the annotated CRFs dated 22 December 2021.

This study is designed to evaluate the efficacy and safety of ANB019 in the treatment of subjects with Hidradenitis Suppurativa (HS). (See Protocol **Sections 2.1** to **2.3** for details).

2. STUDY OBJECTIVES

2.1 Primary Objective

- To evaluate the efficacy of imsidolimab in subjects with HS

2.2 Secondary Objectives

- To evaluate the safety of imsidolimab in subjects with HS
- To further determine the efficacy of imsidolimab on HS signs and symptoms in subjects with HS

2.3 Exploratory Objectives

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

3. STUDY DESIGN

3.1 Study Design

This study is a Phase 2, multicenter, randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of imsidolimab in adult subjects with hidradenitis suppurativa (HS). This study will also characterize the pharmacokinetic (PK) profile of imsidolimab and explore the immune response to imsidolimab in subjects with HS.

To be eligible for this study, subjects must have a clinically confirmed diagnosis of HS with a disease duration of at least 6 months before Day 1. In addition, subjects will have the following characteristics at Screening and Day 1:

1) HS lesions present in at least 2 distinct anatomical areas, 1 of which must be Hurley Stage II (i.e., single or multiple, widely separated, recurrent abscesses with tract formation and cicatrization) or Hurley Stage III (i.e., diffuse or near diffuse involvement, or multiple interconnected tracts and abscesses across the entire area);

2) total abscess and inflammatory nodule (AN) count of ≥ 5;

3) ≤ 20 draining fistulas.

Randomization will be stratified based on Hurley Stage at baseline (Stage II or III).

The maximum study duration per subject is approximately 44 weeks, which includes a screening period of up to 30 days, followed by a 16-week placebo-controlled period, a 16-week treatment extension period, and an 8-week follow up period. The placebo-controlled period ends at Day 113 (Week 16) and the treatment extension period starts when study treatment is administered at the Week 16 visit. Of note, during the extension period all subjects will receive imsidolimab but their treatment will remain blinded.

During the placebo-controlled period, eligible subjects will be randomized (1:1:1) to receive either imsidolimab (at 1 of 2 different regimens) or placebo, subcutaneously (SC) administered on 4 occasions: Day 1, Day 29 (Week 4), Day 57 (Week 8), and Day 85 (Week 12).

The treatment arms during the placebo-controlled period will be as follows:

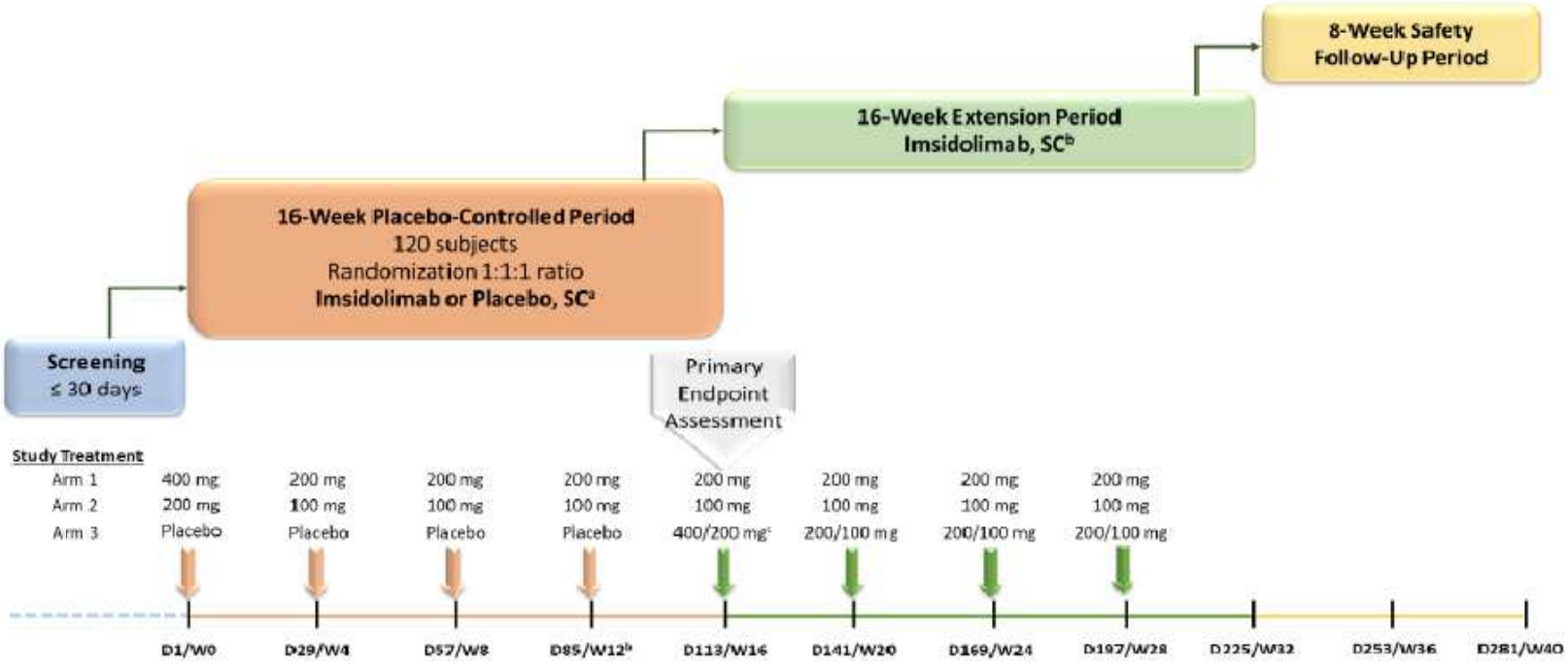
- Imsidolimab 400 mg on Day 1, followed by 200 mg on Days 29, 57, and 85
- Imsidolimab 200 mg on Day 1, followed by 100 mg on Days 29, 57, and 85
- Placebo on Days 1, 29, 57, and 85

During the extension period, all subjects will receive imsidolimab, SC administered on 4 occasions:

- 400 mg dose of imsidolimab on Day 113 for subjects assigned to placebo arm 3A during the placebo-controlled period, followed by 200 mg doses on Days 141, 169, and 197
- 200 mg dose of imsidolimab on Day 113 for subjects assigned to placebo arm 3B during the placebo-controlled period, followed by 100 mg doses on Days 141, 169, and 197
- 200 mg dose of imsidolimab on Days 113, 141, 169, and 197 for subjects assigned to imsidolimab Arm 1 during the placebo-controlled period
- 100 mg dose of imsidolimab on Days 113, 141, 169, and 197 for subjects assigned to imsidolimab Arm 2 during the placebo-controlled period

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

Figure 1 Study Schema



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

[a] During the placebo-controlled period, subjects will be randomized (1:1:1) to receive either imsidolimab (at 1 of 2 different regimens) or placebo, SC administered on 4 occasions: 1) 400-mg dose of imsidolimab on Day 1, 200-mg dose of imsidolimab on Days 29, 57, and 85; 2) 200-mg dose of imsidolimab on Day 1, 100-mg dose of imsidolimab on Days 29, 57, and 85; 3) placebo on Days 1, 29, 57, and 85.

[b] The placebo-controlled period ends on Day 113 (week 16) visit, before study treatment administration. Pre-dose assessments performed on Day 113 (week 16) will be used to evaluate the primary and secondary efficacy endpoints, as well as the safety, tolerability, and immune response of imsidolimab compared with placebo. The extension period starts when the study treatment is administered on Day 113 (week 16) visit. All subjects will receive imsidolimab SC administered on 4 occasions during the extension period.

[c] Subjects in Arm 3 randomized to placebo during the placebo-controlled period will be randomized 1:1 to receive either a 400-mg dose of imsidolimab on Day 113, followed by a 200-mg dose on Days 141, 169, and 197; or a 200-mg dose of imsidolimab on Day 113, followed by a 100-mg dose of imsidolimab on Days 141, 169, and 197. Subjects randomized to imsidolimab in Arms 1 and 2 during the placebo-controlled period will continue to receive the same maintenance dose of imsidolimab (200 mg or 100 mg) on Days 113, 141, 169, and 197.

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 1:1:1 ratio to receive imsidolimab (at 1 of 2 different regimens) or placebo. Subjects randomized to placebo will be randomized in a 1:1 ratio to receive imsidolimab (at 1 of 2 different regimens) in the extension period which begins on Day 113. Randomization will be stratified based on Hurley Stage at baseline (Stage II or III). Subjects who receive the wrong treatment will be analyzed according to the treatment they were supposed to be randomized to in the efficacy analyses; though, in the safety analyses, will be analyzed according to the treatment they actually received.

3.3 Hypothesis Testing

The primary analysis for this study is to compare the mean change from baseline in AN count for imsidolimab vs. placebo at Week 16 of the double-blind treatment period, at a two-sided alpha = 0.10 level. The following hypothesis test will be done separately for each imsidolimab dose arm.

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

Treatment comparisons may be performed for the secondary or exploratory endpoints and will be considered exploratory in nature. Two-sided p-values and 90% confidence intervals will be produced.

3.4 Primary Analysis

A primary analysis will be performed when all subjects have completed Week 16 or have exited study prior. The purpose of this primary analysis is to assist AnaptysBio executive management in making decisions for potential future development of this compound. The primary and secondary efficacy endpoints (defined in **Section 6.2**) of this study will be evaluated in the primary analysis. Listings of the primary and secondary efficacy data will also be provided. Subject disposition, demographics and baseline characteristics will be tabulated and listed as detailed in **Section 7.2 and 7.4.** 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 primary analysis.

Generation of Blinded Reports

In the primary analysis, blinded tables, listings and graphs will be produced by the [redacted] 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 [redacted] standard operating procedures (SOPs) and AnaptysBio 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. Only the Unblinded Statistician and the Unblinded Programmer responsible for the primary analysis will be aware of the treatment assigned to a subject. The Unblinded Statistician and Unblinded Programmer will both be appointed by [redacted] a company external to AnaptysBio. The Unblinded Statistician and Unblinded Programmer 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 will function independently of the investigators and AnaptysBio 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 an Unblinded Data Management Plan.

The Unblinded Statistician and Unblinded Programmer will be in possession of unblinding treatment codes produced for the Interactive Web-based Response System, which is used to randomize subjects to treatment. Upon successful generation of the blinded versions of the datasets and analyses, the Unblinded Statistician and Unblinded Programmer 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 AN count at Week 16. The null hypothesis (H_0) to be tested is that the mean change from baseline in AN count is the same for imsidolimab and placebo. This will be tested separately for each imsidolimab dose arm. Assuming a common standard deviation (SD) of 8.2, and a 10% dropout rate, an enrollment of 40 subjects (leaving 36 after dropout) in each of imsidolimab treatment arms and 40 subjects (leaving 36 after dropout) in the placebo arm will have at least 80% power to detect the overall treatment effect for a two sample t-test using a 2-sided significance level of α=0.10, where the difference in the mean change from baseline between the imsidolimab and placebo group is assumed to be 4.9. The common standard deviation assumption was based on the PIONEER 1 study (Kimball 2014). No adjustments to α are needed in this study for primary analysis or multiple comparisons.

3.6 Study Procedures and Schedule of Activities

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

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Table 1 Schedule of Activities

	Screening Period			Placebo-Controlled Period			Extension Period			Follow-Up Period		
Study visit Window (days)	**(-30 to -1)**	**D1**	**D29 (W4) (±4)**	**D57 (W8) (±4)**	**D85 (W12) (±4)**	**D113 (W16)[a] (±4)**	**D141 (W20) (±4)**	**D169 (W24) (±4)**	**D197 (W28) (±4)**	**D225 (W32) (±4)**	**D253 (W36) (±4)**	**D281 (W40) EOS/ ET[b] (±5)**
Informed consent	X											
Demographics	X											
Fitzpatrick skin type classification[c]	X											
Inclusion and exclusion criteria	X	X										
Medical and surgical history	X	X										
Smoking History[c]		X										
Height and weight[d]	X	X				X				X		X
Complete physical examination[e]	X	X	X	X	X	X				X		X
Vital signs[f]	X	X	X	X	X	X	X	X	X	X	X	X
12-Lead ECG[g]	X	X	X			X	X			X		X
Chest X-ray[h]	X											
Hematology and biochemistry	X	X	X	X	X	X	X	X	X	X	X	X

	Screening Period			Placebo-Controlled Period			Extension Period			Follow-Up Period		
Study visit **Window (days)**	**(-30 to -1)**	**D1**	**D29 (W4) (±4)**	**D57 (W8) (±4)**	**D85 (W12) (±4)**	**D113 (W16)[a] (±4)**	**D141 (W20) (±4)**	**D169 (W24) (±4)**	**D197 (W28) (±4)**	**D225 (W32) (±4)**	**D253 (W36) (±4)**	**D281 (W40) EOS/ ET[b] (±5)**
Urinalysis	X	X	X		X	X	X		X	X		X
TB screening (QuantiFERON®-TB Gold test)	X											
Viral serology	X											
FSH[i]	X											
Serum pregnancy test (WOCBP only)[i]	X											X
Urine pregnancy test (WOCBP only)[i]		X	X	X	X	X	X	X	X	X	X	
HS Pain NRS, PGIB, PGIS, HS-PtGA, DLQI, HiSQoL[j]		X	X	X	X	X	X	X	X	X	X	X
PGIC[j]			X	X	X	X	X	X	X	X	X	X
HS-PGA[j]	X	X	X	X	X	X	X	X	X	X	X	X
Hurley Stage[j]	X	X				X				X		X
AN count, draining fistula count, HiSCR[j]	X	X	X	X	X	X	X	X	X	X	X	X
IHS4[j]		X	X	X	X	X	X	X	X	X	X	X

	Screening Period			Placebo-Controlled Period			Extension Period			Follow-Up Period		
Study visit Window (days)	**(-30 to -1)**	**D1**	**D29 (W4) (±4)**	**D57 (W8) (±4)**	**D85 (W12) (±4)**	**D113 (W16)[a] (±4)**	**D141 (W20) (±4)**	**D169 (W24) (±4)**	**D197 (W28) (±4)**	**D225 (W32) (±4)**	**D253 (W36) (±4)**	**D281 (W40) EOS/ ET[b] (±5)**
Blood samples for PK[k]		X	X	X	X	X	X	X	X	X	X	X
Blood samples for ADA[k]		X	X	X	X	X	X			X		X
Tape strips collection[l]		X	X			X				X		
Drainage fluid collection[l]		X	X	X	X	X	X	X	X	X	X	X
Photography[m]	X	X	X			X				X		X
Randomization[n]		X				X						
Study treatment administration[o]		X	X	X	X	X	X	X	X			
AE/SAE review	X						Continuously					
Concomitant medication review[p]	X						Continuously					

Abbreviations: ADA, anti-drug antibody; AE, adverse event; AN, abscess and inflammatory nodule; D, day; DLQI, Dermatology Life Quality Index; ECG, electrocardiogram; EOS, end of study; ET, early termination; FSH, follicle stimulating hormone; HiSCR, Hidradenitis Suppurativa Clinical Response; HiSQoL, Hidradenitis Suppurativa Quality of Life; HS, Hidradenitis Suppurativa; HS-PGA, Hidradenitis Suppurativa Physician's Global Assessment; HS-PtGA, Hidradenitis Suppurativa Patient's Global Assessment; IHS4, International Hidradenitis Suppurativa Severity Score System; NRS, Numeric Rating Scale; PGI-B, Patient Global Impression of Bother; PGI-C, Patient Global Impression of Change; PGI-S, Patient Global Impression of Severity; PK, pharmacokinetics; SAE, serious adverse event; SC, subcutaneously; SoA, Schedule of Activities; TB, tuberculosis; W, week; WOCBP, woman of childbearing potential.

a All subjects will receive imsidolimab during the extension period starting on Day 113 (Week 16) visit until Day 197 (Week 28) visit. The placebo-controlled period ends on Day 113 (Week 16) visit, before study treatment administration. The extension period starts when the study treatment is administered on Day 113 (Week 16) visit.

b The ET visit will include all procedures to be done at the EOS visit (Day 281/Week 40 visit).

c If the Fitzpatrick skin type and/or Smoking history are not collected at screening and D1 respectively, they may be collected at any subsequent visit.

d Height to be measured at screening only for subjects.

e Refer to Protocol **Section 8.2.4** for details regarding the complete physical examination.

f Refer to Protocol **Section 8.2.5** for details and instructions regarding vital signs.
g 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.
h Bidirectional posterior-anterior view and lateral view chest X-ray will be performed at screening. If a chest X-ray was performed within 6 months of screening and no clinically significant abnormality was observed, it can be skipped at screening.
i The FSH testing is performed for women not of childbearing potential who are postmenopausal (at least 12 months of amenorrhea without an alternative medical cause). Additional pregnancy testing may be performed whenever a menstrual cycle is missed or when pregnancy is otherwise suspected. Refer to **Appendix 11** for details and instructions regarding clinical laboratory parameters.
j Refer to Protocol **Section 8.1** for details and instructions on AN count, draining fistula count, HiSCR, Hurley Stage, HS-PGA, IHS4, Pain NRS, PGI-C, PGI-S, DLQI, HS-PtGA, and HiSQoL. From Screening through Week 32, subjects will not be permitted to use any analgesics related to HS pain within 24 hours of a scheduled study visit. Subjects may use analgesics after the questionnaires are completed at the study visit.
k Sample for PK will be collected pre-dose. See Protocol **Table 5** for PK and ADA sample collection time points.
l Tape stripping will be performed for all randomized subjects as part of this study (not optional). Tape strips will be collected from non-lesional and lesional skin at Day 1 and Week 16 and from lesional skin at Week 4 and Week 32. Drainage fluid may be collected (optional) at any visit after Screening in which HS lesional drainage is present, and stored for future biomarker analysis.
m Photography (of representative lesion[s], fistulas, and scarring) is an optional procedure for all subjects at each of the specified visits at selected site. Two images from two distinct regions of highest density inflammatory nodules/abscesses/fistulas should be taken at baseline if possible. The anatomic regions should be identifiable from the images. These regions should be recorded and consistently photographed throughout the duration of the study if possible.
n Starting at Day 113 (Week 16), subjects who received placebo during the placebo-controlled period will be randomized 1:1 to receive imsidolimab at 1 of 2 different regimens. Subjects who received imsidolimab during the placebo-controlled period will not be randomized at the Week 16 visit.
o During the placebo-controlled period, subjects will receive either imsidolimab or placebo SC administered as follow according to randomization arm:1) 400-mg dose of imsidolimab on Day 1; followed by 200-mg dose of imsidolimab on Days 29, 57, and 85; 2) 200-mg dose of imsidolimab on Day 1; followed by a 100-mg dose of imsidolimab on Days 29, 57, and 85; 3) placebo. The placebo-controlled period ends at the Day 113 (Week 16) visit, before study treatment administration. During the extension period, subjects assigned to imsidolimab during the placebo-controlled period will continue to receive the same maintenance dose of imsidolimab, 200 mg or 100 mg. Subjects assigned to placebo during the placebo-controlled period will receive either a 400-mg dose of imsidolimab on Day 113, followed by 200-mg doses of imsidolimab on Days 141, 169, and 197; or a 200 mg dose of imsidolimab on Day 113, followed by 100-mg doses of imsidolimab on Days 141, 169, and 197.
p At screening, prior medications should be reviewed and documented. Refer to Protocol **Section 6.5**.

4. DATA AND ANALYTICAL QUALITY ASSURANCE

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

The study endpoints and analytic approaches are both prospectively defined and documented in the protocol and in this SAP. The SAP will be finalized prior to the primary analysis data snapshot, and protocol deviations will be identified and decisions for inclusion and exclusion of subjects from the Per-Protocol Analysis Set (**Section 5.4)** will be made prior to the final database lock and data analysis.

5. ANALYSIS SETS

5.1 Intent-to-Treat Analysis Set

The Intent-to-Treat (ITT) analysis set will include all randomized subjects. In this analysis set, treatment will be assigned based upon the treatment arm to which subjects were randomized regardless of which treatment they receive. ITT analysis set will be used for primary, secondary, and exploratory efficacy analyses.

5.2 Safety Analysis Set

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

5.3 Extension Analysis Set

The extension analysis set is a subset of the safety analysis set who receive at least 1 dose of imsidolimab in the extension period. The extension analysis set will be used for summarizing both efficacy and safety data for those subjects who entered the extension period. Subjects will be analyzed as treated.

5.4 Per Protocol Analysis Set

The per protocol analysis set will include all subjects in the ITT analysis set who do not have important protocol deviations that would affect the evaluation of the primary efficacy endpoint. Further details on the determination of protocol deviations are described in **Section 7.3.**

5.5 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 or events

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 primary analysis.

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 [redacted] and AnaptysBio at the blinded data review meeting (BDRM) for inclusion/exclusion into the PK Analysis Set.

5.6 Analysis Sets for Analyses

Demographics will be summarized on the ITT Analysis Set; Per Protocol (PP), PK, Extension, and Safety Analysis Sets will be tabulated only if they are different from ITT Analysis Set for demographics. Extent of exposure, safety, biomarker, and anti-drug antibodies (ADA) data will be summarized on the Safety Analysis Set. Efficacy analyses will be performed on the ITT and (where indicated) PP Analysis Sets.

6. SPECIFICATION OF ENDPOINTS AND VARIABLES

Two baselines will be defined: study baseline and imsidolimab baseline. The study baseline will be the last available measurement taken prior to the first dose of study treatment (either imsidolimab or placebo). The imsidolimab baseline will be the last available measurement taken prior to the first dose of imsidolimab. For subjects assigned to placebo in the placebo-controlled period of this study who continue into the extension period, the imsidolimab baseline will be the value prior to receiving the first dose in the extension period.

For numerical values, change from baseline will be calculated as the difference between the value of interest at a specified visit and the corresponding baseline value.

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

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

6.1 Demographic and Baseline Characteristics

6.1.1 Demography and Physical Characteristics

Subject demographics and baseline disease characteristics 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
- Sex
- Race
- Ethnicity (Hispanic or non-Hispanic)
- Country
- Woman of childbearing potential (yes or no)
- Smoking history (never, current, former)
- Prior history of anti-tumor necrosis factor (TNF; Humira) use (yes or no)
- Weight (kg)

- Height (cm)
- Body mass index (BMI; kg/m^2)
- Hurley Stage at randomization
- Fitzpatrick skin type
- Hidradenitis Suppurativa Patient Global Assessment (HS-PtGA) score at baseline
- Dermatology Life Quality Index (DLQI) at baseline
- Hidradenitis Suppurativa Quality of Life (HiSQoL) score at baseline
- Hidradenitis Suppurativa Physician Global Assessment (HS-PGA) score at baseline
- Total abscess and inflammatory nodule (AN) count at baseline
- Total abscess count
- Total inflammatory nodule count
- International Hidradenitis Suppurativa Severity Score System (IHS4) at baseline
- Draining fistula count at baseline
- Worst pain numeric rating scale (NRS) at Baseline (grade 0 to grade 10)
- Average pain NRS at Baseline (grade 0 to grade 10)
- Patient global impression of severity (PGI-S) at Baseline (no activity, mild, moderate, severe)
- Patient global impression of bother (PGI-B) at Baseline

6.1.2 Medical and Surgical History

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

6.1.3 Prior, Concomitant, and Rescue Medications/Treatments

All medications used to treat HS disease conditions within 6 months prior to Day 1, any prior use of adalimumab (Humira), and all concomitant therapy taken by the patient within 4 weeks prior to enrollment or while on study will be recorded on the Prior or Concomitant Medications CRF page. Use of Humira to treat HS will be identified by concomitant medication records having the World Health Organization Drug Dictionary (WHO-DD) medical coding preferred name “Adalimumab”.

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. Prior and concomitant medications are those which start before the first study treatment but are ongoing or which end after first study treatment.

Rescue medications taken by the subject to control intolerable symptoms of HS during the study will be recorded on the Rescue Medication CRF page.

Rescue procedures performed to control intolerable symptoms of HS will be recorded on the HS Procedures CRF page.

Coding: Verbatim medication or treatment terms will be coded by [redacted] and will be assigned a preferred name and an Anatomical Therapeutic Chemical Class (ATC) term using the version of the WHO-DD 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 names will be coded.

6.2 Efficacy

Endpoints analyzing the placebo-controlled data will use the last pre-dose assessment for all visits and for all study arms. The extension period starts at the Week 16 dose, and endpoints analyzing the extension period data will include pre-dose results from Week 16 as the imsidolimab baseline for the placebo arms, as well as pre-dose results from Weeks 20, 24, and 28, and follow-up results (no dose) from Weeks 32, 36, and 40 for all study arms.

6.2.1 Study Day and Visit Window Definitions

Efficacy data obtained from unscheduled visits [not including the End of Study visit] will be allocated to the scheduled visit corresponding to the visit window they fall in as specified in **Table 2**. Efficacy data will be analyzed based on the nominal visits and nominal time points. If there is no pre-dose assessment for the window, then the closest post-dose assessment may be used instead. Only if the data from the nominal visit or time point is missing or falls outside the visit window will data from unscheduled visits for the same nominal visit or time point be used in analysis. Unscheduled visits will only be considered for use at an analysis time point if they fall within the respective window. If more than one unscheduled visit exists in a given window, the measurement closest to, but not after, the nominal day will be used in analysis. Efficacy data from scheduled and unscheduled visits will be listed.

Table 2 Analysis Visit Windows

Study Period	Nominal Visit	Nominal Day	Visit Window (day)
Screening	Screening	-30 to -1	-30 to -1
Placebo-Controlled, Double-Blind	Day 1	1	1 (Pre-dose)
	Week 4	29	1 (Post-dose) to 42 (Pre-dose)
	Week 8	57	43 to 70 (Pre-dose)
	Week 12	85	71 to 108 (Pre-dose)
	Week 16	113	109 to 136 (Pre-dose)
Treatment Extension	Week 16	113	109 to 136 (Pre-dose)
	Week 20	141	137 to 164 (Pre-dose)
	Week 24	169	165 to 192 (Pre-dose)
	Week 28	197	193 to 220 (Pre-dose)
	Week 32	225	221 to 248
	Week 36	253	249 to 275

	Week 40	281	276 to 286

Study Day and Day of Assessment or Event definitions are provided in **Appendix 1**.

6.2.2 Primary Efficacy Variable

The primary endpoint for this study is the **change from baseline in abscess and inflammatory nodule (AN) count at Week 16**. The AN count is defined as the sum of the number of abscesses and inflammatory nodules (from all locations) from the CRF. For the change from baseline in AN count, the difference in AN count taken between Week 16 and baseline will be computed for each treatment group and overall. The AN count will be assessed at the visits specified in the Schedule of Activities in **Section 3.6**.

6.2.3 Secondary Efficacy Variables

The secondary efficacy endpoints are as follows:

- **Percent change from baseline in AN count at Week 16**
- **Proportion of subjects achieving Hidradenitis Suppurativa Clinical Response 50 (HiSCR50) at Week 16**

  The proportion of subjects with at least a 50% decrease from baseline AN count, and no increase in abscesses or draining fistulas in comparison to baseline (HiSCR50) at Week 16 will be calculated for each treatment group as follows:

  A responder HiSCR50 is defined as a subject with

  a) at least a 50% decrease in AN count from Baseline, and
  b) no increase in abscess count relative to Baseline, and
  c) no increase in draining fistula count relative to Baseline

  Having HiSCR50 data at Week 16 is defined as a subject who is either a responder HiSCR50 or can be confirmed to be a non-responder based on assessed data. Then, the proportion of subjects achieving HiSCR50 is defined as the following ratio:

$$\frac{\#\ of\ subjects\ in\ treatment\ group\ achieving\ HiSCR50\ responder\ status}{\#\ of\ subjects\ in\ treatment\ group\ having\ HiSCR50\ data\ at\ Week\ 16}$$

- **Change from baseline in worst HS Pain NRS scores at Week 16**
- **Percent change from baseline in worst HS Pain NRS scores at Week 16**
- **Change from baseline in average HS Pain NRS scores at Week 16**

- **Percent change from baseline in average HS Pain NRS scores at Week 16**

6.2.4 Exploratory Efficacy Variables

The exploratory efficacy endpoints are as follows:

- **Change from Baseline in AN count at Weeks other than Week 16**
- **Percent change from Baseline in AN count at Weeks other than Week 16**
- **Proportion of subjects achieving AN50 at each visit**

  The number of subjects with at least a 50% decrease from baseline in AN count will be calculated at each visit**.**

$$\frac{\#\ of\ subjects\ in\ treatment\ group\ with\ [\frac{(AN\ count\ at\ baseline - AN\ count\ at\ week\ x)}{(AN\ count\ at\ baseline)}] \geq 50\%}{\#\ of\ subjects\ in\ treatment\ group\ with\ AN\ count\ at\ Week\ x}$$

- **Proportion of subjects achieving AN75 at each visit**

  For each treatment group, the number of subjects with at least a 75% decrease from baseline in AN count will be calculated at each visit. The proportion of such subjects will be calculated for each treatment group at each visit as:

$$\frac{\#\ of\ subjects\ with\ [\frac{(AN\ count\ at\ baseline - AN\ count\ at\ week\ x)}{(AN\ count\ at\ baseline)}] \geq 75\%}{\#\ of\ subjects\ in\ treatment\ group\ with\ AN\ count\ at\ Week\ x}$$

  Proportion of subjects experiencing flare, defined as a $\geq$ 25% increase in AN count with an absolute increase in AN count of $\geq$ 2 relative to Baseline at each visit

  The proportion of subjects experiencing flare will be calculated for each treatment group as follows:

$$\frac{\#\ of\ subjects\ in\ treatment\ group\ experiencing\ flare\ at\ Week\ x}{\#\ of\ subjects\ in\ treatment\ group\ with\ flare\ assessed\ at\ Week\ x}$$

- **Change from baseline in abscess count at each visit**
- **Change from baseline in inflammatory nodule count at each visit**
- **Change from baseline in draining fistula count at each visit**
- **Percent change from baseline in draining fistula count at each visit (for subjects who had non-zero draining fistula counts at baseline)**

- **Change from baseline in calculated composite of abscess, inflammatory nodule, and draining fistula total count at each visit**
- **Percent change from baseline in calculated composite of abscess, inflammatory nodule, and draining fistula total count at each visit**
- **Proportion of subjects achieving HiSCR50 at visits other than Week 16**

  The proportion of subjects with at least a 50% decrease from baseline AN count, and no increase in abscesses or draining fistulas in comparison to baseline (HiSCR50) at visits other than Week 16 will be calculated for each treatment group using the formula in **Section 6.2.3**, but with 'Week 16' replaced with 'Week x'**.**
- **Proportion of subjects achieving Hidradenitis Suppurativa Clinical Response 75 (HiSCR75) at each visit**

  The proportion of subjects with at least a 75% decrease from baseline AN count, and no increase in abscesses or draining fistulas in comparison to baseline (HiSCR75) at visits other than Week 16 will be calculated for each treatment group, with HiSCR75 data defined as in **Section 6.2.3**, but with 'Week 16' replaced with 'Week x', and with 50 replaced with 75.

- **Proportion of subjects achieving an HS-PGA of inactive (0) or almost inactive (1) at each visit**

  For each treatment group, the number of subjects achieving an HS-PGA of inactive (0) or almost inactive (1) will be calculated at each visit. The proportion of such subjects will be calculated for each treatment group at each visit as:

$$\frac{\#\ of\ subjects\ in\ treatment\ group\ achieving\ an\ HS\text{-}PGA\ of\ inactive\ (0)\ or\ almost\ inactive\ (1)\ at\ Week\ x}{\#\ of\ subjects\ in\ treatment\ group\ with\ HS\text{-}PGA\ score\ at\ Week\ x}$$

- **Proportion of subjects with at least 2-point decrease in HS-PGA from baseline at each visit**

  This endpoint measures a 2-point decrease in HS-PGA score at a given time point compared to baseline. For each treatment group, the number of subjects with at least 2-point decrease in HS-PGA will be calculated at each visit. The proportion of such subjects will be calculated for each treatment group at each visit as:

$$\frac{\#\ of\ subjects\ in\ treatment\ group\ with\ at\ least\ 2\ point\ decrease\ in\ HS\text{-}PGA\ at\ Week\ x}{\#\ of\ subjects\ in\ treatment\ group\ with\ baseline\ HS\text{-}PGA\ score \geq 2\ and\ HS\text{-}PGA\ score\ at\ Week\ x}$$

- **Change from Baseline in HS-PGA at each visit**
- **Change from Baseline in calculated composite of abscesses, draining fistulas, and inflammatory and non-inflammatory nodules at each visit**

The change from baseline in calculated composite of abscesses, draining fistulas, and inflammatory and non-inflammatory nodules at Week x will be calculated as the sum of abscesses, draining fistulas, and inflammatory and non-inflammatory nodules at the corresponding visit minus the sum of abscesses, draining fistulas, and inflammatory and non-inflammatory nodules at baseline.

- **Change from baseline in average HS pain NRS at visits other than Week 16**

  The intensity of HS average pain will be assessed using numeric rating scale (NRS). The average HS pain NRS will be assessed at the visits specified in the Schedule of Activities in **Section 3.6.** Subjects will be asked to assign a numerical score representing the average intensity over the last 7 days of their HS pain symptoms on a scale from 0 (no symptoms) to 10 (worst imaginable symptoms).

  Change from baseline will be calculated as the difference between the HS average pain NRS at Weeks x minus the corresponding baseline value.

- **Percent change from baseline in average HS pain NRS at visits other than Week 16**
- **Change from baseline in worst HS pain NRS at visits other than Week 16**

  The intensity of HS worst pain will be assessed using NRS. The worst pain NRS will be assessed at the visits specified in the Schedule of Activities in **Section 3.6.** Subjects will be asked to assign a numerical score representing the HS worst pain intensity over the last 24 hours on a scale from 0 (no symptoms) to 10 (worst imaginable symptoms).

  Change from baseline will be calculated as the difference between the HS worst pain NRS at Weeks x minus the corresponding baseline value.

- **Percent change from baseline in worst HS pain NRS at visits other than Week 16**
- **Proportion of subjects with at least 3-point decrease in worst HS Pain NRS from baseline at each visit**

  For each treatment group, the number of subjects with at least a 3-point decrease in worst HS Pain NRS will be calculated at each visit. The proportion of such subjects will be calculated for each treatment group at each visit as:

$$\frac{\#\ of\ subjects\ in\ treatment\ group\ with\ at\ least\ 3\ point\ decrease\ from\ baseline\ in\ worst\ HS\ Pain\ NRS\ at\ Week\ x}{\#\ of\ subjects\ in\ treatment\ group\ with\ baseline\ worst\ HS\ Pain\ NRS\ score \geq 3}$$

- **Proportion of subjects with at least 3-point decrease average HS Pain NRS from baseline at each visit**

  This endpoint measures a 3-point decrease in average HS Pain NRS at a given time point compared to baseline. For each treatment group, the number of subjects with at least a 3-point decrease in average HS Pain NRS will be calculated at each visit. The proportion of such subjects will be calculated for each treatment group at each visit as:

$$\frac{\#\ of\ subjects\ in\ treatment\ group\ with\ at\ least\ 3\ point\ decrease\ from\ baseline\ in\ average\ HS\ Pain\ NRS\ at\ Week\ x}{\#\ of\ subjects\ in\ treatment\ group\ with\ baseline\ average\ HS\ Pain\ NRS\ score \geq 3}$$

- **Proportion of subjects requiring rescue medication or treatment at each visit**

  For each treatment group, the number of subjects receiving rescue medication or treatment (as defined in **Section 6.1.3**) will be calculated at each visit. The proportion of such subjects will be calculated for each treatment group at each visit as:

$$\frac{\#\ of\ subjects\ in\ treatment\ group\ requiring\ rescue\ medication\ or\ treatment\ by\ Week\ x}{\#\ of\ subjects\ in\ treatment\ group\ at\ Week\ x}$$

- **Change from baseline in DLQI scores at each visit**

  The Dermatology Life Quality Index (DLQI) questionnaire is a simple 10-question validated questionnaire (**Finlay, 1994**). These will be assessed at the visits specified in the Schedule of Activities in **Section 3.6.**. Each item is assigned a value from 0 = not at all to 3 = very much and the score is the sum of the individual items (range from 0 to 30). Additional scoring details are below (Cardiff University School of Medicine, 2021):

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

  Change from baseline in DLQI at each visit will be calculated as the difference between the DLQI at Week x minus the corresponding baseline value.

- **Change from Baseline in IHS4 score at each visit**

  The International Hidradenitis Suppurativa Severity Score System (IHS4) is a composite of the number of nodules, abscesses, and draining tunnels. The IHS4 score is calculated at each visit as:

$$(\#\ of\ nodules\ at\ Week\ x) + 2 * (\#\ of\ abscesses) + 4 * (\#\ of\ draining\ tunnels)$$

  The resulting score is labeled as:

  - ≤ 3 is Mild HS;
  - 4-10 is Moderate HS;
  - ≥ 11 is Severe HS

  The change from baseline in IHS4 score at Week x will be calculated as IHS4 at the corresponding visit minus IHS4 at baseline.

- **Change from Baseline in HiSQoL score at each visit**

  The Hidradenitis Suppurativa Quality of Life (HiSQoL) is a patient-reported 17-item questionnaire aimed to measure how much HS has affected the patient's quality of life during the past 7 days. It will be assessed at the visits specified in the Schedule of Activities in **Section 3.6.** Each item is scored as Extremely, Very Much, Moderately, Slightly, and Not at All (4, 3, 2, 1, and 0, respectively). Scores range from 0 to 68, with higher scores representing a more severe disease impact. If a single question item is missing a value from the eCRF, that question item is scored as Not at All (0). If more than one question item is missing at a given visit for a subject, the entire questionnaire is considered missing.

  The change from baseline in HiSQoL score at Week x will be calculated as HiSQoL at the corresponding visit minus HiSQoL at baseline.

- **Change from Baseline in HS-PtGA score at each visit**

  The Hidradenitis Suppurativa Patient Global Assessment (HS-PtGA) is a single-item questionnaire that asks the subject to assess how HS has influenced their quality of life. Scores are on a 5-point scale from 'Not at all' to 'Extremely', with higher scores indicating more severe impact on quality of life. The change from baseline in HS-PtGA score at Week x will be calculated as HS-PtGA at the corresponding visit minus HS-PtGA at baseline.

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

  The Hidradenitis Suppurativa Patient Global Assessment (HS-PtGA) is a single item, self-administered questionnaire, which asks the patient to rate how HS has influenced their quality of life ("Extremely" to "Not at all").

  For each treatment group, the number of subjects in each response category for the HS-PtGA will be calculated at each visit specified in the Schedule of Activities in **Section 3.6**. The proportion of such subjects will be calculated for each treatment group at each visit as:

$$\frac{\#\ of\ subjects\ in\ treatment\ group\ in\ each\ response\ category\ at\ Week\ x}{\#\ of\ subjects\ in\ treatment\ group\ with\ HS\text{-}PtGA\ score\ at\ Week\ x}$$

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

  The Patient Global Impression of change (PGI-C) is a single item, self-administered questionnaire, which asks the patient 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 visit specified in the Schedule of Activities in **Section 3.6**. The proportion of such subjects will be calculated for each treatment group at each visit as:

$$\frac{\#\ of\ subjects\ in\ treatment\ group\ in\ each\ response\ category\ at\ Week\ x}{\#\ of\ subjects\ in\ treatment\ group\ with\ PGI\text{-}C\ data\ at\ Week\ x}$$

- **Proportion of subjects achieving much improvement according to the PGI-C at each visit**

  For each treatment group, the number of subjects achieving improvement ("Much better", or 'Very much better") according to the PGI-C will be calculated at each visit specified in the Schedule of Activities in **Section 3.6**. The proportion of such subjects will be calculated for each treatment group at each visit as:

$$\frac{\#\ of\ subjects\ in\ treatment\ group\ in\ either\ improvement\ response\ category\ at\ Week\ x}{\#\ of\ subjects\ in\ treatment\ group\ with\ PGI\text{-}C\ data\ at\ Week\ x}$$

- **Proportion of subjects achieving improvement according to the PGI-C at each 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 visit specified in the Schedule of Activities in **Section 3.6**. The proportion of such subjects will be calculated for each treatment group at each visit as:

$$\frac{\#\ of\ subjects\ in\ treatment\ group\ in\ any\ improvement\ response\ category\ at\ Week\ x}{\#\ of\ subjects\ in\ treatment\ group\ with\ PGI\text{-}C\ data\ at\ Week\ x}$$

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

  For each treatment group, the number of subjects in each response category for the PGI-B will be calculated at each visit specified in the Schedule of Activities in **Section 3.6**. The proportion of such subjects will be calculated for each treatment group at each visit as:

$$\frac{\#\ of\ subjects\ in\ treatment\ group\ in\ each\ response\ category\ at\ Week\ x}{\#\ of\ subjects\ in\ treatment\ group\ with\ PGI\text{-}B\ data\ at\ Week\ x}$$

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

- **Proportion of subjects achieving "A little bothered" or "Not at all bothered" for the PGI-B at each visit**

  For each treatment group, the number of subjects "A little bothered" or "Not at all bothered" for the PGI-B will be calculated at each visit specified in the Schedule of Activities in **Section 3.6**. The proportion of such subjects will be calculated for each treatment group at each visit as:

$$\frac{\#\ of\ subjects\ in\ treatment\ group\ achieving\ either\ "A\ little\ bothered"\ or\ "Not\ at\ all\ bothered"\ category\ at\ Week\ x}{\#\ of\ subjects\ in\ treatment\ group\ with\ PGI\text{-}B\ data\ at\ Week\ x}$$

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

The Patient Global Impression of Severity (PGI-S) is a single-item question, which asks the patient to rate the current severity of the HS ("No Activity" / "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 **Section 3.6**. The proportion of such subjects will be calculated for each treatment group at each visit as:

$$\frac{\#\ of\ subjects\ in\ treatment\ group\ in\ each\ response\ category\ at\ Week\ x}{\#\ of\ subjects\ in\ treatment\ group\ with\ PGI\text{-}S\ score\ at\ Week\ x}$$

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

- **Proportion of subjects achieving "Mild" or "No activity" / "Clear skin" for the PGI-S at each visit**

For each treatment group, the number of subjects with either "*Mild*" or "*No activity*" / "Clear Skin" response category for the PGI-S will be calculated at each visit specified in the Schedule of Activities in **Section 3.6**. The proportion of such subjects will be calculated for each treatment group at each visit as:

$$\frac{\#\ of\ subjects\ in\ treatment\ group\ with\ either\ \text{"Mild" or "}No\ activity\text{" / "}Clear\ Skin\text{" response category at Week } x}{\#\ of\ subjects\ in\ treatment\ group\ with\ PGI\text{-}S\ score\ at\ Week\ x}$$

- **Proportion of subjects in each category of Hurley Stage at each visit**

The Hurley system describes 3 clinical stages of HS (Stage I, II, and II). The Hurley stage at a given visit will be determined by the site as the greatest Hurley Stage observed from all involved anatomical regions.

For each treatment group, the number of subjects in each category of Hurley Stage will be calculated at each visit specified in the Schedule of Activities in **Section 3.6**. The proportion of such subjects will be calculated for each treatment group at each visit as:

$$\frac{\#\ of\ subjects\ in\ treatment\ group\ in\ each\ response\ category\ at\ Week\ x}{\#\ of\ subjects\ in\ treatment\ group\ with\ Hurley\ Stage\ scoring\ at\ Week\ x}$$

- **Change from baseline in Hurley Stage at Weeks 16, 32, and 40**

  The change from baseline in Hurley Stage at Weeks 16, 32, and 40 will be calculated as Hurley Stage at the corresponding visit minus the Hurley Stage at baseline.

- **Proportion of subjects with at least 1-stage decrease in Hurley Stage from baseline at each visit**

  This endpoint measures a 1-stage decrease in Hurley Stage at a given time point compared to baseline. For each treatment group, the number of subjects with at least 1-stage decrease in Hurley Stage will be calculated at each visit. The proportion of such subjects will be calculated for each treatment group at each visit as:

$$\frac{\#\ of\ subjects\ in\ treatment\ group\ with\ at\ least\ a\ 1\ stage\ decrease\ in\ Hurley\ Stage\ at\ Week\ x}{\#\ of\ subjects\ in\ treatment\ group\ with\ Hurley\ Stage\ scoring\ at\ Week\ x}$$

6.3 Pharmacokinetic Variables

Serum concentration time data will be collected following imsidolimab administration to evaluate the PK profile of imsidolimab. Samples from subjects who 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 3** below.

Table 3 Pharmacokinetic Sample Collection and Time Points

Study Visit	Pharmacokinetic Sample Time Point (Serum)
Day 1	Pre-dose 2 hr. (± 10 min) post-dose
Day 29	Pre-dose
Day 57	Pre-dose
Day 85	Pre-dose
Day 113	Pre-dose
Day 141	Pre-dose
Day 169	Pre-dose
Day 197	Pre-dose
Day 225	Anytime
Day 253	Anytime
Day 281	Anytime

Abbreviations: hrs., hours; min, minutes; PK, pharmacokinetic.

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

6.4 Immunogenicity Variables

- **Presence of ADA to imsidolimab**

  ADA to imsidolimab will be collected at the time points indicated in **Table 4** below:

Table 4 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 85	Pre-dose
Day 113	Pre-dose
Day 141	Pre-dose
Day 225	Anytime
Day 281	Anytime

Abbreviations: ADA, Anti-drug antibodies.

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-induced or treatment-boosted, relative to all imsidolimab treated subjects
- Titer values

6.5 Biomarker Variables

- **Biomarkers analysis including, but not limited to interleukin (IL)-1, IL-36, Th-17 cytokines such as IL-17A, and markers of neutrophils and dendritic cells infiltration**

  Tape strips and optional noninvasive collection of drainage fluid will be collected at the visits specified in the Schedule of Activities in **Section 3.6** to measure cutaneous biomarkers including, but not limited to, IL-36 receptor (IL-36R), Th-17 cytokines such as IL-17A, and markers of neutrophils and dendritic cells infiltration. The analysis of tape strips biomarkers may 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 on each patient throughout their participation in the study. Adverse Events will be reported by the study period that they occurred in as detailed in the Data Handling Rules Appendix.Safety assessments for other safety variables will occur as detailed in the Schedule of Activities in **Section 3.6**. Safety data assessed per the Schedule of Activities will be allocated according to the rules for efficacy data in **Section 6.2.1.**

6.6.2 Extent of Exposure to Study Medication and Compliance

The number of doses received by the patient for a study treatment will be calculated as the sum of the doses received in the placebo-controlled period, extension period, and overall.

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 entire treatment period (placebo-controlled + extension).

Dose intensity for a specific period is defined as (cumulative total dose received during a period/cumulative total expected per-protocol dose during the same period) x 100%. Dose intensity will be summarized by treatment group and summarized separately for placebo-controlled period, extension period, and overall.

6.6.3 Adverse Events

AEs experienced by the subjects will be collected throughout the entire study and will be coded using the latest version of the MedDRA specified in the approved Data Management Plan. Analysis of adverse events will be carried out on the Safety Analysis Set during the placebo controlled period and the Extension Analysis Set for the extension period.

An adverse event 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 adverse event 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.

AEs 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.

Adverse events will be categorized as serious or non-serious using the definition specified in **Section 8.2.1.2** 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 10** of the study protocol. Local laboratory samples will be collected in the electronic case report form (eCRF) when the central laboratory results are not available immediately, and the Investigator needs to take an immediate decision for any safety concerns. All lab 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 patient data listings will be presented in the International System of Units (SI units). Laboratory data not reported in SI units will be converted to SI units before further processing or data analysis.

Abnormal Values

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

6.6.5 Vital Signs

Vital signs including body temperature (°C), pulse rate (bpm), systolic and diastolic blood pressure (mmHg), respiratory rate (breath/min), weight (kg), and height will be obtained in accordance with the Schedule of Activities in **Section 3.6.** 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)

Changes from baseline in heart rate, as well as RR, PR, QRS, QT, and corrected QT interval by Fredericia (QTcF) intervals will be collected according to the Schedule of Activities in **Section 3.6.** 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, standard deviation, first and third quartiles, median, 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 (calculated as $100\sqrt{}[exp\ (s^2)-1]$, where s is the standard deviation 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.

7.1.1 Sensitivity Analyses

Multiple Imputation with Fully Conditional Specification (FCS) Method

Multiple imputation, using the FCS method will be used as a sensitivity analysis for the analysis of the primary efficacy endpoint. This analysis is described in detail in **Section 7.5.4**.

7.1.2 Tipping Point Analyses

As the primary analysis (mixed effects model for repeated measures [MMRM]) relies on the missing at random (MAR) assumption, to evaluate the robustness of the primary analysis approach, a sensitivity analysis using the tipping-point approach will be conducted. This analysis is described in **Section 7.5.4**.

7.2 Subject Disposition

Disposition for all subjects will be tabulated and listed. The tabulation will include the number of subjects consented, screened, randomized, treated, randomized but not treated, the number of subjects completing the placebo-controlled period, the number of subjects who complete the extension period, the number of subjects who complete the follow-up period, and the number of subjects who discontinue the study early will also be presented. For subjects who discontinue, the reason for discontinuation will also be included. The number and percentage of randomized subjects included in the ITT, PP, Extension, Safety, and PK Analysis Sets will also be tabulated.

Randomization stratification factors 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 double-blind treatment period will be listed. The duration of actual treatment will also be listed.

A listing of reasons why subjects were not randomized will be provided for all subjects who were not randomized. The reason for exclusion of a subject from the PP, Safety, and PK Analysis Sets will be listed for all randomized subjects; Coronavirus disease 2019 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 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 also 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 overall and by treatment and all data will be provided in listings. Continuous baseline demographic and disease characteristics (such as age, height, weight, BMI, AN count, total abscess count, total inflammatory nodule count, draining fistula count, and HS pain NRS), will be summarized descriptively using number of subjects, mean, median, standard deviation, minimum, maximum, first quartile, and third quartile. For categorical baseline disease characteristics and demographic parameters (such as country, reproductive status, sex, ethnicity, race, Hurley Stage, smoking history, Fitzpatrick skin type, HS-PtGA, DLQI, HiSQoL,

HS-PGA, IHS4, PGI-B and PGI-S), the number and frequencies and percentages of subjects will be provided along with descriptive statistics treating them as a continuous variable.

7.4.2 Medical and Surgical History

Medical and surgical history will be summarized for the Safety Analysis Set and listed for all randomized subjects.

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 drugs he/she 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 in the placebo-controlled period. The Extension Analysis Set will be used as the main analysis set for all efficacy analyses in the extension period.

Per protocol analyses will be performed on the primary as well as the following secondary endpoints:

- Percent change from baseline in AN count at each visit
- Proportion of subjects achieving HiSCR50 at each visit
- Change from baseline in HS Pain NRS at each visit
- Percent change from baseline in HS Pain NRS at each visit

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

7.5.1 Primary Efficacy Estimand

The primary estimand, comprising five components, is as follows:

a) The target population is subjects in the United States and Europe diagnosed for at least 6 months with HS, having lesions at Hurley Stage II or III.
b) The primary variable is the change from baseline in AN count of an individual subject at Week 16.
c) To handle intercurrent events such as use of rescue medications, a hypothetical strategy for estimand (**ICH E9, 2019**) will be used such that data collected following receipt of rescue medication (if any) will be considered missing in the analysis. Missing values will be imputed as described in **Section 7.5.4**. The hypothetical scenario envisaged under this estimand is what value the primary variable would have taken if the subject had not taken rescue treatment.

d) The population-level summary measure for the primary endpoint is mean change from baseline in AN count at Week 16. The estimator for between-group comparison of the primary endpoint will be the difference in the primary endpoint between imsidolimab and placebo at Week 16.
e) The treatment conditions of interest, two imsidolimab treatment regimens and one placebo regimen:
    1. Imsidolimab 400 mg injection on Day 1, followed by 200 mg on Days 29, 57, and 85;
    2. Imsidolimab 200 mg injection on Day 1, followed by 100 mg on Day 29, 57, and 85;
    3. Placebo on Days 1, 29, 57, and 85

A linear mixed model will be used for the repeated measures (MMRM) with treatment, visit, treatment by visit interaction, and Hurley Stage at baseline as a categorical covariate and baseline AN count as a continuous covariate. An unstructured correlation (UN) matrix will be used to model correlation within a patient; if convergence is an issue, a Toeplitz structure may be considered. If convergence issue persists, elimination of post-baseline visits other than Week 16 may be considered. Subjects with missing data at Week 16 due to early discontinuation will be included in the model.

The least squares (LS) mean and the standard error of this mean with the corresponding two-sided 90% confidence interval will be provided for each treatment based on the model. The LS mean difference between treatments (imsidolimab - placebo), as well as the corresponding two-sided 90% confidence interval will be provided based on the model. Summary statistics and the results of statistical testing in AN count at Week 16 will be tabulated. The LS mean change from baseline in AN count will be plotted against post-baseline visits for each treatment group. The LS mean difference and corresponding confidence intervals will also be plotted.

7.5.2 Secondary Efficacy Analyses

7.5.2.1 Percent change from baseline in AN count at Week 16

This secondary endpoint will be analyzed using a similar MMRM model as for the primary endpoint. The percent change from baseline in AN count at Week 16 will be the response variable.

7.5.2.2 Proportion of subjects achieving HiSCR50 at Week 16

The frequency and percentage of subjects with HiSCR50 will be summarized at Week 16. The unadjusted risk difference and 90% exact unconditional confidence intervals will be reported between the imsidolimab and placebo groups for all subjects and Hurley Stage at randomization (Stage II or III). The common risk difference will also be tested using a generalized Cochran-Mantel-Haenszel test (ANOVA for row means), adjusting for Hurley Stage at randomization.

A sensitivity analysis will be conducted for this endpoint on the ITT Analysis Set where subjects received rescue medications between Week 4 and Week 16 will be considered as failure to achieve HiSCR50 at Week 16.

An additional exploratory analysis will be performed for the proportion of subjects achieving HiSCR50 by visit. A repeated-measures generalized estimating equations (GEE) with the logit link will be used. The model will include treatment, visit, treatment by visit interaction, race, gender, Fitzpatrick skin type, Hurley Stage at baseline, and baseline inflammatory lesion count as covariates. Data from protocol specified visits up to Week 16 will be included in the analysis. An unstructured correlation matrix will be used to model correlation within a patient; if convergence is an issue, a Toeplitz structure may be considered. An odds ratio resulting from this model along with 90% CI will be reported.

7.5.2.3 Change from Baseline in Average HS pain NRS at Week 16

Change from baseline in Average HS pain NRS at Week 16 will be analyzed using a similar MMRM model as for the primary endpoint, but changing baseline AN count to HS pain NRS in the model as the response.

7.5.2.4 Percent change from Baseline in Average HS pain NRS at Week 16

Percent change from baseline in Average HS pain NRS at Week 16 will be analyzed similarly to percent change from baseline in AN count at Week 16, as described in **Section 7.5.2.1**.

7.5.2.5 Change from Baseline in Worst HS pain NRS at Week 16

Change from baseline in Worst HS pain NRS at Week 16 will be analyzed using a similar MMRM model as for the primary endpoint, but changing baseline AN count to HS pain NRS in the model as the response.

7.5.2.6 Percent change from Baseline in Worst HS pain NRS at Week 16

Percent change from baseline in Worst HS pain NRS at Week 16 will be analyzed similarly to percent change from baseline in AN count at Week 16, as described in **Section 7.5.2.1**.

7.5.3 Exploratory Efficacy Analyses

Protocol Specified Exploratory Efficacy Analyses

The change from baseline in Hurley Stage, HS-PGA, HS-PtGA, PGI-B, and PGI-S 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 time point. Agreement between the baseline score and each post-baseline score will be estimated with a weighted Kappa coefficient and corresponding 90% CI (**Cohen, 1968**) A test of treatment difference for agreement will be done separately for each treatment group and will consist of a CMH test (ANOVA for row means) applied to a 2x2xR table (baseline Hurley Stage x treatment x agreement score), where the agreement score is the Cicchetti-Allison weight (**Cicchetti, 1971**) used for the weighted Kappa coefficient, which is 1-|difference|/(R-1) where R is the number of categories in the endpoint.

The change from baseline and percent change (shown as *) from baseline in each continuous exploratory variable (AN count*, abscess count, inflammatory nodule count, draining fistula count at each visit, calculated composite of abscess, inflammatory nodule and draining fistula count, calculated composite of abscesses, draining fistulas, and inflammatory and non-inflammatory nodules, HS Pain NRS* at visits other than Week 16, worst HS pain NRS, DLQI scores at each visit, IHS4 score at each visit, HiSQOL score at each visit) will be analyzed using a similar MMRM model as described for the primary efficacy analysis in **Section 7.5.1**, but changing baseline AN count to baseline of the outcome. Summary statistics and the results of statistical testing at each visit will be provided for each continuous exploratory variable.

The frequency and percentage of subjects for each categorical exploratory variable (proportion of subjects achieving AN50 and AN75 responses, percentage of subjects experiencing flare, proportion of subjects achieving HiSCR50 and HiSCR75 at each visit, proportion of subjects achieving HS-PGA of inactive (0) or almost inactive (1) at each visit, proportion of subjects achieving at least 2-point decrease in HS-PGA at each visit, proportion of subject with a 2 point reduction from baseline on HS-PGA at each visit, proportion of subjects achieving a 3-point reduction on the HS Worst Pain NRS for subjects with baseline HS Worst Pain NRS of at least 3, proportion of subjects achieving a 3-point reduction on the HS Average Pain NRS

for subjects with baseline HS Average Pain NRS of at least 3, proportion of subjects requiring rescue medication or treatment at each visit, proportion of subjects in each response category for the HS-PtGA at each visit, proportion of subjects in each response category for the PGI-C at each visit, proportion of subjects achieving much improvement in PGI-C at each visit, proportion of subects achieving improvement at each visit, proportion of subjects in each response category for the PGI-S at each visit, proportion of subjects achieving "Mild" or "No activity" / "Clear skin" for the PGI-S at each visit, proportion of subject in each response category for the PGI-B at each visit, proportion of subjects achieving "A little bothered" or "Not at all bothered" for the PGI-B at each visit, proportion of subjects in each category of Hurley Stage at each visit, proportion of subjects achieving at least a 1-stage improvement (decrease) in Hurley Stage) will be summarized at each visit.

For PGI-S, PGI-B, HS-PtGA, HS-PGA, and PGI-C, the difference in distribution between the imsidolimab and placebo groups will be compared separately for each treatment group by using a Wilcoxon rank-sum test and Somers' d statistic, which may be interpreted as a generalized risk difference (**Edwardes, 2000**). This will be performed over all subjects for each comparison, and within each stratum for Hurley Stage. The difference in distribution between the imsidolimab and placebo groups (stratified by baseline Hurley Stage) will be compared using a Cochran-Mantel-Haenszel test as described in **Section 7.5.2.2**. For PGI-S, PGI-B, HS-PtGA, and HS-PGA, the change from baseline will also be analyzed using an ordinal logistic regression model with treatment and baseline Hurley Stage as categorical covariates. Odds ratios resulting from this model along with 90% CI will be reported. The proportional odds assumption will also be tested, and the corresponding p-value will be reported.

Additional Exploratory Efficacy Analyses

To estimate the treatment effect while accounting for a subject knowing they are on study drug, the primary endpoint analysis will be repeated comparing the estimated change from Day 1 imsidolimab baseline to Week 16 (for active dose subjects in the placebo-controlled period) to the estimated change from Week 16 imsidolimab baseline to Week 32 (for placebo → imsidolimab subjects). This comparison will be done separately for like doses (arm 1 to arm 3A, and arm 2 to arm 3B.)

To further estimate the treatment effect while accounting for a subject knowing they are on study drug and while also accounting for inter-subject variability, the primary endpoint analysis model as described in **Section 7.5.1**, will be fitted. A binary indicator variable will be added to the model to indicate visits at which the subject knows they are on study drug. The change from imsidolimab baseline between Week 16 and Week 32 for the placebo → imsidolimab group will be compared within treatment regimen. The overall treatment effect at 16 weeks will be estimated with the primary independent group contrast at Week 16 as well as the cross-over contrast between Week 16 and Week 32 for the placebo → imsidolimab group. Furthermore, the effect of 32 weeks of exposure compared to 16 weeks of exposure will be estimated comparing like doses.

The change from baseline and percent change from baseline in the calculated composite total of abscess, inflammatory nodule, and draining fistula count at each visit, and percent change from baseline in the draining fistula count at each visit will be analyzed using a similar MMRM model as described for the primary efficacy analysis in **Section 7.5.1**, but changing baseline AN count to baseline of the outcome variable and adding Hurley Stage at baseline as an additional covariate. Summary statistics and the results of statistical testing at each visit will be provided for each continuous exploratory variable.

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 specified MMRM model but including additional covariates of race, smoking, age, and Fitzpatrick skin type as model convergence allows.
- Multiple imputation with FCS method (described below).
- Tipping point analysis (described below).
- Prior to database lock and unblinding, the assumption of normality in the change from baseline in AN count will be checked by visually inspecting the distribution of the residuals. If the normality assumption is not met, a repeated-measure GEE approach with an appropriate distribution (e.g. logarithm or generalized logit transformation) will be considered. An unstructured correlation matrix will be used in the model if GEE is decided to be used. However, the results from the primary efficacy analysis will be considered the primary efficacy results.

Multiple Imputation with Fully Conditional Specification (FCS) Method

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

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

a) If there is any missing value at Week 4, it will be imputed using a regression-based predictive mean matching method. A randomization seed of 20225678 will be used. For AN counts, the regression will include the covariates age, treatment group, race, gender, Hurley Stage at baseline (Stage II vs. III), and the baseline measurement of AN counts.

b) All remaining missing visits will be imputed sequentially by the same regression, with covariates specified above in Step (a) and the values (including the imputed values) from earlier visits.

c) For the final Week 16 imputed values, the imputed values will be rounded to the nearest integer for AN count. For intermediate imputed values, the exact values will be kept for the purpose of imputation for the next visit.

The linear mixed model for repeated measures (MMRM) for continuous endpoints as described in **Section 7.5.1** will be applied to each imputed dataset. At least 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.

Tipping Point Analyses

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

a) Intermittent missing values will be imputed using the Monte Carlo Markov Chain (MCMC) approach to create a monotone missing pattern. The imputation will be implemented separately for each treatment and each Hurley Stage at baseline (Stage II or III), under the assumption that

different treatments may have distinct posterior distributions. The imputation will include the all post-baseline values, with age, race, gender, Fitzpatrick skin type, and baseline value of the corresponding endpoint as covariates.

b) If there is any missing value at timepoint 1 (Week 4), it will be imputed using a regression based MI method for monotone missingness. Covariates included in the modelling are age, race, gender, Fitzpatrick skin type, and baseline value of the corresponding endpoint.

c) A delta score will be added to the imputed value at timepoint 1 for subjects missing data at timepoint 1 in the imsidolimab treatment groups, thus worsening the imputed value. The delta value will start at 0 and will be increased in a repeated process until the comparison of imsidolimab to placebo is no longer significant at 0.10 level in step (f).

d) All remaining timepoints will be imputed sequentially by repeating Steps (b) and (c) for each timepoint, including values from earlier timepoints in the imputation model, which include imputed values from the previous step, in addition to the covariates specified above in Step (b). Data from subjects who have already had their responses increased by delta in the previous step(s) will not be further increased by delta again since the regression on the previous value carries this increase forward. This principle also extends to the preliminary step of imputing intermittently missing visits. Thus, if an intermittent missing value is encountered for a subject in the imsidolimab treatment groups, delta adjustment will not apply for the subsequent imputations of the monotone part of the missing visits, for that subject.

e) For each imputed dataset, perform the same primary analysis (MMRM) as described in **Section 7.5.1** to estimate treatment differences between each dose of imsidolimab and placebo. Results across the imputed datasets will then be combined using SAS PROC MIANALYZE.

f) Step (c) to (e) will be repeated with gradually increased delta values until the tipping point is reached.

At least one hundred (100) independent dataset replications will be done with SAS PROC MI. The resulting 100 estimates of the treatment differences and standard errors will then be combined into the final estimate using SAS PROC MIANALYZE.

Study Dates and Day of Assessment or Event

Study Day and Day of Assessment or Event definitions are provided in **Appendix 1**.

Incorrect Stratification

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

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:

- Smoking status:
    - Current

  - Not Current
- Prior history of anti-TNF (Humira) use for HS indication:
  - Yes
  - No
- AN count at baseline:
  - <= median
  - > median
- Age groups:
  - [18, 65) years
  - [18, 30) years
  - [30, 45) years
  - [45, 65) years
  - [65, 75) years
- Sex groups:
  - Male
  - Female
- Hurley Stage at baseline:
  - Stage II
  - Stage III
- 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, 113, 141, 169, 197, will be tabulated as well as graphically presented as scatter plots. Nominal collection times will be used for graphs.

A subject listing of all concentration-time data following SC injections will be presented by subject and scheduled sample collection time. All concentration data of imsidolimab will be summarized by day and nominal time point using the number of observations, arithmetic mean, SD, coefficient of variation (CV), minimum, median, maximum, geometric mean, and CV of geometric mean. Concentrations that are below the limit of quantitation will be treated as zero for the computation of descriptive statistics.

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 of the titer values by treatment group and visit, where possible, will be provided. Neutralizing antibodies, if assayed and present, will also be summarized. The relationship between changes in PK profile and treatment-emergent positive responses will be evaluated to identify a potential impact ADA on imsidolimab exposure. Box plots of ADA status relative to trough concentrations will be plotted. Where possible, evaluation of ADA impact on efficacy and safety may be performed and summarized separately. All immunogenicity results will be listed.

7.8 Biomarker Analyses

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

7.9 Safety Analyses

Safety analyses will be performed using the Safety Analysis Set for data from the placebo-controlled period, and the Extension Analysis Set for data from the extension period. 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.

Data Imputation for Adverse Events Summaries by Severity and Relationship to Study Drug

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

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

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

Data Imputation (All Laboratory, Immunogenicity and Biomarker Summaries)

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

7.9.1 Extent of Exposure to Study Medication and Compliance

Descriptive statistics (n, mean, standard deviation, median, minimum and maximum) will be presented for the number of doses received, the number of days of exposure to study treatment, total dose received, total dose expected, and dose intensity by treatment group and summarized separately for placebo-controlled period, extension period, and overall. Dose intensity will be defined for each study period as doses received divided by doses scheduled in the period. In addition to summary statistics on the dose intensity as a continuous variable, this will also be categorized into bins. For the placebo-controlled and extension periods separately: 0-25%, >25%-50%, >50%-75%, >75%-100%, and >100%. For the both periods overall: 0-12.5%, >12.5%-25%, >25%-37.5%, >37.5%-50%, >50%-62.5%, >62.5%-75%, >75%-87.5%, >87.5%-100%, and >100%. Dosing information will be listed by study period and by placebo-controlled period and extension period.

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 Event 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 SOC. 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
- 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 resulting in study withdrawal

7.9.3 Laboratory Data

Summary statistics (n, mean, median, standard deviation, minimum, and maximum) for the baseline assessment and for the observed value and change from baseline at each post-baseline visit for scheduled lab 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 patient data listings for Safety Analysis Set.

7.9.4 Vital Signs

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

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

7.9.5 Electrocardiogram (ECG)

ECG data (Heart Rate, PR Interval, RR Interval, QRS Interval, QT Interval, and QTcF Interval) will be tabulated with descriptive statistics by visit for both the raw values as well as the changes from baseline.

Number and percentage of subjects with clinically significant abnormalities in all ECG parameters will be summarized for normal, abnormal - not clinically significant and abnormal - clinically significant categories by treatment group. Three-by-three contingency tables will be presented to summarize the shift from the baseline category to the worst post-baseline value. Summary results will include the count and percentage of subjects within each shift category and treatment group.

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 by-subject listings.

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. All physical examination results for the subjects with abnormal finding(s) will be listed. No AEs of special interest will be defined.

8. CHANGES FROM METHODS PLANNED IN THE PROTOCOL

- The protocol uses the following spelling for the patient global impression questionnaires: “PGIS”, “PGIC”, and “PGIB”. This SAP uses the following spelling for the patient global impression questionnaires: “PGI-S”, “PGI-C”, and “PGI-B”.

- The protocol uses the term 'major protocol violations' in the definition of the Per Protocol Analysis Set. This SAP uses the term 'important protocol deviations' throughout.

- The protocol states that the primary estimand is comprised of four components. This SAP includes a fifth component, treatment condition, per ICH E9 (R1) addendum.

- The protocol has two secondary endpoints for PGI-C data with titles that begin "Proportion of subjects achieving improvement…". This SAP uses the following titles to better distinguish between the two: "Proportion of subjects achieving much improvement…", and "Proportion of subjects achieving improvement…".

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. Cardiff University School of Medicine. Quality of Life Questionnaires. https://www.cardiff.ac.uk/medicine/resources/quality-of-life-questionnaires/dermatology-life-quality-index. Accessed 15APR2021.
2. Cicchetti, D. V., and Allison, T. (1971). "A New Procedure for Assessing Reliability of Scoring EEG Sleep Recordings." *American Journal of EEG Technology* 11:101–109.
3. Cochran WG. The Comparison of Percentages in Matched Samples. Biometrika. 1950;37(3/4):256–266.
4. Cohen, J. Weighted kappa: Nominal scale agreement with provision for scaled disagreement or partial credit. Psychol Bull. 1968;70(4):213–220.
5. Edwardes MD, M Baltzan. The generalization of the odds ratio, risk ratio and risk difference to r x k tables. Stat Med. 2000 ;19(14):1901-14.
6. Finlay AY, Khan GK. Dermatology Life Quality Index (DLQI): A simple practical measure for routine clinical use. Clin Exper Dermatol. 1994;19:210-216.
7. International Council for Harmonisation. *Addendum on estimands and sensitivity analysis in clinical trials to the guideline om statistical principles for clinical trials E9(R)* 2019.
8. Kimball AB, Jemec GB, Yang M, et al. Assessing the validity, responsiveness and meaningfulness of the hidradenitis suppurativa clinical response (HiSCR) as the clinical endpoint for hidradenitis suppurativa treatment. Br J Dermatol 2014;171: 1434–42.
9. SAS® 9.4 and SAS® Viya® 3.5 Programming Documentation. "The FREQ Procedure: Cochran-Mantel-Haenszel Statistic.", SAS Institute Inc., Cary, NC. https://documentation.sas.com/doc/en/pgmsascdc/9.4_3.5/procstat/procstat_freq_details92.htm. Accessed April 21, 2021.

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 Beginning Date of Condition	• Missing day of begin date of condition will be imputed as the 1st of the month for the purpose of computing the onset day. • Missing month of begin date of condition will be imputed as June for the purpose of computing the onset day
	Medical 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 would be 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).

Category	Description	Data Handling Rules
	Last Dose Day	**Last Dose Day** in the study is defined as the study day of the last dose of study treatment in the study (defined as the last date of dosing from the Dosing CRF pages).
	Last Study Day	**For subjects who did not receive study treatment in the study (e.g., Non-Randomized subjects)**, Last Study Day is defined as (the later of the last visit date and the date of study completion or discontinuation from the End of Study CRF) – Date of Screening Visit + 1. **For subjects who received study treatment in the study,** Last Study Day is defined as (the later of the last visit date and the date of study completion or discontinuation from the End of Study CRF) – first dose date in the study + 1.
	Days Since Last Dose for event (e.g., Death)	**Days Since Last Dose** is defined as date of event – date of last dose of study treatment.
6. Duration of event	The duration of any event	The duration of any event is defined as (stop date – start date + 1).
7. Prior and concomitant, medication / treatment	Prior and concomitant medication/treatment	**1.** Prior medication/treatment is any medication/treatment stopped prior to the first dose of study treatment (or the date of the randomization visit, Day 1, if the date of the start of study medication is missing). Medication/treatment continued into the treatment period will not be considered prior. **2.** A medication/treatment will be identified as a concomitant medication/treatment if any of the following are true: ○ The start date or the end date is on or after the date of the start of study treatment (or the date of randomization, Day 1, if missing). ○ The medication/treatment is checked as 'Ongoing', and the start date of the medication/treatment is prior to the first dose of study treatment (or the date of the randomization visit, Day 1, if the date of the start of study medication is missing). ○ The start date and the end date are both missing
8. Adverse event	Treatment-emergent adverse event	If the AE start date is partial/missing, then • If AE start date is completely missing, then the AE is considered as treatment-emergent. • If both AE start month and day are missing and AE start year is the same or after the first dose year, then the AE is considered as treatment-emergent. • If AE start day is missing and AE start year and month are the same or after the first dose year and month, then the AE is considered as treatment-emergent.

Category	Description	Data Handling Rules
		Missing/incomplete (partial) AE start and end dates will not be imputed for data listings.
	Assignment of TEAE to Placebo-Controlled vs. Extension and Follow Up Period	Report the TEAE in placebo-controlled period if AP01SDT < AESTDTC; Else report the TEAE in extension and follow-up period if AP02SDT < AESTDTC
	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. Efficacy	Change from baseline	Endpoint value at Week x – endpoint value at baseline
	Percent change from baseline	(Endpoint value at Week x – endpoint value at baseline)/ endpoint value at baseline

	Scoring rules for DLQI questionnaires	• If one question left unanswered, assign a score of 0 for that question.
		• If two or more questions are left unanswered the questionnaire is not scored.
		• For question 7,
		  ○ "Yes" is assigned a score of 3
		  ○ "Not Relevant" is assigned a score of 0
		  ○ "No" and "A lot" is assigned a score of 2
		  ○ "No" and "A little" is assigned a score of 1

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 BASEHSSTAGE; MODEL Y = BASE TRT VISIT TRT|VISIT/ DDFM=KR SOLUTION OUTP=OUT; REPEATED VISIT / TYPE = UN SUBJECT = SUBJECT; LSMEANS TRT|VISIT / PDIFF CL ALPHA=0.1; ODS OUTPUT LSMEANS=MEANS; ODS OUTPUT DIFFS=DIFF; RUN; Where TRT is treatment, VISIT is the study visit number, BASEHSSTAGE is the baseline Hurley Stage, and BASE is the baseline of outcome variable.
General Estimating Equation Repeated Measures with Generalized Logit Transformation	PROC GENMOD; CLASS SUBJECT TRT VISIT BASEHSSTAGE; MODEL Y= BASE TRT VISIT TRT*VISIT / LINK=LOGIT DIST=NEGBIN; REPEATED SUBJECT=SUBJECT / TYPE=UN; LSMEANS TRT|VISIT / DIFF CL ALPHA=0.1; ODS OUTPUT LSMEANDIFFS = LSDIFS ESTIMATES=EST LSMEANS=LSMEANS PARAMETERESTIMATES=PE; Where TRT is treatment, VISIT is the study visit number, BASEHSSTAGE is the baseline Hurley Stage, and BASE is the baseline of outcome variable.
General Estimating Equation Repeated Measures for secondary and exploratory endpoints	PROC GENMOD; CLASS SUBJECT TRT VISIT; MODEL Y = TRT VISIT TRT*VISIT/ DIST=BIN LINK=LOGIT; REPEATED SUBJECT = SUBJECT /TYPE=UN; RUN; Where TRT is treatment and VISIT is the study visit number.

Test	Template SAS Code for Modeling (SAS Version 9.4)
Impute Intermittent Missing using the Monte Carlo Markov Chain (MCMC) approach	PROC MI DATA=data_in SEED=2330710 NIMPUTE=100 OUT=LESION_MONO; BY BASEHSSTAGE TRT; /*Assuming different treatment, baseline Hurley Stage has different distribution*/ MCMC CHAIN=MULTIPLE IMPUTE=MONOTONE; /*Only impute intermittent missing values*/ VAR AGE BASE AN1 – AN5; /*Impute AN count from Week 4 to Week 16, with age and baseline as covariates*/ RUN;
Multiple Imputation with FCS Method	PROC MI MIN=0 ROUND=1; CLASS BASEHSSTAGE TRT SEX; FCS REGPMM(AN2 = AN1 AGE SEX TRT BASE BASEHSSTAGE); FCS REGPMM(AN3 = AN1 AN2 AGE SEX TRT BASE BASEHSSTAGE); FCS REGPMM(AN4 = AN1-AN3 AGE SEX TRT BASE BASEHSSTAGE); FCS REGPMM(AN5 = AN1 AN4 AGE SEX TRT BASE BASEHSSTAGE); VAR AN1 – AN5 AGE SEX TRT BASE BASEHSSTAGE; RUN;
Combine Parameter Estimates for LSmeans	PROC MIANALYZE DATA=OUTREG; BY VISIT; MODELEFFECTS TRT; /* TRT IS THE VARIABLE FOR LS TREATMENT DIFFERENCES */ STDERR TRTERR; /* TRTERR IS THE STANDARD ERROR FOR TREATMENT DIFFERENCES */ RUN;
Cochran-Mantel-Haenszel ANOVA statistics (row means score)	PROC FREQ; TABLES BASEHSSTAGE *TRT*X/CMH2 ALPHA=0.1 SCORE=RANK; RUN; Where BASEHSSTAGE is randomized Hurley Stage, TRT is treatment, and X is the outcome variable.
Ordinal Logistic Regression using PROC LOGISTIC	PROC LOGISTIC; CLASS TRT BASE; MODEL Y = TRT BASE; RUN; Where Y is the ordinal outcome variable, TRT is treatment, BASE the baseline of outcome variable.
Exact unconditional CI	PROC FREQ; TABLES TRT*X; EXACT OR; RUN;

Test	Template SAS Code for Modeling (SAS Version 9.4)
	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 confidence interval	PROC FREQ; WEIGHT COUNT; TABLES BASEHSSTAGE*TRT*X/AGREE ALPHA=0.1; RUN; Where BASEHSSTAGE is Hurley Stage at baseline, TRT is treatment, and X is the outcome variable.
Test of treatment difference for agreement	PROC FREQ; TABLES BASEHSSTAGE*TRT*X/CMH2; RUN; Where BASEHSSTAGE is Hurley Stage at baseline, TRT is treatment, and X is the Cicchetti-Allison weight of outcome variable. Cicchetti-Allison weight = 1-abs(CHG)/(k-1), where k = number of categories of the outcome variable.

APPENDIX 3 MOCKUP TABLES, LISTINGS, AND GRAPHS (TLGS)

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

DocUUID : 836d20b1-e1e9-4b7d-a768-d68cc088dae1

Validation Report

1

Subject CN	TAIGLE LLC
Subject DN	EMAILADDRESS=operations@msbdocs.com,CN=TAIGLE LLC,OU=MSB,O=TAIGLE LLC,L=Irvine,ST=California,C=US
Email	operations@msbdocs.com
Serial #	132378441527873428230597372186267991 46
Issuer DN	CN=Entrust Class 3 Client CA - SHA256,OU=(c) 2015 Entrust, Inc. - for authorized use only,OU=See www.entrust.net/legal-terms,O=Entrust, Inc.,C=US
Signing Time	17 Aug 2022 09:51:28 (-07:00)

- The Certificate chain was successfully built to a Trusted Root Certificate.
- The Signer's identity is valid.
- The Document has not been modified since the signature was applied.

2

Signature invalid, document has been modified.

Subject CN	TAIGLE LLC
Subject DN	EMAILADDRESS=operations@msbdocs.com,CN=TAIGLE LLC,OU=MSB,O=TAIGLE LLC,L=Irvine,ST=California,C=US
Email	operations@msbdocs.com
Serial #	132378441527873428230597372186267991 46
Issuer DN	CN=Entrust Class 3 Client CA - SHA256,OU=(c) 2015 Entrust, Inc. - for authorized use only,OU=See www.entrust.net/legal-terms,O=Entrust, Inc.,C=US
Signing Time	17 Aug 2022 09:26:02 (-07:00)

- The Certificate chain was successfully built to a Trusted Root Certificate.
- The Signer's identity is valid.
- The Document has been altered or corrupted since the signature was applied.

Audit Trail Report

Document Name	ANB019_208_SAP_v1 0.pdf
Document ID	836d20b1-e1e9-4b7d-a768-d68cc088dae1
Document Source	MSB

Time Stamp	User	Action	Details
16 Aug 2022 16:39:30 (-07:00)	[redacted]	Started	The custodian composed the ePak succesfully. Subject: ANB019_208_SAP_v1.0 ePak UUID: 50b24462-f15c-4cab-a042-31bc8e487c13
16 Aug 2022 16:39:30 (-07:00)	[redacted]	RequestSent	Sign request sent to ePak recipient.
16 Aug 2022 16:39:30 (-07:00)	[redacted]	RequestSent	Sign request sent to ePak recipient.
16 Aug 2022 16:39:30 (-07:00)	[redacted]	RequestSent	Sign request sent to ePak recipient.
16 Aug 2022 16:39:30 (-07:00)	[redacted]	RequestSent	Sign request sent to ePak recipient.
16 Aug 2022 16:39:30 (-07:00)	[redacted]	RequestSent	Sign request sent to ePak recipient.
16 Aug 2022 16:39:30 (-07:00)	[redacted]	RequestSent	Sign request sent to ePak recipient.
16 Aug 2022 16:39:37 (-07:00)	[redacted]	DocumentViewed	Document viewed by signer.
16 Aug 2022 16:42:46 (-07:00)	[redacted]	SignerTagFilled	The signer filled Signer Text. Value: 16-Aug-2022
16 Aug 2022 16:43:09 (-07:00)	[redacted]	Signed	The recipient signed the document after authentication via login password. Comments: None Reason: I approve this document. Consent: I understand that my Electronic Signature is Equivalent to my Handwritten Signature and is therefore legally binding. My Electronic Signature will remain unique to me, and under no circumstance I am allowed to disclose my password to any individual which may allow unauthorized access to system. I understand that I am accountable and responsible for all actions associated with my Electronic Signature.

16 Aug 2022 16:46:11 (-07:00)	[redacted]	DocumentViewed	Document viewed by signer.
16 Aug 2022 16:47:14 (-07:00)	[redacted]	SignerTagFilled	The signer filled Signer Text. Value: 16Aug2022
16 Aug 2022 16:47:20 (-07:00)	[redacted]	Signed	The recipient signed the document after authentication via login password. Comments: None Reason: I approve this document. Consent: I understand that my Electronic Signature is Equivalent to my Handwritten Signature and is therefore legally binding. My Electronic Signature will remain unique to me, and under no circumstance I am allowed to disclose my password to any individual which may allow unauthorized access to system. I understand that I am accountable and responsible for all actions associated with my Electronic Signature.
16 Aug 2022 17:43:28 (-07:00)	[redacted]	DocumentViewed	Document viewed by signer.
16 Aug 2022 17:43:54 (-07:00)	[redacted]	SignerTagFilled	The signer filled Signer Text. Value: 08/16/2022
16 Aug 2022 17:44:05 (-07:00)	[redacted]	Signed	The recipient signed the document after authentication via login password. Comments: None Reason: I approve this document. Consent: I understand that my Electronic Signature is Equivalent to my Handwritten Signature and is therefore legally binding. My Electronic Signature will remain unique to me, and under no circumstance I am allowed to disclose my password to any individual which may allow unauthorized access to system. I understand that I am accountable and responsible for all actions associated with my Electronic Signature.
16 Aug 2022 19:34:01 (-07:00)	[redacted]	DocumentViewed	Document viewed by signer.

16 Aug 2022 19:34:23 (-07:00)	[redacted]	SignerTagFilled	The signer filled Signer Text. Value: 16-Aug-2022
16 Aug 2022 19:35:03 (-07:00)	[redacted]	Signed	The recipient signed the document after authentication via login password. Comments: None Reason: I approve this document. Consent: I understand that my Electronic Signature is Equivalent to my Handwritten Signature and is therefore legally binding. My Electronic Signature will remain unique to me, and under no circumstance I am allowed to disclose my password to any individual which may allow unauthorized access to system. I understand that I am accountable and responsible for all actions associated with my Electronic Signature.
16 Aug 2022 20:00:57 (-07:00)	[redacted]	DocumentViewed	Document viewed by signer.
17 Aug 2022 05:42:00 (-07:00)	[redacted]	SignerTagFilled	The signer filled Signer Text. Value: 17-Aug-2022
17 Aug 2022 05:42:26 (-07:00)	[redacted]	Signed	The recipient signed the document after authentication via login password. Comments: None Reason: I approve this document. Consent: I understand that my Electronic Signature is Equivalent to my Handwritten Signature and is therefore legally binding. My Electronic Signature will remain unique to me, and under no circumstance I am allowed to disclose my password to any individual which may allow unauthorized access to system. I understand that I am accountable and responsible for all actions associated with my Electronic Signature.
17 Aug 2022 09:20:39 (-07:00)	[redacted]	StarredByReminder	EPak starred by a reminder to the signer.
17 Aug 2022 09:20:46 (-07:00)	[redacted]	StarredByReminder	EPak starred by a reminder to the signer.
17 Aug 2022 09:20:52 (-07:00)	[redacted]	StarredByReminder	EPak starred by a reminder to the signer.

17 Aug 2022 09:25:14 (-07:00)	[redacted]	DocumentViewed	Document viewed by signer.
17 Aug 2022 09:25:50 (-07:00)	[redacted]	SignerTagFilled	The signer filled Signer Text. Value: 17-Aug-2022
17 Aug 2022 09:26:02 (-07:00)	[redacted]	Signed	The recipient signed the document after authentication via login password. Comments: None Reason: I approve this document. Consent: I understand that my Electronic Signature is Equivalent to my Handwritten Signature and is therefore legally binding. My Electronic Signature will remain unique to me, and under no circumstance I am allowed to disclose my password to any individual which may allow unauthorized access to system. I understand that I am accountable and responsible for all actions associated with my Electronic Signature.