1.0 Title Page

Statistical Analysis Plan

Study M15-573

A Phase 3 Multicenter, Open-Label, Single Arm Study of the Safety and Efficacy of Adalimumab in Japanese Subjects with Moderate to Severe Hidradenitis Suppurativa

Date: 07 NOV 2017

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List of Abbreviations

AAA	Anti-Adalimumab Antibody
AE	Adverse Event
AESI	Adverse Event of Special Interest
AN	Abscess and inflammatory Nodule
BCG	Bacille Calmette-Guérin
bid	Twice a day
CDA	Clinical Drug Accountability
CL/F	Apparent serum clearance
CRF	Case Report Form
CRP	C-Reactive Protein
CXR	Chest X-ray
DLQI	Dermatology Life Quality Index
DNA	Deoxyribonucleic acid
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EMA	European Medicines Agency. European Agency for the Evaluation of Medicinal Products.
eow	Every Other Week
EQ-5D	Descriptive system of health-related quality of life states consisting of five dimensions
EU	European Union
ew	Weekly
FDA	US Food and Drug Administration
GCP	Good Clinical Practice
HBcAb	Hepatitis B Core Antibody
HBsAb	Hepatitis B Surface Antibody
HBsAg	Hepatitis B Surface Antigen
HBV	Hepatitis B Virus
HCV	Hepatitis C Virus
HIV	Human Immunodeficiency Virus
HS	Hidradenitis Suppurativa
HiSCR	Hidradenitis Suppurativa Clinical Response

HS QoL	Hidradenitis Suppurativa Quality of Life
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IP	Investigational Product
IRB	Institutional Review Board
IV	Intravenous
IRT	Interactive response technology
LOCF	Last Observation Carried Forward
LOR	Loss of Response
MedDRA	Medical Dictionary for Regulatory Activities
MI	Myocardial Infarction
NRI	Non-Responder Imputation
NRS	Numeric Rating Scale
NRS30	At least a 30% reduction and at least 1 unit reduction from Baseline in Patient's Global Assessment of Skin Pain
OL	Open-Label
PA	posterior-anterior
PGA	Physician's Global Assessment
pH	Power of Hydrogen Ion Concentration
PK	Pharmacokinetic
po	Oral
PML	Progressive Multifocal Leukoencephalopathy
POR	Proof of Receipt
PPD	Purified Protein Derivative
RA	Rheumatoid Arthritis
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAS	Statistical Analysis Software
SC	Subcutaneous
TA MD	Therapeutic Area Medical Director
TEAEs	Treatment Emergent Adverse Events
TB	Tuberculosis
TNF	Tumor Necrosis Factor
TSQM	Treatment Satisfaction Questionnaire - Medication
US	United States

V/F	Apparent volume of distribution
Wk	Week

3.0 Introduction

This statistical analysis plan (SAP) describes the statistical analysis to be completed by the AbbVie Global Statistics Department for adalimumab study Protocol M15-573 dated 07 July 2016. It provides details to further elaborate statistical methods as outlined in the protocol and describes analysis conventions to guide the statistical programming work.

This is the first version of SAP for Protocol M15-573.

Unless noted otherwise, all analyses will be performed using SAS (SAS Institute Inc., Cary, NC, USA) under the UNIX operating system or in the PC environment.

4.0 Study Objectives, Design and Procedures

4.1 Objectives

The primary objective of this study is to investigate the safety and efficacy of adalimumab in Japanese subjects with moderate to severe hidradenitis suppurativa (HS) after 12 weeks of treatment. A secondary objective is to evaluate the long-term safety, efficacy and tolerability by continuous weekly dosing from Week 12. The pharmacokinetics and immunogenicity of adalimumab following subcutaneous (SC) injection will also be assessed in the study and analyzed in a separate report.

4.2 Design Diagram

This study is an open-label, single arm study designed to investigate the safety and efficacy of adalimumab in Japanese patients with moderate to severe hidradenitis suppurativa after 12 weeks of treatment, and to evaluate long-term safety, efficacy and tolerability. The study will include a 35-day screening period, open-label treatment period and a 70-day follow-up phone call following their last dose of study drug. The treatment period is expected for at least 99 weeks until the time of approval for HS indication, or withdrawal of the marketing application in Japan. A subject's participation in this study is expected up to 38 months. All subjects will receive open-label subcutaneous injection of

adalimumab 40 mg every week (ew) starting at Week 4, after 160 mg at Week 0 (Baseline) and 80 mg at Week 2.

The primary efficacy endpoint is the proportion of subjects achieving Hidradenitis Suppurativa Clinical Response (HiSCR) at Week 12. HiSCR is defined as at least a 50% reduction in the total abscess and inflammatory nodule count (AN count) with no increase in abscess count and no increase in draining fistula count relative to Baseline.

Study visits will occur at Weeks -4 and -2 (in the Screening period), Baseline (Week 0), Weeks 2, 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, and 52 or at the Premature Discontinuation visit. After Week 52, study visits will occur every 12 weeks until the study end.

Additionally, all subjects will be contacted by phone 1 week before and after the Baseline visit to ensure daily pain assessments are being recorded, and at Week 6 and Week 10 to monitor whether any signs or symptoms of infection are present at or near an HS lesion. If any signs or symptoms are reported at the time of the call, an unscheduled study visit will be conducted to assess whether an infection is present.

Adverse events will be collected throughout the study. Subjects who decide not to continue this study will have a 70-day follow-up phone call following their last dose of study drug to determine the status of any ongoing adverse events (AEs) or serious adverse events (SAEs), or the occurrence of any new AEs or SAEs. The 70-day follow-up phone call will not be required for any subject who initiates adalimumab therapy not supplied in the context of the clinical trial after the end of the study participation.

Figure 1. Study Schematic

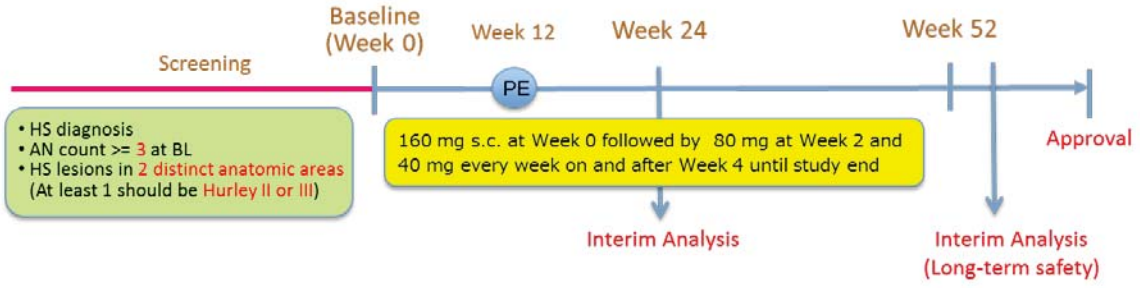

Table 1. Study Activities:

Activity	Screening (Day –35 to Day –1)	Baseline (Day 1)	Wk 2	Wk 4	Wk 8	Wk 12	Wk 16	Wk 20	Wk 24	Wk 28 32	Wk 36	Wk 40 44 48	Wk 52	Every 12 Weeks After Wk 52	Final or Premature Discontinuation Visit	Unscheduled Study Visit	70-Day Call
Informed Consent	X																
Inclusion/Exclusion Criteria	X	X[a]															
Prior and Concomitant Therapy Assessment[b]	X	X[a]	X	X	X	X	X	X	X	X	X	X	X	X	X		
Medical/Surgical History	X	X[a]															
Alcohol Use	X																
Nicotine Use	X					X									X		
Physical Exam	X	X	X[c]	X[c]	X[c]	X[c]	X[c]	X[c]	X[c]	X[c]	X[c]	X[c]	X	X[c]	X	X	
Chest X-ray/ ECG	X												X		X[d]		
TB Screening	X												X				
Vital Signs	X[e]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Pregnancy Tests	X[f]	X[g]		X[g]		X[g]			X[g]		X[g]		X[g]	X[g]	X[g]		
General Labs: Chemistry and Hematology[h]	X	X[h]		X		X			X		X		X	X	X		
Urinalysis[i]	X	X[h]		X		X			X		X		X	X	X		
CRP		X				X									X		
HIV	X																

Table 1. Study Activities: (Continued)

Activity	Screening (Day –35 to Day –1)	Baseline (Day 1)	Wk 2	Wk 4	Wk 8	Wk 12	Wk 16	Wk 20	Wk 24	Wk 28 32	Wk 36	Wk 40 44 48	Wk 52	Every 12 Weeks After Wk 52	Final or Premature Discontinuation Visit	Unscheduled Study Visit	70-Day Call
Hepatitis B/C Screen	X																
HbA1c		X				X									X		
PK Measurements[j]		X	X	X	X	X	X	X	X		X		X		X		
AAA Measurements[j]		X		X		X			X		X		X		X		
ANA/dsDNA[k]	X																
DLQI		X		X		X			X		X		X		X		
EQ-5D		X				X							X		X		
PGA of Skin pain	X[l]	X[l]	X[l]	X[l]	X[l]	X[l]			X		X		X	X	X		
Paper Diary	X	X	X	X	X	X											
HS QOL		X	X	X	X	X			X		X		X		X		
TSQM		X				X			X		X		X		X		
Lesion Counts[m]	**Wk –4** X[n]	**Wk –2** X[n]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Hurley Stage	X[n]	X[n]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Degree of Erythema[o]	X[n]	X[n]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Follow-up Phone Call	X[p]		X[p]		X[q]	X[q]											X[r]
Photographys		X		X		X			X				X		X		
Adverse Events[t]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Dispense Study Drug		X	X	X	X	X	X	X	X	X	X	X	X	X			

Table 1. Study Activities: (Continued)

Footnote for Table 1;

a. Update inclusion/exclusion, prior and concomitant therapy, and medical history information to assure subject eligibility.

b. From Screening through Week 12, subjects will complete a daily diary of their analgesic use using paper diary. After Week 12 and subsequent designated visits including Premature Discontinuation visit, subjects will be required to report if they took any analgesics within 24 hours of their in-office visit at the time of Patient Global Assessment of Skin Pain. Note: Subject may not be allocated to the study drug if pain diaries are not completed for 7 days (at minimum) prior to the Baseline visit.

c. A full physical exam is required at the Screening, Baseline, Week 52 and Final visit or Premature Discontinuation visit. A symptom-directed physical examination should be performed at other visits if, in the opinion of the investigator, it is warranted by the subject's AE status or on review of symptoms.

d. Subjects will have a repeat ECG and CXR at Week 52. Repeat ECG or CXR at Final visit or at Premature Discontinuation visit only if in the opinion of the investigator, clinically significant AEs develop during the study that warrant a repeat.

e. Height will be measured at Screening only.

f. All females of childbearing potential will have a serum pregnancy test at Screening that is performed at the central laboratory.

g. All females of childbearing potential will have a urine sample collected at Baseline and at the designated study visits. Any subject with a positive urine pregnancy test must have a negative serum test performed at the central laboratory prior to enrollment or continuation in the study. Urine pregnancy test at the Baseline will be performed also at site to confirm negative result on site. If the result at site is positive, treatment with study drug should not be started until the serum pregnancy test at the central laboratory is confirmed negative.

h. Refer to the laboratory manual for further instructions.

i. Dipstick urinalysis will be conducted by the central laboratory at required study visits. A microscopic analysis will be performed in the event the dipstick results show protein, ketones or blood greater than negative or glucose greater than normal or in the case of abnormal macroscopic results.

j. Blood samples must be obtained prior to dosing. Blood samples will be collected at the Premature Discontinuation visit if the subject discontinues prior to Week 52.

k. ANA/Anti dsDNA is required at the Screening visit. However, if a subject develops signs and symptoms of lupus, an ANA/Anti-dsDNA test may be repeated based on the investigator's clinical judgment.

l. From Screening through Week 12, subjects will complete a daily diary of their skin pain. See Protocol section 5.3.1.1. No in-office assessment of skin pain will be completed at the Week 12 visit. At the designated study visit after Week 12 until Final visit or Premature Discontinuation visit, subjects will complete skin pain assessments in the office based on a recall period of the last 24 hours. Note: Subject may not be allocated to the study drug if pain diaries are not completed for 7 days (at minimum) prior to the Baseline visit.

Table 1. Study Activities: (Continued)

m. The number, location, longest distance between relevant lesions, and whether the lesions are separated by normal-appearing skin will be measured. The site is responsible for counting lesions that received intervention (Protocol section 5.2.3.2) as permanently present in the lesion counts from the date of the intervention.

n. After IC, evaluation of Lesion Counts, Hurley Stage and Degree of Erythema should be performed twice in the Screening period by site visit. Time point will be Week –4 (Day –28) and Week -2 (Day -14).

o. At every visit, for each affected anatomic region, the investigator will assess the overall degree of erythema using a four-point ordinal scale ranging between 0 and 3.

p. Sites are encouraged to contact Subjects 1 week prior to the Baseline visit to confirm compliance with daily pain collection. Subjects will be contacted 1 week following the Baseline visit to ensure daily pain assessments are being recorded.

q. Subjects will be contacted 2 weeks following the Week 4 and 8 visits (i.e., Week 6 and Week 10) to obtain information on any signs of an infection at or near an HS lesion.

r. Site personnel will contact all subjects by phone approximately 70 days after the last dose of study drug to determine the status of any ongoing AEs/SAEs or the occurrence of any new AE/SAEs. The 70-day follow-up phone call will not be required for any subject who initiates adalimumab therapy not supplied in the context of the clinical trial after the end of study participation.

s. Subjects at pre-selected sites will have photographs taken at Baseline, Week 4, Week 12, Week 24, Week 52 and Final visit or at the Premature Discontinuation visit.

t. All AEs reported from the time of study drug administration until approximately 70 days following discontinuation of study drug administration will be collected. SAEs and protocol-related AEs will be collected from the time the subject signed the study-specific informed consent until approximately 70 days following discontinuation of study drug administration.

4.3 Sample Size

This study is designed to enroll approximately 15 subjects due to quite limited number of patients with HS in Japan, considering the feasibility of the study conduct. But study result will provide adequate information to characterize the safety profile of adalimumab.

In the global placebo-controlled studies (Studies M11-810 and M11-313), the response rates of HiSCR at Week 12 were 59% and 42% in the adalimumab ew group, and 28% and 26% in the placebo group, respectively. Assuming the threshold response rate at Week 12 of 25% (response rate with no medication) and the expected clinical response rate of 60%, a sample size of 13 subjects will have 80.1% power to detect the difference of 35% in the primary endpoint and using one sample Chi-square test at one-sided 2.5% significant level.

4.4 Interim Analysis

Interim analysis is planned at Week 24 and repeated at appropriate time after Week 52.

Measurements on or before the study drug dosing date at planned interim analysis time point (Week 24 or appropriate time after Week 52) will be included in the analysis. For subjects who do not take study drug at planned interim analysis time point, the last non-missing measurement collected on or before the date of the vital signs measurement will be used.

5.0 Analysis Populations

5.1 Definition for Analysis Populations

Full Analysis Set:

Full Analysis Set (FAS) population includes all subjects who complied with GCP and received at least one dose of study drug and had at least one post-treatment efficacy assessment. FAS is the primary population for the efficacy analysis.

Safety Dataset:

Safety Population is defined as all subjects who receive at least one dose of study drug in the study, and will be used for safety analysis.

5.2 Variables Used for Stratification of Randomization

Not applicable.

6.0 Analysis Conventions

Unless otherwise specified, the efficacy and safety continues variables will be summarized using the descriptive statistics (including mean, standard deviation, median, minimum and maximum), and for qualitative variables, the number (n) and percentage (%) of subjects with non-missing data per category will be the default summary presentation.

Definition of Terms

Abscess	A circumscribed collection of purulent exudate frequently associated with swelling and other signs of inflammation, such as fluctuance, tenderness and pain.
HiSCR	Hidradenitis Suppurativa Clinical Response, defined as at least a 50% reduction in the AN count with no increase in abscess count and no increase in draining fistula count relative to Baseline.
Hurley Staging	Stage I: Abscess formation, single or multiple, without sinus tracts and cicatrization (scarring). Stage II: One or more widely separated recurrent abscesses with tract formation and cicatrization (scars). Stage III: Multiple interconnected tracts and abscesses across the entire area, with diffuse or near diffuse involvement.
Hypertrophic Scar	Enlargement or overgrowth of a scar so that it extends above the surrounding skin surface

Inadequate Response to Antibiotics	An adequate trial of oral antibiotic therapy is considered to be at least 90 days in duration. If, after at least 90 days (≥ 90 days) of oral antibiotic therapy, any of the following has occurred, subject will be considered to have had inadequate response, or loss of response, to oral antibiotics: • Progression of Hurley Stage (i.e., the Hurley Stage of at least one affected anatomic region has progressed from I – II, II – III, or I – III); • Subject requires at least one intervention (e.g., incision and drainage or intralesional injection of corticosteroid); • Subject experiences pain interfering with activities of daily living, with unsatisfactory relief from over-the-counter analgesics (e.g., ibuprofen or acetaminophen); • Subject experiences pain requiring opioids, including tramadol; • Subject experiences drainage interfering with activities of daily living (e.g., requires multiple dressing changes and/or changes of clothes daily); • Subject experiences an increase in the number of anatomic regions affected by HS; • Subject experiences at least one new abscess or one new draining fistula. • Sites are encouraged to contact AbbVie TA MD to confirm if the definition of inadequate response or loss of response has been met.
Inflammatory nodules	A tender, erythematous well-defined nodule. The lesion has no evidence of fluctuance. A pyogenic granuloma lesion is considered an inflammatory nodule; a papule or pustule is not considered an inflammatory nodule.
Intolerance to Antibiotics	A subject is defined as intolerant to oral antibiotic when oral antibiotic therapy has been discontinued by a physician as a result of a significant adverse reaction to oral antibiotic administration. A reaction will be considered significant if the adverse reaction is at least moderately severe (i.e., the adverse event causes the subject discomfort and interrupts the subject's usual activities or function). Examples of significant adverse reactions include, but are not limited to: • nausea resulting in decreased oral intake; • macular or papular eruption or erythema associated with pruritus or other associated symptoms; • dizziness/disequilibrium/lightheadedness/vertigo interfering with function; • allergic reaction manifesting as rash, flushing, urticaria, dyspnea, or drug fever ≥ 38°C; • diarrhea manifesting as an increase in stool frequency of at least 4 stools per day over Baseline. Sites are encouraged to contact AbbVie TA MD to confirm if the definition of intolerance has been met.

Loss of Response (LOR)	An AN count that is greater than the average of AN counts at Baseline and Week 12. It is a loss of at least 50% of the improvement (reduction) in the AN count achieved from baseline to Week 12. Calculation: AN > ½ * (Baseline AN count + Week 12 AN count)		
Baseline AN Count	**Week 12 AN Count**	**Average of AN Counts**	**Minimum Count to Meet LOR**
10	1	½ * (10 + 1) = 5.5	6
10	4	½ * (10 + 4) = 7	8
Fistula	Pathologic passageway connecting to the skin surface from dermis or subcutaneous tissue. Draining fistulas are fistulas that drain serous or purulent fluid, either spontaneously or by gentle palpation. Sinus tracts are a sub-type of (non draining) fistula in which the passageway links two or more areas underneath the skin surface, but does not communicate with the skin surface.		
Non-inflammatory nodules	Non-tender or minimally tender, non-erythematous nodules.		
Protocol Allowed Intervention	A protocol-allowed intervention is defined as incision and drainage, or injection of intralesional triamcinolone acetonide suspension (at a dose of 50 mg/5 mL, up to 0.5 mL).		
Worsening or Absence of Improvement (WOAI)	An AN count that has been ≥ Baseline AN count at two consecutive visits occurring ≥ 14 days apart.		

Definition of Baseline

The last non-missing measurement collected on or before the day of the first dose of study drug injection will be used as Baseline for summary of demographics and disease characteristics, the safety analysis and all the efficacy analysis, with the following exception.

For Patient's Global Assessment of Skin Pain (Numerical Rating Scale, Skin Pain NRS), the average of the last 7 assessments BEFORE the date of first dose of study drug injection will be used as Baseline. If there are only 4 to 6 daily assessments available, the average of the available assessments will be used. If there are 3 or less assessments available, the subject's Baseline will be considered as missing.

Definition of Final Observation Value

Final observation for safety analyses is defined as the last non-missing observation collected on or prior to the cut-off date.

- For subjects who did not discontinue the study before the interim cut-off date, final observation is defined as the last non-missing observation collected after the first dose of study drug and on the dose of study drug at Week 24 or Week 52.
- For subjects who discontinued the study before cut-off date, final observation is defined as the last non-missing observation collected after the first dose of study drug and within 70 days after the last dose.

Definition of Rx Days (Days Relative to the First Dose of Study Drug)

Rx Days are calculated for each time point of interest and it provides a quantitative measure of days between the event and the first dose date. That is, the Rx Day is calculated as the event date minus the date of first dose of study drug plus 1. The Rx Day will be a negative value when the time point of interest is prior to the date of first dose of study drug, and the Rx Day will be a positive value when the time point of interest is after the first dose date. By this calculation algorithm the first dose day is Rx Day 1, while the day prior to the date of first dose is defined as Rx Day –1 (there is no Rx Day 0). Rx days are used to map actual study visits to the protocol specified study visits.

Definition of Analysis Windows

Since subjects do not always adhere to the study visit schedule, the following rules will be applied to assign actual visits to protocol-specified visits including early termination visits. For each study visit mentioned in the protocol, a nominal or target day will be selected to represent the corresponding visit along with a window around the target day. Windows will be selected in a non-overlapping fashion so that a date collected on the CRF does not correspond to multiple visit windows. Moreover, windows will not discard any post baseline measurement recorded on the CRF. If a subject had two or more actual visits in one visit window, the visit closest to the target will be used as the study visit for that

window. If two visits are equal distance to the nominal day, then the later visit will be used in analysis. If more than one assessment is included on the same day, then the worst assessment on that day will be used in analyses.

For the visit-wise analysis of Skin Pain NRS through Week 12, the weekly averages of pain will be summarized for the two items (Pain at-worst and Pain on-average) separately. The weekly average score will be calculated based on the 7 available daily scores from the days within each visit window that are closest to the nominal day. If there are 4 to 6 assessments in the visit window, the average of the available assessments will be used. If more than one assessment is included on the same day, the worst assessment on that day will be chosen as the daily score. If there are more than 7 daily scores available and the 7th and 8th observations (ranked based on distance from the nominal day) are equidistant to the nominal day, the one after the nominal day will be used to calculate the weekly score. For any visit with less than 4 diary entries within the visit window, the weekly average will be recorded as missing. Of note, Skin Pain NRS is not to be collected on the day of Week 12 visit; if collected, the data point will not be used in the Week 12 summary because it will be unclear if the assessment is before or after the Week 12 dose.

Rolling weekly average Skin Pain NRS (both pain at-worst and pain on-average) will be analyzed daily from Day 7 through the minimum of Day 98 and the day prior to week 12 drug injection. The rolling weekly average score is calculated as follows. Let P_{m-6}, P_{m-5},…, P_{m-1}, P_m be the daily pain scores from day $m - 6$ to day m (P_i, $m - 6 \leq i \leq m$, will be set as 0 if the pain score on day i is missing for the following calculation purpose) and N_m be the number of days with non-missing pain scores from day $m - 6$ to day m, then the rolling weekly average for day m is:

$$\frac{\sum_{i=m-6}^{m} P_i}{N_m}$$

If there are less than 4 daily entries available ($N_m < 4$), then the rolling weekly average of day m will be counted as missing. If more than one assessment is included on the same day, the worst assessment on that day will be chosen as the daily score.

Table 2. Visit Windows for Analysis of Efficacy Variables (Lesion Count, Hurley Stage, Degree of Erythema)

Scheduled Week	Nominal Day	Time Window (Rx Day Range)
Week -4	-	-35 - -22
Week -2	-	-21 - -1
Baseline	1	1
Week 2	15	2 – 22
Week 4	29	23 – 43
Week 8	57	44 – 71
Week 12	85	72 – 99
Week 16	113	100 – 127
Week 20	141	128 – 155
Week 24	169	156 – 183
Week 28	197	184 – 211
Week 32	225	212 – 239
Week 36	253	240 – 267
Week 40	281	268 – 295
Week 44	309	296 – 323
Week 48	337	324 – 351
Week 52	365	352 – 407
Week K[$]	K*7 + 1	K*7-40 – K*7+43

[$:] Every 12 weeks thereafter

Table 3. Visit Windows for Analysis of Vital Signs

Scheduled Week	Nominal Day	Time Window (Rx Day Range)
Baseline	1	≤ 1
Week 2	15	2 – 22
Week 4	29	23 – 43
Week 8	57	44 – 71
Week 12	85	72 – 99
Week 16	113	100 – 127
Week 20	141	128 – 155
Week 24	169	156 – 183
Week 28	197	184 – 211
Week 32	225	212 – 239
Week 36	253	240 – 267
Week 40	281	268 – 295
Week 44	309	296 – 323
Week 48	337	324 – 351
Week 52	365	352 – 407
Week K[$]	K*7 + 1	K*7-40 – K*7+43

[$:] Every 12 weeks thereafter

Table 4. Visit Windows for Analysis of Efficacy Variables (PGA of skin pain)

Scheduled Week	Nominal Day	Time Window (Rx Day Range)
Baseline	-1	≤ -1
Week 2	14	1 – 21
Week 4	28	22 – 42
Week 8	56	43 – 70
Week 12	84	71 – 126
Week 24	169	127 – 211
Week 36	253	212 – 309
Week 52	365	310 – 407
Week K[$]	K*7 + 1	K*7-40 – K*7+43

[$]: Every 12 weeks thereafter

Table 5. Visit Windows for Analysis of HbA1c and CRP

Scheduled Week	Nominal Day	Time Window (Rx Day Range)
Baseline	1	≤ 1
Week 12	85	2 – Final or Premature Discontinuation after Week 12 - 1
Final or Premature Discontinuation after Week 12		

Table 6. Visit Windows for Analysis of Efficacy Variables (HS QOL)

Scheduled Week	Nominal Day	Time Window (Rx Day Range)
Baseline	1	≤ 1
Week 2	15	2 – 22
Week 4	29	23 – 43
Week 8	57	44 – 71
Week 12	85	72 – 127
Week 24	169	128 – 211
Week 36	253	212 – 309
Week 52	365	310 – Final or Premature Discontinuation after Week 52 - 1
Final or Premature Discontinuation after Week 52		

Table 7. Visit Windows for Analysis of Efficacy Variables (DLQI)

Scheduled Week	Nominal Day	Time Window (Rx Day Range)
Baseline	1	≤ 1
Week 4	29	2 – 57
Week 12	85	58 – 127
Week 24	169	128 – 211
Week 36	253	212 – 309
Week 52	365	310 – Final or Premature Discontinuation after Week 52 - 1
Final or Premature Discontinuation after Week 52		

Table 8. Visit Windows for Analysis of Efficacy Variables (EQ-5D)

Scheduled Week	Nominal Day	Time Window (Rx Day Range)
Baseline	1	≤ 1
Week 12	85	2 – 225
Week 52	365	226 – Final or Premature Discontinuation after Week 52 - 1
Final or Premature Discontinuation after Week 52		

Table 9. Visit Windows for Analysis of Efficacy Variables (TSQM)

Scheduled Week	Nominal Day	Time Window (Rx Day Range)
Baseline	1	≤ 1
Week 12	85	2 – 127
Week 24	169	128 – 211
Week 36	253	212 – 309
Week 52	365	310 – Final or Premature Discontinuation after Week 52 - 1
Final or Premature Discontinuation after Week 52		

Table 10. Visit Windows for Analysis of General Laboratory Parameters

Scheduled Week	Nominal Day	Time Window (Rx Day Range)
Baseline	1	≤ 1
Week 4	29	2 – 57
Week 12	85	58 – 127
Week 24	169	128 – 211
Week 36	253	212 – 309
Week 52	365	309 – 407
Week K[$]	K*7 + 1	K*7-40 – K*7+43

[$]: Every 12 weeks thereafter

Analysis time windows for study drug injections are constructed using the following algorithm:

- Determine the nominal Rx day for each scheduled injection (e.g., Week 0 [first dose of adalimumab] equals Rx Day 1. Week 1 [1 week after first dose of adalimumab] equals Rx Day 8).
- Determine the window around a specific nominal Rx day by adding or subtracting half of the interval between adjacent scheduled injections (e.g., the number of days between Week 0 and Week 1 is 7). The threshold between adjacent scheduled injections is determined by splitting the interval evenly between the injections (e.g., the split between Week 0 and Week 1 would be between Rx Days 4 and 5).

The following time window specified will be used for the summary of study drug injections.

Table 11. Visit Windows for Summary of Study Drug Injections

Scheduled Week	Nominal Day	Time Window (Rx Day Range)
Week 0 (Baseline)	1	1
Week 2	15	2 – 22
Week 4	29	23 – 32
Week 5	36	33 – 39
Week 6	43	40 – 46
Week 7	50	47 – 53
Week 8	57	54 – 60
Week 9	64	61 – 67
Week 10	71	68 – 74
Week 11	78	75 – 81
Week 12	85	82 – 88
Week 13	92	89 – 95
Week 14	99	96 – 102
Week 15	106	103 – 109
Week 16	113	110 – 116
Week 17	120	117 – 123
Week 18	127	124 – 130
Week 19	134	131 – 137
Week 20	141	138 – 144
Week 21	148	145 – 151
Week 22	155	152 – 158
Week 23	162	159 – 165
Week 24	169	166 – 172
Week K[$]	K*7 + 1	K*7-2 – K*7+4

[$:] Every weeks thereafter

Baseline Value is Missing

Subjects will be excluded from analysis which is based on change or percent change from baseline if baseline evaluation is missing.

When no baseline value is available (i.e. missing baseline) for a subject, percent change from baseline cannot be calculated and therefore percent change values will be set to missing.

When the baseline value is 0, the percent change from baseline will be calculated based on the post-baseline value using the following general rules:

- If the post-baseline value is missing, then the percent change will be missing.
- If the post-baseline value is 0, then the percent change will be set to 0.
- If the post-baseline value is non-missing and not 0, then the percent change will be set to missing.

Definition of Missing Data Imputation

The following imputation methods will be used to impute missing values in the efficacy analyses. In general, missing Baseline and safety data will not be imputed. In addition, an observed case analysis will be performed.

- Non-Responder Imputation (NRI)

  The NRI analysis will categorize any subject who has missing value at a specific visit as non-responder for that visit. The NRI will be the primary approach in the analysis of categorical variables.

- Last Observation Carried Forward (LOCF)

  The LOCF analyses will use the completed evaluation from the previous visit within the particular period for efficacy measures assessed to impute missing data at later visits in the same period. Baseline efficacy evaluations will not be carried forward.

LOCF will be the primary approach in the analysis of continuous variable, and the secondary approach in the analysis of categorical variables.

- As-observed:

  The As-observed analysis will not impute values for missing evaluations, and thus a subject who did not have an evaluation on a scheduled visit will be excluded from the as observed analysis for that visit. As observed analysis will be the secondary approach in the analysis of continuous variables.

Lesions that received intervention will be counted as permanently present from the date of the intervention.

- Imputation of Missing Dates

For baseline, efficacy and safety parameters, if the day and/or month are missing, the following conventions will be used to impute the missing dates:

- 01 for missing start day
- End of month for missing end day
- January 1st for missing start month
- December 31st for missing end month

In case of missing or partially missing dosing dates, the dates will not be imputed.

In case of missing or partially missing adverse event start and stop dates, the dates will be imputed by comparing to the first dosing date so that the corresponding adverse events will be made treatment-emergent, whenever possible.

Rounding of Numeric Results

Rounding will be performed only for presentation of results. No rounding will be performed before or during analyses/calculations. The ROUND function of SAS will be used to round results for presentation. The mean and median will be rounded for presentation to 1 decimal more than the data were entered into the database.
For example, mean systolic blood pressure will be presented to one decimal place (125.2

mmHg) when it is recorded to integer level in the database (110 mmHg). The standard deviation will be rounded to 2 decimal places more than the data were entered into the database (e.g., 25.31 mmHg for systolic blood pressure). The minimum and maximum values will be presented as entered into the database.

For the calculation of HiSCR, the percent change in AN count will be rounded to 3 decimal places using usual rounding rules (e.g., –19.9955% = – 19.996%). Then the rounded result will be used to compare with –50% to determine the HiSCR (responder versus non-responder).

Percentages will be rounded for presentation to one decimal place; e.g., the proportion 0.1244 will be reported in percent as 12.4.

7.0 Demographics, Baseline Characteristics, Medical History, and Previous/Concomitant Medications

7.1 Demographic and Baseline Characteristics

All demographic and baseline variables will be described with summary statistics. Categorical data will be summarized using the frequency and percentage; continuous data will be summarized using the mean, standard deviation, first quartile (Q1), median, third quartile (Q3), minimum, and maximum. The number of non-missing values will also be summarized.
All summaries will be presented for the analysis populations defined in Section 5.1.
No statistical test will be performed.

The following demographic and baseline values will be summarized.

Continuous variables:

- Age (years) defined as the number of years from birth to the first study visit
- Body Weight (kg)
- Height (cm)
- Body mass Index (kg/m2)

- Blood Pressure (systolic/diastolic) (mmHg)
- Pulse (bpm)
- Respiratory Rate (bpm)
- Body Temperature (°C)
- Duration of Hidradenitis Suppurativa (HS) [year]
- Modified Sartorius scale
- AN count, nodule (non-inflammatory, inflammatory), abscess, fistula (non-draining, draining) count, and hypertrophic scar count – among all subjects and among subjects with non-zero count
- Number of anatomic regions affected
- Dermatology Life Quality Index (DLQI) [0-30]
- Numeric Rating Scale (NRS) for Patient's Global Assessment of Skin Pain (at worst and on-average)
- Treatment Satisfaction Questionnaire – Medication (TSQM)
- C-Reactive Protein
- $HbA1_c$
- Cigarette use
- HSQoL
- EQ-5D Index
- EQ-5D VAS

Categorical variables:

- Sex (male/female)
- Race (White, Black or African American, Asian, American Indian or Alaska Native, Native Hawaiian or Other Pacific Islander, Other)
- Ethnicity (Japanese, Chinese, Korean, Taiwanese, Other)
- Age categories (< 40, 40–64, ≥ 65, if less than 10% of subjects in the ≥ 65 group, that group will be combined with 40–64 group.)

- Body Weight categories (< Median, ≥ Median)
- Body Mass Index (BMI) category: normal (< 25), over weight (25 – < 30), obese (30 – < 40), Morbid obesity (≥ 40)
- Family history of HS (yes, no)
- Screen failure (status [yes, no], experience SAE during screening [yes, no])
- Current smoking status (yes/no)
- Duration of Hidradenitis Suppurativa (HS) (< Median, ≥ Median)
- Tobacco use (Current, Former, Never, Unknown)
- Alcohol use (Current, Former, Never, Unknown)
- Hurley Stage (the worst level across all anatomic regions)
- Prior HS surgery history (yes, no)
- Time from prior HS surgery to the first dose of study drug (< Median, ≥ Median)
- CRP level (< Median, ≥ Median)
- AN count (≤ 5, 6 – 10, 11+)
- AN count (< Median, ≥ Median)
- Degree of Erythema by anatomic region and for the worst among all anatomic regions
- Concomitant use of oral antibiotics (yes/no)
- ECG assessment at screening visit (normal, abnormal-not clinically significant, abnormal-clinically significant)
- Chest x-ray (finding [normal, abnormal], Calcified granulomas [absent, present], pleural scarring [absent, present], pleural thickening [absent, present])
- Tuberculin PPD skin test result (negative [< 5 mm], positive [≥ 5 mm])
- QuantiFERON-TB Gold test result (negative, indeterminate, positive)
- TB Prophylaxis (enrolled [yes, no], [INH, Other TB Prophylaxis])
- TB history (high risk of TB [yes, no], former BCG immunization [yes, no, unknown])

- Hepatitis B surface antigen (HBsAg [positive, negative])
- Hepatitis B core antibody Total (HBcAb, Total [positive, negative])
- Hepatitis B surface antibody (HBsAb [positive, negative, indeterminate])
- HBV DNA PCR (positive, negative) among subjects with positive HBcAb or HBsAb
- HbA1c (< 7%, ≥ 7%)
- Antinuclear antibody (ANA) (positive, negative)
- Anti-double stranded DNA (dsDNA) (positive, negative)
- Lesion Counts by anatomic region

The duration of HS will be calculated relative to the date of the screening visit (i.e., duration = [date of first study visit – date of onset] + 1). Duration of HS will be expressed in years, by dividing the result in days by 365.25, and then rounding to the nearest tenth.

7.2 Medical History

For the FAS population, the medical history data will be summarized and presented using body systems and conditions/diagnoses as captured on the eCRF. The body systems will be presented in alphabetical order and the conditions/diagnoses will be presented in alphabetical order within each body system. The number and percentage of subjects with a particular condition/diagnosis will be summarized. Subjects reporting more than one condition/diagnosis within a body system will be counted only once for that body system.

7.3 Prior and Concomitant Therapy

Prior and concomitant therapy using drug generic name coded using World Health Organization (WHO) dictionary will be summarized by the generic name with counts and percentages.

A prior medication is defined as any medication taken prior to the first dose of the

analysis period of each analysis population. A concomitant medication is defined as any medication that started prior to the first dose of the analysis period and continued to be taken after the first dose of the analysis period or any medication that started after the first dose of the analysis period, but not after the last dose of the analysis period. The number and percentage of subjects who had taken medications will be summarized by generic drug name for both prior and concomitant medications.

Prior HS treatment received and discontinued (including reason for discontinuation) prior to screening will be summarized as well.

Prior HS related surgery will be summarized. Subjects with prior HS related surgery will be identified per medical review prior to database lock.

8.0 Patient Disposition

Subject disposition will be present for subjects in the safety analysis set using the following information

- Number of subjects in each analysis population
- Number of screening failure
- Subjects who completed the study
- Subjects who prematurely discontinued study drug

In addition, the reasons for premature discontinuation (primary reason and all reasons) will be summarized with frequencies and percentages. Subjects with multiple reasons for premature discontinuation will be counted once in the calculation of the number and percentage of total discontinuations ("Premature Discontinuation").

9.0 Study Drug Exposure and Compliance

For the Safety Analysis Set population, study drug exposure will be summarized through the study as follows:

9.1 Study Drug Exposure

The duration (days) of exposure to study drug will be summarized using the number of subjects treated, mean, standard deviation, median, minimum, and maximum. It will also be summarized in weekly intervals with frequencies and percentages for the number of subjects receiving study drug doses in each interval. In addition cumulative exposure of adalimumab (including total patient years) will be summarized.

Duration of exposure is defined the number of days since first dose of study drug through the last dose date plus 14 days. For interim analysis mentioned in Section 4.4, the Week 24/appropriate time after Week 52 dosing date will be used instead of last dose plus 14 days only for ongoing subjects. For subjects who missed the Week 24/appropriate time after Week 52 study drug injection but continued after the Week 24/appropriate time after Week 52, the study drug exposure = (date of the first available study drug injection after the Week 24/appropriate time after Week 52 - date of first study drug injection).

9.2 Compliance

Compliance (%) is defined as the number of injections received divided by the number of injections planned during the subject's participation in the study (rounded to 0.1%). In addition, at each scheduled time point (i.e., Week 0, Week 2, every week from Week 4), the number of injections received will be summarized with frequencies and percentages. Compliance will be summarized by descriptive statistics, including the mean, standard deviation, Q1, median, Q3, minimum, and maximum.

When computing compliance at each scheduled time point, the denominator for each week will include all subjects in each analysis population who have not prematurely discontinued prior to the scheduled study drug injection.

9.3 Study Drug Dose

160 mg starting at Baseline (Week 0) and 80 mg Week 2 followed by 40 mg every week (ew) starting at Week 4.

10.0 Efficacy Analysis

This section provides the details of the efficacy analysis for the study.

10.1 General Considerations

This study is an open-label study without any comparator. No formal statistical test will be conducted, and descriptive statistics will be provided. These include the number of observations, mean, standard deviation, minimum, median, and maximum for continuous variables; discrete variables will be summarized by counts and percentages with 95% confidence intervals.

All efficacy analyses and subgroup analyses will be performed on the FAS populations.

10.2 Primary Efficacy Analysis

The primary efficacy endpoint is the proportion of subjects achieving HiSCR at Week 12. HiSCR is defined as at least a 50% reduction in the total abscess and inflammatory nodule count (AN count) with no increase in abscess count and no increase in draining fistula count relative to Baseline.

Imputation Method Used for the Primary Efficacy Analysis

Missing data will be imputed using the non-responder imputation (NRI) approach. For details on missing data imputation methods, refer to Section 6. Sensitivity analyses will be performed for the primary efficacy variable by using LOCF and modified NRI.

Modified NRI (mNRI): counting all subjects with any add-on antibiotics (any antibiotics other than the Baseline concomitant ones) or with dose increase on Baseline concomitant antibiotics prior to Week 12, regardless the reason for use, as non-responders.

10.3 Secondary Efficacy Analyses

Discrete variables will be summarized by counts and percentages, and continuous variables will be summarized by descriptive statistics on the items below at each visit.

The subjects who have missing data for any reason such as early terminated subjects will be included into analysis using NRI for discrete variables or LOCF for continuous variables.

For the analysis of Patient's Global Assessment of Skin Pain (NRS), daily assessment will be evaluated and weekly average will be used. For analysis, subjects who received analgesics other than ibuprofen or acetaminophen (e.g., Tramadol) or received ibuprofen or acetaminophen that exceeds the maximum allowed dose (to be determined prior to database lock), for skin pain, or have undergone intervention will be counted as non-responder for categorical variables, and have their last pain assessment before the start date of the analgesic or date of the intervention carried forward for continuous variables, from the start day of the analgesics or the day of the intervention until fourteen (14) days after the stop of analgesic use or the day of the intervention. LOCF and As-Observed analysis will be the sensitivity analyses for categorical variables and for continuous variables, respectively.

Concomitant medication for treatment of HS or pain will be reviewed; confounding medications (those considered as having potential effect on the pain assessments) and the time periods affected by such medications will be determined. Subjects will be counted as non-responder for categorical variables, and have their last pain assessment before the start of the confounding medications carried forward for continuous variables for these periods.

Do not take the following exclusionary medication:

- Using any antibiotics for the treatment of HS (except the protocol allowed baseline concomitant antibiotics)
- Protocol allowed baseline concomitant antibiotics that are not a stable dose
- Using Methotrexate (MTX), cyclosporin, corticosteroids, and retinoids for any reason, or other medication for treatment of their HS

The following secondary efficacy variables will be analyzed:

- Proportion of subjects achieving AN count of 0, 1, or 2 at Week 12
- Proportion of subjects achieving at least 30% reduction and at least 1 unit reduction from Baseline in Patient's Global Assessment of Skin Pain (NRS30) – at worst at Week 2 among subjects with baseline NRS ≥ 3
- Change in modified Sartorius scale from Baseline to Week 12 including screening period (Week -4, Week -2)

Other efficacy variables will be analyzed at each scheduled visit, including the primary or secondary variables for visits other than Week 2 or 12.

- Proportion of subject achieving HiSCR
- Proportion of subject achieving HiSCR (first screening date as baseline)
- Proportion of subjects achieving AN count of 0, 1, or 2
- Proportion of subjects achieving NRS30 – at worst, among subjects with baseline Patient's Global Assessment of Skin Pain (NRS) ≥ 3
- Proportion of subjects achieving NRS30 – on average, among subjects with baseline Patient's Global Assessment of Skin Pain (NRS) ≥ 3
- Change in modified Sartorius scale from Baseline including screening period (Week -4, Week -2)
- Proportion of subjects achieving complete elimination of abscesses at each visit, among subjects who have any abscess at Baseline
- Percentage change from Baseline in number of abscesses, among subjects who have at least one abscess at Baseline
- Change from Baseline in number of abscesses
- Proportion of subjects achieving complete elimination of draining fistulas at each visit, among subjects who have any draining fistulas at Baseline
- Percentage change from Baseline in number of draining fistulas, among subjects who have at least one draining fistula at Baseline
- Change from Baseline in number of draining fistulas

- Percentage change from Baseline in number of inflammatory nodules, among subjects who have at least one inflammatory nodule at Baseline
- Proportion of subjects achieving complete elimination of inflammatory nodules at each visit, among subjects who have any inflammatory nodules at Baseline
- Change from Baseline in number of inflammatory nodules
- Number of interventions until Week 12
- Proportion of subjects with DLQI = 0
- Proportion of subjects with DLQI = 0 or 1
- Change from Baseline in DLQI
- Percentage change from Baseline in Patient's Global Assessment of Skin Pain (NRS) – at worst, among subjects who have baseline NRS ≥ 3
- Percentage change from Baseline in Patient's Global Assessment of Skin Pain (NRS) – on average, among subjects who have baseline NRS ≥ 3
- Change from Baseline in Patient's Global Assessment of Skin Pain (NRS) – at worst
- Change from Baseline in Patient's Global Assessment of Skin Pain (NRS) – on average
- Proportion of subjects achieving AN50 (at least 50% reduction in the AN count relative to Baseline)
- Proportion of subjects achieving AN75 (at least 75% reduction in the AN count relative to Baseline)
- Proportion of subjects achieving AN100 (100% reduction in the AN count relative to Baseline)
- Absolute and percentage change from Baseline in AN count including screening period (Week -4, Week -2)
- Proportion of subjects achieving erythema score of 1 or 0 in all affected anatomic regions among subjects who have erythema score of 2 or more in at least one anatomic region at Baseline
- Proportion of subjects who experience worsening by at least one Hurley Stage in at least 1 affected anatomic region

- Proportion of subjects who experience improvement by at least one Hurley Stage in at least 1 affected anatomic region
- Change from baseline in TSQM
- Change from baseline in EQ-5D index
- Change from baseline in EQ-5D VAS
- Change from baseline in HSQoL
- Proportion of subjects who experience flare, defined as an at least 25% increase in AN counts with a minimum increase of 2 relative to Baseline
- Number of days on flare, calculated from the day when flare is observed to the day prior to the observation that flare is no long present. Of note, there could be multiple periods that flares are observed, in which case, the total days from the multiple periods will be used
- Proportion of subjects who experience at least 25% increase in abscess counts with a minimum increase of 2 relative to Baseline
- Proportion of subjects who experience at least 25% increase in inflammatory nodule counts with a minimum increase of 2 relative to Baseline
- Proportion of subjects who experience at least 25% increase in draining fistula counts with a minimum increase of 2 relative to Baseline
- Change from Baseline in CRP
- Percentage change from Baseline in CRP
- Time to the second incidence of the two-consecutive visits with AN count ≥ Baseline AN count (will be calculated from the date of the Week 12 to the second incidence of the two consecutive visits that lead to WOAI)
- Time to LOR (will be calculated from the date of the Week 12 to the first visits that lead to LOR)

Minimal clinically important difference (MCID) for all patient reported outcomes are defined in Appendix B.

Additional Secondary Efficacy Variables

- Cumulative density plot of percent change from Baseline in AN count at Week 12

- Plot of proportion of subjects achieving HiSCR by visit
- Proportion of subjects achieving MCID in DLQI
- Proportion of subjects achieving MCIDs in TSQM
- Proportion of subjects achieving MCID in HSQoL
- Proportion of subjects achieving MCID in EQ-5D index
- Proportion of subjects achieving MCID in EQ-5D VAS
- Proportion of subjects achieving NRS30 – at worst based on rolling weekly average, among subjects with Baseline Skin Pain NRS ≥ 3.
- Proportion of subjects achieving NRS30 – on average based on rolling weekly average, among subjects with Baseline Skin Pain NRS ≥ 3.
- Change from Baseline in Patient's Global Assessment of Skin Pain (NRS) – at worst based on rolling weekly average, among subjects with Baseline Skin Pain NRS ≥ 3.
- Change from Baseline in Patient's Global Assessment of Skin Pain (NRS) – on average based on rolling weekly average, among subjects with Baseline Skin Pain NRS ≥ 3.
- Percent change from Baseline in Patient's Global Assessment of Skin Pain (NRS) – at worst, based on rolling weekly average, among subjects with Baseline Skin Pain NRS ≥ 3.
- Percent change from Baseline in Patient's Global Assessment of Skin Pain (NRS) – on average, based on rolling weekly average, among subjects with Baseline Skin Pain NRS ≥ 3.

Table 12. Summary of Efficacy Variables and Statistical Analyses

Efficacy Variables		Derivation
Categorical Efficacy Variables (Proportion of Responders at Each Visit)		
1.	HiSCR response	• Responder: percent reduction from baseline in AN ≥ 50% and absolute change in abscess count ≤ 0 and absolute change in draining fistulas count ≤ 0 • Non-responder: otherwise
2.	AN012	• Responder: total number of abscess counts and inflammatory nodule counts < 3 • Non-responder: otherwise
3.	NRS30 – at worst. At least 30% reduction and 1 unit absolute reduction in Patient's Global Assessment of Skin Pain – at worst	• Among subjects with baseline value ≥ 3: Responder: percent reduction from baseline ≥ 30% and absolute reduction from baseline ≥ 1 • Non-responder: otherwise
4.	NRS30 – on average. At least 30% reduction and 1 unit absolute reduction in Patient's Global Assessment of Skin Pain	• Among subjects with baseline value ≥ 3: Responder: percent reduction from baseline ≥ 30% and absolute reduction from baseline ≥ 1 • Non-responder: otherwise
5.	Modified Sartorius Score	The derivation of modified Sartorius Score will be provided in the SAP.
6.	Complete elimination of abscesses	Among subjects with baseline value ≥ 1: • Responder: abscesses count = 0 • Non-responder: otherwise
7.	Complete elimination of draining fistulas	Among subjects with baseline value ≥ 1: • Responder: draining fistulas count = 0 • Non-responder: otherwise
8.	Complete elimination of inflammatory nodules	Among subjects with baseline value ≥ 1: • Responder: inflammatory nodule count = 0 • Non-responder: otherwise

Table 12. Summary of Efficacy Variables and Statistical Analyses (Continued)

Efficacy Variables	Derivation
Categorical Efficacy Variables (Proportion of Responders at Each Visit) (Continued)	
9. DLQI0	• Responder: DLQI = 0 • Non-responder: otherwise
10. DLQI01	• Responder: DLQI = 0 or 1 • Non-responder: otherwise
11. AN50	• Responder: percent reduction from Baseline ≥ 50% • Non-responder: otherwise
12. AN75	• Responder: percent reduction from Baseline ≥ 75% • Non-responder: otherwise
13. AN100	• Responder: abscesses count = 0 and inflammatory nodule count = 0 • Non-responder: otherwise
14. Erythema01	Among subjects who have erythema score ≥ 2 in at least one anatomic region at Baseline • Responder: erythema score = 1 or 0 in all anatomic regions • Non-responder: otherwise
15. Worsening in Hurley Stage	• Experiencing worsening: the minimum increase from baseline in Hurley Stage among all anatomic regions > 0 • Not experiencing worsening: otherwise
16. Improvement in Hurley Stage	• Responder: the minimum reduction from baseline in Hurley Stage among all anatomic regions > 0 • Non-responder: otherwise

Table 12. Summary of Efficacy Variables and Statistical Analyses (Continued)

Efficacy Variables		Derivation
Categorical Efficacy Variables (Proportion of Responders at Each Visit) (Continued)		
17.	Abscess count	
18.	Draining fistula count	
19.	Inflammatory nodule count	
20.	AN count	
21.	Patient's Global Assessment of Skin Pain – at worst	Among subjects with baseline value ≥ 3
22.	Patient's Global Assessment of Skin Pain – on average	Among subjects with baseline value ≥ 3
23.	DLQI	The derivation of DLQI will be provided in the SAP.
24.	TSQM	Total score is calculated by summing the scores from all 13 items.

10.4 Handling of Multiplicity

No adjustment for multiplicity will be done.

10.5 Efficacy Subgroup Analysis

To evaluate the consistency of the efficacy in the primary efficacy variable over demographic and other baseline characteristics, summaries and analyses will be performed for the following subgroups:

- Baseline Hurley Stage (II/III)
- Concomitant use of oral antibiotics (yes/no)
- Age group (< 40, 40–64, ≥ 65, if less than 10% of subjects in the ≥ 65 group, that group will be combined with 40–64 group.)
- Sex (male, female)

- Duration of HS (< median, ≥ median)
- Weight (< median, ≥ median)
- Body Mass Index (BMI) category: normal (< 25), over weight (25 – < 30), obese (30 – < 40), Morbid obesity (≥ 40)
- Current smoking status (yes/no)
- Baseline CRP level (< median, ≥ median)
- Baseline AN count (≤ 5, 6 – 10, 11+)
- Baseline AN count (< median, ≥ median)

11.0 Safety Analysis

11.1 General Considerations

Unless otherwise specified, all safety analysis will be performed on the Safety dataset. Missing safety data will not be imputed.

11.2 Analysis of Adverse Events

11.2.1 Treatment-Emergent Adverse Events

Treatment-emergent adverse events (TEAE) are defined as any event with an onset or worsening date that is after the first dose of study drug and with an onset date no more than 70 days after the last dose of study drug. Events where the onset date is the same as the study drug start date are assumed to be treatment emergent, unless the study drug start time and the adverse event start time are collected and the adverse event start time is prior to the study drug start time. If an incomplete onset date is collected for an adverse event, the event will be assumed to be treatment emergent unless there is other evidence that confirms that the event is not treatment emergent (e.g., the event end date is prior to the study drug start date).

For the interim analysis, treatment-emergent adverse events are defined as below:

- For subjects who did not discontinue the study before the interim cut-off date, treatment-emergent adverse events are defined as the events collected after the first dose of study drug and on or prior the dose of study drug at Week 24 or Week 52.
- For subjects who discontinued the study before cut-off date, treatment-emergent adverse events are defined as the events collected after the first dose of study drug and within 70 days following the last dose of study drug and before the cut-off date. If the discontinued subject's adverse event onset date is within 70 days following the last dose of study drug but after the cut-off date will be excluded from interim analysis.

Treatment-emergent adverse events will be summarized and presented using the Medical Dictionary for Regulatory Activities (MedDRA®) system organ classes (SOCs) and preferred terms (PTs) according to the version of the MedDRA coding dictionary used for the study at the time of database lock. The actual version of the MedDRA coding dictionary used will be noted in the clinical study report. The system organ classes will be presented in alphabetical order and the preferred terms will be presented in alphabetical order within each system organ class.

The number and percentage of subjects experiencing treatment-emergent adverse events will be summarized for the following adverse event categories and by Week 12 HiSCR status.

Adverse Event Overview

- Any treatment-emergent adverse event
- Any treatment-emergent adverse event that was rated as reasonable possibility to study drug by the investigator (Reasonable Possibility)
- Any treatment-emergent severe adverse event
- Any treatment-emergent serious adverse event
- Any treatment-emergent adverse event leading to discontinuation of study drug

- Any treatment-emergent serious adverse event that was rated as reasonable possibility to study drug by the investigator (Reasonable Possibility)
- Any treatment-emergent adverse event leading to death
- Any treatment-emergent adverse event of special interest
- Any Deaths

Adverse Events by SOC and PT

The number and percentage of subjects experiencing adverse events will be tabulated according to the primary MedDRA system organ class (SOC) and preferred term (PT). Subjects reporting more than one adverse event for a given MedDRA PT will be counted only once for that term (most severe incident for the severity tables and most related incident for the relationship tables). Subjects reporting more than one type of adverse event within a MedDRA SOC will be counted only once for that SOC. Subjects reporting more than one type of adverse event will be counted only once in the overall total.

The following AEs will be summarized using the conventions described above:

- Any treatment-emergent adverse event
- Any treatment-emergent adverse event that was rated as reasonable possibility to study drug by the investigator (Reasonable Possibility)
- Any treatment-emergent adverse event by maximum severity
- Any treatment-emergent adverse event by maximum relationship to study drug
- Any treatment-emergent serious adverse event
- Any treatment-emergent adverse event leading to discontinuation of study drug
- Any treatment-emergent serious adverse event that was rated as reasonable possibility to study drug by the investigator (Reasonable Possibility)
- Any treatment-emergent adverse event leading to death
- Any treatment-emergent adverse event of special interest

Adverse Events by Maximum Severity

Adverse events will also be summarized by maximum severity. If a subject has an adverse event with unknown severity, then the subject will be counted in the severity category of "unknown," even if the subject has another occurrence of the same adverse event with a severity present. The only exception is if the subject has another occurrence of the same adverse event with the most extreme severity – "Severe." In this case, the subject will be counted under the "Severe" category.

Adverse Events by Maximum Relationship

Adverse events will also be summarized by maximum relationship to study, as assessed by the investigator. If a subject has an adverse event with unknown relationship, then the subject will be counted in the relationship category of "unknown," even if the subject has another occurrence of the same adverse event with a relationship present. The only exception is if the subject has another occurrence of the same adverse event with a relationship assessment of "Reasonable Possibility." In this case, the subject will be counted under the "Reasonable Possibility" category, respectively.

Adverse Event Rates per 100 Patient Years of Study Drug Exposure

Incidence rates per 100 patient years of exposure to study drug will be presented for adverse event overviews and for adverse events by SOC and PT.

The treatment-emergent adverse event rate per 100 patient years of exposure will be calculated overall, for each primary SOC, and each PT. For this calculation, 1 year will be considered to be 365.25 days. The numerator of the overall rate, the SOC rate, or the PT rate, will be the total number of treatment-emergent adverse events reported overall, for the SOC, or for the PT, respectively; i.e., a subject can be counted more than once overall, for a SOC, and for a PT. The denominator of the rates will be the total number of days exposed to study drug summed across all treated subjects divided by 365.25, and rounded to 1 decimal place. The adverse event rate per 100 subject-years of exposure will be

calculated as [(numerator/denominator)]*100. The number of adverse events reported (numerator), the total number of years of study drug exposure (denominator), and the adverse event rate per 100 subject-years will be presented overall, for each SOC, and for each PT.

Adverse Events of Special Interest (AESI)

The list of AEs of Special Interest will be based on the most updated final version of Humira Product Safety Statistical Analysis Plan, which is consistent to the most updated Humira Risk Management Plan.
The current list of AEs of special interest for treatment with adalimumab is:

- Any Infections AE
- Any Serious Infection AE
- Any Legionella Infection AE
- Any Diverticulitis AE
- Any Opportunistic Infection (Excluding Oral Candidiasis and TB) AE
- Any Oral Candidiasis AE
- Any Tuberculosis AE
- Any Active Tuberculosis AE
- Any Latent Tuberculosis AE
- Any Parasitic Infection AE
- Any Reactivation of Hepatitis B AE
- Any Progressive Multifocal Leukoencephalopathy (PML) AE
- Any Malignancy AE
- Any Lymphoma AE
- Any Hepatosplenic T-Cell Lymphoma (HSTCL) AE
- Any Non-Melanoma Skin Cancer (NMSC) AE
- Any Melanoma AE
- Any Leukemia AE
- Any Other Malignant (Excluding NMSC, Melanoma, Lymphoma, HSTCL, and Leukemia) AE

- Any Allergic Reaction (Including Angioedema/Anaphylaxis) AE
- Any Lupus-Like Reactions and Systemic Lupus Erythematosus AE
- Any Vasculitis AE
- Any Cutaneous Vasculitis AE
- Any Non-Cutaneous Vasculitis AE
- Any Sarcoidosis AE
- Any Autoimmune Hepatitis AE
- Any Myocardial Infarction Related AE
- Any Cerebrovascular Accident Related AE
- Any Congestive Heart Failure Related AE
- Any Pulmonary Embolism Related AE
- Any Interstitial Lung Disease AE
- Any Intestinal Perforation AE
- Any Pancreatitis AE
- Any Stevens-Johnson Syndrome AE
- Any Erythema Multiforme Related AE
- Any Worsening/New Onset of Psoriasis AE
- Any Demyelinating Disorder AE
- Any Amyotrophic Lateral Sclerosis AE
- Any Reversible Posterior Leukoencephalopathy Syndrome (RPLS) AE
- Any Hematologic Disorders (Including Pancytopenia) AE
- Any Liver Failure and Other Liver Event AE
- Any Humira Administration Related Medication Errors AE
- Any Injection Site Reaction AE
- Any AE Leading to Death
- Any AE Leading to Discontinuation of Study Drug.
- Any Deaths

Additional AEs may be considered for tabulation/summary based on recommendations from Clinical and Safety as deemed appropriate.

11.2.2 Listing of Adverse Events

The following additional summaries of adverse events will be prepared.

- Listing of treatment-emergent adverse events
- Listing of subject numbers associated with each PT for treatment-emergent adverse events
- Listing of treatment-emergent serious adverse events
- Listing of pre-treatment serious adverse events
- Listing of treatment-emergent adverse events that led to discontinuation of study drug
- Listing of treatment-emergent fatal adverse events.
- Listing of deaths
- Listing of treatment-emergent adverse events of special interest

11.2.3 Safety Subgroup Analysis

The AE overview and AE by SOC and PT will also be analyzed with respect to the following Baseline characteristics. The subgroups are:

- Current smoking status at Baseline (yes, no)
- HbA1c (< 7%, ≥ 7%)
- BMI (< 40, ≥ 40)
- Prior HS surgery history (yes, no)

11.3 Analysis of Laboratory Data

All summaries will be conducted for the safety analysis populations and Laboratory test variables will use standard units.

11.3.1 Variables and Criteria Defining Abnormality

Laboratory test variables are specified in Table 13.

Note: For urinalysis, only specific gravity, pH will be summarized.

Table 13. Clinical Laboratory Tests

Hematology	Clinical Chemistry	Urinalysis
Hematocrit Hemoglobin Red Blood Cell (RBC) count White Blood Cell (WBC) count Neutrophils Lymphocytes Monocytes Basophils Eosinophils Platelet count (estimate not acceptable)	Blood Urea Nitrogen (BUN) Creatinine Total bilirubin Serum glutamic-pyruvic transaminase (SGPT/ALT) Serum glutamic-oxaloacetic transaminase (SGOT/AST) Alkaline phosphatase Sodium Potassium Calcium Inorganic phosphorus Uric acid Total protein Glucose Albumin Cholesterol Triglycerides LDL HDL	Specific gravity Ketones pH Protein Blood Glucose Microscopic analysisa
Other		**Pregnancy Test**
QuantiFERON-TB Gold CRP HIV Hepatitis B Screening Hepatitis C Screening HbA1c Antinuclear Antibody (ANA)/Anti-dsDNA (if positive for ANA) Pharmacokinetic AAA		Serum HCG Urine HCG

a. A microscopic analysis will be performed by the central laboratory, in the event the dipstick results show protein, ketones or blood greater than negative or glucose greater than normal, or in the case of abnormal macroscopic results.

Potentially Clinically Significant Laboratory Values

Potentially Clinically Significant Laboratory Findings (Common Toxicity Criteria CTC Grades 2 or higher) will be assessed.

11.3.2 Statistical Methods

Analysis of Quantitative Laboratory Parameters (Hematology, Chemistry and Urinalysis)

Changes from baseline to each scheduled visit and to the final value in continuous laboratory parameters will be summarized with the mean, standard deviation, median, minimum value and maximum value.
The baseline and visit/final value means will also be presented for subjects who have both the baseline and visit/final values.

Shift Tables

Shift tables for changes from baseline according to the normal range will be provided for each hematology, clinical chemistry and urinalysis (specific gravity and pH only) parameter. Shifts from baseline to the following endpoints will be considered: minimum value, maximum value and final value. Categories of "low or normal" and "high or normal" will be included at baseline in addition to the categories of "low," "normal," "high" and "missing."

Potentially Clinically Significant Laboratory Values

Frequencies and percentages of subjects with post baseline lab values that are Grade 2 or above, and separately for Grade 3 or above, according to the CTC toxicity criteria will be summarized. A separate listing will be provided that presents all of the subjects and values that are CTC toxicity Grade 2 or above. For each of these subjects, the whole course of the respective parameter will be listed.

Liver Function Tests

Additional summaries will be presented for liver function tests including serum glutamic-pyruvic transaminase (SGPT/ALT), serum glutamic-oxaloacetic transaminase (SGOT/AST), alkaline phosphatase (ALP), and total bilirubin.
Each laboratory value will be categorized as follows:

- < 1.5 × ULN
- ≥ 1.5 × ULN – < 3.0 × ULN
- ≥ 3.0 × ULN – < 5.0 × ULN
- ≥ 5.0 × ULN – < 8.0 × ULN
- ≥ 8.0 × ULN

where ULN is the upper normal limit.

Shift tables of baseline to the maximum (relative to the normal range, i.e., the largest multiple relative to the upper limit of normal) values, and from baseline to final value will be presented using these five categories. A listing of potentially clinically significant liver function laboratory values will be provided. The listing will include all subjects who met any of the following four criteria:

- ALT ≥ 2.5 × ULN, or
- AST ≥ 2.5 × ULN, or
- Alkaline phosphatase ≥ 2.5 × ULN, or
- Total bilirubin ≥ 1.5 × ULN

Table 14. Potentially Clinically Significant Laboratory Findings

Laboratory Parameter	CTC Grade 1	CTC Grade 2	CTC Grade 3	CTC Grade 4
Hemoglobin – Low (G/L)	< LLN – 100	< 100 – 80	< 80	–
Hemoglobin – High (G/L)	CH > 0.0 – 20	CH > 20 – 40	CH > 40	–
Platelet count (× 10^9/L)	< LLN – 75	< 75 – 50	< 50 – 25	< 25
WBC (× 10^9/L)	< LLN – 3.0	< 3.0 – 2.0	< 2.0 – 1.0	< 1.0
Neutrophils (× 10^9/L)	< LLN – 1.5	< 1.5 – 1.0	< 1.0 – 0.5	< 0.5
Lymphocytes (× 10^9/L)	< LLN – 0.8	< 0.8 – 0.5	< 0.5 – 0.2	< 0.2
ALT	> ULN - 3.0 × ULN	> 3.0 - 5.0 × ULN	> 5.0 - 20.0 × ULN	> 20.0 × ULN
AST	> ULN - 3.0 × ULN	> 3.0 - 5.0 × ULN	> 5.0 - 20.0 × ULN	> 20.0 × ULN
Alkaline phosphatase	> ULN - 2.5 x ULN	> 2.5 - 5.0 x ULN	> 5.0 - 20.0 x ULN	> 20.0 x ULN
γ-GTP	> ULN – 2.5 × ULN	> 2.5 – 5.0 × ULN	> 5.0 – 20.0 × ULN	> 20.0 × ULN
Total bilirubin	> ULN - 1.5 × ULN	> 1.5 - 3.0 × ULN	> 3.0 - 10.0 × ULN	> 10.0 × ULN
Albumin (G/L)	< LLN – 30	< 30 – 20	< 20	–
CPK	> ULN – 2.5 × ULN	> 2.5 × ULN – 5.0 × ULN	> 5.0 × ULN – 10.0 × ULN	> 10.0 × ULN
Creatinine*	> ULN – 1.5 × ULN; or > 1 - 1.5 × BL	> 1.5 – 3.0 × ULN or > 1.5 – 3.0 × BL	> 3.0 – 6.0 × ULN or > 3.0 × BL	> 6.0 × ULN
Uric Acid (MCMOL/L)	> ULN – 590	–	–	> 590
Calcium – Low (MMOL/L)	< LLN – 2.0	< 2.0 – 1.75	< 1.75 – 1.5	< 1.5
Calcium – High (MMOL/L)	> ULN – 2.9	> 2.9 – 3.1	> 3.1 – 3.4	> 3.4
Sodium – Low (MMOL/L)	< LLN – 130	–	< 130 – 120	< 120

Table 14. Potentially Clinically Significant Laboratory Findings (Continued)

Laboratory Parameter	CTC Grade 1	CTC Grade 2	CTC Grade 3	CTC Grade 4
Sodium – High (MMOL/L)	> ULN – 150	> 150 – 155	> 155 – 160	> 160
Potassium – Low (MMOL/L)	< LLN – 3.0	–	< 3.0 – 2.5	< 2.5
Potassium – High (MMOL/L)	> ULN – 5.5	> 5.5 – 6.0	> 6.0 – 7.0	> 7.0
Inorganic Phosphorus (MMOL/L)	< LLN – 0.8	< 0.8 – 0.6	< 0.6 – 0.3	< 0.3
Magnesium - Low (MMOL/L)	< LLN – 0.5	< 0.5 – 0.4	< 0.4 – 0.3	< 0.3
Magnesium - High (MMOL/L)	> ULN – 1.23	–	> 1.23 – 3.30	> 3.30
Glucose – Low (MMOL/L)	< LLN – 3.0	< 3.0 – 2.2	< 2.2 – 1.7	< 1.7
Glucose – High (MMOL/L)	> ULN – 8.9	> 8.9 – 13.9	> 13.9 – 27.8	> 27.8
Cholesterol (MMOL/L)	> ULN – 7.75	> 7.75 – 10.34	> 10.34 – 12.92	> 12.92
Triglycerides (MMOL/L)	1.71 – 3.42	> 3.42 – 5.7	> 5.7 – 11.4	> 11.4

CH = change in ULN or change in baseline, if baseline > ULN; ULN = upper limit of normal range; LLN = lower limit of normal range; BL = baseline;
* = identify by ULN if baseline is normal else use BL if baseline is abnormal;

11.4 Analysis of Vital Signs and Weight

11.4.1 Variables and Criteria Defining Abnormality

Vital sign variables are sitting systolic blood pressure, sitting diastolic blood pressure, sitting pulse, respiratory rate, body temperature and weight. The following table presents the Criteria for Potentially Clinically Significant Vital Sign Findings.
The following vital signs are measured at the designated study visits in Table1.

Table 15. Criteria for Potentially Clinically Significant Vital Sign Findings

Vital Sign	Category	Criteria for Potential Clinically Significant Vital Signs
Systolic blood pressure	Low	Value ≤ 90 mmHg and/or decrease ≥ 20 mmHg from Baseline
	High	Value ≥ 180 mmHg and/or increase ≥ 20 mmHg from Baseline
Diastolic blood pressure	Low	Value ≤ 50 mmHg and/or decrease ≥ 15 mmHg from Baseline
	High	Value ≥ 105 mmHg and/or increase ≥ 15 mmHg from Baseline
Pulse	Low	Value ≤ 50 bpm and/or decrease ≥ 15 bpm from Baseline
	High	Value ≥ 120 bpm and/or increase ≥ 15 bpm from Baseline

11.4.2 Statistical Methods

Mean changes from Baseline to post-baseline visits will be summarized with the baseline mean, visit mean, change from baseline mean, standard deviation, median, minimum value and maximum value. The number and percentage of subjects meeting the criteria for potentially clinically significant vital sign values will be summarized.

Vital sign results satisfying the criteria for potentially clinically significant vital sign findings will be identified in a listing. For each of these subjects, the whole course of the respective parameter will be listed.

11.5 Analysis of ECG Parameters

ECG results will be listed in the data listings.

11.6 Analysis of Potentially Clinically Significant ECG Values

Not applicable.

12.0 Summary of Changes

None.

13.0 Appendices

Appendix A. Calculation of the Modified Sartorius Scale

	Number	Coefficient	Total
1 Anatomical region involved: armpit, breast, inguino-femoral, perianal and perineal	I__I	x 3	I__I__I
2 Lesions: – Nodules	I__I	x 2	I__I__I
– Abcess or fistulas	I__I	x 4	I__I__I
– Hypertrophic scars	I__I	x 1	I__I__I
– Others (folliculitis, pustules ...)	I__I	x 0.5	I__I__I
3 The longest distance between two relevant lesions or size if only one lesion. *< 5 cm = 2; < 10 cm = 4; ≥ 10 cm = 6; if no active lesions = 0*	I__I	x 1	I__I
4 Are all lesions clearly separated by normal skin? *Yes = 0; No = 6*	I__I	x 1	I__I
TOTAL			I__I__I__I

Reference: Revus J, Hidradenitis Suppurativa. JEADV. 23, pp985-998, 2009

Appendix B. Minimally Clinically Important Difference (MCID) Determination in Dermatology

Overall Suggestion: Instruments included in each of the clinical trials are documented below with published MCIDs where available. The current suggestion is to include these MCIDs in the statistical analysis plans but to also include the ½ standard deviation criteria for each domain and each instrument. This criteria is a well-accepted and published norm in outcomes studies when clinically meaningful criteria have not been established. This will allow for the evaluation of each endpoint on a similar measure across instruments.

PRO NAME	MCID	Reference	Link to Reference
DLQI	Decrease of ≥ 5.0 points will be considered a responder	Shikiar R, Willian MK, Okun MM, et al. The validity and responsiveness of three quality of life measures in the assessment of psoriasis patients: results of a phase II study. Health Qual Life Outcomes. 2006;4:71. Strand V, Fiorentino D, Hu C, et al. Improvements in patient-reported outcomes with apremilast, an oral phosphodiesterase 4 inhibitor, in the treatment of moderate to severe psoriasis: results from a phase IIb randomized, controlled study. Health Qual Life Outcomes. 2013;11:82.	http://www ncbi nlm nih.gov/pmc/articles/PMC1615869/ http://www hqlo.com/content/11/1/82

PRO NAME	MCID	Reference	Link to Reference
TSQM	≥ ½ SD increase from Baseline to be considered a responder	Atkinson, Mark J., PhD; Hass, Steven L., PhD "Effectiveness" scale of the Treatment Satisfaction Questionnaire for Medication (TSQM): the mean scale score for the "Effectiveness" items on the TSQM (version II).	http://www.qualitymeasures.ahrq.gov/content.aspx?id=26828
HS QoL	≥ ½ SD increase from Baseline to be considered a responder		
EQ-5D-Index Score	An increase of ≥ 0.1 points will be considered a responder	Shikiar R, Willian MK, Okun MM, et al. The validity and responsiveness of three quality of life measures in the assessment of psoriasis patients: results of a phase II study. Health Qual Life Outcomes. 2006;4:71.	http://www ncbi nlm nih.gov/pmc/articles/PMC1615869/ http://www ncbi nlm nih.gov/pmc/articles/PMC1615869/table/T8/
EQ-5D-VAS	An increase of ≥3.82 will be considered a responder	See above	

SD = standard deviation calculated based on Baseline values.

Document Approval

Study M15573-Statistical Analysis Plan Version 1.0 - 07Nov2017 (E3 16.1.9)

Version: 1.0 **Date:** 08-Nov-2017 07:52:25 PM **Company ID:** 11082017-00F9F683B26A08-00001-en

Signed by:	Date:	Meaning Of Signature:
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	07-Nov-2017 06:37:38 AM	Approver
	08-Nov-2017 07:52:25 P	Approver