1.0 Title Page

Clinical Study Protocol M15-574

A Phase 4, Double-Blind, Randomised, Placebo-Controlled Multicenter Study to Assess the Safety and Efficacy of Adalimumab Used in Conjunction with Surgery in Subjects with Moderate to Severe Hidradenitis Suppurativa

Incorporating Administrative Change 1, and Amendments 1, 2, and 3

AbbVie Investigational Product:	Adalimumab
Date:	13 December 2017
Development Phase:	4
Study Design:	Double-Blind, Randomised, Placebo-Controlled
EudraCT Number:	2015-005161-23
Investigators:	Multicenter Trial (Investigator information on file at AbbVie)
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* The specific contact details of the AbbVie legal/regulatory entity (person) within the relevant country are provided within the clinical trial agreement with the Study Investigator/Institution and in the Clinical Trial Application with the Competent Authority.

This study will be conducted in compliance with the protocol, Good Clinical Practice and all other applicable regulatory requirements, including the archiving of essential documents.

1.1 Protocol Amendment: Summary of Changes

Previous Protocol Versions

Protocol	Date
Original	04 February 2016
Amendment 1	05 May 2016
Amendment 2	30 November 2016

The purpose of this amendment is to:

- Section 1.2, Add the planned number of sites for this study of 56.

  Rationale: *Clarify number of sites in the study.*
- Section 8.1.4.1, Add that the 95% confidence intervals of treatment difference will also be provided.

  Rationale: *The protocol was updated to include clarifications requested by regulatory Authorities.*
- Section 8.1.4.1, Add a sensitivity analysis controlling for change from baseline in body weight using logistic regression models, for the primary efficacy endpoint. Analysis details will be specified in the SAP prior to study unblinding and prior to database lock.

  Rationale: *The protocol was updated to include clarifications requested by regulatory Authorities.*
- Update Study Designated Physician in Section 1.0 and Section 6.1.5

  Rationale: *Update information from Administrative Change 1.*
- Update Alternate Contact in Section 7.0

  Rationale: *Update information from Administrative Change 1.*
- Update List of Protocol Signatories in Appendix B

  Rationale: *Update information from Administrative Change 1.*

An itemized list of all changes made to this protocol amendment can be found in Appendix S.

1.2 Synopsis

AbbVie Inc.	**Protocol Number:** M15-574
Name of Study Drug: Adalimumab	**Phase of Development:** 4
Name of Active Ingredient: Adalimumab	**Date of Protocol Synopsis:** 13 December 2017
Protocol Title: A Phase 4, Double-Blind, Randomized, Placebo-Controlled, Multicenter Study to Assess the Safety and Efficacy of Adalimumab used in Conjunction with Surgery in Subjects with Moderate to Severe Hidradenitis Suppurativa	
Objective: Assess the safety and efficacy of adalimumab prior to surgery in subjects with moderate to severe Hidradenitis Suppurativa (HS) who are surgical candidates.	
Investigators: Multicenter	
Study Sites: The planned number of sites for this study is 56.	
Study Population: Male or female subjects between the ages of 18 and 65, inclusive, with moderate to severe HS having • at least 3 distinct anatomical regions involved with inflammatory HS lesions; • either one axilla or one inguinal region that requires excisional surgery with healing by secondary intention, and containing at least one active HS lesion; and • the non-surgical HS sites must have a total AN count ≥ 3, with at least one of these sites rated Hurley Stage II or III.	
Number of Subjects to be Enrolled: 200 The study is designed to enroll approximately 200 subjects. Assuming the true treatment difference in this study population is at least 20%, 100 subjects per arm will provide at least 80% power to detect the treatment difference at the alpha level of 0.05. The study also has at least 80% power to demonstrate the point estimate of the treatment difference of at least 15%. The response rates observed in combined PIONEER I and II studies (Studies M11-313 and M11-810) for the Hidradenitis Suppurativa Clinical Response (HiSCR, defined as at least a 50% reduction in the HS abscess plus inflammatory nodule [AN] count with no increase in abscess count and no increase in draining fistula count relative to Baseline) at Week 12 were 50.6% and 26.8% in the adalimumab every week group and placebo group, respectively. Due to the potential differences between the population of moderate-to-severe HS patients who are surgical candidates and the general moderate-to-severe HS patient population, a conservative estimate of 20% treatment difference is used for the power calculation.	
Methodology: This double-blind, placebo-controlled study consists of a 7 – 30-day Screening Period followed by 24-weeks of active treatment. The eligible subject must have a requirement for surgery of HS lesions in a single axilla or unilateral inguinal region. Subjects will be randomised 1:1 with stratification for Hurley Stage (II versus III worst stage across all body regions) and anatomical location of the planned surgery for HS lesions (axilla versus inguinal region). Study drug treatment will follow the approved dosage for HS, including loading doses at the beginning of the 12-week pre-surgery period (Period A), followed by a 2-week peri-surgery period (Period B) with surgery scheduled for Week 13 and a 10-week post-surgery period (Period C).	

Methodology (Continued):

Study visits will occur as follows:

- Period A (pre-surgery) study visits will occur at Day 1 (Week 0) and Weeks 2, 4, 8, and 12.
- Period B (peri-surgery) the subject will be under the care of the designated surgeon.
- Period C (post-surgery) study visits will occur at Weeks 15, 17, 20, and 24.

Evaluation for safety and efficacy throughout the 24-week study period will include

1) clinical observations of the HS lesions (both in the planned surgical site and at least two other distinct anatomical regions with HS lesions),
2) laboratory measurements of serum and plasma samples, and
3) patient reported outcomes (PROs).

Optional participation in exploratory research and validation studies will include the collection of serum and plasma samples, and tissue samples (both of non-lesional skin and HS lesional skin, specifically at the planned surgical site) at specified various time points throughout the study.

In selected study sites Doppler ultrasound and digital imaging may be performed with optional participation by the study subject.

Diagnosis and Main Criteria for Inclusion/Exclusion:

Main Inclusion:

1. Male and female subjects between the ages of 18 and 65, inclusive;
2. Subject must have a skin lesions that are diagnostic of HS for at least 1 year (365 days) prior to the Baseline visit;
3. Subject must have at least 3 distinct anatomical regions involved with inflammatory (also termed 'active') HS lesions; including
    a. either an axilla or unilateral inguinal region (limited to the inguino-crural fold and adjacent areas that requires excisional surgery (hereinafter designated the 'HS surgical site'), and
    b. with at least one of the other affected HS regions (e.g., contralateral axilla, contralateral inguinal region, buttocks, inframammary region; hereinafter designated the 'HS non-surgical sites') rated as Hurley Stage II or III;
4. Subject must have a total abscess and inflammatory nodule (AN) count of greater than or equal to 3 at the Baseline visit within the HS non-surgical sites;
5. The HS surgical site must contain at least one active HS lesion;
6. The HS surgical site must require excisional surgery and is large enough to require healing by secondary intention as assessed by the designated surgeon;

Diagnosis and Main Criteria for Inclusion/Exclusion (Continued):

Main Inclusion (Continued):

7. If female subject, is either
   - not of childbearing potential, defined as
     - postmenopausal for at least 1 year (365 days) or
     - surgically sterile (bilateral tubal ligation, bilateral oophorectomy, and/or hysterectomy);
   - of childbearing potential and is practicing an approved method of birth control throughout the study and for 150 days after last dose of study drug.

   Examples of approved methods of birth control include the following (see local informed consent for more detail):
     - Intrauterine device (IUD) or Intrauterine hormone-releasing system (IUS); or
     - Hormonal contraceptives at least 30 days prior to study drug administration; and/or
     - A vasectomized partner; and/or
     - True abstinence.
8. Females of childbearing potential must have a negative serum pregnancy test result (conducted at the central lab) at Screening and a negative urine pregnancy test (conducted at the site) at Day 1;
   - Females of non-childbearing potential (either postmenopausal or permanently surgically sterile as defined above) at Screening do not require pregnancy testing.
9. Subject must agree to daily use of one of the following over-the-counter topical antiseptics on their HS lesions (excepting the post-surgical wound): chlorhexidine gluconate, triclosan, benzoyl peroxide, or dilute bleach with shower or bath throughout the entirety of the study;
10. Subject has a negative tuberculosis (TB) screening assessment (see test to be performed in paragraph below) and negative chest x-ray (CXR) (posterior anterior and lateral view) at Screening. If the subject has evidence of a latent TB infection; the subject must initiate and complete a minimum of 12 weeks (or per local guidelines, whichever is longer) of an ongoing TB prophylaxis or have documented completion of a minimum of 4 weeks of TB prophylaxis prior to the Baseline visit and should be evaluated by a physician experienced in the evaluation and treatment of TB patients before entering the trial;
    - In patients treated with corticosteroids (equivalent to Prednisone 5 mg or above – with ongoing treatment or treatment within 1 month prior to TB screening), TB screening must be performed using a QuantiFERON-TB Gold In-tube test or equivalent.
    - In patients NOT treated with corticosteroids (equivalent to Prednisone 5 mg or above – with ongoing treatment or treatment within 1 month prior to TB screening), PPD or QuantiFERON-TB tests may be used.
11. Subject is judged to be in good general health, as determined by the Study Investigator based upon the results of a medical history, physical examination, laboratory profile, CXR and a 12-lead electrocardiogram (ECG) performed during the Screening period and confirmed at the Baseline visit;
12. Subject must be able and willing to self-administer subcutaneous (SC) injections or have a qualified person available to administer SC injections; and
13. Subject must be able and willing to provide written informed consent and comply with the requirements of this study protocol.

Diagnosis and Main Criteria for Inclusion/Exclusion (Continued):

Main Exclusion:

1. Subject has a draining fistula count of greater than 20 at the Baseline visit;
2. Subject requires surgery at any anatomical site other than an unilateral axilla or inguinal region site;
3. Subject requires surgical management prior to Week 13; based on the designated surgeon's assessment;
4. Subject requires, based on the designated surgeon's assessment, excisional surgery with primary closure, partial surgical reduction of the excised area with surgical suture, or reconstruction techniques as the method of closure being most beneficial for the subject;
5. Subject has any other active skin disease or condition (e.g., bacterial, fungal or viral infection) that may interfere with assessment of HS;
6. Subject is taking high-dose systemic corticosteroids at the Baseline visit (see Section 5.2.3.3), or has taken high-dose systemic corticosteroids (see Section 5.2.3.3) within five half-lives of that specific corticosteroid prior to the Baseline visit;
7. Subject received biologic therapies with potential therapeutic impact for HS less than 6 months (178 days) prior to the Baseline visit;
8. Subject received prescription topical therapies (excluding over-the-counter topical antiseptics) for the treatment of HS within 14 days prior to the Baseline visit;
9. Subject received systemic clindamycin or rifampin within 28 days prior to the Baseline visit;
10. Infection(s) requiring treatment with intravenous (IV) anti-infectives (antibiotics, antivirals, antifungals) within 30 days prior to the Baseline visit, except as required as part of an anti-TB regimen;
11. Prior exposure to biologics that have a potential or known association with progressive multifocal leukoencephalopathy (PML i.e., natalizumab or rituximab);
12. Subject has been treated with any investigational drug of chemical nature within a minimum of 30 days or five half-lives (whichever is longer) of the drug prior to the Baseline visit;
13. Known hypersensitivity to adalimumab or its excipients;
14. History of demyelinating disease (including myelitis) or neurologic symptoms suggestive of demyelinating disease;
15. Subject has suspicion of sepsis, cytomegalovirus infection, listeriosis or other opportunistic infections, or has history of invasive infection (e.g., listeriosis, histoplasmosis), human immunodeficiency virus (HIV);
16. Subject has an active systemic viral infection or any active viral infection that based on the Study Investigator's clinical assessment make the subject an unsuitable candidate for the study;
17. Hepatitis B: HBsAg positive (+) or detected sensitivity on the HBV-DNA PCR qualitative test for HBcAb/HBsAb positive subjects;
18. Chronic recurring infections or active TB;
19. History of moderate to severe congestive heart failure (NYHA class III or IV), recent cerebrovascular accident, interstitial lung disease (ILD) and any other condition which, in the opinion of the investigator, would put the subject at risk by participation in the protocol;
20. Evidence of dysplasia or history of malignancy (including lymphoma and leukemia) other than a successfully treated non-metastatic cutaneous squamous cell carcinoma, basal cell carcinoma or localized carcinoma in situ of the cervix;

Diagnosis and Main Criteria for Inclusion/Exclusion (Continued):

Main Exclusion (Continued):

21. Females who are breastfeeding or considering becoming pregnant during the study and during the 5 months following the last dose of adalimumab;
22. History of clinically significant drug or alcohol abuse in the previous 12 months;
23. Clinically significant abnormal screening laboratory results as evaluated by the Investigator; and
24. Subject is considered by the Study Investigator, for any reason, to be an unsuitable candidate for the study.

Active Study Drug:	Adalimumab
Doses:	160 mg/3.2 mL Day 1 (Week 0), 80 mg/1.6 mL Day 15 (Week 2) and 40 mg/0.8 mL every week from Week 4 to Week 23.
Mode of Administration:	Subcutaneously (SC)
Reference Therapy:	Placebo
Doses:	3.2 mL Day 1 (Week 0), 1.6 mL Day 15 (Week 2), and 0.8 mL every week from Week 4 to Week 23.
Mode of Administration:	Subcutaneously (SC)

Duration of Treatment: 23 weeks

Criteria for Evaluation:

Efficacy:

The primary efficacy variable is the proportion of subjects achieving HiSCR at Week 12. The secondary endpoints include the proportion of subjects achieving HiSCR-es (defined as the HiSCR excluding the HS surgical site) at Weeks 12 and 24, the change in surface area of the HS surgical site at Week 12, and the proportion of subjects at Week 12 that require less extensive surgery than the surgical plan (determined at Baseline) or no surgery. Other parameters will be collected and may be analysed, including C-reactive protein (CRP), active HS lesion count, and patient reported outcomes (PROs).

Pharmacokinetic:

Blood samples will be collected for the measurement of serum adalimumab concentrations at Baseline and Weeks 4, 8, 12, 15, 17, 20, 24/Premature Discontinuation visit if the subject discontinues prior to Week 24. Blood samples will be collected for the measurement of anti-adalimumab antibody (AAA) at Baseline, and Weeks 4, 8, 12, 15, 20, and 24/Premature Discontinuation visit if the subject discontinues prior to Week 24.

Safety:

Adverse events, adverse events of special interest and adverse events concerning the surgical site, laboratory data and vital signs will be assessed throughout the study.

Exploratory Research Variables and Validation Studies (Optional):

Prognostic, predictive, and pharmacodynamic biomarker signatures may be investigated. Samples for different applications including, but not limited to, pharmacogenetic, epigenetic, transcriptomic, proteomic, and targeted investigations will be collected at various time points.

Statistical Methods:

Efficacy:

The primary analysis will be the comparison of the adalimumab treatment group versus the placebo treatment group in the proportion of subjects achieving HiSCR at Week 12.

Ranked secondary endpoints with comparison of the adalimumab treatment group versus the placebo treatment group include:

1. Proportion of subjects achieving HiSCR-es (HiSCR evaluation excluding the HS surgical site) at Week 12;
2. Proportion of subjects achieving HiSCR-es at Week 24;
3. Percent change in surface area of the planned surgical site from Baseline to Week 12; and
4. Proportion of subjects that require a less extensive surgery than the surgical plan documented at Baseline, or no longer require surgery as determined by the designated surgeon.

Other efficacy endpoints for which data will be collected and may be analysed include:

1. C-reactive protein (CRP) and white cell count;
2. PROs including DLQI, EQ5D™, HS-PGA-SP, HS-PGIC, HSIA, HSSA, SF-12, TSQM (treatment efficacy subscale), and WPAI:SHP;
3. Proportion of subjects that experience a flare of active HS lesions, during Period A and during the study; and
4. Proportion of subjects that experience at least 25% increase in each lesion type relative to Baseline at each study visit, during Period A and during the study.

The primary efficacy analysis will be carried out in the Intent-to-Treat (ITT) Population in the Period A, defined as all patients who are randomised at the Baseline visit. Treatment difference in response rates between adalimumab and placebo will be conducted by Cochran-Mantel-Haenszel (CMH) test, stratified by the stratification factors used for randomisation. All other secondary efficacy variables in Period A will be analysed by ANCOVA (for continuous variables) with treatment, baseline value and stratification factors in the model, or by CMH (categorical variables) adjusting for stratification factors.
Non-responder imputation will be used as the primary approach to impute the missing values with last-observation-carried-forward and Multiple Imputation as sensitivity analyses for the primary endpoint.

Pharmacokinetic:

Adalimumab trough serum concentrations will be summarized at each time point using descriptive statistics. In addition, pharmacokinetic-pharmacodynamic (PK-PD) model-based analyses will be performed to evaluate adalimumab PK and exposure-response relationships.

Statistical Methods (Continued):

Safety:

All adverse events (AE), serious adverse events (SAE), AEs leading to discontinuation, and pre-specified AEs of special interest and adverse events concerning the surgical site will be collected during the study and up to approximately 70 days after the last dose of study drug, for subjects who do not elect to treat his/her HS disease with commercial adalimumab.

Safety analyses will be carried out using the Safety Population, which consists of subjects who received at least one dose of study drug. Pretreatment AEs will be summarized. A treatment-emergent AE (TEAE) is defined as an event with onset or worsening after the first study drug injection and within approximately 70 days after the last study drug injection, for subjects who do not elect to treat his/her HS disease with commercial adalimumab.

The number and percent of subjects experiencing TEAEs will be tabulated using the Medical Dictionary for Drug Regulatory Activities (MedDRA®) system organ class and preferred term. Comparisons of the percentages of subjects experiencing an AE in the adalimumab group versus the placebo group will be performed using Fisher's exact test for data collected in the entire study, and separately for Period A, Period B, and Period C. Summaries (including percentages and event per 100 patient-years) of SAEs, deaths, AEs leading to discontinuation from the study, and pre-specified AEs of special interest will be provided as well. Mean change in laboratory variables and vital sign variables at each visit will be summarized; the comparison between the adalimumab treatment group and placebo group will be carried out using a one-way ANOVA.

Immunogenicity:

Anti-Adalimumab Antibody (AAA) will be evaluated for each subject and rates of AAA positive will be calculated. As appropriate, the effect on adalimumab PK, efficacy, and treatment-emergent adverse events may be evaluated.

1.3 List of Abbreviations and Definition of Terms

Abbreviations

AAA	Anti-Adalimumab Antibody
AE	Adverse Event
AESI	Adverse Event of Special Interest
ANCOVA	Analysis of covariance
ANOVA	Analysis of variance
AN	Abscess and inflammatory Nodule
ANA	Anti-Nuclear Antibody
BCG	Bacille Calmette-Guérin
CDA	Clinical Drug Accountability
CDC	Centers for Disease Control and Prevention
CO2	Carbon dioxide
CRA	Clinical Research Associate
CRF	Case Report Form
CRP	C-Reactive Protein
CXR	Chest X-Ray
DLQI	Dermatology Life Quality Index
DNA	Deoxyribonucleic acid
dsDNA	Double-stranded deoxyribonucleic acid
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EMA	European Medicines Agency
EMEA	European Agency for the Evaluation of Medicinal Products
EQ-5D	EuroQoL™
EU	European Union
ew	Every Week
FDA	US Food and Drug Administration
GCP	Good Clinical Practice
HbA1c	Hemoglobin A1c
HBcAb	Hepatitis B Core Antibody
HbsAb	Hepatitis B Surface Antibody

HbsAg	Hepatitis B Surface Antigen
HBV	Hepatitis B Virus
HIV	Human Immunodeficiency Virus
HS	Hidradenitis Suppurativa
HiSCR	Hidradenitis Suppurativa Clinical Response
HiSCR-es	Hidradenitis Suppurativa Clinical Response excluding the HS surgical site
hsCRP	High Sensitivity C-Reactive Protein
HSIA	Hidradenitis Suppurativa Impact Assessment
HS-PGA-SP	Hidradenitis Suppurativa Patient's Global Assessment of Skin Pain
HS-PGIC	Hidradenitis Suppurativa Patient's Global Impression of Change
HSSA-7d	Hidradenitis Suppurativa Symptom Assessment-7 day recall
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IgG1	Immunoglobulin G1
IGRA	Interferon-Gamma Release Assay
ILD	Interstitial Lung Disease
IRB	Institutional Review Board
IRT	Interactive Response Technology
ITT	Intent-to-Treat
IUD	Intrauterine device
IUS	Intrauterine hormone-releasing system
IV	Intravenous
LOCF	Last Observation Carried Forward
LOQ	Limit of Quantification
MedDRA	Medical Dictionary for Regulatory Activities
MI	Multiple Imputation
NONMEM	Linear Mixed Effect Modeling
NRI	Non-Responder Imputation
NRS	Numeric Rating Scale
NYHA	New York Heart Association
PA	posterior-anterior
PBMC	Peripheral blood mononuclear cell
pH	Power of Hydrogen Ion Concentration
PK	Pharmacokinetic

PML	Progressive Multifocal Leukoencephalopathy
POR	Proof of Receipt
PP	Per Protocol
PPD	Purified Protein Derivative
PRN	As Needed
RA	Rheumatoid Arthritis
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAS	Statistical Analysis Software
SC	Subcutaneous
SmPC	Summary of Product Characteristics
TB	Tuberculosis
TEAEs	Treatment-Emergent Adverse Events
TESAEs	Treatment-Emergent Serious Adverse Events
TNF	Tumor Necrosis Factor
TNF-α	Tumor Necrosis Factor-alpha
TSQM	Treatment Satisfaction Questionnaire – Medication
US	United States
Wk	Week
WPAI:SHP	Work Productivity and Activity Impairment Questionnaire: Specific Health

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.
AN Count	The sum of abscesses and inflammatory nodules, each a lesion diagnostic of HS.
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.
HiSCR-es	HiSCR calculated excluding the AN count contained within the HS surgical site.
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.
Inflammatory nodule	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.
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 nodule	Non-tender or minimally tender, non-erythematous nodule.
Protocol Allowed Intervention	A protocol-allowed intervention is defined as incision and drainage, or injection of intra-lesional triamcinolone acetonide suspension (at a dose of 5 mg/mL, up to 1 cc).

2.0 Table of Contents

List of Tables

List of Figures

List of Appendices

3.0 Introduction

3.1 Hidradenitis Suppurativa

Hidradenitis suppurativa (HS), also known as acne inversa is a chronic systemic relapsing inflammatory disease primarily affecting the skin in intertriginuous areas, i.e., axillae, groin, and inframammary regions.[1,2] Hidradenitis suppurativa is characterized by recurrent inflamed deep-seated acneiform nodules that result in abscesses, and chronic draining sinus tract formation leading to scarring, disfigurement, and life-altering disability. Its negative impact on quality of life is extreme, mainly due to the lack of early recognition, accurate diagnosis, and appropriate management. Hidradenitis suppurativa has a profoundly negative impact on patients' physical, social, and economic lives, with a higher morbidity index than urticarial, neurofibromatosis, psoriasis, atopic dermatitis, or alopecia. Many become socially isolated or reclusive due to incorrect diagnosis, the numerous lesions, long and continuous duration, and pelvic area involvement. Patients with HS, mainly women, lose an average of 2 – 7 days of work per year (or they lose their job).[3]

Hidradenitis suppurativa creates a substantial burden of disease, particularly in those subjects with more severe manifestations (in one study, mean Dermatology Life Quality Index (DLQI) scores were 5.77, 13.1, and 20.4 for Hurley Stages I, II, and III classifications, respectively).[4] Comparing the DLQI scores of this study with other studies that employed this qualitative method illustrates that HS has a higher impairment in quality of life (QoL) than chronic skin diseases, such as the average patient with psoriasis, hair loss, pityriasis, rosacea, and bullous pemphigoid, just to name a few. Although HS, like other chronic skin diseases, is not imminently dangerous, its effect on the patient's QoL, society and the healthcare system is comparable to, if not greater than conditions such as hypertension or diabetes.[5,6]

As HS has been an orphan disease for decades and subsequently a highly misdiagnosed and underdiagnosed condition with significant diagnosis delay, the true prevalence has been correspondingly challenging to estimate. Prevalence rates are reported as low as

0.00033% and as high as 4.1%.[7-12] Most authors report no racial differences but the female-to-male ratio is 3.3:1. Comparisons of HS to psoriasis in terms of size and scope of the conditions are worth making. The prevalence of HS may approach that of psoriasis, while the sex ratio in large-scale clinical trials for moderate to severe disease is inverted (i.e., 2:1 female-to-male for HS and 1:2 for psoriasis), patients with either condition are affected by comorbidities, social disability, obesity, and stigma.[13-15]

The mean age of onset is 22.1 years; it lasts about 19 years, can remit or partially remit with pregnancy and breastfeeding, and be very variable. Usually a benign, mild, chronic but intermittently painful disease, HS has acute exacerbations, premenstrual flares, resolution after menopause, remission for weeks to months, or continuous or intermittent flares. Solid plaques of coalescent nodules, sinuses, and scars host smelly discharge, pain, and debility. New, deep, painful nodules last 10 to 30 days. Patients may present with a certain degree of severity and remain in that range, severe disease usually starting with severe disease from the beginning. The difficulty with mobility ranges from minor soreness to inability to walk or sit without pain. Odor from drainage may be significant and require diapers, leading to social withdrawal, depression, and dysfunctional lives.[16,17]

The physical extent of HS can be classified using Hurley's clinical staging (Section 1.3) but remain unclear why HS may remain limited to Hurley Stage I, evolve to the more confluent (Hurley Stage II) or progress even further to the fully confluent (Hurley III). Other available clinical measures for assessing HS disease severity include the modified Sartorius (MSS) and the HS Physician's Global Assessment (HS-PGA). Those scores were designed for an accurate assessment of the extent of inflammation within each stage. To support the development of effective anti-inflammatory treatments for HS, the clinical and research community has called for a validated assessment that can be used to identify treatment response. Using data from a Phase 2 clinical trial that evaluated the safety and efficacy of adalimumab in adults with moderate to severe chronic HS (ClinicalTrials.gov Identifier: NCT00918255) a new practical and straightforward clinical endpoint was proposed and validate: the Hidradenitis Suppurativa Clinical Response (HiSCR). The HiSCR is defined by the status of three types of lesions (defining criteria): abscesses

(fluctuant, with or without drainage, tender or painful), inflammatory nodules (tender, erythematous, pyogenic granuloma lesion), and draining fistulas (sinus tracts, with communication to the skin surface, draining purulent fluid). The proposed definition of responders to treatment (HiSCR achievers) is: i) at least a 50% reduction in the total number of abscesses and inflammatory nodules (AN) count, ii) no increase in the number of abscesses, and iii) no increase in the number of draining fistulas, compared to baseline.[18]

Disease onset is typically after puberty. It affects women from 2 to 5 times more commonly than men. Several factors may predispose a person to HS, including genetics, cigarette smoking, and obesity.[19] The histopathologic characteristics of HS include a dense inflammatory cell infiltrate of neutrophils, lymphocytes, and histiocytes.[20] Tumor necrosis factor-alpha (TNF-α), which induces other pro-inflammatory cytokines and activates neutrophils and lymphocytes, may have a pathogenic role, based on the evident over-expression of tumor necrosis factor (TNF) in HS lesions.[21]

Giamarellos-Bourboulis and co-workers described an altered immune response in patients with HS, suggesting a role for TNF-α and the innate immune system in the pathogenesis of the disease. Later, increased amounts of circulating, as well as bound TNF-α were found, support the previous observations. In parallel, the use of TNF-α blockers for the treatment of HS was being studied in case series.[22]

Although the clinical presentation of HS is strongly reminiscent of bacterial infection, the role of bacteria remains controversial. Studies have isolated an array of different bacterial specimens as well as biofilm formation in lesional HS skin. Although the pathogenesis of inflammation in HS is not fully understood, different types of antibiotics (e.g., tetracyclines, rifampin, clindamycin) are widely and increasingly used to treat HS in the absence of validated efficacy data. Considering the prevalence of HS, this issue is critical because potential antimicrobial resistance may hamper the efficacy of antibiotics and induce co-morbidities associated with altered commensal microflora.[23]

3.2 Current Treatments

Prior to the Adalimumab Clinical Trial program, (Studies M10-467, M11-313, M11-810), the only placebo controlled trial of HS demonstrated modest efficacy with the use of topical clindamycin.[24] Other treatments for HS include: medical treatment (e.g., systemic combination therapy with clindamycin and rifampicin, intra-lesional triamcinolone, systemic cyclosporine, anti-androgen treatment in women, systemic dapsone, systemic retinoids, and metformin),[25-29] surgical treatment (radical excision, marsupialization, and de-roofing),[30-35] and laser treatment (carbon dioxide [CO_2] laser and neodymium-doped yttrium aluminum garnet [Nd:YAG] laser).[36-39] It is difficult to evaluate the efficacy for these interventions because their use is described in open-label, frequently retrospective, case series and case reports, with variable, but typically short term follow-up. Case series and case reports have shown that inhibitors of TNF-α are effective in treating HS.[40-42] Thus AbbVie conducted Phase 2 and Phase 3 clinical trials, demonstrating the clinical efficacy and safety of adalimumab in subjects with moderate to severe HS.[43] In 2015 adalimumab was approved for treatment of moderate to severe HS by the European Medicines Agency (EMA)[44] and will be available for use in many countries with a recommended dose specific for the treatment of HS.

Surgical management is an essential modality of the treatment algorithm for HS, to be used concurrently with other treatments.[12,45,46] Patients treated with surgery generally demonstrate one or more of the following: extensive sinus tract and/or fistula, mutilating HS, contracted scars, and painful scars. Multiple types of surgical procedures may be performed for HS treatment, from a simple incision and drainage to wide surgical excision of the lesions. Use of technologies such as CO_2 laser has also been used with success. Wide surgical excision is the most radical and invasive of the procedures, involving excision of the lesion and surrounding skin, sometimes extending down to deep fascial layers. The remaining surgical area may be extensive, and closure may be primary or secondary. Skin grafting may be utilized and for larger areas, flap repair may need to be performed. Recurrence may still occur after surgical management, with rates ranging from 1% – 70% depending on the type of procedure performed.[12] In addition, though

surgical management may be performed for the most severe lesions, patients may have lesions in other anatomical areas, and therefore require continued medical treatment while undergoing surgical management. Patients undergoing surgery for HS lesions were not studied in the registration trials; therefore there are no placebo-controlled data that inform the physician regarding the impact of adalimumab on HS lesions in the patient who is undergoing surgery as part of therapy to manage the disease.

Surgery to remove HS lesional skin is a key treatment modality and adalimumab has recently been approved for the medical treatment of moderate to severe HS based on safety and efficacy data.

The European S1 HS guideline suggests that the disease should be treated based on its individual subjective impact and objective severity. Locally recurring lesions can be treated by classical surgery or LASER techniques, whereas medical treatment either as monotherapy or in combination with radical surgery is more appropriate for widely spread lesions.[12]

When used in combination with radical resection of grossly evident disease, the immunosuppressive effects of biologics could potentially augment the results achievable through surgical intervention alone. To date, however, there have been no randomized controlled trials investigating the role of neoadjuvant/adjuvant biologic therapy in reducing the size and/or disease progression in patients with moderate-severe HS.

There is a need to adopt a multidisciplinary treatment strategy that facilitates collaboration between the surgeon and dermatologist and integrates established surgical principles with therapy that targets underlying proinflammatory mechanisms that contribute to disease pathogenesis.

This study will be the first large prospective, randomized, double-blind, placebo-controlled clinical trial to evaluate the use of anti-TNF therapy in conjunction with surgery of adults suffering with moderate to severe HS.

3.3 Adalimumab Overview

Adalimumab is a recombinant human immunoglobulin G1 (IgG1) monoclonal antibody containing only human peptide sequences. Adalimumab is produced by recombinant deoxyribonucleic acid (DNA) technology in a mammalian cell expression system. It consists of 1,330 amino acids and has a molecular weight of approximately 148 kilodaltons. Adalimumab is composed of fully human heavy and light chain variable regions, which confer specificity to human TNF-α, and human IgG1 heavy chain and kappa light chain sequences. Adalimumab binds with high affinity and specificity to soluble TNF-α but not to lymphotoxin-α (TNF-β).

TNF-α is a naturally occurring cytokine that is involved in normal inflammatory and immune responses. Elevated levels of TNF-α are thought to play an important role in pathologic inflammation. Adalimumab binds specifically to TNF-α and neutralizes the biological function of TNF-α by blocking its interaction with the p55 and p75 cell surface TNF-α receptors. Adalimumab also modulates biological responses that are induced or regulated by TNF-α. After treatment with adalimumab, levels of acute phase reactants of inflammation (C-reactive protein [CRP] and erythrocyte sedimentation rate [ESR]) and serum cytokines rapidly decrease.

Adalimumab was first approved in the United States (US) and European Union (EU) for the treatment of rheumatoid arthritis in 2002 and 2003, respectively. Additional indications have been approved in the US and EU, including, but not limited to HS, psoriasis, psoriatic arthritis, ankylosing spondylitis, Crohn's disease, ulcerative colitis, polyarticular juvenile idiopathic arthritis, paediatric Crohn's disease, paediatric psoriasis, as well as paediatric enthesitis-related arthritis and non-radiographic axial spondyloarthritis in the EU, and intestinal bowel disease in Japan. Adalimumab received approval in the EU for treatment of active moderate to severe HS in 2015. Additional updates regarding approved indications can be found in the current edition of the Humira Summary of Product Characteristics (SmPC).[44]

The adalimumab clinical development program that obtained efficacy and safety data for adalimumab in adult subjects with moderate to severe HS included a dose-ranging Phase 2 study (Study M10-467) and two Phase 3 studies designated PIONEER I and PIONEER II (Study M11-313 and Study M11-810, respectively). In addition subjects were eligible to enroll in an on-going Phase 3 open-label extension study (Study M12-555). The Phase 2 study demonstrated that after loading doses there was demonstrated HiSCR with 40 mg weekly dosing. PIONEER I and II had similar placebo-controlled 36-week study designs and primary efficacy endpoint (i.e., proportion of subjects achieving HiSCR at Week 12). Following a 12-week two-arm period with adalimumab 40 mg weekly doses versus placebo (Period A), subjects in the active treatment arm were re-randomized to adalimumab 40 mg weekly dosing, adalimumab 40 mg every other week dosing, or placebo from Week 12 to Week 36 (Period B). Subjects in the placebo arm were treated with adalimumab 40 mg weekly in PIONEER I or placebo (PIONEER II) from Week 12 to Week 36. A statistically significant greater proportion of adalimumab-treated subjects achieved HiSCR at Week 12 (Period A), regardless of Hurley Stage or concomitant antibiotic use. At the end of Period B a higher proportion of subjects in the continuous adalimumab 40 mg weekly dose maintained HiSCR as compared to those subjects re-randomized to adalimumab every other week dosing or placebo dosing. There were no safety differences across the treatment groups.[43]

3.4 Safety Information

Adalimumab therapy has a well-established and well-described safety profile based on extensive post-marketing experience and continued clinical trial patient exposure since the first approved indication in 2002 for rheumatoid arthritis. A detailed discussion of the clinical toxicology, metabolism, pharmacology, and safety experience with adalimumab can be found in the current SmPC. AbbVie is committed to continue to collect safety information including those events that may occur in this trial in order to confirm this established safety profile and to identify any unknown potential adverse reactions, rare events and those events with a long latency. AbbVie is participating in the US Food and Drug Administration (FDA) requested, TNF inhibitor class-wide exploration of the rare

appearance of malignancy in subjects who are 30 years of age or younger at the time of diagnosis. The risk of malignancy in this age group has not been established and is difficult to study due to its rarity. AbbVie appreciates your attention to the additional reporting requirements needed in this unlikely event, outlined in Section 6.1.5 under Adverse Event Reporting.

3.5 Differences Statement

While several studies (i.e., Studies M10-467, M11-313, M11-810, and M12-555) have been conducted evaluating the safety and efficacy of the use of adalimumab for the treatment of moderate to severe HS, to date no adequate and well controlled study has included patients who undergo surgical intervention for their HS while being treated with adalimumab.

3.6 Benefits and Risks

Adalimumab therapy has a well-established and well described safety profile based on extensive post-marketing experience and continued clinical trial patient exposure since the first approved indication in 2002 for rheumatoid arthritis. More than 29,000 subjects participating in hidradenitis suppurativa, polyarticular juvenile idiopathic arthritis, pediatric enthesitis related arthritis, Crohn's disease, pediatric Crohn's disease, psoriasis, pediatric psoriasis, rheumatoid arthritis, ankylosing spondylitis, non-radiographic axial spondyloarthritis, peripheral spondyloarthritis, psoriatic arthritis, intestinal Behçet's disease, uveitis and ulcerative colitis clinical studies have been treated with adalimumab. The majority of side effects experienced following administration of adalimumab were mild to moderate in severity.

The most commonly reported adverse reactions are infections (such as nasopharyngitis, upper respiratory tract infection and sinusitis), injection site reactions (erythema, itching, haemorrhage, pain or swelling), headache and musculoskeletal pain.

Serious adverse reactions have been reported for Humira. TNF-antagonists, such as Humira affect the immune system and their use may affect the body's defense against

infection and cancer. Fatal and life-threatening infections (including sepsis, opportunistic infections and TB), HBV reactivation and various malignancies (including leukaemia, lymphoma and HSTCL) have also been reported with use of Humira.

Serious haematological, neurological and autoimmune reactions have also been reported. These include rare reports of pancytopenia, aplastic anaemia, central and peripheral demyelinating events and reports of lupus, lupus-related conditions and Stevens-Johnson syndrome.

Humira is contraindicated in patients with:

- Hypersensitivity to the active substance or to any of its excipients;
- Active tuberculosis or other severe infections such as sepsis, and opportunistic infections;
- Moderate to severe heart failure (NYHA class III/IV)

  In its Summary of Product Characteristics, Special warnings and precautions for use for Humira are the following:
- Infections

  Patients taking TNF-antagonists are more susceptible to serious infections. Impaired lung function may increase the risk for developing infections.
- Serious infections

  Serious infections, including sepsis, due to bacterial, mycobacterial, invasive fungal, parasitic, viral, or other opportunistic infections such as listeriosis, legionellosis and pneumocystis have been reported in patients receiving Humira.
- Tuberculosis

  Tuberculosis, including reactivation and new onset of tuberculosis, has been reported in patients receiving Humira. Reports included cases of pulmonary and extra-pulmonary (i.e., disseminated) tuberculosis.
- Other opportunistic infections

  Opportunistic infections, including invasive fungal infections have been observed in patients receiving Humira. These infections have not

consistently been recognised in patients taking TNF antagonists and this resulted in delays in appropriate treatment, sometimes resulting in fatal outcomes.

- Hepatitis B reactivation

  Reactivation of hepatitis B has occurred in patients receiving a TNF-antagonist including Humira, who are chronic carriers of this virus (i.e., surface antigen positive).

- Neurological events

  TNF-antagonists including Humira have been associated in rare instances with new onset or exacerbation of clinical symptoms and/or radiographic evidence of central nervous system demyelinating disease including multiple sclerosis and optic neuritis, and peripheral demyelinating disease, including Guillain-Barré syndrome.

- Allergic reactions

  Serious allergic reactions associated with Humira were rare during clinical trials. Non-serious allergic reactions associated with Humira were uncommon during clinical trials. Reports of serious allergic reactions including anaphylaxis have been received following Humira administration.

- Immunosuppression

  In a study of 64 patients with rheumatoid arthritis that were treated with Humira, there was no evidence of depression of delayed-type hypersensitivity, depression of immunoglobulin levels, or change in enumeration of effector T-, B, - NK-cells, monocyte/macrophages, and neutrophils.

- Malignancies and lymphoproliferative disorders

  In the controlled portions of clinical trials of TNF-antagonists, more cases of malignancies including lymphoma have been observed among patients receiving a TNF-antagonist compared with control patients. However, the occurrence was rare.

- Haematologic reactions

Rare reports of pancytopaenia including aplastic anaemia have been reported with TNF-antagonists.

Adverse events of the haematologic system, including medically significant cytopoenia (e.g., thrombocytopaenia, leucopaenia) have been reported with Humira.

- Vaccinations

  Patients on Humira may receive concurrent vaccinations, except for live vaccines.

- Congestive heart failure

  In a clinical trial with another TNF-antagonist worsening congestive heart failure and increased mortality due to congestive heart failure have been observed. Cases of worsening congestive heart failure have also been reported in patients receiving Humira.

- Autoimmune processes

  Treatment with Humira may result in the formation of autoimmune antibodies. The impact of long term treatment with Humira on the development of autoimmune diseases is unknown.

- Concurrent administration of biologic DMARDS or TNF-antagonists

  Concomitant administration of adalimumab with other biologic DMARDS (e.g, anakinra and abatacept) or other TNF-antagonists is not recommended based upon the possible increased risk for infections, including serious infections and other potential pharmacological interactions.

- Elderly patients

  The frequency of serious infections among Humira treated subjects over 65 years of age (3.6%) was higher than for those under 65 years of age (1.4%). Some of those had a fatal outcome. Particular attention regarding the risk for infection should be paid when treating the elderly.

- Surgery

  There is limited safety experience of surgical procedures in patients treated with Humira.

  The SmPc states that the long half-life of adalimumab should be taken into consideration if a surgical procedure is planned. A patient who requires

surgery while on Humira should be closely monitored for infections, and appropriate actions should be taken.

Experience of adalimumab used peri-surgically:

This will be the first randomised controlled study assessing the use of adalimumab peri-surgically, and of assessing an anti-TNF therapy peri-surgically.

A meta-analysis performed to conduct a systematic review of studies reporting on the post-operative complications of another anti-TNF use, infliximab, in the pre-operative period for Crohn's disease, concluded that pre-operative infliximab use was not shown to be associated with higher rates of major post-operative complications in patients with Crohn's Disease undergoing intra-abdominal surgery, and evaluated up to 90 days post-surgery.[47] Minor complications, the need for a repeat operation and mortality within the first 30 days were also not affected by pre-operative infliximab therapy. A database analysis has examined the rate of postoperative morbidity in patients with Crohn's disease receiving anti TNF therapy in the perioperative period, including the use of adalimumab.[48] This retrospective analysis was performed in one center, the Division of Colon and Rectal Surgery, Mayo Clinic, Rochester. All patients undergoing surgery for Crohn disease from 2005 till 2008 were abstracted from a prospective database, and patients undergoing surgery which included a suture or staple line at risk for leaking were selected for the study. A retrospective review of medical records was performed.

The study compared the post-operative outcomes of patients treated with perioperative anti TNF therapy (defined as treatment within 8 weeks preoperatively or up to 30 days postoperatively) to those in patients without anti-TNF therapy.

Three hundred and seventy patients were selected for analysis in this study, of which 119 received perioperative anti- TNF therapy (69 infliximab, 47 adalimumab 40 mg eow, 3 Certolizumab), and 251 did not receive any anti-TNF therapy.

The groups were similar in baseline characteristics, perioperative risk factors and procedures.

There was no significant association of perioperative anti TNF therapy and any postoperative complications (27.9% in anti-TNF group versus 30.1% in no anti-TNF group, p = 0.63) nor intra-abdominal infectious complications (5.0% in anti-TNF group versus 7.2% in no anti-TNF group, p = 0.44). Univariate analysis showed that the only factors associated with an increase in postoperative intra-abdominal infections were age and penetrating disease.

The analysis concluded that the use of anti-TNF therapy in the perioperative period is safe and is not associated with an increase in overall or infectious complications in Crohn's disease patients undergoing surgery.

A further study examined the impact of pre-operative anti-TNF-α agents on postoperative outcomes 30 and 60 days after Crohn's disease surgery in a nationwide Danish cohort. Outcomes were death, reoperation, anastomosis leakage, intra-abdominal abscess and bacteraemia.[49] Among surgical procedures for Crohn's disease, 214 were exposed to anti-TNFs and 2079 were not. During the study period, infliximab counted for most of the anti-TNF-α agents given before surgery with 57.0% (122/214), adalimumab with 27.1% (58/214) and other anti-TNF-α agents with 15.9% (34/214).

The authors found no increased relative risks of death or abscess drainage 30 or 60 days after follow-up. Among exposed, 7.5% had a reoperation within 30 days vs. 8.6% among unexposed, adjusted odds ratio (OR) = 0.92, 95% confidence interval (CI): 0.52 – 1.63. Among exposed, 3.8% had an anastomosis leakage within 30 days after surgery vs. 2.8% among unexposed, adjusted OR = 1.33, 95% CI: 0.59 – 3.02. No further cases of anastomosis leakages appeared within 60 days.

Sub-analyses indicated no increased risk of bacteraemia after 30 days and no increased risks when anti-TNF-α agents were given 14 days before surgery.

In conclusion the authors found no significantly increased relative risks of post-operative complications after use of anti-TNF-α agents either 12 weeks or 14 days before surgery for Crohn's disease.

The safety and efficacy of adalimumab in HS has been explored in the Phase 2 trial (Study M10-467) and in two Phase 3 trials (Studies M11-313 and M11-810, PIONEER I and II, respectively). To date, 733 subjects with HS have been studied in adalimumab clinical studies in the HS clinical program, for a total of 836.3 patient-years of adalimumab exposure. Treatment emergent adverse events (TEAEs) were reported in 595 subjects (81.2%) for a rate of 417.6 events/100 patient-years. Worsening hidradenitis, nasopharyngitis, headache, and upper respiratory tract infection were the most frequently reported TEAEs.[50]

The recommended adalimumab dose regimen for adult patients with moderate to severe HS (i.e., 160 mg initially on Day 1, 80 mg on Day 15, and beginning on Day 29, the regimen continues with a dose of 40 mg every week [ew]) was safe and well-tolerated, as evaluated by the incidence and severity of TEAEs, treatment-emergent serious adverse events (TESAEs), premature discontinuations due to TESAEs, and changes in laboratory and vital sign values. The incidence and severity of TEAEs, TESAEs, and premature discontinuations due to TEAEs, as well as laboratory and vital sign results, were generally comparable between the adalimumab and placebo groups, and were consistent with a population of subjects with moderate to severe HS. The rates of treatment-emergent adverse events of special interest (AESI) were generally consistent with previous studies in approved adalimumab indications.[50]

Efficacy data from the adalimumab HS clinical program demonstrate that the recommended adalimumab dosing regimen is an effective treatment for inflammatory lesions and skin pain of HS among moderate to severe HS subjects who had an inadequate response or were intolerant to oral antibiotic therapy. The short-term efficacy of adalimumab (i.e., 12 weeks of therapy) was demonstrated with the primary efficacy measure Hidradenitis Suppurativa Clinical Response (HiSCR) rate; and key secondary efficacy measures including proportion of subjects with total abscess and inflammatory

nodule (AN) counts of 0, 1, or 2; proportion of subjects with clinically relevant pain reduction, and mean improvement in modified Sartorius score. Other efficacy measures included improvement in lesion counts, reduced risk of flare, and improvement in dermatology-specific quality of life. A high proportion of subjects who achieved at least a partial short-term improvement maintained treatment success with long-term therapy (up to 52 weeks).[51]

Subjects enrolled in this study will be eligible patients who will have surgical intervention as part of their routine care. Standard practices regarding perioperative and operative care will be under the direction of the dermatologist and/or surgeon and will not be directed per this protocol. It is expected the routine risks of surgery will be essentially unchanged by participation in this study. The subject will be closely followed for any adverse events, adverse events of special interest, adverse events concerning the surgical site and the relationship to study drug as assessed by the Study Investigator will be recorded and analysed. As described above for active HS lesions, there is the possibility that adalimumab may positively affect the active HS lesions in the planned surgical site, which might then allow for a less extensive surgical intervention. Adalimumab is predicted to have neither a positive or negative impact on fibrotic lesions within the HS surgical site.

4.0 Primary Study Objective

Assess the safety and efficacy of adalimumab prior to surgery in subjects with moderate to severe HS who are surgical candidates, using HiSCR as the assessment measurement.

4.1 Secondary Study Objectives

Assess the impact of adalimumab specifically on the planned HS surgical site before surgery, evaluate the safety and efficacy of adalimumab continued during the perioperative period and after surgery, and evaluate Patient Reported Outcomes (PRO) related to health status, HS-related symptoms (e.g., drainage, swollen skin), physical functioning, treatment satisfaction, and work/activity impairment. The pharmacokinetics (PK) and immunogenicity of adalimumab following subcutaneous (SC) injection in this HS surgical population will also be assessed. The objective is to determine if the

inflammatory status of the HS surgical subject alters the PK profile both prior to and after surgery.

4.2 Objectives for Optional Exploratory Research and Validation Studies

The principal objective of the optional exploratory research and validation studies is to help improve our understanding of how individuals respond to adalimumab and our ability to predict which patient might benefit from receiving such treatment for HS. In addition, exploratory research may help to improve our understanding of how to diagnose and assess/monitor HS by assessing association between disease characteristics, outcomes data, and biomarkers of interest.

4.3 Objectives for Doppler Ultrasound Sub-Study

The objective of the Doppler Ultrasound sub-study is to provide pilot data from a randomized double blind placebo-controlled trial to help determine if evaluation of HS lesions using Doppler ultrasound provides for more accurate staging and response to therapy of the disease than current standard medical diagnosis and evaluation. These data will be evaluated separately from data derived from the main study.

5.0 Investigational Plan

5.1 Overall Study Design and Plan: Description

5.1.1 Description of Study Periods and Study Schematic

This interventional, randomised, double-blind, placebo-controlled study is designed to enroll 200 subjects to meet scientific and regulatory objectives without enrolling an undue number of subjects in alignment with ethical considerations. Therefore, if the target number of subjects has been enrolled, there is a possibility that additional subjects in screening will not be enrolled. Eligible subjects will have active HS disease with an axilla or unilateral inguinal region that requires excisional surgery plus two other anatomical regions with active HS lesions (at least one region at Hurley Stage II or III).

The study duration will include a 30-day Screening Period, an initial 12-week double-blind treatment pre-surgery period (Period A), a 2-week peri-surgery period with continuation of weekly double-blind study drug administration (Period B), and a subsequent 10-week double-blind treatment post-surgery period (Period C).

Screening Period: The duration of the screening period will be a minimum of 7 days and a maximum of 30 days during which time all of the inclusion and exclusion criteria will be evaluated, and at referring sites, an eligibility visit with the designated surgeon will take place. Subjects may enroll into the study after all screening procedures are complete and results are known and verified for eligibility at the Baseline visit (Day 1) to receive 160 mg of adalimumab or matching placebo.

Subjects will have up to 30 days to return to the clinical study site for the Baseline visit from the date of the Screening visit. Study visits will occur according the schedule in Appendix C. In addition, all subjects will be contacted by telephone at Weeks 6 and 10 to monitor whether any signs or symptoms of infection are present at or near an HS lesion. If any signs or symptoms of infection are reported at the time of the call, an unscheduled study visit will be conducted to assess whether an infection is present. The informed consent will include a description of signs and symptoms of infections along with the contact information so that the subject may contact the study site immediately if any such signs or symptoms develop at or near an HS lesion.

Subjects that initially screen fail for the study may be permitted to re-screen following re-consent. All screening procedures with the possible exceptions noted below will be repeated. The subject must meet all inclusion and none of the exclusion criteria at the time of re-screening in order to qualify for the study. There is no minimum period of time a subject must wait to re-screen for the study. If the subject had a complete initial screening evaluation including tuberculosis (TB) screening, chest x-ray (CXR, if applicable), and 12-lead electrocardiogram (ECG), these tests will not be required to be repeated for re-screening provided the conditions noted in Section 5.3.1.1 are met and no more than 3 months (90 days) have passed. As appropriate, study sites are encouraged to contact the AbbVie Medical Monitor to confirm if subjects should or should not be

re-screened. If the subject had a negative human immunodeficiency virus (HIV) result at screening but 30 days have elapsed prior to the re-screen, then the HIV screening test must be repeated and the result handled in a like manner as the original screening test (see Section 5.3.1.1).

Period A: A 12-week double-blind, placebo-controlled treatment period during which subjects are randomised in a 1:1 ratio to receive adalimumab or matching placebo, 160 mg initially at Day 1 (or given as two 40 mg injections per day for 2 consecutive days), followed by 80 mg 2 weeks later at Day 15 (given as two 40 mg injections in 1 day). Two weeks later (Day 29) continue with a dose of 40 mg ew until Week 12. The randomisation will be stratified by baseline Hurley Stage (II versus III) and anatomical location of the surgical site (i.e., axilla versus inguinal region). A subject's Hurley Stage is determined by the worst Hurley Stage (i.e., II versus III) across all affected anatomic regions. The projected size of the surgical excision established by the designated surgeon during the Screening Period (calculated from a tracing of the outer perimeter onto an acetate sheet or equivalent) will be recorded by the study physician in the CRF. On each clinical study visit day, all study procedures scheduled for that visit will be completed prior to study drug administration.

Period B: A 2-week double-blind, placebo-controlled treatment period consisting of Weeks 13 and 14 (the peri-operative period) in which subjects will continue the treatment on the first day of Weeks 13 and 14. The designated surgeon will measure the surface area of the actual surgery and record in source document. Surgery will occur during Week 13. The surgery and post-operative management (e.g., hospitalisation, surgical wound care) will be as per local practice.

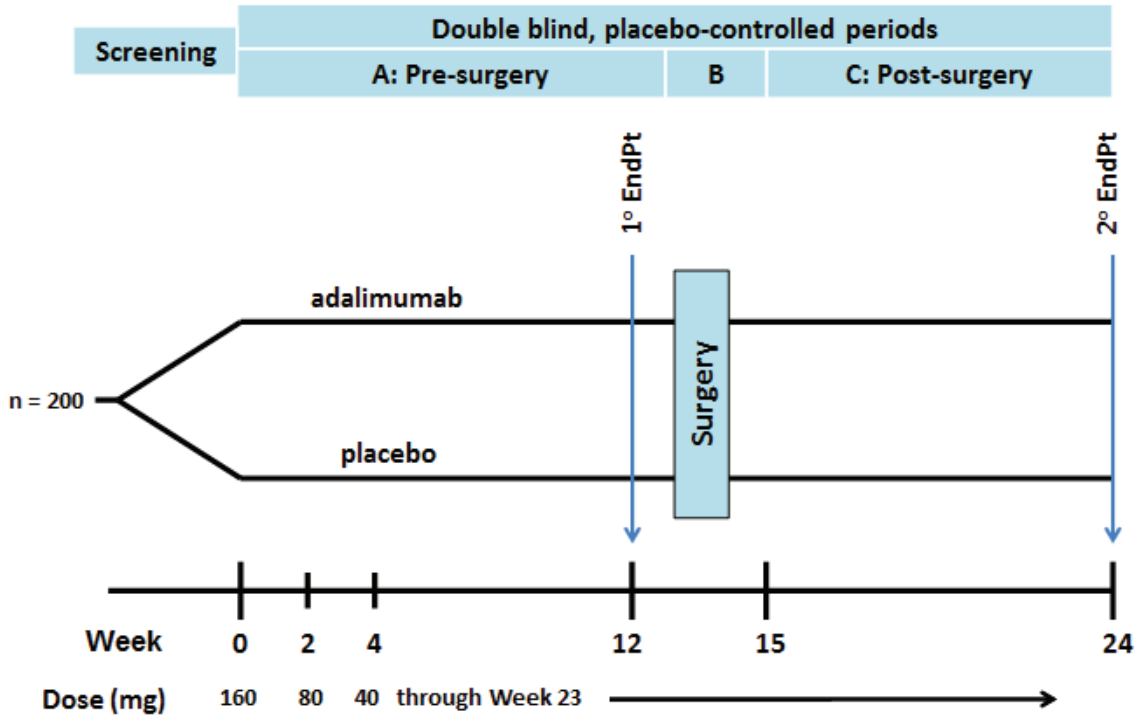
Period C: A 10-week double-blind, placebo-controlled post-operative treatment period will occur from Week 15 through Week 24, during which the subject will continue the treatment assigned at Day 1 from Week 15 through Week 23. No study drug will be administered at Week 24, the final study visit. Subjects may begin commercial product (as prescribed by the subject's physician) after all Week 24 procedures have been completed.

Study procedures throughout the study are listed in Appendix C. Safety and efficacy measurements will be performed throughout the study as described in Section 5.3.1.

The study visit window will be ± 3 days for the Week 2 and Week 4 visits and ± 7 days, relative to Baseline, for all study visits from Week 8 through Week 24. Surgery takes place at Week 13 after all Week 12 evaluations are completed. A subject will be brought back to the original visit schedule (calculated from the Baseline visit [Day 1]) if the subject is out of the visit window.

Subjects may discontinue adalimumab treatment at any time during study participation. Subjects that end study participation early will have a Premature Discontinuation Visit unless consent to participate is withdrawn.

Figure 1. Study Schematic



5.2 Selection of Study Population

Subjects will be screened to determine if they meet all of the inclusion criteria specified in Section 5.2.1 and none of the exclusion criteria specified in Section 5.2.2.

5.2.1 Inclusion Criteria

1. Male and female subjects between the ages of 18 and 65, inclusive;
2. Subject must have skin lesions that are diagnostic of HS for at least 1 year (365 days) prior to the Baseline visit;
3. Subject must have at least 3 distinct anatomical regions involved with inflammatory (also termed 'active') HS lesions; including
   a. either an axilla or unilateral inguinal region (limited to the inguino-crural fold and adjacent areas) that requires excisional surgery (hereinafter designated the "HS surgical site"), and
   b. with at least one of the other affected HS regions (e.g., contralateral inguinal region, buttocks, inframammary region; hereinafter designated the 'HS non-surgical sites) rated as Hurley Stage II or III;
4. Subject must have a total abscess and inflammatory nodule (AN) count of greater than or equal to 3 at the Baseline visit within the HS non-surgical sites;
5. The HS surgical site must contain at least one active HS lesion;
6. The HS surgical site must require excisional surgery and is large enough to require healing by secondary intention as assessed by the designated surgeon;
7. If female subject, is either
   - not of childbearing potential, defined as
     - postmenopausal for at least 1 year (365 days) or
     - surgically sterile (bilateral tubal ligation/occlusion, bilateral oophorectomy, and/or hysterectomy); or

- of childbearing potential and is practicing at least one protocol-allowed method of birth control throughout the study and for 150 days after last dose of study drug.

  Examples of allowed methods of birth control (see Section 5.2.4) include the following (see local informed consent for more detail):

  - Intrauterine device (IUD) or Intrauterine hormone-releasing system (IUS); or
  - Hormonal contraceptives initiated at least 30 days prior to study drug administration;
  - A vasectomised partner; and/or
  - True abstinence

8. Females of childbearing potential must have a negative serum pregnancy test (conducted at central lab) result at Screening, and a negative urine pregnancy test (conducted at site) at Day 1;

   - Females of non-childbearing potential (either postmenopausal or permanently surgically sterile as defined above) at Screening do not require pregnancy testing

9. Subject must agree to daily use of one of the following over-the-counter topical antiseptics on their HS lesions (excepting the post-surgical wound): chlorhexidine gluconate, triclosan, benzoyl peroxide, or dilute bleach with shower or bath throughout the entirety of the study;

10. Subject has a negative TB screening assessment (see test to be performed in paragraph below) and negative CXR (posterior-anterior [PA] and lateral view) at Screening. If the subject has evidence of a latent TB infection; the subject must initiate and complete a minimum of 12 weeks (or per local guidelines, whichever is longer) of an ongoing TB prophylaxis and have documented completion of a minimum of 4 weeks of TB prophylaxis prior to the Baseline visit (see Section 5.3.1) and should be evaluated by a physician experienced in the evaluation and treatment of TB patients before entering the trial;

- In patients treated with corticosteroids (equivalent to Prednisone 5 mg or above – with ongoing treatment or treatment within 1 month prior to TB screening), TB screening must be performed using a QuantiFERON-TB Gold In-tube test or equivalent.
- In patients NOT treated with corticosteroids (equivalent to Prednisone 5 mg or above – with ongoing treatment or treatment within 1 month prior to TB screening), PPD or QuantiFERON-TB tests may be used.

11. Subject is judged to be in good general health, as determined by the Study Investigator based upon the results of a medical history, physical examination, laboratory profile, CXR and a 12-lead ECG performed during the Screening period and confirmed at the Baseline visit;
12. Subject must be able and willing to self-administer subcutaneous (SC) injections or have a qualified person available to administer SC injections; and
13. Subject must be able and willing to provide written informed consent and comply with the requirements of this study protocol.

Rationale for the Inclusion Criteria

1 – 6	To select the appropriate subject population with adequate disease severity for the evaluation
7 – 8	The impact of adalimumab on fetal development has not been formally established
9 – 12	For the safety of the study subject
13	In accordance with harmonised Good Clinical Practice (GCP)

5.2.2 Exclusion Criteria

A subject will not be eligible for study participation if he/she meets any of the following criteria:

1. Subject has a draining fistula count of greater than 20 at the Baseline visit;

2. Subject requires surgery at any anatomical site other than an unilateral axilla or inguinal region site;
3. Subject requires surgical management prior to Week 13, based on the designated surgeon's assessment;
4. Subject requires, based on the designated surgeon's assessment, excisional surgery with primary closure, partial surgical reduction of the excised area with surgical suture, or reconstruction techniques as the method of closure being most beneficial for the subject;
5. Any other active skin disease or condition (e.g., bacterial, fungal or viral infection) that may interfere with assessment of HS;
6. Subject is taking high-dose systemic corticosteroids at the Baseline visit (see Section 5.2.3.3), or has taken high-dose systemic corticosteroids within five half-lives of that specific corticosteroid (see Section 5.2.3.3) prior to the Baseline visit;
7. Subject received biologic therapies with potential therapeutic impact for HS (see Section 5.2.3.3) less than 6 months (178 days) prior to the Baseline visit;
8. Subject received prescription topical therapies (excluding over-the-counter topical antiseptics) for the treatment of HS within 14 days prior to the Baseline visit;
9. Subject received systemic clindamycin or rifampin within 28 days prior to the Baseline visit;
10. Infection(s) requiring treatment with intravenous (IV) anti-infectives (e.g., antibiotics, antivirals, antifungals) within 30 days prior to the Baseline, except as required as part of an anti-TB regimen;
11. Prior exposure to biologics that have a potential or known association with Progressive Multifocal Leukoencephalopathy (PML; i.e., natalizumab or rituximab);

12. Subject has been treated with any investigational drug of chemical nature within a minimum of 30 days or five half-lives (whichever is longer) of the drug prior to the Baseline visit;
13. Known hypersensitivity to adalimumab or its excipients as stated in Section 5.5.2, Table 2;
14. History of demyelinating disease (including myelitis) or neurologic symptoms suggestive of demyelinating disease;
15. Subject has suspicion of sepsis, cytomegalovirus infection, listeriosis or other opportunistic infections, or has history of invasive infection (e.g., listeriosis,histoplasmosis) or human immunodeficiency virus (HIV);
16. Subject has an active systemic viral infection or any active viral infection that based on the Study Investigator's clinical assessment make the subject an unsuitable candidate for the study;
17. Hepatitis B: HBsAg positive (+) or detected sensitivity on the HBV-DNA PCR qualitative test for HBc Ab/HBsAb positive subjects (see Section 5.3.1.1);
18. Chronic recurring infections or active TB;
19. History of moderate to severe congestive heart failure (New York Heart Association [NYHA] class III or IV), recent cerebrovascular accident, interstitial lung disease (ILD) and any other condition that would put the subject at risk by participation in the study;
20. Evidence of dysplasia or history of malignancy (including lymphoma and leukemia) other than a successfully treated non-metastatic cutaneous squamous cell or basal cell carcinoma, or localized carcinoma in situ of the cervix;
21. Female subject who is breastfeeding or is considering becoming pregnant during the study and during the 5 months following the last dose of adalimumab;
22. History of clinically significant drug or alcohol abuse in the previous 12 months;

23. Clinically significant abnormal screening laboratory results as evaluated by the Investigator;

24. Subject is considered by the Study Investigator, for any reason, to be an unsuitable candidate for the study.

Rationale for Exclusion Criteria

1 – 4	To select the appropriate subject population with adequate disease severity for the evaluation
5	To avoid enrollment of subjects who have concomitant skin disease that may interfere with HS assessment
6 – 10	To avoid bias for the evaluation of safety and efficacy by concomitant use of other medications
11 – 13, 19, 22 – 24	To ensure safety of the subject throughout the study
15 – 18, 20	To avoid a possibility of an infectious disease or a malignant tumor progression when administering an anti-TNF drug
14	Demyelinating disorders have been seen in subjects treated with TNF antagonists although a causal relationship has not been conclusively established
21	The impact of adalimumab on fetal development has not been formally established

5.2.3 Prior and Concomitant Therapy

Any medication or vaccine (including over-the-counter or prescription medicines, vitamins and/or herbal supplements) that the subject is receiving at the time of enrollment (i.e., date of signing the informed consent), and/or receives during the study, must be recorded along with the reason for use, date(s) of administration including start and end dates, and dosage information including dose, route and frequency on the appropriate electronic case report form (eCRF).

All analgesics will be allowed as concomitant medications throughout the active phase of the trial. Oral antibiotics (with the restriction of clindamycin and rifampin as described in Section 5.2.3.2) will be allowed as concomitant medications throughout the active phase of the trial provided the dosing regimen (dose and frequency) has been stable for at least 4 consecutive weeks (28 days) prior to the Baseline visit. The AbbVie Study Designated Physician identified in Section 1.0 should be contacted if there are any questions regarding concomitant or prior therapies.

In addition for subjects age ≤ 30 with a reported malignancy adverse event, prior to exposure to, or current of, anti-neoplastics, or other drugs that have a risk of malignancy as stated in their label and other relevant dosing information to estimate total exposure will be collected in the source documents and appropriate eCRF pages (also see Section 6.1.5). At the time of the reported malignancy adverse event, the Study Investigator will be asked if any of the prior and concomitant medications contributed to the event. Any medications used prior to the study will be captured on the appropriate eCRF. Information on the reason for use, date(s) of administration including start and end dates, highest maintained dose, dosage information including dose, route, and frequency, and reason for stopping the medication will be collected in the source documents and appropriate eCRF pages.

Any medication or vaccine (including over-the-counter or prescription medicines, vitamins and/or herbal supplements) that the subject is receiving at the time of enrollment, or receives during the study, must be recorded along with the reason for use, date(s) of administration including start and end dates, and dosage information including dose, route and frequency.

The AbbVie Study Designated Physician should be contacted if there are any questions regarding concomitant or prior therapies.

5.2.3.1 Prior Therapy

Any treatments for HS (as determined through medical history records or through subject interview) prior to study enrollment will be recorded in the source and on the eCRF, along with the reason for discontinuation.

For subjects previously treated with biologics (e.g., infliximab, rituximab, ustekinumab, anakrina) the duration of therapy, maximum dose, reason for use and the reason(s) for termination of treatment with these products should be documented.

A detailed history of prior antibiotic use for HS (topical, oral, IV), response, and reason for discontinuation will be collected.

5.2.3.2 Concomitant Therapy

Antiseptic Therapy

Subjects are required to use a daily antiseptic wash on their active HS lesions beginning at enrollment and continuing throughout the study, except on the surgical wound (unless directed by the Study Investigator or designee). Allowable antiseptic washes are limited to one of the following: chlorhexidine gluconate, triclosan, benzoyl peroxide, or dilute bleach in bathwater.

Wound Care

Concomitant use of wound care dressings on HS wounds and the surgical wound (as per local practice) is allowed, and may include alginates, hydrocolloids, and hydrogels.

Antibiotic Therapy

All oral antibiotics are permitted throughout the study with the restrictions described in the following paragraphs.

Concomitant use of permitted oral antibiotic therapy for treatment of HS is allowed provided the dosing regimen (dose and frequency) has been stable for at least

4 consecutive weeks (28 days) prior to the Baseline visit (see Exclusion Criterion 10). Antibiotics taken on an "as needed" (PRN) basis are not considered a stable dose.

During the peri-operative period (Period B) an antibiotic regimen including systemic clindamycin and/or rifampin is allowed for a maximum of 5 days (see also Section 5.2.3.3).

See Section 6.1.7 for additional discussion on the use of concomitant medications if medically necessitated.

Lesion Intervention

In the event an acutely painful lesion occurs that requires an immediate intervention, the Study Investigator will have the option to perform protocol-allowed interventions.

Only two types of interventions are allowed: injection with intra-lesional triamcinolone acetonide suspension (at a concentration of up to 5 mg/mL, up to 1 cc), and incision and drainage.

If incision and drainage is performed, the required over-the-counter antiseptic wash should continue to be used. Concomitant use of wound care dressings is allowed, which may include alginates, hydrocolloids, and hydrogels. The subject should continue using any ongoing oral and topical therapies during the study. See Section 6.1.7 for additional discussion on the use of concomitant medications if medically necessitated.

Concomitant medications associated with the lesion intervention(s) must be recorded in the source and the appropriate eCRF.

A total of two protocol-allowed interventions are permissible during Period A. An intervention can occur on maximally two different lesions at the same visit or on the same lesion at two different study visits. The same lesion cannot be treated two times at the same visit. If a subject requires more than two interventions within the first 12 weeks, then the subject must be discontinued from the study.

During Period B (including during the excisional surgery) protocol-allowed interventions (i.e., intra-lesional injection, incision and drainage) are not permitted.

During Period C, maximally two interventions every 4 weeks are permitted. An intervention can occur on two different lesions at the same visit or on the same lesion at two different study visits. Within each 4-week period, the same type of intervention cannot be used two times on the same lesion. If a subject requires more than two interventions within a 4-week period or has two of the same interventions on the same lesion within that same 4-weeek period, then a protocol deviation must be recorded in the source and on the appropriate eCRF.

All study visit evaluations must occur before any interventions are performed. Any lesion that undergoes an intervention will be documented in the source. The Study Investigator will be required to count any lesion that undergoes an intervention as permanently present from the date of the intervention, and must record this in the source and on the appropriate eCRF.

Study Drug

Study drug administration will be documented in a separate section of the eCRF. All study visit evaluations must occur before the study drug is administered.

5.2.3.3 Prohibited Therapy

The following are prohibited medications during the study:

- All biologic therapy with a potential therapeutic impact on HS, including but not limited to the following (generic name with brand name, or its biosimilar product):
  - Abatacept (Orencia®);
  - Anakinra (Kineret®);
  - Belimumab (Benlysta®).
  - Certolizumab (Cimzia®);

- Etanercept (Enbrel®);
- Infliximab (Remicade®);
- Natalizumab (Tysabri®);
- Rituximab (Rituxan®);
- Tocilizumab (Actemra®);
- Ustekinumab (Stelara®).

- Any investigational agent
- Any other systemic drug therapies for HS, including but not limited to antibiotics (except as specified in Section 5.2.3.2), systemic cyclosporine, methotrexate, retinoids, and fumaric acid
- Prescription topical therapies for HS, including prescription topical antibiotics
- Surgical or laser intervention for an HS lesion except as outlined in Section 5.2.3.2
- Live vaccine (during the study and for 70 days after the last dose of study drug)
- High-dose oral or injectable corticosteroids

  High-dose systemic corticosteroids and five half-lives are defined as follows:

Steroid	High Dose (/Day)	$t_{1/2}$	5 Half-Lives
Hydrocortisone	20 mg	12 hrs	3 days
Dexamethasone	1 mg	54 hrs	12 days
Methylprednisolone	7.5 mg	36 hrs	8 days
Prednisone	7.5 mg	36 hrs	8 days
Cortisone	25 mg	12 hrs	3 days

5.2.3.4 Rescue Therapy

If the Study Investigator, with agreement of the designated surgeon, determines the subject must undergo excision of the HS surgical site prior to the Week 13 study visit window (i.e., more than 7 days prior to the scheduled Week 13 study visit) all study

procedures scheduled for Week 12 must be performed and recorded, and the subject must be discontinued from the study.

5.2.4 Contraception Recommendations and Pregnancy Testing

If female, the subject must be either postmenopausal, defined as:

- with no menses for 12 or more months without an alternative medical cause; or
- permanently surgically sterile (bilateral oophorectomy, bilateral tubal occlusion, bilateral salpingectomy and/or hysterectomy).

OR

The female subject is of childbearing potential, is participating in heterosexual vaginal intercourse, and is practicing at least one of the following methods of birth control, on Day 1 (or earlier) through at least 150 days (or as dictated by local requirements) after the last dose of study drug:

- Combined (estrogen and progestogen-containing) hormonal contraception (oral, intravaginal, transdermal) associated with the inhibition of ovulation, initiated at least 1 month prior to Day 1;
- Progestogen-only hormonal contraception (oral, injectable, implantable) associated with inhibition of ovulation, excluding low-dose oral gestagens (mini-pills containing either lynestrenol or norestisteron) initiated at least 1 month prior to Day 1;
- Low-dose oral gestagens (mini-pills containing either lynestrenol or norestisteron) are not associated with inhibition of ovulation, and are not considered as effective contraception.
- Vasectomised partner(s), provided the vasectomised partner has received medical assessment of the surgical success;
- Intrauterine device (IUD); and/or
- Intrauterine hormone-releasing system (IUS).

If required per local practices, male or female condom with or without spermicide; or cap, diaphragm, or sponge with spermicide should be used in addition to one of the birth control methods listed above. Barrier methods with or without foams and jellies (such as condom, sponge, and diaphragm, alone or in combination, are not protocol-specified birth control methods.

OR

The female is of childbearing potential and practicing true abstinence from heterosexual vaginal intercourse. (Note: Periodic abstinence [e.g., calendar, ovulation, symptothermal, post-ovulation methods] and withdrawal are not acceptable as abstinence.)

5.3 Efficacy, Safety, and Exploratory Research/Validation Studies Assessments/Variables

5.3.1 Efficacy, Safety, and Exploratory Research/Validation Studies Measurements Assessed and Flow Chart

Study procedures described are listed in the following section of this protocol and are summarized in tabular format in Appendix C.

Study procedures for the optional exploratory research/validation studies are listed in the following section of this protocol and are summarized in tabular format in Appendix D.

5.3.1.1 Study Procedures

The study procedures outlined in Appendix C are discussed in detail in this section, with the exception of drug concentration measurements (Section 5.3.2) and the collection of AE information (Section 6.0).

Informed Consent

An Independent Ethics Committee (IEC)/Institutional Review Board (IRB) approved, study-specific ICF will be reviewed, signed and dated by the subject before any study procedures are undertaken, or before any medications are withheld from the subject in

order to participate in this study. Because subjects are required to be candidates for excisional surgery in order to be eligible for the study (Inclusion Criterion 3), surgical consent is considered a separate, non-study procedure and will be conducted outside of the parameters of the study protocol, per standard of care, with the exception that consent for surgery must be obtained prior to any surgical intervention is undertaken. Details about how informed consent will be obtained and documented are provided in Section 9.3.

Inclusion/Exclusion Criteria

Subjects will be evaluated to ensure they meet all inclusion criteria and none of the exclusion criteria at the Screening and Baseline visits.

Prior and Concomitant Therapy Assessment

See Section 5.2.3.

Medical and Surgical History

A complete medical history (which includes HS-related and non-HS-related medical and surgical history), including history of tobacco and alcohol use, will be obtained from each subject during the Screening visit with the Primary Investigator and designated surgeon. The medical history should also include a detailed history of prior therapies used to treat HS, including antibiotics. Medical history will be reviewed and updated at the Baseline visit to ensure the subject remains qualified for the study.

A detailed medical history with respect to TB exposure needs to be documented. This information needs to include Bacille Calmette-Guérin (BCG) vaccination, cohabitation with individuals who have had TB, and/or who reside or work in TB endemic locations.

If deemed eligible for the study by the Study Investigator, study site personnel will schedule a screening visit with the designated surgeon. The surgeon will verify and complete, if necessary, the surgical history. In addition, the surgeon will complete the surgical Screening assessment by evaluating the planned HS surgical site with regards to the surgical Inclusion and Exclusion Criteria. The surgeon will develop a planned

surgical intervention (hereinafter termed 'surgical plan'). The evaluation and surgical plan will be recorded on the appropriate eCRF pages.

Physical Examination

A full physical exam will be performed at the designated study visits listed in Appendix C. Physical examination findings that are related or part of each subject's medical history should be captured in the source and on the appropriate eCRF page. The designated surgeon will verify and complete, if necessary, any findings regarding examination of the HS surgical site at the Screening visit with the surgeon. The surgeon will enter the findings in the source and on the appropriate eCRF page.

A symptom-directed physical examination should be performed at all other study visits, if warranted. Abnormalities noted after the Baseline visit will be evaluated and documented by the Study Investigator as to whether they are AEs.

Findings from any pre-operative physical exam that is required per standard of care by the subject's personal physician/surgeon, Study Investigator, or designated surgeon, other than AEs/SAEs, will be maintained per local institution policy and will not be recorded on the eCRF. Only those physical findings from the pre-operative physical exam that pertain to a new or ongoing AE/SAE will be recorded on the AE/SAE eCRF (see Section 6.1).

Vital Signs

Vital sign determinations of systolic and diastolic blood pressure, pulse rate (counted for at least 30 seconds after 5 minutes in sitting position), respiratory rate, body weight, and body temperature (oral) will be obtained at each study visit. Blood pressure and pulse rate measurements should be performed prior to the collection of any laboratory specimens.

Height and Waist Circumference Measurements

Height will be measured at Baseline and waist circumference will be measured at Baseline and Week 12 (see Appendix C).

To measure waist circumference, locate the top of the right iliac crest. Place a measuring tape in a horizontal plane around the abdomen at the level of the iliac crest. Before reading the tape measure, ensure that the tape is snug but does not compress the skin and is parallel to the floor. Measurement should be made at the end of a normal expiration.

Electrocardiogram

A resting 12-lead ECG will be performed at the designated study visits listed in Appendix C. A qualified physician will interpret, sign, and date each ECG. Any clinically significant findings will be documented in the source documents and later transcribed on to the appropriate eCRF by the Primary Investigator. Each signed original ECG will be monitored by the AbbVie Clinical Research Associate (CRA) and kept with subject's source documents onsite.

For subjects with a normal ECG taken within 90 days of Screening, a repeat ECG at Screening will not be required, provided all protocol required documentation is available. If there are other findings that are clinically significant, the Study Investigator must contact the Study Designated Physician before enrolling the subject.

Any pre-operative ECG that is required, per standard of care, will be conducted and results maintained per local institution policy and not recorded on the eCRF. Only those findings from the pre-operative ECG that pertain to a new or on-going AE/SAE will be recorded on the AE/SAE eCRF.

Subjects can have a repeat ECG at any time during the study as warranted based on the opinion of the Study Investigator.

Chest X-Ray

All subjects will undergo a standard CXR (PA and lateral views) during the Screening period to rule out the presence of TB or other clinically relevant findings. The CXR will not be required if the subject had a previous normal CXR within 90 days of Screening,

provided all protocol required documentation is available at the study site (as outlined below).

Any pre-operative CXR that is required, per standard of care, will be maintained per local institution policy and will not be recorded on the eCRF. Only those findings from the pre-operative CXR that pertain to a new or on-going AE/SAE will be recorded on the AE/SAE eCRF.

Subjects can have a repeat CXR at any time during the study as warranted based on the opinion of the Study Investigator.

In the assessment of the CXR, a radiologist must specifically note the presence or absence of 1) calcified granulomas, 2) pleural scarring/thickening, and 3) signs of active TB. The Study Investigator will indicate the clinical significance of any findings and will sign and date the CXR report. If the CXR demonstrates changes suggestive of previous TB (e.g., calcified nodule, fibrotic scar, apical or basilar pleural thickening) or other findings that are clinically significant, the Study Investigator must contact the AbbVie Study Designated Physician before enrolling the subject.

TB Screening

In patients treated with corticosteroids (equivalent to Prednisone 5 mg or above – with ongoing treatment or treatment within 1 month prior to TB screening), an Interferon-Gamma Release Assay (IGRA; QuantiFERON-TB Gold In-Tube test or T-SPOT TB test) may be performed locally or by the central lab during the Screening Period for all subjects, including those with a prior history of Bacille Calmette-Guérin (BCG) administration.

In patients NOT treated with corticosteroids (equivalent to Prednisone 5 mg or above – with ongoing treatment or treatment within one month prior to TB screening), a PPD skin test (alternatively, also known as tuberculin skin test) must be placed, or an Interferon-Gamma Release Assay (IGRA; QuantiFERON-TB Gold In-Tube test or T-SPOT TB test)

may be performed locally or the central lab during the Screening Period for all subjects, including those with a prior history of Bacille Calmette-Guérin (BCG) administration.

If a subject had a negative PPD or IGRA test within 90 days prior to Screening, and all protocol required documentation is available, the test does not need to be repeated, provided nothing has changed in the subject's medical history to warrant a repeat test, and that in patients treated with corticosteroids (equivalent to Prednisone 5 mg or above – with ongoing treatment or treatment within 1 month prior to TB screening) the performed screening was an Interferon-Gamma Release Assay. These cases must be discussed with the AbbVie Study Designated Physician.

For the PPD test:

The subject will be required to have the PPD skin test read by a licensed healthcare professional 48 to 72 hours after placement (or as per local guidelines), when the induration is maximal. An induration (not erythema) of 5 mm or greater will be considered as PPD positive, regardless of BCG status or local guidelines. The induration must be recorded in "mm," not as "positive" or "negative." The absence of induration should be recorded, as "0 mm," not "negative." *(If required by specific countries a two-step test may be performed per local guidelines. The result of the second test should be recorded.)*

A subject, who has had an ulcerating reaction to a PPD skin test in the past, as documented in the medical history source and eCRF, should not be re-exposed and should not be tested at Screening but will be considered PPD positive.

If there are study sites where the available testing materials are not accepted, the method must be submitted and approved by the AbbVie Study Designated Physician prior to use with study subjects.

If the PPD or the IGRA test is positive, the subject has a prior history of active or latent TB, or the results of a CXR are indicative of latent TB (see Section 5.3.1.1), the subject will be required to initiate and have taken at least 4 weeks (or per local guideline,

whichever is longer) of an ongoing course of Centers for Disease Control and Prevention (CDC)-recommended prophylaxis or prophylaxis per local guidelines prior to starting study drug therapy and should be evaluated by a physician experienced in the evaluation and treatment of TB patients before entering the trial. Subjects who have a documented completion of the CDC-recommended prophylaxis may be permitted to enroll. The Principle Investigator should contact the AbbVie Study Designated Physician to discuss enrollment of this potential subject.

In the event both a PPD test and an IGRA test are performed, the result of the IGRA test will supersede the result of the PPD test. If the IGRA test is performed and the result is indeterminate, the test should be repeated with a fresh blood sample or perform a PPD test. If the repeat IGRA test is also indeterminate, this should be considered a positive test result and TB prophylaxis should be initiated.

Newly initiated prophylactic treatment should be recorded on the concomitant medications page in the eCRF and in the source documents. Prior therapy should be recorded on the medical history page in the eCRF.

Clinical Laboratory Tests

Samples will be obtained for the laboratory tests listed in Table 1 at the designated study visits listed in Appendix C. For the samples collected at Baseline, Week 12, and Week 24/Premature Discontinuation visits subjects should be fasting before the sample is collected. Please refer to the laboratory manual for further instructions. Blood draws should be performed after questionnaires and vital sign determinations have been completed, but prior to any study drug administration. A certified central laboratory will be utilized to process and provide results for the general laboratory tests. Instructions for urine pregnancy testing can be found in the laboratory manual. All abnormal laboratory test results that are considered clinically significant by the Study Investigator will be followed to a satisfactory resolution.

Any pre-operative laboratory testing that is required, per standard of care, will be read by the local lab and maintained per local institution policy and will not be recorded on the eCRF. Only those findings from the pre-operative laboratory testing that pertain to a new or ongoing AE/SAE will be recorded on the AE/SAE eCRF.

Instructions regarding the collection, processing and shipping of these samples will be provided by the central laboratory.

Pregnancy Testing

A serum pregnancy test (conducted by the central lab) will be performed at the Screening visit for all female subjects of childbearing potential. At the Baseline and Week 24 or Premature Discontinuation visits, female subjects of childbearing potential will have a urine pregnancy test (conducted at the site). *(If required by local regulatory authorities urine pregnancy tests will be performed monthly throughout the study.)* If any urine pregnancy test is positive, a serum pregnancy test will be analysed by the central laboratory. If a serum pregnancy test is positive, the female subject is not eligible for participation or continuation in the study. If the subject is discontinued from the study, every effort will be made to schedule the subject for a Premature Discontinuation Visit.

All female subjects of childbearing potential will have a repeat urine pregnancy test at the final Study Visit performed at the site by designated study personnel.

Females of non-childbearing potential, whether by being postmenopausal or permanently surgically sterile as defined above (Section 5.3.1.1), do not require pregnancy testing at Screening.

Urinalysis

Urine samples will be obtained for urinalysis and nicotine metabolite screening as listed in Appendix C. For urine samples with abnormal macroscopic results, a microscopic test will be performed.

Table 1. Clinical Laboratory Tests

Hematology	**Clinical Chemistry****	**Urinalysis**
Hematocrit Hemoglobin Red Blood Cell (RBC) count White Blood Cell (WBC) count Neutrophils Bands 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 Glucose Blood Urobilinogen Bilirubin Microscopic examination, if needed Leukocytes Nitrite
Other		**Pregnancy Test**
hsCRP Hepatitis B Screening HbA1c Antinuclear Antibody (ANA)/Anti-dsDNA Optional: Exploratory Research/Validation Studies (if informed consent has been obtained) HIV (testing to be conducted at local lab)		Serum HCG Urine HCG

* To be performed only at study visits designated for Lipid Testing.

** Chemistry should be fasting at Baseline and Weeks 12 and 24.

Hepatitis B Screening

All subjects will be tested for the presence of the hepatitis B virus (HBV) at Screening. A positive result for the hepatitis B surface antigen (HBs Ag) will be exclusionary. Samples negative for HBs Ag will be tested for surface antibodies (HBs Ab) and core antibodies (HBc Ab Total). Any subject with HBs Ag (–), HBs Ab (–), and HBc Ab Total (+)

requires PCR qualitative testing for HBV DNA. Any HBV DNA PCR result that meets or exceeds detection sensitivity will be exclusionary.

Subjects with a negative HBs Ag test and tests showing the results below do not require HBV DNA PCR qualitative testing:

- HBs Ab (–) and HBc Ab Total (–)
- HBs Ab (+) and HBc Ab Total (–)
- HBs Ab (+) and HBc Ab Total (+)

Human Immunodeficiency Virus Testing

If required by country regulatory authorities to confirm eligibility, subjects will be tested for antibodies to the HIV at Screening, and document that the test has been performed. The testing is to be done at a local lab. A subject will not be eligible for study participation if test results indicate a positive HIV infection. AbbVie will not receive results from the testing, and will not be made aware of any positive result.

High Sensitivity C-Reactive Protein Testing

Testing for high sensitivity C-reactive protein (hsCRP) will be performed on specimens collected at the designated study visits listed in Appendix C.

Hemoglobin A1c Testing

All subjects will be tested for hemoglobin A1c (HbA1c) at the designated study visits listed in Appendix C.

Antinuclear Antibody/Anti-dsDNA Testing

Study personnel will collect a sample for antinuclear (ANA) and reflex double stranded DNA (dsDNA) antibody testing at the Screening visit. A repeat ANA/Anti-dsDNA would be warranted if a subject has clinical signs and symptoms suggestive of lupus. The Anti-dsDNA antibody testing will be performed in case of positive ANA result. All samples will be sent to the central laboratory for processing.

Exploratory Research and Validation Studies Samples

Subjects will have the option to provide samples for exploratory research and validation studies. Subjects may still participate in the main study even if they decide not to participate in the optional exploratory research/validation studies.

Validation studies, including those related to the development of potential in vitro diagnostic tests, may be carried out retrospectively in order to assess associations between events of interest (i.e., efficacy and/or safety events) and candidate biomarkers.

AbbVie (or people or companies working with AbbVie) will store the exploratory research/validation studies samples in a secure storage space with adequate measures to protect confidentiality. The samples will be retained while research on adalimumab (or drugs of this class) or this disease and related conditions continues, but for no longer than 20 years after study completion.

The following samples will be collected according to Appendix D from each subject who consents to provide samples for exploratory research/validation studies. The procedures for obtaining and documenting informed consent are discussed in Section 9.3.

- DNA samples for pharmacogenetic or epigenetic analyses
- RNA samples for transcriptomic and/or epigenetic analyses
- Serum and plasma samples for systemic analyses including, but not limited to, proteomic and metabolomics
- Blood samples for peripheral blood mononuclear cell (PBMC) investigations including, but not limited to, immunophenotyping and protein expression profiles
- A swab from HS lesional (or healed skin following therapy) and non-lesional skin for microbiome analysis

Samples will be shipped to AbbVie or a designated laboratory for DNA/RNA extraction, if applicable, and/or analyses or long-term storage. Instructions for the preparation and shipment of the samples will be provided in the laboratory manual.

For each subject who consents to provide skin tissue samples, two skin biopsies may be collected at the Baseline visit. For those subjects not undergoing surgery, two additional skin biopsies may be collected at both the Week 12 and Week 24/Premature Discontinuation visit. For those subjects who undergo surgery, remnant tissue will be collected from the excised surgical specimen at Week 13. Six biopsies from HS lesional tissue and six biopsies from non-lesional tissue will be collected and preserved. Also for those subjects who undergo surgery, an additional skin biopsy may be collected at Week 24/Premature Discontinuation visit. Importantly, a subject may still participate in the optional exploratory research/validation studies if the subject decides not to participate in the optional biopsy collections. The procedures for obtaining and documenting informed consent are discussed in Section 9.3.

Samples will be shipped to AbbVie or a designated laboratory for analyses and/or long-term storage of the skin biopsies. Instructions for the preparation and shipment of the samples will be provided in the laboratory manual.

Dermatology Life Quality Index

Subjects will complete a Dermatology Life Quality Index (DLQI) questionnaire (Appendix F) at the designated study visits listed in Appendix C. The DLQI will be used to assess the symptoms and the impact of skin problems on quality of life. The DLQI can be used to evaluate six areas: symptoms and feelings, daily activities, leisure, work and school, personal relationships, and treatment. Subjects will be asked to respond to the 10 items of the DLQI based on a recall period of 'last week.' Decreased scores indicate improved health-related quality of life.

The subject should complete the questionnaire before study site personnel perform any clinic assessments and before any interaction with the site personnel has occurred to avoid biasing the subject's response.

EuroQoL

Subjects will complete the EuroQoL™ (EQ-5D™) questionnaire (Appendix EG) at the designated study visits listed in Appendix C. The EQ-5D™ is a simple generic measure that asks respondents about their current health state "today." The EQ-5D™ contains five dimensions including "mobility," "self-care," "usual activities," "pain/discomfort," and "anxiety/depression."

The subject should complete the questionnaire before study site personnel perform any clinic assessments and before any interaction with the site personnel has occurred to avoid biasing the subject's response.

Hidradenitis Suppurativa Impact Assessment

The Hidradenitis Suppurativa Impact Assessment (HSIA) is an 18-item PRO questionnaire (Appendix H) developed to assess the impact of HS on the daily lives of subjects in the 7 days prior to the assessment. Items 1 – 16 of the HSIA are scored on a 0 to 10 numeric rating score where 0 represents no impact and 10 represents extreme impact. In this way, item scores can be generated to characterize the patient's experience at an individual impact level. Additionally, Items 1 – 16 characterize the overall impact of HS and can be scored together to create a weekly Overall HSIA score. The Overall HSIA score is generated by summing the completed individual impact, item-level scores collected on the same day, and dividing that sum by the total number of completed responses (i.e., the Overall HSIA score is an average). The Overall HSIA score will only be derived if eight or more (i.e., at least 50%) of responses are available (and adjusting the denominator to match the number of completed items). Items 17 and 18 utilize an open field where patients are asked to fill in a number, and are not included in the Overall HSIA score. Instead, a separate mean score for the hours worked (Item 17) or hours missed at school or work (Item 18) will be calculated. If the response is "Non Applicable" for any of the Items 13 – 14 or 16 – 18 then the subject will be deemed as "not applicable" for calculating scores.

The subject should complete the questionnaire before study site personnel perform any clinic assessments and before any interaction with the site personnel has occurred to avoid biasing the subject's response.

Hidradenitis Suppurativa Patient's Global Assessment of Skin Pain

The Hidradenitis Suppurativa Patient's Global Assessment of Skin Pain (HS-PGA-SP) is a two-item PRO questionnaire (Appendix I) designed to assess daily skin pain due to HS at its worst and on the average. The HS-PGA-SP – at worst is a numeric rating scale (NRS). The NRS is an 11-point scale consisting of a 0 – 10 range from which the subject selects the number most representative of his or her experience. Subjects are asked to respond to the items based on a recall period of "the last 24 hours." The scoring for the HS-PGA-SP is based on an 11-point NRS consisting of a 0 – 10 range. Each item is scored independently from the other.

The subject should complete the questionnaire before study site personnel perform any clinic assessments and before any interaction with the site personnel has occurred to avoid biasing the subject's response.

Hidradenitis Suppurativa Patient's Global Impression of Change

Subjects will complete the Hidradenitis Suppurativa Patient's Global Impression of Change (HS PGIC) questionnaire (Appendix J) at the designated study visits listed in Appendix C. The HS PGIC consists of one self-administered item that assesses change in the severity of skin pain due to HS. Subjects are asked to indicate their impression of change compared with their last visit.

The subject should complete the questionnaire before study site personnel perform any clinic assessments and before any interaction with the site personnel has occurred to avoid biasing the subject's response.

Hidradenitis Suppurativa Symptom Assessment

The Hidradenitis Suppurativa Symptom Assessment – 7 day recall (HSSA-7d) is a nine-item PRO questionnaire (Appendix K) developed to assess the primary symptoms of HS in the 7 days prior to assessment. Each item of the HSSA is scored on a 0 to 10 NRS where 0 represents no symptoms and 10 represents extreme symptom experience. In this way, item scores can be generated to characterize the patient's experience at a symptom level. Additionally, Items 1 – 9 can be scored together to create a Total Symptom Score to characterize an overall symptom experience by averaging the scores collected from the non-missing items collected at the same assessment.

The subject should complete the questionnaire before study site personnel perform any clinic assessments and before any interaction with the site personnel has occurred to avoid biasing the subject's response. HSSA scores range from 0 – 90 with higher scores indicating worse symptoms.

Short Form 12

The acute Short Form-12v2™ Health Survey (SF-12) is a 7-day recall, 12-item subset of the Short Form-36v2™ questionnaire (Appendix L) that measures the same eight domains of health including physical functioning, role-function, bodily pain, general health, vitality, social functioning, role-emotional, and mental health. SF-12 is a brief, reliable measure of overall health status with scores general for physical component and mental components. Each item of the SF-12 is scored on 3- or 5-item Likert scales and the domains scales are standardized to a 0 to 100 scale where 0 represents lower quality of life and 100 represents higher quality of life.

The subject should complete the questionnaire before study site personnel perform any clinic assessments and before any interaction with the site personnel has occurred to avoid biasing the subject's response. SF-12 scores range from 0 – 100 with higher scores indicating better quality of life.

Treatment Satisfaction Questionnaire – Medication

Subjects will complete the Treatment Satisfaction Questionnaire – Medication (TSQM) questionnaire (Appendix M) at the designated study visits listed in Appendix C. The TSQM is a 14-item instrument and includes assessments of satisfaction with a medication's effectiveness (three items), lack of side effects (five items), convenience (three items) and the subject's global satisfaction (three items).

The subject should complete the questionnaire before study site personnel perform any clinic assessments and before any interaction with the site personnel has occurred to avoid biasing the subject's response. TSQM scores range from 0 – 100 with higher scores indicating better satisfaction.

Work Productivity and Activity Impairment Questionnaire: Specific Health Problem

The subjects will complete a Work Productivity and Activity Impairment Questionnaire: Specific Health Problem (WPAI:SHP) questionnaire (Appendix N) at the designated study visits listed in Appendix C. The WPAI:SHP (6 items) evaluates four areas: percent work time missed due to HS, percent impairment while working due to HS, percent overall work impairment due to HS, and percent activity impairment due to HS.

The subject should complete the questionnaire before study site personnel perform any clinic assessments and before any interaction with the site personnel has occurred to avoid biasing the subject's response.

Lesion Counts

The number of inflammatory and non-inflammatory nodules, abscesses, draining and non-draining fistulas, and hypertrophic scars, as well as the physical location (e.g., right/left axilla, right/left inframammary, inframammary, right/left buttock, right/left inguino-crural fold, perianal, perineal, other) will be recorded (Appendix E) at the designated study visits listed in Appendix C. The calculation of the HiSCR will be performed by AbbVie at the end of the study based on the lesion counts entered by the

Study Investigators on the appropriate CRFs; thus, treatment decisions made during the conduct of this study will not be based on the HiSCR.

The longest distance between two relevant lesions (if only one lesion, measure diameter of lesion) and whether the lesions are clearly separated by normal-appearing skin ('yes'/'no') will be measured.

Hurley Stage

See Section 1.3 for definition of Hurley Stage. The Study Investigator will determine the Hurley Stage in each affected anatomical region at the designated study visits listed in Appendix C. If more than one stage is present in a region, the worst stage in each region should be entered.

The study site should make every attempt to have the same investigator conduct these assessments throughout the study for each subject.

Dispense Study Drug

Study drug will be dispensed (Appendix O) to subjects at the designated study visits listed in Appendix C. Each subject will receive study drug packaged as described in Section 5.5.2, with adequate supply to be used for weekly injections until the next scheduled study visit.

Digital Imaging

Subjects at prospectively selected study sites will be asked to have photographs taken of their disease response during the study. The study sites will be chosen by AbbVie for their expertise. Subjects who consent will have photographs taken at the designated study visits listed in Appendix C. The cameras for the photographs will be standardized and supplied to the study site by a central photography imaging vendor. Study sites will submit the digital images to the centralized imaging vendor. Training and detailed instructions will be provided by the central imaging vendor. The digital images will be

stored for later reproduction and medical education, and exploratory analyses may be performed of the blinded, annotated digital images.

The designated surgeon (or Study Investigator, dependent on available camera and technical expertise) will photograph each subject's HS surgical site.

Doppler Ultrasound

Subjects at prospectively selected study sites will be asked to have Doppler ultrasound examinations of the HS non-surgical sites throughout the study and the HS surgical site throughout Period A. Subjects who consent will have these examinations performed at the designated study visits listed in Appendix C. The study sites will be selected by AbbVie for their access to appropriate equipment, technical skills, and interpretative expertise to perform these examinations. The results of these evaluations will not be used to count HS lesions (e.g., abscesses, inflammatory nodules, fistulas), calculate the Hurley Stage, or evaluate the HiSCR.

Follow-Up Telephone Calls

Week 6 and Week 10

Subjects will be contacted at Week 6 and Week 10 to obtain information on any signs of an infection at or near an HS lesion. Subjects with signs or symptoms of an infection will be bought into the study site for an unscheduled visit to be evaluated. Study procedures will be performed as outlined in Appendix C.

70 Days Following the Last Dose of Study Drug

Subjects will be contacted approximately 70 days following study drug discontinuation for an assessment of any new or ongoing AEs/SAEs, except for those subjects who continue on adalimumab not supplied in the context of the clinical trial after the end of study participation. These subjects are not required to complete the 70-day follow-up telephone call and any new AEs should be reported through the mechanism used for all post-marketing adverse experience.

5.3.2 Drug Concentration and Anti-Adalimumab Antibody Measurements

Blood samples for adalimumab and Anti-Adalimumab Antibody (AAA) assays will be collected by venipuncture at the designated study visits listed in Appendix C.

5.3.2.1 Collection of Samples for Analysis

Blood samples for PK adalimumab analysis will be collected by venipuncture into appropriately labeled 6 mL evacuated serum collection tubes without gel separator at the designated study visits listed in Appendix C (i.e., at Baseline, and Weeks 4, 8, 12, 14, 15, 17, 20, and 24/Premature Discontinuation Visit if the subject discontinues prior to Week 24). All samples will be obtained immediately prior to study drug administration.

Blood samples for AAA will be split from the PK sample collection after centrifugation to isolate serum. Detailed information will be provided in the laboratory manual. Processing for AAA samples will be done at the designated study visits listed in Appendix C (i.e., at Baseline, and Weeks 4, 8, 12, 15, 20, and 24/Premature Discontinuation Visit if the subject discontinues prior to Week 24).

Collection of Samples for Adalimumab Analysis

A maximum of 8 samples are planned to be collected per subject for PK adalimumab analysis. The total number of PK adalimumab samples planned will not exceed 1600 (8 samples × 200 subjects) for the entire study. Sample calculations are based on the maximum number of subjects.

Collection of Samples for Anti-Adalimumab Antibody Analysis

A maximum of 7 samples are planned to be split from the PK sample collection. The total number of AAA samples planned will not exceed 1400 (7 samples × 200 subjects) for the entire study. Sample calculations are based on the maximum number of subjects.

5.3.2.2 Handling/Processing of Samples

Sufficient blood will be collected to provide approximately 3 mL serum from each sample. The blood will be allowed to clot for 30 minutes at room temperature prior to centrifugation as described in the laboratory manual. The time that each blood sample is collected will be recorded to the nearest minute in the source document and on the appropriate eCRF. Samples will be analysed under the supervision of the AbbVie Drug Analysis Department.

Additional detailed instructions for the handling and processing of samples will be provided from the central laboratory.

5.3.2.3 Disposition of Samples

AbbVie will not supply dry ice for this study. The frozen serum samples for the adalimumab PK and, where applicable, AAA assays will be packed in dry ice (pellet form) sufficient to last 3 days during transport and shipped from the study site to the Central Laboratory. The two splits of each sample set (i.e., adalimumab, AAA) will be shipped in separate shipments in case of transportation problems (i.e., customs delays, damage or loss of shipment) as defined by the Central Laboratory.

5.3.2.4 Measurement Methods

Serum concentrations of adalimumab will be determined using a validated assay methodology under the supervision of the AbbVie Drug Analysis Department.

Serum concentration of AAA will be determined using a validated assay methodology under the supervision of the AbbVie Drug Analysis Department.

5.3.3 Efficacy Variables

5.3.3.1 Primary Variable

The primary efficacy variable is the proportion of subjects achieving HiSCR at Week 12. HiSCR is 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.

5.3.3.2 Secondary Variables

Ranked Secondary Efficacy Variables

The following secondary efficacy variable will be analysed according to the rank order as follows:

1. Proportion of subjects achieving HiSCR-es (defined as the HiSCR excluding the HS surgical site) at Week 12,
2. Proportion of subjects achieving HiSCR-es at Week 24,
3. Percent change in surface area of the HS surgical site from Baseline to Week 12, and
4. Proportion of subjects at Week 12 that require a less extensive surgery than the surgical plan (determined at Baseline) or no surgery as determined by the designated surgeon.

Other Efficacy Variables

Other efficacy variables to be analysed at each scheduled visit in Periods A and C, except for the ones included as the primary or ranked secondary variables that will be analysed for visits other than Weeks 12 and 24 include:

- Change from Baseline in CRP
- Proportion of subjects with DLQI = 0
- Proportion of subjects with DLQI = 0 or 1

- Change from Baseline in DLQI score
- Change from Baseline in EQ-5D index
- Change from Baseline in HS-PGA-SP
- Change from Baseline in HS PGIC
- Change from Baseline in HSIA
- Change from Baseline in HSSA-7d
- Change from Baseline in SF-12
- Change from Baseline in TSQM
- Change from Baseline in WPAI:SHP
- Proportion of subjects that experience a flare, defined as an at least 25% increase in AN count with a minimum increase of 2 relative to Baseline at each study visit, during Period A and during the study
- Proportion of subjects that experience at least 25% increase in each lesion type with a minimum increase of 2 relative to Baseline at each study visit, during Period A and during the study

5.3.4 Safety Variables

Adverse events, laboratory data, physical examinations, and vital signs will be collected, monitored, assessed, and recorded at the designated study visits listed in Appendix C and as described in Section 6.0 and Table 1.

5.3.5 Pharmacokinetic Variables

Adalimumab trough serum concentrations will be summarized at each time point using descriptive statistics. In addition, within subject comparison of adalimumab concentrations before and after surgery will be performed. Percentage of subjects that develop immunogenicity during the 24-week study duration will be calculated. The impact of immunogenicity development on adalimumab PK, efficacy, and safety will be evaluated through comparison of adalimumab concentrations, primary efficacy outcome, and incidence of AEs between AAA+ and AAA– subjects.

5.3.6 Exploratory Research Variables

Biomarker assessments may be used to assess and generate prognostic, predictive, pharmacodynamics, or surrogate biomarker signatures. These assessments may be explored in the context of HS or related conditions, and/or adalimumab or drugs of similar classes. The results from these analyses are exploratory in nature and may not be included with the clinical study report.

The sample may also be used to develop new therapies, research methods, and technologies. In addition, samples from this study may be banked for future use. Samples may then be used to validate putative biomarker signatures obtained from a prospective study, leading to the development of diagnostic tests.

5.4 Removal of Subjects from Therapy or Assessment

5.4.1 Discontinuation of Individual Subjects

A subject may withdraw from the study at any time. The Principle Investigator may discontinue any subject's participation for any reason, including an adverse event, safety concerns, of failure to comply with the protocol.

Subjects will be withdrawn from the study immediately if any one of the following occurs:

- Clinically significant abnormal laboratory result(s) or adverse event(s), as determined by the Study Investigator in consultation with the AbbVie Study Designated Physician;
- The Study Investigator believes it is in the best interest of the subject;
- The subject requests withdrawal from the study;

  Inclusion and exclusion criteria violation was noted after the subject started study drug, when continuation of the study drug would place the subject at risk as determined by the AbbVie Study Designated Physician (see Section 5.2 and Section 7.0);

- Introduction of prohibited medications or dosages when continuation of the study drug would place the subject at risk as determined by the AbbVie Study Designated Physician;
- Subject is non-compliant with TB prophylaxis;
- The subject develops tuberculosis, or any other significant or opportunistic infections;
- The subject becomes pregnant while on study drug;
- Subject has dysplasia of the gastrointestinal tract of a malignancy, except for localized non-melanoma skin cancer. Discontinuation for carcinoma in situ of the cervix is at the discretion of the Study Investigator;
- Subject is diagnosed with lupus-like syndrome, multiple sclerosis, or demyelinating disease;
- Subject is significantly non-compliant with study procedures that would put the subject at risk for continued participation in the trial, as determined by the Study Investigator, in consultation with the AbbVie Study Designated Physician.

If, during the course of study drug administration, the subject prematurely discontinues study drug use, the procedure outlined for the Premature Discontinuation Visit must be completed within 2 weeks of the last dose of study drug, and preferably prior to the initiation of another therapy. However, these procedures should not interfere with the initiation of any new treatments or therapeutic modalities that the Study Investigator thinks are necessary to treat the subject's condition. Following discontinuation of the study drug, the subject will be treated in accordance with the Study Investigator's best clinical judgment.

All attempts must be made to determine the date of the last dose of study drug and the primary reason for premature discontinuation. The information will be recorded on the appropriate eCRF page.

For subjects who are considered lost to follow-up, reasonable attempts must be made to obtain information on the final status of the subject. At a minimum, two telephone calls must be made and one certified letter must be sent.

5.4.2 Discontinuation of Entire Study

AbbVie may terminate this study prematurely, either in its entirety or at any study site, for reasonable cause provided that written notice is submitted in advance of the intended termination. The Study Investigator may also terminate the study at his/her study site for reasonable cause, after providing written notice to AbbVie in advance of the intended termination. Advance notice is not required by either party if the study is stopped due to safety concerns. If AbbVie terminates the study for safety reasons, AbbVie will immediately notify the Study Investigator by telephone and subsequently provide written instructions for study termination.

AbbVie reserves the right to discontinue the study at any time and to remove all study materials from the study site. Possible reasons for termination of the study include, but are not limited to:

- Safety concerns based on reported data
- Unsatisfactory enrollment with respect to quantity or quality
- Inaccurate or incomplete data collection
- Falsification of records
- Failure to adhere to the protocol

5.5 Treatments

5.5.1 Treatments Administered

All treatments administered will be assigned via Interactive Response Technology (IRT) in order to maintain blinding. During Period A (Week 0 through Week 12), all subjects will receive 4 injections initially at Day 1 (or alternatively, given as two 0.8 mL injections per day on 2 consecutive days), 2 injections at Day 15 (Week 2), and one injection weekly

from Week 4 through Week 12. During Period B, all subjects will receive one injection weekly from Week 13 through Week 14. During Period C, all subjects will receive one injection weekly from Week 15 through Week 23. No study drug will be administered at the Week 24 or Premature Discontinuation Visit.

Study drug will be provided as a sterile, preservative-free solution for subcutaneous (SC) administration in 1 mL pre-filled syringes containing adalimumab 40 mg/0.8 mL or placebo (0.8 mL). The subject should be instructed to store the pre-filled syringe in the outer carton (in order to protect from light) in the refrigerator at 2° to 8°C/36° to 46°F, and that syringes should not be stored in a freezer.

Study drug will be administered SC using sterile technique by the subject or designee (e.g., family member, friend, health care professional) at the study site, or at home via self-injection following proper training (Appendix P) or by a qualified designee. At each Study visit qualified research personnel will observe the subject or designee during the injection to ensure proper technique. The subject should place the used syringe in the sharps disposal container, which will be provided to the subject at each study visit (unless prohibited by local regulations) or less frequently depending upon the size of the container.

Period A

Subjects randomised to Arm 1 will receive:

- 160 mg/3.2 mL adalimumab at the Baseline Study visit (Day 1) administered as four 40 mg injections SC (or two 0.8 mL injections on two consecutive days, i.e., Day 1 and Day 2)
- 80 mg/1.6 mL adalimumab at the Week 2 (Day 15) Study visit administered as two 40 mg injections SC
- 40 mg/0.8 mL adalimumab every week (ew) from Week 4 (Day 29) through Week 12 administered (either at the Study visit or at home as appropriate) as one 40 mg injection SC

Subjects randomised to Arm 2 will receive:

- 3.2 mL placebo at the Baseline Study visit (Day 1) administered as four 40 mg injections SC (or two 0.8 mL injections on two consecutive days, i.e., Day 1 and Day 2)
- 1.6 mL placebo at the Week 2 (Day 15) Study visit administered as two 0.8 mL injections SC
- 0.8 mL placebo every week (ew) from Week 4 (Day 29) through Week 12 administered (either at the Study visit or at home as appropriate) as one 0.8 mL injection SC

Period B

Subjects randomised to Arm 1 will receive:

- 40 mg/0.8 mL adalimumab every week (ew) from Week 13 through Week 14 administered (either at the Study visit in clinic, in hospital, or at home as appropriate) as one 40 mg injection SC

Subjects randomised to Arm 2 will receive:

- 0.8 mL placebo every week (ew) from Week 13 through Week 14 administered (either at the Study visit in clinic, in hospital, or at home as appropriate) as one 0.8 mL injection SC

Period C

Subjects randomised to Arm 1 will receive:

- 40 mg/0.8 mL adalimumab every week (ew) from Week 15 through Week 23 administered (either at the Study visit or at home as appropriate) as one 40 mg injection SC

Subjects randomised to Arm 2 will receive:

- 0.8 mL placebo every week (ew) from Week 15 through Week 23 administered (either at the Study visit or at home as appropriate) as one 0.8 mL injection SC

5.5.2 Identity of Study Drug

The individual study drug information is presented in Table 2.

Table 2. Identity of Study Drug

Study Drug	Formulation	Manufacturer
Adalimumab	40 mg/0.8 mL pre-filled syringes Adalimumab/Mannitol, Citric acid monohydrate, Sodium citrate, Disodium phosphate dehydrate, Sodium dihydrogen phosphate dehydrate, Sodium chloride, Polysorbate 80, Water for injection, Sodium hydroxide added as necessary to adjust pH	AbbVie
Placebo	0.8 mL pre-filled syringes Mannitol, Citric acid monohydrate, Sodium citrate, Disodium phosphate dehydrate, Sodium dihydrogen phosphate dehydrate, Sodium chloride, Polysorbate 80, Water for injection, Sodium hydroxide added as necessary to adjust pH	AbbVie

Each study site will be responsible for tracking the lot numbers and expiration dates for all non-investigational medicinal products (e.g., generic name and generic name) that are dispensed.

5.5.2.1 Packaging and Labeling

Adalimumab and placebo will be provided in a 1 mL pre-filled syringe containing adalimumab 40 mg/0.8 mL or matching placebo injection solution and will be packaged in two pre-filled syringes per carton. Each adalimumab/placebo kit carton and syringe will be labeled and have a unique kit ID. The labels for the adalimumab/placebo syringe kit carton will minimally contain the required country information.

Each label must remain affixed to the dosing unit.

5.5.2.2 Storage and Disposition of Study Drugs

Adalimumab/placebo pre-filled syringes are to be stored protected from light at 2° to 8°C/36° to 46°F. Study drug ***must not be frozen*** at any time. A storage temperature log is to be maintained to document proper storage conditions. The refrigerator temperature must be recorded on a temperature log to record proper function. Malfunctions or any temperature excursions must be reported to the Sponsor immediately upon identification. Study medications should be quarantined and not dispensed until AbbVie GPRD or Abbott Temperature Excursion Management System (ATEMS) deems the medications as acceptable.

All clinical supplies must be stored and locked in a secure place until they are dispensed for subject use or are returned to AbbVie.

Study drugs, syringes, and associated products are for investigational use only and are to be used only within the context of this study.

5.5.3 Method of Assigning Subjects to Treatment Groups

The randomisation schedules will be generated at AbbVie before the start of the study and will be provided to the IRT vendor. Before the study site is initiated, the instructions for use of the IRT will be provided to the site. All subjects will be assigned a unique identification number by IRT as they are screened for the study. The subjects will be randomised centrally and stratified by Hurley Stage (II versus III) and anatomical location of the HS surgical site (i.e., axilla versus inguinal region) in a 1:1 ratio to either adalimumab or placebo at Day 1. The number of subjects in Hurley Stage III is not to exceed 50% of the total planned number of subjects (100 subjects). In addition the number of subjects with an AN count of 3 or 4 is not to exceed 40 (20% of the total planned number of subjects).

5.5.4 Selection and Timing of Dose for Each Subject

Subjects should take study medication as outline in Section 5.5.1.

At the Baseline visit, after all assessments have been completed, subjects in Arm 1 will receive four injections of active study drug (40 mg/0.8 mL each) and subjects in Arm 2 will receive four placebo injections (0.8 mL each) as detailed in Section 5.5.1. Appropriate study site personnel will train and then supervise the subject or designee administering at least one injection of the study drug to ensure proper understanding of injection technique (Appendix P). The subject or designee will subsequently dose and be witnessed by study site personnel during their study visits to ensure continued proper technique. When study drug is administered at the Day 1 (Week 0) and Week 2 study visits (see Appendix C), the subject should remain at the study site for approximately 15 to 30 minutes after injection for observation.

For home administration of injection, subjects or qualified designee will be instructed to inject study medication on the same day of the week as their Baseline visit day as detailed in Section 5.5.1. Every kit contains 2 syringes each.

If a subject should forget to administer the injection of study medication on their regularly scheduled dosing date, the subject should take the forgotten injection as soon as she/he remembers the dose was missed up to the day before the next scheduled dose. The subject should not administer two doses on the same day.

Doses not administered (e.g., not taken before the next dose is scheduled), should be recorded as not taken in the source. The extra dose should be returned in its entirety to the study site at the subject's next study visit. Meanwhile, the subject should resume their regular dosing schedule based on the first dosing date at Baseline (Day 1).

In the event the incorrect dose is taken, the entire volume of study drug is not injected, or a dose is missed, the subject should be instructed to contact the study site to determine how to proceed with dosing. The subject must record all dosing information on the Subject-Dosing Diary Sheet.

5.5.5 Blinding

5.5.5.1 Blinding of Study Drug

All AbbVie personnel with direct oversight of the conduct and management of the trial (with the exception of AbbVie's Global Drug Supply Management Team); the Study Investigator, the designated surgeon, and study site personnel; and the subject will remain blinded to each subject's treatment throughout the study. The IRT will provide access to blinded subject treatment information in the case of medical emergency. The procedure for breaking the blind is referenced in the IRT Training Slides provided to each study site.

AbbVie must be notified before the blind is broken unless identification of the study drug is required for medical emergency, i.e., situation in which the knowledge of the specific blinded treatment will affect the immediate management of the subject/patient's conditions (e.g., antidote is available). AbbVie must then be notified within 24 hours of the blind being broken. See Section 7.0 for contact information, including 24/7 physician coverage.

The date and reason that the blind was broken must be conveyed to AbbVie and recorded in the source documentation and on the appropriate eCRF.

5.5.6 Treatment Compliance

The Study Investigator or his/her designated and qualified representatives will administer/dispense study drug only to subjects enrolled in the study in accordance with the protocol. The study drug must not be used for reasons other than that described in the protocol.

The subject or his/her qualified designee will administer all doses of study drug after being appropriately trained (see Section 5.5.4). Appropriate study site personnel will supervise the subject's administration of the study drug at required study visits (see Appendix C) to ensure proper injection technique. In order to document compliance with the treatment regimen, the subject will be given a dosing sheet (Appendix Q) to record all injection dates and times. Compliance information will be document on the appropriate

eCRF. The subject will be counseled on missed doses of study drug. If the subject does not return the dosing sheet, study drug boxes, and/or sharps containers (when applicable), study site personnel should question the subject and obtain as much information as possible as to the dosing of the study drug.

The information should be documented on the source documents as per "best recollection" and when possible, re-verified when the dosing sheet is returned before completing the applicable eCRF page.

If a subject is consistently not returning the dosing sheet, not providing accurate dosing information, or consistently missing doses and/or is deemed non-compliant with no explanation, the situation will be discussed with the AbbVie Study Designated Physician and the subject may be discontinued from the study.

5.5.7 Drug Accountability

The Study Investigator or designee will verify that study drug supplies are received intact, at the appropriate temperature, and in the correct amounts. This will be accomplished by documenting the condition of the shipment, verifying kit numbers in the package against the Proof of Receipt (POR) or similar document included with each drug shipment, and documenting this verification by signing and dating the POR or similar document. The original POR or similar document will be kept in the study site files as a record of what was received.

In addition, an accurate running inventory of study drug will be kept by the study site using the online clinical drug accountability (CDA) system provided by the IRT system. The CDA system will track the following: date received, the lot number, the kit number(s), date dispensed, subject number, and the identification with date of the person dispensing the drug.

All empty study drug boxes and used pre-filled syringes will be inventoried by the study site personnel. Each subject will be given his/her own sharps disposal container to store used pre-filled syringes. Empty study drug boxes and sharps disposal containers should

be returned by the subject at each study visit for accountability and compliance purposes, and new containers will be issued as necessary. Empty study drug boxes and returned sharps disposal containers will be retained (unless prohibited by local regulations) until the AbbVie Medical Monitor is at the study site to confirm the returned study drug. The AbbVie CRA and study site personnel will complete study drug accountability using study drug logs, source documents, and subject dosing sheets plus visual inspection of empty study drug boxes and the syringes in the returned sharps disposal containers. The returned sharps disposal containers should never be opened. Once the AbbVie CRA has verified drug accountability, the study site personnel and AbbVie CRA will document that the used syringes have been destroyed, using appropriate biohazard precautions, when appropriate. A copy of the destruction methodology should be maintained at the study site's facility. Unused study drug will be returned by the AbbVie CRA after drug accountability has been completed at the study site.

In addition to overall drug accountability, the subject and study site will maintain subject dosing and subject drug accountability logs, Appendix Q and Appendix R, respectively.

Non-investigational medicinal and other treatment products (standard of care) (e.g., wound care supplies) must be obtained commercially.

5.6 Discussion and Justification of Study Design

5.6.1 Discussion of Study Design and Choice of Control Groups

The design of this clinical trial is chosen to evaluate adalimumab in HS subjects with active HS lesions who require surgery as part of their standard care. Adalimumab will be compared to placebo during a 12-week period (Period A) prior to surgery, to assess the impact on all anatomic regions with active HS lesions including the HS surgical site and at least two other anatomical regions, one of which is Hurley Stage II or III. The impact on the HS surgical site will be also evaluated. Period B is a 2-week period during which the subject undergoes surgery and immediate post-operative routine care and monitoring. The utility of Period C, a 10-week period, is to assess the impact the adalimumab as compared to placebo in HS subjects who have undergone surgery, including the continued

impact on active HS lesions not within the surgical site (i.e., HS non-surgical sites) and the impact on the surgical wound. Previous clinical trials have not evaluated the use of adalimumab in concert with surgery. This study design will allow direct evaluation of adalimumab in a HS population that requires excisional surgery as part of their routine disease management. The placebo-controlled trial will allow a comparison of safety of adalimumab over a 24-week period including comparisons both before and after excisional surgery.

5.6.2 Appropriateness of Measurements

Standard statistical, clinical, and laboratory procedures will be used in this study. Efficacy measurements have been selected to assess disease activity in subjects with chronic HS. The primary efficacy endpoint (HiSCR, at least a 50% reduction in the AN count plus no increase in abscess count and no increase in draining fistulas) was designed and validated in the Adalimumab Clinical Development Program. The HiSCR has been accepted as a useful score to measure the impact of therapeutic agents in clinical trials as evidenced by the use of this measure in other clinical studies sponsored by entities other than AbbVie. All clinical and laboratory procedures in this study are standard and generally accepted.

5.6.3 Suitability of Subject Population

Males and females 18 years or older with moderate to severe HS requiring excisional surgery as part of routine disease management who meet all inclusion criteria but none of the exclusion criteria are eligible for this study. Adalimumab is approved for the treatment of active moderate to severe HS in adult patients who have not responded to conventional systemic HS therapy. This population in this study is similar to the moderate to severe HS population that was included in the Adalimumab Clinical Development Program, however this population will also have advanced HS lesions such that excisional surgery is required as part of their routine disease management. The population being studied represents normal clinical practice with a spectrum of subjects with high medical need due to great disability and discomfort. This ensures the activity of

adalimumab can be evaluated as part of the integrated medical-surgical management across a distribution of HS severity that has not been previously studied in a placebo-controlled clinical trial.

5.6.4 Selection of Doses in the Study

Adalimumab has been approved for the treatment of adult HS patients and the dose regimen used in this study will be the approved recommended dosing: 160 mg initially at Day 1, followed by 80 mg two weeks later at Day 15. Two weeks later (Day 29) continue with a dose of 40 mg every week as documented in the current SmPC.

6.0 Complaints

A Complaint is any written, electronic, or oral communication that alleges deficiencies related to the physical characteristics, identity, quality, purity, potency, durability, reliability, safety, effectiveness, or performance of a product/device after it is released for distribution.

The active study drug in this trial contains both a:

- biologic compound and
- pre-filled syringe

Complaints associated with any component of this study drug must be reported to the Sponsor (Section 6.2.2). For adverse events, please refer to Section 6.1. For product complaints, please refer to Section 6.2.

6.1 Medical Complaints

The Study Investigator will monitor each subject for clinical and laboratory evidence of AEs on a routine basis throughout the study. The Study Investigator will assess and record any AE in detail including the date of onset, event diagnosis (if known) or sign/symptom, severity, time course (end date, ongoing, intermittent), relationship of the AE to study drug, and any action(s) taken. For an SAE considered as having "no

reasonable possibility" of being associated with study drug, the Study Investigator will provide another cause of the event. For an AEs to be considered intermittent, the repetitive occurrences of the events must be of similar nature and severity. An AE, whether in response to a query, observed by study site personnel, or reported spontaneously by the subject will be recorded.

All AEs will be followed to a satisfactory conclusion.

6.1.1 Definitions

6.1.1.1 Adverse Event

An adverse event (AE) is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not the event is considered causally related to the use of the product.

Such an event can result from use of the drug as stipulated in the protocol or labeling, as well as from accidental or intentional overdose, drug abuse, or drug withdrawal. Any worsening of a pre-existing condition or illness is considered an AE. Worsening in severity of a reported adverse event should be reported as a new AE. Laboratory abnormalities and changes in vital signs are considered to be AEs only if the event results in discontinuation from the study, necessitates therapeutic medical intervention, meets protocol specific criteria (see Section 6.1.7 regarding toxicity management) and/or if the Study Investigator considers the event to be an AE.

An elective surgery or procedure scheduled to occur during a study will not be considered an AE if the surgery or procedure is being performed for a pre-existing condition and the surgery/ or procedure has been pre planned prior to study entry. However, if the pre-existing condition deteriorates unexpectedly during the study (e.g., surgery performed

earlier than planned), then the deterioration of the condition for which the elective surgery/procedure is being done will be considered an AE.

In order to be eligible for this study a subject must require surgery due to HS and the surgery date will determined after enrollment. The need for rescue surgery of the designated HS surgical site (i.e., surgery prior to Week 13) will not be recorded as an AE; rather the reason for surgery will be recorded on the appropriate eCRF as described in Section 5.3.2.4 and the subject will be withdrawn from the study.

6.1.1.2 Serious Adverse Events

If an adverse event meets any of the following criteria, it is to be reported to AbbVie as a serious adverse event (SAE) within 24 hours of the study site being made aware of the SAE.

Death of Subject	An event that results in the death of a subject.
Life-Threatening	An event that, in the opinion of the investigator, would have resulted in immediate fatality if medical intervention had not been taken. This does not include an event that would have been fatal if it had occurred in a more severe form.
Hospitalization or Prolongation of Hospitalization	An event that results in an admission to the hospital for any length of time or prolongs the subject's hospital stay. This does not include an emergency room visit or admission to an outpatient facility.
Congenital Anomaly	An anomaly detected at or after birth, or any anomaly that results in fetal loss.
Persistent or Significant Disability/Incapacity	An event that results in a condition that substantially interferes with the activities of daily living of a study subject. Disability is not intended to include experiences of relatively minor medical significance such as headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle).

Important Medical Event Requiring Medical or Surgical Intervention to Prevent Serious Outcome	An important medical event that may not be immediately life-threatening or result in death or hospitalization, but based on medical judgment may jeopardize the subject and may require medical or surgical intervention to prevent any of the outcomes listed above (i.e., death of subject, life-threatening, hospitalization, prolongation of hospitalization, congenital anomaly, or persistent or significant disability/incapacity). Additionally, any elective or spontaneous abortion or stillbirth is considered an important medical event. Examples of such events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

For SAEs with the outcome of death, the date and cause of death will be recorded on the appropriate case report form.

6.1.1.3 Adverse Events of Special Interest

Adverse events of special interest as defined in Table 3, and adverse events concerning the surgical site will be collected and analysed.

Table 3. Adverse Events of Special Interest

Serious and nonserious opportunistic infections, including the following bacterial, fungal, viral and parasitic infections: Aspergillus, Blastomyces, Candida, Coccidioides, Cryptococcal, Cytomegalovirus, Histoplasma, Listeria, Nocardia, Paracoccidioides, Pneumocystis, Toxoplasma, Tuberculosis, Herpes, Bacillary angiomatosis, Mucormycosis, Progressive Vaccinia, Zygomycosis, BK virus, and JC virus
Lymphoma
Hepatosplenic T-cell lymphoma
Leukemia
Non-melanoma skin cancer (NMSC)
Other malignancies (except lymphoma, leukemia and NMSC)
Immune reactions including lupus, lupus-like reactions, and severe allergic reactions
Congestive heart failure (CHF)
Cerebrovascular accident (CVA)
Myocardial infarction (MI)
CNS demyelinating disorders (including MS and Guillain-Barré syndrome)
Hepatic events that are serious or lead to permanent discontinuation of study drug (e.g., persistent liver function test abnormalities, acute liver failure and other serious hepatic events)
Hematologic events that are serious or lead to permanent discontinuation of study drug (e.g., aplastic anemia, granulocytopenia, Granulocyte Maturation Arrest, leukopenia, neutropenia, nancytopenia and thrombocytopenia)
Worsening of Psoriasis
Vasculitis
Diverticulitis
Intestinal perforation

6.1.2 Adverse Event Severity

The investigator will use the following definitions to rate the severity of each adverse event:

Mild	The adverse event is transient and easily tolerated by the subject.
Moderate	The adverse event causes the subject discomfort and interrupts the subject's usual activities.

Severe	The adverse event causes considerable interference with the subject's usual activities and may be incapacitating or life-threatening.

6.1.3 Relationship to Study Drug

The investigator will use the following definitions to assess the relationship of the adverse event to the use of study drug:

Reasonable Possibility	An adverse event where there is evidence to suggest a causal relationship between the study drug and the adverse event.
No Reasonable Possibility	An adverse event where there is no evidence to suggest a causal relationship between the study drug and the adverse event.

For causality assessments, events assessed as having a reasonable possibility of being related to the study drug will be considered "associated." Events assessed as having no reasonable possibility of being related to study drug will be considered "not associated." In addition, when the investigator has not reported a causality or deemed it not assessable, AbbVie will consider the event associated.

If an investigator's opinion of no reasonable possibility of being related to study drug is given, an Other cause of event must be provided by the investigator for the serious adverse event.

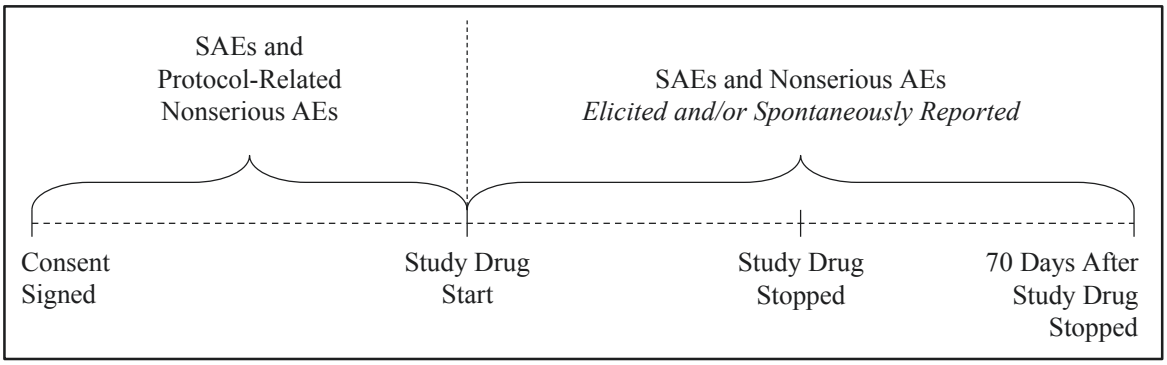
6.1.4 Adverse Event Collection Period

All AEs reported from the time of study drug administration until either the final follow-up telephone call (approximately 70 days following discontinuation of study drug administration) or the date at which the subject initiated commercial adalimumab will be collected, whether solicited or spontaneously reported by the subject. In addition, SAEs and protocol-related nonserious AEs will be collected from the time the subject signed the study-specific informed consent. Adverse event information will be collected and recorded on the appropriate eCRFs.

Subjects will contacted approximately 70 days following study drug discontinuation for an assessment of any new or ongoing AEs/AESI/SAEs as discussed in Section 5.3.1.1.

Adverse event information will be collected as shown in Figure 2.

Figure 2. Adverse Event Collection



6.1.5 Adverse Event Reporting

In the event of an SAE, and additionally, any nonserious event of malignancy in subjects 30 years of age and younger, whether related with study drug or not, the Study Investigator will notify AbbVie Clinical Pharmacovigilance within 24 hours of the study site being made aware of the serious adverse event by entering the SAE or nonserious event of malignancy in subjects 30 years of age or younger data into the electronic data capture (EDC) system. All SAEs and nonserious events of malignancy in subjects 30 years of age and younger that occur prior to the study site having access to the RAVE® system or if RAVE® is not operable, should be documented on the SAE Non-CRF forms and emailed (preferred route) or faxed to AbbVie Clinical Pharmacovigilance within 24 hours of the study site being made aware of the serious adverse event.

Email: [redacted]

FAX to: [redacted]

For safety concerns, contact the Immunology Safety Team at:

[redacted]
AbbVie
[redacted]
1 North Waukegan Road
North Chicago, IL USA 60064

Telephone Contact Information:
[redacted]
Email: [redacted]

For any subject safety concerns, please contact the physician listed below:

Study Designated Physician:

[redacted]
26525 Riverwoods Blvd.
Mettawa, IL 60045

Telephone Contact Information:
Office: [redacted]
Mobile: [redacted]
Email: [redacted]

In emergency situations involving study subjects when the Study Designated Physician is not available by telephone, please contact the 24-hour AbbVie Medical Escalation Hotline where your call will be re-directed to a designated backup AbbVie physician:

Telephone: [redacted]

The sponsor will be responsible for Suspected Unexpected Serious Adverse Reactions (SUSAR) reporting for the Investigational Medicinal Product (IMP) in accordance with Directive 2001/20/EC. For AbbVie IMPs used in Phase 4 studies or for non-AbbVie

IMP, also include: The reference document used for SUSAR reporting in the EU countries will be the most current version of the SmPC.

6.1.6 Pregnancy

Pregnancy in a study subject must be reported to AbbVie within 1 working day of the study site becoming aware of the pregnancy. Subjects who become pregnant during the study must be discontinued (Section 5.4.1). Pregnancies will be collected from the date of the first dose through 150 days following the last dose of study drug.

Information regarding a pregnancy occurrence in a study subject and the outcome of the pregnancy will be collected.

Pregnancy in a study subject is not considered an AE. However, the medical outcome of an elective or spontaneous abortion, stillbirth, or congenital anomaly is considered a SAE and must be reported to AbbVie within 24 hours of the study site becoming aware of the event.

6.1.7 Toxicity Management

Subjects who develop a new infection while undergoing treatment with adalimumab should be monitored closely. Administration of study injections should be interrupted if subject develops an infection requiring IV anti-infective treatment or if an infection meets the definition of "serious" (refer to Section 6.0 for definitions). Study medication may be restarted once the physician determines that the infection has been successfully treated. Otherwise prohibited concomitant medications may be given if medically necessitated. Specifically, if a subject develops an inter-current infection, then topical and/or oral antibiotic usage is permitted. Prior to use, every attempt should be made to contact the AbbVie Study Designated Physician for direction on re-introduction of adalimumab therapy after prohibited medication administration.

6.2 Product Complaint

6.2.1 Definition

A Product Complaint is any Complaint (see Section 6.0 for the definition) related to the biologic or drug component of the product or to the pre-filled syringe.

For a product this may include, but is not limited to, damaged/broken product or packaging, product appearance whose color/markings do not match the labeling, labeling discrepancies/inadequacies in the labeling/instructions (example: printing illegible), missing components/product, device (i.e., syringe not working properly, or packaging issues.

For a medical device (i.e., pre-filled syringe), a product complaint also includes deaths of a patient using the device, any illness, injury, or adverse event in the proximity of the device, an adverse event that could be a result of using the device, any event needing medical or surgical intervention including hospitalization while using the device and use errors.

Any information available to help in the determination of causality by the device to the events outlined directly above should be recorded.

6.2.2 Reporting

Product Complaints concerning the study drug and/or pre-filled syringes must be reported to the Sponsor within 24 hours of the study site's knowledge of the event via the Product Complaint form. Product Complaints occurring during the study will be followed-up to a satisfactory conclusion. All follow-up information is to be reported to the Sponsor (or an authorized representative) and documented in source as required by the Sponsor. Product Complaints associated with adverse events will be reported in the study summary. All other complaints will be monitored on an ongoing basis.

Product Complaints may require return of the product (i.e., syringe) with the alleged complaint condition. In instances where a return is requested, every effort should be

made by the Study Investigator to return the product within 30 days. If returns cannot be accommodated within 30 days, the study site will need to provide justification and an estimated date of return.

The description of the complaint is important for AbbVie in order to enable AbbVie to investigate and determine if any corrective actions are required.

7.0 Protocol Deviations

AbbVie does not allow intentional/prospective deviations from the protocol unless when necessary to eliminate an immediate hazard to study subjects. The Study Investigator and sub-investigators are responsible for complying with all protocol requirements, and applicable global and local laws regarding protocol deviations. If a protocol deviation occurs (or is identified) after a subject has been enrolled, the Study Investigator is responsible for notifying IEC/IRB regulatory authorities (as applicable), and the following AbbVie CRA(s) or alternate contact:

Primary Contact:	Alternate Contact:
AbbVie Site Monitor (contact information per country to be provided)	[redacted] 1 North Waukegan Road North Chicago, IL USA 60064 Office: [redacted] Mobile: Email:

Such contact must be made as soon as possible to permit a review by AbbVie to determine the impact of the deviation on the subject and/or the study. Any significant protocol deviation affecting subject eligibility and/or safety must be reviewed and/or approved by the IEC/IRB and regulatory authorities, as applicable prior to implementation.

For the purposes of this protocol, reportable deviations are defined as:

- subject entered into the study even though she/he did not satisfy entry criteria,
- subject developed withdrawal criteria during the study but was not withdrawn,
- subject received the wrong study drug or an incorrect dose of study drug, or
- subject received excluded or prohibited concomitant treatment (e.g., medication, surgical intervention)

8.0 Statistical Methods and Determination of Sample Size

8.1 Statistical and Analytical Plans

The objectives of the statistical analyses are to evaluate the clinical safety and efficacy of adalimumab compared to placebo in subjects with moderate to severe HS who are scheduled to undergo excisional surgery for the 12-week period prior to surgery (Period A), the 2-week perioperative period (Period B) and during a 10-week post-surgical period (Period C). Complete, specific details of the statistical analysis will be described and fully documented in the Statistical Analysis Plan (SAP). The SAP will be finalized prior to the database lock and blind break.

8.1.1 Analysis Populations

The Intent-to-Treat (ITT) Population is defined as all subjects who randomised at the Baseline visit. A Per-protocol Population (PP), which excludes patients with significant protocol violations, will be defined if deemed necessary. The ITT Population and the PP population, if defined, will be used for the efficacy analysis. Of note, the surgery-related endpoints during Periods B and C will be analysed among the subjects who undergo surgery.

The Safety Population is defined as all subjects who are in the ITT Population and receive at least one dose of study drug. The Safety Population in each period will be used for

safety analysis. Of note, the surgery-related safety endpoints during Periods B and C will be analysed among the subjects who undergo surgery.

For efficacy analysis, subjects included in the ITT population will be analysed by treatment group as randomised. That is, all subjects will be included in the treatment group to which they are randomised, regardless of which treatment the subject actually received. Subjects included in the PP Population, if defined, will be analysed as treated. That is, if a subject receives that treatment that is not the randomised assignment during the entire participation of a period or study, the subject will be analysed according to the treatment that the subject actually received.

For safety analysis, subjects included in the Safety Population will be analysed by treatment group as treated. That is, if a subject receives treatment that is not the randomized assignment during the entire participation of a period or study, the subject will be analysed according to the treatment the subject actually received.

8.1.2 Planned Methods of Statistical Analysis

All statistical tests will be two-tailed with the significance level 0.05. All *P* values will be rounded to three decimal places. Descriptive statistics will be provided. These include the number of observations, mean, and standard deviation for continuous variables; and counts and percentages for discrete variables.

The analyses will be performed using Statistical Analysis Software (SAS®, SAS Institute Inc., Cary, NC, USA).

8.1.3 Demographic and Baseline Characteristics

Demographic and Baseline characteristics of the study subjects will be summarized for each arm of the study using descriptive statistics. Statistical tests will be performed to assess the comparability of the two arms. Continuous variable will be analysed using one-way analysis of variance (ANOVA), and discrete variable will be analysed using Fisher's exact test.

8.1.4 Statistical Analyses of Efficacy

The efficacy analysis will be conducted in the ITT Population and PP Population, if defined.

Visit windows and the data handling convention for summarizing efficacy results will be defined in the SAP.

Missing data will be imputed using the following methods for the efficacy analyses in the ITT Population:

- Non-Responder Imputation (NRI): the NRI analysis will categorize any subject who has a missing value at a specific visit as non-responder for that visit. The NRI will be the primary approach in the analyses of categorical variables. For analyses up to Week 12, NRI will be applied using evaluations within the period.
- 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 analyses of continuous variables, and the secondary approach in the analyses of categorical variables.
- As-Observed: The As-observed analyses 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 analyses will be the secondary approach in the analyses of continuous variables.

Multiple Imputation (MI) for missing values will be performed for the primary efficacy variable.

Lesions that receive intervention (e.g., contained within the excised surgical specimen, protocol-allowed minor interventions including incision and drainage) will be counted as permanently present from the date of the intervention.

In order to evaluate the impact of major protocol violations on the results of the trial, efficacy assessments obtained after the start of a major protocol-disallowed treatment will be excluded from the analysis. Subjects will be counted as non-responders for the categorical variable from the date of the major protocol-disallowed treatment and have their LOCF for continuous variables. The exclusion of efficacy assessments will be determined via classification prior to the database lock.

Additional analyses may be performed for the primary efficacy variable adjusting for baseline covariates in addition to the stratification factors.

8.1.4.1 Primary Analysis of Efficacy

The primary analysis will be the comparison of the adalimumab ew treatment group versus the placebo treatment group in the proportion of subjects achieving HiSCR at Week 12. The number and percentage of subjects achieving HiSCR will be computed for each treatment arm and the difference in response rates (adalimumab – placebo) will be analysed using the Cochran-Mantel-Haenszel (CMH) test, stratified by the stratification factors used for randomization. The 95% confidence intervals of treatment difference will also be provided.

The primary analysis will be carried out in the ITT Population and the PP Population, if defined. Non-responder imputation will be used as the primary approach for missing values. LOCF and MI will be performed as sensitivity analyses for the primary efficacy variable.

In addition, a sensitivity analysis controlling for change from baseline in body weight using logistic regression models, for the primary efficacy endpoint. Analysis details will be specified in the SAP prior to study unblinding and prior to database lock.

8.1.4.2 Secondary Analyses of Efficacy

Categorical variables will be analysed by CMH adjusting for the stratification factors for randomisation. Continuous variables will be analysed by analysis of covariance

(ANCOVA) with Baseline value and the stratification factors used randomization in the model.

The analyses of the adalilmumab ew group versus placebo group will be carried out in the ITT Population.

Additional analyses may be performed for the primary efficacy variable adjusting for baseline covariates. Results from any additional analyses will not be used as a substitute for the planned analyses, but may be used as supplemental information for the study report.

To evaluate the consistency of the efficacy over demographic and other baseline characteristics, summaries and analyses will be performed for selected subgroups for the primary endpoint and ranked secondary endpoints. The detailed subgroups will be outlined in the SAP.

8.1.5 Statistical Analyses of Safety

All AEs, SAEs, AEs leading to discontinuation, pre-specified AEs of special interest (AESIs) and adverse events concerning the surgical site will be collected during the study and up to approximately 70 days after the last dose of the study drug for subjects who do not elect to treat his/her HS disease with commercial adalimumab.

Safety analyses will be carried out using the Safety Population. Pretreatment AEs will be summarized. Any TEAE is defined as an event with onset or worsening after the first study drug administration and within approximately 70 days after the last study drug administration for subjects who do not elect to treat his/her HS disease with commercial adalimumab.

The number and percent of subjects experiencing treatment-emergent TEAEs will be tabulated using the Medical Dictionary for Drug Regulatory Activities (MedDRA®) system organ class and preferred term. Comparisons of the percentages of subjects experiencing an AE in the adalimumab group versus the placebo group will be performed

using Fisher's exact test for data collected in the entire study, and separately for Period A, Period B, and Period C. Summaries (including percentages and event per 100 patient-years) of SAEs, deaths, AEs leasing to discontinuation from the study, AESIs, and adverse events concerning the surgical site will also be provided.

8.2 Determination of Sample Size

The study is designed to enroll approximately 200 subjects. Assuming the true treatment difference in this study population is at least 20%, 100 subjects per arm will provide at least 80% power to detect the treatment difference at the alpha level of 0.05. The study also has at least 80% power to demonstrate the point estimate of the treatment difference of at least 15%.

The response rates observed in the combined PIONEER I and II studies (Studies M11-313 and M11-810, respectively) for the HiSCR at Week 12 were 50.6% and 26.8% in the adalimumab ew group and placebo group, respectively. Due to the potential differences between the population of moderate-to-severe HS patients who are surgical candidates and the general moderate-to-severe HS patient population, a conservative estimate of 20% treatment difference is used for the power calculation.

8.3 Randomisation Methods

An IRT will be used to determine the randomisation of subjects. Detailed instructions for using the IRT will be provided to the study site personnel.

Subjects who are eligible based on inclusion and exclusion criteria and have had all pre-randomisation procedures performed will be randomised in a 1:1 double-blind fashion to adalimumab 40 mg or placebo using baseline Hurley Stage (II versus III) and anatomic location of planned HS surgical site (axilla versus inguinal region). The number of subjects in Hurley Stage III is not to exceed 50% of the total planned number of subjects (100 subjects). The randomisation schedule will be prepared by the Statistics Department of AbbVie, USA and provided to drug supply for adequate packaging.

8.4 Pharmacokinetic Analysis

Adalimumab serum concentrations will be summarized by treatment group at each time point using descriptive statistics including number of subjects, number of non-missing observations (n_{nmiss}), mean, median, standard deviation, coefficient of variation (CV), minimum, and maximum as appropriate. Individual subject concentrations versus time plots and mean concentration versus time plots by treatment group will be provided. Data listing will be generated for individual subjects. For the calculation of summary statistics and plots, concentration values below limit of quantification (LOQ) will be set to zero.

Population-based pharmacokinetic analysis will be performed based on the actual sampling times, instead of using the protocol-specified times. Pharmacokinetic models will be built using a non-linear mixed-effect modeling approach with the Non-Linear Mixed Effect Modeling (NONMEM) software (Version VII, or a higher version). The evaluation criteria described below will be used to examine the performance of different models.

1. The objective function value of the best model is significantly smaller than the alternative model(s) based on the Likelihood Ratio test.
2. The observed and predicted serum adalimumab concentration levels from the preferred model are more randomly distributed across the line of unity (a straight line with zero intercept and a slope of one) than the base model.
3. Visual inspection of model fits, standard errors of model parameters and change in inter-subject and random residual error.

Once appropriate base pharmacokinetic model (including inter- and intra-individual error models) is developed, empirical Bayesian estimates of individual model parameters will be calculated by the posterior conditional estimation technique (post-hoc) on NONMEM. Covariates (such as demographics) will be tested with NONMEM in a stepwise parameter addition and deletion method until no more significant covariate-parameter relationships are found. For the stepwise inclusion step of the model-finding process, all covariates

will be assessed at a significant level of $P \leq 0.01$ (corresponding to a decrease in objective function > 6.63 for 1 degree of freedom).

The final model will be used to produce empirical Bayesian estimates of the pharmacokinetic parameters for each individual, using the post-hoc option in NONMEM. Individual pharmacokinetic parameters will be listed and summarized with appropriate statistical methods.

9.0 Ethics

9.1 Independent Ethics Committee or Institutional Review Board

Good Clinical Practice (GCP) requires that the clinical protocol, any substantial protocol amendments, the SmPC (or package insert), the informed consent and all other forms of subject information related to the study (e.g., advertisements used to recruit subjects) and any other necessary documents be reviewed by an IEC/IRB. The IEC/IRB will review the ethical, scientific and medical appropriateness of study the before it is conducted. IEC/IRB approval of the protocol, informed consent, and subject information and/or advertising, as relevant, will be obtained prior to the authorization of drug shipment to a study site.

Any substantial amendments to the protocol will require IEC/IRB approval prior to implementation of any changes made to the study design. The Study Investigator will be required to submit, maintain, and archive study essential documents according to International Conference on Harmonisation Good Clinical Practice (ICH GCP).

Any serious adverse events that meet the reporting criteria, as dictated by local regulations, will be reported to both responsible Ethics Committees and Regulatory Agencies, as required by local regulations. During the conduct of the study, the Study Investigator should promptly provide written reports (e.g., ICH Expedited Reports, and any additional reports required by local regulations) to the IEC/IRB of any changes that

affect the conduct of the study and/or increase the risk to subjects. Written documentation of the submission to the IEC/IRB should also be provided to AbbVie.

9.2 Ethical Conduct of the Study

The study will be conducted in accordance with the protocol, International Conference on Harmonisation (ICH) guidelines, applicable regulations and guidelines governing clinical study conduct and the ethical principles that have their origin in the Declaration of Helsinki. Responsibilities of the clinical investigator are specified in Appendix A.

9.3 Subject Information and Consent

The Study Investigator or his/her representative will explain the nature of the study to the subject, and answer all questions regarding this study. Prior to any study-related screening procedures being performed on the subject, the informed consent statement will be reviewed, signed, and dated by the subject, the person who administered the informed consent, and any other signatories according to local requirements. A copy of the informed consent form will be given to the subject and the original will be placed in the subject's medical record. An entry must also be made in the subject's dated source documents to confirm that informed consent was obtained prior to any study-related procedures and that the subject received a signed copy.

Information regarding incentives for subjects and information regarding provisions for treating and/or compensating subjects who are harmed as a consequence of participation in the study can be found in the informed consent form.

Samples for exploratory research/validation studies will only be collected if the subject has voluntarily signed and dated the separate written consent for exploratory research/validation studies, approved by an IEC/IRB, after the nature of the testing has been explained and the subject has had an opportunity to ask questions. The separate written consent must be signed before the exploratory research/validation study samples are collected and testing is performed. If the subject does not consent to the exploratory research/validation studies, it will not impact the subject's participation in the main study.

In the event a subject withdraws from the main study, optional exploratory research/validation studies samples will continue to be stored and analysed unless the subject specifically withdraws consent for the optional samples. If consent is withdrawn for the optional sampling, the subject must inform their study investigator, and once AbbVie is informed, the optional samples will be destroyed. However, if the subject withdraws his/her consent and the samples have already been tested, those results will still remain as part of the overall research data.

10.0 Source Documents and Case Report Form Completion

10.1 Source Documents

Source documents are defined as original documents, data, and records. These may include hospital records, clinical and office charts, laboratory data/information, subjects' diaries or evaluation checklists, paper PRO's, pharmacy dispensing and other records, recorded data from automated instruments, microfiches, photographic negatives, microfilm or magnetic media, and/or x-rays. Data collected during this study must be recorded on the appropriate source documents.

The investigator(s)/institution(s) will permit study-related monitoring, audits, IEC/IRB review, and regulatory inspection(s), providing direct access to source data documents.

The following paper assessments completed by the subject or Study Investigator will be considered source documentation:

- Dermatology Life Quality Index (DLQI)
- EuroQoL (EQ-5D™)
- Hidradentis Suppurativa Patient's Global Impression of Change (HS-PGIC)
- Hidradenitis Suppurativa Patient's Global Assessment Skin Pain (HS-PGA-SP)
- Hidradenitis Suppurativa Impact Assessment (HSIA)
- Hidradenitis Suppurativa Symptom Assessment – 7 day recall (HSSA-7d)
- Short Form 12 (SF-12)

- Treatment Satisfaction Questionnaire (TSQM)
- Work Productivity and Activity Impairment Questionnaire: Specific Health Problem (WPAI:SHP)

Once collected, these outcome assessment sheets will be entered by delegated study site personnel into the EDC system and will be available for viewing by study site personnel.

The AE/SAE eCRF data segments of alternate etiology, severity, frequency, and relationship to study drug may also be used as source documentation and will require the Study Investigator's approval on the eCRF as verification of the accuracy of the information.

10.2 Case Report Forms

Electronic and paper CRFs must be completed for each subject screened/enrolled in this study. These forms will be used to transmit information collected during the study to AbbVie and regulatory authorities, as applicable. The CRF data for this study are being collected with an EDC system called Rave® provided by the technology vendor Medidata Solutions Incorporated, NY, USA. The EDC system and the study-specific eCRFs will comply with Title 21 CFR Part 11. The documentation related to the validation of the EDC system is available through the vendor, Medidata, while the validation of the study-specific CRFs will be conducted by AbbVie and will be maintained in the Trial Master File at AbbVie.

The Study Investigator will document subject data in his/her own subject files. These subject files will serve as source data for the study. All electronic and paper CRF data required by this protocol will be recorded by study site personnel in the EDC system. All data entered into the EDC system will be supported by source documentation (Section 10.1).

The Study Investigator or an authorized member of the study site personnel will make any necessary corrections to the eCRF. All change information, including the date and person performing the corrections, will be available via the audit trail, which is part of the EDC

system. For any correction, a reason for the alteration will be provided. The eCRFs will be reviewed periodically for completeness, legibility, and acceptability by AbbVie personnel (or their representatives). AbbVie (or their representatives) will also be allowed access to all source documents pertinent to the study in order to verify eCRF entries. The Study Investigator will review the eCRFs for completeness and accuracy, and provide his/her electronic signature and date to eCRFs as evidence thereof.

Medidata will provide access to the EDC system for the duration of the trial through a password-protected method of internet access. Such access will be removed from study sites at the end of the site's participation in the study. Data from the EDC system will be archived on appropriate data media (CD-ROM, etc.) and provided to the Study Investigator at that time as a durable record of the study site's CRF data. It will be possible for the investigator to make paper printouts from that media.

11.0 Data Quality Assurance

Computer logic and manual checks will be created to identify items such as inconsistent study dates. Any necessary corrections will be made to the eCRF.

An Investigator's Meeting will be held with AbbVie personnel, the Study Investigator, study site coordinators, and the AbbVie CRAs for this study. This meeting will include a detailed discussion of the protocol, performance of study procedures, CRFs, completion of logs, and specimen collection methods. In addition to, or instead of, the Investigator's Meeting, the study site personnel may be trained on the study procedures by an AbbVie CRA at the study initiation visit. Each study site will be given a CRF completion guideline and laboratory manual for reference.

The AbbVie CRAs will monitor each study site throughout the study. Source document review will be performed against entries in the EDC system and a quality assurance check will be performed to ensure that the Study Investigator is complying with the protocol and all global and local regulations.

All data recorded on paper CRFs will be hand-entered in the database and verified by a double-key entry procedure at AbbVie.

All central laboratory results will be electronically transferred from the central laboratory to the study database.

A review of the data will be conducted by a physician and clinical review team at AbbVie as specified in the safety review plan.

12.0 Use of Information

12.1 Use of Information

All information concerning adalimumab and AbbVie's operations, such as AbbVie's patent applications, formulas, manufacturing processes, basic scientific data, or formulation information, supplied by AbbVie and not previously published is considered confidential information.

The information developed during the conduct of this clinical study is also considered confidential and will be used by AbbVie in connection with the development of adalimumab. This information is disclosed as deemed necessary by AbbVie to other clinical investigators, other pharmaceutical companies, and to regulatory agencies and other governmental agencies. To allow for the use of the information derived from this clinical study, and to ensure complete and thorough analyses, the Study Investigator is obligated to provide AbbVie with complete test results and all data developed in this study and to provide direct access to all source data/documents for trial-related monitoring, audits, IEC/IRB review, and regulatory inspection.

This confidential information shall remain the sole property of AbbVie, shall not be disclosed to others without the written consent of AbbVie.

The Study Investigator will maintain a confidential subject identification code list of all subjects enrolled in the study (by name and subject number). This will be maintained at the study site and will not be retrieved by AbbVie.

Any exploratory research/validation studies that may be done using samples from this study will be experimental in nature and the results will not be suitable for clinical decision making or patient management. Hence, the Study Investigator, the designated surgeon, the subject, and the subject's physician (if different from the Study Investigator or designated surgeon) will not be informed of individual results should analyses be performed, nor will anyone not directly involved in this research. Correspondingly, researchers will not have access to subject identifiers. Individual results will not be reported to anyone not directly involved in this research other than for regulatory purposes. Aggregate data from optional exploratory research/validation studies from this study may be used in scientific publications or presented at medical conventions. Exploratory research/validation studies data will be published or presented only in a way that does not identify any individual subject.

12.2 Publication

Core publication(s) will be authored by Study Investigator(s) and study designated surgeons specified by AbbVie who contribute significantly to the implementation and conduct of the study and non-study site personnel who contribute substantially to the design, interpretation, or analysis of the study (e.g., AbbVie personnel, consultants). AbbVie scientists making significant contributions to the study will be included in the list of authors.

Development of the core publication will be coordinated by a publication committee, whose membership will include Study Investigators and surgeons who provided significant input into study design, implementation, conduct, and interpretation, in addition to AbbVie personnel responsible for study conduct and/or analyses.

A name author approach will be utilized if this is a requirement of the journal selected for publication, or if additional publications are agreed (authors to be agreed upon by the publication committee). The named author approach will need sanction of the publication committee.

13.0 Completion of the Study

The investigator will conduct the study in compliance with the protocol and complete the study within the timeframe specified in the contract between the Study Investigator and AbbVie. Continuation of this study beyond this date must be mutually agreed upon in writing by both the Study Investigator and AbbVie. The Study Investigator will provide a final report to the IEC/IRB following conclusion of the study, and will forward a copy of this report to AbbVie.

AbbVie will select the Coordinating Investigator from the Study Investigators who participate in the study. Selection criteria for this investigator will include level of participation as well as significant knowledge of the clinical research, study drug, and study protocol. The Coordinating Investigator for the study will review and sign the final study report in accordance with the European Agency for the Evaluation of Medicinal Products (EMEA) Guidance on Investigator's Signature for Study Reports.

The end-of-study is defined as the date of the last subject's last visit or the actual date of follow-up contact, whichever is later.

14.0 Investigator's Agreement

1. I have received and reviewed the Summary of Product Characteristics for Humira.
2. I have read this protocol and agree that the study is ethical.
3. I agree to conduct the study as outlined and in accordance with all applicable regulations and guidelines.
4. I agree to maintain the confidentiality of all information received or developed in connection with this protocol.
5. I agree that all electronic signatures will be considered the equivalent of a handwritten signature and will be legally binding.

Protocol Title	A Phase 4, Double-Blind, Randomised, Placebo-Controlled Multicenter Study to Assess the Safety and Efficacy of Adalimumab Used in Conjunction with Surgery in Subjects with Moderate to Severe Hidradenitis Suppurativa
Protocol Date:	13 December 2017

Signature of Study Investigator | Date

Name of Study Investigator (printed or typed)

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Appendix A. Responsibilities of the Clinical Investigator

Clinical research studies sponsored by AbbVie are subject to the Good Clinical Practices (GCP) and local regulations and guidelines governing the study at the site location. In signing the Investigator Agreement in Section 14.0 of this protocol, the investigator is agreeing to the following:

1. Conducting the study in accordance with the relevant, current protocol, making changes in a protocol only after notifying AbbVie, except when necessary to protect the safety, rights or welfare of subjects.
2. Personally conducting or supervising the described investigation(s).
3. Informing all subjects, or persons used as controls, that the drugs are being used for investigational purposes and complying with the requirements relating to informed consent and ethics committees (e.g., independent ethics committee [IEC] or institutional review board [IRB]) review and approval of the protocol and substantial amendments.
4. Reporting adverse experiences that occur in the course of the investigation(s) to AbbVie and the site director.

   Reading the information in the Summary of Product Characteristics (or local regulatory label), including the instructions for use and the potential risks and side effects of adalimumab.
5. Informing all associates, colleagues, and employees assisting in the conduct of the study about their obligations in meeting the above commitments.
6. Maintaining adequate and accurate records of the conduct of the study, making those records available for inspection by representatives of AbbVie and/or the appropriate regulatory agency, and retaining all study-related documents until notification from AbbVie.
7. Maintaining records demonstrating that an ethics committee reviewed and approved the initial clinical investigation and all substantial amendments.

8. Reporting promptly, all changes in the research activity and all unanticipated problems involving risks to human subjects or others, to the appropriate individuals (e.g., coordinating investigator, institution director) and/or directly to the ethics committees and AbbVie.
9. Following the protocol and not make any changes in the research without ethics committee approval, except where necessary to eliminate apparent immediate hazards to human subjects.

Appendix B. List of Protocol Signatories

Name	Title	Functional Area
[redacted]	[redacted]	Global Medical Affairs
		Clinical
		Statistics
		Regulatory Affairs
		Clinical Program Development

Appendix C. Schedule of Activities

Activity	Period A						Period B		Period C				Unscheduled Study Visit	70-Day Call
	Screening (Day –30 to Day –7)	Baseline (Day 1)	Wk 2	Wk 4	Wk 8	Wk 12	Wk 13	Wk 14	Wk 15	Wk 17	Wk 20	Wk 24 or Premature Discontinuation Visit		
Informed Consent	X													
Inclusion/Exclusion Criteria	X	X[a]												
Medical/Surgical History	X	X[a]												
Eligibility Visit with Surgeon	X													
Prior and Concomitant Therapy Assessment[b]	X	X[a]	X	X	X	X	X	X	X	X	X	X	X	
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	X[c]	
Vital Signs	X	X	X	X	X	X			X	X	X	X	X	
Height		X[d]												
Waist Circumference		X				X								
CXR/ECG	X											X[e]		
TB Screening	X													
General Labs: Chemistry and Haematology	X[g]	X[g]		X		X[f]			X	X	X	X[f]		
Pregnancy Tests	X[h]	X[i]										Xi		
Urinalysis[j]	X	X		X		X			X	X	X	X		

Activity	Period A						Period B		Period C				Unscheduled Study Visit	70-Day Call
	Screening (Day –30 to Day –7)	Baseline (Day 1)	Wk 2	Wk 4	Wk 8	Wk 12	Wk 13	Wk 14	Wk 15	Wk 17	Wk 20	Wk 24 or Premature Discontinuation Visit		
Hepatitis B Screen	X													
HIV[k] and ANA/Anti dsDNA	X													
hsCRP		X				X						X		
HbA1c		X				X						X		
Lipid Testing		X[f]				X[f]						X[f]		
PK Measurements[l]		X		X	X	X			X	X	X	X		
AAA Measurements[m]		X		X	X	X			X		X	X		
Monitor Adverse Events[n]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Digital Imaging[o]		X		X		X	X		X	X	X	X		
Doppler Ultrasound[p]		X		X		X				X		X		
Dispense Study Drug[q]				X	X	X[q]			X	X	X			
Administer Study Drug[r]		X	X	X	X	X	X	X	X	X	X			
Hurley Stage	X	X[t]				X						X		
Lesion Counts[s]	X	X	X	X	X	X			X	X	X	X	X	
DLQI[w] (10 items)		X		X		X			X			X		
EQ-5D[w] (5 items)		X		X		X			X	X		X		
HSIA[u,w] (18 items)		X		X		X			X			X		
HS-PGA-SP[w] (2 items)		X	X	X	X	X			X	X	X	X		
HS-PGIC[w] (1 item)			X	X	X	X			X	X		X		
HSSA-7d[u,w] (9 items)		X		X		X			X		X	X		

Activity	Period A						Period B		Period C				Unscheduled Study Visit	70-Day Call
	Screening (Day –30 to Day –7)	Baseline (Day 1)	Wk 2	Wk 4	Wk 8	Wk 12	Wk 13	Wk 14	Wk 15	Wk 17	Wk 20	Wk 24 or Premature Discontinuation Visit		
SF-12[W] (12 items)		X				X			X			X		
TSQM[V,W] (14 items)		X				X			X	X		X		
WPAI:SHP[W] (6 items)		X				X			X			X		
Surgical/ICU/Hospital Days							X	X	X	X	X	X		
Follow-Up Telephone Call														X[X]

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

b. Confirm ongoing antiseptic wash requirement at every visit on the concomitant medication page.

c. A full physical exam is required at the Screening, Baseline and Week 24 or the Premature Discontinuation Visit if subject discontinues prior to Week 24. A symptom directed physical examination should be performed at other visits if, in the opinion of the Study Investigator, it is warranted by the subject's AE status or on review of symptoms.

d. Height will be measured at Baseline and Waist Circumference will be measured at Baseline and Week 12.

e. Subjects will have a repeat ECG or CXR at Week 24 or the Premature Discontinuation Visit, only if in the opinion of the Study Investigator clinically significant AEs develop during the study that warrant a repeat ECG or CXR.

f. Subject should be fasting at Baseline and Weeks 12 and 24. Please refer to the laboratory manual for further instructions.

g. Lab assessments will only need to be repeated at Baseline if the time between Screening and Baseline is greater than 14 days, or if the subject's health status has changed to warrant a repeat test. The chemistry at Baseline should be fasting. If the screening period is 14 days or less, and lab assessments are not repeated, then Screening labs should be fasting.

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

i. All females of childbearing potential will have a urine sample collected at Baseline and at Week 24 or the Premature Discontinuation Visit (conducted by the site). (If required by local regulatory authorities, monthly urinary pregnancy tests will be performed locally by designated study personnel.) 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.

j. 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.

k. If required by country regulatory authorities to confirm eligibility, subjects will be tested for antibodies to the HIV, and document that the test has been performed. The testing is to be done at a local lab. A subject will not be eligible for study participation if test results indicate a positive HIV infection. AbbVie will not receive results from the testing and not be made aware of any positive results.

l. Blood samples must be obtained prior to dosing.

m. AAA samples are not collected as separate venipuncture; they are pipetted from the PK serum.

n. All AEs reported from the time of study drug administration until approximately 70 days following discontinuation of study drug administration will be collected. SAEs will be collected from the time the subject signed the study-specific informed consent until approximately 70 days following discontinuation of study drug administration (See Sections 5.3.1.1 Study Procedures – Follow-up telephone call and Section 6.1.4 Adverse Event Collection Period).

o. A subset of subjects at pre-selected study sites will have photographs taken of their HS surgical site at Baseline, Weeks 4, 12, 13 (post-surgical), 15, 17, 20 and 24 or at the Premature Discontinuation Visit if the subjects discontinues prior to Week 24.

p. A subset of subjects at pre-selected study sites will undergo Doppler Ultrasound examination Baseline, Week 4, Week 12, Week 17, and Week 24 or at the Premature Discontinuation Visit if the subjects discontinues prior to Week 24. During Period A (pre-surgery) examination will be performed on all HS-affected anatomical regions. During Period C (post-surgery) examination will be performed on all non-surgical HS-affected anatomical regions.

q. Study drug will be dispensed via Interactive Response Technology (IRT) at each Study Visit. An adequate amount should be dispensed in order to ensure enough study drug to cover the weekly injections until the next Study Visit. At Week 12, the Study Investigator should dispense study drug for Weeks 13 and 14, if the investigator is not the designated surgeon.

r. At Study Visits the study drug will be administered by the subject with observation by qualified study personnel to ensure proper technique.

s. 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 (Section 5.2.3.2) as permanently present in the lesion counts from the date of intervention.

t. Study site must enter worst Hurley stage across all body regions into IRT.

u. The questionnaire shall not be used for any research purposes whatsoever without express prior written permission from AbbVie.

v. Only the treatment efficacy subscale of the TSQM will be used.

w. It is preferred that the staff that assists patients with PRO completion should not be the same staff member that administers the injections at clinic visits.

x. Study site personnel will contact all subjects by telephone at Weeks 6 and 10 to monitor whether any signs and symptoms of a skin or soft tissue infection are present near or at any HS lesion (see Section 5.1.1) and approximately 70 days after the last dose of study drug (except as described in Section 5.3.1.1 Study Procedures – Follow-up telephone call) to determine the status of any ongoing AEs/SAEs or the occurrence of any new AE/SAE.

Appendix D. Optional Exploratory Research and Validation Studies – Schedule of Activities

Activity	Period A						Period B		Period C				Unscheduled Study Visit	70-Day Call
	Screening (Day –30 to Day –7)	Baseline (Day 1)	Wk 2	Wk 4	Wk 8	Wk 12	Wk 13	Wk 14	Wk 15	Wk 17	Wk 20	Wk 24 or Premature Discontinuation Visit		
Informed Consent for Exploratory Research and Validation Studies[a]	X													
Pharmacogenetic Sample[a,b]		X												
Epigenetic Sample[a,b]		X	X			X				X		X		
Transcriptomic Sample[a,b]		X	X			X				X		X		
Serum and Plasma[a,b]		X	X			X				X		X		
Peripheral Blood Mononuclear Cells[a,b]		X	X			X				X		X		
Microbiome Swab[a,b]		X	X			X				X		X		
Surgical Resection Punch Biopsies[a,b]							X							
Skin Punch Biopsies[a,b]		X				X[c]						X		

a. Subjects must sign and date the separate informed consent before any of these optional exploratory research and validation studies samples may be collected (see Section 9.3). A subject may participate in the main study whether or not that subject volunteers to the collection of these optional samples.

b. Blood and tissue samples must be obtained prior to dosing.

c. Collected only from subjects who will not undergo surgery.

Appendix E. Lesion Counts – Sample

Lesion Counts[a]	Abscess	Non-Draining Fistula	Draining Fistula	Non-Inflammatory Nodule	Inflammatory Nodule	Hypertrophic Scar	Longest Distance (mm) Between 2 Relevant Lesions[b]	Intervening Normal Appearing Tissue (Yes or No)[c]
Left Axilla								
Right Axilla								
Left Sub/inframammary Area								
Right Sub/inframammary Area								
Intermammary Area								
Left Buttock								
Right Buttock								
Left Inguino-crural Fold[d]								
Right Inguino-crural Fold[d]								
Perianal								
Perineal								
Other								
Totals								

a. Lesion counts are to be recorded at every Study Visit in Period A and Period C.

b. If only 1 lesion, record diameter of that single lesion.

c. Are all lesions in this area clearing separated by normal appearing tissue? Answer: 'Yes' or 'No'

d. Includes the immediate adjacent area.

Appendix F. Dermatology Life Quality Index (DLQI) – Example

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

Question	Response	
1. Over the last week, how **itchy**, **sore**, **painful** or **stinging** has your skin been?	Very much ☐ A lot ☐ A little ☐ Not at all ☐	
2. Over the last week, how **embarrassed** or **self-conscious** have you been because of your skin?	Very much ☐ A lot ☐ A little ☐ Not at all ☐	
3. Over the last week, how much has your skin interfered with you going **shopping** or looking after your **home** or **yard**?	Very much ☐ A lot ☐ A little ☐ Not at all ☐	Not relevant ☐
4. Over the last week, how much has your skin influenced the **clothes** you wear?	Very much ☐ A lot ☐ A little ☐ Not at all ☐	Not relevant ☐
5. Over the last week, how much has your skin affected any **social** or **leisure** activities?	Very much ☐ A lot ☐ A little ☐ Not at all ☐	Not relevant ☐
6. Over the last week, how much has your skin made it difficult for you to do any **sport**?	Very much ☐ A lot ☐ A little ☐ Not at all ☐	Not relevant ☐

7. Over the last week, has your skin prevented you from **working** or **studying**? If "No," over the last week how much has your skin been a problem at **work** or **studying**?	Very much ☐ A lot ☐ A little ☐ Not at all ☐	Not relevant ☐
8. Over the last week, how much has your skin created problems with your **partner** or any of your **close friends** or **relatives**?	Very much ☐ A lot ☐ A little ☐ Not at all ☐	Not relevant ☐
9. Over the last week, how much has your skin caused any **sexual difficulties**?	Very much ☐ A lot ☐ A little ☐ Not at all ☐	Not relevant ☐
10. Over the last week, how much of a problem has the **treatment** for your skin been, for example by making your home messy, or by taking up time?	Very much ☐ A lot ☐ A little ☐ Not at all ☐	Not relevant ☐

Please check you have answered EVERY question. Thank you.

Appendix G. EuroQoL EQ-5D – Example

By placing a checkmark in one box in each group below, please indicate which statements best describe your own health state today.

Mobility

I have no problems in walking about ☐
I have some problems in walking about ☐
I am confined to bed ☐

Self-Care

I have no problems with self-care ☐
I have some problems washing or dressing myself ☐
I am unable to wash or dress myself ☐

Usual Activities *(e.g., work, study, housework, family or leisure activities)*

I have no problems with performing my usual activities ☐
I have some problems with performing my usual activities ☐
I am unable to perform my usual activities ☐

Pain/Discomfort

I have no pain or discomfort ☐
I have moderate pain or discomfort ☐
I have extreme pain or discomfort ☐

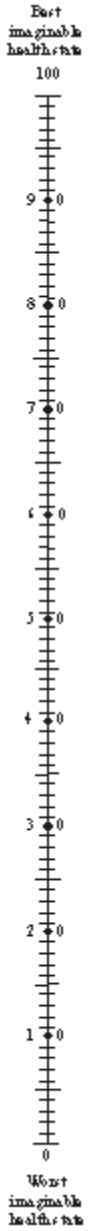
Anxiety/Depression

I am not anxious or depressed ☐
I am moderately anxious or depressed ☐
I am extremely anxious or depressed ☐

To help people say how good or bad a health state is, we have drawn a scale (rather like a thermometer) on which the best state you can imagine is marked 100 and the worst state you can imagine is marked 0.

We would like you to indicate on this scale how good or bad your own health is today, in your opinion. Please do this by drawing a line from the box below to whichever point on the scale indicates how good or bad your health state is today.

Your own health state today



Appendix H. Hidradenitis Suppurativa Impact Assessment – Example

Instructions: This questionnaire includes 18 questions about the impacts that you may experience associated with your Hidradenitis Suppurativa (HS). Hidradenitis Suppurativa is a skin condition that affects areas with sweat glands such as the underarms, breasts, inner thighs, groin, and buttocks. People often refer to their HS as boils, cysts, or lesions on their skin.

Please clearly mark an **"x" in the box ( )** that best describes how you have been affected by your **HS** in the **past 7 days**. There are no right or wrong answers to any of the questions.

[Example of HSIA in process of being reformatted for this protocol.]

Appendix I. Hidradenitis Suppurativa Patient's Global Assessment of Skin Pain – Example

Please answer the questions below before you go to bed.

Please mark an "X" in the box that best describes the severity of your skin pain in the last 24 hours.

No skin pain										Worst skin pain ever
0	1	2	3	4	5	6	7	8	9	10

In the last 24 hours, mark an "X" in the box that best describes your skin pain on average due to your HS.

No skin pain										Worst skin pain ever
0	1	2	3	4	5	6	7	8	9	10

Appendix J. Hidradenitis Suppurativa Patient Global Impression Change – Example

1. Since your last visit, how would you rate your pain due to your Hidradenitis Suppurativa (HS)?

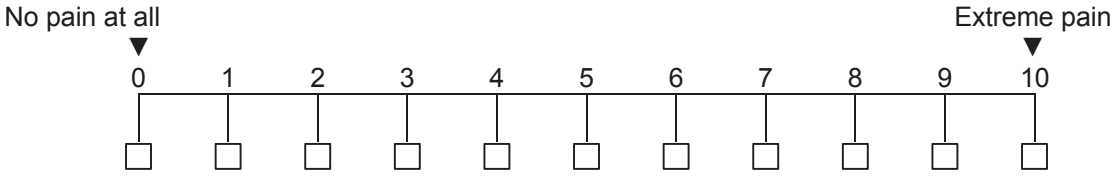
   ☐ Very much worse
   ☐ Much worse
   ☐ A little worse
   ☐ No change
   ☐ A little better
   ☐ Much better
   ☐ Very much better

Appendix K. Hidradenitis Suppurativa Symptom Assessment – 7 Day Recall – Example

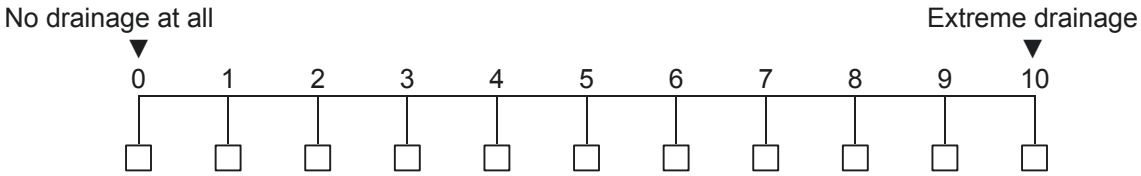
Instructions: This questionnaire includes nine questions about the symptoms you may experience associated with your Hidradenitis Suppurativa (HS). Hidradenitis Suppurativa is a skin condition that affects areas with sweat glands such as the underarms, breasts, inner thighs, groin, and buttocks. People often refer to their HS as boils, cysts, or lesions on their skin.

Please clearly mark an "x" in the box (☒) that best describes how severe your HS symptoms were over the **past 7 days**. There are no right or wrong answers to any of the questions.

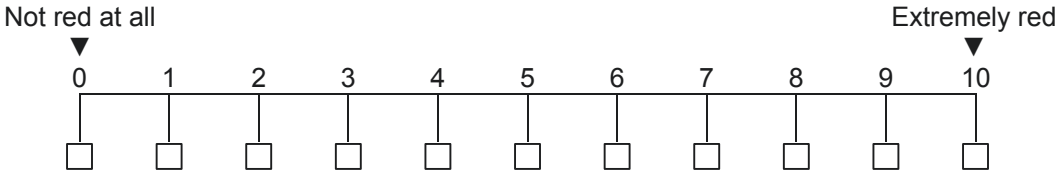
1. Over the **past 7 days**, what was the worst pain you felt in the area(s) affected by your HS?



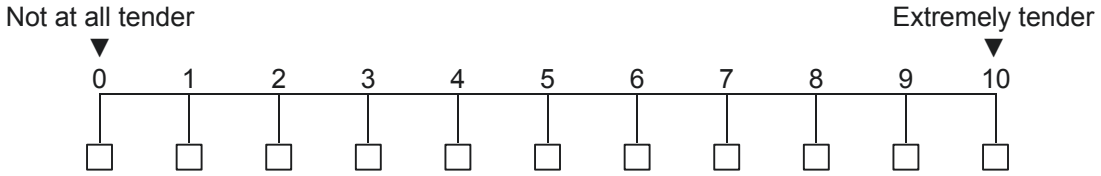
2. Over the **past 7 days**, what was the worst drainage you had in the area(s) affected by your HS?



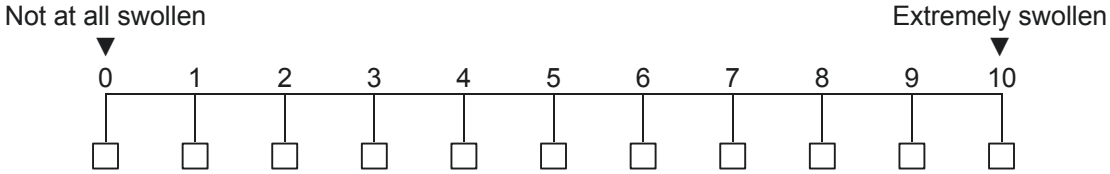
3. Over the **past 7 days**, how red was your skin in the area(s) affected by your HS?



4. Over the **past 7 days**, how tender was your skin in the area(s) affected by your HS?

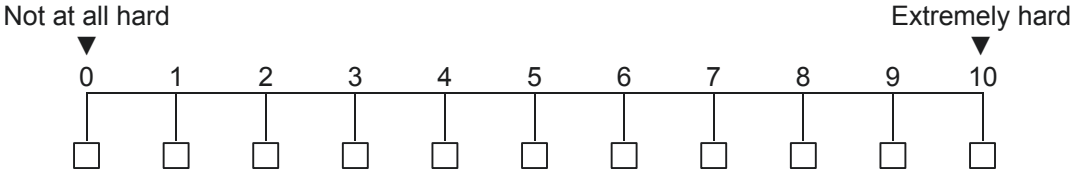


5. Over the **past 7 days**, how swollen was your skin in the area(s) affected by your HS?

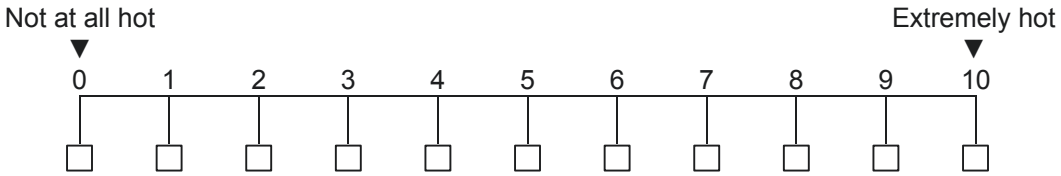


6. Over the **past 7 days**, how hard did you skin feel in the area(s) affected by your HS?

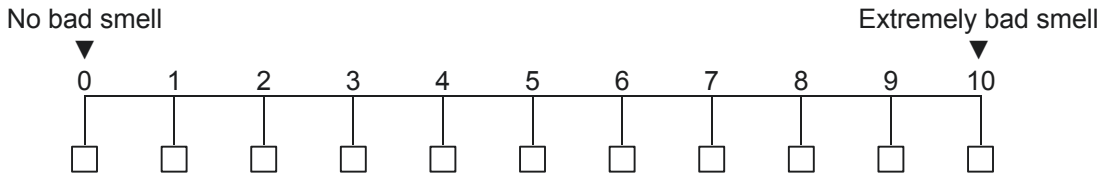
   Note: Please do not consider any hardness that you may have from the scars left on your skin from HS.



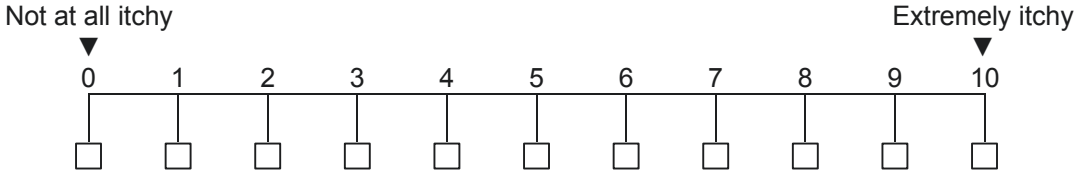
7. Over the **past 7 days**, how hot was your skin in the area(s) affected by your HS?



8. Over the **past 7 days**, how bad was the smell coming from the area(s) affected by your HS?



9. Over the **past 7 days**, how itchy was your skin in the area(s) affected by your HS?



Appendix L. Short Form-12 – Example

[Sample not available, licensing in process.]

Appendix M. Treatment Satisfaction Questionnaire for Medication – Example

TSQM (Version1.4)

Treatment Satisfaction Questionnaire for Medication

Instructions: Please take some time to think about your level of satisfaction or dissatisfaction with the medication you are taking in this clinical trial. We are interested in your evaluation of the effectiveness, side effects, and convenience of the medication *over the last two to three weeks, or since you last used it.* For each question, please place a single check mark next to the response that most closely corresponds to your own experiences.

1. How satisfied or dissatisfied are you with the ability of the medication to prevent or treat your condition?

O1 Extremely Dissatisfied
O2 Very Dissatisfied
O3 Dissatisfied
O4 Somewhat Satisfied
O5 Satisfied
O6 Very Satisfied
O7 Extremely Satisfied

2. How satisfied or dissatisfied are you with the way the medication relieves your symptoms?

O1 Extremely Dissatisfied
O2 Very Dissatisfied
O3 Dissatisfied
04 Somewhat Satisfied
O5 Satisfied
O6 Very Satisfied
O7 Extremely Satisfied

3. How satisfied or dissatisfied are you with the amount of time it takes the medication to start working?

O1 Extremely Dissatisfied
O2 Very Dissatisfied
O3 Dissatisfied
O4 Somewhat Satisfied
O5 Satisfied
O6 Very Satisfied
O7 Extremely Satisfied

 [Clinical Trial Version]

Appendix N. Work Productivity and Activity Impairment Questionnaire: Specific Health Problem – Example

The following questions ask about the effect of your hidradenitis suppurativa on your ability to work and perform regular activities. Please fill in the blanks or circle a number, as indicated.

1. Are you currently employed (working for pay)? _____NO____YES

   If NO, check "NO" and skip to question 6.

The next questions are about the **past 7 days**, not including today.

2. During the past seven days, how many hours did you miss from work because of problems associated with your hidradenitis suppurativa*? Include hours you missed on sick days, times you went in late, left early, etc. because of your hidradenitis suppurativa. Do not include time you missed to participate in this study.*

_____ HOURS

3. During the past seven days, how many hours did you miss from work because of any other reason, such as vacation, holidays, time off to participate in this study?

_____ HOURS

4. During the past seven days, how many hours did you actually work?

_____ HOURS *(If "0," write "0" and skip to question 6.)*

5. During the past seven days, how much did hidradenitis suppurativa affect your productivity while you were working?

Think about days you were limited in the amount or kind of work you could do, days you accomplished less than you would like, or days you could not do your work as carefully as usual. If hidradenitis suppurativa affected your work only a little, choose a low number. Choose a high number if hidradenitis suppurativa affected your work a great deal.

Hidradenitis suppurativa had no effect on my work	0 1 2 3 4 5 6 7 8 9 10 CIRCLE A NUMBER	Hidradenitis suppurativa completely prevented me from working

6. During the past seven days, how much did hidradenitis suppurativa affect your ability to do your regular daily activities, other than work at a job?

By regular activities, we mean the usual activities you do, such as work around the house, shopping, child care, exercising, studying, etc. Think about times you were limited in the amount or kind of activities you could do and times you accomplished less than you would like. If hidradenitis suppurativa affected your activities only a little, choose a low number. Choose a high number if hidradenitis suppurativa affected your activities a great deal.

Hidradenitis suppurativa had no effect on my daily activities	0 1 2 3 4 5 6 7 8 9 10 CIRCLE A NUMBER	Hidradenitis suppurativa completely prevented me from doing my daily activities

WPAI:SHP (US English)

Appendix O. Clinical Study Site Personnel – Study Drug Dispensing Table

Visit	Dose	Dispense Study Drug for Weeks**	Number of Syringes Used Day of Visit	Number of Kits and Syringes per Kit Dispensed for Between Visits
Baseline	160 mg (1st loading dose)	Week 1 (D1 or split over D1+D2)	4 (or 2 if split on two days)	2 kits (4 syringes)
Week 2	80 mg (2nd loading dose)	Week 2 (Day 15) 40 mg/week	2	1 kit (2 syringes)
Week 4	40 mg/week	Weeks 4, 5, 6 and 7	1	2 kits (4 syringes)
Week 8	40 mg/week	Weeks 8, 9, 10, and 11	1	2 kits (4 syringes)
Week 12	40 mg/week	Weeks 12, 13, 14 and 15	1	2 kits (4 syringes)
Week 15	40 mg/week	Weeks 16 and 17	1	1 kit (2 syringes)
Week 17	40 mg/week	Weeks 18, 19, 20 and 21	1	2 kits (4 syringes)
Week 20	40 mg/week	Weeks 22, and 23	1	2 kits (4 syringes) resulting in 1 kit/2 PFS* left over at study's end which should be destroyed if not being used as replacement.

* PFS = Pre-filled syringes.

** Study Investigators will ensure that enough study drug is dispensed at each visit to cover the subject until their next visit.

Appendix P. Subject Injection Instructions – Example Pre-Filled Syringe

1. You will not administer injections to yourself at home on clinic visit days. You or your helper will be taught on a clinic visit day how to give injections subcutaneously (under the skin, not in the muscle) and you will be asked to show the study staff you or your helpers ability to self-inject in the clinic.
2. You will administering injections at home on Day 2 of Week 0 (if directed by your study doctor), on the first day of Weeks 5, 6, 7, 9, 10, 11, (ask your study doctor about Weeks 13 and 14), and on the first day of Weeks 16, 18, 19, 21, 22 and 23 (last dose).
3. Check your dosing chart to make sure you are giving yourself the injection on the same day of the week as your last injection and check the location of the last injection on your home chart so you choose a different location for the current injection
4. Remove your carton from the refrigerator and remove **one** pre-filled syringe (there will be two syringes in the carton). Put the other syringe (syringe 2) back in the carton and place the carton back in the refrigerator.
5. If your pre-filled syringe accidentally becomes frozen, do not use the syringe and contact your study doctor.
6. Prepare a clean area where you will not be distracted.
7. You may self-administer your injection or have a helper, someone who has been approved by the study staff, do so.
8. Check the syringe to make sure the fluid in the syringe is clear and colorless. If you notice anything unusual about the pre-filled syringe, such as the liquid is cloudy, discolored or has flakes in it or the syringe itself doesn't look right to you, contact your study doctor before administering your injection. If there is a question or something unusual suspected by your study doctor, you may be required to return the carton with the full liquid amount in the syringe to your study doctor if requested to do so.

9. Wash your hands with soap and warm water or have your helper do the same. Clean medical gloves are not necessary but may be preferred by your helper.

10. If you or your helper is ready to administer your injection, have your alcohol swab, sharps container (a safe place to put your used syringes) and gauze or cotton ball ready.

    a. As you or your helper was taught in the clinic, you will first swab the area with alcohol, being careful to go from the inside out in a circular motion, trying not to put alcohol on the same area of your skin twice.

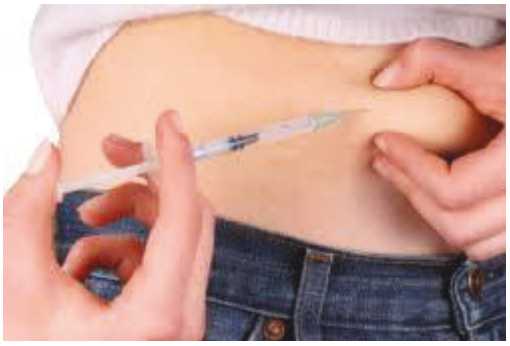
    b. You will pinch together about 1 inch of skin on either side of your stomach or your upper thighs, remove the needle cap (do not try to put the cap back on after your injection) and stick the needle in with the needle slightly sideways at an angle as shown (see the pictures below).

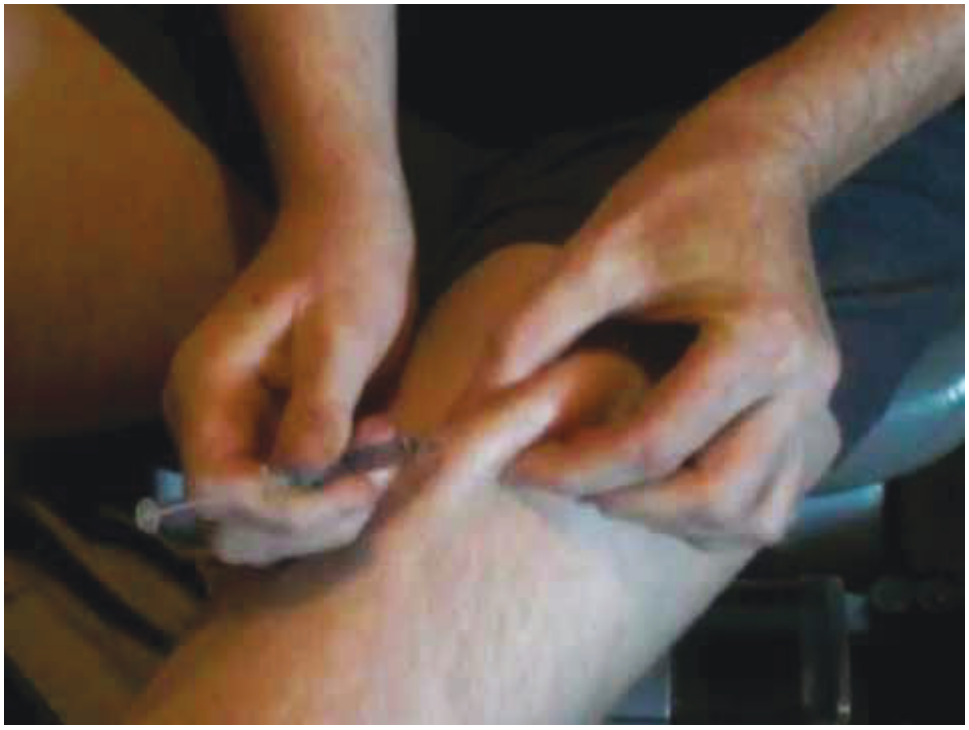
    c. Pull back slightly on the plunger.

    d. If blood does not appear push the plunger until all of the liquid is gone.

    e. If blood appears in the syringe it means the tip of the needles has entered a blood vessel. Do not begin the injection of the liquid. Pull the needle out of the skin and dispose of that pre-filled syringe.

    f. Repeat the step 10 to choose and clean a new injection site. Do not use the same syringe; instead use a new pre-filled syringe (syringe 2).





11. Remove the syringe and apply pressure with a cotton ball to the injected area.

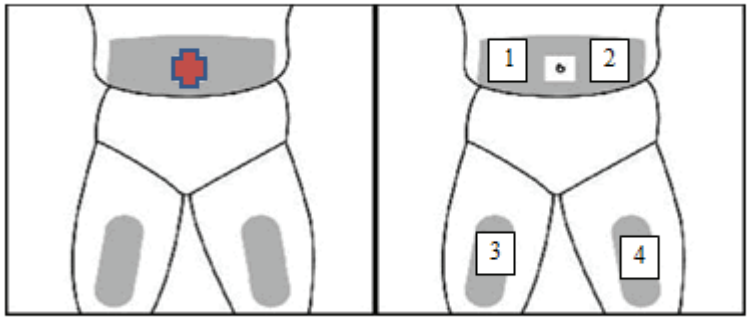
12. Immediately put the used syringe in your sharps container.

13. Please return all used and unused syringes and empty boxes to the clinic on your next visit.

14. If an injection is missed or something occurs where the full dose cannot be injected, contact your study doctor immediately for further instructions. Please record any missed doses on your subject dosing sheet.

15. Remember to complete your dosing sheet after each injection and to call the study doctor if you are having problems administering your study medication.

Sample Home Chart for Injections



Avoid the area around your navel (belly button), and rotate your weekly injections, see examples 1-4 and start over after 4 injections

Appendix Q. Subject Dosing Chart – Example

M15-574 Sample Subject Dosing Chart for Subject Number:									
Week	Day of Week	Scheduled Date of Injection	Actual Date of Injection	Kit Number	Syringe Number	Time of Injection	Was full dose administered	Person Giving Injection if not Subject	Problems with syringe or liquid?
6	1	7/6/16	7/6/16	12345	1	9AM	Yes	Tom	No

Appendix R. Study Site Drug Accountability (by Subject) Log – Example

Subject Number	Kit Number	Date Dose Administered	Total Dose Administered (mg)	Total Volume Administered (mL)	Start Time of Dose	End time of Dose
					:	:
					:	:
					:	:
		Administered By (Sign and Date)			Verified By (Sign and Date)	

I attest that the subject identified by number above, or designated helper (documented in source document as having been trained), has demonstrated safe administration of study drug on Date: _____ Time: _____ and the subject is approved to self-administer or have study drug administered by their designated (trained) helper.

_____

Name of Study Investigator or Designee

_____

Signature of Study Investigator Designee

Appendix S. Protocol Amendment: List of Changes

The summary of changes is listed in Section 1.1.

Specific Protocol Changes

Section 1.0 Title Page
"Sponsor/Emergency Contact:" previously read:

Sponsor/Emergency Contact:	[redacted]	Phone: Cell:	[redacted]

Global Medical Affairs
10, rue d'Arcueil
94150 RUNGIS
France

Has been changed to read:

Sponsor/Emergency Contact:	[redacted]	Phone: Cell:	[redacted]

Global Medical Affairs
[redacted]
26525 Riverwoods Blvd.
Mettawa, IL 60045

Section 1.2 Synopsis
Subsection Study Sites:
Previously read:

Investigator information is on file at AbbVie.

Has been changed to read:

The planned number of sites for this study is 56.

Section 6.1.5 Adverse Event Reporting
"Study Designated Physician:" previously read:

[redacted]
10, rue d'Arcueil
94150 RUNGIS France

Telephone Contact Information:
Office: [redacted]
Mobile:
Email:

Has been changed to read:

[redacted]
26525 Riverwoods Blvd.
Mettawa, IL 60045

Telephone Contact Information:
Office: [redacted]
Mobile:
Email:

Section 7.0 Protocol Deviations
"Alternate Contact:" previously read:

[redacted]
1 North Waukegan Road
North Chicago , IL USA 60064

Office: [redacted]
Email:

Has been changed to read:

[redacted]

1 North Waukegan Road
North Chicago, IL USA 60064

Office: [redacted]
Mobile: [redacted]
Email: [redacted]

Section 8.1.4.1 Primary Analysis of Efficacy
First paragraph
Add: new last sentence

The 95% confidence intervals of treatment difference will also be provided.

Section 8.1.4.1 Primary Analysis of Efficacy
Add: new last paragraph

In addition, a sensitivity analysis controlling for change from baseline in body weight using logistic regression models, for the primary efficacy endpoint. Analysis details will be specified in the SAP prior to study unblinding and prior to database lock.

Appendix B. List of Protocol Signatories
Previously read:

Name	Title	Functional Area
[redacted]		Global Medical Affairs
		Global Medical Affairs
		Statistics
		CPPM
		Regulatory Affairs
		Biologics
		Clinical Program Development

Has been changed to read:

Name	Title	Functional Area
[redacted]		Global Medical Affairs
		Clinical
		Statistics
		Regulatory Affairs
		Clinical Program Development

Document Approval

Study M15574 - A Phase 4, Double-Blind, Randomised, Placebo-Controlled Multicenter Study to Assess the Safety and Efficacy of Adalimumab Used in Conjunction with Surgery in Subjects with Moderate to Severe Hidradenitis Suppurativa - Amendment 3 - EudraCT 2015-005161-23 - 13Dec2017

Version: 1.0 **Date:** 14-Dec-2017 07:09:35 PM **Company ID:** 12142017-00F9F683B82C34-00001-en

Signed by:	Date:	Meaning Of Signature:
[redacted]	13-Dec-2017 02:41:46 PM	Approver
	13-Dec-2017 03:47:25 PM	Approver
	13-Dec-2017 04:00:01 PM	Approver
	13-Dec-2017 07:20:57 PM	Approver
	14-Dec-2017 07:09:35 PM	Approver