1.0 Title Page

Clinical Study Protocol M15-573

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

AbbVie Investigational Product:	Adalimumab
Date:	07 July 2016
Development Phase:	3
Study Design:	Non-randomized, Open-label, Single-arm
EudraCT Number:	N/A
Investigators:	Multicenter Trial (Investigator information on file at AbbVie)
Sponsor:	AbbVie GK,
Sponsor/Emergency Contact:	[redacted]

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 Synopsis

AbbVie Inc.	**Protocol Number:** M15-573
Name of Study Drug: Adalimumab	**Phase of Development:** 3
Name of Active Ingredient: Adalimumab	**Date of Protocol Synopsis:** 07 July 2016
Protocol Title: A Phase 3 Multicenter, Open-Label, Single Arm Study of the Safety and Efficacy of Adalimumab in Japanese Subjects with Moderate to Severe Hidradenitis Suppurativa	
Objective: The primary objective of this study is to evaluate the safety and efficacy of adalimumab in Japanese subjects with moderate to severe hidradenitis suppurativa (HS).	
Investigators: Multicenter	
Study Sites: Approximately 10 centers.	
Study Population: Male or female Japanese subjects age 18 years or older with moderate to severe HS.	
Number of Subjects to be Enrolled: Approximately 15	
Methodology: This study is an open-label, single arm study designed to investigate the safety and efficacy of adalimumab in Japanese patients with moderate to severe hidradenitis suppurativa after 12 weeks of treatment, and to evaluate long-term safety, efficacy and tolerability. The study will include a 35-day screening period, open-label treatment period and a Day 70 follow-up phone call following their last dose of study drug. The treatment period is expected for at least 99 weeks until the time of approval for HS indication, or withdrawal of the marketing application in Japan. All subjects will receive open-label subcutaneous injection of adalimumab 40 mg every week (ew) starting at Week 4, after 160 mg at Week 0 (Baseline) and 80 mg at Week 2. The primary efficacy endpoint is the proportion of subjects achieving Hidradenitis Suppurativa Clinical Response (HiSCR) at Week 12. HiSCR is defined as at least a 50% reduction in the total abscess and inflammatory nodule count (AN count) with no increase in abscess count and no increase in draining fistula count relative to Baseline. Study visits will occur at Weeks -4 and -2 (in the Screening period), Baseline (Week 0), Weeks 2, 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, and 52 or at the Premature Discontinuation visit. After Week 52, study visits will occur every 12 weeks until the study end. Additionally, all subjects will be contacted by phone 1 week before and after the Baseline visit to ensure daily pain assessments are being recorded, and at Week 6 and Week 10 to monitor whether any signs or symptoms of infection are present at or near an HS lesion. If any signs or symptoms are reported at the time of the call, an unscheduled study visit will be conducted to assess whether an infection is present. Adverse events will be collected throughout the study. Subjects who decide not to continue this study will have a Day 70 follow-up phone call following their last dose of study drug to determine the status of any ongoing adverse events (AEs) or serious adverse events (SAEs), or the occurrence of any new AEs or SAEs. The Day 70 follow-up phone call will not be required for any subject who initiates adalimumab therapy not supplied in the context of the clinical trial after the end of the study participation.	

Diagnosis and Main Criteria for Inclusion/Exclusion:

Main Inclusion:

- Subjects must have a diagnosis of HS;
- Subjects must have any HS symptom at least 6 months prior to Baseline;
- HS lesions must be present in at least two distinct anatomic areas, one of which must be at least Hurley Stage II or Hurley Stage III;
- Subject must have stable HS for at least 2 months (60 days) prior to Screening and also at the Baseline visit as determined by the investigator through subject interview and review of medical history;
- Subject must have a total abscess and inflammatory nodule (AN) count of greater than or equal to 3 at the Baseline visit;
- Subject has a negative TB screening assessment (including a PPD test or QuantiFERON-TB Gold test, or equivalent) and negative chest x-ray (CXR) (posterior-anterior [PA] and lateral view) at Screening;
- Subject is judged to be in good general health, as determined by the Principal 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 Baseline.

Main Exclusion:

- Prior treatment with adalimumab or other anti-TNF therapy (e.g., infliximab or etanercept), or participation in an adalimumab trial;
- Subject received antibiotic treatment for HS within 28 days prior to the Baseline visit other than those allowed per protocol. Subjects on permitted oral antibiotic treatment (doxycycline or minocycline only) for HS who have not been on a stable dose for at least 28 days prior to the Baseline visit;
- Subject received oral concomitant analgesics (non-opioids and opioids) for HS-related pain within 14 days prior to the Baseline visit;
- If entering the study on concomitant oral analgesics for non-HS-related pain:
  - Subject on opioid analgesics within 14 days prior to Baseline visit (opioid analgesics are not allowed);
  - Subject not on a stable dose of non-opioid oral analgesics for at least 14 days prior to the Baseline visit (PRN is not considered a stable dose).
- Subject requires, or is expected to require, opioid analgesics for any reason (excluding tramadol);
- Subject received prescription topical therapies for the treatment of HS within 14 days prior to the Baseline visit;
- Subject received systemic non-biologic therapies for HS with potential therapeutic impact for HS less than 28 days prior to Baseline visit (other than permitted oral antibiotics);
- Subject has a draining fistula count of greater than 20 at the Baseline visit;
- Infection(s) requiring treatment with intravenous (IV) anti-infectives (antibiotics, antivirals, antifungals) within 30 days prior to Baseline or oral anti-infectives (antibiotics, antivirals, antifungals) within 14 days prior to Baseline, except as required as part of an anti-TB regimen;
- Any other active skin disease or condition (e.g., bacterial, fungal or viral infection) that may interfere with assessment of HS;

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

Main Exclusion (Continued):

- History of demyelinating disease (including myelitis) or neurologic symptoms suggestive of demyelinating disease;
- History of invasive infection (e.g., listeriosis, histoplasmosis), human immunodeficiency virus (HIV);
- Subject has an active systemic viral infection or any active viral infection including Hepatitis C that based on the investigator's clinical assessment make the subject an unsuitable candidate for the study;
- Hepatitis B: HBsAg positive (+) or detected sensitivity on the HBV-DNA PCR qualitative test for HBc Ab/HBsAb positive subjects;
- Chronic recurring infections or active TB;
- History of moderate to severe congestive heart failure (NYHA class III or IV), recent cerebrovascular accident and any other condition which, in the opinion of the investigator, would put the subject at risk by participation in the protocol;
- 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;
- Female subjects who is pregnant, breastfeeding or is considering becoming pregnant during the study and for approximately 150 days after the last dose of study drug;
- Subject currently has an adequate response to oral antibiotic treatment for HS.

Investigational Product:	Adalimumab
Doses:	160 mg Week 0 and 80 mg Week 2 followed by 40 mg every week (ew) starting at Week 4.
Mode of Administration:	Subcutaneously (SC)

Duration of Treatment: Until approval of HS indication in Japan (at least 99 weeks)

Criteria for Evaluation:

Efficacy:

The primary efficacy endpoint is the proportion of subjects achieving HiSCR at Week 12. The study will provide long-term efficacy as well.

Pharmacokinetic:

Blood samples will be collected for the measurement of serum adalimumab concentrations at Baseline (Week 0) and Weeks 2, 4, 8, 12, 16, 20, 24, 36, and 52, or at the Premature Discontinuation visit if the subject discontinues prior to Week 52. Blood samples will be collected for the measurement of anti-adalimumab antibody (AAA) at Baseline (Week0), Weeks 4, 12, 24, 36, and 52, or at the Premature Discontinuation visit if the subject discontinues prior to Week 52.

Safety:

Adverse events, laboratory data and vital signs will be assessed throughout the study.

Statistical Methods:

Efficacy:

The primary analysis will be the proportion of subjects achieving HiSCR at Week 12.

Secondary endpoints include:

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

The degree of erythema will be assessed in each affected anatomic region as an additional secondary endpoint.

Efficacy variables will be analyzed at all scheduled visits.

The primary efficacy analysis will be carried out in the FAS Population, defined as all patients who received at least one dose of study drug and had at least one-post-treatment efficacy assessment in this study. Non-responder imputation will be used as primary approach to impute the missing values, with last-observation-carried-forward. Primary efficacy variable will be summarized by baseline value, baseline Hurley Stage (II/III), and antibiotic use (Y/N), if appropriate.

Secondary and other efficacy variables will be summarized in the FAS Population.

Considering quite limited number of patients with HS in Japan and feasibility of the study conduct, 15 subjects is set for sample size of this study. The response rates of HiSCR at Week 12 in Study M11-810 and M11-313 were 59 % and 42% in the adalimumab ew group, and 28% and 26% in the placebo group, respectively. Assuming the threshold clinical response rate of 25% and expected clinical response rate of 60% in adalimumab at Week 12, a sample size of 13 subjects will have 80.1% power to detect the difference of 35% in the primary endpoint and using one sample Chi-square test at one-sided 2.5% significant level.

Pharmacokinetic:

Adalimumab trough serum concentrations will be summarized at each time point using descriptive statistics. The results may be incorporated into a population pharmacokinetic analysis if the data warrants in order to estimate parameters such as apparent clearance (CL/F) and apparent volume of distribution (V/F) of adalimumab.

Immunogenicity:

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

Statistical Methods: (Continued):

Safety:

All adverse events (AE), serious adverse events (SAE), AEs leading to discontinuation, and pre specified AEs of special interest will be collected during the study and up to approximately 70 days after the last dose of study drug for subjects who prematurely discontinue the study. Safety analyses will be carried out using the Safety Population (subjects who received at least one dose of study drug). Pretreatment AEs will be summarized as well. A treatment-emergent AE 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. The number and percent of subjects experiencing treatment-emergent AEs will be tabulated using the Medical Dictionary for Drug Regulatory Activities (MedDRA®) system organ class and preferred term.

Summaries (including percentages and event per 100 patient-years) of SAEs, deaths, AEs leading to discontinuation from the study, and prespecified AEs of special interest will be provided. Mean change in laboratory variables and vital sign variables at each visit will be summarized for all treated subjects. For selected parameters, a listing of all subjects with any laboratory determination meeting Common Toxicity Criteria (CTC) of Grade 2 or higher will be provided. Shift tables for changes from Baseline according to the normal range will also be provided.

1.2 List of Abbreviations

Abbreviations

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

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

TSQM	Treatment Satisfaction Questionnaire - Medication
US	United States
V/F	Apparent volume of distribution
Wk	Week

1.3 Definition of Terms

Abscess	A circumscribed collection of purulent exudate frequently associated with swelling and other signs of inflammation, such as fluctuance, tenderness and pain.
HiSCR	Hidradenitis Suppurativa Clinical Response, defined as at least a 50% reduction in the AN count with no increase in abscess count and no increase in draining fistula count relative to Baseline.
Hurley Staging	Stage I: Abscess formation, single or multiple, without sinus tracts and cicatrization (scarring). Stage II: One or more widely separated recurrent abscesses with tract formation and cicatrization (scars). Stage III: Multiple interconnected tracts and abscesses across the entire area, with diffuse or near diffuse involvement.
Hypertrophic Scar	Enlargement or overgrowth of a scar so that it extends above the surrounding skin surface
Inadequate Response to Antibiotics	An adequate trial of oral antibiotic therapy is considered to be at least 90 days in duration. If, after at least 90 days (≥ 90 days) of oral antibiotic therapy, any of the following has occurred, subject will be considered to have had inadequate response, or loss of response, to oral antibiotics: • Progression of Hurley Stage (i.e., the Hurley Stage of at least one affected anatomic region has progressed from I – II, II – III, or I – III); • Subject requires at least one intervention (e.g., incision and drainage or intralesional injection of corticosteroid); • Subject experiences pain interfering with activities of daily living, with unsatisfactory relief from over-the-counter analgesics (e.g., ibuprofen or acetaminophen); • Subject experiences pain requiring opioids, including tramadol; • Subject experiences drainage interfering with activities of daily living (e.g., requires multiple dressing changes and/or changes of clothes daily); • Subject experiences an increase in the number of anatomic regions affected by HS; • Subject experiences at least one new abscess or one new draining fistula. • Sites are encouraged to contact AbbVie TA MD to confirm if the definition of inadequate response or loss of response has been met.

<table>
<tr><td>Inflammatory nodules</td><td colspan="3">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.</td></tr>
<tr><td>Intolerance to Antibiotics</td><td colspan="3">A subject is defined as intolerant to oral antibiotic when oral antibiotic therapy has been discontinued by a physician as a result of a significant adverse reaction to oral antibiotic administration.
A reaction will be considered significant if the adverse reaction is at least moderately severe (i.e., the adverse event causes the subject discomfort and interrupts the subject's usual activities or function). Examples of significant adverse reactions include, but are not limited to:
• nausea resulting in decreased oral intake;
• macular or papular eruption or erythema associated with pruritus or other associated symptoms;
• dizziness/disequilibrium/lightheadedness/vertigo interfering with function;
• allergic reaction manifesting as rash, flushing, urticaria, dyspnea, or drug fever ≥ 38°C;
• diarrhea manifesting as an increase in stool frequency of at least 4 stools per day over Baseline.
Sites are encouraged to contact AbbVie TA MD to confirm if the definition of intolerance has been met.</td></tr>
<tr><td>Loss of Response (LOR)</td><td colspan="3">An AN count that is greater than the average of AN counts at Baseline and Week 12. It is a loss of at least 50% of the improvement (reduction) in the AN count achieved from baseline to Week 12.
Calculation: AN > ½ * (Baseline AN count + Week 12 AN count)</td></tr>
<tr><td>Baseline AN Count</td><td>Week 12 AN Count</td><td>Average of AN Counts</td><td>Minimum Count to Meet LOR</td></tr>
<tr><td>10</td><td>1</td><td>½ * (10 + 1) = 5.5</td><td>6</td></tr>
<tr><td>10</td><td>4</td><td>½ * (10 + 4) = 7</td><td>8</td></tr>
<tr><td>Fistula</td><td colspan="3">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.</td></tr>
<tr><td>Non-inflammatory nodules</td><td colspan="3">Non-tender or minimally tender, non-erythematous nodules.</td></tr>
<tr><td>Protocol Allowed Intervention</td><td colspan="3">A protocol-allowed intervention is defined as incision and drainage, or injection of intralesional triamcinolone acetonide suspension (at a dose of 50 mg/5 mL, up to 0.5 mL).</td></tr>
<tr><td>Worsening or Absence of</td><td colspan="3">An AN count that has been ≥ Baseline AN count at two consecutive visits occurring ≥ 14 days apart.</td></tr>
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3.0 Introduction

3.1 Differences Statement

Study M15-573 is a Phase 3 clinical study to evaluate the safety and efficacy of adalimumab in the treatment of Japanese subjects with moderate to severe hidradenitis suppurativa (HS). Prior to initiation of this trial, global Phase IIb study (Study M10-467) and pivotal Phase III studies (Studies M11-810 and M11-313) were completed in the Western countries and market authorization of adalimumab was approved in US and EU for the treatment of subjects with HS. The differences between Study M15-573 and global studies include sample size, study design, duration, and race.

3.2 Hidradenitis Suppurativa

HS is a painful, chronic, skin disease characterized by recurrent inflamed nodules and abscesses, which may rupture to form fistulas and subsequent scarring. The most commonly involved anatomic locations are the inguino-crural and axillary folds, with sub-mammary folds (in women) and the perineal area less commonly involved in the Western countries.

Hidradenitis Suppurativa has a severely negative effect on patients' quality of life.[1] It typically presents with painful, deep-seated nodules, which either resolve spontaneously, persist as non-tender nodules, or progress to form abscesses. Abscesses typically rupture and release purulent drainage. Abscesses and nodules may heal with scarring and the formation of fistulas or sinus tracts. Thus, many patients with HS develop permanent sequelae of past inflammation that are only remediable through surgical excision of the involved skin areas. The physical and psycho-social morbidity associated with en bloc excision of scarred axillary, inguinal, or groin skin is substantial. Rare complications of HS include fistula formation into urethra, bladder, rectum, or peritoneum, lymphedema of the limbs or scrotal elephantiasis, and squamous cell carcinomas of the skin originating from HS lesions.

Hidradenitis Suppurativa affects approximately 1% of the general population in the Western countries.[2,3] Disease onset is typically after puberty. Disease prevalence decreases from 1.5% in those < 25 years of age to 0.5% in those older than 55 years of age. 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.[4]

The histopathologic characteristics of HS include a dense inflammatory cell infiltrate of neutrophils, lymphocytes, and histiocytes.[5] Tumor necrosis factor-alpha (TNF-α), which induces pro-inflammatory cytokines and activates neutrophils and lymphocytes, may have a pathogenic role.

In Japan, HS is approximately two times more prevalent in men than in women, and the most commonly involved anatomic locations are buttocks, axillae, and groin. These differences in anatomic area of skin lesion and gender between Japan and the Western countries may represent the different phenotypes of a single disease, as it is reported that HS has 3 phenotypes depending on the anatomic areas involved.[6] Indeed, the histopathological characteristics of HS lesions in Japanese were follicular occlusion followed by neutrophil infiltration into the follicles and were similar to those observed in Western patients.[7] The patient number is quite limited as reported in the questionnaire survey in 2014; 100 cases in 44 hospitals authorized by Japan Dermatology Association.[8]

3.3 Current Treatments

There were no formal treatment guidelines for this condition overseas at the time of study initiation for clinical development in HS in 2010. Current treatments are still driven primarily by expert opinion and isolated case reports or series. Prior to Phase 2 Study M10-467, the only placebo controlled trial of HS demonstrated modest efficacy with the use of topical clindamycin.[9] Treatment of HS depends on the extent and activity of disease.[4] The recommendation by experts for mild or limited forms of the disease consists of topical clindamycin, short courses of systemic antibiotics, or intralesional steroids. Successful use of oral retinoids, anti–androgens, or immunosuppressants for recalcitrant cases has been described in case reports and series, but no controlled studies

have been conducted with these agents. In more advanced cases, a multifaceted approach may be adopted, where surgical therapy is used to remove the chronic components of HS which are not expected to respond to medical therapy (e.g., scarring, fistulas, and sinus tracts), and long-term systemic medical therapy is used to treat the acute or sub-chronic manifestations of HS (e.g., abscesses and inflammatory nodules).

Oral retinoids for treatment of HS appear to offer limited therapeutic benefit, but one small case series reported that the response of HS to isotretinoin is more successful in the milder cases.[10] Other treatments for HS include: 1) Systemic combination therapy with clindamycin and rifampicin, 2) Radical excision, 3) Intralesional triamcinolone (which can add to a significant systemic exposure), 4) Systemic cyclosporine, 5) Anti-androgen treatment in women (which is teratogenic), and 6) systemic dapsone.[11]

Case reports and series have shown that inhibitors of TNF-α are effective in treating HS.[12-14] Based on these observations, the investigation of adalimumab, a fully human anti-TNF monoclonal antibody, for the treatment of moderate to severe HS was considered warranted. AbbVie Inc. conducted Phase 2 and Phase 3 studies in patients with moderate to severe HS and had approval of HS indication in 2015. Then adalimumab was listed on the EU guideline as the first biologic agent.

In Japan, the treatment options for HS are basically the same as those in the Western countries; oral or topical antibiotics and surgery of total removal of skin lesion or incision for drainage of abscess.

3.4 Adalimumab Overview

Adalimumab is a recombinant human immunoglobulin (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, 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 is a naturally occurring cytokine that is involved in normal inflammatory and immune responses. Elevated levels of TNF are thought to play an important role in pathologic inflammation. Adalimumab binds specifically to TNF and neutralizes the biological function of TNF by blocking its interaction with the p55 and p75 cell surface TNF receptors. Adalimumab also modulates biological responses that are induced or regulated by TNF. 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.

The role of elevated levels of TNF in pathologic autoimmune disorders and immune-mediated disorders has led to the study and approval of anti-TNF agents in diseases such as rheumatoid arthritis (RA), juvenile idiopathic arthritis (JIA), psoriatic arthritis (PsA), ankylosing spondylitis (AS), Crohn's disease and psoriasis (Ps). Elevated TNF levels in the synovial fluid of RA, including JIA, PsA, and AS patients, play an important role in both the pathologic inflammation and the joint destruction that are hallmarks of these diseases. In plaque Ps, treatment with adalimumab may reduce the epidermal thickness and infiltration of inflammatory cells. The relationship between these pharmacodynamic activities and the mechanism(s) by which adalimumab exerts its clinical effects is unknown.

Adalimumab also modulates biological responses that are induced or regulated by TNF, including changes in the levels of adhesion molecules responsible for leukocyte migration (ELAM-1, VCAM-1, and ICAM-1 with an IC_{50} of 1 to 2×10^{-10}M).

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 Psoriasis, Psoriatic Arthritis, Ankylosing Spondylitis, Crohn's Disease, Juvenile Idiopathic Arthritis, and Ulcerative Colitis. In 2015, adalimumab was approved for the indication of Hidradenitis Suppurativa with the following clinical data.

A 52-week Phase 2 dose-ranging study (Study M10-467) was conducted to evaluate the short- and long-term clinical efficacy and safety of adalimumab in subjects with moderate to severe HS. The first portion of the study was a 16-week, randomized, double-blinded, placebo-controlled phase in which subjects were randomized to adalimumab 40 mg ew (weekly starting at Week 4, after 160 mg at Week 0 and 80 mg at Week 2), or to adalimumab 40 mg eow (every other week starting at Week 1, after 80 mg at Week 0), or to placebo. The primary endpoint was the proportion of subjects achieving an HS-Physician's Global Assessment (PGA) of clear (0), minimal (1), or mild (2), with a reduction from Baseline of at least 2 grades at Week 16.

The proportion of subjects who achieved a clinical response was significantly higher in the ew arm compared with subjects in the placebo arm at Week 12 and Week 16. The second portion of the study was a 36-week open-label phase in which all subjects received adalimumab 40 mg eow and were eligible to dose escalate to ew dosing if response was sub-optimal. A decline in response rate was seen following decreasing from ew to eow dosing, and dose escalation to ew dosing resulted in improved efficacy.

A Phase 3 Study M11-313 was a 36-week multicenter study designed to evaluate the safety and efficacy of adalimumab in subjects with moderate to severe HS. The study included a 30 day screening period, an initial 12-week double-blind placebo-controlled treatment period (Period A), and a subsequent 24-week double-blind placebo-controlled treatment period (Period B). Subjects were randomized 1:1 at Baseline (Week 0) to either adalimumab 40 mg ew (starting at Week 4 through Week 11, after 160 mg at Week 0 and 80 mg at Week 2), or matching placebo for 12 weeks. The randomization was stratified by Hurley Stage (II versus III). The primary efficacy variable was the proportion of subjects achieving Hidradenitis Suppurativa Clinical Response (HiSCR) at Week 12. After Week 12, subjects who had been randomized to adalimumab during Period A were re-randomized 1:1:1 to 1 of 3 groups: adalimumab 40 mg ew, adalimumab 40 mg eow, or placebo from Week 12 to Week 35. The re-randomization was stratified by Week 12 response (HiSCR responder versus non responder) and by Baseline Hurley Stage (II versus III).

A total of 307 subjects were randomized in this study. In Period A, a statistically significantly higher percentage of subjects in the adalimumab ew group achieved HiSCR at Week 12 (primary efficacy endpoint) compared with subjects in the placebo group (41.8% [64/153] versus 26.0% [40/154]; P = 0.003). Furthermore, a greater proportion of subjects in the adalimumab group achieved HiSCR at each visit in Period A compared with subjects in the placebo group ($P \leq 0.05$ at all visits). Efficacy assessments from subjects who were randomized to adalimumab ew in Period A and re-randomized to Period B as HiSCR responders showed generally better treatment outcomes among those continuing adalimumab ew treatment (ew/ew group) compared with subjects who reduced dosing frequency to eow or to placebo groups through 36 weeks. Overall, the safety profile of adalimumab treatment observed in this study was consistent with the experience in other adalimumab clinical trials.

Another Phase 3 Study M11-810 was a 36-week multicenter study designed to evaluate the safety and efficacy of adalimumab in subjects with moderate to severe HS. The study design and procedures were almost identical to those for Study M11-313. The main differences between the studies are 1) treatment in Period B for the subjects who were allocated to placebo in Period A and 2) permission of use of antibiotics and its related study procedures. The randomization was stratified by Hurley Stage (II versus III) and concomitant antibiotic use (defined as baseline use of antibiotics to be used concomitantly during the study; Yes versus No). The primary efficacy variable was the proportion of subjects achieving HiSCR at Week 12, the same as in Study M11-313.

A total of 326 subjects were randomized in this study. In Period A, a statistically significantly higher proportion of subjects randomized to adalimumab ew achieved HiSCR at Week 12 (primary efficacy endpoint), as compared to subjects randomized to placebo (58.9% [96/163] versus 27.6% [45/163], respectively). Consistent treatment effects were observed for subjects in each Hurley Stage and in each baseline antibiotic use strata. Furthermore, a greater proportion of subjects in the adalimumab group achieved HiSCR than subjects in the placebo group at each visit during Period A ($P < 0.001$ at all visits). Results of the secondary endpoints support the primary efficacy endpoint results.

Efficacy assessments from subjects who were randomized to adalimumab ew in Period A and re-randomized to adalimumab ew (ew/ew group) in Period B showed generally better treatment outcomes than subjects who reduced dosing frequency to eow (ew/eow group) or who were re-randomized to placebo (ew/placebo) for both HiSCR responders and HiSCR nonresponders. Overall, the safety profile of adalimumab treatment observed in this study was consistent with that expected for the study population of moderate to severe HS.

3.5 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. The safety and efficacy of adalimumab in HS has been demonstrated in the Phase 3 pivotal Studies M11-810 and M11-313. At Week 12 of the double blind period, the proportion of subjects who achieved HiSCR at Week 12 were 50.6% and 26.8% in adalimumab and placebo ($P < 0.001$) in the integrated analysis, respectively, which demonstrated statistically significant superiority of efficacy to placebo. The necessity of ew dosing was also confirmed to maintain the efficacy in both studies. The safety profile of adalimumab in HS does not appear different from that previously observed with adalimumab in the other indications.

Regarding safety data from the initial DB period of Phase 2 Study M10-467 (first 16 weeks) and Period A of Phase 3 Studies M11-810 and M11-313 (first 12 weeks), the percentages of subjects reporting AEs were comparable between the placebo (63.7%) and total adalimumab (eow and ew) groups (58.2%) during the placebo-controlled period of the Phase 2 and 3 studies. Similar percentages of subjects in the placebo and total adalimumab groups reported AEs that were considered by the investigator to be possibly or probably related to study drug (27.0% and 29.1%, respectively) and severe AEs (6.6% and 5.7%, respectively).

The most frequently reported TEAEs for the adalimumab total and placebo groups in the placebo-controlled period were headache, hidradenitis, and nasopharyngitis. The percentage of subjects who reported headache was higher in the adalimumab total group than in the placebo group (11.9% versus 10.4%). The percentages of subjects who reported hidradenitis and nasopharyngitis were lower in the adalimumab total group than in the placebo group (7.6% versus 12.8% for hidradenitis and 7.4% versus 8.7% for nasopharyngitis).

The most frequently reported TEAEs in the adalimumab ew/ew and ew/placebo groups in the maintenance period were headache, nasopharyngitis, hidradenitis, and upper respiratory tract infection. The most frequently reported TEAEs in the adalimumab ew/eow group were hidradenitis, upper respiratory tract infection, headache, and pyrexia. The percentage of subjects who reported hidradenitis was significantly lower in the adalimumab ew/ew group, as compared to the adalimumab ew/eow and ew/placebo groups (P = 0.007 and P = 0.002, respectively).

The potential benefit of the proposed study in HS is that it is designed to demonstrate whether adalimumab therapy is associated with a reduction in the extent of inflammation in Japanese patients with moderate to severe HS, manifested as a specific reduction in the number of inflammatory nodules and abscesses. As these inflammatory lesions are associated with considerable pain and impairment in quality of life, a reduction in the number of such lesions could directly benefit patients. Subjects with a draining fistula count of greater than 20 at the Baseline visit are excluded from enrolling in the study to exclude the most severe forms of the disease that may place subjects at a higher risk.

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 an FDA-requested, TNF inhibitor class wide exploration of the rare appearance of malignancy in patients 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.

Given that (a) the abscesses and inflammatory nodules of HS cause pain and malodor, and may culminate in scar formation; (b) there are no approved medical therapies for the abscesses and inflammatory nodules of HS; and (c) surgical therapies are associated with significant post-operative morbidity, there is a significant unmet medical need for therapies to treat this condition. Based on the current treatment options and unmet medical need, AbbVie considers that adalimumab will provide safe and effective therapy also for Japanese patients with moderate to severe HS and is thus conducting Phase 3 clinical trial for this indication in Japan.

4.0 Study Objective

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

5.0 Investigational Plan

5.1 Overall Study Design and Plan: Description

The study is a Phase 3, multicenter, open-label, single arm study of adalimumab, and designed to enroll 15 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.

The study duration will include a 35-day Screening Period, open-label treatment period, and a Day 70 follow-up phone call approximately 70 days after the last dose of study drug administration. The treatment period is expected for at least 99 weeks until the time of approval for HS indication, or withdrawal of the marketing application in Japan. A subject's participation in this study is expected up to 38 months.

The duration of the screening period will be a maximum of 35 days during which time all of the inclusion and exclusion criteria will be evaluated. Subjects may enroll into the study after all screening procedures are complete, at least 7 days of pain diaries are completed, and results are known and verified for eligibility at Baseline.

All subjects will receive open-label subcutaneous injection of adalimumab 40 mg every week (ew) starting at Week 4, after 160 mg at Week 0 (Baseline) and 80 mg at Week 2.

Subjects will have to return to the site once (Week –2) in the Screening period after the date of the Screening visit (Week –4). Study visits for clinical and safety assessment will occur at Baseline, Week 2, Week 4, Week 8, Week 12, Week 16, Week 20, Week 24, Week 28, Week 32, Week 36, Week 40, Week 44, Week 48, and Week 52 or at the Premature Discontinuation visit. After Week 52, study visits should be every 12 weeks until the study end.

The primary efficacy endpoint is the proportion of subjects achieving Hidradenitis Suppurativa Clinical Response (HiSCR) at Week 12. HiSCR is defined as at least a 50% reduction in the total abscess and inflammatory nodule count (AN count) with no increase in abscess count and no increase in draining fistula count relative to Baseline. Safety and efficacy measurements will be performed throughout the study as described in Section 5.3.1.

Blood samples will be collected for clinical laboratory test, adalimumab serum concentrations and anti-adalimumab antibody (AAA) levels, as indicated in Table 1. Photography of skin lesions will also be performed in subjects who consent in pre-selected sites.

Additionally, all subjects will be contacted by phone 1 week before and after the Baseline visit to ensure daily pain assessments are being recorded, and at 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 are reported at the time of the call, an unscheduled study visit will be conducted to assess whether an infection is present. Each subject will also be

given an information card (Appendix O) describing signs and symptoms of infections with instructions to contact the site immediately if any such signs or symptoms develop at or near an HS lesion.

The visit window will be + or –3 days for the Week –4, Week –2,Week 2 and Week 4 visits, and + or –7 days for all study visits from Week 8 until the study end. Subjects will be brought back to their original visit schedule (calculated from Baseline) if they are out of the visit window. Baseline is defined as the date of first administration of study drug (Day 1). The phone calls at Weeks 1, 6 and 10 should be completed as close to the scheduled date as possible, but minimally prior to the next study visit.

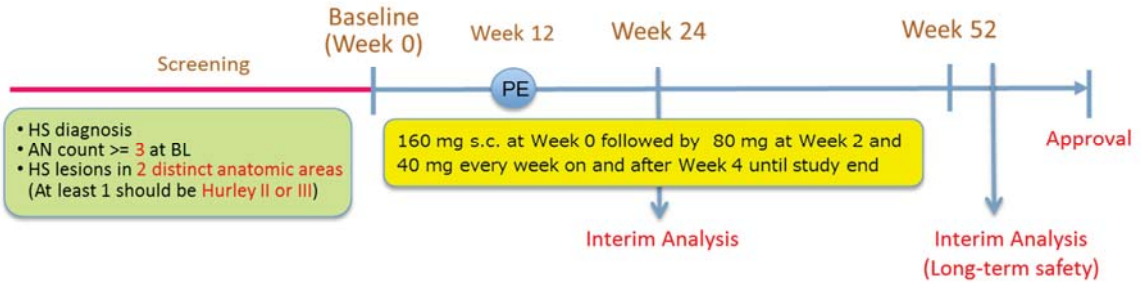
No study drug will be administered or injected at the final visit.

Subjects may discontinue treatment at any time during study participation. Subjects who prematurely discontinue the study, will have a Premature Discontinuation visit. All subjects will have a follow-up phone call approximately 70 days after the last administration of study drug to determine the status of any ongoing AEs or SAEs, or the occurrence of any new AEs or SAEs. The 70-day follow-up phone call will not be required for any subject who initiates adalimumab therapy not supplied in the context of the clinical trial after the end of study participation.

Subjects who 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 the assessment of an electrocardiogram (ECG) and a complete TB screen (PPD/QuantiFERON-TB Gold test or T-SPOT [or equivalent] and CXR), these tests will not be required to be repeated for the re screening visit provided the conditions noted in Section 5.3.1.1 are met and no more than 90 days have passed. Sites are encouraged to contact AbbVie TA MD to confirm if subjects should or should not be re screened.

A schematic of the study design is presented in Figure 1.

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 have none of the exclusion criteria specified in Section 5.2.2.

5.2.1 Inclusion Criteria

1. Male and female subjects ≥ 18 years of age at the Screening visit;
2. Subjects must have a diagnosis of HS;
3. Subjects must have any HS symptom at least 6 months prior to Baseline;
4. HS lesions must be present in at least two distinct anatomic areas (e.g., left and right axilla; or left axilla and left inguino-crural fold), one of which must be Hurley Stage II or Hurley Stage III;
5. Subject must have stable HS for at least 2 months (60 days) prior to Screening and also at the Baseline visit as determined by the investigator through subject interview and review of the medical history;
6. Subject must have a total abscess and inflammatory nodule (AN) count of greater than or equal to 3 at the Baseline visit;

7. If female, subject must be either postmenopausal, OR permanently surgically sterile, OR for Women of Childbearing Potential practicing at least one protocol specified method of birth control (Section 5.2.4), starting at Study Day 1 through at least 150 days after the last dose of study drug;
8. Females of childbearing potential must have a negative serum pregnancy test result at Screening, and negative urine pregnancy test prior to starting of study drug (at Study 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 has a negative tuberculosis (TB) Screening Assessment (including a PPD test or QuantiFERON-TB Gold test, or equivalent) 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 3 weeks of anti-TB therapy, or have documented completion of a course of anti TB therapy, prior to Baseline (Section 5.3.1.1);
10. Subject is judged to be in good general health, as determined by the Principal 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 Baseline;
11. Subject must be able and willing to self-administer subcutaneous (SC) injections or have a qualified person(s) who can reliably administer SC injections;
12. Subjects must voluntarily sign and date an informed consent, approved by an Independent Ethics Committee (IEC)/Institutional Review Board (IRB), prior to the initiation of any screening or study-specific procedures, and be able to comply with the requirements of this study protocol. If the subject is < 20 years old, a subject's parent or legal guardian must be willing to give written informed consent.

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 – 11	For the safety of the study subjects
12	In accordance with harmonized GCP

5.2.2 Exclusion Criteria

1. Prior treatment with adalimumab or other anti-TNF therapy (e.g., infliximab, etanercept), or participation in an adalimumab trial;
2. Any other active skin disease or condition (e.g., bacterial, fungal or viral infection) that may interfere with assessment of hidradenitis suppurativa;
3. Subject received antibiotic treatment for HS within 28 days prior to the Baseline visit other than those allowed per protocol. Subjects on permitted oral antibiotic treatment (doxycycline or minocycline only) for HS who have not been on a stable dose for at least 28 days prior to the Baseline visit (see Section 5.2.3 for permitted medications);
4. Subject received prescription topical therapies for the treatment of HS within 14 days prior to the Baseline visit;
5. Subject received systemic non-biologic therapies with potential therapeutic impact for HS less than 28 days prior to Baseline visit (other than permitted oral antibiotics – see Section 5.2.3);
6. Subject received oral concomitant analgesics (non-opioids and opioids) for HS-related pain within 14 days prior to the Baseline visit;
7. If entering the study on concomitant oral analgesics for non-HS-related pain:

- Subject on opioid analgesics within 14 days prior to Baseline visit (opioid analgesics are not allowed);
- Subject not on a stable dose of non-opioid oral analgesics for at least 14 days prior to the Baseline visit (PRN is not considered a stable dose).

8. Subject requires or is expected to require, opioid analgesics for any reason (excluding tramadol);
9. Subject has a draining fistula count of greater than 20 at the Baseline visit;
10. Subject has been treated with any investigational drug of chemical or biologic nature within a minimum of 30 days or 5 half-lives (whichever is longer) of the drug prior to the Baseline visit or is currently enrolled in another clinical study;
11. Prior exposure to biologics that have a potential or known association with PML (i.e., natalizumab [Tysabri®], rituximab [Rituxan®], or efalizumab [Raptiva®]);
12. Infection(s) requiring treatment with intravenous (IV) anti-infectives (antibiotics, antivirals, antifungals) within 30 days prior to Baseline or oral anti-infectives (antibiotics, antivirals, antifungals) within 14 days prior to Baseline, except as required as part of an anti-TB regimen;
13. History of moderate to severe congestive heart failure (New York Health Association [NYHA] class III or IV), recent cerebrovascular accident and any other condition which, in the opinion of the investigator would put the subject at risk by participation in the study;
14. History of demyelinating disease (including myelitis) or neurologic symptoms suggestive of demyelinating disease;
15. 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 including Hepatitis C that based on the investigator's clinical assessment makes 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 (Section 5.3.1.1);
18. Chronic recurring infections or active TB;
19. Known hypersensitivity to adalimumab or its excipients as stated in Section 5.5.2, Table 3.
20. Positive pregnancy test at Screening or Baseline;
21. Female subjects who is pregnant, breastfeeding or is considering becoming pregnant during the study and for approximately 150 days after the last dose of study drug;
22. 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;
23. History of clinically significant drug or alcohol abuse in the last 12 months;
24. Clinically significant abnormal screening laboratory results as evaluated by the investigator;
25. Subject is considered by the investigator for any reason, to be an unsuitable candidate for the study and not able to comply with the study protocol.
26. Subject currently has an adequate response to oral antibiotic treatment for HS.

Rationale for the Exclusion Criteria

1, 26	To avoid bias for the evaluation of safety and efficacy
2	To avoid enrollment of subjects who have concomitant skin disease that may interfere with HS assessment
3–8, 10	To avoid bias for the evaluation of safety and efficacy by concomitant use of other medications
9	Excludes the most severe forms of the disease that may place subjects at a higher risk

11, 15 – 19, 23 – 25	To ensure safety of the subjects throughout the study.
12, 22	To avoid a possibility of an infectious disease or a malignant tumor progression when administering an anti-TNF drug
13	To avoid a possibility of heart failure process 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
20, 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, but not limited to, over-the-counter or prescription medicines such as aspirin, antacids, vitamins, mineral supplements and/or herbal supplements) that the subject is receiving at the time of screening/enrollment, or receives during the study, must be recorded in the source and on the appropriate electronic case report form (eCRF), along with the reason for use, date(s) of administration including start and end dates, and dosage information including dose, route and frequency.

Prophylaxis treatment for TB (e.g., isoniazid) will be recorded. Even if a subject prematurely discontinues this study, the treatment should be continued for a certain period considering the best interest of the subject at the discretion of the Investigator. Any vaccine (except for live vaccine) administered during the study will be recorded in the eCRF as a concomitant medication.

The AbbVie TA MD identified in Section 6.1.5 should be contacted if there are any questions regarding prior, concomitant and/or prohibited therapy(ies).

In addition for patient's age ≤ 30 with a reported malignancy adverse event, prior exposure to, or current use of antineoplastics or other drugs which 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. At the time of the reported malignancy adverse event, sites 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.

5.2.3.1 Prior Therapy

Any treatments for HS since initial diagnosis (as determined through medical history records or through subject interview) prior to study entry will be recorded in the source and on the eCRF, along with the reason for discontinuation. A detailed history of prior antibiotic use for HS, response and reason for discontinuation will be collected.

For subjects previously treated with biologics other than anti-TNF therapy, the duration of therapy, maximum dose, reason for use and reason(s) for termination of treatment with these products should be documented.

5.2.3.2 Concomitant Therapy

Antiseptic Therapy

Use of any antiseptic washes for HS lesion is not allowed, except for the treatment of wound after lesion intervention (incision and drainage), described below.

Wound Care

Concomitant use of wound care dressings on HS wounds is allowed, and options are alginates, hydrocolloids, hydrogels, polyurethane film, polyurethane foam, hydrofiber and hydropolymer.

Antibiotic Therapy

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 Baseline (See Exclusion Criterion 3). The dosing regimen must remain stable throughout study participation. Antibiotics taken on an "as needed" (PRN) basis are not considered a stable dose.

Permitted oral concomitant antibiotics include:

- Oral:
  - doxycycline (at a dose of up to 100 mg po bid);
  - minocycline (at a dose of up to 100 mg po bid).

If another Baseline oral concomitant antibiotic for HS is medically necessitated, AbbVie TA MD must be contacted for approval.

Subjects taking permitted oral concomitant antibiotics for HS at Baseline (doxycycline or minocycline at a dose of up to 100 mg po bid, or other oral concomitant antibiotic previously approved by AbbVie TA MD) may continue their dose; however, starting, stopping or changing the dose is not allowed, with the following exceptions:

- If a subject develops an intolerance to the oral antibiotic, the antibiotic may be discontinued (see definition of Intolerance in Section 1.2).
- If at any time after Week 52, a subject achieves HiSCR, and the physician and subject mutually decide that the risk/benefit of continuing oral antibiotic is unfavorable, then the oral antibiotic dose may be reduced. Subject is not obligated to reduce the dose; rather, he/she has the option to reduce the dose. If at any time after dose reduction the subject experiences a loss of HiSCR response, subject may resume his/her previous antibiotic dose. This decrease/increase in dose is permitted one time only without prior contact with AbbVie TA MD. AbbVie TA MD should be contacted if additional dose adjustments are needed.

- If a subject is receiving an oral antibiotic dose less than the maximal permitted dose (e.g., doxycycline at a dose of up to 100 mg po bid or minocycline at a dose of up to 100 mg po bid) and if, at any time after Week 52, a subject does not achieve HiSCR response and the physician and subject mutually decide that the risk/benefit of increasing the oral antibiotic is favorable, then the subject may increase the dose up to the maximal permitted dose. Subject is not obligated to increase the dose; rather, he/she has the option to increase the dose. This increase in dose is permitted one time only. No decrease in dose is subsequently permitted, unless the subject develops an intolerance to the oral antibiotic, in which case he/she may either resume his/her previous dose, or discontinue the oral antibiotic.

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

Analgesic Therapy

Most subjects will be required to washout of all analgesics for 14 days prior to Baseline. This includes analgesics for HS-related pain and other pain (non-HS-related). However, if a subject is on a stable dose of a non-opioid analgesic (PRN is not considered stable) for a non-HS medical condition (e.g., osteoarthritis), the subject may continue the analgesic, provided the dose is stable for 14 days prior to Baseline and is anticipated to remain stable throughout study participation.

If a subject's pain (HS-related or non-HS-related) worsens after Baseline, they may initiate analgesic therapy at any time as follows:

For HS-related pain, permitted analgesics are limited to:

- ibuprofen (at a dose of up to 200 mg po TID) not to exceed 600 mg/day; AND/OR
- acetaminophen (at a dose of 300 – 1000 mg po every 4 to 6 hours) not to exceed 4000 mg/day; AND/OR

- If HS-related pain is uncontrolled with ibuprofen or acetaminophen at the above dosing regimens after the Baseline visit, subjects can be prescribed tramadol (at a dose of up to 100 mg po every 4 hours), not to exceed 400 mg/day

Dose adjustments of ibuprofen, acetaminophen, or tramadol, and use of these analgesics on an "as needed" (PRN) basis for HS-related pain up to the maximum permitted dose and frequency, are allowed during the study.

From Screening through Week 12, subjects will complete a daily diary of their analgesic use (Appendix G) using paper or an electronic diary. After Week 12 and subsequent designated visits including Premature Discontinuation visit, subjects will be required to report if they took any analgesics within 24 hours of their in-office visit at the time of Patient Global Assessment of Skin Pain. All analgesics and dose adjustments will be captured in the source and on the appropriate eCRF.

For non-HS-related pain:

- Opioid analgesics are prohibited
- All other analgesics (including tramadol) are allowed at the recommended or prescribed dose

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

Lesion Intervention

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

Only two types of interventions are allowed: injection with intralesional triamcinolone acetonide suspension (at a concentration of 50 mg/5 mL and up to 0.5 mL, or equivalent) and incision and drainage.

New systemic and topical therapies following incision and drainage (including antibiotics) are prohibited, except antiseptic wash limited for the wound intervened. Concomitant use of wound care dressings is allowed, however options are limited to shown in Section 5.2.3.2. Subjects should continue using any ongoing oral therapies (including antibiotics, with the constraints as described in Section 5.2.3.2) 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 captured in the source and on the appropriate eCRF.

A total of two protocol-allowed interventions are permissible until Week 12. 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 (i.e., two types of intervention) at the same visit. If a subject requires more than two interventions within the first 12 weeks, then they must be discontinued from the study.

After Week 12 until the study end, 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 period, then he or she must be discontinued from the study.

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

HS Surgery

In the event a subject undergoes a surgical procedure for medically irreversible stigmata of chronic HS (i.e., non-draining fistula, sinus tract, or hypertrophic scarring) after

Week 52, the procedure and other surgery detail must be collected on the appropriate eCRF.

As with lesion interventions, the site will be required to count any lesion that undergoes an HS surgical procedure as permanently present from the date of the procedure and must account for it in the source and on the appropriate eCRF.

Study Drug

Study drug administration will be documented in a separate section of the eCRF.

5.2.3.3 Prohibited Therapy

The following treatments are prohibited for all subjects during the study:

- Phototherapy (PUVA and/or UVB)
- All biologic therapy with a potential therapeutic impact on the disease being studied, including but not limited to the following:
  - Abatacept (Orencia®)
  - Anakinra (Kineret®)
  - Natalizumab (Tysabri®)
  - Ustekinumab (Stelara®)
  - Etanercept (Enbrel®)
  - Infliximab (Remicade®)
  - Rituximab (Rituxan®)
  - Tocilizumab (Actemra®)
  - Efalizumab (Raptiva®)
  - Golimumab (Simponi®)
  - Certolizumab (Cimzia®)
  - Belimumab (Benlysta®)
  - Secukinumab (Cosentyx®)
  - Ixekizumab (Taltz®)

- Brodalumab
- Vedolizumab

- Any investigational agents
- Any other systemic drug therapies for HS, including but not limited to antibiotics (except as specified in Section 5.2.3.2), methotrexate (MTX), cyclosporine, retinoids, fumaric acid esters, and JAK inhibitors
- Live vaccines (during the study and for 70 days after the last dose of study drug)
- Oral or injectable corticosteroids (except as allowed per Section 5.2.3.2)
- Oral analgesics for HS not listed in Section 5.2.3.2
- Oral opioid analgesics
- New prescription topical therapies for HS
- Over-the-counter topical antiseptic washes, creams, soaps, ointments, gels and liquids containing antibacterial agents to treat HS
- Surgical or laser intervention for an HS lesion except as outlined in Section 5.2.3.2

The investigator should contact AbbVie TA MD identified in Section 1.0 if there are any questions regarding concomitant or prior therapy.

5.2.4 Contraception Recommendations

A woman who is postmenopausal or permanently surgically sterile (bilateral oophorectomy, bilateral salpingectomy or hysterectomy) is not considered to be a woman of childbearing potential and is not required to follow contraception recommendations.

Postmenopausal is defined as:

- Age > 55 years with no menses for 12 or more months without an alternative medical cause; or
- Age < 55 years with no menses for 12 or more months without an alternative medical cause AND an FSH level > 40 IU/L.

A woman who does not meet the definition of postmenopausal or permanently surgically sterile is considered a woman of childbearing potential and is required to practice at least one of the following highly effective method of birth control, on Study Day 1 (or earlier) through at least 150 days after the last dose of study drug.

- Combined (estrogen and progestogen containing) oral hormonal contraception associated with the inhibition of ovulation, initiated at least 1 month prior to Study Day 1.
- Progestogen-only oral hormonal contraception associated with inhibition of ovulation, initiated at least 1 month prior to Study Day 1.
- Bilateral tubal ligation.
- Vasectomized partner(s), provided the vasectomized partner has received medical assessment of the surgical success and is the sole sexual partner of the WOCBP trial participant.
- Intrauterine device (IUD).
- Intrauterine hormone-releasing system (IUS).
- True abstinence: Refraining from heterosexual intercourse when this is in line with the preferred and usual lifestyle of the subject (periodic abstinence [e.g., calendar, ovulation, symptothermal, post-ovulation methods] and withdrawal are not acceptable)

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 excluding true abstinence.

5.3 Efficacy, Pharmacokinetic, and Safety Assessments/Variables

Study procedures will be performed at the designated study visits listed in Table 1.

5.3.1 Safety and Efficacy Measurements Assessed and Flow Chart

Table 1. Study Activities

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

Table 1. Study Activities (Continued)

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

Table 1. Study Activities (Continued)

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

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

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

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

e. Height will be measured at Screening only.

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

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

h. Refer to the laboratory manual for further instructions.

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

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

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

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

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

Table 1. Study Activities (Continued)

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

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

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

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

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

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

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

5.3.1.1 Study Procedures

The study procedures outlined in Table 1 are discussed in detail in this section, with the exception of the collection of prior and concomitant medication information (Section 5.2.3), drug concentration measurements (Section 5.3.2) and the collection of AE information (Section 6.1). All study data will be recorded in source documents and on the appropriate eCRFs.

Informed Consent

An Independent Ethics Committee (IEC)/Institutional Review Board (IRB) approved, study-specific informed consent 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. Written consent will be required for each subject in order to take photography of the skin lesion. Subjects can withdraw informed consent at any time.

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, Alcohol and Nicotine Use

A complete medical history (which includes HS-related and non-HS-related medical and surgical history), including history of alcohol and tobacco (nicotine) use, will be obtained from each subject during the Screening visit. Tabacco use will be checked also at Week 12 and Final/PD visit. The medical history should also include a detailed history of

prior therapies used to treat HS, including antibiotics. The prior doses and reasons for discontinuation of antibiotic therapy will be recorded. Medical history will be reviewed and updated at the Baseline visit to ensure that 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.

Physical Examination

A full physical exam will be performed at the designated study visits listed in Table 1. 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.

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

Chest X-ray (CXR)

All subjects will undergo a standard CXR (posterior-anterior [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 chest x-ray within 90 days of Screening, provided all protocol required documentation is available at the site (as outlined below).

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

In the assessment of the CXR, a radiologist or internist must specifically note the presence or absence of 1) calcified granulomas, 2) pleural scarring/thickening, and 3) signs of active TB. The Principal Investigator will indicate the clinical significance of any findings and will sign and date the report.

Subject will have a repeat CXR at Final visit or at the Premature Discontinuation visit, only if in the opinion of the investigator, clinically significant AEs develop during the study that warrant a repeat exam. If subject successfully continues at Week 52, CXR will be performed.

Electrocardiogram (ECG)

A resting 12-lead ECG will be performed at the designated study visits listed in Table 1. 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 using the following conventions as appropriate: Normal, Abnormal – not clinically significant, Abnormal – clinically significant, or Unable to evaluate. Each signed original ECG will be monitored by the responsible Monitor and kept with subject's source documents onsite.

Subject will have a repeat ECG at Final visit or at the Premature Discontinuation visit, only if in the opinion of the investigator, clinically significant AEs develop during the study that warrant a repeat exam. If subject successfully continues at Week 52, ECG testing will be performed.

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 Principal Investigator must contact AbbVie TA MD before enrolling the subject.

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

TB Screening/TB Prophylaxis

The TB screening tests are diagnostic test results to be interpreted in the context of the subject's epidemiology, history, exam findings, etc., and it is the responsibility of the Investigator to determine if a subject has previous, active, or latent TB.

At Screening, all subjects will be assessed for evidence of increased risk for TB by a risk assessment form (Appendix C) and tested for TB infection by an Interferon-Gamma Release Assay (IGRA; QuantiFERON®-TB Gold, T-spot, or equivalent). The PPD skin test should be utilized only when an IGRA is not possible for any reason. The site staff will complete the TB risk assessment form and enter the data into an appropriate eCRF. The assessment for TB risk and TB test will be repeated at Week 52.

- QuantiFERON®-TB Gold Test will be analyzed by the central laboratory (QuantiFERON® test is preferred over PPD skin test).
- If the QuantiFERON®-TB Gold Test is NOT possible: the PPD skin test (also known as a TB skin test) will be performed according to standard clinical practice. The TB skin test should be read by a licensed healthcare professional between 48 and 72 hours after administration. A subject who does not return within 72 hours will need to be rescheduled for another skin test. The reaction will be measured in millimeters (mm) of induration and induration ≥ 5 mm is considered a positive reaction. The absence of induration will be recorded as "0 mm" not "negative." Subjects who have had an ulcerating reaction to the TB skin test in the past should not be re-exposed and should not be tested by a PPD skin test.

If a subject had a negative QuantiFERON®-TB Gold (and/or PPD) test (or IGRA equivalent such as T-SPOT TB test) within 90 days prior to Screening and source 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. The results of the TB test(s) will be retained at the site as the original source documentation.

In the event both a PPD test and a QuantiFERON®-TB Gold test (or equivalent) are performed, the result of the QuantiFERON®-TB Gold test will supersede the result of the PPD test unless otherwise required by local guidelines. If the QuantiFERON®-TB Gold test is indeterminate, the site should repeat the test with another blood sample and/or perform a PPD test. If the second QuantiFERON®-TB Gold test is also indeterminate, the subject is considered to be positive.

Subjects with a negative QuantiFERON®-TB Gold test (and/or negative PPD TB skin test) and chest x-ray (CXR) not suggestive of active TB or prior TB exposure may be enrolled.

If the subject has evidence of latent TB infection (QuantiFERON®-TB Gold test and/or the PPD test positive) and has a CXR not suggestive of active TB, prophylactic treatment must be initiated at least 3 weeks prior to administration of study drug per local guideline in Japan. The prophylaxis needs to be completed, however, the full course of prophylaxis does not need to be completed prior to the first dose of study drug.

Subjects with a prior history of latent TB that have documented completion of a full course of anti-TB therapy within 1 year prior to first study drug administration will be allowed to enter the study provided nothing has changed in the subject's medical history to warrant repeat treatment.

Subjects with documented completion of a full course of anti-TB therapy greater than 1 year prior to first study drug administration may be allowed to enter the study only after consultation with the AbbVie TA MD.

Newly initiated prophylactic treatment should be captured in the eCRF and in the source documents. Prior therapy should be captured in the eCRF.

Vital Signs

Vital sign determinations of systolic and diastolic blood pressure, pulse (counted for at least 30 seconds after 5 minutes in sitting position), respiratory rate, body weight, and body temperature will be obtained at each visit. Blood pressure and pulse should be performed before blood draws are performed. Height will be measured at the Screening visit only.

Pregnancy Tests

A serum pregnancy test will be performed at the Screening visit on all female subjects of childbearing potential by the central laboratory. At the Baseline visit and at the

designated study visits listed in Table 1, all female subjects of childbearing potential will have a urine pregnancy test by the central laboratory.

Urine pregnancy test at the Baseline will be performed also at the site to confirm negative result on site prior to start of study drug. If the result is positive, treatment with study drug must not be started until the serum pregnancy test at the central laboratory is confirmed negative.

If any urine pregnancy test is positive, a serum pregnancy test will be analyzed by the central laboratory. At each visit, the study staff should review the pregnancy avoidance recommendations with each subject of childbearing potential.

A pregnant or breastfeeding female will not be eligible for participation or continuation in this study.

Females of non-child bearing potential (either postmenopausal or permanently surgically sterile, defined as in Section 5.2.4) at Screening do not require pregnancy testing.

Clinical Laboratory Tests

Samples will be obtained for the laboratory tests listed in Table 2 at the designated study visits listed in Table 1. 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 investigator will be followed to a satisfactory resolution.

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

Urinalysis

Urine samples will be obtained for urinalysis as noted in Table 1. For samples with abnormal macroscopic results, or in the event the dipstick results show protein, ketones or blood greater than negative or glucose greater than normal, or in the case or abnormal macroscopic results, a microscopic test will be performed.

C-reactive Protein (CRP) Testing

Testing for CRP will be performed on specimens collected at the designated study visits listed in Table 1.

Human Immunodeficiency Virus (HIV) Testing

Subjects with a known history of HIV infection are excluded from study participation. Subjects will be tested for antibodies to the Human Immunodeficiency Virus (HIV) at Screening, and document that the test has been performed. The testing is to be done at the Central 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.

Table 2. Clinical Laboratory Tests

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

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

Hepatitis B Screening

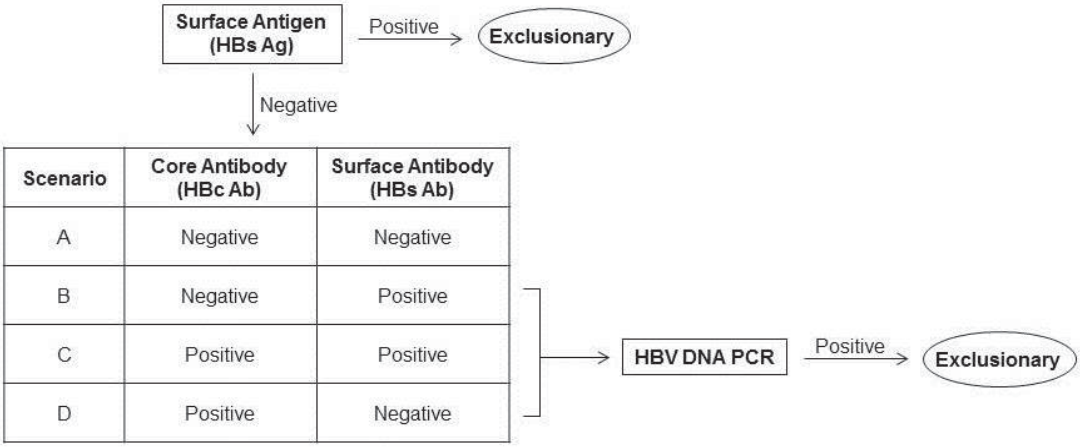
All subjects will be tested for the presence of the hepatitis B virus (HBV) at Screening. A positive result for the hepatitis B surface antigen (HBsAg) will be exclusionary. Samples negative for HBsAg will be tested for surface antibodies (HBsAb) and core antibodies

(HBcAb). If test results are positive for HBcAb or HBsAb, then HBV DNA PCR will be performed and any result that meets or exceeds detection sensitivity will be exclusionary.

- A negative test result for HBc Ab and HBs Ab does not require HBV DNA PCR qualitative testing and the subject may be enrolled (Figure 2, Scenario A).

  For a subject who has had a HBV vaccination (should document in the medical history), a positive test result for HBs Ab is expected and the subject may be enrolled.
- A positive test result for HBc Ab or HBs Ab requires HBV DNA PCR testing (automatic reflex testing) (Figure 2, Scenarios B, C and D).
  - A positive result for HBV DNA or a result that exceeds detection sensitivity will be exclusionary.
  - A subject with a negative result for HBV DNA may be enrolled.

Figure 2. Criteria for HBV DNA PCR Qualitative Testing



Hepatitis C Screening

All subjects will be tested for the presence of the Hepatitis C Virus (HCV) at Screening. A positive result for the hepatitis C will be exclusionary.

HbA1c

All subjects will be tested for HbA1c at the designated study visits listed in Table 1.

PK and AAA Measurement

See Section 5.3.2.

Antinuclear Antibody (ANA)/Anti-dsDNA Testing

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

All samples will be sent to the central laboratory for processing.

Dermatology Life Quality Index (DLQI)

Subjects will complete a DLQI questionnaire (Appendix D) at the designated study visits listed in Table 1. 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 'the last week.' Decreased scores indicate improved health-related quality of life.

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

EuroQoL (EQ-5D)

Subjects will complete the EQ-5D questionnaire (Appendix E) at the designated study visits listed in Table 1. 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 site personnel perform any clinic assessments and before any interaction with the site personnel has occurred to avoid biasing the subject's response.

Patient Global Assessment of Skin Pain (Numeric Rating Scale)

The Patient Global Assessment of Skin Pain (Appendix F) will be completed on a daily diary by subjects from Screening through Week 12. If pain diaries are not completed for at least the seven consecutive days just prior to the Baseline visit, the subject may not be qualified.

The Patient Global Assessment of Skin Pain will be used to assess the worst skin pain and the average skin pain due to HS. Ratings for the two items will range from 0 (no skin pain) to 10 (skin pain as bad as you can imagine). For the daily assessments being completed from Screening to Week 12, subjects should be instructed to complete the assessment before they go to bed, and respond to the items based on a recall period of the "last 24 hours."

No in-office assessment of skin pain will be completed at the Week 12 visit. At the designated study visit after Week 12 until Final visit or Premature Discontinuation visit listed in Table 1, subjects will complete skin pain assessments in the office based on a recall period of the last 24 hours. For these in-office assessments, the subject should complete the assessment before site personnel perform any clinic assessments and before any interaction with the site personnel has occurred to avoid biasing the subject's response.

Patient's Diary

Sites should adhere to the following schedule when dispensing of paper diaries and collecting daily pain assessments by completing them;

- Screening visit: Dispense Booklet and instruct subject on completion of daily pain assessments beginning at bedtime the day of the Screening visit through bedtime, the day prior to the Baseline visit;
- Baseline visit: Collect assessments that were completed beginning at bedtime the day of the Screening visit through bedtime, the day prior to the Baseline visit. Dispense Booklet and instruct subject on completion of daily pain assessments beginning at bedtime the day of the Baseline visit through bedtime, the day prior to Week 2 visit;
- Week 2 visit: Collect assessments that were completed beginning at bedtime the day of the Baseline visit through bedtime, the day prior to Week 2. Instruct subject continuously on completion of daily pain assessments beginning at bedtime the day of the Week 2 visit through bedtime, the day prior to Week 4 visit;
- Week 4 visit: Collect assessments that were completed beginning at bedtime the day of the Week 2 visit through bedtime, the day prior to Week 4. Dispense Booklet and instruct subject on completion of daily pain assessments beginning at bedtime the day of the Week 4 visit through bedtime, the day prior to Week 8 visit;
- Week 8 visit: Collect assessments that were completed beginning at bedtime the day of the Week 4 visit through bedtime, the day prior to Week 8. Dispense Booklet and instruct subject on completion of daily pain assessments beginning at bedtime the day of the Week 8 visit through bedtime, the day prior to Week 12 visit;
- Week 12 visit: Collect assessments that were completed beginning at bedtime the day of the Week 8 visit through bedtime, the day prior to Week 12.

Subjects should bring the paper diary to each visit. Data collected using the paper diary will be entered by the site into the EDC system and will be available for viewing by site personnel. Subjects will use paper diaries to complete pain assessments and document analgesic use, and site personnel have been appropriately trained.

See Section 10.0 for a description of source documents and case report form completion.

Analgesic Use

From Screening through Week 12, subjects will complete a daily diary of their analgesic use (Appendix G) using paper diary. At the subsequent designated visits including Premature Discontinuation visit after Week 12, subjects will be required to report if they took any analgesics within 24 hours of their in-office visit at the time of Patient Global Assessment of Skin Pain. All analgesics and dose adjustments will be captured in the source and on the appropriate eCRF.

HS Quality of Life (HS QOL)

Subjects will complete the HS QoL questionnaire (Appendix H) at the designated study visits listed in Table 1. The HS QoL item will be used to assess the quality of life with HS. Ratings for the items will range from 0 (worst possible) to 10 (best possible). The subject should complete the questionnaire before site personnel perform any clinic assessments and before any interaction with the site personnel has occurred to avoid biasing the subject's response.

Treatment Satisfaction Questionnaire – Medication (TSQM)

Subjects will complete the TSQM questionnaire (Appendix I) at the designated study visits listed in Table 1. 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 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.

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 (right/left axilla,

right/left inframammary, intermammary, right/left buttock, right/left inguino-crural fold, perianal, perineal, other) will be recorded at the designated study visits listed in Figure 1 (Appendix J).

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.

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

Hurley Stage

See Section 1.3 for definition. The investigator will determine the Hurley Stage in each affected anatomical region at the designated study visits listed in Table 1. If more than one stage is present in a region, the worst stage in each region should be entered.

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

Degree of Erythema

At the designated study visits listed in Table 1, for each anatomic region affected by HS, the investigator will assess the overall degree of erythema (Appendix K) affecting this region on a four-point ordinal scale, ranging between 0 (no redness), 1 (faint but discernible pink coloration), 2 (moderate red coloration), or 3 (very red or bright red coloration).

Follow-up Calls

One Week Prior to the Baseline Visit

Sites are encouraged to contact Subjects 1 week prior to the Baseline visit to confirm compliance with daily pain collection. The phone call will be recorded in source document.

One Week Following the Baseline Visit

Subjects will be contacted 1 week following the Baseline visit to ensure daily pain assessments are being recorded. The phone call will be recorded in source document.

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. The phone calls will be recorded in source document. Subjects with signs or symptoms of an infection will be brought into the study site for an unscheduled visit to be evaluated. Study procedures for an unscheduled visit will be performed as outlined in Table 1.

70 Days Following the Last Dose of Study Drug

Subjects will be contacted approximately 70 days following the last dose of study drug to determine the status of any ongoing AEs or SAEs, or the occurrence of any new AEs or SAEs. The Day 70 follow-up phone call will be recorded in source document only and confirmation of the contact will be submitted to AbbVie (Appendix L). Any updates to ongoing AEs/SAEs, or new AEs/SAEs, should be submitted on the eCRF. Information on any ongoing or new AEs/SAEs will be included in the database for the study.

Photography

Subjects at prospectively selected sites will be asked to have photographs taken of their disease response during the study. Subjects who consent will have photographs taken at the designated study visits listed in Table 1. Photographs will be taken by procedures standardized by each site in the daily clinical practice. Sites will submit the digital images to AbbVie.

Adverse Events

See Section 6.1.

Dispense Study Drug

Study drug will be dispensed to subjects, who perform self-injection or receive the subcutaneous injection of study drug by a qualified person at the designated study visits listed in Table 1.

5.3.2 Drug Concentration Measurements

Blood samples for adalimumab and Anti-Adalimumab Antibody (AAA) assays will be collected by venipuncture at the designated study visits listed in Table 1.

5.3.2.1 Collection of Samples for Analysis

Blood samples for pharmacokinetic (PK) adalimumab analysis will be collected by venipuncture into appropriately labeled 6-mL evacuated serum collection tubes without gel separator at the required visits. All samples will be obtained prior to study drug administration at the designated study visits listed in Table 1 (Baseline, Weeks 2, 4, 8, 12, 16, 20, 24, 36, and 52, or at the Premature Discontinuation visit if the subject discontinues prior to Week 52).

Blood samples for AAA will be collected by venipuncture into appropriately labeled 6 mL evacuated serum collection tubes without gel separator at the required visits. All samples will be obtained prior to dosing at the designated study visits listed in Table 1 (Baseline, Weeks 4, 12, 24, 36, and 52, or at the Premature Discontinuation visit if the subject discontinues prior to Week 52).

The date and time that each blood sample is collected will be recorded to the nearest minutes in the source document and on the appropriate eCRF.

Collection of Samples for Adalimumab Analysis

A maximum of 10 samples are planned to be collected per subject for PK adalimumab analysis. The total number of PK adalimumab samples planned will not exceed

150 (10 samples × 15 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 6 samples are planned to be collected per subject for AAA analysis. The total number of AAA samples planned will not exceed 90 (6 samples × 15 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 2 mL serum from each sample. Allow the blood to clot for 30 minutes at room temperature before centrifugation.

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

5.3.2.3 Disposition of Samples

The frozen serum samples will be packed in dry ice (pellet form) sufficient to last 3 days during transport. Samples will be shipped by central laboratory pursuant to instructions from the sponsor. An inventory of the samples will be included in the package for shipment.

5.3.2.4 Measurement Methods

Serum concentrations of adalimumab and AAA will be determined using a validated assay methodology (Ligand Binding Assay, LBA) under the supervision of the Drug Analysis Department at AbbVie.

5.3.3 Efficacy Variables

5.3.3.1 Primary Variable

The primary efficacy endpoint is the proportion of subjects achieving HiSCR at Week 12. HiSCR is defined as at least a 50% reduction in the total abscess and inflammatory nodule

count (AN count) with no increase in abscess count and no increase in draining fistula count relative to Baseline.

5.3.3.2 Secondary Efficacy Variables

The following secondary efficacy variables will be analyzed:

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

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

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

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

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

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 Table 1 and as described in Section 6.0 and Table 2.

5.3.5 Pharmacokinetic Variables

Adalimumab trough serum concentrations will be summarized at each time point using descriptive statistics.

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 investigator may discontinue any subject's participation for any reason, including an adverse event, safety concerns or 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 investigator in consultation with AbbVie TA MD.
- The investigator believes it is in the best interest of the subject.
- The subject requests withdrawal from the study.
- Inclusion and exclusion criteria violation is noted after the subject started study drug, when continuation of the study drug would place the subject at risk as determined by AbbVie TA-MD (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 AbbVie TA MD.
- Subject is non-compliant with TB prophylaxis.
- The subject becomes pregnant while on study medication.
- Subject has known dysplasia of the gastrointestinal tract (a colonoscopy is not required to enter the study) or a malignancy, except for localized non melanoma skin cancer. Discontinuation for carcinoma in-situ of the cervix is at the discretion of the investigator.
- Subject is diagnosed with lupus-like syndrome, multiple sclerosis or demyelinating disease.
- Subject is significantly non-compliant with study procedures which would put the subject at risk for continued participation in the trial, as determined by the investigator, in consultation with AbbVie TA MD.
- Subject requires or receives more than 2 interventions until Week 12.

- Subject requires or receives more than 2 interventions on the same lesion or 2 of the same type of intervention on the same lesion within a 4-week period after Week 12.

If, during the course of study drug administration, the subject prematurely discontinues study drug use, the procedures 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 investigator feels are necessary to treat the subject's condition. Following discontinuation of the study drug, the subject will be treated in accordance with the investigator's best clinical judgment.

A final phone call will be made to the subject approximately 70 days after the last dose of study drug to determine the status of any ongoing AEs/SAEs or the occurrence of any new AEs/SAEs. The Day 70 follow-up phone call will not be required for any subject who initiates adalimumab therapy not supplied in the context of the clinical trial after the end of study participation.

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 in the source and 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 phone 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 investigator may also terminate the study at his/her 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 investigator by phone 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 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 by the interactive response technology (IRT). All subjects will receive 4 injections at Week 0 (160 mg), 2 injections at Week 2 (80 mg) and 1 injection weekly from Week 4 (40 mg) until the study end.

Study drug will be provided as a sterile, preservative-free solution for SC administration solution in 1 mL pre-filled syringes containing adalimumab 40 mg/0.4 mL. Study drug will be administered subcutaneously using sterile technique by the research staff or qualified designee (health care professional, or patient him/herself or family member following proper training) at the study site or at home.

5.5.2 Identity of Investigational Product

The individual study drug information is presented in Table 3.

Table 3. Identity of Investigational Product

Study Drug	Formulation	Manufacturer
Adalimumab	40 mg/0.4 mL pre-filled syringes Adalimumab/Mannitol, Polysorbate 80, Water for injection,	AbbVie

Study drug is not blinded in this study. As per country regulations, investigational product (IP) will be labeled with the following information:

- Sponsor's name and address
- Study protocol number
- Study drug name
- Storage conditions
- Manufacturing number
- Display of "for clinical trial"

Each site will be responsible for tracking the lot numbers and expiration dates for all non-investigational medicinal products that are dispensed.

5.5.2.1 Packaging and Labeling

Investigational product will be provided in a 0.4 mL pre-filled syringe containing adalimumab 40 mg/0.4 mL and will be packaged in two pre-filled syringes per carton. Each adalimumab kit carton and syringe will be labeled and have a unique kit ID on the carton. The labels for the adalimumab 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 medication 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. Study medication should be quarantined and not dispensed until AbbVie GPRD or AbbVie Temperature Excursion Management System (ATEMS) deems the medication 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.

Investigational 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 Group

Before the site is initiated, the instructions for 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.

5.5.4 Selection and Timing of Dose for Each Subject

Subjects should take study medication as outlined in Section 5.5.1.

At Baseline, after all assessments have been completed, subjects will receive four injections of study drug (40 mg each) as detailed in Section 5.5.1. Appropriate site personnel will train and then supervise the subject or designee administering at least one injection of the study drug at the Baseline visit to ensure proper understanding of injection technique, if the subject wants to perform self-injection of the study drug (Appendix M). Subject or designee will subsequently dose and be witnessed by site staff during their study visits to ensure continued proper technique. When study drug is administered in the office, subjects should remain at the site for approximately 15 to 30 minutes after injection for observation.

For home administration of injections, 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 forgets to administer the injection of study medication at their regularly scheduled dosing date, they should take the forgotten injection as soon as she/he remembers the dose was missed up to the day of their next scheduled dose. The subject should not administer two doses on the same day, except at Week 2.

In the event the incorrect dose is taken, the entire volume of study medication is not injected, or a dose is missed, the subject should contact the site to determine how to proceed with dosing. The subject must record all dosing information on the subject-dosing sheet.

Doses not administered (e.g., not taken before next dose is scheduled) should be recorded in the source documentation as not taken. The unused dose should be returned full to the study site, and the subject should administer the next regularly scheduled dose. The subject should then resume their regular dosing schedule based on the first dosing date at Baseline (Week 0).

5.5.5 Treatment Compliance

The investigator or his/her designated and qualified representatives will dispense study drug only for use by 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 their qualified designee will administer all doses of study drug when not at the site. Appropriate site staff will supervise the subject's administration of the study drug at required in-office study visits to ensure proper injection technique. In order to document compliance with the treatment regimen, the subject will be given a dosing sheet (Appendix N) to record all injection dates and times. Compliance information will be documented on the appropriate eCRF. Subjects will be counseled on missed doses of medication.

If the subject does not return the dosing sheet, IP boxes and sharp containers (when applicable), the site 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 subjects are consistently not returning the dosing sheet, not providing accurate dosing information, or consistently missing doses and/or are deemed non-compliant with no explanation, the situation will be discussed with AbbVie TA MD and the subject may be discontinued from the study.

5.5.6 Drug Accountability

The 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 the 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 Note or similar document will be kept in the site files as a record of what was received.

In addition, an accurate running inventory of study drug will be kept by the 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, kit number(s), date dispensed, subject number, and the identification with date of the person dispensing the drug.

For Subjects Dosing at Home (Self-Injection)

Each subject will be given his/her own sharps disposal container to store used pre-filled syringes. Empty IP boxes and returned Sharps containers should be returned by the subject at each visit for accountability and compliance purposes and new containers issued as necessary. Empty Boxes and returned Sharps containers will be retained (unless

prohibited by local law or site regulation) until the Monitor is on site to confirm the returned medication. Monitors and site staff will complete study medication accountability via study medication logs, source documents, subject dosing sheets, empty IP boxes and by visually inspecting the syringes in the Sharps container whenever possible. Used Sharps containers should never be opened. Once the Monitor has verified drug accountability at the site, the site staff and Monitor will document that the used pre-filled syringes have been destroyed, using appropriate biohazard precautions, when appropriate. If the destruction of the used study drug is not feasible at the site, the site staff or Monitor will send them to the destruction facilities designated by AbbVie. A copy of the destruction methodology should be maintained at the site's facility or kept by AbbVie. Unused medication will be returned by the Monitor after drug accountability has been completed at the site.

Non-investigational medicinal products (standard of care) must be obtained commercially by each site.

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 was chosen to evaluate adalimumab in subjects with moderate to severe HS. The first 12-week period (Weeks 0 to 12) is to provide clinical data demonstrating the safety and efficacy of adalimumab 160 mg at Week 0 and 80 mg at Week 2 and 40 mg weekly starting at Week 4 for treatment of HS. The subsequent period (after Weeks 12 until the study end) is to provide information on long-term safety and maintenance of efficacy for subjects on adalimumab weekly dosing. This is a single arm study and no control group is set.

5.6.2 Appropriateness of Measurements

Standard statistical, clinical and laboratory procedures will be utilized in this study. Efficacy measurements in this study have been selected or designed to assess disease

activity in subjects with chronic HS. 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 (abscess and inflammatory nodule count of greater than or equal to 3) who meet all inclusion criteria and who do not meet any of the exclusion criteria are eligible for this study. The population being studied represents normal clinical practice with a broad spectrum of subjects with a high medical need due to great physical disability and discomfort. This ensures the activity of adalimumab can be evaluated across a distribution of disease severity in the study.

5.6.4 Selection of Doses in the Study

In the global Phase 3 Studies M11-810 and M11-313, used dosing regimen (40 mg weekly starting at Week 4, after 160 mg at Week 0 and 80 mg at Week 2) was demonstrated the statistical superiority of efficacy compared to placebo. Assessment of the comparative safety and efficacy of ew dosing and eow dosing confirmed that ew dosing provides a better benefit risk balance in the treatment of HS, based on the better efficacy with ew dosing and on the fact that the AE profile for ew dosing, eow dosing, and placebo in the Phase 3 studies were similar over the next 24 week placebo controlled period.

The amount of safety data to be generated, along with the existing safety data generated in the existing other indications (Western patients with HS, Japanese patients with UC and CD for the initial high dose at Baseline and Week 2, and dose escalation to 80 mg eow in Japanese patients with RA, AS and Ps for the maintenance dose, where PK of 40 mg ew is comparable to that of 80 mg eow), supports the proposed indication with the proposed dose regimen.

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 investigational product in this trial contains both

- Biologic compound and
- Device components (pre-filled syringe)

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

6.1 Medical Complaints

The Investigator will monitor each subject for clinical and laboratory evidence of AEs on a routine basis throughout the study. The 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 SAEs considered as having "no reasonable possibility" of being associated with study drug, the Investigator will provide other cause(s) of the event. For AEs to be considered intermittent, the events must be of similar nature and severity. AEs, whether in response to a query, observed by 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 (investigational) 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 AE should be reported as a new AE. Laboratory abnormalities and changes in vital signs are considered to be AEs only if they result in discontinuation from the study, necessitate therapeutic medical intervention, (meets protocol specific criteria [see Section 6.1.7 regarding toxicity management]) and/or if the investigator considers them to be AEs.

An elective surgery/procedure scheduled to occur during the study will not be considered an AE if the surgery/procedure is being performed for a pre-existing condition and the surgery/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.

6.1.1.2 Serious Adverse Events

If an AE meets any of the following criteria, it is to be reported to AbbVie as an SAE within 24 hours of the 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 still birth 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.

6.1.2 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.

The CTCAE v4.0 – JCOG (Japanese translation JCOG version on 09 April 2013) can be used as a reference as appropriate.

6.1.3 Relationship to Study Drug

The Investigator will use the following definitions to assess the relationship of the AE 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 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 SAE.

6.1.4 Adverse Event Collection Period

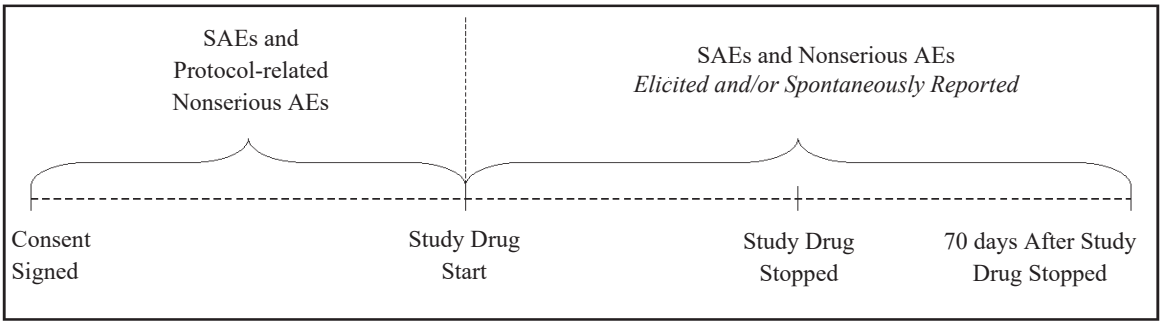
All AEs reported from the time of study drug administration until approximately 70 days following discontinuation of study drug administration have elapsed, as well as the medication for AEs/SAEs, will be collected, whether solicited or spontaneously reported by the subject. In addition, SAEs and protocol-related 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 be contacted approximately 70 days following study drug discontinuation for an assessment of any new or ongoing AEs/SAEs (Appendix L) as discussed in protocol Section 5.3.1.1, except for those subjects who initiate adalimumab therapy 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 call and any new AEs should be reported through the mechanism used for all post-marketing adverse experiences.

All SAEs or Adverse Events of Special Interest, as defined by AbbVie, reported during the 70 day follow-up phone call must be captured in the clinical database.

Adverse event information will be collected as shown in Figure 3.

Figure 3. Adverse Event Collection



6.1.5 Adverse Event Reporting

In the event of a SAE, and additionally, any non-serious event of malignancy in patients 30 years of age and younger, whether related to study drug or not, the Investigator will notify Clinical Pharmacovigilance within 24 hours of the site being aware of the event by entering the SAE or non-serious event of malignancy in patients 30 years of age and younger data into the RAVE® electronic data capture (EDC) system. SAEs and non-serious events of malignancy in patients 30 years of age and younger, that occur prior to the site having access to the RAVE® system, or if the RAVE® system is not operable, should be documented on the SAE Non-case report form and emailed (recommended) or faxed to Clinical Pharmacovigilance within 24 hours of being made aware of the serious adverse event.

Email:	[redacted]
FAX to:	[redacted]

For safety concerns, contact Medical Science Group at:

[redacted]

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

Primary Therapeutic Area Medical Director:

Secondary Contact (Regional Medical Monitor):

In emergency situations involving study subjects when the primary Therapeutic Area Medical Director (TA-MD) is not available by phone, please contact the 24-hour AbbVie Medical Escalation Hotline where your call will be re-directed to a designated backup AbbVie TA MD:

Phone: 

The Principal Investigator will provide documentation of all SAEs to the Director of the investigative site and the Sponsor.

6.1.6 Pregnancy

Pregnancy in a study subject must be reported to AbbVie within 1 working day of the 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 site becoming aware of the event.

6.1.7 Toxicity Management

Subjects who develop a new infection while undergoing treatment with study drug should be monitored closely. Administration of study injections should be interrupted if a subject develops an infection requiring IV anti-infective treatment or if an infection meets the definition of "serious" (refer to Section 6.1.1.2 for definitions). Study medication may be restarted once the Investigator determines that the infection has been successfully treated. Otherwise prohibited concomitant medications may be given if medically necessitated. Specifically, if a patient develops an intercurrent infection, then topical and/or oral antibiotic usage is permitted. If a patient experiences an intercurrent illness associated with pain for which oral analgesia is required, then otherwise-prohibited oral analgesics are permitted. Topical and/or oral antibiotic usage and oral analgesia are not permitted for worsening of HS (except as specified in Section 5.2.3.2). Prior to use, every attempt should be made to contact the AbbVie TA-MD for direction on re introduction of study drug after prohibited medication administration.

If the subject must undergo elective surgery, the study injections must be interrupted 2 weeks prior to the surgery. If the subject must undergo emergency surgery, the study injections must be interrupted at the time of the surgery. The injectable study medication can recommence at least 2 weeks after surgery once the physician has examined the surgical site and determined that it has healed and there is no sign of infection.

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 medical device component(s).

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 not working properly or packaging issues.

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

6.2.2 Reporting

Product Complaints concerning the investigational product and/or device 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 with the alleged complaint condition (prefilled syringe). In instances where a return is requested, every effort should be made by the Investigator to return the product within 30 days. If returns cannot be

accommodated within 30 days, the 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 principal investigator is 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 principal investigator is responsible for notifying Independent Ethics Committee (IEC)/Independent Review Board (IRB) regulatory authorities (as applicable), and the following AbbVie Clinical Monitor(s):

Primary Contact:	Alternate Contact:
[redacted]	

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.

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 who developed withdrawal criteria during the study and was not withdrawn
- Subject who received wrong treatment or incorrect dose
- Subject who received excluded or prohibited concomitant treatment

The Investigator will record all protocol deviations in the appropriate medical records at site.

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 in Japanese subjects with moderate to severe HS after 12 weeks of treatment, and to evaluate long-term safety and efficacy for continuous weekly dosing from Week 12. Complete, specific details of the statistical analysis will be described and fully documented in the Statistical Analysis Plan (SAP). The SAP will be finalized by first interim analysis.

8.1.1 Analysis Populations

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

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

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, minimum, median, and maximum for continuous variables; and counts and percentages for discrete variables.

The analysis will be performed using SAS® (SAS Institute Inc., Cary, NC, USA).

8.1.3 Demographics and Baseline Characteristics

Demographics and Baseline characteristics of the study subjects will be summarized using descriptive statistics.

8.1.4 Statistical Analyses of Efficacy

The efficacy analysis will be conducted in the FAS Population.

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

Missing data will be imputed using the following methods for the efficacy analyses in the FAS Populations:

- Non-Responder Imputation (NRI): the NRI analysis will categorize any subject who has missing value at a specific visit as non-responder for that visit. The NRI will be the primary approach in the analysis of categorical variables.
- Last Observation Carried Forward (LOCF): The LOCF analyses will use the completed evaluation from the previous visit within the particular period for efficacy measures assessed to impute missing data at later visits in the same period. Baseline efficacy evaluations will not be carried forward. LOCF will be the primary approach in the analysis of continuous variable, and the secondary approach in the analysis of categorical variables.
- As-observed: The As-observed analysis will not impute values for missing evaluations, and thus a subject who did not have an evaluation on a scheduled visit will be excluded from the as observed analysis for that visit. As observed analysis will be the secondary approach in the analysis of continuous variables.

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

8.1.4.1 Primary Analysis of Efficacy

The primary analysis is to describe the proportion of subjects achieving HiSCR at Week 12. The number and percentage of subjects achieving HiSCR will be calculated.

The primary analysis will be carried out in the FAS Population. Non responder imputation will be used as primary approach for missing values.

8.1.4.2 Secondary Analysis of Efficacy

Secondary analyses of efficacy will be carried out in the FAS Population

For the analysis of Patient's Global Assessment of Skin Pain (NRS), daily assessment will be evaluated and weekly average will be used. For analysis, subjects who received analgesics other than ibuprofen or acetaminophen (e.g., Tramadol) for skin pain will be counted as non-responder for categorical variables, and have their last pain assessment before the start of the analgesic carried forward for continuous variables, from the start day of the analgesics until fourteen (14) days after the stop of analgesic use. Concomitant medication for treatment of HS or pain will be reviewed; confounding medications (those considered as having potential effect on the pain assessments) and the time periods affected by such medications will be determined. Subjects will be counted as non-responder for categorical variables, and have their last pain assessment before the start of the confounding medications carried forward for continuous variables for these periods.

Additional analyses may be performed for the primary efficacy variable. Results from any additional analyses may be used as supplemental information for the study report.

Subgroup Analysis of Efficacy

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

1. Baseline Hurley Stage (II/III)

2. Concomitant use of oral antibiotics (yes/no)
3. Age group (< 40, 40–64, ≥ 65, if less than 10% of subjects in the ≥ 65 group, that group will be combined with 40–64 group.)
4. Sex (male, female)
5. Duration of HS (< median, ≥ median)
6. Weight (< median, ≥ median)
7. Body Mass Index (BMI) category: normal (< 25), over weight (25 – < 30), obese (30 – < 40), Morbid obesity (≥ 40)
8. Current smoking status (yes/no)
9. Baseline CRP level (< median, ≥ median)
10. Baseline AN count (≤ 5, 6 – 10, 11+)
11. Baseline AN count (< median, ≥ median)

8.1.5 Statistical Analysis of Safety

All AEs, SAEs, and AEs leading to discontinuation will be collected during the study and up to approximately 70 days after the last dose of the study drug. Safety analyses will be carried out using the Safety Population. SAEs and protocol-related AEs will be summarized as well. A treatment-emergent AE 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. The number and percent of subjects experiencing treatment emergent AEs will be tabulated using the Medical Dictionary for Drug Regulatory Activities (MedDRA®) system organ class and preferred term. Summaries (including percentages and event per 100 patient-year) of SAEs, deaths, AEs leading to discontinuation from the study, and AEs of Special Interest according to the most updated Humira Risk Management Plan will be provided as well. Mean change in laboratory variables and vital sign variables will be summarized at each visit. The last evaluation prior to the first dose of study drug will be used as Baseline for all analyses. For selected

parameters, a listing of all subjects with any laboratory determination meeting Common Toxicity Criteria (CTC) of Grade 2 or higher will be provided. Shift tables for changes from Baseline according to the normal range will also be provided.

8.1.6 Interim Analysis

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

8.2 Determination of Sample Size

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

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

8.3 Study Drug Allocation Methods

An IRT will be used to allocate study drug to subjects. Detailed instructions for using the IRT will be provided to the site personnel.

Subjects who are eligible based on inclusion and exclusion criteria and have had all pre enrollment procedures performed will be allocate to the study drug.

8.4 Pharmacokinetic Analysis

Adalimumab trough serum concentrations will be summarized 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 will be provided. Data listings 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.

The results may be incorporated into a population pharmacokinetic analysis if the data warrants in order to estimate parameters such as apparent clearance (CL/F) and apparent volume of distribution (V/F) of adalimumab.

As for the immunogenicity, serum AAA concentrations will be listed. A subject will be considered to be AAA+ when the subject has at least one AAA concentration greater than 20 ng/mL (confirmed with confirmatory assay) and the sample will be collected within 30 days after an adalimumab dose. The number and percentage of subjects who developed AAA will be determined. As appropriate, the effect of AAA on adalimumab pharmacokinetics, efficacy variable(s), and treatment-emergent adverse events may be evaluated.

9.0 Ethics

9.1 Independent Ethics Committee (IEC) or Institutional Review Board (IRB)

Good Clinical Practice (GCP) requires that the clinical protocol, any protocol amendments, the Investigator's Brochure, 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 the study 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 amendments to the protocol will require IEC/IRB approval prior to implementation of any changes made to the study design. The investigator will be required to submit, maintain and archive study essential documents according to 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 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 Harmonization (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 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, including the acceptability of photography of skin lesion, will be reviewed and signed and dated by the subject, the person who administered the informed consent. If the subject is < 20 years old, a subject's parent or legal guardian must be explained and willing to give written informed consent. 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.

9.3.1 Informed Consent Form and Explanatory Material

The Principal Investigator will prepare the consent form and explanatory material required to obtain subject's consent to participate in the study with the cooperation of the sponsor and will revise these documents as required. The prepared or revised consent forms and explanatory material will be submitted to the sponsor. Approval of the IRB will be obtained prior to use in the study.

9.3.2 Revision of the Consent Form and Explanatory Material

When important new information related to the subject's consent becomes available, the Principal Investigator will revise the consent form and explanatory material based on the information without delay and will obtain the approval of the IRB prior to use in the study. The Investigator will provide the information without delay to each subject already participating in the study, and will confirm the intention of each subject to continue in the study or not. The Investigator will also provide further explanation using the revised consent form and explanatory material and will obtain written consent from each subject of their own free will to continue participating in the study. If the subject is < 20 years old, a subject's parent or legal guardian must be explained and willing to give written informed consent.

10.0 Source Documents and Case Report Form Completion

10.1 Source Documents

Source documents are defined as original documents, data and records. This may include hospital records, clinical and office charts, laboratory data/information, subjects' diaries or evaluation checklists, 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 following assessments that will be completed by the subject on paper will be considered source documentation:

- DLQI
- EQ-5D
- Patient's Global Assessment of Skin Pain (NRS)
- HS QoL
- TSQM

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

The following contents recorded in eCRF may also be used as source, and will require an Investigator's approval on the eCRF as verification of the accuracy of the information:

- Route of drug administration
- Diagnostics, time course, severity, frequency and relationship to study drug, alternative etiology, medication for recovery, and seriousness for either SAEs or Nonserious AEs
- Investigator's comments
- Reason for Premature discontinuation for subject
- Reason why the physician or nurse performed injection of study drug, after self-injection started (if applicable)

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.

10.2 Case Report Forms

Case report forms (CRF) 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 electronic data capture (EDC) system called Rave® provided by the technology vendor Medidata Solutions Incorporated, NY, USA. The EDC system and the study-specific electronic case report forms (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 eCRFs will be conducted by AbbVie and will be maintained in the Trial Master File at AbbVie.

The investigator will document subject data in his/her own subject files. These subject files will serve as source data for the study. All eCRF data required by this protocol will be recorded by investigative site personnel in the EDC system, except for subject-completed questionnaires, which will be completed on paper by the subject then transcribed into the EDC system by site personnel. All data entered into the eCRF will be supported by source documentation except as noted in Section 10.1.

The investigator or an authorized member of the investigator's staff 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 Principal Investigator will review the eCRFs for completeness and accuracy and provide his or 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 investigator 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 investigator at that time as a durable record of the site's eCRF data. It will be possible for the investigator to make paper printouts from that media. The following assessments will be completed by subjects on paper:

- DLQI
- EQ-5D
- Patient's Global Assessment of Skin Pain (NRS)
- HS QoL
- TSQM

Site staff will verify completion of these forms. All questionnaires must be legible and completed in indelible ballpoint ink. Any necessary corrections are to be made by drawing a single line through the incorrect entry and writing in the revision, the date of the correction, the reason for the correction, and the initials of the study subject who is making the correction. Data are not to be obliterated by blacking out, using correction fluid or by erasing the original entry.

11.0 Data Quality Assurance

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

An Investigator's Meeting and/or Start-up Meeting at the site will be held with AbbVie personnel, the investigators and their study coordinators and the Monitors for the study. This meeting will include a detailed discussion of the protocol, performance of study procedures, eCRF and Subject Diary and log completion, and specimen collection methods. In addition to or instead of the Investigator's Meeting, the study personnel at each site may be trained on the study procedures by a Monitor at a study initiation visit and will be given an eCRF completion guideline for reference.

The Monitors will monitor each site throughout the study. Source document review will be performed against entries in the eCRF database and a quality assurance check will be performed to ensure that the investigator is complying with the protocol and regulations.

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 may be disclosed as deemed necessary by AbbVie to other clinical investigators, other pharmaceutical companies, to the FDA and to other governmental agencies. To allow for the use of the information derived from this clinical study and to ensure complete and thorough analysis, the 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 investigator will maintain a confidential subject identification code list of all subjects enrolled in the study (by name and subject number). This list will be maintained at the

site. When a copy is provided to AbbVie, the site should carefully consider that it never include any subject identifying information by obscuring subject's name with a heavy black marker until the relevant information can no longer be seen.

12.2 Publication

Core publication(s) will be authored by Principal Investigator(s) specified by AbbVie who contribute significantly to the implementation and conduct of the study and non-site personnel who contribute substantially to the design, interpretation or analysis of the study (e.g., AbbVie personnel or 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 investigators who provided significant input into study design, implementation, conduct and interpretation, in addition to AbbVie scientific personnel responsible for study conduct.

A named 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 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 Director of the Site and the sponsor. Continuation of this study beyond this date must be mutually agreed upon in writing by both the Director of the Site and the sponsor. The investigator will provide a final report to the Director of the Site following conclusion of the study, and the Director of the Site will inform the summary of the report to IRB and the sponsor.

The Director of the Site must retain any records related to the study according to local requirements. If the Director of the Site is not able to retain the records, he/she must notify the sponsor to arrange alternative archiving options.

AbbVie will select the signatory investigator from the 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, investigational drug and study protocol. The signatory investigator for the study will review and sign the final study report in accordance with the European Medicines Agency (EMA) 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 Investigator's Brochure for adalimumab.
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 3 Multicenter, Open-Label, Single Arm Study of the Safety and Efficacy of Adalimumab in Japanese Subjects with Moderate to Severe Hidradenitis Suppurativa
Protocol Date:	07 July 2016

Signature of Principal Investigator | Date

Name of Principal Investigator (printed or typed)

15.0 Reference List

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14. Giamarellos-Bourboulis EJ, Pelekanou E, Antonopoulou A, et al. An open-label phase II study of the safety and efficacy of etanercept for the therapy of hidradenitis suppurativa. Br J Dermatol. 2008;158(3):567-72.

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 amendments.
4. Reporting adverse experiences that occur in the course of the investigation(s) to AbbVie and the site director.
5. Reading the information in the Investigator's Brochure/safety material provided, including the instructions for use and the potential risks and side effects of the investigational product(s).
6. Informing all associates, colleagues, and employees assisting in the conduct of the study about their obligations in meeting the above commitments.
7. 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.
8. Maintaining records demonstrating that an ethics committee reviewed and approved the initial clinical investigation and all amendments.

9. 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.
10. 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]	Clinical
		Clinical
		Statistics
		Clinical
		Clinical Pharmacology & Pharmacometrics
		Bioanalysis
		Clinical, Author
		Clinical

Appendix C. Latest TB Risk Assessment Form Example

1. Have you or an immediate family member or other close contact ever been diagnosed or treated for tuberculosis?
2. Have you lived in or had prolonged travels to countries in the following regions:
   - Sub-Saharan Africa
   - India
   - China
   - Mexico
   - Southeast Asia or Micronesia
   - The former Soviet Union
3. Have you lived or worked in a prison, homeless shelter, immigration center, or nursing home?
4. Have you, or an immediate family member, had any of the following problems for the past 3 weeks or longer:
   - Chronic Cough
   - Production of Sputum
   - Blood-Streaked Sputum
   - Unexplained Weight Loss
   - Fever
   - Fatigue/Tiredness
   - Night Sweats
   - Shortness of Breath

From: http://www.mayoclinic.com/health/tuberculosis/DS00372/DSECTION=risk-factors
http://www.in.gov/fssa/files/Tuberculosis_Questionnaire.pdf

Appendix D. 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**?	yes ☐ no ☐	Not relevant ☐
If "No", over the last week how much has your skin been a problem at **work** or **studying**?	A lot ☐ A little ☐ Not at all ☐	
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 E. EuroQoL (EQ-5D questionnaire) – 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	☐

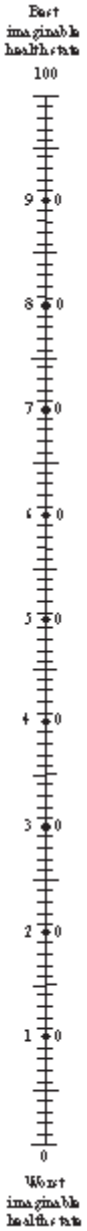
Anxiety/Depression

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.

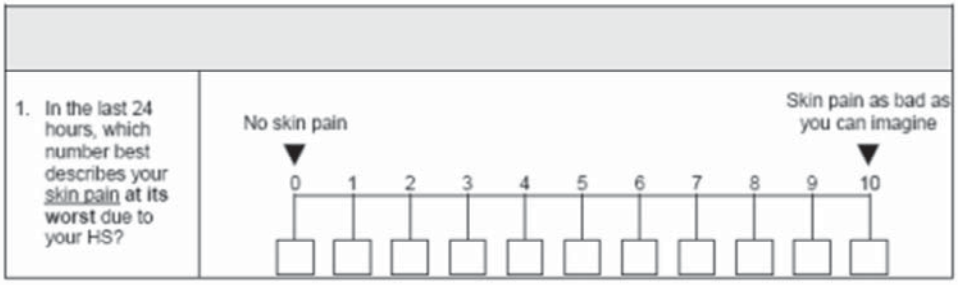
We would like you to indicate on this scale how good or bad your own health is today, in your opinion. Please do this by drawing a line from the box below to whichever point on the scale indicates how good or bad your health state is today.

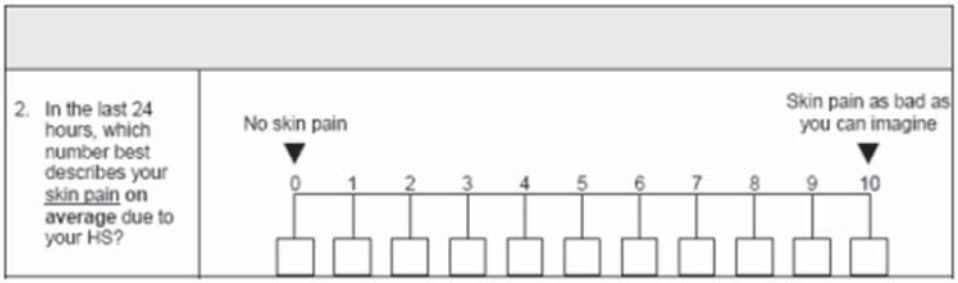
Your own health state today



Appendix F. Patient's Global Assessment of Skin Pain – NRS – Example

Please answer the questions below before you go to bed. Please mark an "X" in the box (☒) which best describes the severity of your skin pain in the last 24 hours.





Appendix G. Daily Subject Analgesic (Pain) Use Diary – Example

Please answer the questions below before you go to bed. Provide your response based on the past 24 hours.

Did you take any pain medication in the past 24 hours? □ Yes □ No

If YES:

Fill in the chart with the information about the pain medication you took. If "Other" write in the name of the pain medication you took.

Pain Medication	Type of Pain Medication Taken (CHECK BOX)	Was the Pain Medication for HS?	Dose and Unit (example: 325 mg)	Number of Pills Taken (example: 2 pills)
Ibuprofen	□	□ Yes □ No		
Acetaminophen	□	□ Yes □ No		
Tramadol	□	□ Yes □ No		
Other Pain Medication:	□	□ Yes □ No		
Other Pain Medication:	□	□ Yes □ No		
Other Pain Medication:	□	□ Yes □ No		

Appendix H. Hidradenitis Suppurativa Quality of Life – Example

Overall, how would you rate your quality of life with Hidradenitis Suppurativa (HS)	**Worst Possible** ⇩									**Best Possible** ⇩
	0 ☐	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐	6 ☐	7 ☐	8 ☐	9 ☐	10 ☐

Appendix I. Treatment Satisfaction Questionnaire for Medication – Example

TSQM *Version 1.4*

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 one 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?

☐1 Extremely Dissatisfied
☐2 Very Dissatisfied
☐3 Dissatisfied
☐4 Somewhat Satisfied
☐5 Satisfied
☐6 Very Satisfied
☐7 Extremely Satisfied

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

☐1 Extremely Dissatisfied
☐2 Very Dissatisfied
☐3 Dissatisfied
☐4 Somewhat Satisfied
☐5 Satisfied
☐6 Very Satisfied
☐7 Extremely Satisfied

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

☐1 Extremely Dissatisfied
☐2 Very Dissatisfied
☐3 Dissatisfied
☐4 Somewhat Satisfied
☐5 Satisfied
☐6 Very Satisfied
☐7 Extremely Satisfied

4. As a result of taking this medication, do you experience any side effects at all?

☐1 Yes
☐0 No (If No, then please skip to Question 9)

5. How bothersome are the side effects of the medication you take to treat your condition?

☐1 Extremely Bothersome
☐2 Very Bothersome
☐3 Somewhat Bothersome
☐4 A Little Bothersome
☐5 Not at All Bothersome

6. To what extent do the side effects interfere with your physical health and ability to function (i.e., strength, energy levels, etc.)?

☐1 A Great Deal
☐2 Quite a Bit
☐3 Somewhat
☐4 Minimally
☐5 Not at All

7. To what extent do the side effects interfere with your mental function (i.e., ability to think clearly, stay awake, etc.)?

☐1 A Great Deal
☐2 Quite a Bit
☐3 Somewhat
☐4 Minimally
☐5 Not at All

8. To what degree have medication side effects affected your overall satisfaction with the medication?

☐1 A Great Deal
☐2 Quite a Bit
☐3 Somewhat
☐4 Minimally
☐5 Not at All

9. How easy or difficult is it to use the medication in its current form?

☐1 Extremely Difficult
☐2 Very Difficult
☐3 Difficult
☐4 Somewhat Easy
☐5 Easy
☐6 Very Easy
☐7 Extremely Easy

10. How easy or difficult is it to plan when you will use the medication each time?

☐1 Extremely Difficult
☐2 Very Difficult
☐3 Difficult
☐4 Somewhat Easy
☐5 Easy
☐6 Very Easy
☐7 Extremely Easy

11. How convenient or inconvenient is it to take the medication as instructed?

☐1 Extremely Inconvenient
☐2 Very Inconvenient
☐3 Inconvenient
☐4 Somewhat Convenient
☐5 Convenient
☐6 Very Convenient
☐7 Extremely Convenient

12. Overall, how confident are you that taking this medication is a good thing for you?

☐1 Not at All Confident
☐2 A Little Confident
☐3 Somewhat Confident
☐4 Very Confident
☐5 Extremely Confident

13. How certain are you that the good things about your medication outweigh the bad things?

☐1 Not at All Certain
☐2 A Little Certain
☐3 Somewhat Certain
☐4 Very Certain
☐5 Extremely Certain

14. Taking all things into account, how satisfied or dissatisfied are you with this medication?

☐1 Extremely Dissatisfied
☐2 Very Dissatisfied
☐3 Dissatisfied
☐4 Somewhat Satisfied
☐5 Satisfied
☐6 Very Satisfied
☐7 Extremely Satisfied

Appendix J. Lesion Counts – Example

Lesion Counts (to be assessed at every visit)	Hurley Stage	Abscess	Non-Draining Fistula	Draining Fistula	Non-Inflammatory Nodule	Inflammatory Nodule	Hypertrophic Scar	Longest distance (mm) between 2 relevant lesions (If only 1 lesion, measure diameter of lesion)	Are all lesions clearly separated by normal-appearing skin? (yes/no)
Left Axilla									
Right Axilla									
Left Sub/Inframammary Area									
Right Sub/Inframammary Area									
Intermammary Area									
Left Buttock									
Right Buttock									
Left Inguino-crural Fold									
Right Inguino-crural Fold									
Perianal									
Perineal									
Other									
Totals									
Worst Hurley									

Note: Lesions that received intervention (Section 5.2.3.2) will be counted as permanently present from the date of the intervention and must be accounted for on the appropriate eCRF. For a definition of terms, see Section 1.3

Appendix K. Degree of Erythema – Example

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

Region (to be assessed at every visit)	Degree of Erythema
Left Axilla	
Right Axilla	
Left Sub/Inframammary Area	
Right Sub/Inframammary Area	
Intermammary Area	
Left Buttock	
Right Buttock	
Left Inguino-crural Fold	
Right Inguino-crural Fold	
Perianal	
Perineal	
Other	

0 = no redness

1 = faint but discernible pink coloration

2 = moderate red coloration

3 = very red or bright red coloration

Appendix L. Day 70 Follow-Up Call – Example

Subject Number: _____

Please contact Subjects 70 days after study drug discontinuation.

Date of Call: _____

☐ Lost to Follow-up (Please check this box if subject was not willing to provide any follow-up information or you were unable to speak to the subject following at least one attempt.)

☐ No Events Reported

☐ Adverse Events/ Serious Adverse Events Reported

List any new Adverse Events (AE) and/or Serious Adverse Events (SAE) that occurred since the subject was last seen in the clinic for this study. Please also update the status of any ongoing AEs and/or SAEs. If needed, provide AE/SAE details on the AE worksheet attached. (Please report all SAEs to AbbVie within 24 hours of being made aware of the event.) Any medications taken as a result of the events should be entered on the eCRF.

_____	_____
_____	_____
_____	_____
_____	_____
_____	_____
_____	_____
_____	_____

If events are listed above, your Monitor will review and retrieve the appropriate eCRF pages during their next visit.

Please fax all completed forms to:

To Be Determined

Appendix M. Injection Instructions – Example Pre-Filled Syringe

Subject Instructions

0.4 mL dose (40 mg)

(Administered as a single dose-pre-filled syringe)

Protocol M15-573

Tables of Contents

Study Drug Dosing Schedule

Subject Number _____

You will require subcutaneous (SC) injections throughout the study.

You will receive the following number of injections during this study:

- Baseline visit (the first visit to receive study medication for this study) you will receive 4 injections at the clinic. You will not be given any kits to take home. The kit for Week 2 dosing will be dispensed at the Week 2 visit.
- You will return for your Week 2 visit, at which time one kit will be dispensed (2 syringes total). At the Week 2 visit, you will have a sample of blood drawn for PK, then the kit will be used to administer both injections in the office. You will not be given any kits to take home. The kit for Week 4 dosing will be dispensed at the Week 4 visit.
- You will return for your Week 4 visit, at which time two kits will be dispensed (4 syringes total). At the Week 4 visit, you will have a sample of blood drawn for PK/AAA, then one of the kits will be used to administer 1 injection in the office. You will take home the kits for your Week 5 (one injection), 6 (one injection) and 7 (one injection) doses, if you have qualified to conduct self-injection of study drug after you signed for the IC.
- You will return for your Week 8 visit, at which time two kits will be dispensed (4 syringes total). At the Week 8 visit, you will have a sample of blood drawn for PK, then one of the kits will be used to administer 1 injection in the office. You will take home the kits for your Week 9 (one injection), 10 (one injection) and 11 (one injection) doses.
- You will return for your Week 12 visit, at which time two kits will be dispensed. At the Week 12 visit, you will have a sample of blood drawn for PK/AAA, then you may take your Week 12 (1 injection) dose in the office. You will take home the kits for your Week 13 (one injection), 14 (one injection) and 15 (one injection) doses.
- You will return for your Week 16 visit, at which time two kits will be dispensed (4 syringes total). At the Week 16 visit, you will have a sample of

blood drawn for PK, then one of the kits will be used to administer 1 injection in the office. You will take home the kits for your Week 17 (one injection), 18 (one injection) and 19 (one injection) doses.

- You will return for your Week 20 visit, at which time two kits will be dispensed (4 syringes total). At the Week 20 visit, you will have a sample of blood drawn for PK, then one of the kits will be used to administer 1 injection in the office. You will take home the kits for your Week 21 (one injection), 22 (one injection) and 23 (one injection) doses.
- You will return for your Week 24 visit, at which time two kits will be dispensed (4 syringes total). At the Week 24 visit, you will have a sample of blood drawn for PK/AAA, then one of the kits will be used to administer 1 injection in the office. You will take home the kits for your Week 25 (one injection), 26 (one injection) and 27 (one injection) doses.
- You will return for your Week 28 visit, at which time two kits will be dispensed (4 syringes total). At the Week 28 visit, one of the kits will be used to administer 1 injection in the office. You will take home the kits for your Week 29 (one injection), 30 (one injection) and 31 (one injection) doses.
- You will return for your Week 32 visit, at which time two kits will be dispensed (4 syringes total). At the Week 32 visit, one of the kits will be used to administer 1 injection in the office. You will take home the kits for your Week 33 (one injection), 34 (one injection) and 35 (one injection) doses.
- You will return for your Week 36 visit, at which time two kits will be dispensed (4 syringes total). At the Week 36 visit, you will have a sample of blood drawn for PK/AAA, then one of the kits will be used to administer 1 injection in the office. You will take home the kits for your Week 37 (one injection), 38 (one injection) and 39 (one injection) doses.
- You will return for your Week 40 visit, at which time two kits will be dispensed (4 syringes total). At the Week 40 visit, one of the kits will be used to administer 1 injection in the office. You will take home the kits for your Week 41 (one injection), 42 (one injection) and 43 (one injection) doses.
- You will return for your Week 44 visit, at which time two kits will be dispensed (4 syringes total). At the Week 44 visit, one of the kits will be used

to administer 1 injection in the office. You will take home the kits for your Week 45 (one injection), 46 (one injection) and 47 (one injection) doses.

- You will return for your Week 48 visit, at which time two kits will be dispensed (4 syringes total). At the Week 48 visit, one of the kits will be used to administer 1 injection in the office. You will take home the kits for your Week 49 (one injection), 50 (one injection) and 51 (one injection) doses.
- You will return for your Week 52 visit, at which time six kits will be dispensed (12 syringes total). At the Week 52 visit, you will have a sample of blood drawn for PK/AAA, then one of the kits will be used to administer 1 injection in the office. You will take home the kits for your Week 53 (one injection), 54 (one injection), 55 (one injection), Week 56 (one injection), 57 (one injection), 58 (one injection), Week 59 (one injection), Week 60 (one injection), 61 (one injection), Week 62 (one injection), and 63 (one injection) doses.
- The above every 12-week visit will be repeated until the study end or the time you want to withdraw the study participation.

Please return all used and unused syringes and empty boxes to the clinic on your next visit. Used syringes should be placed in the special sharps container provided. All unused syringes should be returned in the original box.

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

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

General Information

- Pre-filled syringes will be labeled "Adalimumab" versus Placebo.
- Store all adalimumab pre-filled syringes in your refrigerator NOT in the freezer. Should the syringes accidentally become frozen, call your study doctor's office.

- Study medication should be taken at about the same time of day, on the same day of the week as directed by your study doctor.
- **USE A NEW SYRINGE EVERY INJECTION DAY.** There may be medication left in the syringe. **DO NOT RE-USE.**
- Save all study medications. ***Pre-filled syringes (used and unused) & empty boxes must be returned to the study center at each visit.*** Used syringes will be disposed of in a sharps container provided to you.
- Call your doctor IMMEDIATELY if you experience any itching, hives, shortness of breath, or any symptom that has you concerned. If you are unable to reach your doctor or if you experience life-threatening symptoms **call**, _____ or proceed to your nearest emergency room.

Injection Procedures (Pre-filled Syringe)

1. Setting up for an injection

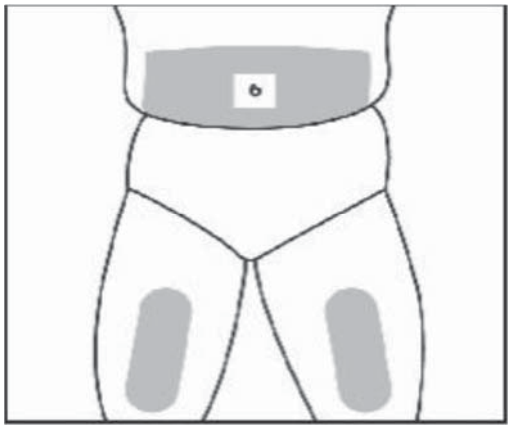
    - Find a clean flat surface.
    - Do not use if the seals on the carton are broken or missing. Contact your study doctor's office if the seals are broken.
    - Take one kit with the pre-filled syringe(s) of adalimumab from the refrigerator. Do not use a pre-filled syringe that has been frozen or if it has been left in direct sunlight.
    - Return any unused syringe(s) to the refrigerator.
    - You will need the following items for each dose:
        - study medication in pre-filled syringe(s)
        - alcohol prep(s)
        - cotton ball or gauze pad(s)

If you do not have all of the items you need to give yourself an injection, call your study physician. Use only the items provided in the box your adalimumab comes in.

- Make sure the liquid in the pre-filled syringe is clear and colorless. Do not use a pre-filled syringe if the liquid is cloudy or discolored or has flakes or particles in it.
- Have a special sharps (puncture proof) container nearby for disposing of used needles and syringes.

For your protection, it is important that you follow these instructions.

2. **Choosing and preparing an injection site**



- Wash your hands well.
- Choose a site on the front of your thighs or your stomach area (abdomen). If you choose your abdomen, you should avoid the area 2 inches around your belly button (navel).
- Choose a different site each time you give yourself an injection. Each new injection should be given at least one inch from a site you used before. Never inject into areas where the skin is tender, bruised, red or hard or where you have scars or stretch marks.
- If you have psoriasis, you should try not to inject directly into any raised, thick, red or scaly skin patches or lesions.
- You may find it helpful to keep notes on the location of your injection sites.
- Wipe the site where adalimumab is to be injected with an alcohol prep (swab), using a circular motion. Do not touch this area again until you are ready to inject.

3. How to prepare your adalimumab dose for injection with a Pre-filled Syringe

- Hold the syringe upright with the needle facing down. Check to make sure that the amount of liquid in the syringe is the same or close to the 0.4 mL line for the 40 mg pre-filled syringe. The top of the liquid may be curved. If the

syringe does not have the correct amount of liquid, do not use that syringe. Call your study doctor.

- Remove the needle cover taking care not to touch the needle with your fingers or allow it to touch any surface.
- Turn the syringe so the needle is facing up and slowly push the plunger in to push the air in the syringe out through the needle. If a small drop of liquid comes out of the needle that is okay.
- Do not shake the syringe.

4. Injecting Adalimumab

- With your other hand, gently squeeze an area of the cleaned area of skin and hold it firmly.
- You will inject into this raised area of skin. Hold the syringe like a pencil at about a 45° angle (see picture) to the skin.
- With a quick, short, "dart-like" motion, push the needle into the skin.
- After the needle is in, let go of the skin. Pull back slightly on the plunger. If blood appears in the syringe it means that you have entered a blood vessel. Do not inject adalimumab. Pull the needle out of the skin and repeat the steps to choose and clean a new injection site. Do not use the same syringe. Dispose of it in your special sharps container. If no blood appears, slowly push the plunger all the way in until all of the adalimumab is injected.
- When the syringe is empty, remove the needle from the skin keeping it at the same angle it was when it was pushed into the skin.

- Press a cotton ball or gauze pad over the injection site and hold it for 10 seconds. Do not rub the injection site. You may have slight bleeding. This is normal.
- Dispose of the syringe right away into your special sharps container.

Appendix N. Subject Dosing Sheet – Adalimumab Example

To be completed for every study dose taken at home. Study medication should be taken at about the same time of day, on the same day of the week as directed by your study doctor. Please record the date, time of study drug administration, if the full dose was administered, your initials, and any comments. Instructions on proper study medication administration will be provided by your study doctor and should be followed for every injection. Call the doctor's clinic if you are having problems administering your study medication.

For rows that are italicized and shaded, do not record the information. These represent study visits for which injections will occur at the clinic. The study personnel will record this information at the time of your study visit.

Please bring your Sheet with you to each clinic visit.

If you have any questions or concerns at any time, please call the study coordinator or physician at the following number(s):

Study M15-573 – Sample
Week 0 to Week 11

Subject Initials: _____ Subject Number: _____

Week	Scheduled Date[a] day/mm/yr	Actual Date of Injection[b] day/mm/yr	Kit No.	Time of Study Drug Administration (if known)	Was full dose Administered? Yes/No	Initials of Person Administering Study Medication	Notes Problems with the needle
EXAMPLE	**8/June/16**	**8/June/2016**	**600101**	**9:35 am**	**Yes**	**MM**	**No**
Baseline/Wk 0							
Baseline/Wk 0							
Baseline/Wk 0							
Baseline/Wk 0							
Week 2							
Week 2							
Week 4							
Week 5							
Week 6							
Week 7							
Week 8							
Week 9							
Week 10							
Week 11							

a. Site personnel should record the scheduled date of injection for the subject in the first column.

b. Subjects will write the actual date the study drug was injected in the second column.

Study M15-573 – Sample
Week 12 to Week 27

Subject Initials: _____ Subject Number: _____

Week	Scheduled Date[a] day/mm/yr	Actual Date of Injection[b] day/mm/yr	Kit No.	Time of Study Drug Administration (if known)	Was full dose Administered? Yes/No	Initials of Person Administering Study Medication	Notes Problems with the needle
EXAMPLE	**8/June/16**	**8/June/2016**	**600101**	**9:35 am**	**Yes**	**MM**	**No**
Week 12							
Week 13							
Week 14							
Week 15							
Week 16							
Week 17							
Week 18							
Week 19							
Week 20							
Week 21							
Week 22							
Week 23							
Week 24							
Week 25							
Week 26							
Week 27							

a. Site personnel should record the scheduled date of injection for the subject in the first column.

b. Subjects will write the actual date the study drug was injected in the second column.

Study M15-573 – Sample

Week 28 to Week 43 (after Week 44, please prepare as needed according to the length of the study)

Subject Initials: _____ Subject Number: _____

Week	Scheduled Date[a] day/mm/yr	Actual Date of Injection[b] day/mm/yr	Kit No.	Time of Study Drug Administration (if known)	Was full dose Administered? Yes/No	Initials of Person Administering Study Medication	Notes Problems with the needle
EXAMPLE	**8/June/16**	**8/June/2016**	**600101**	**9:35 am**	**Yes**	**MM**	**No**
Week 28							
Week 29							
Week 30							
Week 31							
Week 32							
Week 33							
Week 34							
Week 35							
Week 36							
Week 37							
Week 38							
Week 39							
Week 40							
Week 41							
Week 42							
Week 43							

a. Site personnel should record the scheduled date of injection for the subject in the first column.

b. Subjects will write the actual date the study drug was injected in the second column.

Appendix O. Infection Subject Information Card – Example

It is possible that you may be at increased risk for an infection at or near your HS area. If you develop any of the following signs or symptoms, you should contact your study doctor (number noted below) immediately for an additional examination.

Possible Signs of an Infection:

- Fever
- Chills
- Unusual **warmth** at or near an HS area
- Unusual **redness** at or near an HS area
- Unusual **swelling** at or near an HS area
- Unusual **pain** at or near an HS area
- Unusual amounts of **pus** at or near an HS area

Call your study Dr. at (XXX) XXX–XXXX

If you notice any of the above symptoms for further evaluation.

Document Approval

Study M15573 - A Phase 3 Multicenter, Open-Label, Single Arm Study of the Safety and Efficacy of Adalimumab in Japanese Subjects with Moderate to Severe Hidradenitis Suppurativa - 07Jul2016

Version: 1.0 **Date:** 11-Jul-2016 01:59:59 PM **Company ID:** 07112016-00F9F6812DD14C-00001-en

Signed by:	Date:	Meaning Of Signature:
[redacted]	08-Jul-2016 06:46:55 AM	Author
	08-Jul-2016 12:51:35 PM	Approver
	08-Jul-2016 02:54:28 PM	Approver
	08-Jul-2016 02:55:47 PM	Approver
	10-Jul-2016 08:43:13 AM	Approver
	11-Jul-2016 12:45:14 PM	Approver
	11-Jul-2016 01:30:36 PM	Approver
	11-Jul-2016 01:59:55 PM	Approver