25 June 2015
EMA/CHMP/364731/2015
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Invented name: Humira

International non-proprietary name: adalimumab

Procedure No. EMEA/H/C/000481/II/0137

Marketing authorisation holder (MAH): AbbVie Ltd.

Note

Variation assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

AAA	Anti-adalimumab antibody
AE	Adverse event
AESI	Adverse event of special interest
AN	Abscess and inflammatory nodule
ANCOVA	Analysis of covariance
ANOVA	Analysis of variance
BID	Twice a day
BL	Baseline
BMI	Body mass index
CMH	Cochran-Mantel-Haenszel
CRP	C-reactive protein
CSR	Clinical study report
CXR	Chest x-ray
DB	Double-blind
DLQI	Dermatology Life Quality Index
DMARD	Disease-modifying antirheumatic drug
ECG	Electrocardiogram
eow	Every other week
EU	European Union
ew	Weekly
GCP	Good Clinical Practice
HiSCR	Hidradenitis Suppurativa Clinical Response
HS	Hidradenitis suppurativa
HS QoL	Hidradenitis Suppurativa Quality of Life
hsCRP	High sensitivity C-reactive protein
ICH	International Conference on Harmonization
ISE	Integrated Summary of Efficacy
ITT	Intent-to treat
IXRS	Interactive Voice Response System/Interactive Web Response System
LOCF	Last observation carried forward
LOR	Loss of response
LS	Least squares
MCID	Minimal clinically important difference
MMRM	Mixed-effects model repeated measurement
MTX	Methotrexate
NRI	Non-responder imputation
NRS	Numeric rating scale
OC	Observed case
OL	Open-label
OLE	Open-label extension
pbo	Placebo
PGA	Physician's Global Assessment
PP	Per protocol
PPD	Purified protein derivative
SAE	Serious adverse event
SAP	Statistical analysis plan
SC	Subcutaneous
TNF	Tumour necrosis factor
TSQM	Treatment Satisfaction Questionnaire for Medication
US	United States
Wk	Week
WOAI	Worsening or absence of improvement
WPAI:SHP	Work Productivity and Activity Impairment Questionnaire: Specific Health Problem

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, AbbVie Ltd. submitted to the European Medicines Agency on 11 November 2014 an application for a variation.

This application concerns the following medicinal product:

Centrally authorised Medicinal product: **For presentations: See Annex A**	**International non-proprietary name**
Humira	adalimumab

The following variation was requested:

Variation requested		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

The Marketing authorisation holder (MAH) applied for a new indication for the treatment of active moderate to severe hidradenitis suppurativa (acne inversa) in adult patients, including treatment of inflammatory lesions and prevention of worsening of abscesses and draining fistulas. Consequently, the MAH proposed the update of sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC. The Package Leaflet was proposed to be updated in accordance.

The variation proposed amendments to the Summary of Product Characteristics and Package Leaflet.

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) P/0121/2013 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P0121/2013 was not yet completed as some measures were deferred.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the MAH did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Scientific advice

The MAH received Scientific Advice from the CHMP on 18 November 2010 and 19 May 2011. The Scientific Advices pertained to clinical aspects of the dossier.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP and the evaluation teams were:

Rapporteur: Kristina Dunder Co-Rapporteur: Daniela Melchiorri

Timetable	Actual dates
Rapporteur's preliminary assessment report circulated on:	19 January 2015
Co-Rapporteur's preliminary assessment report circulated on:	14 January 2015
Joint Rapporteur's updated assessment report circulated on:	20 February 2015
Request for supplementary information and extension of timetable adopted by the CHMP on:	26 February 2015
MAH's responses submitted to the CHMP on:	26 April 2015
Rapporteur's preliminary assessment report on the MAH's responses circulated on:	26 May 2015
Joint Rapporteur's updated assessment report on the MAH's responses circulated on:	18 June 2015
PRAC RMP advice and assessment overview adopted by PRAC:	11 June 2015
CHMP opinion:	26 June 2015

2. Scientific discussion

2.1. Introduction

Adalimumab is a recombinant, fully human immunoglobulin (IgG1) monoclonal antibody that binds specifically to the soluble and transmembrane forms of tumor necrosis factor (TNF)-α and inhibits the binding of TNF-α to its receptors.

Adalimumab is approved for the treatment of moderate to severe rheumatoid arthritis, active juvenile idiopathic arthritis, active and progressive psoriatic arthritis, severe ankylosing spondylitis, moderate to severe chronic plaque psoriasis (in adults), severe chronic plaque psoriasis in children and adolescents from 4 years of age, moderate to severe Crohn's disease, and moderate to severe ulcerative colitis (UC).

Hidradenitis suppurativa (HS) is a serious, chronic, inflammatory, recurrent, debilitating skin disease that usually presents with painful, deep-seated, inflamed lesions in the apocrine gland-bearing areas of the body, most commonly the axillary, inguinal, and anogenital regions.

Disease onset is typically after puberty and affects women 2 to 5 times more commonly than men. Various factors including genetics, cigarette smoking, and obesity may predispose a person to HS. The disease is characterized by recurrent inflamed nodules and abscesses, which may rupture to form fistulas and ooze purulent drainage and cause subsequent scarring. HS is also associated with several complications (e.g. the development of anal, urethral and rectal strictures and fistulas). The excessive scarring and fibrosis produced by HS lesions can lead to contractures and limitations in limb mobility, especially in the axilla. In addition, inflammation and scarring in the genitofemoral region may predispose to anal, urethral, and rectal strictures. Other comorbidities associated with HS include anaemia, secondary infection, malignancies (such as non-melanoma skin cancer; NMSC), metabolic syndrome, spondyloarthritis, depression and anxiety.

The 1-year prevalence of symptomatic HS, including mild to severe disease, has been estimated to be 0.97% in France and 1.0% in Copenhagen County, Denmark. Two recent studies suggest that the diagnosed prevalence of HS in the US is approximately 0.05%.

The diagnosis of HS is established by the characteristic clinical presentation, without the need for a confirmatory skin biopsy. HS is described clinically using the Hurley Stages classification, first proposed in 1989, which represent the levels of severity of HS disease. The stages are based on the extent of cicatrisation and sinus tract involvement, as follows:

- Hurley Stage I: Abscess formation (single or multiple) without sinus tracts and cicatrisation
- Hurley Stage II: One or more widely separated recurrent abscesses with tract formation and scars
- Hurley Stage III: Multiple interconnected tracts and abscesses throughout an entire area

Hurley Stage I patients are typically treated with topical or systemic antibiotics. Patients who fail these treatments generally receive retinoid therapy, short-term corticosteroid treatments, or cryotherapy. Hurley Stage II and III disease often requires long-term immunosuppression or surgical intervention. HS may be a progressive disease in some patients and risk factors that predispose patients to progression include smoking and obesity.

The Sartorius scale is also often used to grade severity of HS and a modified version (MSS) is commonly used.

Table 1. Modified Sartorius Scale (MSS)

Anatomical Region	**Region Involved?** (circle yes or no for each area)		**Number of Lesions by Region and Type**	**Longest Distance Between 2 relevant Lesions** (If only 1 lesion, measure diameter of lesion)
• Right Axilla	Yes	No	_____(#) Abscesses _____(#) Nodules _____(#) Fistulas	_____ mm
• Right Groin	Yes	No	_____(#) Abscesses _____(#) Nodules _____(#) Fistulas	_____ mm
• Right Gluteal Region	Yes	No	_____(#) Abscesses _____(#) Nodules _____(#) Fistulas	_____ mm
• Right Inframammary	Yes	No	_____(#) Abscesses _____(#) Nodules _____(#) Fistulas	_____ mm
• Left Axilla	Yes	No	_____(#) Abscesses _____(#) Nodules _____(#) Fistulas	_____ mm
• Left Groin	Yes	No	_____(#) Abscesses _____(#) Nodules _____(#) Fistulas	_____ mm
• Left Gluteal Region	Yes	No	_____(#) Abscesses _____(#) Nodules _____(#) Fistulas	_____ mm
• Left Inframammary	Yes	No	_____(#) Abscesses _____(#) Nodules _____(#) Fistulas	_____ mm
• Other Please Specify: _____	Yes	No	_____(#) Abscesses _____(#) Nodules _____(#) Fistulas	_____ mm
Hurley Stage (Circle 1)	I	II	III	

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HS has a severely negative effect on patients' quality of life. Patients who suffer from moderate to severe HS have substantial and often persistent morbidity due to pain and sequelae from uncontrolled inflammation. Compared to other skin diseases, the impact of HS on health-related quality of life is worse. The baseline mean Dermatology Life Quality Index (DLQI) scores (which range from 0 for no impairment to 30 for maximal impairment) were 14 for moderate to severe HS patients in a Phase 2 HS trial compared to 11 for moderate to severe plaque psoriasis patients in a Phase 3 psoriasis trial.

A diverse range of symptoms are associated with HS, with skin pain being the most frequently reported and bothersome. Adults with HS experience considerable impact on activities of daily living, work/school attendance, physical activities, and emotional states. The impairment that HS patients suffer is often greater than the impairment experienced by patients with other dermatologic conditions, including chronic urticaria, psoriasis, atopic dermatitis and neurofibromatosis. Patients with HS, especially those with moderately to severely active disease, often have poor work productivity.

Patients with HS often have needs of frequent healthcare contacts. Over a 3-year period, approximately 1 in 4 patients (27%) with HS were admitted to the emergency room and 16% were hospitalized.

Current treatment options

Understanding of the pathogenesis of HS has progressed rapidly in the last years. The inflammation in HS is associated with increased levels of pro-inflammatory cytokines such as IL-1β and TNF-α. Most experts believe that bacterial infection is a secondary event in the disease process, and that antibiotics do not cure the disease but may relieve symptoms through either an antibacterial or an anti-inflammatory effect.

There are no approved medicinal products for the treatment of HS and there are few randomized, controlled trials of medical therapies, or surgical or laser interventions in the treatment of HS. So far, the only randomized placebo-controlled study of HS demonstrating efficacy was with the use of topical clindamycin. This was a single-centre, small (N = 30 patients) study that demonstrated a mean reduction of 1.3 inflammatory nodules after 3 months of therapy.

Since there are no robust data and no approved products for HS, treatments vary widely and are not well characterised. These include medical treatments (e.g. systemic combination therapy with clindamycin and rifampicin, tetracyclines including doxycycline and minocycline, intralesional triamcinolone, systemic cyclosporine, anti-androgen treatment in women, systemic dapsone, systemic retinoids, and metformin), surgical treatments (radical excision, marsupialization and deroofing) and laser treatment (CO_2 laser and Nd:YAG laser). Their use is described in open-label, frequently retrospective case series and case reports, with typically short-term follow-up and varying eligibility criteria and surgical techniques. Retrospective studies of oral clindamycin and rifampicin have not provided definitive evidence to establish the optimal duration of therapy, however, a range of 2 to 4 months has been mentioned.

There is an unmet medical need in this condition, given that (a) the abscesses and inflammatory nodules of HS are malodorous, cause pain and may culminate in scar formation; (b) there are no approved medical therapies for the abscesses and inflammatory nodules of HS; and (c) surgical and laser therapies can be associated with significant post-procedure morbidity and uncertain long-term disease control.

The MAH has submitted a type II variation application to add a new indication for Humira for the:" treatment of active moderate to severe hidradenitis suppurativa (acne inversa) in adult patients, including treatment of inflammatory lesions and prevention of worsening of abscesses and draining fistulas".

The application is based on data from Studies M10-467, M11-810, M11-313, and M12-555 in adult subjects with moderate to severe hidradenitis suppurativa (HS).

The proposed dose for adult patients with moderate to severe HS is an initial dose of 160 mg at Week 0, 80 mg at Week 2, and 40 mg every week (ew) starting at Week 4.

There is no European guideline available for the clinical development of products for the treatment of hidradenitis suppurativa. CHMP Scientific Advice (EMEA/H/SA/127/8/2010/II) and Follow-up Scientific Advice (EMEA/H/SA/127/8/FU/1/2011/II) for the development of Humira in HS were received by the MAH and were taken into consideration when designing the phase 3 clinical programme.

In the first CHMP advice, issues were raised regarding the target population (e.g. disease severity, previous and ongoing antibiotic use) and the proposed primary efficacy end-point AN50 (a 50% reduction in abscess and/or nodule count), which was not considered sufficient to address a clinically relevant effect. The choice of dose, study duration and size of the safety data base were also addressed.

In the follow-up advice, the MAH had revised the proposed inclusion criteria in order to include a sufficiently severe HS population. They had also developed a new composite end-point, the Hidradenitis Suppurativa Clinical Response (HiSCR), that requires a 50% or more reduction in total count of abscess and inflammatory nodule count with no increase in abscess count or draining fistula count vs. baseline. This was deemed a more relevant end-point by the CHMP, however, the need for validation was stressed. The importance of relevant secondary efficacy end-points to capture other aspects of HS was emphasized. Issues related to previous and ongoing antibiotic treatment were further discussed and it was recommended to perform sub-group analyses with respect to smoking status and obesity (BMI) as these factors are known to affect HS.

The MAH has in general followed the CHMP Scientific advice in the clinical development of Humira in HS.

2.2. Non-clinical aspects

No new non-clinical data have been submitted in this application, which was considered acceptable by the CHMP.

2.3. Clinical aspects

2.3.1. Introduction

GCP

The Clinical trials were performed in accordance with GCP as claimed by the MAH.

The MAH has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- Tabular overview of clinical studies

Study No.	No. Patients Enrolled	Location	Study Design / Duration	Key Efficacy Variables	Status
M10-467	154	USA, NLD, DNK, DEU	Phase 2, randomized, DB, placebo-controlled period followed by an OL period/ 52 weeks	Proportion of subjects achieving HS-PGA of clear, minimal, or mild with at least 2 grades improvement (reduction) from Baseline at Week 16 (primary)	Completed
M11-810	326	AUS, CAN, DNK, FRA, GRC, NLD, SWE, CHE, TUR, USA	Phase 3, randomized, DB, placebo-controlled, 2-period/36 weeks	Proportion of subjects achieving HiSCR at Week 12 (primary); AN count of 0/1/2, NRS30, modified Sartorius score (ranked secondaries)	Completed
M11-313	307	AUS, CAN, CZE, DEU, HUN, USA	Phase 3, randomized, DB, placebo-controlled, 2-period/36 weeks	Proportion of subjects achieving HiSCR at Week 12 (primary); AN count of 0/1/2, NRS30, modified Sartorius score (ranked secondaries)	Completed
M12-555	497[a]	CAN, AUS, DEU, CZE, FRA, CHE, DNK, GRC, HUN, NLD, SWE, USA	OL extension/ at least 60 weeks	HiSCR, AN count, modified Sartorius score, NRS30	Ongoing

ada = adalimumab; AN = abscess and inflammatory nodule; AUS = Australia; CAN = Canada; CHE = Switzerland; CZE = Czech Republic; DB = double-blind; DEU = Germany; DNK = Denmark; eow = every other week; ew = every week; FRA = France; GRC = Greece; HiSCR = Hidradenitis Suppurativa Clinical Response; HS = hidradenitis suppurativa; HS-PGA = HS physician's global assessment; HUN = Hungary; NLD = Netherlands; NRS30 = at least a 30% reduction and at least 1 unit reduction from baseline in Patient's Global Assessment of Skin Pain – at worst –among subjects with baseline numeric rating scale (NRS) ≥ 3; pbo = placebo; PK = pharmacokinetics; SWE = Sweden; TUR = Turkey; USA = United States of America

a. Enrollment is complete and study is ongoing. Results are presented from an interim analysis of data through 29 April 2014.

Note: AN count is the total abscess and inflammatory nodule count. HiSCR is defined as at least a 50% reduction in the AN count with no increase in abscess count and no increase in draining fistula count relative to Baseline.

2.3.2. Pharmacokinetics

The pharmacokinetic properties of adalimumab have been characterized previously in healthy subjects and in patients with rheumatoid arthritis (RA), Crohn's disease (CD), active ulcerative colitis (UC) and chronic plaque psoriasis (Ps).

After subcutaneous administration of a single 40 mg dose, absorption and distribution of adalimumab was slow, with Tmax of about 5 days. The average absolute bioavailability of adalimumab is estimated to 64%. After single intravenous doses ranging from 0.25 to 10 mg/kg, concentrations were dose proportional, and clearances (CL) were typically under 12 ml/hour. The distribution volume (Vss) ranged from 4.7 to 6.0 litres. The mean terminal phase half-life was approximately two weeks.

Following subcutaneous administration of 40 mg of Humira every other week to patients with rheumatoid arthritis, accumulation of adalimumab was predictable based on the half-life, with mean steady-state concentrations of approximately 5 ug/ml (without concomitant methotrexate) and 8 to 9 ug/ml (with concomitant methotrexate), respectively. Methotrexate reduces adalimumab apparent clearance by approximately 40%.

The serum adalimumab trough levels at steady-state increased approximately proportionally with dose following 20, 40 and 80 mg every other week and every week subcutaneous dosing. In long-term studies with dosing more than two years, there was no evidence of changes in clearance over time.

Population pharmacokinetic analyses with data from over 1200 patients revealed a trend toward higher apparent clearance of adalimumab with increasing body weight and in the presence of anti adalimumab antibodies. After adjustment for weight differences, gender and age appeared to have a minimal effect on adalimumab clearance.

To support the current application the pharmacokinetics and immunogenicity of adalimumab were evaluated in subjects with moderate to severe Hidradenitis Suppurativa (HS) in a Phase 2 study (Study M10-467) and two Phase 3 studies (Studies M11-313 and M11-810). The population pharmacokinetics of adalimumab was also evaluated for HS subjects using a non-linear mixed effects modeling approach. The impact of covariates on adalimumab pharmacokinetics was assessed. Exposure-response analyses were conducted to evaluate the efficacy and safety of adalimumab in Phase 3 studies in the withdrawal phase.

The pharmacokinetics and immunogenicity results in subjects with HS were compared with results from previous studies in subjects with active CD (Study M02-403), UC (Study M06-827) and Ps (Study M02-528).

Analytical methods

The human serum samples were analysed by using a validated ELISA method over an analytical range of 3.125 ng/mL to 50.0 ng/mL. The minimum required dilution was 1:10 in sample buffer (-). Therefore, the LLOQ was 31.25 ng/mL in human serum. Inter-assay precision and bias for calibration standards were adequate.

Immunogenicity of adalimumab in the HS population was assessed in Studies M10-467, M11-313 and M11-810 using a double antigen sandwich enzyme-linked immunosorbent assay (ELISA) method. A sample was classified as AAA+ if the anti-adalimumab antibody (AAA) concentration in serum was >20 ng/mL and the serum sample was collected within 30 days after an adalimumab dose.

Pharmacokinetic data analysis

Descriptive statistics of adalimumab concentrations were presented for within and between study comparisons. In addition, a population pharmacokinetic (PPK) analysis has been performed. Subjects with moderate to severe HS in Studies M10-467, M11-313 and M11-810 who had adalimumab treatment and with at least one measurable adalimumab concentration were included in the population PK analyses (n=600). In study M10-467 blood samples for the measurement of serum adalimumab concentrations were obtained at Baseline, Weeks 4, 8, 16, 28, 31, 39, 45 and Week 52, and at ET visit if the subject discontinued prior to Week 52. Blood samples for the measurement of AAA were also obtained at Baseline, Weeks 4, 8, 16, 28, 31, 39, 45 and Week 52/ET. In studies M11-313 and M11-810 pre-dose blood samples for the measurement of serum adalimumab concentrations were obtained at Baseline, Weeks 2, 4, 8, 12, 14, 16, 20, 24, 32, 36, and at the ET visit if the subject discontinued prior to Week 36. Blood samples for measurement of AAA were obtained at Baseline, Weeks 4, 12, 16, 24 and Week 36/ET.

For the PPK analysis, adalimumab concentration values below LLOQ during active treatment were set to LLOQ/2. Both population PK and exposure-response models were built using nonlinear mixed effect modeling based on NONMEM 7.3 compiled with the GNU Fortran compiler. The PK model was fit to the data using the first-order conditional estimation method with INTERACTION within NONMEM. Inter-individual variability in PK parameters was modeled using an exponential error model. During the process of model

development standard graphical as well as numerical/statistical methods (including the likelihood ratio test to discriminate among alternative nested models) were employed to assess model goodness-of-fit. Inter-individual and residual variability were described and correlations between parameters were investigated.

Pharmacokinetics in target population

The population PK model included a one-compartment model with correlated exponential terms for inter-individual variability on CL/F and V2/F, a combined residual error model, and covariates on CL/F and V2/F.

The estimated PK parameter values, the effects of covariates on these parameters and their associated variability for the final adalimumab PK model are listed in **Table 2.** The model fit is illustrated in **Figure 1** and **Figure 2.**

Table 2. Parameter estimates for the final PPK model

Parameter	Population Estimate (SEE)	%RSE	95% CI
CL/F (L/day)	0.667 (0.018)	2.65	0.632 – 0.702
V_2/F (L)	13.5 (0.459)	3.40	12.6 – 14.4
k_a (1/day)	0.195 (0.019)	9.90	0.157 – 0.233
AAA on CL/F	6.76 (0.751)	11.1	5.29 – 8.23
CRP on CL/F	0.173 (0.021)	12.0	0.132 – 0.214
WTKG on CL/F	0.888 (0.107)	12.1	0.678 – 1.10
WTKG on V_2/F	0.707 (0.097)	13.7	0.516 – 0.898
Inter-Individual Variability on CL/F (%CV)	0.346 (58.8)	NA	NA
Inter-Individual Variability on V_2/F (%CV)	0.091 (30.2)	NA	NA
Residual Error Term – Proportional	0.052 (0.004)	NA	NA
Residual Error Term – Additive	2.06 (0.139)	NA	NA

NA = not applicable
SEE = Standard Error of Estimate
%RSE was estimated as the SEE divided by the population estimate multiplied by 100.
95% CI = 95% Confidence Interval = Estimate ± 1.96•SEE
%CV = SQRT(ETA) multiplied by 100

Figure 1. Individual (Upper Left) and Population Predicted (Upper Right) Versus Observed Concentrations and Conditional Weighted Residuals Versus Predicted Concentrations (Lower Left) and Versus Time (Lower Right) for Final Population Pharmacokinetic Model

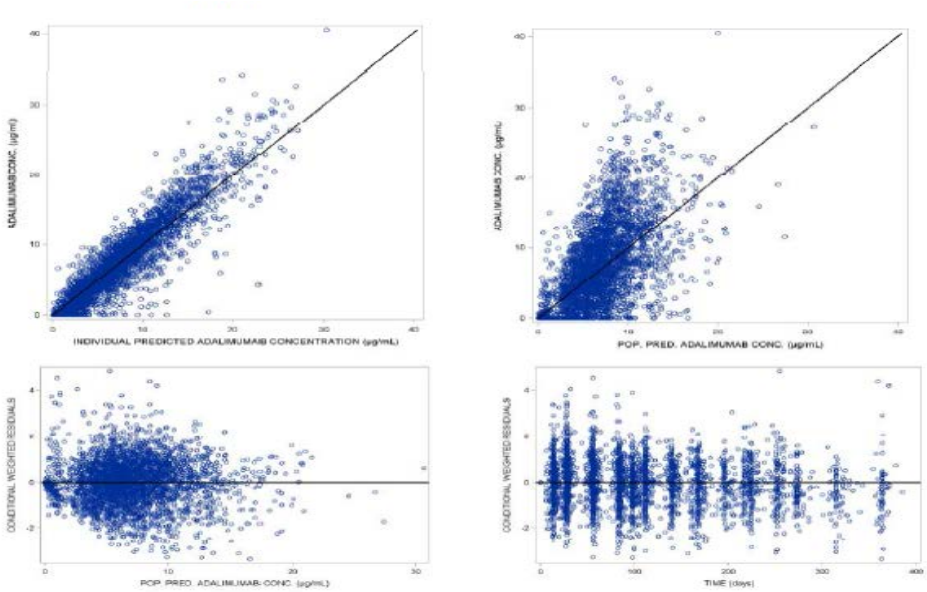
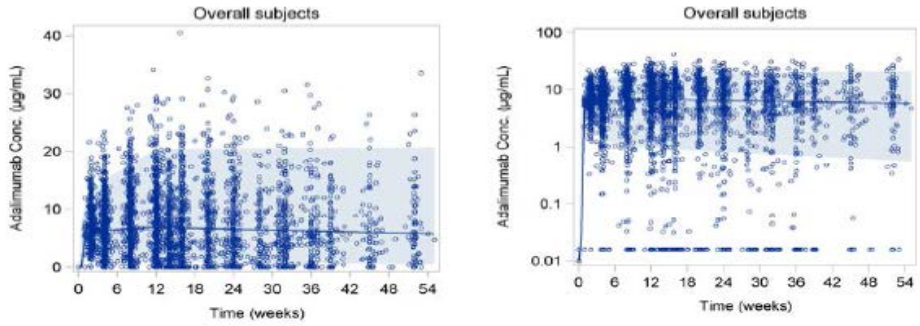


Figure 2. Visual Predictive Checks for Final Population Pharmacokinetic Model



Circles = observed data; solid line = median of the predicted concentrations; band = 90% prediction interval
Left Plot: Linear scale; Right Plot: Log-linear scale

Special populations

Impact of covariates

There was ~116% increase in median CL/F from subjects with the lowest weight quartile of 43 – 78 kg to subjects with the highest weight quartile of 110 – 221 kg. CL/F doubled from subjects with the lowest baseline CRP quartile of 0.1 – 3.875 mg/L to subjects with the highest CRP quartile of 20.9 – 189 mL/h.

There was a significant impact on CL/F in AAA+ patients. Median CL/F was about 6-fold higher in the AAA+ subjects compared to the AAA– subjects. The frequency of AAA+ in the three studies is reported in **Table 3**.

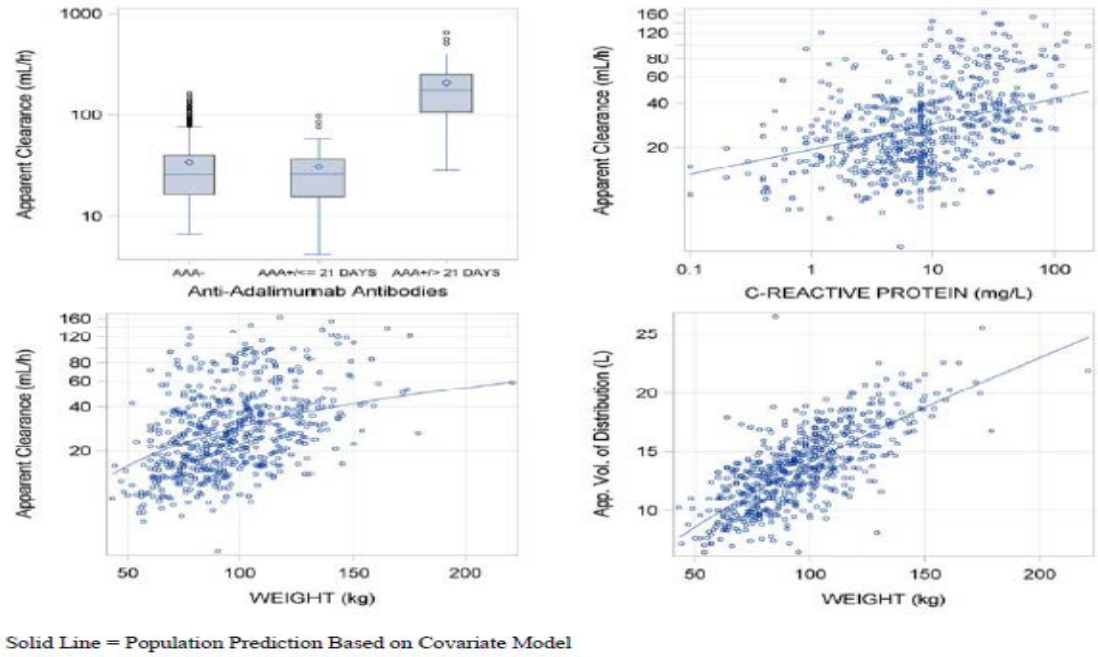
The impacts of AAA status and baseline CRP on CL/F, as well as baseline body weight on CL/F and V2/F are further illustrated in **Figure 3**.

Table 3. AAA positive rates (Phase III studies M11-313 and M11-810)

Treatment Group	Study M11-313	Study M11-810	Total
Period A (Weeks 0 – 12)			
Adalimumab 40 mg ew	5.2%, 8/153	1.2%, 2/163	3.2%, 10/316
Period B (Weeks 12 – 36)			
Adalimumab 40 mg ew/ew	10.4%, 5/48[a]	9.8%, 5/51[b]	10.1%, 10/99
Adalimumab 40 mg ew/eow	16.7%, 8/48[c]	9.4%, 5/53[d]	12.9%, 13/101
Adalimumab 40 mg ew/pbo	4.1%, 2/49[e]	0.0%, 0/51[f]	2%, 2/100
pbo/Adalimumab 40 mg ew	2.8%, 4/145	--	2.8%, 4/145
Periods A + B (Weeks 0 – 36)	**6.7%, 20/298**	**6.1%, 10/163**	**6.5%, 30/461**

a. Three subjects became AAA+ after Week 12.
b. Two subjects became AAA+ in Period A.
c. Five subjects became AAA+ after Week 12.
d. In addition, one subject's AAA+ sample was taken > 30 days from the last adalimumab dose and was not counted.
e. The subjects were AAA+ from Period A. In addition, 14 subjects had measurable AAA concentration during placebo treatment in Period B only. Since those samples were taken > 30 days of the last adalimumab dose, they were not counted as AAA+.
f. Twelve subjects had measurable AAA concentrations during placebo treatment in Period B only. Since these samples were taken > 30 days from the last adalimumab dose, they were not counted as AAA+.

Figure 3. Impact of Covariates on Pharmacokinetic Parameters: Final Model



Solid Line = Population Prediction Based on Covariate Model

Comparison of PK across indications

The proposed dosing regimen for subjects with moderate to severe HS consisted of an initial dosing regimen (adalimumab 160 mg at Week 0 and 80 mg at Week 2) and a maintenance dosing regimen (adalimumab 40 mg ew). Pharmacokinetic data obtained from Phase 3 studies in HS (Studies M11-313 and M11-810) were combined and compared with results from previous studies in other indications for these two regimens.

The same initial dosing regimen was tested in subjects with CD (Study M02 -403) and UC (Study M06-827). Adalimumab concentrations were lower in subjects with HS (approximately 7.5 µg/mL) compared to subjects with CD and UC (approximately 12 µg/mL) following the initial doses of 160 mg/80 mg administered at Week 0/Week 2. Similarly adalimumab concentrations following 40 mg ew treatment were lower in subjects with HS (8.8 µg/mL at Week 12) compared to those observed in subjects with Ps (17.6 µg/mL at Week 11) (Study M02-528).

Simulations to support alternative dosing

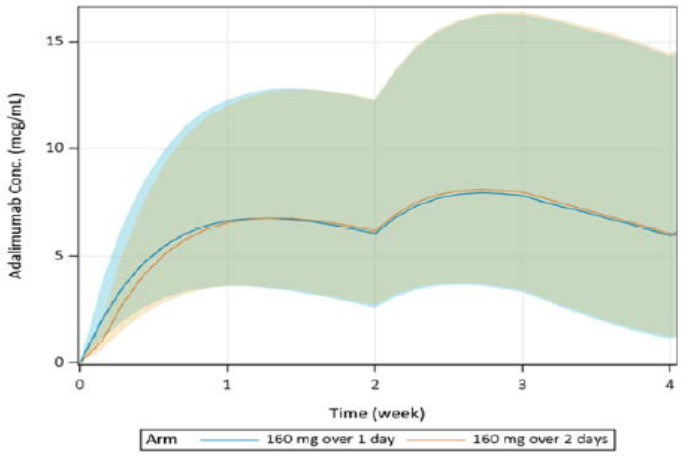
Patients in Studies M11-313 and M11-810 received 160 mg adalimumab at Week 0 and 80 mg at Week 2. The 160 mg dose requires 4 injections of 40 mg each on a single day, which may be inconvenient and difficult for subjects to tolerate. Thus an alternative initial dosing regimen was evaluated using the established PPK model of adalimumab in HS: the current regimen (Current), in which 160 mg of adalimumab was administered on Day 0, and 80 mg on Day 14. The simulated alternative regimen (Alternative) split the 160 mg dose over 2 days as shown in **Table 4Error! Reference source not found.** The simulated serum adalimumab concentrations following the administration of initial doses are shown in

Figure 4.

Table 4. Simulated dosing regimens

		Treatment Days		
		Day 0	Day 1	Day 14
Scenario	Current	160	--	80
	Alternative	80	80	80

Figure 4. Comparison of Simulated Serum Adalimumab Concentrations of 160 mg Adalimumab Given Over 1 or 2 Days



Shaded area = simulated 5th and 95th percentile of serum adalimumab concentrations; Solid line = simulated median of serum adalimumab concentrations

2.3.3. Pharmacodynamics

Mechanism of action

Adalimumab is a recombinant, fully human immunoglobulin (IgG1) monoclonal antibody that binds specifically to the soluble and transmembrane forms of tumour necrosis factor (TNF)-α and inhibits the binding of TNF- α to its receptors.

Primary and secondary pharmacology

No new data have been submitted within the scope of this variation which was considered acceptable by the CHMP.

The histopathologic characteristics of HS include a dense inflammatory cell infiltrate of neutrophils, lymphocytes, and histiocytes (Layton 2006). TNF-á, which induces other pro-inflammatory cytokines and activates neutrophils and lymphocytes, is believed to have a pathogenic role in HS, based on the evident over-expression of TNF in HS lesions (van der Zee 2011).

2.3.4. PK/PD modelling

At the end of Period A (Week 12) in the Phase 3 studies, subjects were evaluated for the primary efficacy endpoint of HiSCR. In subjects that received adalimumab 40 mg ew, HiSCR responders had slightly higher adalimumab concentrations compared to non-responders (8 – 11 µg/mL versus 6 – 7 µg/mL) in both Phase 3 studies (**Figure 5**). In addition, graphical exploration of the the observed loss of response (LOR) and HS as an adverse event in the withdrawal phase of Phase 3 studies (**Figure 6**) suggested a drug effect; the placebo group showing apparently higher LOR compared to the active treatment groups.

Figure 5. Mean (SD) Serum Adalimumab Concentrations Versus Time in Subjects with HS in Period A by HiSCR Response at Week 12 (Studies M11-313 and M11 –810)

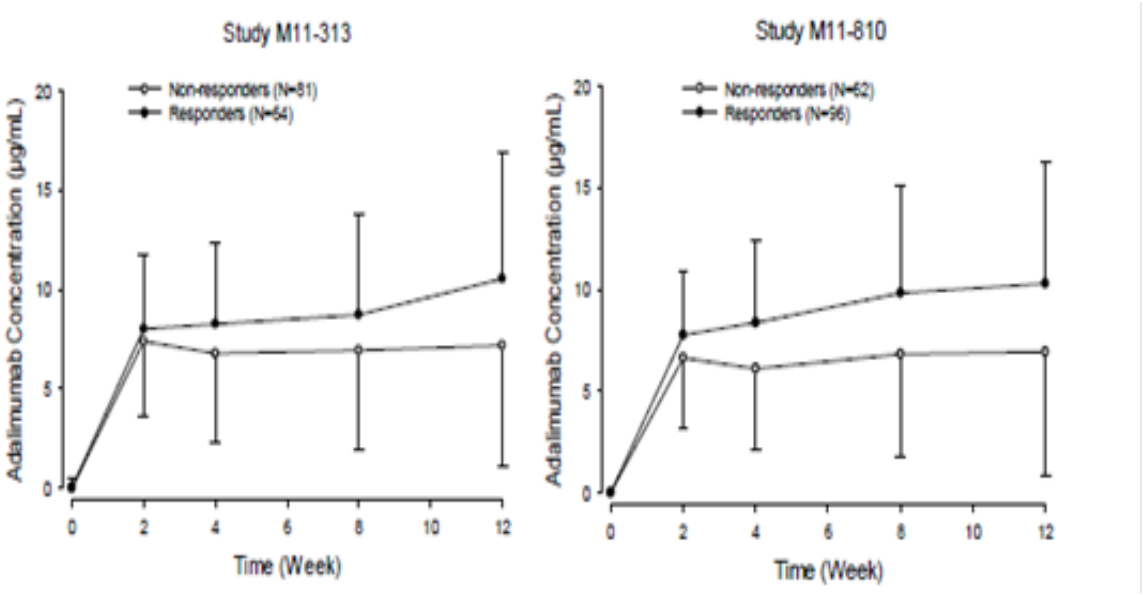


Figure 6. Kaplan-Meier Plot for Observed Loss of Response in the Withdrawal Phase Stratified by Treatment Group in Period B

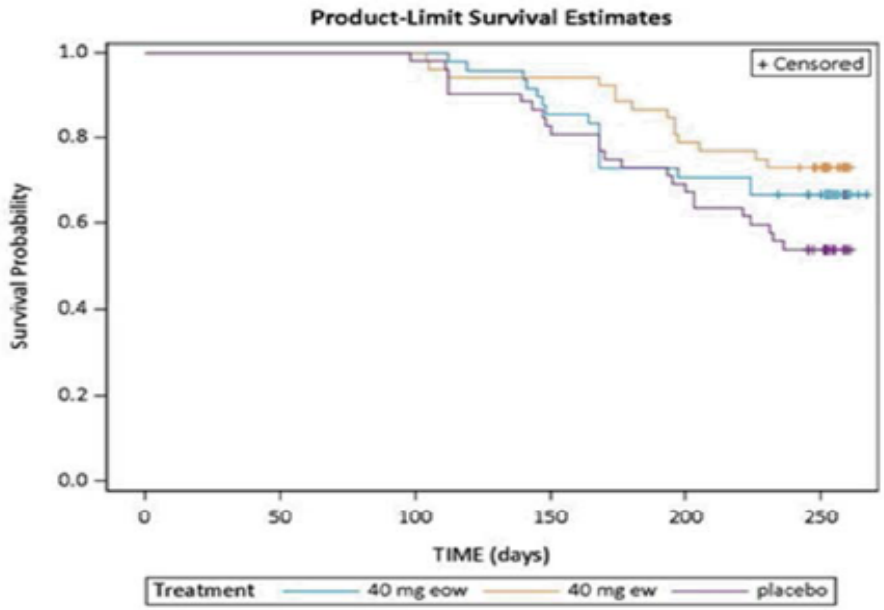
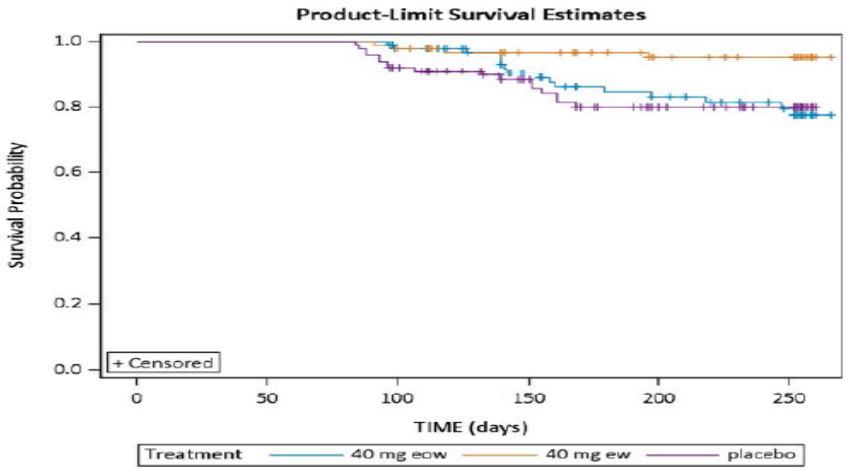


Figure 7. Kaplan-Meier Plot of First HS adverse event in the Withdrawal Phase Stratified by Treatment Group in Period B

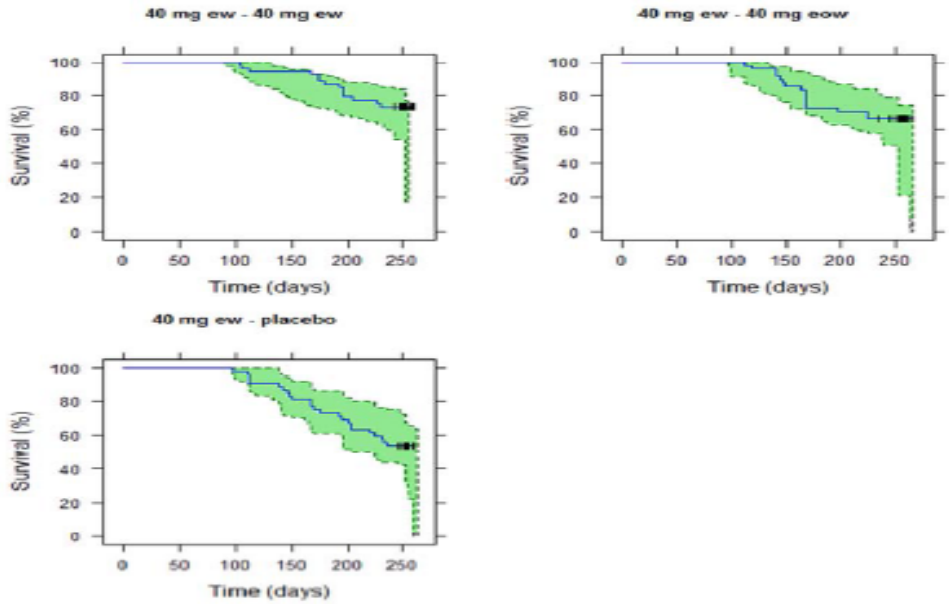


For the exposure-response modeling of efficacy and safety of adalimumab during the withdrawal phase of Phase 3 studies, parametric time-to-event (TTE) models were developed to explore potential effects of adalimumab treatment frequency on these endpoints. For efficacy, Loss of response (LOR) in responders and worsening or absence of improvement (WOAI) in non-responders were evaluated. For safety, HS as an AE and infection AEs were evaluated. The exposure-response models were fit to the data using the Laplacian Conditional Estimation method within NONMEM. The following covariates were investigated: AN count at baseline (AN_BL), AN count at Week 12 (AN_W12), draining fistula at Week 12 (DRFI_W12), CRP at Week 12 (CRP_W12), Sartorius scale at Week 12 (SART_W12), Hurley Stage at baseline (HUST_BL), tobacco use, body weight (WTKG), SEX, AGE, and antibiotics use at baseline (BANTIB).

Model of Loss of response

The Hazard function for Loss of Response (LOR) was fixed to zero for Period A to analyze the withdrawal phase in Period B only. The Visual Predictive Checks (VPCs) were performed using Perl Speaks NONMEM 4.2.0 and are shown as Kaplan-Meier plots in **Figure 8.** The observed LOR together with 95% prediction intervals were plotted separately for each treatment arm. The results indicated that the model appropriately describes the LOR over time for the different treatment arm. No covariates significantly improved the model.

Figure 8. Visual Predictive Checks for LOR Stratified by Treatment (Final Model)

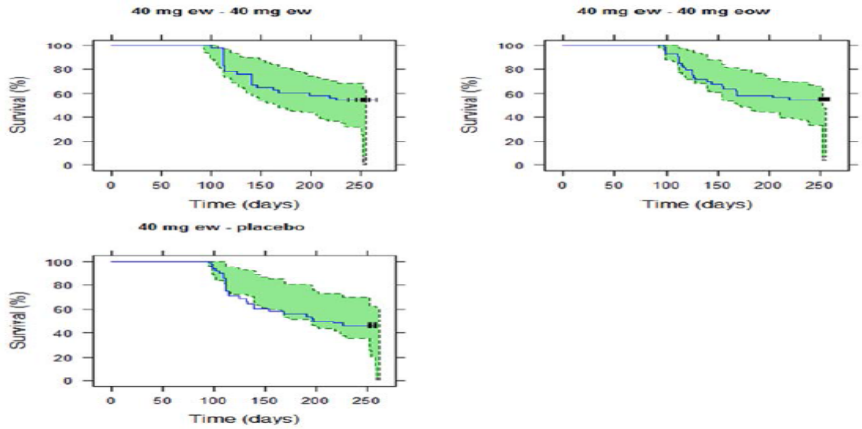


Note: Blue lines indicate observed LOR, black vertical lines indicate censoring events, and the green shaded regions denote 95% prediction intervals. Titles indicate treatment in Period A – Period B, respectively.

Model of absence of improvement

There was no significant correlation between adalimumab concentration and WOAI. Higher CRP values resulted in a more likely WOAI. There were no additional significant covariates identified. Model run12 was chosen as the final model.

Figure 9. Visual Predictive Checks for WOAI Stratified by Treatment (Final Model)

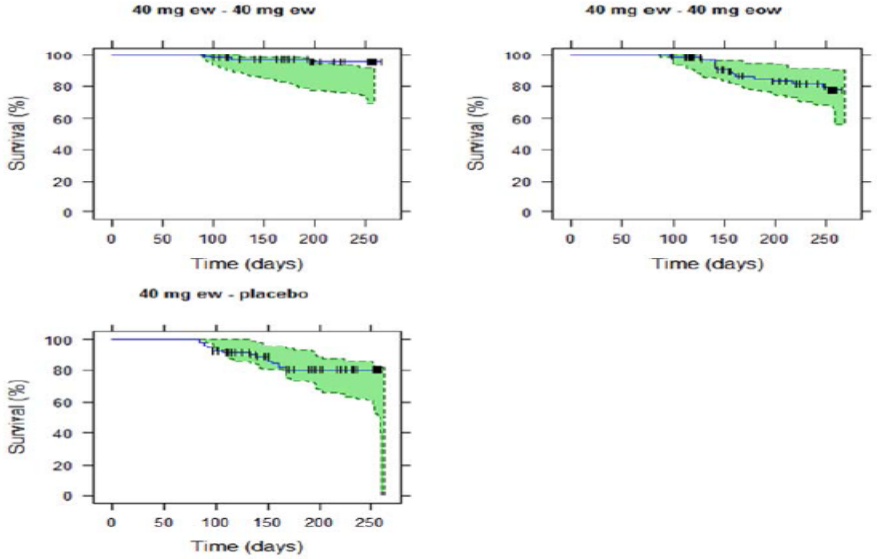


Note: Blue lines indicate observed WOAI, black vertical lines indicate censoring events, and the green shaded regions denote 95% prediction intervals. Titles indicate treatment in Period A – Period B, respectively.

Model for HS as an Adverse Event

None of the tested covariates significantly improved the fit which is illustrated in **Figure 10**.

Figure 10. Visual Predictive Checks for First HS AE Stratified by Treatment (Final Model)



Note: Blue lines indicate observed first HS AE, black vertical lines indicate censoring events, and the green shaded regions denote 95% prediction intervals. Titles indicate treatment in Period A – Period B, respectively.

2.3.5. Discussion on clinical pharmacology

Descriptive statistics of adalimumab concentrations at steady state have been presented for the three studies, however, the PPK model is considered the primary analysis. The PPK model has been developed according to current standard practices.

The VPCs could have been made more illustrative and easy to interpret by stratifying into separate plots according to covariate status. However, the presented plots suggested that the model adequately describes the data and the model is fit for purpose.

The alternative dosing causes only a small and transient difference in exposure. The proposed alternative dosing is endorsed by the CHMP.

No specific pharmacodynamic data have been submitted to support the use of adalimumab in HS. However, elevated TNF-á levels are implicated in several pathologic autoimmune conditions, including HS, based on observations of over-expression of TNF in HS lesions.

High initial loading doses and weekly 40 mg maintenance doses have been chosen for this indication, which are higher in comparison with most other indications already approved for Humira. No clear pharmacodynamic rationale for the need for high adalimumab concentrations in the treatment of HS has been presented. However, it is acknowledged that the recommended posology differs across indications for Humira, and in the phase 2 dose ranging study M10-467, both a high and low dose level regimen were investigated. In addition, HS patients were found to have a lower exposure compared to CD and Ps patients at the same doses. The lower exposure supports the need for a relatively high dose in this population.

The VPCs of the pharmacodynamics models presented suggest a considerable uncertainty in the exposure-response correlation (for LOR and HS) as well as for the correlation between CRP at week 12 and WOAI. However, the general conclusions regarding the statistical associations are endorsed.

In summary, the TTE modeling suggested that serum adalimumab concentration was a statistically significant predictor for LOR in Hidradenitis Suppurativa Clinical Response (HiSCR) responders (p-values = 0.015) and for HS as AE (p-values = 0.008). Higher adalimumab concentrations were associated with less probability for LOR or developing HS as an AE.

There was no apparent relationship between adalimumab concentration and WOAI, or between adalimumab concentration and infection AE in the exposure-response analyses. CRP at Week 12 was identified as a statistically significant covariate for WOAI (higher CRP values resulting in more likely WOAI). No covariate was identified for infection AEs.

Given the identified correlation between anti-adalimumab antibody formation and reduced efficacy, it appears likely that AAA+ HS patients are at risk of LOR as described in the SmPC (Section 5.1, Immunogenicity).

Available data indicate that in the initial treatment (Period A) a relationship exists between ADA levels and response. Taking into account that baseline CRP has a marked effect on the drug clearance, it is expected that CL/F baseline CRP levels may influence the clinical response. At CHMP's request, the MAH analyses the potential influence of baseline CRP levels on clinical response at week 2, 4, 8 and 12. The results suggested that baseline CRP levels affect the response rate, particularly in subjects with Hurley Stage III. In this group, the difference vs. placebo in response rates was 42.3% and 19.7%, in the sub-groups with lower (<8.4 mg/L) and higher (>8.4 mg/L) baseline CRP levels, respectively. The MAH argued that because the randomization was not stratified by baseline CRP levels, differences in response to treatment in the 2 CRP subgroups could be confounded by other factors. Given this and the small sample size, a multivariate approach that takes multiple factors into account and evaluates all time points simultaneously was considered to be more appropriate. For these reasons the Markov Chain Pharmacokinetic/Pharmacodynamic (PK/PD) modeling analysis was conducted and analysing VPC it could be concluded that the model adequately describe the observed data across treatment groups. The results of the PK/PD modelling analysis showed that none of the tested covariates was a significant predictor of treatment response. This indicates that, although higher disease markers may reduce placebo response to active treatment due to higher disease burden, they do not appear to affect response in subjects receiving adalimumab. Importantly, results of the performed analysis indicate that even in the subgroup in which the influence of baseline CRP levels was more evident (i.e., Hurley Stage III subjects with higher baseline CRP level), adalimumab was superior to placebo. Therefore, the provided data supports the conclusion that CRP levels are not very significant predictors of response per se and that baseline CRP levels do not influence clinical response.

2.3.6. Conclusions on clinical pharmacology

The PK properties of adalimumab have been characterized previously in healthy subjects and in patients with rheumatoid arthritis (RA), Crohn's disease (CD), active ulcerative colitis (UC) and chronic plaque psoriasis (Ps). The PK of adalimumab in patients with HS were evaluated in three clinical studies. Weight, CRP and AAA+ were identified as significant covariates of adalimumab CL/F. Particularly AAA+ had a significant impact on adalimumab exposure.

HS patients were found to have a lower exposure compared to CD and Ps patients at the same doses. This finding may be explained by the covariate effects described. The HS population had a mean weight >90 kg and the CRP appears also to be high in this group. The lower exposure supports the need for a relatively high dose in this population.

Simulations using the established PPK model suggest that splitting the 160 mg initial dose into two 80 mg doses administered over 2 days has only a small, transient impact on the exposure profile and should not alter the efficacy in subjects with HS compared to administering the 160 mg initial dose on a single day.

No specific pharmacodynamic data have been submitted to support the use of adalimumab in HS. However, elevated TNF-α levels are implicated in several pathologic autoimmune conditions, including HS, based on observations of over-expression of TNF in HS lesions.

High initial loading doses and weekly 40 mg maintenance doses have been chosen for this indication, which are higher in comparison with most other indications already approved for Humira. No clear

pharmacodynamic rationale for the need for high adalimumab concentrations in the treatment of HS has been presented. However, it is acknowledged that the recommended posology differs across indications for Humira, and in the phase 2 dose ranging study M10-467, both a high and low dose level regimen were investigated.

In summary, the TTE modelling showed that serum adalimumab concentration was a statistically significant predictor for LOR in Hidradenitis Suppurativa Clinical Response (HiSCR) responders and for HS as AE. Higher adalimumab concentrations were associated with less probability for LOR or developing HS as an AE. There was no apparent relationship between adalimumab concentration and WOAI, or between adalimumab concentration and infection AE in the exposure-response analyses. CRP at Week 12 was identified as a statistically significant covariate for WOAI (higher CRP values resulting in more likely WOAI). No covariate was identified for infection AEs.

2.4. Clinical efficacy

The end-point chosen for phase 3 was the "Hidradenitis Suppurativa Clinical Response", HiSCR, defined as at least a 50% reduction in the AN count with no increase in abscess count and no increase in draining fistula count, at Week 12 relative to baseline.

The psychometric performance and interpretability of HiSCR scores are based on data from Phase 2 Study M10-467 and one stand-alone, observational study. The application included a "HiSCR Measurement Report", which is summarized and assessed below:

Hidradenitis Suppurativa Clinical Response, HiSCR

The aim of the measurement report was to provide evidence supporting the HiSCR as an appropriate endpoint to evaluate efficacy for adalimumab for the treatment of adults with moderate to severe hidradenitis suppurativa (HS). The primary signs and symptoms of HS are abscesses, inflammatory nodules or draining fistulas and these are assessed by the HiSCR. The measurement of skin pain and other impacts of HS were addressed via other end-points.

Hidradenitis Suppurativa Clinical Response (HiSCR) definition
HiSCR is defined by the status of three-criteria lesions, including the sum of abscesses, the sum of inflammatory nodules (which are added for the total AN count) and the number of draining fistulas.
The definition of a HiSCR achiever is: (1) at least a 50% reduction in AN count, (2) with no increase in the number of abscesses, and (3) no increase in the number of draining fistulas.

The lesions are counted by the clinician in 12 different anatomical regions of the subject´s body, as detailed in a worksheet. Investigators were trained on the use of the HS Lesion and Degree of Erythema Assessments worksheet, including how to assess and record lesion counts. Every effort was made to have the same assessor perform the lesion count assessment at every study visit. Lesion counts were completed during Period A (Screening, Baseline Day 1, Weeks 2, 4, 8, and 12) and Period B (Weeks 14, 16, 20, 24, 28, 32, and 36 or Premature Discontinuation visit).

Content validity

The content validity of the HiSCR is supported by literature, which documents that inflammatory lesions (abscesses, inflammatory nodules, and draining fistulas) are important and relevant aspects of HS. HS patients experience impacts relating to interpersonal contact due to smell and appearance of skin resulting from the lesions. Emotional impacts (e.g. shame, irritation, feelings of lack of control, fear of stigmatization) and the possibility of isolation are other impacts experienced. The location of the lesions and the number of skin areas involved in HS lesions were major factors affecting the QoL of HS patients. The location of lesions could lead to being socially embarrassed and the failure to seek medical treatment. Specifically, the anogenital location of lesions has been shown to have a psychological impact as well as to result in physical impairment (pain, tenderness, flows, odor, or limited movements). It has been found that the clinical stage of disease activity was the most important factor related to QoL impairment in HS.

Psychometric evaluation and score interpretation

Psychometric evaluation of the HiSCR was performed using data from a Phase 2 clinical study and an observational study, to support the HiSCR's reliability (intra- and inter-rater reliability), validity (construct and predictive validity) and ability to detect change.

Study M10-467 (assessed below) included a 16-week, double-blind, placebo-controlled period (Period 1) followed by a 36- week, open-label period (Period 2). During Period 1, patients were randomized in a 1:1:1 ratio to adalimumab 40 mg every week, adalimumab 40 mg every other week or placebo. Pooled Period 1 data from all treatment arms were used for evaluating HiSCR (Baseline and Week 16 abscess, inflammatory nodule, and draining fistula counts were used to determine subject HiSCR responder status). Patients with AN count <3 at Baseline were excluded to eliminate the possibility that a one-unit reduction in AN count could lead to HiSCR response.

Three physician-rated HS disease severity measures were used as criteria measures for HiSCR validation: Hurley Stage, MSS (modified Sartorius score) and HS-PGA. Three patient-reported outcome (PRO) instruments were also used to demonstrate the association between HiSCR and PRO results: the Visual Analogue Scale for HS skin pain (Pain-VAS), the Dermatology Life Quality Index (DLQI) and the Work Productivity and Activity Impairment Questionnaire: Specific Health Problem (WPAI-SHP).

A total of 138 subjects with AN count ≥3 at Baseline were included for analyses. The majority were female, white and current smokers, with a mean age of 37 years. The mean disease duration was 12 years, with an average AN count of 13.1 at Baseline. The mean Baseline MSS was 125. The average DLQI score was 15.6, indicating that the disease had a large effect on patients. More than half of patients (54%) had Hurley Stage II, while 31% had Hurley Stage III lesions. The rationale for including 21 patients (15%) with Hurley Stage I was to provide evidence that the HiSCR performed throughout the spectrum of HS disease severities.

Construct-related validity

Construct-related validity is concluded when the associations between concepts measured by a specified instrument and concepts measured by other instruments are as expected. Construct-related validity is typically assessed via a correlation coefficient, which can range from –1.0 (a perfectly negative relationship) to 1.0 (a perfectly positive relationship), with 0.0 indicative of no relationship among the evaluated variables. There are no universally accepted rules for the interpretation of correlation coefficients (r); however, the following guidelines were considered based on the absolute value of r: negligible relationship, r=0.0-0.09, small relationship, r=0.1-0.29; medium relationship, r=0.30-0.49; and strong relationship, r=0.50 or larger.

Spearman´s rank-order correlations between HiSCR and the six existing ClinRO and PRO measures (Hurley Stage, MSS, HS-PGA, Pain-VAS, DLQI, WPAI-SHP) were assessed at Week 16. Correlations with HiSCR were calculated separately for two subscores of the WPAI-SHP (WPAI-TWI and WPAI-TAI).

HiSCR converged well with criteria measures, correlating significantly with all ClinRO and PRO assessments (Spearman's rho ranging between −0.64 and −0.38, all p<0.001) (Table). The highest correlations with HiSCR were observed with the HS-PGA, Pain-VAS, and MSS (Spearman's rho=−0.64, −0.53, and −0.51, respectively).

Table 5. Convergent validity: Spearman's correlation between HiSCR and criteria measures at Week 16

Assessment	Spearman's rho correlation with HiSCR	P value	N
Hurley Stage	-0.49	<0.001	127
MSS	-0.51	<0.001	127
HS-PGA	-0.64	<0.001	127
Pain-VAS	-0.53	<0.001	125
DLQI	-0.38	<0.001	124
WPAI-TWI	-0.47	<0.001	80
WPAI-TAI	-0.47	<0.001	123

DLQI=Dermatology Life Quality Index; HS-PGA=Hidradenitis Suppurativa Physician's Global Assessment; HiSCR=Hidradenitis Suppurativa Clinical Response; Pain-VAS=Visual Analogue Scale for HS skin pain; PRO=patient-reported outcome; MSS=modified Sartorius scale; WPAI-TAI=Work Productivity and Activity Impairment Questionnaire Total Activity Impairment; WPAI-TWI=Work Productivity and Activity Impairment Questionnaire Total Work Impairment

The predictive validity of the HiSCR was assessed using logistic regression to examine how well Week 16 HiSCR achievement predicted three dichotomized outcomes at Week 52: a) HiSCR achievement (yes/no); b) being "clear" or "minimal" with HS lesions based on HS-PGA (versus "mild"/"moderate"/"severe"/"very severe"); and c) having "no effect" (score of 0-1) or "small effect" (score of 2-5) based on DLQI scores (versus "moderate effect"/"large effect"/"very large effect").

Baseline characteristics, including age, gender, race (white/non-white), current smoker (yes/no), body mass index, and employment status (yes/no), along with a dichotomized variable indicating dose escalation during Period 2, were used in the regression models for predictive validity.

A total of 125 patients had AN counts at both Week 16 and Week 52 or their respective early termination visit. Logistic regression models showed that HiSCR responders at Week 16 were 4.7 times more likely to be responders at Week 52 when compared to non-responders, after adjusting for patient characteristics and dose escalation. These patients were 5.1 times more likely than the non-responders to have HS-PGA assessed as "clean" or "minimal" with HS lesions at Week 52. They were also 2.8 times more likely to report the skin disease had no effect or a small effect, based on DLQI scores.

Responsiveness (ability to detect change)

The responsiveness of HiSCR was evaluated by examining the difference in the mean changes of ClinRO and PRO measures between HiSCR achievers (responders) and non-achievers (non-responders) at Week 16 and at Week 52. The mean changes from Baseline to Week 16 in ClinRO and PRO measures were compared between the groups using Wilcoxon rank-sum tests. The patient distribution across three Hurley Stages between the groups was compared using the Cochran- Mantel-Haenszel statistic test. In addition, the standardized response mean (SRM) was computed for HiSCR responders and non-responders on each of the outcomes of interest.

Table presents the changes in ClinRO and PRO outcomes by HiSCR status at Week 16 and Week 52. A very large effect was observed by Week 16 on both ClinRO measures (HS-PGA and MSS) and moderately large to large effects were observed on all PROs among HiSCR responders. Among HiSCR non-responders, a small effect was observed on the DLQI and WPAI-TAI. At Week 52, most assessments had a greater extent of responsiveness among HiSCR responders. The extent of the improvements in score changes were all greater than the minimally importance difference of the respective PRO assessments, which include 10-14 (Pain-VAS), 5.0 (DLQI) and 7% (WPAI).

By Week 16, significantly more responders were in Hurley Stage I than in Hurley Stage II or III, (responders by Hurley Stage I, II, III: 61%, 35%, 4%; non-responders: 17%, 49%, 35%, p<0.001).

Table 6. Mean change in ClinRO and PRO measures by responder status Change From Baseline (mean±SD) SRM* Change From Baseline (mean±SD)

	Change From Baseline (mean±SD)	SRM*	Change From Baseline (mean±SD)	SRM*	Difference in Means	P value†
Week 16	**HiSCR Responders (n=49)**		**HiSCR Non-responders (n=78)**			
MSS	−46.5±40.1	1.16	−1.1±194.8	0.01	−45.45	<0.001
HS-PGA	−1.3±1.0	1.33	−0.1±0.7	0.16	−1.15	<0.001
Pain-VAS	−15.7±23.7	0.66	−1.7±25.9	0.04	−13.66	0.005
DLQI	−5.4±6.1	0.89	−2.9±6.4	0.45	−2.52	0.030
WPAI-TWI	−17.4±23.6	0.74	−2.6±19.9	0.13	−14.84	0.017
WPAI-TAI	−20.2±24.4	0.83	−6.1±24.8	0.24	−14.21	0.004
Week 52	**Responders (n=64)**		**Non-responders (n=62)**			
MSS	−66.3 ± 91.3	0.73	6.6 ± 99.5	0.07	−72.92	<0.001
HS-PGA	−1.6 ± 1.0	1.57	0.1 ± 0.7	0.16	−1.75	<0.001
Pain-VAS	−29.5 ± 29.6	1.00	−1.3 ± 29.5	0.04	−28.21	<0.001
DLQI	−7.4 ± 6.8	1.09	−2.4 ± 7.5	0.32	−5.03	0.003
WPAI-TWI	−19.2 ± 27.6	0.70	−5.7 ± 32.6	0.18	−13.50	0.116
WPAI-TAI	−23.6 ± 27.1	0.87	−9.3 ± 32.0	0.29	−14.31	0.013

DLQI=Dermatology Life Quality Index; HS-PGA=Hidradenitis Suppurativa Physician's Global Assessment; HiSCR=Hidradenitis Suppurativa Clinical Response; PRO=patient-reported outcome; Pain-VAS=Visual Analogue Scale for HS skin pain; MSS=modified Sartorius scale; SD=standard deviation; SRM=Standardized Response Measure; WPAI-TAI=Work Productivity and Activity Impairment Questionnaire Total Activity Impairment; WPAI-TWI=Work Productivity and Activity Impairment Questionnaire Total Work Impairment.
Treatment responders achieved HiSCR (defined as at least a 50% reduction in AN count with no increase in the number of abscesses and no increase in the number of draining fistulas relative to Baseline).
*SRM is computed by dividing the mean change in a score between two visits by the SD of that change. SRM (absolute values) of 0.2, 0.5, and 0.8 represent small, medium, and large degrees of change, respectively.[25]
†P values were calculated using Wilcoxon rank-sum tests

Assessment of Clinical meaningfulness to patients

To test whether a 50% reduction in AN count was the appropriate threshold for defining HiSCR achievement, mean changes from Baseline to Week 16 in PROs were calculated using alternative thresholds for the percentage changes in AN count. Patients were still required to have no worsening in abscess count and no worsening in draining fistula count.

Patients with worsening disease or minimal improvement in AN count (<30% reduction) did not have a meaningful improvement on the DLQI (Figure 11). They also reported worsening pain (Figure 11) and exhibited some improvement in WPAI-TWI and WPAI-TAI (Figure 12). However, no substantial incremental benefits were observed on PRO assessments beyond the AN count reduction threshold for HiSCR.

Figure 11. Mean changes from Baseline to Week 16 in Pain‑VAS and DLQI using alternative thresholds for the percentage changes in AN count

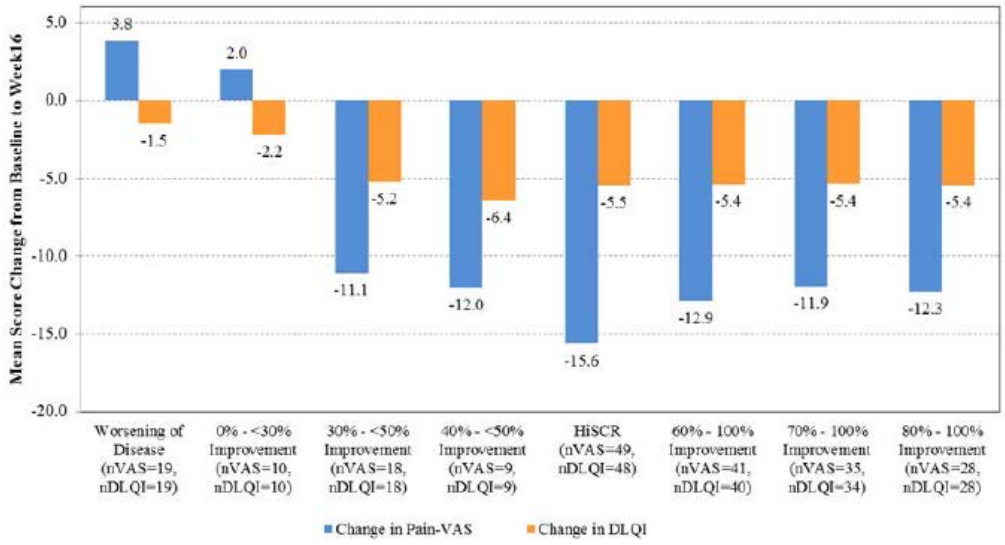
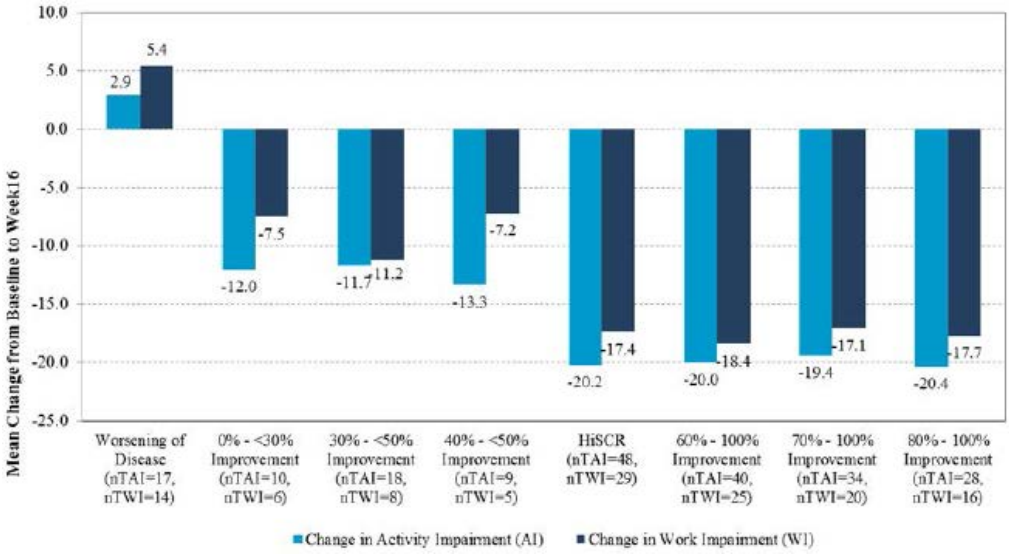


Figure 12. Mean changes from Baseline to Week 16 in WPAI using alternative thresholds for the percentage changes in AN count



Among HiSCR responders at Week 16, the impact on PROs of sustaining versus losing HiSCR achievement by Week 52 (or the last available observation after Week 16) was assessed using Wilcoxon rank-sum tests. Similarly, the Week 52 impact of achieving versus not achieving HiSCR response was compared among patients without HiSCR at Week 16. The majority of the HiSCR responders at Week 16 sustained the response to Week 52 (n=36/48). These patients experienced continued improvement between Week 16 and Week 52 (change of −7.9, −1.9, −3.8 for Pain - VAS, DLQI, and WPAI - TAI, respectively), with only WPAI - TWI being numerically worse (change of 2.7). Those Week 16 responders who lost HiSCR response at Week 52 experienced worse outcomes (change of 8.3, 2.1, 5.2, and 12.5 for Pain - VAS, DLQI, WPAI - TWI, and WPAI - TAI, respectively). Patients who did not achieve HiSCR at Week 16 but achieved HiSCR at Week 52 experienced significant improvements (change of −29.0, −5.0, −25.6 and −17.8 for Pain - VAS, DLQI, WPAI - TWI, and WPAI - TAI, respectively) compared to those who remained non-responders at Week 52.

Reliability assessment (Non-interventional study)
Reliability of the HiSCR was evaluated in a stand-alone, multi-center, prospective, non-interventional observational study. This study involved 22 clinically-confirmed HS subjects at two sites in the US, with two clinicians (dermatologists) participating at each site. These 4 clinicians had been treating patients with HS for over five years and they were all currently treating five to six HS patients per month on average. The subjects were to be between 18 to 65 years of age; have a diagnosis of HS for at least one year; and their HS was to have been stable for two months prior to screening as determined by the investigator through subject interview and review of the medical history.

Eligible subjects who provided consent to participate in the study had an in-office visit (Timepoint 1) to confirm eligibility and complete assessments. Two clinicians at the site evaluated the subjects using the HS Lesion Count Tool. At Timepoint 2, 7 days after Timepoint 1, subjects returned to the clinician's office to complete the Patient Global Impression of Change (PGI-C). Additionally, at Timepoint 2, the subjects were assessed by the same two clinicians using the HS Lesion Count Tool.

Among the 22 subjects that completed the study, most were female (n=19) and Caucasian (n=18). The mean age was 34 years. The self-reported HS severity of the patients was well distributed between mild, moderate and severe. Most of the patients reported use of antibacterial soaps, topical medications and antibiotics for treatment of their HS. The majority of patients were diagnosed with HS within the last one to two years. On average, almost 60% of patients used four or more treatments to control their HS.

As an indicator of reproducibility and consistency, score reliability (both inter- and intra-rater) for the HS Lesion Count Tool was evaluated. The inter-rater reliability of lesion counts was assessed by examining the intra-class correlation coefficients (ICCs) of lesion counts between pairs of clinicians.

Inter-rater reliability

Inter-rater reliability examined the degree to which two or more independent raters agree on the rating of the same subject. Inter-rater reliability was calculated between the first set of clinicians (i.e. combined data from Clinician 1 from Site 1 and Clinician 3 from Site 2) and the second set of clinicians (i.e. combined data from Clinician 2 from Site 1 and Clinician 4 from Site 2). These statistics were computed separately at Timepoints 1 and 2. The inter-rater reliability using ICC (1,1) for total draining fistula count, total inflammatory nodule count and total abscess/inflammatory nodule count was ≥0.61 for Timepoint 1 and Timepoint 2. The ICC for total abscess count was 0.38 and 0.67 for Timepoint 1 and Timepoint 2, driven primarily by a frequent rating of 0 abscesses by one clinician at Timepoint 1.

Due to the sensitivity of the inter-rater reliability statistics to the limited sample size at each timepoint, an exploratory model was proposed that combined both timepoints into the same model. This approach was based on a general linear model with subject, clinician and time as independent variables and the ICC computed as the proportion of variance attributable to clinician out of overall variance. Using this approach, the ICCs for each of the examined HS lesion counts were ≥0.68.

Table 7. Exploratory inter-rater reliability (N=88)

Comparison	ICC Reliability*	95% Confidence Interval
Total Abscess Count	0.68	(0.37, 0.85)
Total Draining Fistula Count	0.78	(0.55, 0.90)
Total Inflammatory Nodule Count	0.91	(0.80, 0.96)
Total Abscess/ Inflammatory Nodule Count	0.92	(0.82, 0.97)

*ICC computed using Shrout-Fleiss reliability one-way single score statistic (1,1) using data from baseline and follow-up across both sites.
Note: 6 out of 22 respondents (27.3%) reported no change in HS.

Intra-rater reliability

Intra-rater reliability (also known as test-retest reliability) is the degree to which an instrument yields similar scores at different time points in stable subjects (i.e. when no change is expected in the underlying concept).

Test-retest reliability was computed between Timepoints 1 and 2 using the sample combined across study site. As there was no treatment intervention, all subjects were assumed to be “stable” on scores between the first and the second assessment. This approach was based on a general linear model with subject, clinician, and time as independent variables and the ICC computed as the proportion of variance attributable to time out of overall variance. The intra-rater reliability using ICC (1,1) for total abscess count, total draining fistula count, total inflammatory nodule count, and total abscess/inflammatory nodule count was ≥0.70, showing an acceptable test-retest reliability.

Table 8. Intra-rater reliability (N=88)

Comparison	ICC Reliability*	95% Confidence Interval
Total Abscess Count	0.70	(0.42, 0.87)
Total Draining Fistula Count	0.78	(0.55, 0.90)
Total Inflammatory Nodule Count	0.91	(0.80, 0.96)
Total Abscess/Inflammatory Nodule Count	0.92	(0.83, 0.97)

*ICC computed using Shrout-Fleiss reliability one-way single score statistic (1,2) using data from baseline and follow-up across both sites.
Note: 6 out of 22 respondents (27.3%) reported no change in HS.

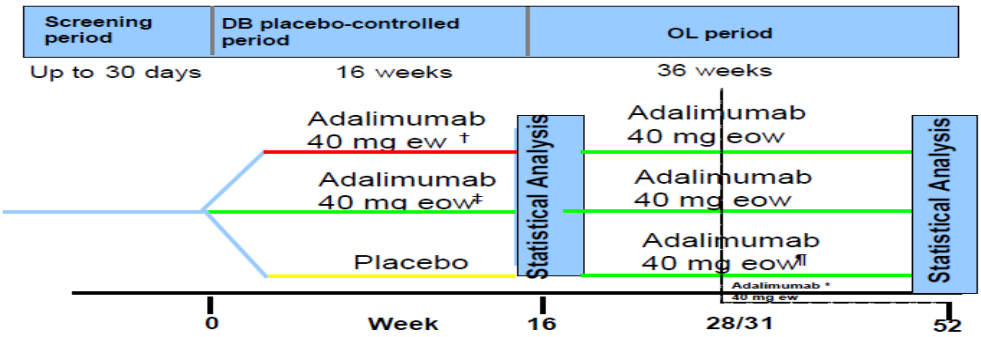
2.4.1. Dose response study

Study M10-467: Phase 2 Multicenter Study of the Safety and Efficacy of Adalimumab in Subjects with Moderate to Severe Chronic Hidradenitis Suppurativa

Methods

This was a Phase 2, double-blind (DB), placebo-controlled, randomized study with an open-label (OL) phase conducted in the US and Europe in subjects with moderate to severe chronic HS. The study consisted of 2 periods: a 16-week DB placebo-controlled period assessed adalimumab at 2 dosing regimens. In the 36-week OL period, all subjects received adalimumab 40 mg eow and those who failed to achieve HS-PGA < 3 were permitted to dose escalate at Week 28 or Week 31 to 40 mg ew through Week 51.

Figure 13. Study Design Schematic



† From Week 4, after 160 mg dose at Week 0, 80 mg at Week 2.
‡ From Week 1, after 80 mg dose at Week 0.
¶ From Week 17, after 80 mg dose at Week 16.
* At Week 28 or Week 31 subjects may have dose escalated to 40 mg ew.

- **Study participants**

Key inclusion and exclusion criteria are outlined below:

Inclusion criteria

- Male and female subjects ≥ 18 years of age.
- Subjects must have had a diagnosis of HS for ≥ 6 months prior to Baseline that involved ≥ 2 distinct anatomic areas (e.g., left and right axilla or left axilla and left inguinal-crural fold).
- Subjects must have been unresponsive or intolerant, as determined by the investigator, to oral antibiotics for treatment of their HS.
- Subjects must have had stable HS for ≥ 2 months before Screening and also at Baseline as determined by subject interview of his/her medical history.
- Subjects must have had a PGA of at least moderate disease (score of ≥ 3) at Baseline.
- If female, subject was either not of childbearing potential or was practicing an approved method of birth control throughout the study and for 150 days after last dose of study drug
- Subjects must have had a negative PPD test (or equivalent) and CXR (posterior-anterior [PA] and lateral view) at Screening. If the subject had a positive PPD test (or equivalent), had a past ulcerative reaction to PPD placement, and/or a CXR consistent with prior tuberculosis (TB) exposure, the subject must have initiated, or have documented completion of a course of anti-TB therapy.
- Subjects must have been judged to be in good general health, as determined by the investigator.

Exclusion criteria

- Subjects must not have had prior treatment with adalimumab or other anti-TNF therapy (e.g., infliximab or etanercept), or participation in an adalimumab trial.
- Subjects must not have had any other active skin disease or condition (e.g., bacterial, fungal, or viral infection) that may have interfered with assessment of HS.
- Subjects must not have been on allowable oral and/or topical antibiotic treatment for HS who had not been on a stable dose for ≥ 4 weeks prior to Baseline
- Subjects must not have received systemic non-biologic therapies with potential therapeutic impact for HS < 4 weeks prior to Baseline visit (other than oral and/or topical antibiotics).
- Subjects must not have received ultraviolet B (UVB) phototherapy within 2 weeks of Baseline or ultraviolet A and psoralen (PUVA) phototherapy within 4 weeks of Baseline.

Concomitant use of permitted oral and/or topical antibiotic therapy for treatment of HS was allowed provided the dosing regimen had been stable for ≥ 4 consecutive weeks prior to Baseline. The dosing regimen was to remain stable through study participation. Permitted concomitant antibiotics included: Topical: Clindamycin twice per day at a 1% concentration (weight/volume); Oral: Tetracycline (at a dose of up to 500 mg by mouth twice a day), Doxycycline (at a dose of up to 100 mg po bid) or Minocycline (at a dose of up to 100 mg po bid). Several medications were prohibited during the study, e.g. phototherapy (PUVA and/or UVB), biologic therapy including other anti-TNFs, other systemic drug therapies for HS, including MTX, cyclosporine, retinoids, and fumaric acid esters, live vaccines and oral or injectable corticosteroids.

• Treatments

Period 1 was a 16-week DB placebo-controlled period. Adalimumab was administered at 2 dosing regimens:

- 40 mg ew starting at Week 4 after a 160 mg dose at Week 0 and an 80 mg dose at Week 2 or
- 40 mg eow starting at Week 1 after an 80 mg dose at Week 0

Subjects randomized to placebo received placebo injections at Baseline (Day 1), Week 1 (Day 8), Week 2 (Day 15) and ew from Week 3 (Day 22) through Week 15.

In the 36-week OL period, all subjects received adalimumab 40 mg eow and those who failed to achieve HS-PGA < 3 were permitted to dose escalate at Week 28 or Week 31 to 40 mg ew through Week 51.

• Objectives

The primary objective was to determine the efficacy and safety of adalimumab in subjects with moderate to severe chronic HS after 16 weeks of treatment.

The secondary objective was to determine maintenance of efficacy and continued safety of adalimumab 40 mg for an additional 36 weeks. The PK and immunogenicity of adalimumab following subcutaneous (SC) injection were also assessed.

• Outcomes/endpoints

Primary efficacy variable

The primary efficacy variable was the proportion of subjects achieving clinical response, defined as achieving a PGA of clear, minimal, or mild, with a minimum of 2 grades improvement (reduction) from Baseline on the PGA at Week 16. Thus, a subject who entered with PGA of 3 must have achieved PGA of 0 or 1, and a subject who entered with PGA of 4 or 5 must have achieved PGA of 0, 1, or 2.

Secondary efficacy variables (ITT population) included:

- Proportion of subjects who achieved a clinical response at each visit (other than at Week 16)

- Proportion of subjects who achieved at each visit: a PGA of clear or minimal; a PGA of clear, minimal, or mild; a PGA of clear; ≥ 1 grade of improvement in PGA relative to Baseline.
- Proportion of subjects achieving complete clearance of abscesses and complete elimination of draining fistulas at each visit, among subjects who had any abscesses or draining fistula at Baseline
- Absolute and percent change at each visit from Baseline in numbers of different lesions, e.g. non-inflammatory and inflammatory nodules, total number of nodules, number of abscesses, number of draining and non-draining fistulas
- Change from Baseline in Sartorius scale at Week 16 and Week 52
- DLQI (0 at each visit, 0 or 1 at each visit, change from Baseline in DLQI)
- Change from Baseline in Patient's Global Assessment of skin pain at each visit, PHQ-9 at Week 16 and Week 52 and EQ-5D scores at Week 16 and Week 52

• Sample size

Approximately 150 subjects were planned to be enrolled. The study was designed to detect a clinically relevant difference between active treatment and placebo treatment groups with 80% power. The sample size was based on the hypothesis tests for primary efficacy endpoint. The expected clinical response rate for placebo treatment was 10%, and 35% for active treatment.

• Randomisation

The randomization schedules were generated at AbbVie and were provided to the IVR/IWR vendor. At Week 0 eligible subjects were randomized centrally, stratified by Hurley Stage (Stage III vs. Stage I or II) in a 1:1:1 ratio to either adalimumab ew, adalimumab eow, or placebo. The proportion of enrolled subjects with Hurley stage III was not to exceed 50% of the total study population.

• Blinding (masking)

The MAH's team responsible for the conduct of the study, the investigator, site study personnel, and the subject remained blinded to each subject's randomized treatment group throughout the course of the study. All subjects who completed Period 1 were eligible to participate in Period 2. Subjects from the placebo arm in Period 1 received a blinded dose of 80 mg adalimumab at Week 16. To maintain the blind of Period 1, 54subjects from Arm C (placebo) received two injections of adalimumab (80 mg) at Week 16 while subjects from the active treatment groups, Arm A and B, received 2 placebo injections.

Starting at Week 17 and through Week 28, all subjects received one injection of 40 mg adalimumab SC eow.

• Statistical methods

All statistical tests were 2-tailed with a significance level of 0.05.

The Intent-to-Treat (ITT) Population in each Period was used for analyses of efficacy with the ITT Population in Period 1 (ITT-1) defined as all subjects who were randomised at Week 0. The ITT Population in Period 2 (ITT-2) included all subjects who received ≥1 dose of study drug in Period 2. For subjects who were dose escalated, all evaluations after dose escalation were excluded. In addition, the ITT Population for integrated analysis across Period 1 and Period 2 (ITT-Int) included subjects who were randomized to adalimumab 40 mg ew or eow at Week 0. The ITT-Int population was used for evaluation of the 2 dosing strategies, adalimumab ew/eow (step-down) versus continued adalimumab 40 mg eow dosing. The ITT-Int population was analysed in 2 ways, with and without the option of dose escalation.

In period 1 pairwise comparisons of each adalimumab dose arm versus placebo were performed. In period 2 adalimumab eow/eow versus adalimumab ew/eow was compared to evaluate the long-term dosing strategy.

The primary analysis was the comparison of each adalimumab treatment group versus the placebo treatment group. An initial overall comparison across the 3 treatment groups was performed. If statistically significant, pairwise comparisons of each adalimumab dose group versus placebo were to be performed. A global test controls the overall type I error and is, with three treatment arms including a placebo considered sufficient for control regarding also each pairwise comparison.

The analysis of the primary endpoint, the proportion of subjects achieving clinical response at Week 16, was based on a Cochran-Mantel-Haenszel (CMH) test with factors of treatment and baseline Hurley Stage, hence taking the stratification factor into account. A non-responder imputation was used as primary approach to impute missing values with sensitivity analyses planned using Last Observation Carried Forward (LOCF). The primary non-responder imputation is agreed with. Additional sensitivity analyses could be performed on the per-protocol (PP) population, which, if defined, were to exclude subjects with major protocol deviations. No PP analyses were however performed.

Analyses of secondary efficacy endpoints were performed using the CMH test, analysis of covariance (ANCOVA), and stratified Log-rank test with factors of treatment and Hurley Stage as appropriate.

Three analysis populations were defined for analyses of safety, the Safety population, the All Adalimumab population and the Eow population. The Safety Population included all subject in the ITT population who received at least one dose of study drug.

Results

- **Participant flow**

A total of 154 subjects who met entry criteria were enrolled and almost all of the subjects (93%) in the ITT-1 population completed Period 1.

Table 9. Disposition of Subjects in Period 1 (ITT-1 Population)

	Number (%) of Subjects by Randomization Group			
		Adalimumab		
	Placebo N = 51	eow N = 52	ew N = 51	Total N = 154
Randomized and dosed	51 (100)	52 (100)	51 (100)	154 (100)
Completed Period 1	46 (90.2)	52 (100)	45 (88.2)	143 (92.9)
Discontinued from Period 1	5 (9.8)	0	6 (11.8)	11 (7.1)
Discontinuations due to all reasons[a]				
Adverse event	0	0	1 (2.0)	1 (0.6)
Withdrew consent	2 (3.9)	0	1 (2.0)	3 (1.9)
Lack of efficacy	0	0	1 (2.0)	1 (0.6)
Lost to follow-up	2 (3.9)	0	1 (2.0)	3 (1.9)
Exceeded protocol specified number of interventions	1 (2.0)	0	0	1 (0.6)
Did not meet entry criteria	0	0	0	0
Protocol violation	0	0	0	0
Other	0	0	2 (3.9)	2 (1.3)
Completed Period 1 but did not enter Period 2	0	1 (1.9)	0	1 (0.6)

eow = every other week; ew = every week

a. No subjects discontinued for multiple reasons in Period 1.

Note: Percent based on the number of subjects randomized and dosed.

A total of 143 subjects completed Period 1 and 142 subjects entered Period 2. The majority (72.5%) of the ITT-2 population completed Period 2. The most common primary reasons for premature discontinuation from the study in the ITT-2 population were "withdrew consent" (7.7%) and "lack of efficacy" (7.7%).

Eighty-nine subjects dose escalated in Period 2 at Week 28 or Week 31. Of these, 75.3% completed Period 2. The most common reason for premature discontinuation from the study among subjects who dose escalated was "lack of efficacy" (10%).

- **Recruitment**

A total of 154 subjects with HS were randomized across 26 sites in the US, Netherlands, Denmark, and Germany. The first subject's first visit occurred on 22 April 2009 and the last subject's last visit occurred on 09 November 2010.

- **Conduct of the study**

The original protocol had 2 amendments. The protocol changes described in the amendments and administrative changes did not affect the interpretation of the results in the study. The option for dose escalation in period 2 was included in the second amendment.

A total of 34 (22%) subjects had major protocol deviations. Three subjects had received major protocol-prohibited treatment for HS and their efficacy assessments after the prohibited treatment were excluded from efficacy analyses. The subjects were counted as non-responders in the NRI analysis and had their last assessments prior to the start of prohibited medications carried forward in the LOCF analysis. None of the major protocol deviations were deemed to have impacted the analysis or interpretation of the efficacy and safety results of the study.

Subjects in the ITT-1 population had an overall mean compliance of >97% across treatment groups and the compliance was similarly high (>96%) in the ITT-2 population.

- **Baseline data**

Table 10. Demographic Characteristics (ITT-1 Population)

Demographic Characteristic	Placebo N = 51	Adalimumab eow N = 52	Adalimumab ew N = 51	Total N = 154	*P* value
Mean age ± SD (years)	37.8 ± 12.10	36.1 ± 12.50	35.1 ± 10.69	36.3 ± 11.76	0.525[a]
Age group (n [%])					
< 40 years	34 (66.7)	31 (59.6)	33 (64.7)	98 (63.6)	0.759[b]
≥ 40 years	17 (33.3)	21 (40.4)	18 (35.3)	56 (36.4)	
Sex (n [%])					
Female	36 (70.6)	38 (73.1)	36 (70.6)	110 (71.4)	0.950[b]
Male	15 (29.4)	14 (26.9)	15 (29.4)	44 (28.6)	
Race (n [%])					
White	37 (72.5)	36 (69.2)	37 (72.5)	110 (71.4)	0.925[b,c]
Black	8 (15.7)	12 (23.1)	9 (17.6)	29 (18.8)	
Asian	0	0	2 (3.9)	2 (1.3)	
American Indian/Alaska Native	0	0	1 (2.0)	1 (0.6)	
Native Hawaiian or other Pacific Islander	0	0	0	0	
Other	5 (9.8)	2 (3.8)	2 (3.9)	9 (5.8)	
Multi Race	1 (2.0)	2 (3.8)	0	3 (1.9)	
Hispanic or Latino (n [%])					
Yes	7 (13.7)	5 (9.6)	2 (3.9)	14 (9.1)	0.232[b]
No	44 (86.3)	47 (90.4)	49 (96.1)	140 (90.9)	
Body weight (kg)					
Mean ± SD	96.5 ± 24.80	99.8 ± 26.75	95.4 ± 22.94	97.2 ± 24.80	0.649[a]
Median (min – max)	96.0 (48.0 – 161.0)	100.0 (54.0 – 172.0)	90.0 (57.0 – 143.0)	96.5 (48.0 – 172.0)	
BMI					
Mean ± SD	33.8 ± 7.92	35.2 ± 9.40	33.1 ± 8.31	34.0 ± 8.56	0.438
Median (min – max)	32.6 (18.1 – 49.7)	34.8 (18.9 – 64.7)	31.6 (18.6 – 51.6)	32.8 (18.1 – 64.7)	

About 55% of the total population were current nicotine users, 30% were non-users and 15% ex-users. With respect to alcohol consumption, 60% were drinkers and 36% non-drinkers.

No statistically significant differences were observed in demographic characteristics across treatment groups in the ITT-1 population. The demographics for the other populations (ITT-2, ITT-Int, All Adalimumab treated, eow, and Dose Escalation populations) were generally similar to the ITT-1 population.

With respect to disease history, the mean duration of HS was 11.9 years and approximately 28% of subjects reported a family history of HS in the ITT-1 population with no statistically significant differences observed across treatment groups.

Table 11. Hurley Stage and Sartorius Scale Assessments (ITT-1 Population)

		Adalimumab			
Disease Activity Assessment	**Placebo N = 51**	**eow N = 52**	**ew N = 51**	**Total N = 154**	***P* value**
Hurley Stage(n [%])					
I	7 (13.7)	9 (17.3)	8 (15.7)	24 (15.6)	0.995[a]
II	29 (56.9)	28 (53.8)	28 (54.9)	85 (55.2)	
III	15 (29.4)	15 (28.8)	15 (29.4)	45 (29.2)	
Sartorius scale					
N	51	51	51	153	
Mean ± SD	104.7 ± 106.44	97.6 ± 122.32	114.4 ± 150.94	105.6 ± 127.24	0.723[b]
Median (min – max)	66 (0 – 498)	61 (12 –721)	70 (19 – 759)	64 (0 – 759)	

eow = every other week; ew = every week

a. *P* value is based on Fisher's exact test.

b. *P* value for differences among treatment groups is from Kruskal-Wallis test.

Note: Percent based on non-missing values.

Table 12. Physician's Global Assessment and Patient's Global Assessment (ITT-1)

	Number (%) of Subjects				
		Adalimumab			
Disease Activity Assessment	**Placebo N = 51**	**eow N = 52**	**ew N = 51**	**Total N = 154**	***P* value**
Physician's Global Assessment (n [%])					
Clear	0	0	0	0	0.998[a]
Minimal	1 (2.0)	0	0	1 (0.6)	
Mild	0	1 (1.9)	0	1 (0.6)	
Moderate	33 (64.7)	35 (67.3)	35 (68.6)	103 (66.9)	
Severe	5 (9.8)	5 (9.6)	5 (9.8)	15 (9.7)	
Very severe	12 (23.5)	11 (21.2)	11 (21.6)	34 (22.1)	
Patient's Global Assessment (n [%])					
Complete disease control	0	1 (1.9)	0	1 (0.6)	0.598[a]
Good disease control	4 (7.8)	6 (11.5)	4 (7.8)	14 (9.1)	
Limited disease control	15 (29.4)	17 (32.7)	22 (43.1)	54 (35.1)	
Uncontrolled disease	32 (62.7)	28 (53.8)	25 (49.0)	85 (55.2)	

The majority of subjects in the ITT-1 population had a PGA of moderate disease at Baseline. Subjects in the 3 treatment groups had similar HS severity at Baseline as judged also by the similarity in their individual PGA components.

The most frequently reported conditions/diagnosis were hypertension, depression, and obesity.

A majority (82%) of all subjects had been on some type of medication (not specifically for HS) prior to enrolment into the study. The most frequently reported prior medications were ibuprofen, minocycline, clindamycin, and doxycycline. Prior medications taken for treatment of HS were common and consisted of both topical and systemic treatments (corticosteroids, retinoids, antibiotics). Prior treatment, either topical or systemic, was generally ineffective and unsatisfactory response was a common reason for discontinuation of previous treatment.

Almost all subjects (93.5%) used concomitant medication during the study. The most frequently reported concomitant medications were ibuprofen (20%), paracetamol (16%), triamcinolone (10%) and minocycline (7%).

- **Numbers analysed**

Seven populations were used to analyse the data from this study.

The ITT population in Period 1 (ITT-1) included all subjects who were randomised at Week 0 (N = 154; placebo n=51, adalimumab eow n=52, adalimumab ew n=51).

The ITT population in Period 2 (ITT-2) included all subjects who received ≥1 dose of study drug in Period 2 (N = 142; placebo/eow n=46, adalimumab eow/eow n=51, adalimumab ew/eow n=45).

The ITT population for integrated analysis across Period 1 and Period 2 (ITT-Int) included all subjects who were randomised to adalimumab eow or ew at Week 0 (N = 103; adalimumab eow/eow n=52, adalimumab ew/eow n=51).

The Safety population for each period was the same as the ITT population in each period (Period 1 N = 154, Period 2 N = 142). The Safety population for the integrated analysis across Period 1 and Period 2 included all subjects who were in the ITT-Int population and received ≥ 1 dose of study drug in the study (N = 103). Since all randomised subjects received at 1 dose of study drug, the Safety population was the same as the ITT population in each period and ITT-Int.

The All Adalimumab treated population included all subjects who received ≥1 dose of adalimumab in the study (N = 149).

The Dose Escalation population included all subjects who dose escalated from adalimumab 40 mg eow to 40 mg ew (N = 89).

The eow population (N = 98) included subjects who received adalimumab 40 mg eow in Period 1 (n=52) and who switched from placebo in Period 1 to adalimumab 40 mg eow in Period 2 (n=46).

• **Outcomes and estimation**

Primary Efficacy Variable

Table 13. Proportion of Subjects Achieving Clinical Response at Week 16 (NRI and LOCF, ITT-1 Population)

Variable Baseline Hurley Stage	Placebo n/N (%)	Adalimumab eow n/N (%)	*P* value[a]	Adalimumab ew n/N (%)	*P* value[a]
Clinical responders at Week 16 (NRI)					0.022[b]
All stages	2/51 (3.9)	5/52 (9.6)	0.252	9/51 (17.6)	0.025
Stage I/II	2/36 (5.6)	5/37 (13.5)	0.430	8/36 (22.2)	0.085
Stage III	0/15	0/15	N/A	1/15 (6.7)	1.000
Clinical responders at Week 16 (LOCF)					0.004[b]
All stages	2/50 (4.0)	5/52 (9.6)	0.252	11/50 (22.0)	0.006
Stage I/II	2/36 (5.6)	5/37 (13.5)	0.430	10/35 (28.6)	0.012
Stage III	0/14	0/15	N/A	1/15 (6.7)	1.000

eow = every other week; ew = every week; LOCF = last observation carried forward; NRI = non-responder imputation, in which subjects with missing PGA scores are counted as non-responders; PGA = Physician's Global Assessment

a. *P* value for pairwise comparison (adalimumab ew versus placebo and adalimumab eow versus placebo) is from CMH test adjusted for Baseline Hurley Stage.

b. *P* value for comparison across all treatment groups is from CMH test adjusted for Baseline Hurley Stage.

Note: A clinical responder is a subject with a PGA score of 0/1/2 and $\geq$ 2 grades of reduction in PGA score relative to Baseline.

Secondary Efficacy Variables

Table 14. Proportion of Subjects Achieving Clinical Response at each Visit in Period 1 (NRI, ITT-1 Population)

	Number (%) of Subjects		
		Adalimumab	
Visit	Placebo N = 51	eow N = 52	ew N = 51
Week 2	1 (2.0)	5 (9.6)	1 (2.0)
Week 4	1 (2.0)	3 (5.8)	6 (11.8)
Week 8	4 (7.8)	3 (5.8)	4 (7.8)
Week 12	3 (5.9)	4 (7.7)	11 (21.6)[a]
Week 16	2 (3.9)	5 (9.6)	9 (17.6)[a]

eow = every other week; ew = every week; NRI = non-responder imputation, in which subjects with missing PGA scores are counted as non-responders; PGA = physician's global assessment

a. $P \leq 0.05$ for pairwise comparison versus placebo is from CMH test adjusted for Baseline Hurley Stage.

Note: A clinical responder is a subject with a PGA score of 0/1/2 and ≥ 2 grades of reduction in PGA score relative to Baseline.

Table 15. Proportion of Subjects Achieving PGA Scores of Clear, Minimal, and/or Mild and Improvement in PGA at each Visit in Period 1 (NRI, ITT-1 Population)

	Number (%) of Subjects		
		Adalimumab	
PGA Score/Improvement Visit	Placebo N = 51	eow N = 52	ew N = 51
Clear			
Week 2	1 (2.0)	2 (3.8)	0
Week 4	0	2 (3.8)	1 (2.0)
Week 8	0	1 (1.9)	0
Week 12	0	1 (1.9)	1 (2.0)
Week 16	1 (2.0)	2 (3.8)	4 (7.8)
Clear or minimal			
Week 2	1 (2.0)	6 (11.5)	1 (2.0)
Week 4	1 (2.0)	3 (5.8)	3 (5.9)
Week 8	4 (7.8)	2 (3.8)	2 (3.9)
Week 12	2 (3.9)	3 (5.8)	8 (15.7)[a]
Week 16	2 (3.9)	5 (9.6)	7 (13.7)
Clear, minimal, or mild			
Week 2	8 (15.7)	9 (17.3)	12 (23.5)
Week 4	6 (11.8)	15 (28.8)[a]	19 (37.3)[a]
Week 8	14 (27.5)	13 (25.0)	19 (37.3)
Week 12	15 (29.4)	17 (32.7)	24 (47.1)
Week 16	12 (23.5)	11 (21.2)	25 (49.0)[a]
≥ 1 grade improvement[b]			
Week 2	8 (15.7)	15 (28.8)	18 (35.3)[a]
Week 4	9 (17.6)	25 (48.1)[a]	24 (47.1)[a]
Week 8	15 (29.4)	22 (42.3)	24 (47.1)
Week 12	16 (31.4)	23 (44.2)	27 (52.9)[a]
Week 16	14 (27.5)	21 (40.4)	29 (56.9)[a]
≥ 2 grades improvement[b]			
Week 2	1 (2.0)	8 (15.4)[a]	5 (9.8)
Week 4	2 (3.9)	9 (17.3)[a]	8 (15.7)[a]
Week 8	4 (7.8)	7 (13.5)	6 (11.8)
Week 12	3 (5.9)	9 (17.3)	13 (25.5)[a]
Week 16	2 (3.9)	11 (21.2)[a]	11 (21.6)[a]

eow = every other week; ew = every week; NRI = non-responder imputation, in which subjects with missing PGA scores are counted as non-responders; PGA = physician's global assessment

a. $P \leq 0.05$ for pairwise comparison with placebo using CMH test adjusted for Baseline Hurley Stage.

b. Reduction in PGA relative to Baseline.

With respect to proportions of subjects achieving complete clearance or elimination of abscesses, draining fistulas and inflammatory nodules, the differences across groups were overall small. For complete clearance of abscesses, a slightly higher proportion of subjects achieved complete clearance at Week 16 in the

adalimumab ew (50%) and eow (48%) groups compared with the placebo group (45%). At Week 16, a higher proportion of subjects receiving adalimumab ew had complete clearance of draining fistulas (43%) vs. eow (25%) or placebo (27%) as well as complete clearance of inflammatory nodules (20% for ew vs. 21% for eow versus 8% for placebo). These differences were not statistically significant.

The Percent Change from Baseline in Lesion Counts (nodules, abscesses and draining fistulas) in subjects with ≥ 1 such lesion at Baseline was generally numerically higher for the adalimumab groups vs. placebo, although statistical significance could not be shown for all comparisons across different time points. Fewer than 10% of subjects in each treatment group had incision and drainage of lesions or intralesional injection of corticosteroids during Period 1.

The proportion of subjects achieving AN50, defined as a ≥50% reduction in total AN count relative to Baseline, at each visit is shown in **Table** for subjects with > 2 AN and ≤20 draining fistulas at Baseline.

Table 16. Proportion of Subjects Achieving AN50 Response at each Visit in Period 1 Among Subjects with Baseline AN > 2 and Draining Fistulas ≤ 20 (NRI, ITT-1 Population)

	n/N (%) of Subjects		
		Adalimumab	
Visit	Placebo N = 51	eow N = 52	ew N = 51
Week 2	6/43 (14.0)	12/45 (26.7)	19/44 (43.2)[a]
Week 4	8/43 (18.6)	19/45 (42.2)[a]	23/44 (52.3)[a]
Week 8	18/43 (41.9)	23/45 (51.1)	25/44 (56.8)
Week 12	14/43 (32.6)	19/45 (42.2)	28/44 (63.6)[a]
Week 16	15/43 (34.9)	22/45 (48.9)	25/44 (56.8)[a]

AN = abscesses and inflammatory nodules; AN50 = ≥ 50% reduction in total AN count relative to Baseline; eow = every other week; ew = every week; NRI = nonresponder imputation in which subjects with missing values are counted as nonresponders

a. $P \leq 0.05$ for pairwise comparison with placebo using Cochran-Mantel-Haenszel test adjusted for Baseline Hurley Stage.

Mean change from Baseline in Patient's Global Assessment of skin pain score was assessed. Skin pain scores decreased (indicating reduced pain levels) in all treatment groups at Week 16, with the largest mean change from Baseline in the adalimumab ew group (–12.68), followed by the adalimumab eow group (–6.11) and the placebo group (–3.75).

Period 2 results

Loss of response during Period 2 was observed in many subjects who had achieved a favourable clinical response in Period 1. Among those subjects who achieved a PGA < 3 during Period 1, 64% of those treated with adalimumab eow in Period 1 and 63% of those treated ew with adalimumab in Period 1 were unable to maintain this level of response throughout Period 2 while receiving adalimumab eow. Among those subjects who had achieved a PGA < 3 while receiving placebo in Period 1, 25% lost their response while receiving adalimumab eow in Period 2.

Overall, 89 subjects dose escalated from adalimumab 40 mg eow to ew in Period 2. Among these subjects, 68 provided Week 52 PGA assessments and 13 of them achieved clinical response (NRI: 13/89, 15%; as observed: 13/68, 19%) at Week 52. All but 1 of these subjects was Hurley Stage I/II at Baseline.

The proportion of subjects achieving clinical response (PGA score of 0/1/2 and ≥2 grades of reduction in PGA score relative to Baseline) was low at Week 52, regardless of whether subjects had initiated therapy with eow dosing or ew dosing. At Week 52, the highest proportion of clinical responders (20%) was observed among those subjects who had been randomized to the adalimumab ew group during Period 1 and had dose escalated back to ew dosing during Period 2.

Table 17. Proportion of Subjects Achieving Clinical Response at each Visit Including and Excluding Dose Escalation Data (NRI, ITT-INT Population)

	Number (%) of Subjects			
	Excluding Dose Escalation Data		Including Dose Escalation Data	
Period Visit	eow/eow N = 52	ew/eow N = 51	eow/eow/ew N = 52	ew/eow/ew N = 51
Period 1				
Week 2	5 (9.6)	1 (2.0)	5 (9.6)	1 (2.0)
Week 4	3 (5.8)	6 (11.8)	3 (5.8)	6 (11.8)
Week 8	3 (5.8)	4 (7.8)	3 (5.8)	4 (7.8)
Week 12	4 (7.7)	11 (21.6)	4 (7.7)	11 (21.6)
Week 16	5 (9.6)	9 (17.6)	5 (9.6)	9 (17.6)
Period 2				
Week 20	4 (7.7)	7 (13.7)	4 (7.7)	7 (13.7)
Week 24	7 (13.5)	13 (25.5)	7 (13.5)	13 (25.5)
Week 28	7 (13.5)	8 (15.7)	7 (13.5)	8 (15.7)
Week 31	2 (3.8)	4 (7.8)	3 (5.8)	4 (7.8)
Week 39	6 (11.5)	2 (3.9)	10 (19.2)	6 (11.8)
Week 45	5 (9.6)	2 (3.9)	8 (15.4)	5 (9.8)
Week 52	3 (5.8)	5 (9.8)	6 (11.5)	10 (19.6)

eow = every other week; ew = every week; NRI = non-responder imputation, in which subjects with missing PGA scores are counted as non-responders

Note: A clinical responder is a subject with a PGA score of 0/1/2 and ≥ 2 grades of reduction in PGA score relative to Baseline.

Post-hoc results for mITT population

The purpose of the revision to the Phase 2 study report was to examine efficacy endpoints in the modified ITT population in Period 1 (mITT-1 population), which was similar to the population in the Phase 3 studies (Studies M11-810 and M11-313). The mITT-1 population included subjects in the ITT-1 Population who met all of the following criteria:

- Baseline total abscess and inflammatory nodule (AN) count was ≥ 3;
- Baseline draining fistula count was ≤ 20;
- Hurley Stage II or III at Baseline.

The additional analyses included:

- Proportion of subjects achieving HiSCR, 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.
- Proportion of subjects achieving an AN count of 0, 1, 2 among subjects with Hurley Stage II at Baseline.
- Proportion of subjects achieving at least a 30% reduction and at least a 10 mm reduction in skin pain (VAS), among subjects who had a Baseline pain assessment ≥ 30 mm. This corresponds to the proportion of subjects achieving at least a 30% reduction and at least 1 unit reduction from Baseline in Patient's Global Assessment of Skin Pain Numeric Rating Scale (NRS30), which was evaluated in the Phase 3 program.
- Change from Baseline in modified Sartorius scale.

A total of 111 subjects were included in the mITT-1 population, 37 in the placebo group, 38 in the adalimumab eow group, and 36 in the adalimumab ew group.

Table 18. Proportion of Subjects Achieving HiSCR at Week 12 (NRI) (mITT-1 Population)

Strata	Placebo n/N (%)	Adalimumab ew n/N (%)	Difference %	(95% CI)[a]	*P* Value[b]
All	6/37 (16.2)	22/36 (61.1)	44.4	(21.9, 66.8)	<0.001*
Hurley Stage II	4/24 (16.7)	17/25 (68.0)	51.3	(27.7, 74.9)	<0.001*
Hurley Stage III	2/13 (15.4)	5/11 (45.5)	30.1	(-5.3, 65.4)	0.182

ew = every week; CI = confidence interval; NRI = nonresponder imputation

a. For overall strata, 95% CI for strata-adjusted difference (Hurley Stage II versus III) based on CMH test corresponding to the extended Mantel-Haenszel statistic. Within each stratum, 95% CI for difference based on normal approximation to the binomial distribution.

b. *P* value for pairwise comparison: ew versus placebo.

Note: Across overall strata, *P* values are calculated from the Cochran Mantel Haenszel test adjusted for strata; within each stratum, *P* values are calculated from Fisher's exact test. * denotes $P \leq 0.05$

Table 19. Statistical Results for Post Hoc Analyses Corresponding to Ranked Secondary Endpoints in Studies M11-810 and M11-313 (mITT-1 population)

Secondary Variable	Adalimumab ew vs. placebo
Proportion of subjects who achieved an AN count of 0, 1, or 2 at Week 12, among subjects with Hurley Stage II at Baseline	60.0% vs. 20.8% *P* = 0.009*
Proportion of subjects who achieved at least 30% reduction and at least 10 mm reduction from Baseline in Patient's Global Assessment of Skin Pain (VAS)[a] at Week 12 among subjects with baseline VAS ≥ 30 mm	60.7% vs. 21.9% *P* = 0.003*
Mean change in modified Sartorius scale from Baseline to Week 16[b]	–38.2 vs. –20.4 *P* = 0.036*

AN = abscesses and inflammatory nodules; ew = every week; VAS = visual analog scale

a. Corresponds to the proportion of subjects who achieved at NRS30 in Studies M11-810 and M11-313.

b. Modified Sartorius scale was only collected at Baseline and Week 16 in Study M10-467.

Note: * denotes $P \leq 0.05$

2.4.2. Main studies

Title of Study

The phase 3 studies performed to support the use of Humira in HS were **M11-313** and **M11-810**.

Since the pivotal studies had an almost identical design, the methods are not described for each study separately. Differences are indicated, where relevant. The efficacy results are presented for each study separately (for Part A of the studies for most end-points) and results from integrated analyses are presented in the paragraph *Analysis performed across trials* below.

Study M11-313: A Phase 3 Multicenter Study of the Safety and Efficacy of Adalimumab in Subjects with Moderate to Severe Hidradenitis Suppurativa – PIONEER I

Study M11-810: Phase 3 Multicenter Study of the Safety and Efficacy of Adalimumab in Subjects with Moderate to Severe Hidradenitis Suppurativa – PIONEER II

Methods

Studies M11-313 and M11-810 were both multi-center, randomized, double-blind, placebo-controlled, 2-period studies with the aim to determine the clinical safety and efficacy of adalimumab compared to placebo in subjects with moderate to severe HS.

- **Study participants**

The phase 3 studies were performed in the US, Europe, Australia and Canada.

Main inclusion criteria:

- Male and female subjects ≥18 years of age;
- Subject had a diagnosis of HS for at least 1 year prior to Baseline;
- HS lesions were present in at least 2 distinct anatomic areas (e.g., left and right axilla; or left axilla and left inguino-crural fold), one of which was Hurley Stage II or Hurley Stage III.
- Subject had an inadequate response to at least a 3-month (90 days) trial of oral antibiotics for treatment of HS (or demonstrated intolerance to, or had a contraindication to, oral antibiotics for treatment of their HS).
- Subject had 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;
- Subject had a total AN count of greater than or equal to 3 at the Baseline visit;
- If female, subject was either not of childbearing potential, defined as postmenopausal for at least 1 year or surgically sterile (bilateral tubal ligation, bilateral oophorectomy and/or hysterectomy) or of childbearing potential and practicing an approved method of birth control throughout the study and for 150 days after last dose of study drug. The results of the serum pregnancy test performed during the Screening period and urine pregnancy test performed at the Baseline visit must have been negative.
- Subject must have agreed to daily use (throughout the entirety of the study) of 1 of the following over-the-counter topical antiseptics on their body areas affected with HS lesions: chlorhexidine gluconate, triclosan, benzoyl peroxide, or dilute bleach in bathwater;
- Subject had a negative TB screening assessment (including a PPD test or QuantiFERON-TB Gold test, or equivalent) and negative CXR (posterior-anterior and lateral view) at Screening. If the subject had evidence of a latent TB infection, the subject must have initiated and completed a minimum of 4 weeks of anti-TB therapy, or have documented completion of a course of anti-TB therapy, prior to Baseline;
- Subject was 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;
- Subject must have been able and willing to self-administer SC injections or had a qualified person(s) who could reliably administer SC injections;
- Subject must have been able and willing to provide written informed consent and comply with the requirements of the study protocol.

Definition of inadequate response to antibiotics
An adequate trial of oral antibiotic therapy was considered to be at least 90 days in duration. If, after at least 90 days of oral antibiotic therapy, any of the following has occurred, subject was 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 progressed from I→II, II→III, or I→III);
- ✓ Subject required at least one intervention (e.g., incision and drainage or intralesional injection of corticosteroid);
- ✓ Subject experienced pain interfering with activities of daily living, with unsatisfactory relief from over-the-counter analgesics (e.g., ibuprofen or acetaminophen);
- ✓ Subject experienced pain requiring opioids, including tramadol;
- ✓ Subject experienced drainage interfering with activities of daily living (e.g., requires multiple dressing changes and/or changes of clothes daily);
- ✓ Subject experienced an increase in the number of anatomic regions affected by HS;
- ✓ Subject experienced at least one new abscess or one new draining fistula.

Definition of intolerance to antibiotics
A subject was defined as intolerant to oral antibiotic when oral antibiotic therapy had been discontinued by a physician as a result of a significant adverse reaction to oral antibiotic administration. A reaction was considered significant if the adverse reaction was at least moderately severe (i.e., the adverse event causes the subject discomfort and interrupts the subject's usual activities or function).

Main exclusion criteria:

- Prior treatment with adalimumab or other anti-TNF therapy (e.g., infliximab, etanercept), or participation in an adalimumab trial;
- Any other active skin disease or condition (e.g., bacterial, fungal or viral infection) that could have interfered with assessment of HS;
- *Study M11-313 only:* Subject received any oral antibiotic treatment for HS within 28 days prior to the Baseline visit;
- *Study M11-810 only:* Subjects on permitted oral antibiotic treatment (doxycycline or minocycline only) for HS who had not been on a stable dose for at least 28 days prior to the baseline visit;
- Subject received prescription topical therapies for the treatment of HS within 14 days prior to the Baseline visit;
- Subject received systemic non-biologic therapies with potential therapeutic impact for HS < 28 days prior to Baseline visit;
- Subject received oral concomitant analgesics (including 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 was on opioid analgesics within 14 days prior to Baseline visit;
  - Subject was not on a stable dose of non-opioid oral analgesics for at least 14 days prior to the Baseline visit ("as needed" [PRN] was not considered a stable dose).
- Subject required or was expected to require, opioid analgesics for any reason (excluding tramadol);
- Subject had a draining fistula count of greater than 20 at the Baseline visit;
- Subject had been treated with any investigational drug of chemical or biologic nature within a minimum of 30 days or 5 half-lives (whichever was longer) of the drug prior to the Baseline visit;
- Prior exposure to biologics that had a potential or known association with progressive multifocal leukoencephalopathy (PML; i.e. natalizumab; Tysabri, rituximab; Rituxan or efalizumab; Raptiva);
- Subject had had infections that required treatment with intravenous 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;
- History of moderate to severe congestive heart failure (New York Health Association 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;
- 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 had an active systemic viral infection or any active viral infection that, based on the investigator's clinical assessment, made the subject an unsuitable candidate for the study;
- Hepatitis B surface antigen (HBsAg) positive (+) or detected sensitivity on the hepatitis B virus (HBV)-DNA polymerase chain reaction (PCR) qualitative test for hepatitis B core antibody (HBcAb)/hepatitis B surface antibody (HBsAb) positive subjects;
- Chronic recurring infections or active TB;
- Positive pregnancy test at Screening or Baseline;
- Female subjects who were breastfeeding or considering becoming pregnant during the study;

- Evidence of dysplasia or history of malignancy (including lymphoma and leukaemia) other than a successfully treated non-metastatic cutaneous squamous cell carcinoma, basal cell carcinoma or localized carcinoma in situ of the cervix;
- Clinically significant abnormal screening laboratory results as evaluated by the investigator;

Wound care

Concomitant use of wound care dressings on HS wounds was allowed, with options limited to alginates, hydrocolloids and hydrogels.

Analgesic use

Most subjects were required to washout of all analgesics for 14 days prior to Baseline. If a subject's pain (HS-related or non-HS-related) worsened after Baseline, the subject was allowed to initiate analgesic therapy at any time; for *HS-related pain*, permitted analgesics were limited to Ibuprofen (at a dose of up to 800 mg by mouth every 6 hours) not to exceed 3.2 grams/24 hours; AND/OR Acetaminophen as per local labelling; AND/OR if HS-related pain was uncontrolled with ibuprofen or acetaminophen at the above dosing regimens after the Baseline visit, subjects could be prescribed tramadol (at a dose of up to 100 mg po every 4 hours), not to exceed 400 mg/24 hours.

Dose adjustments of ibuprofen, acetaminophen, or tramadol, and use of these analgesics on a PRN basis for HS-related pain up to the maximum permitted dose and frequency, were allowed during the study. From screening through Week 12, subjects were to complete a daily diary of their analgesic use.

For *Non-HS-related pain* opioid analgesics were prohibited but all other analgesics (including tramadol) were allowed at the recommended or prescribed dose.

Lesion Intervention

In the event that an acutely painful lesion occurred that required an immediate intervention, physicians had the option to perform protocol-allowed interventions. Only 2 types of interventions were allowed: injection with intralesional triamcinolone acetonide suspension and incision and drainage. If incision and drainage was performed, the required over-the-counter antiseptic wash was to continue to be used. New systemic and topical therapies following incision and drainage (including antibiotics), were prohibited.

A total of 2 protocol-allowed interventions were permissible during Period A. If a subject required more than 2 interventions within the first 12 weeks, then that subject was to be discontinued from the study. Similarly, during Period B, maximally 2 interventions every 4 weeks were permitted.

Prohibited Therapy
A number of treatments were prohibited for all subjects during the study, e.g. phototherapy (psoralen plus ultraviolet A and/or ultraviolet B), all biologic therapy with a potential therapeutic impact on the disease being studied, any other systemic drug therapies for HS, including but not limited to antibiotics (except as allowed for rescue in study M11-313 and as allowed for concomitant treatment in study M11-810, see below), methotrexate (MTX), cyclosporine, retinoids, and fumaric acid esters, live vaccines (during the study and for 70 days after the last dose of study drug), oral or injectable corticosteroids (except as allowed for rescue; intralesional triamcinolone acetonide), oral analgesics for HS not listed in the protocol, 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 not listed in the protocol, surgical or laser intervention for an HS lesion except as outlined in the protocol.

Antibiotic Rescue Therapy (Study M11-313)
At Week 4 or Week 8, if a subject experienced an increase in their AN count such that the total count was greater-than-or equal-to 150% of their Baseline AN count, antibiotic rescue medication could be initiated. Subjects who qualified could initiate treatment with minocycline or doxycycline up to 100 mg bid. The dosing regimen was to remain stable throughout study participation. Otherwise, concomitant use of oral antibiotic therapy for treatment of HS was not allowed. Rescue antibiotic therapy was to be captured in the source and on the appropriate eCRF. The proportion of subjects who started oral antibiotic rescue therapy was defined

as a secondary efficacy endpoint and was also to be taken into account in a sensitivity analysis of the primary endpoint.

Antibiotic Therapy (Study M11-810)
Concomitant use of permitted oral antibiotic therapy for treatment of HS was allowed provided the dosing regimen (dose and frequency) had been stable for at least 4 consecutive weeks prior to Baseline. The dosing regimen was to remain stable throughout study participation. Permitted oral concomitant antibiotics included:

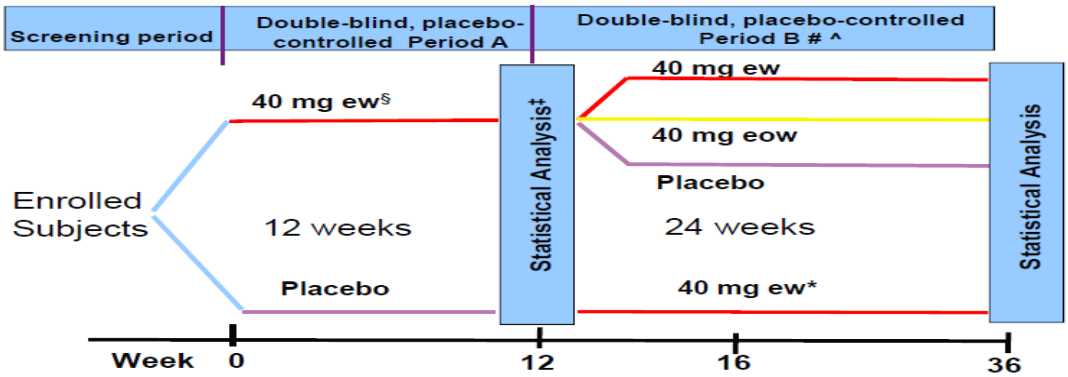
- doxycycline (at a dose up to 100 mg by mouth [p.o.] twice-a-day [b.i.d.])
- minocycline (at a dose up to 100 mg p.o. b.i.d.)

- **Treatments and study procedures**

Both studies included a 30-day screening period, an initial 12-week double-blind treatment period (Period A), and a subsequent 24-week double-blind treatment period (Period B), plus a Day 70 follow-up phone call approximately 70 days after the last dose of study drug administration. The week numbers provided are defined relative to the first dose of study drug in the study.

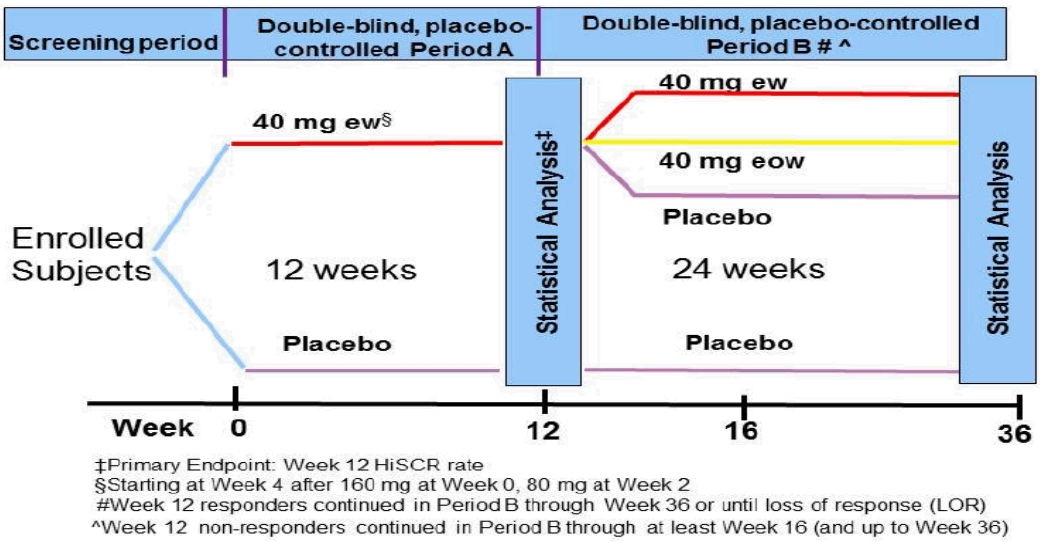
The study designs are depicted below.

Figure 14. Study Design Schematic (Study M11-313)



‡Primary Endpoint: Week 12 HiSCR rate
§Starting at Week 4 after 160 mg at Week 0, 80 mg at Week 2
#Week 12 responders continued in Period B through Week 36 or until loss of response (LOR)
^Week 12 non-responders continued in Period B through at least Week 16 (and up to Week 36)
* Blinded adalimumab load of 160 mg at Week 12, 80 mg at Week 14

Figure 15. Study Design Schematic (Study M11-810)



‡Primary Endpoint: Week 12 HiSCR rate
§Starting at Week 4 after 160 mg at Week 0, 80 mg at Week 2
#Week 12 responders continued in Period B through Week 36 or until loss of response (LOR)
^Week 12 non-responders continued in Period B through at least Week 16 (and up to Week 36)

Period A (M11-313): A 12-week double-blind, placebo-controlled treatment period during which subjects were randomized at Day 1, in a 1:1 ratio to receive blinded adalimumab 160 mg at Week 0, 80 mg at Week 2, and 40 mg ew or matching placebo starting at Week 4 for an evaluation of safety and efficacy. The randomization was to be stratified by Baseline Hurley Stage (II versus III). A subject's Hurley Stage was determined by the worst Hurley Stage across all affected anatomic regions.

Subjects randomized to Arm 1 were to receive:

- 160 mg adalimumab at Baseline (Day 1) administered as four 40 mg injections SC
- 80 mg adalimumab at Week 2 administered as two 40 mg injections SC
- 40 mg adalimumab ew from Week 4 through Week 11 administered as one 40 mg injection SC

Subjects randomized to Arm 2 were to receive:

- Four 0.8 mL placebo injections at Baseline (Day 1)
- Two 0.8 mL placebo injections at Week 2
- One 0.8 mL placebo injection ew from Week 4 through Week 11

Period A (M11-810): A 12-week double-blind, placebo-controlled treatment period during which subjects were randomized at Day 1, in a 1:1 ratio, to receive blinded adalimumab 40 mg ew (following loading doses of 160 and 80 mg at weeks 0 and 2) or matching placebo for an evaluation of safety and efficacy. The dosing schedule was the same as in Study M11-313.

Period B (M11-313): A 24-week double-blind, placebo-controlled treatment period. All subjects who continued to Period B, regardless of the treatment in Period A, were to be re-randomized at Week 12 to maintain the blind. Subjects randomized to adalimumab in Period A were re-randomized in a 1:1:1 ratio to receive adalimumab 40 mg ew, adalimumab 40 mg eow, or matching placebo. Subjects randomized to placebo in Period A were assigned (using re-randomization numbers) to receive adalimumab 40 mg ew.

All subjects enrolled in this study who completed Period A were eligible to participate in Period B. At Week 12, subjects from the adalimumab arm in Period A (Arm 1) were to be re-randomized 1:1:1 to 1 of 3 blinded treatment groups:

- adalimumab 40 mg ew,
- adalimumab 40 mg eow,

– or placebo from Week 12 to Week 35.

The re-randomization was to be stratified by Week 12 Hidradenitis Suppurativa Clinical Response (HiSCR) response (responder versus non-responder) and by Baseline Hurley Stage (II versus III). At Weeks 12 through 15, these subjects were to receive matching placebo to blind the loading doses administered to subjects who had been randomized to placebo in Period A (Arm 2).

Subjects from the placebo arm in Period A (Arm 2) were to receive adalimumab 160 mg at Week 12, 80 mg at Week 14, matching placebo at Week 13 and Week 15, and adalimumab 40 mg ew from Week 16 to Week 35.

- All subjects (Arm 1 and Arm 2) who achieved HiSCR at Week 12 were to continue in Period B through Week 36. Subjects who experienced a loss of response (LOR) in Period B, defined as an abscess and inflammatory nodule (AN) count that was greater than the average of AN counts at Baseline and Week 12, were to be discontinued from the study and had the opportunity to enter the open-label extension (OLE) Study M12-555 to receive open-label adalimumab 40 mg ew.
- All subjects (Arm 1 and Arm 2) who did not achieve HiSCR at Week 12 were to continue in Period B through Week 36. Starting at or after Week 16, subjects who experienced a Worsening or Absence of Improvement, defined as an AN count that was greater than or equal to the AN count at Baseline on 2 consecutive visits (excluding Week 12) that occurred at least 14 days apart, were to be discontinued from the study and had the opportunity to enter the OLE Study M12-555 to receive open-label adalimumab 40 mg ew.

Starting at Week 4 or Week 8, if AN counts were greater-than-or equal-to 150% of Baseline AN counts, antibiotic rescue medication was permitted.

Period B (M11-810): A 24-week double-blind, placebo-controlled treatment period, largely similar to Study M11-313. All subjects who continued to Period B, regardless of the treatment in Period A, were re-randomized at Week 12 to maintain the blind. Subjects randomized to adalimumab in Period A (Arm 1) were re-randomized in a 1:1:1 ratio to receive adalimumab 40 mg ew, adalimumab 40 mg eow or matching placebo. Subjects randomized to placebo in Period A were assigned (using re-randomization numbers) to continue on placebo. All subjects enrolled in this study who completed Period A were eligible to participate in Period B. The re-randomization was to be stratified by Week 12 HiSCR (responder vs. non-responder) and by baseline Hurley Stage (II vs. III).

Subjects from the placebo group in Period A (Arm 2) were to continue on blinded placebo from Week 12 to Week 35.

Similar to Study M11-313, all subjects (Arm 1 and Arm 2) who achieved HiSCR at Week 12 were to continue in Period B through Week 36 and those who experienced loss of response (defined as in study M11-313) were to be discontinued from the study and had the opportunity to enter the open-label extension Study M12-555 to receive open-label adalimumab 40 mg ew. All subjects (Arm 1 and Arm 2) who did not achieve HiSCR at Week 12 were to continue in Period B through Week 36. Starting at or after Week 16, subjects who experienced a worsening or absence of improvement were to be discontinued from the study and had the opportunity to enter the OLE Study M12-555 to receive open-label adalimumab 40 mg ew.

In both studies, at Week 36, all subjects had the opportunity to enter in the OLE Study M12-555 where they were to receive adalimumab 40 mg ew.

- **Objectives**

The primary objective of the pivotal studies was to determine the clinical safety and efficacy of adalimumab compared to placebo in subjects with moderate to severe HS after 12 weeks of treatment.

A secondary objective was to evaluate safety and explore efficacy for continuous weekly dosing versus dose reduction versus maintenance of response off-therapy from Week 12 to Week 36.

The pharmacokinetics and immunogenicity of adalimumab following subcutaneous (SC) injection were also assessed.

- **Outcomes / endpoints**

Primary efficacy variable

The primary efficacy variable in both studies was the proportion of subjects who achieved HiSCR, defined as at least a 50% reduction in AN count with no increase in abscess count and no increase in draining fistula count relative to Baseline, at Week 12.

Ranked Secondary Efficacy Variables (for both studies)

1. Proportion of subjects who achieved AN count of 0, 1, or 2 at Week 12, among subjects with Hurley Stage II at Baseline.
2. Proportion of subjects who achieved 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 12 among subjects with Baseline NRS ≥ 3.
3. Change in modified Sartorius score from Baseline to Week 12.

Other Secondary Efficacy Variables in Period A

Other secondary efficacy variables were analysed at each scheduled visit in Period A. Primary and ranked secondary variables were also analysed at visits other than Week 12. These variables were similar for the two studies with a few exceptions (indicated below).

- Proportions of subjects who achieved HiSCR; AN count of 0, 1, or 2, among subjects with Hurley Stage II at Baseline; NRS30 – at worst and on average, among subjects with Baseline Patient's Global Assessment of Skin Pain (NRS) ≥ 3
- Change in modified Sartorius score from Baseline
- Proportion of subjects who achieved complete elimination of abscesses at each visit and percentage change from Baseline in number of abscesses, among subjects who had any abscess at Baseline
- Change from Baseline in number of abscesses
- Proportion of subjects who achieved complete elimination of draining fistulas at each visit and percentage change from Baseline in number of draining fistulas, among subjects who had any draining fistulas at Baseline
- Change from Baseline in number of draining fistulas
- Proportion of subjects who achieved complete elimination of inflammatory nodules at each visit and percentage change from Baseline in number of inflammatory nodules, among subjects who had at least 1 inflammatory nodule at Baseline
- Change from Baseline in number of inflammatory nodules
- Number of interventions during Period A
- Proportion of subjects with DLQI = 0, DLQI = 0 or 1 and change from Baseline in DLQI
- Change from Baseline in WPAI:SHP (Work Productivity and Activity Impairment Questionnaire: Specific Health Problem)
- Percentage change from Baseline in Patient's Global Assessment of Skin Pain NRS – at worst and on average, among subjects who had Baseline (NRS) ≥ 3
- Change from Baseline in Patient's Global Assessment of Skin Pain NRS – at worst and on average
- Proportions of subjects who achieved at least 50%, 75% and 100% reductions in the AN count relative to Baseline (AN50, AN75, AN100)
- Absolute and percentage change from Baseline in AN count

- Proportion of subjects who achieved erythema score of 1 or 0 in all affected anatomic regions among subjects who had erythema score of 2 or more in at least 1 anatomic region at Baseline
- Proportion of subjects who experienced worsening or improvement by at least one Hurley Stage in at least 1 affected anatomic region
- Absolute and percentage change from Baseline in SF-36 (Short Form 36) (only Study M11-313)
- Change from Baseline in HADS (Hospital Anxiety and Depression Scale) (only Study M11-313) and TSQM (Treatment Satisfaction Questionnaire for Medication) (both studies)
- Change from Baseline in EQ-5D index and change from Baseline in EQ-5D visual analog scale (Study M11-810)
- Change from Baseline in Proportion of subjects who experienced flare, defined by at least a 25% increase in AN counts with a minimum increase of 2 relative to Baseline; number of days on flare
- Proportion of subjects who experienced at least 25% increase in abscess counts with a minimum increase of 2 relative to Baseline
- Proportion of subjects who experienced at least 25% increase in inflammatory nodule counts with a minimum increase of 2 relative to Baseline
- Proportion of subjects who experienced at least 25% increase in draining fistula counts with a minimum increase of 2 relative to Baseline
- Proportion of subjects who started oral antibiotic rescue therapy (only Study M11-313)
- Change from Baseline in CRP and percentage change from Baseline in CRP

In addition, the progression of lesions denoted as representative (3-6 per patient) was evaluated.

Other Secondary Efficacy Variables for Period B

Efficacy was explored for Period B.

- The secondary efficacy variables listed above were summarized for each subpopulation in the Intent-to-Treat (ITT) population in Period B (ITT_B). The treatment comparisons were performed in ITT_B subjects who were randomized to adalimumab in Period A and were Week 12 HiSCR responders (ITT_B_R Population). In addition, change from re-randomization was analyzed for continuous variables for ITT_B_R Population.
- Time to LOR (loss of response) was analyzed for the ITT_B_R Population.
- Time to the second incidence of the two-consecutive visits with AN count ≥ Baseline AN count was summarized for the ITT_B subjects who were randomized to adalimumab in Period A and were Week 12 HiSCR non-responders (ITT_B_NR).

In addition, for safety evaluation, adverse events, laboratory data, physical examinations and vital signs were collected, monitored, assessed and recorded at the designated study visits. Blood samples for adalimumab and anti-adalimumab antibody (AAA) assays were collected by venipuncture at designated study visits.

- **Sample size**

Approximately 300 subjects were planned to be enrolled in Study M11-313 and M11-810 respectively, in order to provide adequate information to characterize the adalimumab safety profile as well to have sufficient power for the primary efficacy endpoint. For the primary efficacy endpoint, the power calculation was based on the response rates observed in the phase 2 Study M10-467 where HiSCR response rates at Week 12 were 61% and 16% in the adalimumab ew group and placebo group, respectively. With a sample size of 150 per group each study had more than 90% power to detect the treatment difference with a 2-sided alpha level of 0.05.

Period B was considered for exploratory purposes and no power calculation was performed.

- **Randomisation**

Randomization schedules were generated at AbbVie and were provided to the Interactive Voice Response System/Interactive Web Response System vendor. In both Study M11-313 and Study M11-810, subjects were randomized at Week 0 in a 1:1 ratio to receive adalimumab 40 mg every week (ew) or matching placebo. Randomisation was stratified by Baseline Hurley Stage (II versus III). The number of subjects in Hurley Stage III were to be limited to 150 (50% of the total planned number of subjects).

In study M11-810 randomisation was also stratified by Baseline concomitant antibiotic use (Yes versus No) where the number of subjects on baseline concomitant antibiotics were to be limited to 90 (30% of the total planned number of subjects). In addition and concerning both studies, the number of subjects with an AN count of 3 or 4, were to be limited to 60 (20% of the total planned number of subjects).

All subjects who completed Period A were eligible for Period B and those who continued to Period B, were to be re-randomized at Week 12 to maintain the blind. Subjects randomized to adalimumab in Period A were to be re-randomized in a 1:1:1 ratio to receive adalimumab 40 mg ew, adalimumab 40 mg eow, or matching placebo.

Among subjects from the adalimumab arm of Period A, the re-randomization was stratified by Week 12 Hidradenitis Suppurative Clinical Response (HiSCR) (responder versus non-responder) and by baseline Hurley Stage (II versus III).

For subjects receiving placebo in Period A, the Period B treatment in the 2 studies differed. In Study M11-313 subjects receiving placebo in Period A were assigned (using re-randomized numbers to adalimumab 40 mg ew). In Study M11-810 subjects receiving placebo in Period A were assigned (using re-randomization numbers) to continue to receive placebo.

- **Blinding (masking)**

All AbbVie personnel with direct oversight of the conduct and management of the trial (with exception of the Drug Supply Management Team), the investigator, study site personnel and the subject remained blinded to each subject's treatment (adalimumab or placebo) throughout the blinded periods of the study.

Masking of treatments was to be achieved by matching placebo to adalimumab dosing regimen in both period A and B. During Period A, all subjects were to receive 4 injections at Week 0, 2 injections at Week 2 and 1 injection weekly from Week 4 through Week 11. In Period B, all subjects were to receive 1 injection weekly from Week 12 through Week 35.

In order to maintain blinding during Period A (Week 0 to Week 11), all subjects were to receive 4 injections of study drug (40 mg each) or placebo at Week 0, 2 injections at Week 2 and 1 injection weekly from Week 4 through Week 11. In Period B, all subjects were to receive 4 injections at Week 12, 1 injection at Week 13, 2 injections at Week 14 and 1 injection weekly from Week 15 through Week 35.

- **Statistical methods**

The Intent-to-Treat Population in each Period was used for analyses of efficacy with the ITT Population in Period A (ITT_A) defined as all subjects who were randomized at Baseline (Week 0).

In period A the primary analysis was the comparison of adalimumab versus placebo in the proportion of subjects who achieved HiSCR at Week 12. The number and percentage of subjects who achieved HiSCR was computed for each treatment arm and the difference in response rates was compared using a Cochran-Mantel-Haenszel (CMH) test, stratified by Baseline Hurley Stage (II versus III) and, in Study

M11-810 also Baseline concomitant use of oral antibiotics (Y/N). In the primary analysis a non-responder imputation (NRI) approach was used. Several sensitivity analyses were planned including modification of the NRI approach, e.g. counting all subjects with any add-on antibiotics or with dose increase on baseline concomitant antibiotics (Study M11-810 only) prior to Week 12 as non-responders, the use of LOCF and multiple imputation.

In addition, analyses of the primary efficacy endpoint and ranked secondary efficacy endpoints were repeated based on the Per-protocol population defined for Period A.

Regarding handling of multiplicity, the analyses of the primary efficacy variable and the ranked secondary variables were performed in a hierarchical order and using a step-down procedure with each comparison tested at a significance level of 0.05. A statistically significant result for the comparison in the higher rank (primary, then ranked secondary variables) was required for testing of the next comparison in the lower rank.

In Period B, the analyses of each adalimumab arm versus placebo, and between the 2 adalimumab arms, were performed for the ITT Population in Period B including all subjects who were re-randomized at the entry of Period B. Three subpopulations were also defined based on whether a subject was randomised to adalimumab or placebo in period A and, if a HiSCR responder or non-responder at re-randomisation, i.e. week 12. ITT_B_R (randomized to adalimumab in Period A/HiSCR responder), ITT_B_NR (randomized to adalimumab in Period A/HiSCR non-responders) and ITT_B_EW (randomized to placebo in Period A).

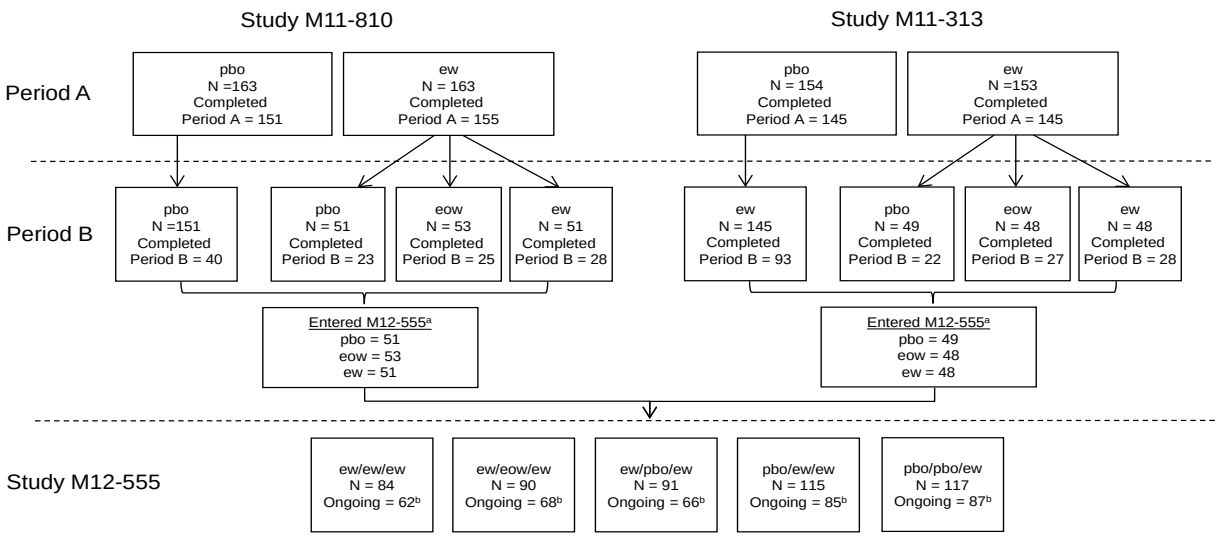
Safety analyses were carried out using the safety population in each period and the All Adalimumab Treated Population. No interim analysis was planned nor performed in any of the studies. Safety data, the primary efficacy endpoints and ranked secondary endpoints were in both studies however periodically reviewed by the IDMC.

Results

- **Participant flow**

The following figure depicts the subject disposition for Studies M11-810, M11-313 and also includes study M12-555, the open-label extension study.

Figure 16. Flow Chart of Phase 3 Studies (All Randomized Subjects)



eow = adalimumab every other week; ew = adalimumab every week; pbo = placebo

a. Subjects who achieved HiSCR at Week 12 continued in Period B through Week 36, or until loss of response (LOR), defined as an AN count that was greater than the average AN counts at Baseline and Week 12. Subjects with LOR were discontinued from Studies M11-810 and M11-313 and were eligible to enter the OLE Study M12-555 to receive open-label (OL) adalimumab 40 mg ew. Subjects who did not achieve HiSCR at Week 12 were to continue in Period B through at least Week 16 (and up to Week 36).
At or after Week 16, subjects who experienced a worsening or absence of improvement (WOAI), defined as an AN count that was greater than or equal to the Baseline AN count at 2 consecutive visits (excluding Week 12) occurring at least 14 days apart, were discontinued from the study and were eligible to enter the OLE Study M12-555 to receive OL adalimumab 40 mg ew. At Week 36, all subjects were eligible to enroll in the OLE Study M12-555 to receive OL adalimumab 40 mg ew.

b. Ongoing as of 29 April 2014.

Study M11-313

Table 20. Overall Subject Disposition in Period A (ITT_A Population) Study M11-313

Subject Disposition in Period A	Placebo (N = 154) n (%)	Adalimumab ew (N = 153) n (%)	Total (N = 307) n (%)
Number of randomized subjects	154	153	307
Number of subjects who discontinued without dose[a]	2 (1.3)	0	2 (0.7)
Number of subjects randomized and dosed	152 (98.7)	153 (100)	305 (99.3)
Number of subjects who completed Period A	145 (94.2)	145 (94.8)	290 (94.5)
Number of subjects who discontinued from Period A	7 (4.5)	8 (5.2)	15 (4.9)
Discontinuation due to (primary reason):			
Adverse event	1 (0.6)	0	1 (0.3)
Withdrew consent	4 (2.6)	4 (2.6)	8 (2.6)
Lack of efficacy	0	0	0
Lost to follow-up	2 (1.3)	1 (0.7)	3 (1.0)
Exceeded protocol-specified number of interventions	0	0	0
Protocol violation	0	1 (0.7)	1 (0.3)
Other	0	2 (1.3)	2 (0.7)
Discontinuation due to (all reasons):			
Adverse event	2 (1.3)	0	2 (0.7)
Withdrew consent	4 (2.6)	4 (2.6)	8 (2.6)
Lack of efficacy	1 (0.6)	1 (0.7)	2 (0.7)
Lost to follow-up	2 (1.3)	1 (0.7)	3 (1.0)
Exceeded protocol-specified number of interventions	0	0	0
Protocol violation	0	1 (0.7)	1 (0.3)
Other	1 (0.6)	2 (1.3)	3 (1.0)
Number of subjects who completed Period A but did not enter Period B	0	0	0

Ew = every week
a. One subject was randomized but discontinued without taking any study drug due to protocol violation. One subject was randomized but discontinued without taking any study drug due to withdrawal of consent.
Note: Percentage is calculated based on number of subjects randomized.

Table 5. Overall Subject Disposition in Period B (ITT_B Population) Study M11-313

Subject Disposition in Period B	placebo/ew	ew/placebo	ew/eow	ew/ew
Number of subjects who were re-randomized	145	49	48	48
Number of subjects who discontinued without dose in Period B	0	0	0	0
Number of subjects re-randomized and dosed in Period B	145 (100)	49 (100)	48 (100)	48 (100)
Number of subjects who completed Period B	93 (64.1)	22 (44.9)	27 (56.3)	28 (58.3)
Number of subjects who discontinued from Period B	52 (35.9)	27 (55.1)	21 (43.8)	20 (41.7)
Discontinuation due to (primary reason):				
Adverse event	6 (4.1)	1 (2.0)	2 (4.2)	1 (2.1)
Withdrew consent	5 (3.4)	0	0	2 (4.2)
Lack of efficacy	1 (0.7)	1 (2.0)	0	2 (4.2)
Lost to follow-up	5 (3.4)	1 (2.0)	0	0
Per IVRS instruction[a]	30 (20.7)	23 (46.9)	18 (37.5)	13 (27.1)
Exceeded protocol-specified number of interventions	0	0	0	0
Protocol violation	0	0	0	0
Other	5 (3.4)	1 (2.0)	1 (2.1)	2 (4.2)
Discontinuation due to (all reasons):				
Adverse event	6 (4.1)	2 (4.1)	2 (4.2)	1 (2.1)
Withdrew consent	6 (4.1)	0	1 (2.1)	2 (4.2)
Lack of efficacy	1 (0.7)	3 (6.1)	2 (4.2)	2 (4.2)
Lost to follow-up	6 (4.1)	1 (2.0)	1 (2.1)	0
Per IVRS instruction[a]	31 (21.4)	24 (49.0)	18 (37.5)	14 (29.2)
Exceeded protocol-specified number of interventions	0	0	0	0
Protocol violation	0	0	0	0
Other	7 (4.8)	1 (2.0)	1 (2.1)	3 (6.3)

eow = every other week; ew = every week; HiSCR = hidradenitis suppurativa clinical response; LOR = loss of response; WOAI = worsening or absence of improvement
a. Subjects meeting criteria of LOR or WOAI were requested by the IXRS system to discontinue from the study and enter the open-label extension, Study M12-555.
Note: Percentages based on the number of subjects who were re-randomized.

Study M11-810

Table 22. Overall Subject Disposition in Period A (ITT_A Population) Study M11-810

Subject Disposition in Period A	Placebo n (%)	Adalimumab ew n (%)	Total n (%)
Number of randomized subjects	163	163	326
Number of subjects who discontinued without dose	0	0	0
Number of subjects randomized and dosed	163 (100)	163 (100)	326 (100
Number of subjects who completed Period A	151 (92.6)	155 (95.1)	306 (93.9
Number of subjects who discontinued from Period A	12 (7.4)	8 (4.9)	20 (6.1)
Discontinuation due to (primary reason):			
Adverse event	5 (3.1)	3 (1.8)	8 (2.5)
Withdrew consent	3 (1.8)	4 (2.5)	7 (2.1)
Lack of efficacy	0	0	0
Lost to follow-up	3 (1.8)	0	3 (0.9)
Exceeded protocol-specified number of interventions	0	0	0
Protocol violation	0	0	0
Other	1 (0.6)	1 (0.6)	2 (0.6)
Discontinuation due to (all reasons):			
Adverse event	6 (3.7)	3 (1.8)	9 (2.8)
Withdrew consent	5 (3.1)	4 (2.5)	9 (2.8)
Lack of efficacy	2 (1.2)	0	2 (0.6)
Lost to follow-up	3 (1.8)	0	3 (0.9)
Exceeded protocol-specified number of interventions	0	0	0
Protocol violation	0	0	0
Other	1 (0.6)	1 (0.6)	2 (0.6)
Number of subjects who completed Period A, but did not enter Period B	0	0	0

ew = every week. Note: Percentage is based on the number of subjects randomized.

Table 23. Overall Subject Disposition in Period B (ITT_B Population) Study M11-810

Subject Disposition in Period B	Placebo/Placebo n (%)	ew/Placebo n (%)	ew/eow n (%)	ew/ew n (%)
Number of subjects who were re-randomized	151	51	53	51
Number of subjects who discontinued without dose in Period B	0	0	0	0
Number of subjects re-randomized and dosed in Period B	151 (100)	51 (100)	53 (100)	155 (100)
Number of subjects who completed Period B	40 (26.5)	23 (45.1)	25 (47.2)	28 (54.9)
Number of subjects who discontinued from Period B	111 (73.5)	28 (54.9)	28 (52.8)	23 (45.1)
Discontinuation due to (primary reason):				
Adverse event	3 (2.0)	0	2 (3.8)	1 (2.0)
Withdrew consent	9 (6.0)	1 (2.0)	1 (1.9)	1 (2.0)
Lack of efficacy	9 (6.0)	2 (3.9)	0	1 (2.0)
Lost to follow-up	3 (2.0)	0	2 (3.8)	0
Per IXRS instruction[a]	84 (55.6)	25 (49.0)	22 (41.5)	20 (39.2)
Exceeded protocol-specified number of interventions	0	0	0	0
Protocol violation	0	0	0	0
Other	3 (2.0)	0	1 (1.9)	0
Discontinuation due to (all reasons):				
Adverse event	4 (2.6)	0	2 (3.8)	1 (2.0)
Withdrew consent	11 (7.3)	2 (3.9)	1 (1.9)	1 (2.0)
Lack of efficacy	17 (11.3)	2 (3.9)	1 (1.9)	3 (5.9)
Lost to follow-up	3 (2.0)	0	2 (3.8)	0
Per IXRS instruction[a]	88 (58.3)	26 (51.0)	22 (41.5)	21 (41.2)
Exceeded protocol-specified number of interventions	0	0	0	0
Protocol violation	0	0	0	0
Other	4 (2.6)	0	1 (1.9)	0

eow = every other week; ew = every week; OLE = open-label extension; IXRS = interactive voice response system/interactive web response system
a. Subjects meeting criteria of LOR or WOAI were requested by the IXRS system to discontinue from the study and enter the OLE, Study M12-555. Note: Percentage is based on the number of subjects re-randomized.

- **Recruitment**

In study M11-313, the first subject's first visit occurred on 29 November 2011 and the last subject's last visit was 28 January 2014. A total of 307 subjects at 48 study sites were randomized in Period A.

In study M11-810, the first subject's first visit occurred on 28 December 2011 and the last subject's last visit was 28 April 2014. A total of 326 subjects at 53 sites were randomized in Period A.

The number of subjects in Hurley Stage III was not to exceed 150 (50% of the total planned number of subjects) and the number of subjects who were on baseline concomitant antibiotics was not to exceed 90 (30% of the total planned number of subjects). These percent limits were not exceeded.

Table 24. Number of Subjects by Hurley Stage and Antibiotic Use, Study M11-810

		Baseline Concomitant Antibiotic Use	
	N	Yes, n (%)	No, n (%)
Hurley Stage II	172 (52.8)	23 (13.4)	149 (86.6)
Hurley Stage III	154 (47.2)	40 (26.0)	114 (74.0)
Total	326	63 (19.3)	263 (80.7)

- **Conduct of the study**

Protocol amendments

For study M11-313, the original protocol (dated 24 August 2011) had 2 amendments and 4 administrative changes. One hundred six subjects were enrolled under the original protocol, 199 subjects were enrolled under Amendment No. 1, and 2 subjects under Amendment No. 2.

Amendment No. 1 included addition of lesion count assessments at unscheduled visits after Week 12, provided clarification of TB testing at the screening and revised recommendation related to anti-TB therapy, added collection of NRS pain and analgesic use using an electronic device and increased baseline requirement for subject inclusion from baseline NRS ≥ 1 to baseline NRS ≥ 3 for assessment of NRS30.

Amendment No. 2 included addition of new Safety Monitoring language (related to a FDA-requested TNF inhibitor class wide exploration of appearance of malignancy in patients ≤ 30 years of age), added prohibited

therapy (recently approved biologics), update to antibiotic rescue therapy and added changes from Baseline in CRP.

For study M11-810, the original protocol (dated 25 August 2011) had 3 amendments and 4 administrative changes. One hundred and eight subjects were enrolled under the original protocol, 20 subjects were enrolled under Amendment No. 1, and 198 subjects under Amendment No. 2. The amendments covered largely the same aspects as for study M11-313.

Protocol deviations

Table 25. Protocol Deviations (ITT_A Population), Study M11-313

	Placebo (N = 154) n (%)	Adalimumab ew (N = 153) n (%)	Total (N = 307) n (%)
Total subjects with any inclusion/exclusion criterion violated or protocol deviations	32 (20.8)	32 (20.9)	64 (20.8)
Subjects with any inclusion/exclusion criterion violated as evaluated at study entry	3 (1.9)	6 (3.9)	9 (2.9)
Subjects who had at least one protocol deviation reported via SDI	31 (20.1)	29 (19.0)	60 (19.5)
Subjects entered into the study even though she/he did not satisfy entry criteria	20 (13.0)	18 (11.8)	38 (12.4)
Subject developed withdrawal criteria during the study and was not withdrawn	0	0	0
Subject received wrong treatment or incorrect dose	5 (3.2)	4 (2.6)	9 (2.9)
Subject received excluded concomitant treatment	13 (8.4)	9 (5.9)	22 (7.2)

ew = every week

Table 26. Protocol Deviations (ITT_A Population), Study M11-810

	Placebo (N = 163) n (%)	Adalimumab ew (N = 163) n (%)	Total (N = 326) n (%)
Total subjects with any inclusion/exclusion criterion violated or protocol deviations	49 (30.1)	55 (33.7)	104 (31.9)
Subjects with any inclusion/exclusion criterion violated as evaluated at study entry	23 (14.1)	23 (14.1)	46 (14.1)
Subjects who had at least one protocol deviation reported via SDI	37 (22.7)	46 (28.2)	83 (25.5)
Subjects entered into the study even though she/he did not satisfy entry criteria	28 (17.2)	33 (20.2)	61 (18.7)
Subject developed withdrawal criteria during the study and was not withdrawn	0	0	0
Subject received wrong treatment or incorrect dose	1 (0.6)	6 (3.7)	7 (2.1)
Subject received excluded concomitant treatment	12 (7.4)	13 (8.0)	25 (7.7)

ew = every week

Compliance

The subject or a qualified designee was to administer all doses of study drug when not at the site. Appropriate site staff were to 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 was given a dosing sheet to record all injection dates and times.

Compliance with study drug administration was high in both periods in both studies, with a mean compliance above 96% for all treatment groups across Periods A and B.

- • **Baseline data**

Study M11-313

Table 27. Demographic Characteristics (ITT_A Population) Study M11-313

Demographic Variable	Placebo (N = 154)	Adalimumab ew (N = 153)	Total (N = 307)	*P* value[a]
Sex (n [%])				
Female	105 (68.2)	91 (59.5)	196 (63.8)	
Male	49 (31.8)	62 (40.5)	111 (36.2)	0.123
Race (n [%])				
White	118 (76.6)	116 (75.8)	234 (76.2)	
Black	29 (18.8)	33 (21.6)	62 (20.2)	
Asian	3 (1.9)	1 (0.7)	4 (1.3)	
American Indian/ Alaska native	1 (0.6)	1 (0.7)	2 (0.7)	
Other	2 (1.3)	2 (1.3)	4 (1.3)	
Multi race	1 (0.6)	0	1 (0.3)	0.894
Ethnicity				
Hispanic/Latino	3 (1.9)	6 (3.9)	9 (2.9)	
No ethnicity	151 (98.1)	147 (96.1)	298 (97.1)	0.336
Age (year)				
Mean ± SD	37.8 ± 11.33	36.2 ± 10.83	37.0 ± 11.10	
Median (min – max)	35.5 (18 – 67)	35.0 (19 – 65)	35.0 (18 – 67)	0.205
Age group (n [%])				
< 40	89 (57.8)	102 (66.7)	191 (62.2)	
40 – ≤ 64	63 (40.9)	50 (32.7)	113 (36.8)	
≥ 65	2 (1.3)	1 (0.7)	3 (1.0)	0.258
Weight (kg)				
Mean ± SD	99.3 ± 25.13	97.1 ± 24.90	98.2 ± 25.00	
Median (min – max)	97.0 (52.0 – 221.0)	93.0 (44.0 – 179.0)	95.0 (44.0 – 221.0)	0.445
Height (cm)[b]				
Mean ± SD	169.7 ± 10.69	171.3 ± 10.33	170.5 ± 10.53	
Median (min – max)	168.5 (149.0 – 207.0)	170.0 (148.0 – 198.0)	170.0 (148.0 – 207.0)	0.184
BMI (kg/m^2)[b]				
Mean ± SD	34.5 ± 7.94	33.0 ± 7.62	33.8 ± 7.80	
Median (min – max)	33.6 (16.4 – 69.8)	32.1 (18.3 – 54.5)	32.5 (16.4 – 69.8)	0.107
Nicotine Use (n [%])				
User	92 (59.7)	81 (52.9)	173 (56.4)	
Ex-user	22 (14.3)	22 (14.4)	44 (14.3)	
Non-user	40 (26.0)	50 (32.7)	90 (29.3)	0.251
Alcohol Use (n [%])				
User	79 (51.3)	85 (55.6)	164 (53.4)	
Ex-user	8 (5.2)	3 (2.0)	11 (3.6)	
Non-user	67 (43.5)	65 (42.5)	132 (43.0)	0.493

BMI = body mass index; ew = every week

a. *P* value for differences between treatment groups from Fisher's exact test for sex, race, ethnicity, nicotine use, and alcohol use; chi-square test for age and BMI categories; and one-way ANOVA for age, weight, height, and BMI.Non-white races were combined for analysis of race.
b. Adalimumab ew N = 152.
Note: A subject may be a user of 1 type of tobacco (or nicotine-containing product), an ex-user of another type of nicotine and a non-user of another type of nicotine. A subject was counted in the category closest to user.
Percentages were calculated on non-missing values.

Table 28. Baseline Disease Characteristics (ITT_A Population) Study M11-313

Demographic Variable	Placebo (N = 154)	Adalimumab ew (N = 153)	Total (N = 307)	*P* value
Hurley Stage (n [%])[a]				
II	81 (52.6)	80 (52.3)	161 (52.4)	
III	73 (47.4)	73 (47.7)	146 (47.6)	0.957
Family history of HS (n [%])				
Yes	32 (20.8)	39 (25.5)	71 (23.1)	
No	122 (79.2)	114 (74.5)	236 (76.9)	0.328
Duration of HS (years)				
< 9.17 (median)	73 (47.4)	80 (52.3)	153 (49.8)	
≥ 9.17 (median)	81 (52.6)	73 (47.7)	154 (50.2)	0.392
Baseline AN count (n [%])				
≤ 5	36 (23.4)	24 (15.7)	60 (19.5)	
6 – 10	33 (21.4)	54 (35.3)	87 (28.3)	
≥ 11	85 (55.2)	75 (49.0)	160 (52.1)	0.018*
Abscess count				
Mean ± SD	2.7 ± 3.69	2.8 ± 3.47	2.8 ± 3.47	
Median (min – max)	2.0 (0 – 24.0)	2.0 (0 – 17.0)	2.0 (0 – 24.0)	0.864
Draining fistula count				
Mean ± SD	3.8 ± 4.40	4.6 ± 5.20	4.2 ± 4.82	
Median (min – max)	2.0 (0 – 20.0)	3.0 (0 – 20.0)	2.0 (0 – 20.0)	0.152
Inflammatory nodule count				
Mean ± SD	11.6 ± 13.85	11.5 ± 10.92	11.6 ± 12.46	
Median (min – max)	7.0 (0 – 138.0)	8.0 (0 – 76.0)	8.0 (0 – 138.0)	0.937
Hypertrophic scar count				
Mean ± SD	7.5 ± 10.25	10.1 ± 33.86	8.8 ± 24.97	
Median (min – max)	4.0 (0 – 50.0)	5.0 (0 – 324.0)	4.0 (0 – 324.0)	0.370
AN count				
Mean ± SD	14.4 ± 14.80	14.3 ± 11.92	14.3 ± 13.42	
Median (min – max)	11.0 (3 – 141.0)	10.0 (3 – 78.0)	11.0 (3 – 141.0)	0.977
Erythema (worst among all body regions)				
No redness	1 (0.6)	0	1 (0.3)	
Faint but discernable pink coloration	19 (12.3)	14 (9.2)	33 (10.7)	
Moderate red coloration	70 (45.5)	74 (48.4)	144 (46.9)	
Very red or bright red coloration	64 (41.6)	65 (42.5)	129 (42.0)	0.661
Modified Sartorius score				
Mean ± SD	147.3 ± 97.16	151.0 ± 131.17	149.1 ± 115.19	
Median (min – max)	190.0 (29 – 531.0)	179.0 (19 – 1093.0)	180.0 (19 – 1093.0)	0.774
NRS (daily pain at worst)[b]				
Mean ± SD	4.8 ± 2.68	5.1 ± 2.51	5.0 ± 2.60	
Median (min – max)	4.7 (0 – 10.0)	5.3 (0 – 9.6)	5.1 (0 – 10.0)	0.341
Prior surgery for HS				
Yes	13 (8.4)	21 (13.7)	34 (11.1)	
No	141 (91.6)	132 (86.3)	273 (88.9)	0.140

ADA = adalimumab; AN = abscess and inflammatory nodule; eow = every other week; ew = every week;
HS = hidradenitis suppurativa; NRS = numeric rating scale of skin pain due to HS in the past 24 hours; PBO = placebo;
SD = standard deviation

a. Hurley Stage presented in the demographic tables may differ from the Hurley Stage stratum used for the purposes of the efficacy analyses. Hurley Stage stratum used for efficacy analyses was determined at the time of randomization. Subsequent updates to a subject's Hurley Stage did not affect the stratum, but are reflected in the demographic tables.

b. placebo N = 146; adalimumab ew N = 151.

Note: * denotes $P \leq 0.05$.

Study M11-810

Table 29. Demographic Characteristics (ITT_A Population) Study M11-810

Demographic Variable	Placebo (N = 163)	Adalimumab ew (N = 163)	Total (N = 326)	*P* Value[a]
Sex (n [%])				
Female	113 (69.3)	108 (66.3)	221 (67.8)	
Male	50 (30.7)	55 (33.7)	105 (32.2)	0.636
Race (n [%])[b]				
White	130 (79.8)	143 (87.7)	273 (83.7)	
Black	20 (12.3)	9 (5.5)	29 (8.9)	
Asian	4 (2.5)	6 (3.7)	10 (3.1)	
American Indian/ Alaska native	1 (0.6)	0	1 (0.3)	
Native Hawaiian or other Pacific Islander	1 (0.6)	0	1 (0.3)	
Other	6 (3.7)	3 (1.8)	9 (2.8)	
Multi-race	1 (0.6)	2 (1.2)	3 (0.9)	0.071
Ethnicity				
Hispanic/Latino	7 (4.3)	12 (7.4)	19 (5.8)	
No ethnicity	156 (95.7)	151 (92.6)	307 (94.2)	0.345
Age (year)				
Mean ± SD	36.1 ± 12.18	34.9 ± 9.96	35.5 ± 11.13	
Median (min – max)	34.0 (19.0 – 69.0)	35.0 (18.0 – 67.0)	34.5 (18.0 – 69.0)	0.299
Age group (n [%])				
< 40	108 (66.3)	115 (70.6)	223 (68.4)	
40 – 64	52 (31.9)	47 (28.8)	99 (30.4)	
≥ 65	3 (1.8)	1 (0.6)	4 (1.2)	0.482
Weight (kg)				
Mean ± SD	95.7 ± 25.87	90.2 ± 21.74	92.9 ± 24.01	
Median (min – max)	92.0 (41.0 – 184.0)	90.0 (43.0 – 153.0)	90.0 (41.0 – 184.0)	0.039*
Height (cm)[c]	170.2 ± 10.52	169.8 ± 9.72		
Mean ± SD	169.0 (148.0 –	168.0 (147.0 –	170.0 ± 10.11	
Median (min – max)	208.0)	197.0)	168.0 (147.0 – 208.0)	0.697
BMI (kg/m^2)[c]				
Mean ± SD	32.9 ± 7.94	31.3 ± 7.41	32.1 ± 7.71	
Median (min – max)	31.8 (16.7 – 60.1)	30.5 (17.4 – 54.2)	31.5 (16.7 – 60.1)	0.065
Nicotine use (n [%])				
User	109 (67.3)	105 (64.4)	214 (65.8)	
Ex-user	18 (11.1)	22 (13.5)	40 (12.3)	
Non-user	35 (21.6)	36 (22.1)	71 (21.8)	
Unknown	1	0	1	0.640
Alcohol use (n [%])				
User	97 (59.5)	95 (58.3)	192 (58.9)	
Ex-user	4 (2.5)	5 (3.1)	9 (2.8)	
Non-user	62 (38.0)	63 (38.7)	125 (38.3)	0.910

BMI = body mass index; ew = every week; SD = standard deviation
a *P* value for differences between treatment groups from Fisher's exact test for sex, race, ethnicity, nicotine use, and alcohol use.
P value for differences between treatment groups from 1-way ANOVA for age, weight, height, and BMI.
b Non-white races were combined for analysis of race.
c Placebo group N = 161.
Notes: Ex-users and non-users of nicotine were combined for analysis of nicotine and ex-users and non-users of alcohol were combined for analysis of alcohol.
Percentages were calculated on non-missing values.

* denotes $P \leq 0.05$.

Table 30. Baseline Disease Characteristics (ITT_A Population) Study M11-810

Demographic Variable	Placebo (N = 163)	Adalimumab ew (N = 163)	Total (N = 326)	*P* Value
Hurley Stage (n [%])[a]				
II	89 (54.6)	86 (52.8)	175 (53.7)	
III	74 (45.4)	77 (47.2)	151 (46.3)	0.739
Family history of HS (n [%])				
Yes	43 (26.4)	39 (24.1)	82 (25.2)	
No	120 (73.6)	123 (75.9)	243 (74.8)	
Missing	0	1	1	0.632
Duration of HS (years)				
< 9.31 (median)	79 (48.5)	84 (51.5)	163 (50.0)	
≥ 9.31 (median)	84 (51.5)	79 (48.5)	163 (50.0)	0.580
AN count (n [%])				
≤ 5	50 (30.7)	47 (28.8)	97 (29.8)	
6 – 10	51 (31.3)	61 (37.4)	112 (34.4)	
≥ 11	62 (38.0)	55 (33.7)	117 (35.9)	0.495
Abscess count				
Mean ± SD	2.4 ± 3.34	2.0 ± 2.60	2.2 ± 3.00	
Median (min – max)	1.0 (0.0 – 16.0)	1.0 (0.0 – 13.0)	1.0 (0.0 – 16.0)	0.223
Draining fistula count				
Mean ± SD	3.7 ± 5.20	3.0 ± 4.11	3.4 ± 4.70	
Median (min – max)	1.0 (0.0 – 20.0)	1.0 (0.0 – 20.0)	1.0 (0.0 – 20.0)	0.157
Inflammatory nodule count				
Mean ± SD	9.4 ± 9.60	8.6 ± 6.92	9.0 ± 8.36	
Median (min – max)	6.0 (0.0 – 62.0)	6.0 (0.0 – 42.0)	6.0 (0.0 – 62.0)	0.379
Hypertrophic scar count				
Mean ± SD	7.0 ± 11.86	6.4 ± 14.18	6.7 ± 13.06	
Median (min – max)	3.0 (0.0 – 75.0)	3.0 (0.0 – 146.0)	3.0 (0.0 – 146.0)	0.642
AN count				
Mean ± SD	11.9 ± 11.02	10.7 ± 8.10	11.3 ± 9.68	
Median (min – max)	8.0 (3.0 – 66.0)	8.0 (3.0 – 50.0)	8.0 (3.0 – 66.0)	0.255
Erythema (worst among all body regions)				
No redness	1 (0.6)	2 (1.2)	3 (0.9)	
Faint, but discernable pink coloration	10 (6.1)	8 (4.9)	18 (5.5)	
Moderate red coloration	77 (47.2)	67 (41.1)	144 (44.2)	
Very red or bright red coloration	75 (46.0)	86 (52.8)	161 (49.4)	0.583
Modified Sartorius score				
Mean ± SD	122.6 ± 88.00	107.5 ± 80.03	115.0 ± 84.32	
Median (min – max)	95.0 (20.0 – 468.0)	91.0 (18.0 – 483.0)	93.5 (18.0 – 483.0)	0.106
NRS (daily pain at worst)[b]				
Mean ± SD	4.8 ± 2.73	4.3 ± 2.62	4.5 ± 2.69	
Median (min – max)	5.0 (0.0 – 10.0)	4.1 (0.0 – 10.0)	4.4 (0.0 – 10.0)	0.058
Prior surgery for HS				
Yes	18 (11.0)	27 (16.6)	45 (13.8)	
No	145 (89.0)	136 (83.4)	281 (86.2)	0.148

AN = abscess and inflammatory nodule; ew = every week; HS = hidradenitis suppurativa; NRS = numeric rating scale; SD = standard deviation

a. Hurley Stage presented in the baseline characteristics tables may differ from the Hurley Stage stratum used for the purposes of the efficacy analyses. Hurley Stage stratum used for efficacy analyses was determined at the time of randomization. Subsequent updates to a subject's Hurley Stage did not affect the stratum, but are reflected in the baseline disease characteristics tables.

b. N = 155 (placebo), 159 (adalimumab ew), and 314 (total).

Medical history

In Study **M11-313,** the most frequently reported (≥ 10% of all subjects) medical history findings at baseline were hypertension, surgery in another body system, depression, asthma, gastroesophageal reflux disease, and musculoskeletal surgery. These medical history findings were generally balanced across the adalimumab and placebo treatment groups.

No subjects in Period A had any signs of active TB at screening. Overall, 10 subjects (7 adalimumab ew and 3 placebo) enrolled in Period A while receiving TB prophylaxis for signs of latent TB.

In Study **M11-810**, the most frequently reported co-morbidities in this HS population were surgery of the skin and other body systems, depression, hypertension, and diabetes mellitus. The findings were generally balanced across the adalimumab and placebo treatment groups.

The majority of subjects tested negative for TB; 21 subjects (10 in the placebo group and 11 in the adalimumab ew group) tested positive for TB. All subjects with a positive or indeterminant test result enrolled in the TB prophylaxis program. No subjects had any signs or symptoms of active TB.

Prior and concomitant medications

In Study **M11-313**, all subjects reported prior antibiotic use for treatment of HS, doxycycline and clindamycin being the most commonly used prior oral antibiotics. Approximately 1/3 of the subjects reported prior use of both topical and systemic therapies to treat HS. The majority of subjects discontinued use due to inadequate response (overall about 80%).

In Study **M11-810**, nearly all subjects reported prior antibiotic use for treatment of HS, which had been discontinued for various reasons. Doxycycline and clindamycin were the most frequently reported prior oral antibiotics. The majority of subjects discontinued use of prior antibiotic therapy because of inadequate response (>80%).

All subjects in both studies received concomitant medications, including the protocol-required antiseptic wash, during the study. The most common medications were ibuprofen, chlorhexidine, paracetamol, corticosteroids and retinoids for treatment of acne.

In Study **M11-810**, a total of 38 subjects (12%) had doxycycline as a concomitant medication and 27 subjects (8.3%) received minocycline (the two allowed antibiotics). These treatments were fairly well balanced between the adalimumab and placebo groups.

- **Numbers analysed**

Study M11-313

The ITT population in Period A (ITT_A) included all subjects who were randomised at Week 0 (N=307; placebo n=154, adalimumab ew n=153).

The Safety population in period A (Safety_A) included all subjects who received at least 1 dose of study drug. Two subjects randomised to placebo did not receive study drug and were excluded in the safety analyses (N=305; placebo n=152, adalimumab ew n=153).

The PP Population in Period A (PP_A) included a total of 280 subjects (placebo n=136, adalimumab ew n=144).

The ITT population in Period B (ITT_B) included all subjects who were re-randomized (received a re-randomization number) at entry to Period B (N = 290; placebo/ew n=145, adalimumab ew/placebo n=49, adalimumab ew/eow n=48, adalimumab ew/ew n=48).

The ITT_B_R population (period B) included all subjects randomised to adalimumab ew in period A and was re-randomised in period B as HiSCR responders (adalimumab ew/placebo n=22, adalimumab ew/eow n=20, adalimumab ew/ew n=21).

The ITT_B_NR population (period B) included all subjects randomised to adalimumab ew in period A and was re-randomised in period B as HiSCR non-responders (adalimumab ew/placebo n=27, adalimumab ew/eow n=28, adalimumab ew/ew n=27).

The Safety_B population included all subjects who received at least 1 dose of study drug in period B and was the same as the ITT_B population (N=290).

Study M11-810

The ITT population in Period A (ITT_A) included all subjects who were randomised at Week 0 (N=326; placebo n=163, adalimumab ew n=163).

The Safety population in period A (Safety_A) included all subjects who received at least 1 dose of study drug and was the same as the ITT_A population (N=326).

The PP Population in Period A (PP_A) included a total of 302 subjects (placebo n=151, adalimumab n=151).

The ITT population in Period B (ITT_B) included all subjects who were re-randomized (received a re-randomization number) at entry to Period B (N = 306; placebo/placebo n=151, adalimumab ew/placebo n=51, adalimumab ew/eow n=53, adalimumab ew/ew n=51).

The ITT_B_R population (period B) included all subjects randomised to adalimumab ew in period A and was re-randomised in period B as HiSCR responders (adalimumab ew/placebo n=31, adalimumab ew/eow n=32, adalimumab ew/ew n=31).

The ITT_B_NR population (period B) included all subjects randomised to adalimumab ew in period A and was re-randomised in period B as HiSCR non-responders (adalimumab ew/placebo n=20, adalimumab ew/eow n=21, adalimumab ew/ew n=20).

The Safety_B population included all subjects who received at least 1 dose of study drug in period B and was the same as the ITT_B population (N=306).

- **Outcomes and estimation**

Primary end-point

HiSCR

The primary efficacy variable was the proportion of subjects achieving HiSCR, defined as at least a 50% reduction in AN count with no increase in abscess count and no increase in draining fistula count relative to Baseline, at Week 12.

Study M11-313

Table 31. Proportion of Subjects Achieving HiSCR at Week 12 (NRI) (ITT_A Population), Study M11-313

Strata	Placebo n/N (%)	Adalimumab ew n/N (%)	Difference %	(95% CI)[a]	*P* value[b]
All	40/154 (26.0)	64/153 (41.8)	15.9	(5.3, 26.5)	0.003*
Hurley Stage II	25/84 (29.8)	37/83 (44.6)	14.8	(0.3, 29.3)	0.048*
Hurley Stage III	15/70 (21.4)	27/70 (38.6)	17.1	(2.2, 32.1)	0.027*

CI = confidence interval; ew = every week; NRI = non-responder imputation
a. Across all strata, 95% CI for adjusted difference was calculated according to the extended Mantel-Haenszel statistic for the comparison of 2 treatment groups; within each stratum of baseline Hurley Stage, 95% CI for difference was calculated based on normal approximation to the binomial distribution.
b. Across all strata, *P* value was calculated from the Cochran-Mantel-Haenszel test adjusted for strata; within each stratum of Baseline Hurley Stage, *P* value was calculated based on chi-square test (or Fisher's exact test if ≥ 20% of the cells have expected cell count < 5).
Note: * denotes $P \leq 0.05$.

Results were consistent for the following analyses: LOCF, modified NRI (mNRI), which counted all subjects with any add-on antibiotics prior to Week 12, regardless the reason for use, as non-responders and for multiple imputation (MI). The treatment difference was also similar between the ITT and PP populations.

Study M11-810

Table 32. Proportion of Subjects Achieving HiSCR at Week 12 (NRI) (ITT_A Population), Study M11-810

Strata	Placebo n/N (%)	Adalimumab n/N (%)	Difference %	(95% CI)[a]	*P* Value[b]
All	45/163 (27.6)	96/163 (58.9)	31.5	(20.7, 42.2)	< 0.001*
Antibiotic use	7/32 (21.9)	20/31 (64.5)	42.6	(17.8, 67.5)	<0.001
No antibiotic use	38/131 (29.0)	76/132 (57.6)	28.6	(16.9, 40.6)	<0.001
Hurley Stage II	32/87 (36.8)	53/85 (62.4)	25.5	(10.5, 40.5)	< 0.001*
Antibiotic use	3/12 (25.0)	7/11 (63.6)	38.6	(1.1, 76.2)	0.004*
No antibiotic use	29/75 (38.7)	46/74 (62.2)	23.5	(7.9, 39.1)	< 0.001*
Hurley Stage III	13/76 (17.1)	43/78 (55.1)	38.1	(22.8, 53.3)	< 0.001*
Antibiotic use	4/20 (20.0)	13/20 (65.0)	45.0	(17.7, 72.3)	0.004*
No antibiotic use	9/56 (16.1)	30/58 (51.7)	35.7	(19.6, 51.7)	< 0.001*

a. CI = confidence interval; HiSCR = Hidradenitis suppurativa clinical response; NRI = nonresponder imputation a. 95% CI for adjusted difference was calculated according to the extended Mantel-Haenszel statistic adjusted for baseline Hurley Stage (II/III) and baseline antibiotic use (Y/N); for each stratum of baseline Hurley Stage, 95% CI for adjusted difference was calculated according to the extended Mantel-Haenszel statistic adjusted for baseline antibiotics use (Y/N).
b. *P* value was calculated from the Cochran-Mantel-Haenszel test adjusted for baseline Hurley Stage (II/III) and baseline antibiotic use (Y/N); for each stratum of baseline Hurley Stage, *P* value was calculated from the Cochran-Mantel-Haenszel test adjusted for baseline antibiotics use (Y/N).
Note: * denotes $P \leq 0.05$.

Results from different sensitivity analyses were consistent with the results from the primary analysis using NRI. The treatment difference was also similar between the ITT and PP populations.

LOCF, modified NRI_1 (mNRI1), counting all subjects with any add-on antibiotics (any antibiotics other than those used at Baseline) or with dose increase in baseline concomitant antibiotics prior to Week 12, regardless of the reason for use, as non-responders, modified NRI_2 (mNRI2): Among all subjects in the strata of non-concomitant antibiotics of the ITT Population in Period A, counting all subjects that have an add-on antibiotics prior to Week 12, regardless of the reason for use, as non-responders. If any subject was randomized according to a wrong stratum, a sensitivity analysis was performed for the primary endpoint based on the subjects' actual baseline Hurley Stage and actual baseline concomitant use of antibiotics with NRI as the imputation method. Multiple imputation (MI) was also performed.

Ranked secondary end-points (studies M11-313 and M11-810 including *post hoc* analysis of Study M10-467)

A summary of the results for the three ranked secondary end-points for both pivotal studies and the results from the *post hoc* analysis of the phase 2 study M10-467 is presented below.

Table 33. Summarized results of Ranked Secondary Endpoints for Individual Studies (ITT_A Population, Study M11-810 and Study M11-313; mITT-1 Population, Study M10-467)

		ew vs. pbo		
Rank	**Secondary Variable**	**Study M11-810**	**Study M11-313**	**Study M10-467**
1	Proportion of subjects who achieved AN count of 0, 1, or 2 at Week 12, among subjects with Hurley Stage II at baseline (NRI)	51.8% vs. 32.2% *P* = 0.010*	28.9% vs. 28.6% *P* = 0.961	60.0% vs. 20.8% *P* = 0.009*,[a]
2	Proportion of subjects who achieved 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 12 among subjects with baseline skin pain NRS ≥ 3 (NRI)[a]	45.7% vs. 20.7% *P* < 0.001*	27.9% vs. 24.8% *P* = 0.628	60.7% vs. 21.9% *P* = 0.003*,[a]
3	Change in modified Sartorius score from baseline to Week 12 (LOCF)[b]	–28.9 vs. –9.5 *P* < 0.001*	–24.4 vs. –15.7 *P* = 0.124	–38.2 vs. –20.4 *P* = 0.036*,[c]

a. In Study M10-467, patient global assessment of skin pain was examined using a 100-point scale, and only subjects with a baseline value ≥ 30 were included.

b. Modified Sartorius measurement was collected at Week 16 for Study M10-467.

c. Post hoc analysis; all other analyses were prespecified.

* Denotes *P* ≤ 0.05.

Other secondary end-points

HiSCR at Each Visit

Study M11-313

Table 34. Proportion of Subjects Achieving HiSCR by Visit in Period A (NRI) (ITT_A Population, Study M11-313)

	Response, n (%)		Treatment Difference[a,b]	
Visit	**pbo N = 154**	**ew N = 153**	**%**	**(95% CI)**
Week 2	22 (14.3)	36 (23.5)	9.3*	(0.7, 17.9)
Week 4	29 (18.8)	45 (29.4)	10.6*	(1.1, 20.1)
Week 8	31 (20.1)	63 (41.2)	21.1*	(10.8, 31.3)
Week 12	40 (26.0)	64 (41.8)	15.9*	(5.3, 26.5)

a. 95% CI for adjusted difference calculated according to the extended Mantel-Haenszel statistic adjusted for baseline Hurley Stage.

b. *P* value was calculated from the CMH test adjusted for baseline Hurley Stage.

* Denotes *P* ≤ 0.05.

Study M11-810

Table 35. Proportion of Subjects Achieving HiSCR by Visit in Period A (NRI) (ITT_A Population), Study M11-810

	Response, n (%)		Treatment Difference[a,b]	
Visit	pbo N = 163	ew N = 163	%	(95% CI)
Week 2	19 (11.7)	73 (44.8)	33.2*	(23.5, 42.9)
Week 4	36 (22.1)	84 (51.5)	29.6*	(19.3, 40.0)
Week 8	41 (25.2)	89 (54.6)	29.7*	(19.2, 40.2)
Week 12	45 (27.6)	96 (58.9)	31.5*	(20.7, 42.2)

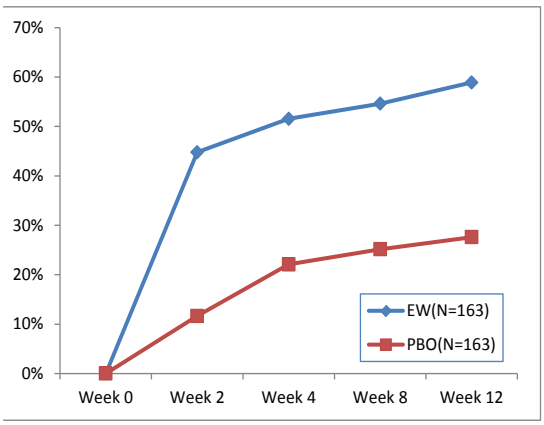
a. 95% CI for adjusted difference was calculated according to the extended Mantel-Haenszel statistic adjusted for baseline Hurley Stage (II/III) and baseline antibiotic use (Y/N).

b. *P* value was calculated from the CMH test adjusted for baseline Hurley Stage (II/III) and baseline antibiotic use (Y/N).

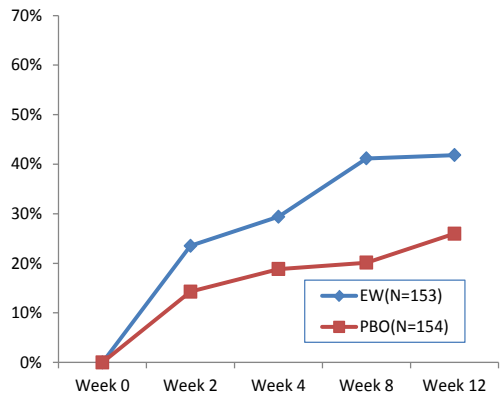
* Denotes $P \leq 0.05$.

Figure 17. Proportions of Subjects Achieving HiSCR (NRI) (Panel A, Study M11-810), (Panel B, Study M11-313) (ITT_A Population)

Panel A (Study M11-810):



Panel B (Study M11-313):



Reduction in Inflammatory Lesions

Study M11-313

The overall proportions of subjects achieving complete elimination of AN (AN = 0) and AN of 0/1 (counts of 0 or 1) at Week 12 were higher for subjects randomized to adalimumab ew compared with subjects randomized to placebo (p ≤0.05).

The treatment effect for the proportion of subjects who achieved AN count of 0, 1, or 2 as well as those who achieved AN count of 0 or 1 was generally larger for subjects with Hurley Stage III at baseline compared to subjects with Hurley Stage II at baseline of Study M11-313. The proportion of subjects who achieved AN count of 0, 1, or 2 at Week 12 among subjects with Hurley Stage II at baseline (first ranked secondary endpoint) did not reach statistical significance while the treatment difference was larger among subjects with Hurley Stage III (P ≤ 0.05).

Table 36. Proportion of Subjects Achieving AN Count of 0, AN Count of 0/1, or AN Count of 0/1/2 at Week 12 (NRI) (ITT_A Population, Study M11-313)

	Response, n (%)		Treatment Difference[a,b]	
Variable	pbo N = 154	ew N = 153	%	(95% CI)
AN count of 0	6 (3.9)	16 (10.5)	6.6*	(0.8, 12.3)
AN count of 0/1	16/154 (10.4)	29/153 (19.0)	8.6*	(0.6, 16.5)
AN count of 0/1/2	32/154 (20.8)	43/153 (28.1)	7.4	(-2.2, 16.9)

a. 95% CI calculated according to the extended Mantel-Haenszel statistic adjusted for baseline Hurley Stage.

b. *P* value calculated from the CMH test adjusted for baseline Hurley Stage. * Denotes $P \leq 0.05$.

The mean reduction and mean percent reduction from baseline in AN count and inflammatory nodule count was higher for subjects in the adalimumab ew group compared with subjects in the placebo group at Week 12 ($p \leq 0.05$).

Table 37. Change from Baseline in Lesion Counts at Week 12 (LOCF) (ITT_A Population, Study M11-313)

				Within Group Change	Between Group Change		
Lesion Type/ Treatment Group	N	BL Mean	Week 12 Mean	LS Mean ± SE	LS Mean	(95% CI)	*P* value[a]
AN count							
Placebo	151	14.2	11.4	–2.7 ± 0.67			
Adalimumab ew	153	14.3	8.7	–5.5 ± 0.67	–2.7	(–4.6, –0.9)	0.004*
Inflammatory nodule count							
Placebo	151	11.6	9.5	–1.9 ± 0.59			
Adalimumab ew	153	11.5	7.2	–4.2 ± 0.59	–2.4	(–4.0, –0.7)	0.005*
Abscess count							
Placebo	151	2.7	1.8	–0.8 ± 0.18			
Adalimumab ew	153	2.8	1.6	–1.2 ± 0.18	–0.3	(–0.8, 0.2)	0.181
Draining fistula count							
Placebo	151	3.7	3.4	–0.3 ± 0.41			
Adalimumab ew	153	4.6	3.7	–0.8 ± 0.41	–0.5	(–1.6, 0.7)	0.412
All fistula count[b]							
Placebo	151	10.7	9.9	–0.8 ± 0.51			
Adalimumab ew	153	11.5	10.4	–1.0 ± 0.51	–0.2	(–1.6, 1.2)	0.782

a. *P* values were calculated from ANCOVA with stratum, baseline value, and treatment in the model.

b. All fistula includes draining and nondraining fistulas.

* Denotes $P \leq 0.05$.

The *percent* change from baseline in lesion counts at Week 12 showed corresponding results, with between 10-35% decreases in different lesion counts for adalimumab ew vs. between <1% up to 25% decreases for placebo.

Study M11-810

The overall proportions of subjects achieving complete elimination of AN (AN = 0), AN count of 0/1 (AN = 0 or 1), and AN count of 0/1/2 (AN = 0, 1, or 2) at Week 12 were higher for subjects randomized to adalimumab ew compared to subjects randomized to placebo (P ≤0.05).

Table 38. Proportion of Subjects Achieving AN Count of 0, AN Count of 0/1, or AN Count of 0/1/2 at Week 12 (NRI) (ITT_A Population), Study M11-810

	Response, n (%)		Treatment Difference[a,b]	
Variable	pbo N = 163	ew N = 163	%	(95% CI)
AN count of 0	10 (6.1)	25 (15.3)	9.2*	(2.5, 16.0)
AN count of 0/1	23 (14.1)	50 (30.7)	16.6*	(7.6, 25.6)
AN count of 0/1/2	37 (22.7)	70 (42.9)	20.4*	(10.4, 30.4)

a. 95% CI for adjusted difference was calculated according to the extended Mantel-Haenszel statistic adjusted for baseline Hurley Stage (II/III) and baseline antibiotic use (Y/N).

b. *P* value was calculated from the CMH test adjusted for baseline Hurley Stage (II/III) and baseline antibiotic use (Y/N).

* Denotes $P \leq 0.05$.

The mean reduction and mean percent reduction from Baseline in AN, inflammatory nodule, abscess, draining fistula, and all fistula (draining and non-draining) counts at Week 12 were greater for subjects randomized to adalimumab ew than for subjects randomized to placebo ($p \leq 0.009$ for all lesion types, except for mean change in "all fistula") (LOCF).

Table 39. Change from Baseline in Lesion Counts at Week 12 (LOCF) (ITT_A Population, Study M11-810)

Lesion Type / Treatment Group	N	BL Mean	Week 12 Mean	Within Group Change	Between Group Change		
				LS Mean ± SE	LS Mean	(95% CI)	*P* value[a]
AN count							
Placebo	162	11.9	9.7	–2.4 ± 0.62	-	-	-
Adalimumab ew	163	10.7	5.1	–6.3 ± 0.62	–3.8	(–5.3, –2.3)	< 0.001*
Inflammatory nodule count							
Placebo	162	9.5	7.6	–2.0 ± 0.37	-	-	-
Adalimumab ew	163	8.6	4.1	–4.9 ± 0.38	–3.0	(–4.2, –1.8)	< 0.001*
Abscess count							
Placebo	162	2.4	2.1	–0.4 ± 0.22	-	-	-
Adalimumab ew	163	2.0	1.0	–1.3 ± 0.22	–0.9	(–1.4, –0.4)	< 0.001*
Draining fistula count							
Placebo	162	3.7	4.1	0.5 ± 0.35	-	-	-
Adalimumab ew	163	3.0	2.2	–0.7 ± 0.35	–1.2	(–2.1, –0.4)	0.005*
All fistula[b] count							
Placebo	162	8.7	8.5	–0.2 ± 0.47	-	-	-
Adalimumab ew	163	7.2	6.1	–1.2 ± 0.47	–1.0	(–2.1, 0.1)	0.083

d. *P* values were calculated from ANCOVA with stratum (baseline Hurley Stage and antibiotics use), baseline value, and treatment in the model.

e. All fistula includes draining and nondraining fistulas.

* Denotes $P \leq 0.05$.

The *percent* change from baseline in lesion counts at Week 12 showed corresponding results, with between 25-55% decreases in different lesion counts for adalimumab ew vs. 8-25% decreases for placebo.

Improvement in Lesion Severity

Changes in the severity of the lesions were evaluated by follow-up of representative lesions. Up to 6 baseline representative lesions were identified per patient and evaluated for lesion type, tenderness, size, and degree of erythema, and the Patient's Lesion Severity Score was calculated based on these evaluations.

Study M11-313

The mean reduction from Baseline in the Patient's Lesion Severity Score and the degree of in erythema and tenderness, but not lesion size, were greater for subjects in the adalimumab ew group than for subjects in the placebo group.

Table 40. Change from Baseline in Lesion Severity Scores by Score Type at Week 12 (LOCF) (ITT_A Population, Study M11-313)

Lesion Severity Score Type / Treatment Group	N	BL Mean	Week 12 Mean	Within Group Change	Between Group Change		
				LS Mean ± SE	LS Mean Diff	(95% CI)	*P* value[a]
Patient's lesion severity score							
Placebo	150	15.9	10.0	–6.0 ± 0.58			
Adalimumab ew	151	16.8	8.8	–7.8 ± 0.58	–1.8	(–3.4, –0.2)	0.029*
Average lesion severity score in erythema							
Placebo	150	7.0	4.4	–2.6 ± 0.26			
Adalimumab ew	151	7.3	3.7	–3.4 ± 0.26	–0.8	(–1.5, –0.1)	0.025*
Average lesion severity score in tenderness							
Placebo	150	6.3	3.8	–2.6 ± 0.25			
Adalimumab ew	151	6.8	3.2	–3.4 ± 0.25	–0.9	(–1.6, –0.2)	0.014*
Average lesion severity score in size							
Placebo	150	2.6	1.8	–0.8 ± 0.14			
Adalimumab ew	151	2.7	1.9	–0.8 ± 0.14	0.0	(–0.4, 0.4)	0.976

a. *P* values were calculated from ANCOVA with stratum, baseline value, and treatment in the model.

* Denotes $P \leq 0.05$.

Study M11-810

The mean reduction from Baseline in the various lesion-related parameters were greater for subjects randomized to adalimumab ew, than for subjects randomized to placebo (p ≤0.012) (LOCF).

Table 6. Change from Baseline in Lesion Severity Scores by Score Type at Week 12 (LOCF) (ITT_A Population, Study M11-810)

Lesion Severity Score Type / Treatment Group	N	BL Mean	Week 12 Mean	Within Group Change	Between Group Change		
				LS Mean ± SE	LS Mean Diff	(95% CI)	*P* value[a]
Patient's lesion severity score							
Placebo	158	15.9	9.6	–5.9 ± 0.57			
Adalimumab ew	163	15.3	6.3	–8.9 ± 0.57	–2.9	(–4.3, –1.6)	< 0.001*
Average lesion severity score in erythema							
Placebo	158	7.1	4.2	–2.7 ± 0.26			
Adalimumab ew	163	6.9	2.8	–4.0 ± 0.26	–1.3	(–1.9, –0.7)	< 0.001*
Average lesion severity score in tenderness							
Placebo	158	6.2	3.5	–2.5 ± 0.25			
Adalimumab ew	163	5.9	2.2	–3.7 ± 0.25	–1.2	(–1.8, –0.6)	< 0.001*
Average lesion severity score in size							
Placebo	158	2.6	1.9	–0.7 ± 0.16			
Adalimumab ew	163	2.5	1.3	–1.2 ± 0.16	–0.5	(–0.9, –0.1)	0.012*

a. *P* values were calculated from ANCOVA with stratum (baseline Hurley Stage and antibiotics use), baseline value, and treatment in the model.

* Denotes $P \leq 0.05$.

Improvement in Modified Sartorius Score

Mean change in modified in modified Sartorius score from Baseline to Week 12 was the third ranked secondary endpoint for the pivotal studies.

Study M11-313

Table 42. Mean Change from Baseline in Modified Sartorius Score by Visit (LOCF) (ITT_A Population) Study M11-313

Visit/ Treatment Group	N	Baseline Mean	Visit Mean	Between Group Change	
				LS Mean	*P* value[a]
Week 2					
Placebo	151	146.7	139.6		
Adalimumab ew	152	150.7	135.6	–7.7	0.014*
Week 4					
Placebo	151	146.7	139.1		
Adalimumab ew	153	151.0	131.5	–11.7	0.002*
Week 8					
Placebo	151	146.7	138.5		
Adalimumab ew	153	151.0	125.7	–17.0	< 0.001*
Week 12					
Placebo	151	146.7	130.5		
Adalimumab ew	153	151.0	125.8	–8.7	0.124

ew = every week; LOCF = last observation carried forward

a. *P* values were calculated from ANCOVA with stratum, baseline value, and treatment in the model.

Note: * denotes $P \leq 0.05$.

Study M11-810

Table 43. Mean Change from Baseline in Modified Sartorius Score by Visit (LOCF) (ITT_A Population), Study M11-810

Visit/ Treatment Group	N	Baseline Mean	Visit Mean	Between Group Change	
				LS Mean	*P* Value[a]
Week 2					
Placebo	162	122.5	119.4	-	-
Adalimumab ew	161	107.7	90.7	–14.8	< 0.001
Week 4					
Placebo	162	122.5	115.9	-	-
Adalimumab ew	163	107.5	87.4	–14.2	< 0.001*
Week 8					
Placebo	162	122.5	114.3	-	-
Adalimumab ew	163	107.5	83.8	–15.9	< 0.001*
Week 12					
Placebo	162	122.5	115.2	-	-
Adalimumab ew	163	107.5	81.4	–19.4	< 0.001*

ew = every week; LOCF = last observation carried forward

a. *P* values were calculated from ANCOVA with stratum (baseline Hurley Stage and antibiotics use), baseline value, and treatment in the model.

Note: * denotes $P \leq 0.05$.

Risk of Flare

Study M11-313

The proportion of subjects who experienced disease flare, defined as at least a 25% increase in AN count with a minimum increase of 2 relative to Baseline, was lower at all visits during Period A for subjects randomized to adalimumab ew than for subjects randomized to placebo (NRI). At least 1 occurrence of flare was experienced by 14% of subjects in the adalimumab ew group and 36% of subjects in the placebo group ($p<0.001$).

Study M11-810
The proportion of subjects who experienced disease flare was lower for subjects randomized to adalimumab ew at all visits during Period A than for subjects randomized to placebo (11% vs. 35%, $p<0.001$).

Improvement in Patient-Reported HS-Related Skin Pain

The proportion of subjects who achieved NRS30 – at worst at Week 12 among subjects with baseline skin pain NRS ≥3 was the second ranked secondary endpoint. Since the protocols of both studies were amended to include only subjects with baseline skin pain NRS ≥ 3 in this analysis, the numbers included in the following analyses are smaller than those for other end-points.

Study M11-313
A greater proportion of subjects achieved NRS30 in the adalimumab ew group compared with the placebo group during Period A (p≤0.05 for all visits except at Week 12)

To assess improvement in skin pain over the entire treatment period, the average skin pain treatment effect across all visits in Period A was analyzed. When the proportion of subjects with baseline skin pain NRS ≥3 who achieved NRS30 – at worst among subjects with baseline skin pain NRS ≥ 3 at each visit was analyzed using a MMRM approach, which included treatment (ew/placebo), visit (Week 2, 4, 8, and 12), and baseline Hurley Stage (II/III), the overall treatment effect between adalimumab 40 mg ew and placebo was 40.3% versus 24.9% (odds ratio = 2.03, P = 0.004).

Table 44. Proportion of Subjects Achieving NRS30 – at Worst Among Subjects with Baseline NRS at Worst ≥ 3 in Period A (NRI) (ITT_A Population, Study M11-313)

	Response, n (%)		Treatment Difference[a]		
Visit	pbo N = 109	ew N = 122	%	(95% CI)	Treatment Effect *P* value
Week 2	20 (18.3)	48 (39.3)	20.5	(8.8, 32.2)	< 0.001*[,b]
Week 4	24 (22.0)	47 (38.5)	16.4	(4.4, 28.3)	0.007*[,b]
Week 8	26 (23.9)	47 (38.5)	14.2	(2.2, 26.2)	0.020*[,b]
Week 12	27 (24.8)	34 (27.9)	2.8	(-8.6, 14.2)	0.628[b]
Overall[c]	(24.9)	(40.3)	--	--	0.004*

a. 95% CI for adjusted difference calculated according to the extended Mantel-Haenszel statistic adjusted for baseline Hurley stage.

b. *P* value calculated from the CMH test adjusted for baseline Hurley stage.

c. *P* value is calculated from repeated measure analysis, using observed data (for subjects who received analgesic other than ibuprofen or acetaminophen, or received ibuprofen or acetaminophen that exceeded the maximum dose allowed, for skin pain or underwent intervention, pain assessment from the start until 14 days after the stop of these treatments were excluded from the analyses) across Period A, adjusted for treatment (ew versus pbo), visit (Week 2, 4, 8, and 12), and Hurley stages (II versus III), using unstructured correlation matrix. The response rate for each treatment group was estimated from the model. Of note, 20/109 (18.3%) and 18/122 (14.8%) subjects in the pbo and ew groups, respectively, had at least 1 day excluded in Period A due to taking analgesics.

* Denotes $p\leq0.05$.

Study M11-810
The proportion of subjects achieving NRS30 in the adalimumab ew group was higher than that in the placebo group at every visit during Period A ($p\leq0.001$).

Table 45. Proportion of Subjects Achieving NRS30 – at Worst Among Subjects with Baseline NRS at Worst ≥ 3 in Period A (NRI) (ITT_A Population, Study M11-810)

	Response, n (%)		Treatment Difference[a]		
Visit	pbo N = 111	ew N = 105	%	(95% CI)	Treatment Effect *P* value
Week 2	21 (18.9)	54 (51.4)	32.9	(20.3, 45.6)	< 0.001*[,b]
Week 4	20 (18.0)	61 (58.1)	40.0	(27.1, 53.0)	< 0.001*[,b]
Week 8	24 (21.6)	57 (54.3)	33.3	(20.3, 46.2)	< 0.001*[,b]
Week 12	23 (20.7)	48 (45.7)	25.1	(12.7, 37.6)	< 0.001*[,b]
Overall[c]	(24.8)	(61.2)	--	--	< 0.001*

a. 95% CI for adjusted difference was calculated according to the extended Mantel-Haenszel statistic adjusted for baseline Hurley Stage (II/III) and baseline antibiotic use (Y/N).

b. *P* value calculated from the CMH test adjusted for baseline Hurley Stage and baseline antibiotics use.

c. *P* value is calculated from repeated measures analysis, using observed data (for subjects who received analgesic other than ibuprofen or acetaminophen, or received ibuprofen or acetaminophen that exceeded the maximum dose allowed, for skin pain or underwent intervention, pain assessment from the start until 14 days after the stop of these treatments were excluded from the analyses) across Period A, adjusted for treatment (ew versus pbo), visit (Week 2, 4, 8, and 12), and Hurley stages (II versus III), using unstructured correlation matrix. The response rate for each treatment group was estimated from the model. Of note, 5/111 (4.5%) and 0/105 subjects in the pbo and ew groups, respectively, had at least 1 day excluded in Period A due to taking analgesics.

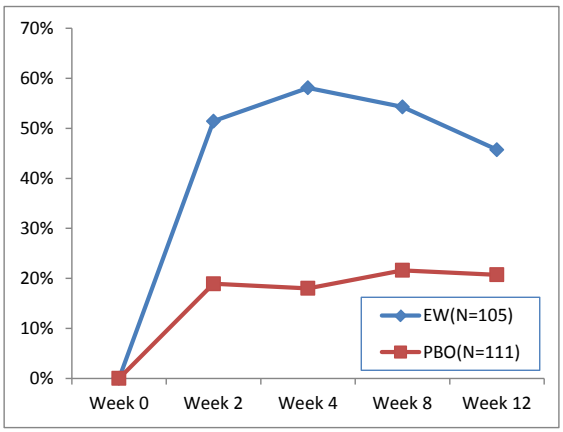
* Denotes $p \leq 0.05$.

When the proportion of subjects achieving NRS30 – at worst among subjects with baseline skin pain NRS ≥ 3 at each visit was analyzed using a Mixed-Effects Model Repeated Measures (MMRM) approach, including covariates of treatment (ew/placebo), visit (Weeks 2, 4, 8, and 12), baseline Hurley Stage (II/III), and baseline antibiotic use (Yes/No), a statistically significant difference for overall treatment effect was shown between adalimumab 40 mg ew and placebo (61% versus 25%; odds ratio = 4.78, p < 0.001).

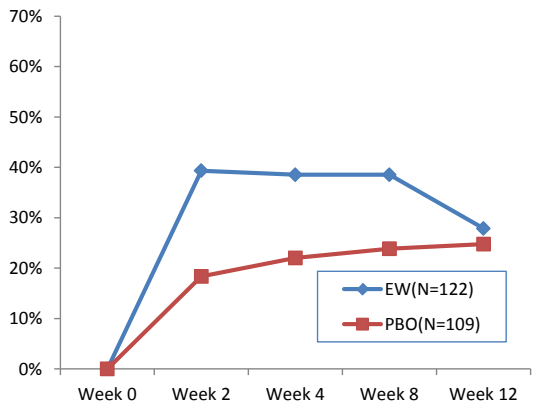
Additionally, the mean percent improvement in skin pain at worst was larger for subjects in the adalimumab ew group compared with subjects in the placebo group at every visit (p<0.001). Improvement in average skin pain was consistent with these results.

Figure 18. Proportions of Subjects Achieving NRS30 – At Worst Among Subjects with Baseline Skin Pain NRS ≥ 3 (NRI) (Panel A, Study M11-810) (Panel B Study M11-313) (ITT_A Population)

Panel A (Study M11-810):



Panel B (Study M11-313):



Quality of Life end-points

SF-36 (Short Form-36 Health Status Survey)

Subjects in the adalimumab ew group generally reported greater mean improvement in their physical health status than subjects in the placebo group, as measured by change from Baseline to Week 12 in SF-36. In particular, subjects in the adalimumab group experienced greater improvement in the PCS (physical component summary) domain and the role-physical and bodily pain subdomains, indicating improved physical health.

Results from Part B of the pivotal studies

Analyses from part B of the two pivotal studies are presented below in the parapgraph *Analysis performed across trials* for the pre-specified integrated analysis. Since there was a difference between the studies with respect to the treatment in Part B for the groups who received placebo in Part A, these results are presented briefly for each study separately.

Study M11-313, ITT_EW Population

At Week 36, 41% of subjects who received placebo in Period A and were treated with adalimumab ew in Period B (ITT_B_EW Population) were HiSCR responders. These results were consistent with HiSCR rates in the adalimumab ew group in Period A. Improvements from week 12 to 36 were also observed for other efficacy endpoints, e.g. AN count and NRS30.

Study M11-810, ITT_B_PBO Population

The ITT_B_PBO Population included subjects who were randomized to placebo in Period A and continued on placebo in Period B. Subjects in the ITT_B_PBO Population in Period B showed a low level HiSCR rate that decreased from Week 12 (29%) to Week 36 (16%) (NRI).

Summary of main studies

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 46: Summary of Efficacy for trial M11-313 and M11-810

Title: A Phase 3 Multicenter Study of the Safety and Efficacy of ADA in Subjects with Moderate to Severe Hidradenitis Suppurativa		
Study identifier	M11-313 (PIONEER I) and M11-810 (PIONEER II)	
Design	Phase 3 multicenter, randomized, DB, PBO-controlled studies of the safety and efficacy of ADA in subjects with moderate to severe HS	
	Duration of main phase:	Period A, 12 weeks
Hypothesis	Superiority	
Treatment groups (N=307 for M11-313; N=326 for M11-810)	Placebo	12 weeks n=154 for M11-313 n=163 for M11-810

	ADA ew		160 mg at week 0, 80 mg at week 2, 40 mg ew starting at week 4 until week 12, 12 week of treatment, SC n=153 for M11-313 n=163 for M11-810
Endpoints and definitions	Primary endpoint	HiSCR	Proportion of subjects achieving HiSCR, defined as at least a 50% reduction in AN count with no increase in abscess count and no increase in draining fistula count relative to baseline at Week 12.
	First secondary ranked endpoint (SRE)	AN0, 1 or 2	Proportion of subjects achieving inflammatory nodule and abscess count of 0, 1, or 2 at Week 12, among subjects with Hurley Stage II at baseline (it was considered too strict to be applied to subjects with Hurley stage III).
	Second SRE	NRS30	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 12 among subjects with Baseline skin pain NRS (numerical rating scale) ≥ 3.
	Third SRE	Modified Sartorius score	Change in modified Sartorius score from Baseline to Week 12.
Database lock	M11-313: 5 February 2014; M11-810: 23 May 2014		

Results and analysis

Analysis description	**Primary analysis**					
Analysis population and time point description	ITT-A (N=307 for M11-313; N=326 for M11-810)					
Descriptive statistics and estimate variability	Study		M11-313		M11-810	
	Treatment group		PBO	ew	PBO	ew
	Number of subjects		154	153	163	163
	Primary endpoint	**HiSCR**%	26.0	41.8	27.6	58.9
	SRE	**AN0, 1 or 2** %	28.6	28.9	32.2	51.8
		NRS30 %	24.8	27.9	20.7	45.7
		Modified Sartorius score	-15.7	-24.4	-9.5	-28.9
Effect estimate per	**Primary endpoint**		Comparison groups		PBO *vs* EW	

comparison		Test statistic	Cochrane-Mantel-Haenszel (CMH) test, statistical test was 2-tailed with the significance level 0.05.
		P-value	M11-313 P=0.003 M11-810 P<0.001
	SRE	Comparison groups	PBO *vs* EW
		Test statistic	Cochrane-Mantel-Haenszel (CMH) test, statistical test was 2-tailed with the significance level 0.05.
		P-value	M11-313 P=0.961 (AN0,1 or 2) P=0.628 (NRS30) P=0.124 (Sartorius) M11-810 P=0.010 (AN0,1 or 2) P<0.001 (NRS30) P<0.001 (Sartorius)

Analysis performed across trials (pooled analyses and meta-analysis)

An integrated analysis of data from the three Phase 3 studies (Studies M11-810, M11-313, and M12-555) was pre-specified in the SAP for the ISE. Data from the Phase 2 study (Study M10-467) were analyzed separately because the study protocol differs from those of the Phase 3 studies in several details (e.g. subjects in Study M10-467 were not required to use antiseptic washes and Hurley Stage I patients were allowed).

Integrated results from Part A of Studies M11-810 and M11-313

Primary Endpoint

Both studies met their primary endpoint (Week 12 HiSCR rate).

A logistic regression analysis of the integrated data, adjusted for baseline weight and baseline draining fistula count (both of which were identified using stepwise selection), found the treatment-by-study interaction to be non-significant (p>0.10). This finding suggests that differences in baseline characteristics in part account for the observed different magnitudes of treatment effect between the 2 studies and was considered to provide justification for the pooling of data from the 2 studies.

Table 47. Proportion of Subjects Achieving HiSCR at Week 12 (NRI) (ITT_A Population, Integrated Analyses)

	Response, n (%)		Treatment Difference[a,b]	
Strata	pbo n/N (%)	ew n/N (%)	%	(95% CI)
All	85/317 (26.8)	160/316 (50.6)	23.9*	(16.4, 31.4)
Hurley Stage II	57/171 (33.3)	90/168 (53.6)	20.2*	(9.7, 30.8)
Hurley Stage III	28/146 (19.2)	70/148 (47.3)	28.1*	(17.3, 38.9)

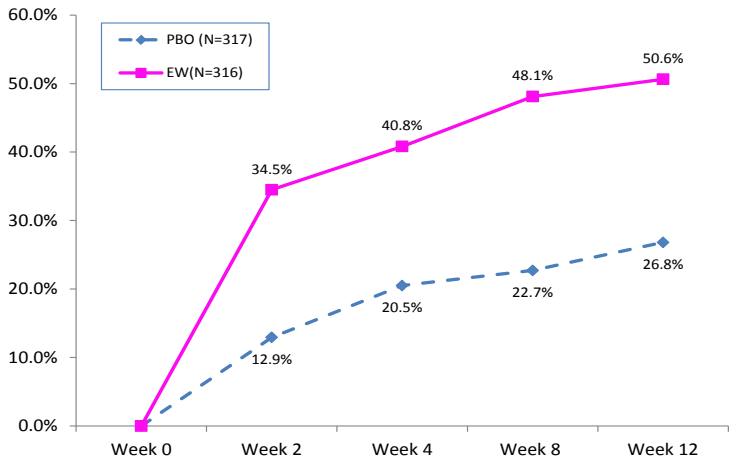
a. 95% CI for adjusted difference for all subjects calculated according to the extended Mantel-Haenszel statistic adjusted for study, baseline Hurley stage, and antibiotics use. 95% CI for adjusted difference by Hurley stage subgroup calculated according to the extended Mantel-Haenszel statistic adjusted for study and antibiotics use.

b. *P* value for all subjects calculated from the CMH test adjusted for study, baseline Hurley stage and antibiotics use. *P* value for comparison by Hurley Stage subgroup was calculated from the CMH test adjusted for study and antibiotics use.

* Denotes $p \leq 0.05$.

With respect to HiSCR over time (secondary end-point), a higher proportion of subjects in the adalimumab ew group achieved HiSCR compared with the placebo group, starting at Week 2 ($p < 0.001$), and remained consistent throughout Period A (NRI) ($p < 0.001$ at all visits) in the integrated ITT_A Population.

Figure 19. Proportion of Subjects Achieving HiSCR by Visit in Period A (NRI) (ITT_A Population, Integrated Analyses)



Ranked Secondary Efficacy Endpoints

The results of all the ranked secondary endpoints in both studies showed greater improvement in the adalimumab group as compared with the placebo group; however, the differences were statistically significant only in Study M11-810. Integrated results from the ranked secondary endpoints are presented in **Table .** Because the first ranked secondary endpoint (AN count of 0, 1, or 2 in Hurley Stage II subjects at Week 12) missed statistical significance (P = 0.051), none of the secondary ranked endpoints is interpreted as confirmatory.

Table 48. Statistical Results for Ranked Secondary Endpoints Presented in Rank Order (ITT_A Population, Integrated Analyses)

Rank	Secondary Variable	ew vs. pbo
1	Proportion of subjects who achieved AN count of 0, 1, or 2 at Week 12, among subjects with Hurley Stage II at baseline (NRI)	40.5% vs. 30.4% *P* = 0.051[a]
2	Proportion of subjects who achieved 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 12 among subjects with baseline skin pain NRS ≥ 3 (NRI)	36.1% vs. 22.7% *P* = 0.002[b]
3	Change in modified Sartorius score from baseline to Week 12 (LOCF)	–27.1 vs. –12.5 *P* < 0.001[c]

a. *P* value calculated from the CMH test adjusted for study and antibiotic use.

b. *P* value calculated from the CMH test adjusted for study, baseline Hurley stage, and antibiotic use.

c. *P* value calculated from ANCOVA with baseline value, stratum (study, baseline Hurley stage, and antibiotic use) and treatment in the model.

Health-Related Quality of Life

Different QoL scales were used in the two pivotal studies, however, DLQI and TSQM were used in both studies and results are presented for the integrated ITT_A Population.

Adalimumab ew subjects had greater improvement in DLQI, compared to placebo-treated subjects, as measured by mean change in DLQI, from Baseline to Week 12 (P ≤ 0.05). Among subjects with a baseline DLQI ≥ 5, a higher proportion of adalimumab ew subjects than placebo subjects (50% vs. 34%) achieved the MCID, defined as a decrease of ≥5.0 points at Week 12 (NRI; p<0.001).

Table 49. Change from Baseline in DLQI at Week 12 (LOCF) (ITT_A Population, Integrated Analyses)

Treatment Group	N	Baseline Mean	Week 12 Mean	Within Group Change	Between Group Change[a]	
				LS Mean ± SE	LS Mean	(95% CI)
pbo	310	15.4	12.8	–2.6 ± 0.39		
ew	312	15.2	10.1	–5.2 ± 0.39	–2.6*	(–3.6, –1.7)

a. *P* values were calculated from ANCOVA with stratum (study, baseline Hurley stage, and antibiotic use), baseline value, and treatment in the model.

* Denotes *P* ≤ 0.05.

TSQM scores range from 0 to 100, with higher scores indicating better treatment satisfaction. Subjects in the adalimumab ew group had greater increases in overall treatment satisfaction and effectiveness than subjects in the placebo group at Week 12 (p ≤ 0.05). Satisfaction with the side effects and convenience were similar between the placebo and treatment groups.

Table 50. Change from Baseline in TSQM at Week 12 (LOCF) (ITT_A Population, Integrated Analyses)

Component / Treatment Group	N	Baseline Mean	Week 12 Mean	Within Group Change	Between Group Change[a]	
				LS Mean ± SE	LS Mean	(95% CI)
TSQM Global Satisfaction						
pbo	243	36.9	47.2	8.8 ± 1.78		
ew	230	39.6	58.9	20.1 ± 1.81	11.3*	(6.9, 15.6)
Effectiveness						
pbo	246	30.9	41.4	10.9 ± 1.75		
ew	231	31.3	54.0	23.6 ± 1.79	12.6*	(8.3, 16.9)

a. *P* values were calculated from ANCOVA with stratum, baseline value, and treatment in the model.

* Denotes $p \leq 0.05$.

Integrated results from Part B of Studies M11-810 and M11-313

While analyses in Period B was specified as exploratory in each individual study due to the limited sample size, the period B integrated analysis was pre-specified as confirmatory.

All re-randomized subjects received at least 1 dose of study drug. Of the 596 subjects who were re-randomized in Period B, 286 (48%) subjects completed Period B and 310 (52%) subjects discontinued from the study. The most frequently reported primary reason for discontinuation from Period B was per IXRS instruction, which instructed subjects who experienced LOR or WOAI to discontinue from the study and enter the OLE, Study M12-555. The highest percentage of discontinuation primarily per IXRS instruction was in the pbo/pbo (56%) and ew/pbo (48%) groups.

Table 51. Overall Subject Disposition in Period B (ITT_B Population, Integrated Analyses)

Subject Disposition in Period B	pbo/pbo (N = 151)	pbo/ew (N = 145)	ew/pbo (N = 100)	ew/eow (N = 101)	ew/ew (N = 99)	ew All[a] (N =300)
Number of subjects who were re-randomized	151	145	100	101	99	300
Number of subjects who discontinued without dose in Period B	0	0	0	0	0	0
Number of subjects re-randomized and dosed in Period B	151 (100)	145 (100)	100 (100)	101 (100)	99 (100)	300 (100)
Number of subjects who completed Period B	40 (26.5)	93 (64.1)	45 (45.0)	51 (51.5)	56 (56.6)	153 (51.0)
Number of subjects who discontinued from Period B	111 (73.5)	52 (35.9)	55 (55.0)	49 (48.5)	43 (43.4)	147 (49.0)
Discontinuation due to (primary reason):						
Adverse event	3 (2.0)	6 (4.1)	1 (1.0)	4 (4.0)	2 (2.0)	7 (2.3)
Withdrew consent	9 (6.0)	5 (3.4)	1 (1.0)	1 (1.0)	3 (3.0)	5 (1.7)
Lack of efficacy	9 (6.0)	1 (0.7)	3 (3.0)	0	3 (3.0)	6 (2.0)
Lost to follow-up	3 (2.0)	5 (3.4)	1 (1.0)	2 (2.0)	0	3 (1.0)
Per IXRS instruction[b]	84 (55.6)	30 (20.7)	48 (48.0)	40 (39.6)	33 (33.3)	121 (40.3)
Exceeded protocol-specified number of interventions	0	0	0	0	0	0
Protocol violation	0	0	0	0	0	0
Other	3 (2.0)	5 (3.4)	1 (1.0)	2 (2.0)	2 (2.0)	5 (1.7)

eow = every other week; ew = every week; HiSCR = hidradenitis suppurativa complete response; LOR = loss of response; WOAI = worsening or absence of improvement

a. All subjects who were randomized to adalimumab ew in Period A and were re-randomized in Period B.

b. Subjects meeting criteria of LOR or WOAI were requested by the IXRS system to discontinue from the study and enter the open label extension, Study M12-555.

Note: Percentages based on the number of subjects who were re-randomized.

Period B: Combined ITT_B_R and ITT_B_NR Population

When *all* subjects who were re-randomized after the adalimumab ew treatment in Period A were analyzed (ITT_B_R and ITT_B_NR Populations combined), the proportion of subjects with HiSCR at Week 36 was higher for subjects in the ew/ew group compared with the ew/eow and ew/pbo groups **(Table).**

All treatment groups experienced reduction to some extent in the HiSCR rate over time during Period B, which may in part be due to the study design. Any subject who experienced LOR or WOAI during Period B, was discontinued from the study and counted as non-responders in Period B, after roll-over to Study M12-555.

Table 52. Proportion of Subjects Achieving HiSCR by Visit in Period B (NRI) (Combined ITT_B_R and ITT_B_NR Populations, Integrated Analyses)

	Response, n (%)			Treatment Difference[a,b]		
Visit	ew/pbo (N = 100)	ew/eow (N = 101)	ew/ew (N = 99)	ew/eow vs. ew/pbo	ew/ew vs. ew/pbo	ew/ew vs. ew/eow
Entry to Period B	53 (53.0)	52 (51.5)	53 (53.5)	--	--	--
Week 24	30 (30.0)	37 (36.6)	44 (44.4)	7.1 (–5.3, 19.6)	14.4* (1.6, 27.3)	7.4 (–5.3, 20.1)
Week 36	28 (28.0)	31 (30.7)	43 (43.4)	3.1 (–9.2, 15.4)	15.3* (2.1, 28.6)	12.4 (–0.6, 25.4)

a. 95% CI for adjusted difference calculated according to the extended Mantel-Haenszel statistic adjusted for study, baseline Hurley stage, and HiSCR status at re-randomization (responder/nonresponder) at entry of Period B.

b. *P* value calculated from the CMH test adjusted for study, baseline Hurley stage, and HiSCR status at re-randomization (responder/nonresponder) at entry of Period B.

* Denotes $p \leq 0.05$.

Period B: ITT_B_R Population (HiSCR responders at entry to Period B)

The primary endpoint for the integrated analysis was the proportion of subjects achieving HiSCR at Week 36 in the ITT_B_R Population. Pairwise comparisons were performed in the rank order EW/EW vs. EW/PBO followed by EW/EOW vs. EW/PBO. The proportion of ITT_B_R subjects who retained HiSCR at Week 36 was higher for subjects who were re-randomized to adalimumab compared to those re-randomized to placebo.

Table 53. Proportion of Subjects Achieving HiSCR by Visit in Period B (NRI) (ITT_B_R Population, Integrated Analyses)

	Response, n (%)			Treatment Difference[a,b]		
Visit	ew/pbo (N = 53)	ew/eow (N = 52)	ew/ew (N = 52)	ew/eow vs. ew/pbo	ew/ew vs. ew/pbo	ew/ew vs. ew/eow
Entry to Period B	52 (98.1)	52 (100)	52 (100)	--	--	--
Week 24	21 (39.6)	29 (55.8)	32 (61.5)	16.2 (–3.0, 35.5)	21.6* (2.7, 40.6)	5.7 (–13.6, 24.9)
Week 36	17 (32.1)	24 (46.2)	25 (48.1)	14.2 (–4.5, 33.0)	15.7 (–2.9, 34.3)	1.4 (–17.7, 20.5)

a. 95% CI for adjusted difference calculated according to the extended Mantel-Haenszel statistic adjusted for study and baseline Hurley stage.

b. *P* value calculated from the extended CMH test adjusted for adjusted for study and baseline Hurley stage.

* Denotes $p \leq 0.05$.

Note: One subject was randomized in the HiSCR responder strata although the subject did not achieve HiSCR at Week 12.

Additional efficacy measures assessed in Period B for the ITT_B_R Population demonstrated that subjects benefit by continuing to receive ew treatment rather than de-escalating to an eow regimen. The proportion of subjects with worsening of their draining fistula count (≥ 25% increase with minimum increase of 2 relative to baseline) at any time during Period B was 13% in the ew/pbo group and 15% in the ew/eow group compared to 6% in the ew/ew group. Reduction from Baseline in skin pain was greater for both the ew/ew group and the ew/eow group compared to ew/pbo (P ≤ 0.05). For these endpoints, subjects in the ew/ew group consistently numerically outperformed subjects in the ew/eow group.

Period B: ITT_B_NR Population (HiSCR non-responders at entry to Period B)
In the ITT_NR Population (i.e. HiSCR non-responders at entry to Period B), the HiSCR rate was higher by Week 36 for subjects in the ew/ew group (38%) compared to subjects in ew/eow (14%) and ew/pbo (23%) groups.

The majority of subjects in the ITT_B_NR Population who achieved HiSCR by Week 36 on continuous adalimumab ew therapy in Period B belonged to a subgroup who achieved at least AN25 improvement on adalimumab ew by Week 12. A *post-hoc* analysis was performed, showing that for these AN25 responders, Week 36 HiSCR response rates were higher for the ew/ew group (78%) compared to both the ew/eow (22%) and ew/pbo (25%) groups at Week 36 (p≤0.05). In contrast, among subjects who were AN25 non-responders at the end of Period A, the majority in each treatment group did not achieve HiSCR, regardless of treatment group.

Table 54. Proportion of Subjects Achieving HiSCR by Visit in Period B (NRI) (ITT_B_NR Population, Integrated Analyses)

	Response n (%)			Treatment Difference % (95% CI)[a,b]		
Visit	ew/pbo (N = 47)	ew/eow (N = 49)	ew/ew (N = 47)	ew/eow vs. ew/pbo	ew/ew vs. ew/pbo	ew/ew vs. ew/eow
Entry to Period B	1 (2.1)	0	1 (2.1)	--	--	--
Week 24	9 (19.1)	8 (16.3)	12 (25.5)	–2.8 (–18.2, 12.6)	6.4 (–10.7, 23.5)	9.4 (–6.9, 25.6)
Week 36	11 (23.4)	7 (14.3)	18 (38.3)	–9.1 (–24.8, 6.6)	14.9 (–4.0, 33.8)	24.3* (6.7, 41.8)

a. 95% CI for adjusted difference calculated according to the extended Mantel-Haenszel statistic adjusted for study and baseline Hurley stage.

b. *P* value calculated from the extended CMH test adjusted for adjusted for study and baseline Hurley stage.

* Denotes *p*≤0.05.

Note: Two subjects were randomized in the HiSCR non-responder strata although they achieved HiSCR at Week 12.

Period B: ITT_B_PRR Population (HiSCR responders <u>and</u> partial responders achieving AN25)
Post-hoc analyses revealed that subjects who achieved a partial responses (≥ 25% reduction in AN count relative to baseline in the ITT_B_NR Population) and HiSCR responders (in the ITT_B_R Population) had greater potential to achieve or maintain HiSCR with longer treatment of 40 mg ew until Week 36. In this population, HiSCR at Week 36 was achieved by a higher proportion of subjects in the ew/ew group compared to the ew/eow or ew/pbo groups (refer to table and figure below).

Table 55. Proportion of Subjects Achieving HiSCR by Visit in Period B (NRI) (ITT_B_PRR Population, Integrated Analyses)

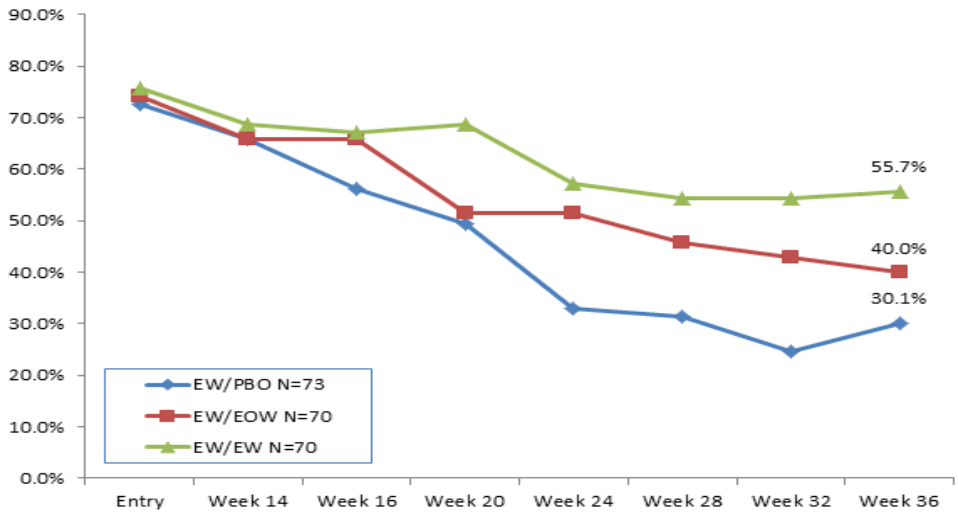
	Response n (%)			Treatment Difference % (95% CI)[a,b]		
Visit	ew/pbo (N = 73)	ew/eow (N = 70)	ew/ew (N = 70)	ew/eow vs. ew/pbo	ew/ew vs. ew/pbo	ew/ew vs. ew/eow
Entry to Period B	53 (72.6)	52 (74.3)	53 (75.7)	--	--	--
Week 24	24 (32.9)	36 (51.4)	40 (57.1)	18.3* (2.1, 34.5)	23.7* (7.5, 40.0)	5.4 (–11.1, 21.9)
Week 36	22 (30.1)	28 (40.0)	39 (55.7)	11.2 (–4.4, 26.8)	26.8* (10.5, 43.1)	15.1 (–1.4, 31.5)

a. 95% CI for adjusted difference calculated according to the extended Mantel-Haenszel statistic adjusted for study and HiSCR status at re-randomization (responder/nonresponder).

b. *P* value calculated from the extended CMH test adjusted for study and HiSCR status at re-randomization (responder/nonresponder).

* Denotes $P \leq 0.05$.

Figure 20. Proportion of Subjects Achieving HiSCR by Visit in Period B (NRI) (ITT_B_PRR Population, Integrated Analyses)



Results were also presented for other end-points (all referring to the ITT_B_PRR Population):

For the "Improvement from Baseline in AN count" (mean and mean percent change), there was a numerical trend favoring the ew/ew group over the ew/eow group and greater improvement for the ew/ew group compared to the ew/pbo group ($P \leq 0.05$) in the ITT_B_PRR Population at Week 36.

For "Achievement of AN Count of 0, 1, 2", there was a numerical trend in achievement of AN count of 0, 1, or 2 favoring the ew/ew group over the ew/eow group in Period B. The ew/ew group demonstrated greater improvement ($P \leq 0.05$) at Weeks 24 and 36 compared to the ew/pbo group.

The proportion of subjects who experienced "Flare" (defined as at least a 25% increase in AN counts with a minimum increase of 2 relative to Baseline) in the ITT_B_PRR Population, was lower overall for subjects in the ew/ew group (1 subject) compared to the ew/eow and ew/pbo groups (9 and 6 subjects, respectively). The risk of worsening of disease was based on all occurrences (i.e. not excluding any cases after a subject used rescue medication in Study M11-313.

With respect to “Improvement in patient-reported HS-related skin pain”, a higher NRS30 rate was demonstrated in the ew/ew group by the end of Period B ($P \leq 0.05$) as compared to the ew/eow and ew/pbo groups.

With respect to “DLQI”, subjects in the ew/ew group had numerically greater improvement in DLQI, as measured by mean change in DLQI, from Baseline to Week 36 compared to subjects in the ew/eow and ew/pbo groups.

Supportive study

Study M12-555: Phase 3 Open-Label Study of the Safety and Efficacy of Adalimumab in Subjects with Moderate to Severe Hidradenitis Suppurativa – PIONEER (Open-Label Extension)

Is an ongoing study that enrolled subjects who participated in a prior Phase 3 HS study and either

(a) completed the study;

(b) achieved HiSCR at the entry to Period B then experienced LOR (defined as loss of at least 50% of the improvement (reduction) in the AN count achieved from Baseline to Week 12); or

(c) did not achieve HiSCR at the entry to Period B then experienced WOAI (defined as an AN count ≥ Baseline AN count at 2 consecutive visits, excluding Week 12, occurring ≥ 14 days apart) on or after Week 16 of the prior Phase 3 study.

Starting at Baseline, all subjects received open-label adalimumab 40 mg ew regardless of treatment assignment in a prior Phase 3 study. If at any time on or after Week 24 of the open-label extension (OLE), a subject meets the following criteria, the dosing regimen may be reduced to adalimumab 40 mg eow:

- Achieved hidradenitis suppurativa clinical response (HiSCR) during the OLE relative to the Baseline visit of the prior Phase 3 study; AND
- Achieved an abscess and inflammatory nodule (AN) count of 0 or 1 on at least 2 consecutive study visits; AND
- The physician and subject mutually decided that the risk/benefit of reducing adalimumab dosing to eow was favorable.

In this study, subjects must have agreed to daily use (and throughout the entirety of the study) of one over-the-counter topical antiseptics (specified in the protocol) on their body areas affected with HS lesions. The exclusion criteria also specified that subjects should not have received any oral antibiotic treatment for HS within 28 days prior to the Baseline visit of Study M12-555, except for antibiotics permitted in a prior Phase 3 study. Restrictions were also applied for topical therapies for the treatment of HS, systemic non-biologic therapies with potential therapeutic impact for HS and oral concomitant analgesics (including opioids) for HS-related pain.

The original protocol (dated 30 November 2011) had 2 amendments. One hundred seven subjects were enrolled under the original protocol, 136 subjects were enrolled under Amendment No. 1, and 254 subjects were enrolled under Amendment No. 2.

Results

Data from an interim analysis are available in this submission. Subjects entered Study M12-555 at different time points and not all subjects had reached the later visits as of the data cut-off date. Therefore, missing data were handled using LOCF as the primary approach, and the number of subjects at the later visits are noted below the tables.

As of 29 April 2014, 497 subjects received at least 1 dose of study drug in Study M12-555 at 94 study sites in the US, Canada, Australia, Germany, Czech Republic, France, Switzerland, Denmark, Greece, Hungary, Netherlands, and Sweden. A total of 368 (74%) subjects remained ongoing. Enrollment in the study is closed. A flow chart summarizing subject disposition for Studies M11-810, M11-313 and M12-555 presented above (**Figure 16**).

- In the EW/EW/EW Population (subjects who received adalimumab 40 mg ew in both Period A and Period B of the prior Phase 3 HS study and received at least 1 dose of study drug in Study M12-555), the proportion of subjects achieving HiSCR was maintained above 50% at all visits (range: 51% to 60%).

- Among subjects whose adalimumab treatment was withdrawn during Period B of the prior Phase 3 study and reintroduced upon entry into Study M12-555 (EW/PBO/EW Population), the proportion who achieved HiSCR increased soon after retreatment, reaching 56% at Week 12 of Study M12-555.

- Among subjects whose dose was reduced to 40 mg eow during Period B of the prior Phase 3 study and returned to 40 mg ew upon entry into Study M12-555 (EW/EOW/EW Population), the proportion who achieved HiSCR from the time of dose escalation increased over time, reaching 61% at Week 48 of Study M12-555.

Table 56. Proportion of Subjects Achieving HiSCR Over Time During Study M12-555 (LOCF) (EW/EW/EW, EW/EOW/EW, and EW/PBO/EW Populations in Study M12-555)

Visit[a]	EW/EW/EW N = 84 n (%)	EW/EOW/EW N = 90 n (%)	EW/PBO/EW N = 91 n (%)
Entry of Study M12-555	43 (51.2)	33 (36.7)	28 (30.8)
Week 4×	46 (56.8)	36 (42.9)	41 (48.8)
Week 8×	46 (56.1)	44 (51.8)	43 (51.2)
Week 12×	45 (54.9)	43 (50.6)	47 (56.0)
Week 24×	45 (54.9)	50 (58.8)	48 (57.1)
Week 36×[b]	49 (59.8)	53 (62.4)	41 (48.8)
Week 48×[b]	47 (57.3)	52 (61.2)	44 (52.4)

a. "×" indicates visit in extension study.

b. The number of observations at Weeks 36 and 48 are 40 and 22 for EW/EW/EW, 43 and 23 for EW/EOW/EW, and 39 and 20 for EW/PBO/EW

Note: The data cutoff date was 29 April 2014. Results after Week 48 (from start of Study M12-555) are available for fewer than 20% of subjects.

With continuous treatment with adalimumab ew, at least 55% of subjects maintained HiSCR up to 48 weeks in Study M12-555. Dose interruption and dose reduction were associated with reductions in HiSCR rate from entry of Study M12-555 up to Week 8 or Week 12. Re-treatment, however, seems still beneficial, as HiSCR rates were above 50% in all 3 populations at Week 48.

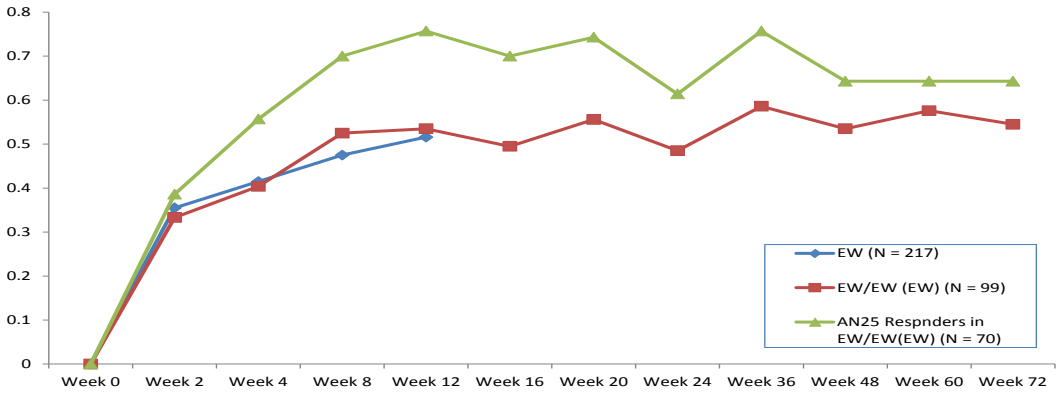
Continuous ew Dosing

The ew Population includes a total of 316 subjects who were randomized to receive adalimumab 40 mg ew in Period A of Studies M11-810 or M11-313: 217 subjects, the ew group, either did not enter Period B or entered Period B to receive adalimumab 40 mg eow or placebo, and 99 subjects, the ew/ew (ew) group, were re-randomized to continuous ew treatment in Period B regardless of whether the subjects entered Study M12-555.

The results from the ew/ew (ew) group show the long-term efficacy of adalimumab 40 mg ew treatment among those who had the opportunity to continue ew treatment by integrating data from both the initial studies (Studies M11-313 and M11-810) and Study M12-555. This group represents the overall

adalimumab-treated subjects since HiSCR rates in this group during the first 12 weeks were similar to those of subjects who did not have the opportunity to continue beyond Week 12 (ew). The HiSCR rate was above 50% at Week 8 and was maintained around this level up to Week 72. Among subjects who achieved at least AN25 response (partial responders or HiSCR responders) at Week 12, the HiSCR rate was above 60% from Week 8 through Week 72 **(Figure 21).**

Figure 21. Proportion of Subjects Achieving HiSCR by Visit (LOCF) (EW Population, Integrated Analyses)



Note: ew = subjects randomized to adalimumab 40 mg ew in Period A who either did not enter Period B or entered Period B to receive adalimumab 40 mg eow or placebo. ew/ew (ew) = subjects randomized to adalimumab 40 mg ew in both Period A and Period B, regardless of entry into Study M12-555. As of the data cutoff date for Study M12-555 (29 April 2014), not all ongoing subjects had visits beyond Week 36 ew. The number of subjects with observations at later weeks is as follows: 70 at Week 48ew, 42 at Week 60 ew, and 28 at Week 72 ew. Results after Week 72 ew are available for fewer than 20% of subjects.

Dose Reduction and Dose Interruption

Efficacy data were also integrated across Periods A and B of Studies M11-810 and M11-313, as well as the open-label treatment in Study M12-555, to compare the overall strategies of continuous weekly dosing (EW/EW/EW Population) with the alternatives of:

- Reducing dose frequency to eow at Week 12 and returning to ew in the event of LOR, WOAI, or at Week 36 (EW/EOW/EW Population), or
- Dose interruption at Week 12 and re-initiation in the event of LOR, WOAI, or at Week 36 (EW/PBO/EW Population).

The difference between the ew/ew (ew) group presented above and the EW/EW/EW Population in Study M12-555 is that the EW/EW/EW Population did not include 15 subjects in the ew/ew (ew) group who did not receive a dose of adalimumab in Study M12-555.

The proportion of HiSCR responders at Week 36 was higher for subjects in the EW/EW/EW Population (63.1%) compared with those in the EW/EOW/EW Population (54.4%) or EW/PBO/EW Population (52.7%). These results demonstrate the benefit of continuous treatment with adalimumab ew, as dose interruption and dose reduction strategies were associated with temporary decreases in HiSCR, until adalimumab 40 mg ew dosing was resumed. Among subjects whose adalimumab treatment was halted at Week 12 (EW/PBO/EW Population), the HiSCR rate dropped to 42.9% at Week 24. Following re-introduction of (40 mg) ew dosing at Week 36 (without initial 160 mg and 80 mg doses), the proportion of subjects achieving HiSCR increased over time, reaching 58.2% at Week 48.

Table 57. Proportion of Subjects Achieving HiSCR Over Time (LOCF) (EW/EW/EW, EW/EOW/EW, and EW/PBO/EW Populations, Study M12-555)

Weeks of Adalimumab Treatment[a]	EW/EW/EW N = 84 n (%)	EW/EOW/EW N = 90 n (%)	EW/PBO/EW N = 91 n (%)
Week 2	27 (32.1)	35 (39.8)	31 (34.4)
Week 4	31 (36.9)	37 (41.1)	36 (39.6)
Week 8	42 (50.0)	44 (48.9)	44 (48.4)
Week 12	42 (50.0)	50 (55.6)	46 (50.5)
Week 16	41 (48.8)	51 (56.7)	41 (45.1)
Week 20	47 (56.0)	41 (45.6)	41 (45.1)
Week 24	41 (48.8)	43 (47.8)	39 (42.9)
Week 36	53 (63.1)	49 (54.4)	48 (52.7)
Week 48[b]	48 (57.1)	48 (53.3)	53 (58.2)
Week 60[b]	52 (61.9)	54 (60.0)	52 (57.1)
Week 72[b]	49 (58.3)	56 (62.2)	50 (54.9)

a. Weeks were relative to the first dose of adalimumab in Study M11-313 or Study M11-810.

b. As of the data cutoff date, not all ongoing subjects had visits beyond Week 36. The number of subjects with observations at Weeks 48, 60, and 72 was 70, 42, and 28, respectively for EW/EW/EW; 70, 55, and 31, respectively, for EW/EOW/EW; and 67, 45, and 27, respectively, for EW/PBO/EW.

Note: The data cut-off date was 29 April 2014. Results after Week 72 (from start of prior study) are available for fewer than 20% of subjects.

Clinical studies in special populations

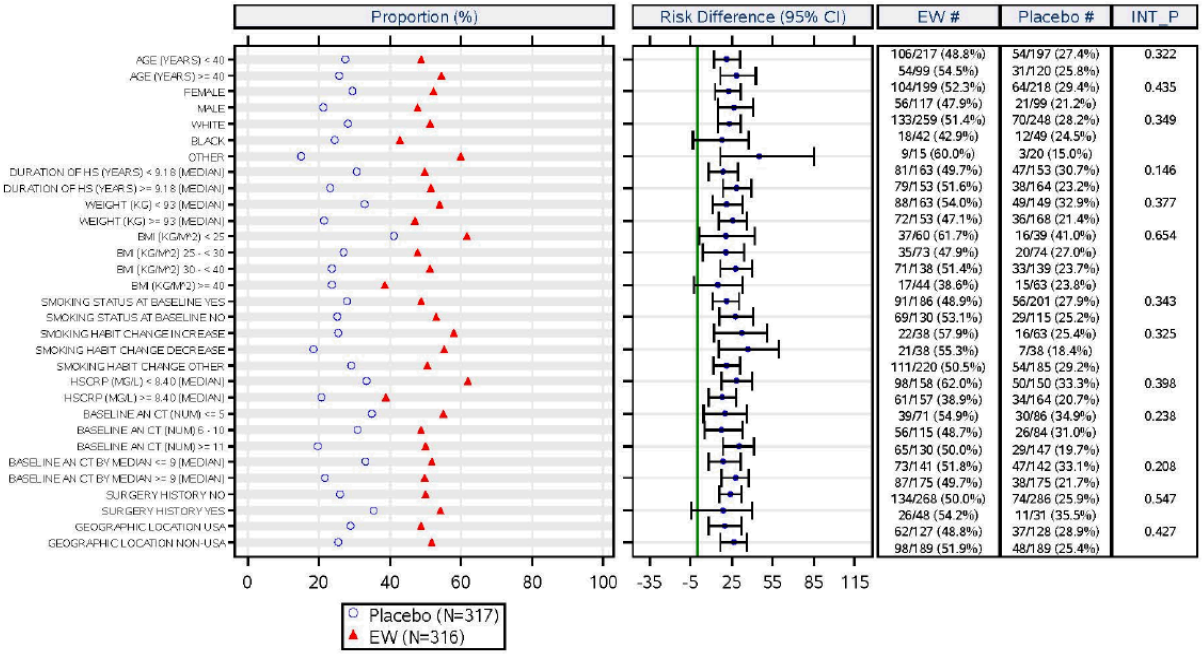
There were no dedicated studies in special populations. Sub-group analyses were performed both within the separate studies and for the studies combined and the integrated results will be presented here.

Baseline Hurley stage and baseline concomitant antibiotic use (Study M11-810 only) were stratification factors in the Period A randomization for the Phase 3 studies. The primary efficacy variable (HiSCR) was analyzed for each stratum based on Hurley Stage (II/III) and antibiotic use at Baseline (yes/no) for the integrated ITT_A Population. A significantly higher HiSCR rate in the adalimumab ew group compared to the placebo group was observed in each stratum at each visit in Period A. Also, as presented above (primary efficacy end-point) greater treatment differences were observed among subjects with Hurley Stage III than those with Hurley Stage II and among subjects who received concomitant antibiotics compared to those who did not.

Primary efficacy results (HiSCR rate) in the integrated ITT_A Population analysis set were also summarized by demographic characteristics (including BMI, weight, smoking status at Baseline, and smoking habit), and disease characteristics (including duration of HS, hsCRP, Baseline AN category, and prior HS surgery history).

The higher HiSCR rate in the adalimumab ew group compared to the placebo group at Week 12 was consistent in every subgroup (**Figure 22**). The confidence intervals for the treatment difference excluded zero in almost all subgroups; the exceptions were subgroups black and prior HS surgery "yes" for which sample sizes were very small (less than 15% of the total). There were no treatment by subgroup interactions associated with $p \leq 0.10$.

Figure 22. Proportion of Subjects Achieving HiSCR at Week 12 (NRI) by Subgroup (ITT_A Population, Integrated Analyses)



***, **, *Statistically significant at 0.001, 0.01, and 0.05 level, respectively.

EW and Placebo represents n/N (%).

Note: INT_P is the *P* value for treatment*subgroup interaction, and it is calculated using a logistic regression with HiSCR at Week 12 as response variable, and treatment, subgroup, Hurley stage, and treatment*subgroup interaction as factors.

Sub-group analyses were also performed within each of the two studies:

In study M11-313, efficacy (HiSCR at Week 12) among subjects in the adalimumab group generally was above 35% (ranging from 30% to 50%) and a consistent treatment effect was generally observed. Some exceptions were noted; subjects with BMI ≥ 40 in both the adalimumab and placebo groups had similar HiSCR rates; larger treatment difference was observed among subjects with Hurley Stage III than those with Hurley Stage II and larger treatment difference was observed among subjects with lower hsCRP than those with higher hsCRP. The sample sizes in these subgroups were small.

In study M11-810, the HiSCR rate was higher in the adalimumab ew group than in the placebo group in all subgroups. The lower bound of the 95% confidence interval for the treatment difference exceeded 0, except for the subgroups of black, BMI< 25, AN count ≤5, and prior surgical history. The numbers of subjects were relatively small in these 4 subgroups. Treatment by subgroup interactions were not significant (p>0.1), except for median baseline AN count, where subjects who had higher than median AN count at Baseline experienced a larger adalimumab treatment effect.

Impact of Immunogenicity on Efficacy

The primary efficacy endpoint was the proportion of subjects who achieved HiSCR (responders/non-responders) at Week 12. None of the AAA+ subjects in Period A from Study M11-313 (0%, 0/8 subjects) and Study M11-810 (0%, 0/2 subjects) achieved HiSCR at Week 12. In the AAA– subjects, 64 of 145 subjects (44.1%) in Study M11-313 and 96 of 161 subjects (59.6%) in Study M11-810 achieved HiSCR.

The number of subjects being AAA+ was overall low and firm conclusions are difficult to make. It is, however, noted that none of the AAA+ subjects was a HiSCR responder.

2.4.3. Discussion on clinical efficacy

Design and conduct of clinical studies

The clinical development program for Humira in HS comprises 4 clinical studies: a Phase 2, placebo-controlled, dose-ranging study (Study M10-467), two Phase 3 double-blind (DB), placebo-controlled studies (Studies M11-810 and M11-313), and one Phase 3 open-label extension (OLE) study (Study M12-555; still ongoing).

In the phase 2 dose-ranging study M10-467, a high and a low dose regimen were compared, in addition to placebo. Experience from other, approved indications for adalimumab shows that for some conditions (e.g. RA, Ps, PsA) loading and maintenance doses in a lower dose range are sufficient, while in other conditions (CD, UC) higher loading and maintenance doses are necessary. The efficacy results in this study showed that across all Hurley stages, a statistically significantly higher proportion of subjects in the adalimumab ew (every week) treatment group achieved clinical response, compared with placebo at Week 16 (18% vs. 4%, P = 0.025). The proportion of subjects who achieved clinical response in the adalimumab eow treatment group at Week 16 (10%) was numerically higher but not statistically significant compared to placebo. With respect to safety results, no major differences were observed between the two dose levels.

Based on the efficacy and safety results of this study and the fact that high loading and maintenance doses of adalimumab have shown to be necessary in other indications, the choice of dosing regimen for the phase 3 HS studies is considered justified. The body weight and BMI of subjects with HS are generally high (median BMI was >30 in both pivotal studies) and in population PK analyses it has been found that weight is a covariate for CL/F, with lower exposures in overweight subjects. Thus, based on these considerations, a high dose of adalimumab is considered necessary in HS.

The pivotal phase 3 studies M11-810 and M11-313 were both multi-center, randomized, double-blind, placebo-controlled, 2-period studies with the aim to determine the clinical safety and efficacy of adalimumab compared to placebo in subjects with moderate to severe HS. The studies were performed in the US, Europe, Australia and Canada.

The inclusion and exclusion criteria were adequate and ensured that subjects with moderate to severe HS were included, i.e. by requiring involvement of at least 2 distinct anatomic areas (at least one with Hurley Stage II or III), inadequate response to at least a 3-month course of oral antibiotics for treatment of HS (or with intolerance or contraindication to oral antibiotics) and a total AN count $\geq$ 3 at Baseline while excluding patients with very severe HS (e.g. draining fistula count greater than 20 at Baseline).

The inclusion and exclusion criteria were overall the same for both studies except concerning oral antibiotic use; in Study M11-313 subjects were not to have received any oral antibiotic treatment for HS within 28 days prior to the Baseline visit, while in Study M11-810 specified oral antibiotics (doxycycline or minocycline only) were permitted if the dose had been stable for at least 28 days prior to baseline.

In both studies, subjects must have agreed to daily use throughout the study of an over-the-counter topical antiseptic on their body areas affected with HS lesions. It is acknowledged that use of topical antiseptics can be part of the routine treatment of HS, possibly with regional differences. From an efficacy perspective, this is not likely to have affected the interpretation of the results since all subjects (adalimumab and placebo) were to use antiseptics.

Both studies included a 30-day screening period, an initial 12-week double-blind treatment period (Period A), and a subsequent 24-week double-blind treatment period (Period B), plus a Day 70 follow-up phone call approximately 70 days after the last dose of study drug administration. The design of both studies is considered adequate, with an initial 12-week placebo-controlled part with assessment of the primary end-point (HiSCR) at week 12. In both studies, a loading dose regimen was used, with adalimumab 160 mg at Week 0, 80 mg at Week 2 followed by 40 mg ew or matching placebo starting at Week 4.

In part B of both studies, subjects in the adalimumab arm were re-randomized in a 1:1:1 ratio to receive adalimumab 40 mg ew (i.e. continue with 40 mg ew treatment), adalimumab 40 mg eow (i.e. reduced dosing frequency) or matching placebo (i.e. withdrawal of active treatment). HiSCR responders who lost response and non-responders who experienced a worsening or absence of improvement were discontinued and had the opportunity to enter Study M12-555 to receive open-label adalimumab 40 mg ew. The studies differed to some extent during part B, e.g. with subjects from the placebo group in Period A of Study M11-810 were continued on blinded placebo from Week 12 to Week 35 while in Study M11-313, subjects from the placebo arm in Period A received adalimumab 40 mg ew from Week 16 to Week 35 (with adalimumab 160 mg at Week 12 and 80 mg at Week 14).

The primary end-point in both studies was the “Hidradenitis Suppurativa Clinical Response”, HiSCR, developed by the MAH. HiSCR is defined as at least a 50% reduction in the AN (abscess and inflammatory nodule count) count with no increase in abscess count and no increase in draining fistula count, at Week 12 relative to baseline.

There is no European guideline available for the clinical development of products for the treatment of HS and to date there have been few published randomised, controlled studies for other HS treatments. The MAH has received advice from both the FDA and the EMA during the clinical development for Humira in HS. Advice was given with respect to the primary end-point as well as other end-points. The MAH originally proposed to use “AN50” (a 50% reduction in abscess and inflammatory nodule count) as the primary efficacy end-point. However, the SAWP/CHMP had concerns that this endpoint would not adequately account for disease progression. Thus, the end-point chosen for phase 3 was the “Hidradenitis Suppurativa Clinical Response”, HiSCR, that requires at least a 50% reduction in the AN count, that may not be associated with increases in abscess count or draining fistula count.

A comprehensive work has been done by the MAH to develop and validate the HiSCR. In this work, data from one phase 2 study as well as data from a small, non-interventional study were used. From the phase 2 study, assessment of construct - related validity, predictive validity and responsiveness to change were assessed for HiSCR. Correlations between HiSCR and six other measures, e.g. Hurley Stage, modified Sartorius score, Pain - VAS, HS - PGA and DLQI, were assessed and it was found that HiSCR was well correlated with the other assessments. The HiSCR was also found able to detect changes in HS, based on the difference in the mean changes of other measures between HiSCR responders and non - responders at Week 16 and at Week 52.

The clinical meaningfulness for patients of the chosen cut-off of 50 % reduction in AN count for the definition of HiSCR response was assessed using alternative thresholds for the percentage changes in AN count. Patients with worsening disease or minimal improvement in AN count (<30% reduction) did not have a meaningful improvements of DLQI or pain and had only slight improvements in other patient-reported outcomes. A 50% reduction in AN count was found to be an appropriate threshold to define a HiSCR responder, which is agreed. In the non-interventional study, 22 HS patients and 4 dermatologists experienced in treating HS patients participated. Both intra- and inter-rater reliability in assessment of lesion counts was found adequate with intra-class correlation coefficients (ICCs) ranging from 0.68 up to 0.92, with the lowest ICCs observed for total abscess counts. In conclusion, the HiSCR is considered to have been adequately described and validated for its intended purpose as the primary end-point in the pivotal studies.

There were three ranked secondary end-points in the studies, assessing AN counts, skin Pain (NRS30) and change in modified Sartorius score from Baseline to Week 12. These are also endorsed and were discussed in the CHMP scientific advice. In addition, a full range of other secondary efficacy variables were explored, covering several aspects of HS, e.g. lesion counts and severity as well as several patient-reported outcomes (e.g. DLQI, TSQM, EQ-5D).

The sample size in the phase 3 studies seems foremost to have been chosen based on safety data considerations. Based on the observed difference in phase 2, the power for the primary comparison was >99% at the planning stage thus allowing a smaller difference to be detected. The sample size per se is, however, supported also from an efficacy perspective considering the studies confirmatory status.

The randomisation procedure used in the phase 3 studies seems appropriate. In both studies, stratification was made by Hurley stage to balance for severity of HS disease, which is endorsed. In study M11-810 concomitant use of permitted oral antibiotic therapy for treatment of HS was allowed (provided the dosing regimen was stable) and stratification was made for antibiotic use in this study, which is agreed. The methods used to achieve and maintain blinding during the two periods in each study seem appropriate.

Concerning the statistical methods, the methods planned and the analyses performed are in general considered appropriate. Stratification factor(s) was/were taken into account in the analyses. The primary approach for handling missing data is supported and also, that several sensitivity analyses were pre-planned. Main analyses included all randomised subjects with analyses of the primary endpoint and ranked secondary endpoints repeated based on the per-protocol population. The sensitivity modified NRI approaches are also supported while the use of LOCF is foremost considered conservative where its use implied treatment failure.

The procedures to handle multiplicity for primary and key (ranked) secondary endpoints were acceptable. No method or discussion regarding the pairwise comparisons in period B has been found. It is however acknowledged that period B (both studies) was considered for exploratory analyses only. The assessment of continued adalimumab treatment/adalimumab as maintenance was however to be a part of the integrated analyses where statistical testing was to be performed in ranked order. Study protocol amendments (while the studies were ongoing) implied foremost minor statistical changes. Changes were however also implemented post-hoc (after final SAP and code break). None of the changes affected primary analyses in period A but one of the ranked secondary endpoints. This added analysis is considered for supportive purposes.

The application also contained interim results from the on-going, open-label extension study M12-555, in which subjects previously participating in the pivotal phase 3 studies were included. This study enrolled subjects who participated in a prior Phase 3 HS study and either (a) completed the study; (b) achieved HiSCR at the entry to Period B then experienced LOR (defined as loss of at least 50% of the improvement (reduction) in the AN count achieved from Baseline to Week 12); or (c) did not achieve HiSCR at the entry to Period B then experienced WOAI (defined as an AN count $\geq$ Baseline AN count at 2 consecutive visits, excluding Week 12, occurring $\geq$ 14 days apart) on or after Week 16 of the prior Phase 3 study.

Starting at Baseline, all subjects received open-label adalimumab 40 mg ew regardless of treatment assignment in a prior Phase 3 study. If at any time on or after Week 24 of the open-label extension (OLE), a subject met certain criteria, the dosing regimen could be reduced to adalimumab 40 mg eow; if the subject achieved HiSCR during the OLE relative to Baseline of the prior Phase 3 study; AND achieved an AN count of 0 or 1 on at least 2 consecutive study visits; AND the physician and subject mutually decided that the risk/benefit of reducing adalimumab dosing to eow was favorable. Also in this study, subjects must have agreed to daily use of topical antiseptics on body areas affected with HS lesions. The exclusion criteria also specified that subjects should not have received any oral antibiotic treatment for HS within 28 days prior to the Baseline visit of Study M12-555, except for antibiotics permitted in a prior Phase 3 study. Restrictions were also applied for other HS therapies.

The indication initially applied for by the MAH was the treatment of active moderate to severe hidradenitis suppurativa (acne inversa) in adult patients, including treatment of inflammatory lesions and prevention of worsening of abscesses and draining fistulas. The CHMP acknowledged that no other medicinal product is currently approved for the treatment of HS and that the evidence of efficacy from the therapies commonly used in HS today is limited. However, considering that adalimumab is associated with some important safety concerns, the CHMP considered that population of patients that may benefit most from treatment with

Humira should be more clearly defined. The CHMP also noted that, from a mechanistic point of view, it is expected that adalimumab treatment would preferably display an anti-inflammatory effect on HS preferentially targeting inflammatory nodules rather than abscesses and clinical chronic sequelae such as draining fistula. Furthermore, the patient population in the pivotal trials had a higher prevalence of inflammatory nodules compared to abscesses, and a limited number of draining fistulas.

Therefore the CHMP requested that the indication should reflect the fact that patients with moderate to severe HS may have been treated with other therapies prior to the decision to initiate treatment with a biologic and that the "prevention" claim with respect to abscesses and fistulas should be removed to which the MAH agreed.

Efficacy data and additional analyses

In study M11-313, 307 subjects were enrolled and randomized, 154 to placebo and 153 to adalimumab. In study M11-810, 326 subjects were enrolled and randomized, 163 each to placebo and adalimumab, respectively. The number of subjects who completed period A of both studies was high (overall 94%). The numbers of subjects who completed period B were much lower (26 to 64% across groups), which was mainly due to the study design, since subjects meeting criteria for loss of response, worsening or absence of improvement were to discontinue from the study and enter the open-label extension Study M12-555.

With respect to baseline data, both demographic and disease characteristics were overall well balanced between the adalimumab and the placebo groups in both studies, with some exceptions. The population included reflects a typical HS population, with the majority being female (>63%), with a mean age below 40 years and high BMI (>32). The majority of subjects were white (>76% in study 313 and >83% in study 810). There were more black subjects in study 313 vs. study 810 (20% vs. 9%). The numbers of subjects using nicotine and alcohol were rather high.

Concerning baseline disease characteristics, the percentages with Hurley stage II or III were about equal, around one fourth had a family history of HS, the mean AN count was about 14 in study 313 and 11 in study 810. The mean number of draining fistulas was also slightly higher in study 313 vs. study 810 (4.2 vs. 3.4) and so was the mean modified Sartorius score (149 vs. 115).

In accordance with the inclusion criteria, all subjects (or nearly all in Study M11-810) reported prior antibiotic use for treatment of HS, doxycycline and clindamycin being most common and the majority of subjects discontinued use due to inadequate response (overall about 80%). Definitions were included in the study protocols to define inadequate response and intolerance to oral antibiotics.

In study M11-810, the number of subjects treated with stable doses of allowed oral antibiotics (doxycycline and minocycline) was 63 (19%), 32 in the placebo group and 31 in the adalimumab group.

No subjects were excluded in the primary ITT analyses (period A) and almost all subjects (94%) irrespective of study, continued to and were included in the ITT population in Period B. The low drop-out rate in period A contributed to a small difference between the ITT population and PP population (period A). Primary and secondary analyses were repeated based on the PP_A population, but considering the small difference between the ITT_A and the PP_A, these did generally not offer any meaningful comparisons with the analyses based on the ITT_A population.

Results Period A

The primary end-point, HiSCR (the proportion of subjects achieving HiSCR, defined as at least a 50% reduction in AN count with no increase in abscess count and no increase in draining fistula count relative to Baseline) at Week 12, was met in both studies. The size of the effect differed between the two studies, though, with differences between adalimumab and placebo of 16% in study M11-313 and 31.5% in study M11-810, respectively. Baseline Hurley stage and baseline concomitant antibiotic use (Study M11-810 only) were stratification factors in the Period A randomization for both studies. A significantly higher HiSCR rate in

the adalimumab ew group compared to the placebo group was observed in eachstratum and at each vist in Period A. The treatment difference between adalimumab and placebo were greater among subjects with Hurley Stage III than those with Hurley Stage II and among subjects who received concomitant antibiotics compared to those who did not.

In the integrated ITT_A Population for both studies combined, 51% of subjects in the adalimumab group achieved HiSCR at Week 12 compared to 27% of subjects in the placebo group ($P < 0.001$).

For the three, ranked secondary end-points (proportion of subjects who achieved AN count of 0, 1, or 2 in Hurley Stage II subjects; pain reduction assessed by NRS30 in subjects with baseline skin pain NRS ≥ 3 and Change in modified Sartorius score; all assessed at week 12), Study M11-810 met all these endpoints with statistically significant differences between adalimumab 40 mg ew and placebo. In contrast, none of these end-points achieved statistical significance in Study M11-313. All outcomes in Study M11-313 were, however, numerically in favour of adalimumab ew, although borderline regarding the first endpoint, AN count of 0, 1, or 2 in Hurley stage II subjects (the difference in the point estimate for adalimumab versus placebo was <1%). Post-hoc analyses for these end-points performed on data from the phase 2 Study M10-467 showed statistically significant differences between adalimumab ew and placebo, in favour of adalimumab.

The MAH has discussed possible reasons for the failure to achieve statistical significance for the ranked secondary end-points in study M11-313. Some between-study differences in baseline characteristics can be noted, e.g. in body weight (mean weight was higher, 98 kg, in; Study M11-313 compared with 93 kg in Study M11-810) and weight was a significant covariate for CL/F for adalimumab in HS patients, with higher CL/F in heavy subjects.

Factors indicating HS severity also differed between studies (higher mean draining fistula count, higher mean AN count, slightly worse mean pain score in Study, higher mean modified Sartorius score and higher mean DLQI score in Study in Study M11-313 compared with Study M11-810). The percentage of black subjects was higher in Study M11-313 compared with Study M11-810 (20% vs. 9%). The percentage of current smokers was lower in Study M11-313 (56%) compared with Study M11-810 (66%). Similar to obesity, smoking is considered another risk factor for HS. However, for this factor the number of smokers was overall lower in study M11-313, and thus, this does not seem to be a factor explaining the poorer efficacy outcome in this study compared with study M11-810.

The primary efficacy end-point in this study (HiSCR), was, however, statistically significant and the study may not be regarded as a failed study in this respect even if the effect size was smaller in this study compared with Study M11-810.

A large number of other secondary efficacy variables were assessed. With respect to lesion counts, the percent change from baseline in different lesion counts at Week 12 showed decreases in the range 10 to 55% for adalimumab ew vs. maximally 25% decreases for placebo across the two studies. A small number of subjects (10% in study M11-313 and 15% in M11-810) achieved complete elimination of AN (AN = 0) with adalimumab ew treatment.

For the assessment of representative HS lesions, the mean reduction from Baseline in the Patient's lesion Severity Score and the degree of in erythema and tenderness, were greater for subjects in the adalimumab ew group than for subjects in the placebo group in both studies. In Study M11-313, adalimumab showed no effect on lesion size vs. placebo.

Risk of flare was assessed, defined as at least a 25% increase in AN count with a minimum increase of 2 relative to Baseline. In both studies, the risk of flare was lower at all visits during Period A for subjects randomized to adalimumab ew than for subjects randomized to placebo (NRI). At least 1 occurrence of flare was experienced by 11% (Study M11-810) and 14% (Study M11-313) of subjects in the adalimumab ew group and approximately 35% of subjects in the placebo group ($P < 0.001$, in both studies).

Several different Quality of Life scales were used in the pivotal studies, with DLQI (a validated QoL score used in other dermatological conditions) and TSQM (Treatment Satisfaction Questionnaire for Medication) being used in both studies and results are presented for the integrated ITT_A Population.

Adalimumab ew subjects had greater improvement in DLQI, compared to placebo-treated subjects, as measured by mean change in DLQI, from Baseline to Week 12 ($P \leq 0.05$). Among subjects with a baseline DLQI ≥ 5, a higher proportion of adalimumab ew subjects than placebo subjects (50% vs. 34%) achieved the MCID, defined as a decrease of ≥ 5.0 points at Week 12 (NRI; $P < 0.001$).

TSQM scores range from 0 to 100, with higher scores indicating better treatment satisfaction. Subjects in the adalimumab ew group had greater increases in overall treatment satisfaction and effectiveness than subjects in the placebo group at Week 12 ($P \leq 0.05$) (Table 28). Satisfaction with the side effects and convenience were similar between the placebo and treatment groups.

Results Period B

Analyses were performed for HiSCR at different time points up to week 36 for different populations, defined on the basis of the outcome at the end of Part A in the pivotal studies, e.g. responders, non-responders (separately and combined) and a post-hoc defined population (ITT_B_PRR Population) defined as HiSCR responders and partial responders achieving AN25 (a $\geq$ 25% reduction in AN count relative to baseline) at week 12.

Regardless of the population analysed, the HiSCR rates decreased over time in all treatment groups. However, as pointed out by the MAH, this may in part be explained by the study design, since any subject who experienced loss of response (LOR), worsening or absence of improvement (WOAI) during Period B was discontinued from the study, counted as a non-responder in Period B and then went to Study M12-555. Thus, these subjects did not have the opportunity to demonstrate if they could have regained HiSCR in a subsequent visit during Period B. Even if the overall HiSCR rates decreased over time (for reasons outlined above), the response rates at weeks 24 and 36 were highest with the ew/ew treatment in all analysis populations. Although acknowledged that almost all discontinuations were “by design” the Applicant was asked for an analysis of time to LOR/WOAI based on all subjects re-randomised to period B and, irrespective of responders status at week 12 (i.e. the ITT-B population) to further illustrate the time point for discontinuations in each randomised treatment group. In the MAH´s response, additional analyses of time to LOR/WOAI have been provided clarifying also time to discontinuations as per IXRS instruction due to loss of response (LOR)/worsening or absence of improvement (WOAI). As clear from previously reported data, the proportion of subjects who experienced LOR/WOAI was lowest in the adalimumab ew/ew group as compared to the adalimumab ew/placebo and adalimumab ew/eow groups. The difference between ew/ew and ew/eow was numerically in favour of ew/ew but provide no clear evidence in support of ew/ew over ew/eow.

In Study M11-810, the ITT_B_PBO Population included subjects who were randomized to placebo in Period A and continued on placebo in Period B, thus, this group had a very long duration of placebo treatment. Subjects in the ITT_B_PBO Population in Period B showed a low level HiSCR rate that decreased from Week 12 (29%) to Week 36 (16%) (NRI).

In the post-hoc analyses of the sub-group of AN25 responders (partial responders), it was found that among the group of HiSCR non-responders, this sub-group was able to reach HiSCR, in particular with adalimumab 40 mg ew/ew. Based on this, the MAH considers the statement in the SmPC section 4.2. that “Continued therapy beyond 12 weeks is recommended except in those patients without any improvement for whom continued therapy should be reconsidered” to be supported. This wording was revised in the final SmPC and was found acceptable to the CHMP.

Overall the CHMP considered that the available data were sufficient to support the dosing regimen of 160 mg initially at Day 1, followed by 80 mg two weeks later at Day 15 and to continue with a dose of 40 mg every week from Day 29 onwards.

2.4.4. Conclusions on the clinical efficacy

The application for Humira in the indication Hidradenitis suppurativa is supported by two adequately designed and performed phase 3 studies performed in subjects with moderate to severe HS.

The primary end-point, HiSCR, was met in both studies, albeit with some differences in the size of the effect of adalimumab vs. placebo between the studies. For the three, ranked secondary end-points, Study M11-810 met all these endpoints with statistically significant differences between adalimumab 40 mg ew and placebo. In contrast, none of these end-points achieved statistical significance in Study M11-313, however, all outcomes except one were numerically in favour of adalimumab ew.

Outcomes related to patient-reported Quality of Life showed an effect of adalimumab vs. placebo for both DLQI and TSQM.

For inclusion in the pivotal studies, patients were required to have had insufficient response or intolerance to oral antibiotics. It is acknowledged that no other medicinal product is currently approved for the treatment of HS (including oral antibiotics) and most of the therapies commonly used in HS today have not demonstrated in a clinical trial setting, evidence of efficacy. However, adalimumab is a TNF alfa-blocker with a well-known and not entirely benign safety profile. Therefore, the initially proposed indication by the MAH, for Humira as a first-line treatment for HS, was not considered acceptable.

Instead, the CHMP requested that Humira should be indicated for the treatment of active moderate to severe hidradenitis suppurativa (acne inversa) in adult patients with an inadequate response to conventional systemic HS therapy.

In addition, given the biological mechanism of action of adalimumab and the specific patient characteristics in the HS trials, which had a higher prevalence of inflammatory nodules compared to abscesses, the CHMP also requested that the prevention of abscesses and fistulae should not be included in the indication of Humira. The applicant agreed to amend the indication in line with the CHMP proposal and reference to claims related to worsening of abscesses and draining fistulae were removed.

2.5. Clinical safety

Introduction

Up to 29 April 2014, 727 subjects with HS (635.7 patient years [PYs]) had been exposed to at least 1 dose of adalimumab with 576 subjects exposed for more than 6 months and 336 subjects exposed for more than 1 year in the HS clinical program.

Patient exposure

Four analysis sets were used for the integrated safety analyses as summarized in **Table** .

Table 58. Definition of Analysis Sets

Analysis Sets	Studies Included	Study Population	Treatment Groups and Treatment Group Comparisons
Placebo-Controlled Analysis Set[a]	M10-467 M11-313 M11-810	All subjects who received at least 1 dose of study drug (adalimumab or placebo) in Period A of Studies M10-467, M11-810, or M11-313.	Treatment Groups: • Adalimumab ew • Adalimumab eow • Adalimumab total (adalimumab ew and eow combined)[b] • Placebo

			Pairwise Comparisons: • Adalimumab ew versus placebo • Adalimumab total versus placebo
Maintenance Analysis Set	M11-313 M11-810	All subjects from Period A adalimumab ew group who received at least 1 dose of study drug in Period B of Studies M11-810 or M11-313. Subgroups include: • HiSCR responders at the entry of Period B • HiSCR nonresponders at the entry of Period B • Subjects who achieved AN25 at entry of Period B	Treatment Groups: • Adalimumab ew in Period B following adalimumab ew in Period A (adalimumab ew/ew) • Adalimumab eow in Period B following adalimumab ew in Period A (adalimumab ew/eow) • Placebo in Period B following adalimumab ew in Period A (adalimumab ew/placebo) Pairwise Comparisons: • Adalimumab ew/ew versus adalimumab ew/eow • Adalimumab ew/eow versus adalimumab ew/placebo • Adalimumab ew/ew versus adalimumab ew/placebo
All Adalimumab ew Analysis Set[c]	M10-467 M11-313 M11-810 M12-555	All subjects who received at least 1 dose of adalimumab ew in Studies M10-467, M11-810, M11-313, or M12-555.	Adalimumab ew
All Adalimumab Analysis Set	M10-467 M11-313 M11-810 M12-555	All subjects who received at least 1 dose of adalimumab ew or eow in Studies M10-467, M11-810, M11-313, or M12-555.	Adalimumab

AN25 = 25% reduction in total abscess and inflammatory nodule count; eow = every other week; ew = every week; HiSCR = hidradenitis suppurativa clinical response

Analyses were also conducted using only the subjects from the Phase 3 placebo-controlled studies, Studies M11-810 and M11-313 (called the Phase 3 Placebo-Controlled Analysis Set). The summaries for these Phase 3 placebo-controlled analyses include treatment-emergent adverse event (TEAE) overview, TEAE by system organ class (SOC) and preferred term (PT), treatment-emergent serious adverse event (TESAE) by SOC and PT, infections by SOC and PT, and serious infections by SOC and PT.

The adalimumab ew or eow (adalimumab) treatment group described in the ISS SAP is referred to as "adalimumab total" to clarify that this treatment group contained both the adalimumab ew and eow groups.

In order to assess the safety of continuous adalimumab ew treatment, analyses also were conducted (using the All Adalimumab ew Analysis Set – Continuous Adalimumab ew) and included only those periods where adalimumab treatment was continuous. The summaries for continuous adalimumab ew treatment include TEAE overview, treatment-emergent adverse events of special interest (AESI) overview, and TEAE by SOC and PT.

- The *Placebo-Controlled Analysis Set* allows for assessment of the short-term safety profiles for adalimumab ew, eow, and total (ew and eow combined) treatments, as compared to placebo, and is based on the DB data from Period A of the Phase 2 study, (first 16 weeks) and Period A of the Phase 3 studies, (first 12 weeks) with focus on the comparison between the adalimumab ew and total groups versus the placebo group.
- The *Maintenance Analysis Set* allows for an assessment of the safety profiles for continuous adalimumab ew treatment (i.e., adalimumab ew in both Period A and Period B) and step-down dosing to adalimumab eow (i.e., adalimumab ew in Period A and adalimumab eow in Period B), as compared to withdrawal from adalimumab ew treatment (i.e., adalimumab ew in Period A and placebo in Period B), is based on the DB data from Period B of the Phase 3 studies M11-810 and M11-313.
- The *All Adalimumab ew Analysis Set* allows for an assessment of the safety profile for adalimumab ew treatment that is based on all adalimumab ew exposure across all four studies (M10-467, M11-810, M11-313, and M12-555).
- The *All Adalimumab Analysis Set* allows for an assessment of safety data that is based on all subjects exposed to adalimumab ew and eow in all studies.

In the All Adalimumab Analysis Set, a total of 727 subjects with HS received at least 1 dose of adalimumab as of 29 April 2014, with a cumulative exposure of 635.7 PYs. The exposure data are summarized in the table below.

Table 59. Study Drug Exposure for Studies M10-467, M11-810, M11-313, and M12-555 Through 29 April 2014 (All Adalimumab Analysis Set)

Duration of Exposure (Days)	Adalimumab (N = 727) n (%)
1	727 (100)
183 (6 months)	549 (75.5)
365 (12 months)	281 (38.7)
548 (18 months)	69 (9.5)
730 (24 months)	12 (1.7)

Note: For each subject, the total duration of adalimumab exposure is the sum of the duration of exposure to adalimumab for each phase/study. For a phase/study, duration is defined as the last dose date – first dose date + 14, however, if a subject continues to the next phase/study and the last dose date of the current phase/study + 14 is greater than the first dose date of the next phase/study, then the duration of the current phase/study is defined as the first dose date of the next phase/study – first dose date of current phase/study. The last available dose date prior to 29 April 2014 is used if a subject is still ongoing in a study. Duration for more than 14 days during a protocol-defined gap or during a gap between studies is excluded. Includes Studies M10-467, M11-810, M11-313, and M12-555.

Demographic Characteristics

In the *All Adalimumab Analysis Set*, the majority of subjects were female (67%), white (80%), <40 years of age (64%), and had a BMI ≥30 kg/m^2. Of note, the majority of subjects were either current users or ex-users of nicotine (60% and 14%, respectively). A similar profile of demographics was observed for the other analysis sets.

In the *Placebo-Controlled Analysis Set*, statistically significant differences among treatment groups were observed for mean BMI (p= 0.009) and BMI category (p= 0.031). Mean BMI was highest in the adalimumab

eow group and there were more subjects in the adalimumab eow group that were morbidly obese, as compared to the other treatment groups.

In the *Maintenance Analysis Set*, statistically significant differences among treatment groups were observed for race (p= 0.016) and race category (p= 0.016). No other statistically significant differences among treatment groups were observed with respect to demographic characteristics. There were no clinically meaningful differences among treatment groups in the Placebo-Controlled or Maintenance Analysis Sets that would have influenced the safety conclusions.

Baseline Disease Characteristics

In the All Adalimumab Analysis Set, baseline disease characteristics data were representative of a population with moderate to severe HS. The mean duration of HS was approximately 11.6 years. Most subjects had Hurley Stage II or III HS (53% Hurley Stage II and 44% Stage III). The majority of subjects did not have a family history of HS and did not have prior surgery for HS (75% and 87% for the All Adalimumab Analysis Set).

Study M10-467 was the only study which evaluated adalimumab eow dosing in the initial placebo-controlled phase and enrolled subjects with Hurley Stage I, II, or III disease; Studies M11-810 and M11-313 enrolled mostly subjects with Hurley Stage II or III disease. The baseline disease characteristics were generally balanced between the treatment groups. A similar profile of baseline characteristics was observed for the other analysis sets.

Medical History

In the All Adalimumab Analysis Set, hypertension (19%) and depression (17%) were the most commonly reported conditions/diagnoses during medical history data collection. A small percentage of subjects in the All Adalimumab Analysis Set had a medical history of ischemic cardiovascular events (myocardial infarction [0.7%] and transient ischemic attack [0.7%]) and 2.2% of subjects had a history of psoriasis.

Prior and Concomitant HS Medication Use

Of the subjects who reported prior antibiotic use across analysis sets, the majority discontinued use of their prior antibiotics because of inadequate response. Subjects from the Phase II dose-ranging study, Study M10-467, are not included in this analysis because only antibiotic categories (not antibiotic generic names) were collected in the study.

Continuation of permitted baseline oral antibiotic use for treatment of HS was allowed in Study M11-810, provided the dosing regimen had been stable for at least 4 consecutive weeks prior to Baseline. The dosing regimen was to remain stable throughout study participation. Across analysis sets, the most commonly used concomitant medications were chlorhexidine and ibuprofen (36% and 33% for the All Adalimumab Analysis Set).

In the Phase 3 studies, subjects must have agreed to daily use (throughout the entirety of the study) of 1 of the following over-the-counter topical antiseptics on their body areas affected with HS lesions: chlorhexidine gluconate, triclosan, benzoyl peroxide, or dilute bleach in bathwater.

Adverse events

A TEAE was defined as an event with onset or worsening after the first study drug injection and within 70 days after the last study drug injection. AEs that occurred on the same day of the first study drug injection were considered as TEAEs.

Placebo-Controlled Initial Treatment (Period A; Weeks 0 to 12)

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) are shown in **Table** . Data from the individual studies are consistent, and thus, integrated data are presented.

The percentages of subjects reporting AEs were comparable between the placebo and total adalimumab (eow and ew) groups 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 and severe AEs.

Table 60. Overview of Adverse Events in Studies M10-467, M11-810, and M11-313 (Placebo-Controlled Analysis Set)

		Adalimumab		
	Placebo N = 366 n (%)	**eow N = 52 n (%)**	**ew N = 367 n (%)**	**Total N = 419 n (%)**
Any AE	233 (63.7)	33 (63.5)	211 (57.5)	244 (58.2)
Any SAE	13 (3.6)	3 (5.8)	10 (2.7)	13 (3.1)
Any AE leading to discontinuation of study drug	10 (2.7)	2 (3.8)	7 (1.9)	9 (2.1)
Any severe AE	24 (6.6)	4 (7.7)	20 (5.4)	24 (5.7)
Any AE at least possibly related to study drug[a]	99 (27.0)	16 (30.8)	106 (28.9)	122 (29.1)
Any SAE at least possibly related to study drug[a]	2 (0.5)	1 (1.9)	3 (0.8)	4 (1.0)
Any infection	114 (31.1)	22 (42.3)	96 (26.2)	118 (28.2)
Any serious infection	2 (0.5)	1 (1.9)	3 (0.8)	4 (1.0)
Any malignancy (excluding lymphoma, HSTCL, leukemia, NMSC, and melanoma)	1 (0.3)	0	1 (0.3)	1 (0.2)

a. As assessed by investigator.

Note: Treatment-emergent AE is defined as any adverse event with an onset date on or after the first dose of study drug in Period A and up to the last dose of study drug in Period A + 70 days or the first dose of study drug in Period B, whichever is earlier.

SAEs were experienced by similar proportions of subjects in the total adalimumab and placebo groups. Two (0.5%) subjects in the placebo group had SAEs of suicide attempt, and 7 subjects (2 [0.5%] subjects in the total adalimumab group and 5 [1.4%] subjects in the placebo group) had SAEs of hidradenitis (i.e., worsening of HS); all other SAEs were reported by at most 1 subject each.

AEs led to study drug discontinuation in 2.1% and 2.7% of subjects in the total adalimumab and placebo groups, respectively. Hidradenitis led to discontinuation for 3 (0.7%) adalimumab-treated subjects and 2 (0.5%) placebo-treated subjects.

Serious infections were reported by 4 (1.0%) adalimumab-treated subjects (3 treated with ew and 1 treated with eow) and 2 (0.5%) placebo-treated subjects.

Placebo-Controlled Maintenance Treatment (Period B; Weeks 12 to 36)

Comparison of the safety data from subjects treated with continuous adalimumab ew (adalimumab ew in both Period A and B, referred to as ew/ew group), dose reduction to adalimumab eow (adalimumab ew in Period A and adalimumab eow in Period B, referred to as ew/eow group), or treatment withdrawal from adalimumab ew (adalimumab ew in Period A and placebo in Period B, referred to as ew/pbo group) revealed

few differences in the safety profiles for the different regimens. Overall, the safety profiles were comparable for the adalimumab ew and adalimumab eow groups.

Table 61. Overview of Number and Percentage of Subjects with TEAEs for Studies M11-810 and M11-313 (Maintenance Analysis Set)

	Adalimumab					
	ew/placebo		ew/eow		ew/ew	
	(N = 100) n (%)	(PYs = 31.8) Events (E/100 PYs)	(N = 101) n (%)	(PYs = 33.1) Events (E/100 PYs)	(N = 99) n (%)	(PYs = 35.4) Events (E/100 PYs)
Any TEAE	65 (65.0)	188 (591.2)	58 (57.4)	163 (492.4)	59 (59.6)	167 (471.8)
Any TESAE	2 (2.0)	2 (6.3)	5 (5.0)	7 (21.1)	3 (3.0)	5 (14.1)
Any TEAE leading to discontinuation of study drug	2 (2.0)	2 (6.3)	2 (2.0)	2 (6.0)	2 (2.0)	2 (5.6)
Any severe TEAE	3 (3.0)	3 (9.4)	7 (6.9)	11 (33.2)	4 (4.0)	13 (36.7)
Any TEAE at least possibly related to study drug[a]	23 (23.0)	57 (179.2)	21 (20.8)	33 (99.7)	25 (25.3)	47 (132.8)
Any TESAE at least possibly related to study drug[a]	0	0	2 (2.0)	2 (6.0)	2 (2.0)	4 (11.3)
Any infection	29 (29.0)	55 (173.0)	31 (30.7)	46 (139.0)	32 (32.3)	45 (127.1)
Any serious infection	0	0	0	0	1 (1.0)	1 (2.8)
Any opportunistic infection (excluding oral candidiasis and TB)	0	0	0	0	0	0
Any TB (active or latent)	0	0	0	0	0	0
Any lymphoma	0	0	0	0	0	0
Any NMSC	0	0	1 (1.0)	1 (3.0)	0	0
Any malignancy (excluding lymphoma, HSTCL, leukemia, NMSC, and melanoma)	0	0	0	0	0	0
Any demyelinating disorder	0	0	0	0	0	0
Any TEAE leading to death	0	0	1 (1.0)	1 (3.0)	0	0
Deaths	0	0	1 (1.0)	1 (3.0)	0	0

eow = every other week; ew = every week; HSTCL = hepatosplenic T-cell lymphoma; NMSC = nonmelanoma skin cancer; PYs = patient years; TEAE = treatment-emergent adverse event; TB = tuberculosis; TESAE = treatment-emergent serious adverse event

f. As assessed by investigator.

Note: TEAE is defined as any adverse event with an onset date on or after the first dose of study drug in Period A and up to the last dose of study drug in Period A + 70 days or the first dose of study drug in Period B, whichever is earlier. Any AE with an unknown relationship was considered as study drug-related and any AE with an unknown severity was considered as severe.

Table 7. Overview of Number and Percentage of Subjects with TEAEs for Studies M10-467, M11-810, M11-313, and M12-555 Through 29 April 2014 (All Adalimumab Analysis Set)

	Adalimumab	
Category	(N = 727) n (%)	(PYs = 635.7) Events (E/100 PYs)
Any TEAE	572 (78.7)	2975 (468.0)
Any TESAE	78 (10.7)	115 (18.1)
Any TEAE leading to discontinuation of study drug	70 (9.6)	84 (13.2)
Any severe TEAE	107 (14.7)	169 (26.6)
Any TEAE at least possibly related to study drug[a]	322 (44.3)	958 (150.7)
Any TESAE at least possibly related to study drug[a]	20 (2.8)	26 (4.1)
Any infection	377 (51.9)	789 (124.1)
Any serious infection	21 (2.9)	25 (3.9)
Any opportunistic infection (excluding oral candidiasis and TB)	1 (0.1)	1 (0.2)
Any TB (active or latent)	3 (0.4)	3 (0.5)
Any lymphoma	1 (0.1)	1 (0.2)
Any NMSC	1 (0.1)	1 (0.2)
Any malignancy (excluding lymphoma, HSTCL, leukemia, NMSC, and melanoma)	3 (0.4)	3 (0.5)
Any demyelinating disorder	0	0
Any TEAE leading to death	2 (0.3)	2 (0.3)
Deaths	2 (0.3)	2 (0.3)

HSTCL = hepatosplenic T-cell lymphoma; NMSC = nonmelanoma skin cancer; PYs = patient years; TB = tuberculosis; TEAE = treatment-emergent adverse event; TESAE = treatment-emergent serious adverse event

a As assessed by investigator.

Note: TEAE is defined as any adverse event with an onset date on or after the first adalimumab dose and up to 70 days after the last dose of adalimumab. The last available dose date prior to 29 April 2014 is used if a subject is still ongoing in Study M12-555. AEs with an onset date more than 70 days during a protocol-defined placebo gap or during a gap between studies are excluded. Any AE with an unknown relationship was considered as study drug-related and any AE with an unknown severity was considered as severe.

Common adverse events

A summary of AEs reported by ≥ 2% of subjects in the Placebo-Controlled Analysis Set is presented in **Table 63.** The most frequently reported TEAEs for the adalimumab total and placebo groups 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 percentage of subjects who reported serious events of hidradenitis was lower in the adalimumab total group than in the placebo group (0.5% versus 1.4%).

Table 8. TEAEs Reported in ≥ 2% of Subjects in Any Treatment Group in Order of Decreasing Frequency in the Adalimumab Total Group for Studies M10-467, M11-810, and M11-313 (Placebo-Controlled Analysis Set)

	Placebo		Adalimumab					
			eow		ew		Total	
MedDRA PT	(N = 366) n (%)	(PYs = 85.8) Events (E/100 PYs)	(N = 52) n (%)	(PYs = 16.1) Events (E/100 PYs)	(N = 367) n (%)	(PYs = 87.1) Events (E/100 PYs)	(N = 419) n (%)	(PYs = 103.2) Events (E/100 PYs)
Any TEAE	233 (63.7)	639 (744.8)	33 (63.5)	126 (782.6)	211 (57.5)	583 (669.3)	244 (58.2)	709 (687.0)
Headache	38 (10.4)	49 (57.1)	7 (13.5)	16 (99.4)	43 (11.7)	59 (67.7)	50 (11.9)	75 (72.7)
Hidradenitis	47 (12.8)	58 (67.6)	7 (13.5)	8 (49.7)	25 (6.8)	28 (32.1)	32 (7.6)	36 (34.9)
Nasopharyngitis	32 (8.7)	34 (39.6)	7 (13.5)	9 (55.9)	24 (6.5)	26 (29.9)	31 (7.4)	35 (33.9)
Upper respiratory tract infection	15 (4.1)	15 (17.5)	4 (7.7)	6 (37.3)	17 (4.6)	18 (20.7)	21 (5.0)	24 (23.3)
Nausea	10 (2.7)	11 (12.8)	2 (3.8)	4 (24.8)	14 (3.8)	14 (16.1)	16 (3.8)	18 (17.4)
Diarrhoea	8 (2.2)	8 (9.3)	2 (3.8)	3 (18.6)	12 (3.3)	12 (13.8)	14 (3.3)	15 (14.5)
Dizziness	6 (1.6)	6 (7.0)	1 (1.9)	1 (6.2)	11 (3.0)	14 (16.1)	12 (2.9)	15 (14.5)
Fatigue	9 (2.5)	11 (12.8)	2 (3.8)	2 (12.4)	10 (2.7)	11 (12.6)	12 (2.9)	13 (12.6)
Arthralgia	3 (0.8)	3 (3.5)	0	0	9 (2.5)	9 (10.3)	9 (2.1)	9 (8.7)
Back pain	8 (2.2)	8 (9.3)	1 (1.9)	1 (6.2)	7 (1.9)	7 (8.0)	8 (1.9)	8 (7.8)
Pruritus	3 (0.8)	3 (3.5)	3 (5.8)	3 (18.6)	5 (1.4)	5 (5.7)	8 (1.9)	8 (7.8)
Vomiting	7 (1.9)	7 (8.2)	2 (3.8)	2 (12.4)	6 (1.6)	6 (6.9)	8 (1.9)	8 (7.8)
Oropharyngeal pain	5 (1.4)	5 (5.8)	3 (5.8)	4 (24.8)	4 (1.1)	5 (5.7)	7 (1.7)	9 (8.7)
Urinary tract infection	8 (2.2)	8 (9.3)	1 (1.9)	1 (6.2)	6 (1.6)	6 (6.9)	7 (1.7)	7 (6.8)
Abdominal pain upper	6 (1.6)	6 (7.0)	2 (3.8)	2 (12.4)	4 (1.1)	4 (4.6)	6 (1.4)	6 (5.8)
Hypercholesterolemia	1 (0.3)	1 (1.2)	2 (3.8)	2 (12.4)	3 (0.8)	3 (3.4)	5 (1.2)	5 (4.8)
Pyrexia	6 (1.6)	7 (8.2)	2 (3.8)	2 (12.4)	2 (0.5)	2 (2.3)	4 (1.0)	4 (3.9)
Bronchitis	8 (2.2)	9 (10.5)	0	0	3 (0.8)	3 (3.4)	3 (0.7)	3 (2.9)
Dyspnea	4 (1.1)	4 (4.7)	2 (3.8)	2 (12.4)	1 (0.3)	1 (1.1)	3 (0.7)	3 (2.9)
Pain	2 (0.5)	2 (2.3)	2 (3.8)	2 (12.4)	1 (0.3)	1 (1.1)	3 (0.7)	3 (2.9)
Herpes simplex	1 (0.3)	2 (2.3)	2 (3.8)	2 (12.4)	0	0	2 (0.5)	2 (1.9)
Pilonidal cyst	1 (0.3)	2 (2.3)	2 (3.8)	2 (12.4)	0	0	2 (0.5)	2 (1.9)

eow = every other week; ew = every week; MedDRA = Medical Dictionary for Regulatory Activities; PT = preferred term; PYs = patient years; TEAE = treatment-emergent adverse event

Note: TEAE is defined as any adverse event with an onset date on or after the first dose of study drug in Period A and up to the last dose of study drug in Period A + 70 days or the first dose of study drug in Period B, whichever is earlier.

A summary of AEs reported by ≥ 2% of subjects in the Maintenance Analysis Set is presented in **Table 64**. The most frequently reported TEAEs in the adalimumab ew/ew and ew/placebo groups 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).

Table 9. TEAEs Reported in ≥ 2% of Subjects in Any Treatment Group in Order of Decreasing Frequency in the Adalimumab ew/ew Group for Studies M11-810 and M11-313 (Maintenance Analysis Set)

	Adalimumab					
	ew/placebo		ew/eow		ew/ew	
MedDRA PT	(N = 100) n (%)	(PYs = 31.8) Events (E/100 PYs)	(N = 101) n (%)	(PYs = 33.1) Events (E/100 PYs)	(N = 99) n (%)	(PYs = 35.4) Events (E/100 PYs)
Any TEAE	65 (65.0)	188 (591.2)	58 (57.4)	163 (492.4)	59 (59.6)	167 (471.8)
Headache	8 (8.0)	13 (40.9)	6 (6.0)	8 (24.2)	7 (7.0)	12 (33.9)
Nasopharyngitis	10 (10.0)	16 (50.3)	4 (4.0)	8 (24.2)	6 (6.0)	7 (19.8)
Hidradenitis	20 (20.0)	23 (72.3)	18 (18.0)	19 (57.4)	5 (5.0)	6 (16.9)
Upper respiratory tract infection	7 (7.0)	9 (28.3)	7 (6.9)	8 (24.2)	5 (5.1)	5 (14.1)
Folliculitis	1 (1.0)	1 (3.1)	1 (1.0)	2 (6.0)	4 (4.0)	4 (11.3)
Influenza	2 (2.0)	3 (9.4)	0	0	4 (4.0)	4 (11.3)
Back pain	1 (1.0)	1 (3.1)	1 (1.0)	1 (3.0)	3 (3.0)	3 (8.5)
Cough	1 (1.0)	1 (3.1)	2 (2.0)	2 (6.0)	3 (3.0)	3 (8.5)
Gastritis	0	0	0	0	3 (3.0)	3 (8.5)
Gastroenteritis viral	0	0	2 (2.0)	2 (6.0)	3 (3.0)	3 (8.5)
Intertrigo	1 (1.0)	2 (6.3)	1 (1.0)	1 (3.0)	3 (3.0)	3 (8.5)
Nausea	1 (1.0)	1 (3.1)	1 (1.0)	1 (3.0)	3 (3.0)	3 (8.5)
Pyrexia	1 (1.0)	1 (3.1)	5 (5.0)	5 (15.1)	3 (3.0)	3 (8.5)
Anaemia	2 (2.0)	2 (6.3)	1 (1.0)	2 (6.0)	2 (2.0)	2 (5.6)
Arthralgia	3 (3.0)	3 (9.4)	1 (1.0)	1 (3.0)	2 (2.0)	2 (5.6)
Dermatitis psoriasiform	1 (1.0)	1 (3.1)	0	0	2 (2.0)	2 (5.6)
Diarrhea	2 (2.0)	2 (6.3)	4 (4.0)	4 (12.1)	2 (2.0)	2 (5.6)
Hypertension	3 (3.0)	3 (9.4)	0	0	2 (2.0)	2 (5.6)
Insomnia	0	0	1 (1.0)	1 (3.0)	2 (2.0)	2 (5.6)
Pneumonia	1 (1.0)	1 (3.1)	2 (2.0)	2 (6.0)	2 (2.0)	2 (5.6)
Sinusitis	1 (1.0)	1 (3.1)	0	0	2 (2.0)	2 (5.6)
Urinary tract infection	2 (2.0)	2 (6.3)	3 (3.0)	4 (12.1)	2 (2.0)	3 (8.5)
Viral upper respiratory tract infection	0	0	0	0	2 (2.0)	2 (5.6)
Weight decreased	0	0	0	0	2 (2.0)	2 (5.6)
Alanine aminotransferase increased	2 (2.0)	2 (6.3)	0	0	1 (1.0)	1 (2.8)
ALT increased	2 (2.0)	2 (6.3)	0	0	1 (1.0)	1 (2.8)
Bronchitis	3 (3.0)	6 (18.9)	1 (1.0)	1 (3.0)	1 (1.0)	1 (2.8)
Conjunctivitis	2 (2.0)	2 (6.3)	1 (1.0)	1 (3.0)	1 (1.0)	2 (5.6)
Diabetes mellitus	0	0	3 (3.0)	3 (9.1)	1 (1.0)	1 (2.8)
Gastroenteritis	1 (1.0)	1 (3.1)	2 (2.0)	3 (9.1)	1 (1.0)	2 (2.8)
Oropharyngeal pain	2 (2.0)	2 (6.3)	0	0	1 (1.0)	1 (2.8)
Pharyngitis	0	0	2 (2.0)	2 (6.0)	1 (1.0)	1 (2.8)
Toothache	4 (4.0)	4 (12.6)	0	0	1 (1.0)	1 (2.8)
Vitamin D deficiency	1 (1.0)	1 (3.1)	2 (2.0)	2 (6.0)	1 (1.0)	1 (2.8)
Vomiting	1 (1.0)	1 (3.1)	3 (3.0)	3 (9.1)	1 (1.0)	1 (2.8)
Abdominal pain upper	2 (2.0)	2 (6.3)	0	0	0	0
Asthma	2 (2.0)	2 (6.3)	0	0	0	0
Dermal cyst	2 (2.0)	2 (6.3)	1 (1.0)	1 (3.0)	0	0
Dermatitis contact	2 (2.0)	2 (6.3)	3 (3.0)	3 (9.1)	0	0
Dizziness	1 (1.0)	1 (3.1)	2 (2.0)	2 (6.0)	0	0
Erythema	0	0	2 (2.0)	2 (6.0)	0	0
Lower respiratory tract infection	1 (1.0)	1 (3.1)	2 (2.0)	2 (6.0)	0	0
Muscle spasms	2 (2.0)	2 (6.3)	0	0	0	0

eow = every other week; ew = every week; PT = preferred term; PYs = patient years; TEAE = treatment-emergent adverse event

Note: TEAE is defined as any adverse event with an onset date on or after the first dose of study drug in Period A and up to the last dose of study drug in Period A + 70 days or the first dose of study drug in Period B, whichever is earlier.

Table 10. TEAEs Reported in ≥ 2% of Subjects in Order of Decreasing Frequency for Studies M10-467, M11-810, M11-313, and M12-555 Through 29 April 2014 (All Adalimumab Analysis Set)

	Adalimumab	
MedDRA PT	**(N = 727) n (%)**	**(PYs = 635.7) Events (E/100 PYs)**
Any TEAE	572 (78.7)	2975 (468.0)
Hidradenitis	153 (21.0)	215 (33.8)
Nasopharyngitis	104 (14.3)	151 (23.8)
Headache	97 (13.3)	175 (27.5)
Upper respiratory tract infection	77 (10.6)	103 (16.2)
Nausea	38 (5.2)	42 (6.6)
Urinary tract infection	37 (5.1)	43 (6.8)
Arthralgia	36 (5.0)	40 (6.3)
Diarrhoea	35 (4.8)	38 (6.0)
Influenza	34 (4.7)	43 (6.8)
Back pain	31 (4.3)	35 (5.5)
Fatigue	31 (4.3)	35 (5.5)
Pyrexia	30 (4.1)	42 (6.6)
Sinusitis	30 (4.1)	35 (5.5)
Cough	27 (3.7)	29 (4.6)
Oropharyngeal pain	25 (3.4)	32 (5.0)
Dizziness	23 (3.2)	29 (4.6)
Vomiting	23 (3.2)	23 (3.6)
Bronchitis	22 (3.0)	25 (3.9)
Folliculitis	21 (2.9)	25 (3.9)
Hypertension	21 (2.9)	22 (3.5)
Anaemia	19 (2.6)	22 (3.5)
Gastroenteritis	19 (2.6)	26 (4.1)
Pruritus	19 (2.6)	21 (3.3)
Cellulitis	18 (2.5)	20 (3.1)
Injection site erythema	18 (2.5)	35 (5.5)
Myalgia	17 (2.3)	19 (3.0)
Tonsillitis	15 (2.1)	17 (2.7)
Toothache	15 (2.1)	18 (2.8)

MedDRA = Medical Dictionary of Regulatory Activities; PT = preferred term; PYs = patient years; TEAE = treatment-emergent adverse event

Note: TEAE is defined as any adverse event with an onset date on or after the first adalimumab dose and up to 70 days after the last dose of adalimumab. The last available dose date prior to 29 April 2014 is used if a subject is still ongoing in Study M12-555. AEs with an onset date more than 70 days during a protocol-defined placebo gap or during a gap between studies are excluded.

AESI (Adverse Events of Special Interest)

In the *Placebo-Controlled Analysis Set*, the most frequently reported AESI in both the adalimumab total and placebo groups were injection site reaction, allergic reaction (most were events of urticaria and pruritus generalized; 1 event of drug sensitivity), and hematologic disorder (most events were anemia; 2 events of neutropenia were reported by subjects receiving placebo).

Two subjects in the adalimumab total group had events of infection (infection and pyelonephritis) that were serious and considered by the investigator as at least possibly related to study drug; no subjects in the placebo group reported serious infection at least possibly related to study drug.

Two subjects in the placebo group reported worsening or new onset of psoriasis, as compared to no subjects in the adalimumab total group.

Table 11. Overview of Number and Percentage of Subjects with Treatment-Emergent AESI for Studies M10-467, M11-810, and M11-313 (Placebo-Controlled Analysis Set)

	Placebo		Adalimumab					
Category	(N = 366) n (%)	(PYs = 85.8) Events (E/100 PYs)	eow (N = 52) n (%)	(PYs = 16.1) Events (E/100 PYs)	ew (N = 367) n (%)	(PYs = 87.1) Events (E/100 PYs)	Total (N = 419) n (%)	(PYs = 103.2) Events (E/100 PYs)
Any diverticulitis	1 (0.3)	1 (1.2)	0	0	1 (0.3)	1 (1.1)	1 (0.2)	1 (1.0)
Any oral candidiasis	1 (0.3)	1 (1.2)	0	0	0	0	0	0
Any malignancy	1 (0.3)	1 (1.2)	0	0	1 (0.3)	1 (1.1)	1 (0.2)	1 (1.0)
Any allergic reaction including angioedema/anaphylaxis	3 (0.8)	3 (3.5)	1 (1.9)	1 (6.2)	6 (1.6)	13 (14.9)	7 (1.7)	14 (13.6)
Any vasculitis	1 (0.3)	1 (1.2)	0	0	0	0	0	0
Any non-cutaneous vasculitis	1 (0.3)	1 (1.2)	0	0	0	0	0	0
Any worsening/new onset of psoriasis	2 (0.5)	2 (2.3)	0	0	0	0	0	0
Any hematologic disorder including pancytopenia	5 (1.4)	6 (7.0)	0	0	3 (0.8)	3 (3.4)	3 (0.7)	3 (2.9)
Any liver failure and other liver event	0	0	0	0	1 (0.3)	1 (1.1)	1 (0.2)	1 (1.0)
Any injection site reaction	10 (2.7)	14 (16.3)	1 (1.9)	1 (6.2)	18 (4.9)	35 (40.2)	19 (4.5)	36 (34.9)

AE = adverse event; AESI = adverse event of special interest; eow = every other week; ew = every week; PYs = patient years; TEAE = treatment-emergent adverse event
Note: TEAE is defined as any adverse event with an onset date on or after the first dose of study drug in Period A and up to the last dose of study drug in Period A + 70 days or the first dose of study drug in Period B, whichever is earlier. AEs with unknown severity are counted as severe. AEs with unknown relationship to study drug are counted as study drug-related.

In the *Maintenance Analysis Set*, the most frequently reported AESI were allergic reaction (1 event of drug hypersensitivity), hematologic disorder (anemia), and worsening/new onset psoriasis. Three subjects in the adalimumab ew/eow group, 1 subject in the adalimumab ew/ew and 2 subjects in the adalimumab ew/placebo group reported allergic reaction related AEs.

Three subjects in the adalimumab ew/ew group, 1 subject in the adalimumab ew/eow, and 1 subject in the adalimumab ew/placebo group reported worsening or new onset of psoriasis.

Of the subjects who reported AESI that were serious and considered by the investigator as at least possibly related to study drug, 1 subject in the adalimumab ew/ew group reported a treatment-emergent serious infection (severe pneumonia). In addition, 1 subject in the adalimumab ew/eow group experienced a malignancy (squamous cell carcinoma located on the right nasal slope).

Table 67. Overview of Number and Percentage of Subjects with Treatment-Emergent AESI for Studies M11-810 and M11-313 (Maintenance Analysis Set)

	Adalimumab					
Category	ew/placebo (N = 100) n (%)	(PYs = 31.8) Events (E/100 PYs)	ew/eow (N = 101) n (%)	(PYs = 33.1) Events (E/100 PYs)	ew/ew (N = 99) n (%)	(PYs = 35.4) Events (E/100 PYs)
Any parasitic infection	0	0	0	0	1 (1.0)	1 (2.8)
Any malignancy	0	0	1 (1.0)	1 (3.0)	0	0
Any allergic reaction including angioedema/anaphylaxis	2 (2.0)	2 (6.3)	3 (3.0)	3 (9.1)	1 (1.0)	1 (2.8)
Any lupus-like reactions and SLE	1 (1.0)	1 (3.1)	0	0	0	0
Any MI	0	0	1 (1.0)	1 (3.0)	0	0
Any CHF	0	0	1 (1.0)	1 (3.0)	0	0
Any worsening/new onset of psoriasis	1 (1.0)	1 (3.1)	1 (1.0)	1 (3.0)	3 (3.0)	3 (8.5)
Any hematologic disorders including pancytopenia	2 (2.0)	2 (6.3)	1 (1.0)	2 (6.0)	2 (2.0)	2 (5.6)
Any injection site reaction	1 (1.0)	1 (3.1)	1 (1.0)	1 (3.0)	1 (1.0)	1 (2.8)

AE = adverse event; AESI = adverse event of special interest; eow = every other week; ew = every week; PYs = patient years; TEAE = treatment-emergent adverse event
a As assessed by investigator.
Note: TEAE is defined as any adverse event with an onset date on or after the first dose of study drug in Period A and up to the last dose of study drug in Period A + 70 days or the first dose of study drug in Period B, whichever is earlier. AEs with unknown severity are counted as severe. AEs with unknown relationship to study drug are counted as study drug-related.

In the *All Adalimumab Analysis Set*, the most frequently reported AESI were injection site reaction, allergic reaction (1 event of drug hypersensitivity), worsening/new onset psoriasis, and hematologic disorders (mainly anemia; 2 subjects each reported events of neutropenia and lymphopenia). All other AESI were reported in <1% of subjects each.

Table 68. Overview of Number and Percentage of Subjects with Treatment-Emergent AESI for Studies M10-467, M11-810, M11-313, and M12-555 Through 29 April 2014 (All Adalimumab Analysis Set)

	Adalimumab	
Category	(N = 727) n (%)	(PYs = 635.7) Events (E/100 PYs)
Any diverticulitis	2 (0.3)	2 (0.3)
Any oral candidiasis	3 (0.4)	3 (0.5)
Any latent TB	3 (0.4)	3 (0.5)
Any parasitic infection	3 (0.4)	3 (0.5)
Any malignancy	5 (0.7)	5 (0.8)
Any allergic reaction including angioedema/anaphylaxis	27 (3.7)	35 (5.5)
Any lupus-like reactions and SLE	1 (0.1)	1 (0.2)
Any MI	1 (0.1)	1 (0.2)
Any CVA	2 (0.3)	2 (0.3)
Any CHF	3 (0.4)	3 (0.5)
Any pulmonary embolism	1 (0.1)	1 (0.2)
Any ILD	1 (0.1)	1 (0.2)
Any erythema multiforme	1 (0.1)	1 (0.2)
Any worsening/new onset of psoriasis	23 (3.2)	27 (4.2)
Any hematologic disorders including pancytopenia	22 (3.0)	26 (4.1)
Any liver failure and other liver event	3 (0.4)	3 (0.5)
Any injection site reaction	54 (7.4)	107 (16.8)

AESI = adverse event of special interest; CHF = congestive heart failure; CVA = cerebrovascular accident; ILD = interstitial lung disease; MI = myocardial infarction; PYs = patient years; SLE = systemic lupus erythematosus; TB = tuberculosis

Note: Treatment-emergent AESI is defined as any adverse event of special interest with an onset date on or after the first adalimumab dose and up to 70 days after the last dose of adalimumab. The last available dose date prior to 29 April 2014 is used if a subject is still ongoing in Study M12-555. AESI with an onset date more than 70 days during a protocol-defined placebo gap or during a gap between studies are excluded.

Subjects who reported AESI that were serious and considered by the investigator as at least possibly related to study drug included 10 subjects who reported serious infections (purulent discharge/rash pustular, cellulitis, pneumonia chlamydial, pneumonia, septic shock, pyelonephritis, infection, sepsis, pneumonia viral) and 1 subject each who reported events of malignancy (seminoma), acute MI, pustular psoriasis, and anaemia.

No subjects reported events in the following AESI categories: legionella infection, active TB, reactivation of hepatitis B, PML, HSTCL, melanoma, leukaemia, vasculitis (cutaneous and non-cutaneous), sarcoidosis, intestinal perforation, Stevens-Johnson syndrome, ALS, RPLS, and adalimumab administration-related medication errors.

Infections

In the *Placebo-Controlled Analysis Set*, 28% and 31% of subjects in the adalimumab total and placebo groups, respectively, reported treatment-emergent infections. Overall, the most frequently reported treatment-emergent infections were nasopharyngitis, upper respiratory tract infection, urinary tract infection, and bronchitis. Of the subjects who reported treatment-emergent infections, 40% in both the adalimumab total group and the placebo group reported events that were considered at least possibly related to study drug. Of the subjects who reported treatment-emergent infections, 8 of 118 subjects

(6.8%) in the adalimumab total group and 7 of 114 subjects (6.1%) in the placebo group reported severe events.

In the *Maintenance Analysis Set*, 32% of subjects in the adalimumab ew/ew group, 31% of subjects in the adalimumab ew/eow group, and 29% of subjects in the adalimumab ew/placebo group reported treatment-emergent infections. Of the subjects who reported treatment emergent infections, 12 of 32 subjects (37.5%) in the adalimumab ew/ew group, 7 of 31 subjects (22.6%) in the adalimumab ew/eow group, and 11 of 29 subjects (37.9%) in the adalimumab ew/placebo group reported events that were considered at least possibly related to study drug. Three subjects in the adalimumab ew/ew group reported severe treatment-emergent infections (nasopharyngitis, otitis externa, and pneumonia). No subjects in the two other groups reported severe treatment emergent infections.

In the *All Adalimumab ew Analysis Set*, 47% of subjects reported treatment-emergent infections; 134 of 324 subjects (41.4%) reported events that were considered at least possibly related to study drug and 24 of 324 subjects (7.4%) reported severe infections.

In the *All Adalimumab Analysis Set*, 52% of subjects reported treatment-emergent infections, the most frequent being nasopharyngitis, upper respiratory tract infection, and urinary tract infection. 158 of 377 subjects (42%) reported events that were considered at least possibly related to study drug and 27 of 377 subjects (7.2%) reported severe events.

Serious Infections

In the *Placebo-Controlled Analysis Set*, 1.9% of subjects in the adalimumab eow group, 0.8% of subjects in the adalimumab ew group, 1.0% of subjects in the adalimumab total group, and 0.5% of subjects in the placebo group reported treatment-emergent serious infections. Serious infections considered at least possibly related to study drug were reported in 2 subjects in the adalimumab total group. Serious treatment-emergent infections that were also severe included infection, pilonidal cyst, and pyelonephritis in the adalimumab total group and gastroenteritis and viral infection in the placebo group.

In the *Maintenance Analysis Set*, 1 subject in the adalimumab ew/ew group reported a treatment-emergent serious infection that was also severe (pneumonia) and which was considered by the investigator as probably related to study drug. The pneumonia led to interruption of study drug.

In the *All Adalimumab Analysis Set*, 2.9% of subjects reported treatment-emergent serious infections. 10 of 21 subjects (48%) reported events that were considered at least possibly related to study drug and 18 of 21 subjects (86%) reported severe events.

Skin and Soft Tissue Serious Infections

Events of serious infection were adjudicated post-hoc (after blind break) to identify which were potentially skin and soft tissue infections (SSTIs). SSTIs were defined as microbial invasion of the epidermis, dermis, and/or subcutaneous tissues accompanied by signs and symptoms of inflammation. These SAEs included all SAEs of hidradenitis because they were reported as serious infections. Medical history potentially relevant to the development of the SSTI (i.e., history of other conditions associated with increased risk of infection or history of previously documented skin infections) was noted.

Events were adjudicated as SSTIs based on clinical judgement, e.g. related to findings like rapid onset of symptoms, presence of systemic manifestations of infection (e.g. fever and chills), the culture of a predominant pathogenic organism from purulent drainage or blood, laboratory data (leukocytosis, bandemia, rises in C-reactive protein and erythrocyte sedimentation rate) and clear improvement with antibacterial treatment. For areas of skin not affected by underlying HS disease, new onset of localized warmth, erythema, and tenderness of the skin also was considered as suggestive of infection. Since the adjudications were done retrospectively, limitations exist in regards to varying levels of event detail as well as inherent challenges in assessing the role of infection in the context of baseline inflammation in the case of areas of skin affected by HS.

In the *Placebo-Controlled Analysis Set*, 12 SAEs were reviewed, 8 of which were adjudicated as SSTIs. One SAE was adjudicated as not being a SSTI and, for 3 SAEs (all occurred in subjects receiving placebo), there was insufficient information to adjudicate the events. The SAEs that were determined to be SSTIs included 1 event each of *Escherichia* infection and genital infection bacterial in the same subject who had a history of infection and who was receiving adalimumab; 1 event of pilonidal cyst in a subject with a history of pilonidal cyst and who was receiving adalimumab; and 5 events of hidradenitis, 1 of which occurred in a subject who had a history of diabetes. Three SAEs of hidradenitis occurred in 2 subjects receiving placebo and 2 SAEs of hidradenitis occurred in 2 subjects receiving adalimumab. One of the subjects receiving adalimumab discontinued from study drug because of the event of hidradenitis. All events of hidradenitis, except 1, were reported to have resolved; the outcome of the 1 other event is unknown.

In the *All Adalimumab Analysis Set*, 41 SAEs were reviewed, 30 of which were adjudicated as SSTIs, in 23 subjects (3.2%). Six SAEs (*Escherichia* infection, genital infection bacterial, penile swelling, scrotal swelling, purulent discharge, and rash pustular) occurred in the same subject who had a history of infection.

Thirteen of the SAEs that were determined to be SSTIs were events of hidradenitis, 2 of which occurred in subjects receiving placebo and 11 of which occurred while the subject was receiving adalimumab (4 of these subjects discontinued from study drug because of the event). Of the 2 subjects receiving placebo at the time of the SAE, 1 subject who was initially randomized to adalimumab ew experienced an event following re-randomization to placebo (34 days after the last dose of adalimumab) that led to study discontinuation and 1 subject experienced an event while receiving adalimumab ew and then experienced another event following re-randomization to placebo (63 days after the last dose of adalimumab). All of the events of hidradenitis were reported as resolved, except 1, which was ongoing as of the cut-off date for the analyses. Ten of the 23 subjects with SSTIs had an underlying medical history that may have contributed to the development of the serious infection. Of the 12 subjects with events of hidradenitis, 3 subjects had a history of diabetes and 2 subjects had a history of pilonidal cyst.

Opportunistic and parasitic infections

In the *All Adalimumab Analysis Set*, a few cases of treatment-emergent opportunistic infections were reported; one case of cutaneous coccidioidomycosis, three cases of oral candidiasis, three cases of latent TB (all mild and nonserious). The event of TB for 1 subject was considered by the investigator as probably related to study drug and study drug was discontinued.

In the *All Adalimumab Analysis Set*, 3 subjects reported treatment-emergent parasitic infections (trichomoniasis, acarodermatitis and bed bug infestation), none of which led to discontinuation.

Malignancies

Five subjects (0.7%) in the *All Adalimumab Analysis Set* reported treatment-emergent malignancies (seminoma, breast cancer Stage III, Hodgkin's disease, squamous cell carcinoma, and benign vocal cord neoplasm. Subjects who reported malignancies had received between 81 and 421 days of adalimumab treatment. The seminoma was considered by the investigator as at least possibly related to study drug and led to discontinuation of study drug. The other 4 events were considered by the investigator as probably not related or not related to study drug.

Allergic Reactions

In the *Placebo-Controlled Analysis Set*, 1.7% and 0.8% of subjects in the adalimumab total and placebo groups, respectively, reported treatment-emergent allergic reactions. Treatment-emergent allergic reactions in 2 subjects in the adalimumab total group (pruritus generalized and urticaria) were mild, considered by the investigator as at least possibly related to study drug, and did not result in discontinuation from study drug. All other reported events were considered by as probably not related or not related. Three subjects in the adalimumab total group reported events of asthma and all events were an exacerbation or worsening of a pre-existing condition.

In the *Maintenance Analysis Set*, 1 subject in the adalimumab ew/ew group, 3 subjects in the adalimumab ew/eow group, and 2 subjects in the adalimumab ew/placebo group reported treatment-emergent allergic reactions.

In the *All Adalimumab Analysis Set*, 3.7% of subjects reported treatment-emergent allergic reactions. Treatment-emergent allergic reactions reported in 9 subjects were considered by the investigator as at least possibly related to study drug; none of the reported events led to study drug discontinuation. Seven subjects reported events of asthma; one of which was considered by the investigator as at least possibly related to study drug.

Overall, no subjects reported serious or severe treatment-emergent allergic reactions.

Lupus-Like Reactions/SLE

In the *All Adalimumab Analysis Set*, 1 subject in the adalimumab ew/placebo/ew population reported a non-serious event of severe treatment-emergent cutaneous lupus erythematosus after the last dose of placebo in Period B of Study M11-810 but before the first dose of adalimumab ew in Study M12-555. The event lasted for more than 56 days and was ongoing as of 29 April 2014. The subject had no history of lupus or lupus-like condition. The event did not lead to discontinuation and the subject subsequently began adalimumab ew treatment in Study M12-555.

Autoimmune Hepatitis

In the *All Adalimumab Analysis Set*, 1 subject had an event of autoimmune hepatitis. The event was considered by the investigator as possibly related to study drug and led to interruption of study drug.

Myocardial Infarction

In the *All Adalimumab Analysis Set*, 1 subject reported a treatment-emergent MI, which occurred 4 days after the last dose of adalimumab eow in Study M11-810. The event was considered by the investigator as possibly related to study drug. This subject also had an event of cardio-respiratory arrest 38 days later, which subsequently led to the subject's death.

Cerebrovascular Accident

In the *All Adalimumab Analysis Set*, 2 subjects reported a treatment-emergent CVA; one non-serious and one serious. The serious event, which led to discontinuation from study drug, occurred 3 days after the last dose of adalimumab ew in Study M12-555 and was considered by the investigator as probably not related to study drug. Results from an MRI conducted at the time of the event showed small vessel ischemia.

Congestive Heart Failure

In the *All Adalimumab Analysis Set*, 3 subjects reported treatment-emergent CHF. All events were considered not related or probably not related to study drug. All 3 subjects had diabetes mellitus and were current smokers. One subject was obese and had a family history of cardiomyopathy.

Pulmonary Embolism and Interstitial Lung Disease

In the *All Adalimumab Analysis Set*, 1 subject reported a treatment-emergent pulmonary embolism, which occurred 11 days after the last dose of adalimumab ew in Study M12-555. The same subject also reported a non-serious treatment-emergent Interstitial Lung Disease. The events were considered as not related to study drug and did not lead to discontinuation of study drug.

Pancreatitis

One subject had a serious event of severe autoimmune pancreatitis with fatal outcome. The event was considered by the investigator as not related to study drug.

Erythema Multiforme

In the *All Adalimumab Analysis Set*, 1 subject reported a non-serious, mild event of treatment-emergent erythema multiforme while receiving adalimumab ew, that led to discontinuation from study drug. The event was considered by the investigator as probably related to study drug.

Worsening/New Onset Psoriasis

In the *Placebo-Controlled Analysis Set*, 2 subjects (0.5%; both worsening of psoriasis) in the placebo group and no subjects in the adalimumab total group reported events of psoriasis.

In the *Maintenance Analysis Set*, 3 subjects in the adalimumab ew/ew group and 1 subject each in the adalimumab ew/eow and ew/placebo groups reported treatment-emergent worsening/new onset psoriasis. Four of these events were considered at least possibly related to study drug and one event was considered not related. No subjects reported serious or severe treatment-emergent worsening/new onset psoriasis; 1 of the events (adalimumab ew/placebo group) led to study drug discontinuation.

In the *All Adalimumab Analysis Set*, 23 subjects (3.2%) reported events of psoriasis. The incidence rate was 4.2 E/100 PYs, which was similar to the rate reported for adalimumab ew across other indications of CD, RA and Ps (4.1 E/100 PY). Treatment-emergent worsening/new onset psoriasis in 19 subjects was considered by the investigator as at least possibly related to study drug; 11 of these subjects discontinued study drug due to the events. Of the subjects who reported treatment-emergent worsening/new onset psoriasis, 6 had a prior history of psoriasis. Four subjects reported events that were severe while receiving adalimumab ew treatment; 1 of the reported events, which occurred during Study M12-555, was also serious (pustular psoriasis).Each of these subjects discontinued study drug due to the events. Follow-up for reports of psoriasis in the HS clinical development program included assessment of the specific type of psoriasis (i.e., plaque, guttate, or pustular) and the location of the psoriasis.

Table 69. Treatment-Emergent Worsening/New Onset Psoriasis Reported for Studies M10-467, M11-810, M11-313, and M12-555 Through 29 April 2014 (All Adalimumab Analysis Set)

MedDRA PT	Adalimumab (N = 727) n (%)
Any treatment-emergent worsening/new onset psoriasis	23 (3.2)
Psoriasis	10 (1.4)
Pustular psoriasis	6 (0.8)
Dermatitis psoriasiform	5 (0.7)
Guttate psoriasis	2 (0.3)

AESI = adverse event of special interest; MedDRA = Medical Dictionary of Regulatory Activities; PT = preferred term

Note: Treatment-emergent AESI is defined as any adverse event of special interest with an onset date on or after the first adalimumab dose and up to 70 days after the last dose of adalimumab. The last available dose date prior to 29 April 20 is used if a subject is still ongoing in Study M12-555. AESIs with an onset date more than 70 days during a protocol-defined placebo gap or during a gap between studies are excluded.

In the Humira SmPC, worsening or new onset of psoriasis (including palmoplantar pustular psoriasis) are included as common ADRs. However, pustular psoriasis (generalised) is currently not included. Brief narratives of the events of pustular psoriasis are provided below:

Study M11-810:

- The first subject was a 26-year-old black, very obese, smoking female who was randomized to the placebo/ew treatment group in Period B, and experienced severe pustular psoriasis on Day 183. The subject had a history of plaque psoriasis and was symptomatic at study entry. A biopsy showed

suppurative folliculitis. The subject was treated with medication and discontinued study drug. The event of pustular psoriasis was ongoing as of Day 198.

- The other was a 26-year-old black female randomized to the placebo/ew treatment group in Period B, who experienced moderate pustular psoriasis on Day 183. The subject did not have a history of psoriasis. A biopsy showed folliculitis. This subjects was also obese and a past smoker. The subject was treated with medication and discontinued study drug. The event of pustular psoriasis was ongoing as of Day 167.

The investigator did not consider either of the events to be serious, but both were considered probably related to study drug. Both subjects were prematurely discontinued from the study.

Study M12-555:

- *Serious event:* This subject was a 41-year-old female in the PBO/PBO/EW Population, who had an event of severe pustular psoriasis (reported term: pustular psoriasis scalp and palms) on Day 162, 14 days after the first dose of open-label adalimumab. Study drug was interrupted and the subject received treatment. The event persisted until an SAE of severe pustular psoriasis (reported term: exacerbation of pustular psoriasis) was reported on Day 241, and study drug was discontinued. The event resolved in 8 days. The investigator considered both events to be probably related to study drug. The subject had no history of psoriasis.
- *Severe event:* This subject was a 31-year-old female in the EW/EW/EW Population, who had a severe, non-serious event of pustular psoriasis (reported term: new onset of pustular psoriasis palmar/plantar) on Day 287 (Day 36 of Study M12-555). Study drug was discontinued, and the event was ongoing as of Day 399. The event was considered possibly related to study drug.
- *1 discontinuation due to a pustular psoriasis AE:* This was a 37-year-old female in the PBO/EW/EW Population, who had a moderate event of pustular psoriasis (reported term: pustular psoriasis, bilateral palms and soles) on Day 266 (Day 13 of Study M12-555). The investigator considered the event to be probably related to study drug.

None of these 3 subjects had a history of psoriasis.

Study M10-467:

This was a 44-year-old white male with no history of Ps, who reported treatment-emergent pustular Ps on Day 246, 134 days after switching from ew adalimumab to eow adalimumab. The event was non-serious, mild in severity, and considered by the investigator as possibly related to study drug. The subject prematurely discontinued from the study as a result of this TEAE. As of Day 302 the event was ongoing.

Hematologic Disorders

In the *Placebo-Controlled Analysis Set*, 3 subjects (0.7%) and 5 subjects (1.4%) in the adalimumab total and placebo groups, respectively, reported treatment-emergent hematologic disorders. The events in the adalimumab group were considered as probably not related or not related to study drug. Two subjects reported events that were serious and 2 reported events that were severe; 1 subject had an interruption of study drug because of the event.

In the *Maintenance Analysis Set*, 2 subjects each in the adalimumab ew/placebo and adalimumab ew/ew groups and 1 subject in the adalimumab ew/eow group reported treatment-emergent hematologic reactions (anemia); no subjects reported neutropenia. No events were serious or severe and none led to discontinuation of study drug.

In the *All Adalimumab Analysis Set*, 22 subjects (3.0%) reported treatment-emergent hematologic disorders; the majority of these subjects reported events of anemia. Six subjects reported events that were considered by the investigator as at least possibly related to study drug. Two subjects reported 3 serious events of anemia. Two events reported by 1 of the subjects were considered as possibly related to study drug and led to study drug discontinuation and 1 event reported by the second subject was considered as probably not related to study drug. One subject reported a severe event of anemia.

Liver Failure and Other Liver Events

No events of liver failure were reported. In the All Adalimumab Analysis Set, 3 subjects reported treatment-emergent other liver events; all were non-serious. Two of these subjects, who had a severe event of hepatic steatosis and a moderate event of autoimmune hepatitis, were receiving adalimumab ew in Study M12-555 at the time of the event One of these subjects also had hypercholesterolemia. These events were considered as at least possibly related to study drug and led to interruption of study drug. The subject with autoimmune hepatitis is also discussed above under the category of "Autoimmune Hepatitis". The third subject had an event of drug-induced liver injury while receiving adalimumab ew during Period A of Study M11-810. This event was considered by the investigator as not related to study drug. The subject had been receiving isoniazid for treatment of TB at the time of the event, which was then discontinued.

Injection Site Reactions

In the *Placebo-Controlled Analysis Set*, 19 subjects (4.5%) and 10 subjects (2.7%) in the adalimumab total and placebo groups, respectively, reported treatment-emergent injection site reactions. Of the subjects who reported treatment-emergent injection site reactions, 95% in the adalimumab total group and 100% in the placebo group reported events that were considered at least possibly related to study drug. No subjects reported injection site reactions that were serious or severe; none of the events led to discontinuation.

In the *All Adalimumab Analysis Set*, 54 subjects (7.4%) reported treatment-emergent injection site reactions. Of these, 94% were considered by the investigator as at least possibly related to study drug. No subjects reported treatment-emergent injection site reactions that were serious or severe; none of the events led to discontinuation

Comparison with other indications

The MAH presented data from five studies in the MAH's adalimumab clinical trials database (two studies in CD, one in RA, and two studies in psoriasis) that directly compared adalimumab 40 mg eow and adalimumab 40 mg ew dosing in a blinded, controlled fashion. The overall incidence of AESI in the HS clinical development program was consistent with previous studies in approved adalimumab indications.

A review of the safety data across the 5 studies overall revealed no consistent differences between the safety profile of adalimumab eow and ew dosing. The rate of adverse events in the adalimumab ew dosing group was similar to the eow dosing group for all studies, except in one of the psoriasis studies. In Study M02-528, there were more subjects in the ew dosing group with any SAE, any AE probably or possibly related to study drug, infectious non-serious AEs, and injection site reaction AEs. These results were based on 12 weeks of dosing and all of these trends (except for "any AE probably or possibly related to study drug") were not observed in the follow-up study, Study M02-529, during which subjects received up to 48 weeks of dosing. Overall, across all 5 of the studies examined, there was no clear trend of specific AEs occurring at a greater frequency with ew dosing than eow dosing.

Table 70. Clinical Trials Comparing Adalimumab 40 mg eow and ew Dosing

Study	Title	Indication	Length of Dosing	Adalimumab Doses	Number of Patients (By Dose Group)
DE011	A multicenter, randomized, placebo-controlled Phase 3 study comparing 2 doses and 2 dosing intervals of the fully human anti-TNF antibody, D2E7, versus placebo administered over 6 months as SC injections in patients with RA	RA	26 weeks	20 mg eow 20 mg ew 40 mg eow 40 mg ew	Placebo, N = 110 20 mg eow, N = 106 20 mg ew, N = 112 40 mg eow, N = 113 40 mg ew, N = 103
M02-404	A multicenter, randomized, DB, placebo-controlled study of the human anti-TNF monoclonal antibody adalimumab for the induction and maintenance of clinical remission in subjects with Crohn's disease	Crohn's disease	52 weeks	40 mg eow 40 mg ew	Placebo, N = 261 40 mg eow, N = 260 40 mg ew, N = 257
M02-433	A multicenter, randomized, DB, placebo-controlled study of the human anti-TNF monoclonal antibody adalimumab for the maintenance of clinical remission in subjects with Crohn's disease (OLE)	Crohn's disease	4 weeks; randomized 56+ weeks (OLE)	40 mg eow 40 mg ew	Remitters: N = 55 (placebo, N = 18, adalimumab 40 mg eow, N = 19 adalimumab 40 mg ew, N = 18) Non-remitters: N = 221 (adalimumab 40 mg eow)
M02-528	A Phase 2 multicenter study of the safety and efficacy of adalimumab (D2E7) in subjects with moderate to severe chronic plaque psoriasis	Psoriasis	12 weeks	40 mg eow 40 mg ew	Placebo, N = 52 40 mg eow, N = 45 40 mg ew, N = 50

DB = double-blind; eow = every other week; ew = every week; OLE = open-label extension; RA = rheumatoid arthritis; SC = subcutaneous; TNF = tumor necrosis factor

Table 12. Overview of TEAEs per 100 Patient Years (All Placebo-Controlled Studies with eow and ew Dosing)

Category	Placebo (N = 441) (PYs = 150.9) Events (E/100 PYs)	Adalimumab eow (N = 437) (PYs = 215.2) Events (E/100 PYs)	Adalimumab ew (N = 428) (PYs = 221.1) Events (E/100 PYs)
Any AE	2030 (1345.3)	2487 (1155.7)	2432 (1100.0)
Any SAE	75 (49.7)	49 (22.8)	57 (25.8)
Any AE leading to discontinuation of study drug	41 (27.2)	38 (17.7)	27 (12.2)
Any severe AE	143 (94.8)	103 (47.9)	94 (42.5)
Any AE related to study drug	387 (256.5)	618 (287.2)	546 (246.9)
Any AE leading to death	3 (2.0)	2 (0.9)	1 (0.5)
Any infection	238 (157.7)	337 (156.6)	332 (150.2)
Any serious infection	10 (6.6)	9 (4.2)	10 (4.5)
Any opportunistic infection (excluding oral candidiasis and TB)	2 (1.3)	0	1 (0.5)
Any TB (active or latent)	0	0	0
Any parasitic infection	0	0	0
Any malignancy	0	0	0
Any lymphoma	0	0	0
Any NMSC	1 (0.7)	2 (0.9)	0
Any malignancy (excluding lymphoma, HSTCL, leukemia, NMSC, and melanoma)	1 (0.7)	1 (0.5)	2 (0.9)
Any allergic reaction, including angioedema/anaphylaxis	11 (7.3)	28 (13.0)	23 (10.4)
Any vasculitis	1 (0.7)	2 (0.9)	0
Any cutaneous vasculitis	0	0	0
Any noncutaneous vasculitis	1 (0.7)	2 (0.9)	0
Any MI	0	1 (0.5)	0
Any CHF	2 (1.3)	0	0
Any pulmonary embolism	0	0	1 (0.5)
Any pancreatitis	1 (0.7)	0	0
Any erythema multiforme	1 (0.7)	0	0
Any worsening/new onset of psoriasis	4 (2.7)	5 (2.3)	9 (4.1)
Any hematological disorders, including pancytopenia	11 (7.3)	12 (5.6)	9 (4.1)
Any liver failure and other liver events	1 (0.7)	1 (0.5)	0
Any injection site reaction	45 (29.8)	115 (53.4)	136 (61.5)

eow = every other week; ew = every week; CHF = congestive heart failure; HSTCL = hepatosplenic T-cell lymphoma; MI = myocardial infaction; NMSC = nonmelanoma skin cancer; PT = preferred term; PYs = patient years; AE = adverse event; SAE = serious adverse event; TB = tuberculosis; TEAE = treatment-emergent adverse event

Serious adverse event / deaths / other significant events

Serious adverse events

In the *Placebo-Controlled Analysis Set*, TESAEs were reported in 3.1% of subjects in the adalimumab total group and 3.6% of subjects in the placebo group (

Table 72). TESAEs considered by the investigator as at least possibly related to study drug were reported in 1.0% of subjects in the adalimumab total group and 0.5% of subjects in the placebo group. All TESAEs considered by the investigator as at least possibly related to study drug were reported by 1 subject each in the adalimumab total and placebo groups.

In the *Maintenance Analysis Set*, TESAEs considered by the investigator as at least possibly related to study drug were lymphadenitis and acute MI in the adalimumab ew/eow group (1 subject each) and pneumonia and rash in the adalimumab ew/ew group (1 subject each). No TESAEs at least possibly related to study drug were reported in the adalimumab ew/placebo group.

In the *All Adalimumab ew Analysis Set*, all TESAE considered by the investigator as at least possibly related to study drug were reported by 1 subject each, with the exception of pneumonia, which was reported by 2 subjects.

In the *All Adalimumab Analysis Set*, 10.7% of subjects reported TESAEs (**Table 73**). The following TESAEs were reported in ≥ 2 subjects each: anemia, cellulitis, ectopic pregnancy, hidradenitis, non-cardiac chest pain, palpitations, pilonidal cyst, pneumonia, postoperative wound infection, sepsis, and septic shock. All

other TESAEs were reported in 1 subject each. A total of 2.8% of subjects reported TESAEs that were considered by the investigator as at least possibly related to study drug. Of these, pneumonia was reported in 2 subjects.

Table 13. Number and Percentage of Subjects Who Reported TESAEs for Studies M10-467, M11-810, and M11-313 (Placebo-Controlled Analysis Set)

	n (%)			
		Adalimumab		
MedDRA PT	Placebo (N = 366)	eow (N = 52)	ew (N = 367)	Total (N = 419)
Any TESAE	13 (3.6)	3 (5.8)	10 (2.7)	13 (3.1)
Hidradenitis	5 (1.4)	1 (1.9)	1 (0.3)	2 (0.5)
Anemia	1 (0.3)	0	1 (0.3)	1 (0.2)
Chronic obstructive pulmonary disease	0	0	1 (0.3)	1 (0.2)
Escherichia infection	0	0	1 (0.3)	1 (0.2)
Genital infection bacterial	0	0	1 (0.3)	1 (0.2)
Infection	0	0	1 (0.3)	1 (0.2)
Interstitial lung disease	0	1 (1.9)	0	1 (0.2)
Non-cardiac chest pain	0	0	1 (0.3)	1 (0.2)
Pilonidal cyst	0	1 (1.9)	0	1 (0.2)
Pyelonephritis	0	0	1 (0.3)	1 (0.2)
Renal failure acute	0	0	1 (0.3)	1 (0.2)
Sexual abuse	0	0	1 (0.3)	1 (0.2)
Tendon rupture	0	0	1 (0.3)	1 (0.2)
Vocal cord neoplasm[a]	0	0	1 (0.3)	1 (0.2)
Accidental overdose	1 (0.3)	0	0	0
Diabetes mellitus inadequate control	1 (0.3)	0	0	0
Dizziness	1 (0.3)	0	0	0
Effusion	1 (0.3)	0	0	0
Fatigue	1 (0.3)	0	0	0
Gastroenteritis	1 (0.3)	0	0	0
International normalized ratio increased	1 (0.3)	0	0	0
Intervertebral disc calcification	1 (0.3)	0	0	0
Invasive ductal breast carcinoma	1 (0.3)	0	0	0
Presyncope	1 (0.3)	0	0	0
Small intestinal obstruction	1 (0.3)	0	0	0
Suicide attempt	2 (0.5)	0	0	0
Tendonitis	1 (0.3)	0	0	0
Viral infection	1 (0.3)	0	0	0

eow = every other week; ew = every week; MedDRA = Medical Dictionary of Regulatory Activities;

PT = preferred term; TEAE = treatment-emergent adverse event; TESAE = treatment-emergent serious adverse event

a determined to be benign.

Note: TEAE is defined as any adverse event with an onset date on or after the first dose of study drug in Period A and up to the last dose of study drug in Period A + 70 days or the first dose of study drug in Period B, whichever is earlier. Any AE with an unknown relationship was considered as study drug-related and any AE with an unknown severity was considered as severe.

Table 14. TESAEs Reported by at Least 2 Subjects for Studies M10-467, M11-810, M11-313, and M12-555 Through 29 April 2014 (All Adalimumab Analysis Set)

MedDRA PT	Adalimumab (N = 727) n (%)
Any TESAE	78 (10.7)
Hidradenitis	22 (3.0)
Cellulitis	3 (0.4)
Anaemia	2 (0.3)
Ectopic pregnancy	2 (0.3)
Non-cardiac chest pain	2 (0.3)
Palpitations	2 (0.3)
Pilonidal cyst	2 (0.3)
Pneumonia	2 (0.3)
Postoperative wound infection	2 (0.3)
Sepsis	2 (0.3)
Septic shock	2 (0.3)

MedDRA = Medical Dictionary of Regulatory Activities; PT = preferred term;

TESAE = treatment-emergent serious adverse event

Note: TEAE is defined as any adverse event with an onset date on or after the first adalimumab dose and up to 70 days after the last dose of adalimumab. The last available dose date prior to 29 April 2014 is used if a subject is still ongoing in Study M12-555. AEs with an onset date more than 70 days during a protocol-defined placebo gap or during a gap between studies are excluded. Any AE with an unknown relationship was considered as study drug-related and any AE with an unknown severity was considered as severe.

Deaths

No deaths were reported during the 12-week placebo-controlled treatment periods.

One subject died in Study M11-810. This was a 35-year-old male in the adalimumab ew/eow group who had an event of cardio-respiratory arrest on Day 234, 42 days after the last dose of study drug (Period B). The investigator considered the event not related to adalimumab, but a result of coronary heart disease. The subject had a prior event of non-ST elevation myocardial infarction on Day 196 and there was a family history of early onset coronary heart disease. Other risk factors included a diagnosis of diabetes mellitus since 2008 and heavy smoking for 16 years.

One subject died in Study M12-555. This was a 62-year-old female in the placebo/placebo/ew group (i.e. received placebo throughout Study M11-810 and then received adalimumab ew in the OLE study) with a history of Hashimoto's thyroiditis, who experienced a fatal AE of autoimmune pancreatitis on Day 214 and cardiac arrest/respiratory failure on Day 241 (30 days after the last dose of adalimumab ew). The investigator considered the event not related to adalimumab. Hashimoto's thyroiditis has been associated with autoimmune pancreatitis (Pezzilli 2005). The cause of death was septic shock that developed after an event of ascending cholangitis due to severe autoimmune pancreatitis.

Laboratory findings

Mean changes in hematology, clinical chemistry and urinalysis values from Baseline to the final visit were not considered to be clinically meaningful in the Placebo-Controlled Analysis Set or the All Adalimumab Analysis Set.

Individual Subject Changes

Hematology

In the *Placebo-Controlled Analysis Set*, shifts in hematology values from normal or high at Baseline to low at the final visit or low or normal at Baseline to high at the final visit were generally infrequent and not considered clinically meaningful for the adalimumab total and placebo groups. A total of 17.5% of subjects in the adalimumab eow group experienced shifts in platelet count from low or normal at Baseline to high at the final visit, which was numerically higher than placebo (4.0% of subjects).

Similarly, in the *All Adalimumab Analysis Set*, shifts in hematology values were generally infrequent and not considered clinically meaningful.

Clinical Chemistry

In the *Placebo-Controlled Analysis Set*, shifts in chemistry values from normal or high at Baseline to low at the final visit or low or normal at Baseline to high at the final visit were generally infrequent and not considered clinically meaningful for most parameters for the adalimumab total and placebo groups. A greater percentage of subjects in the adalimumab total group experienced shifts in cholesterol and triglyceride levels from normal or low at Baseline to high at final, as compared to the placebo group (14% vs. 8% and 11% vs. 7%, respectively). None of these shifts were reported as AEs. Although numerically higher, these shifts were not considered to be clinically meaningful. Few shifts (≤9 of 785 subjects) from normal levels in each of SGPT/ALT, SGOT/AST, alkaline phosphatase and total bilirubin were observed; these shifts were not considered to be clinically meaningful.

In the *All Adalimumab Analysis Set*, shifts in chemistry values were also generally infrequent and not considered clinically meaningful for most parameters. A total of 14% and 11% of subjects experienced shifts in cholesterol and triglyceride levels, respectively, from normal or low at Baseline to high at final. None of these shifts were reported as AEs and they were not considered clinically meaningful. Few shifts (≤ 12 of 727 subjects) from normal levels in each of SGPT/ALT, SGOT/AST, alkaline phosphatase and total bilirubin were observed; these shifts were not considered to be clinically meaningful.

Urinalysis

Shifts in urinalysis values from Baseline to the final visit were generally infrequent and not considered clinically meaningful in the adalimumab total and placebo groups in the Placebo-Controlled Analysis Set and All Adalimumab Analysis Set.

Individual Clinically Significant Abnormalities

Hematology

In the *Placebo-Controlled Analysis Set*, hematology values of CTC Grade ≥2 were observed for hemoglobin (1.8% of subjects) and neutrophils (0.5% of subjects) in the adalimumab total group, and for hemoglobin (1.7% of subjects), WBC count (0.3% of subjects), neutrophils (0.8% of subjects), lymphocytes (0.6% of subjects) in the placebo group. Hematology values of CTC Grade ≥ 3 were observed for hemoglobin in 1 subject in the adalimumab total group and for hemoglobin and neutrophils in 2 subjects each in the placebo group.

In the *All Adalimumab Analysis Set*, hematology values of CTC Grade ≥2 were observed for hemoglobin (3.9% of subjects) and WBC count (0.3% of subjects), neutrophils (1.1% of subjects), lymphocytes (0.7% of subjects), and platelets (0.1% of subjects). Hematology values of CTC Grade ≥3 were observed for hemoglobin (0.8% of subjects) and WBC count (0.1% of subjects), neutrophils (0.4% of subjects), lymphocytes (0.3% of subjects), and platelets (0.1% of subjects).

Based on a medical review, none of the above changes were considered clinically meaningful.

Clinical Chemistry

In the *Placebo-Controlled Analysis Set*, chemistry values of CTC Grade ≥2 occurred in less than 2% of subjects for all measured parameters except hypophosphatemia and hypertriglyceridemia (p= 0.005 vs. placebo) in the adalimumab total group, and hyperglycemia in the adalimumab total and placebo groups. Chemistry values of CTC Grade ≥2 occurred in less than 2% of subjects in the placebo group for all measured

parameters, except hypophosphatemia and hyperglycemia. Chemistry values of CTC Grade ≥ 3 occurred in ≤ 1% of subjects in both the adalimumab total and placebo groups. None of these values were considered clinically meaningful. There was no significant difference among the adalimumab total and placebo groups in the proportion of subjects with CTC Grade ≥ 3 elevations in triglycerides.

Concerning clinically significant liver function values, ALT values ≥3 × ULN were experienced by 3 subjects in the adalimumab total group and 2 subjects in the placebo group. ALT values ≥ 5 × ULN were experienced by 1 subject in the adalimumab total group and 2 subjects in the placebo group. AST values ≥3 × ULN were experienced by 1 subject in the adalimumab total group and 2 subjects in the placebo group. AST values ≥5 × ULN and ≥10 × ULN were experienced by a few subjects in the placebo group. Alkaline phosphatase values ≥1.5 × ULN were experienced by 3 subjects each in the adalimumab total group and placebo group. No subjects experienced total bilirubin ≥2 × ULN.

In the *All Adalimumab Analysis Set*, the most frequently occurring chemistry values of CTC Grade ≥ 2 and ≥ 3 were hypophosphatemia, hyperglycemia, and hypertriglyceridemia. A review of the liver function tests did not reveal any potential signal for severe hepatotoxicity. The incidence of potentially clinically significant liver function values is provided below (N = 727):

- ALT values ≥3 × ULN were experienced by 10 subjects; ALT values ≥ 5 × ULN were experienced by 2 subjects; and ALT values ≥ 10 × ULN were experienced by 1 subject.
    - One subject had a non-serious event of severe hepatic steatosis on Day 85 of Study M12-555 that was considered as probably related to study drug. The subject underwent laboratory testing and hepatic echography. ALT values were elevated (505 U/L). Study drug was interrupted and restarted on Day 99. The event was considered resolved on Day 105 and a subsequent ALT value (Day 169) was 28 U/L.
- AST values ≥3 × ULN were experienced by 6 subjects.
- Total bilirubin ≥2 × ULN was experienced by 1 subject.
- Alkaline phosphatase values ≥ 1.5 × ULN were experienced by 13 subjects.
- ALT and/or AST ≥3 × ULN and concurrent total bilirubin ≥ 1.5 × ULN was experienced by 1 subject.
- ALT and/or AST ≥3 × ULN and concurrent total bilirubin ≥ 2 × ULN was experienced by 1 subject.

One subject experienced multiple SAEs, including cholangitis, septic shock, and a fatal event of autoimmune pancreatitis during the OLE study, Study M12-555 (see above, section 4.4)

Vital Signs

In the Placebo-Controlled Analysis Set, the numbers of subjects with potentially clinically significant vital sign values were balanced across the treatment groups. Similarly, in the All Adalimumab Analysis Set, the number of subjects with potentially clinically significant vital sign values was low. Mean changes in vital sign values from Baseline to the final visit and the incidence of potentially clinically significant vital sign values were not considered to be clinically meaningful.

Safety in special populations

Intrinsic Factors

The number and percentage of TEAEs overall, by primary SOC and PT, as well as by AESI overall, were assessed by subgroups of sex, age, race, baseline BMI, baseline Hurley Stage, and prior HS surgery, (Phase 3 studies only).

In the Placebo-controlled Analysis Set, although there were a few statistically significant differences, no clinically meaningful differences were observed. In many cases, the sample sizes were too small to determine whether a difference between subgroups was meaningful. No clinically meaningful differences were observed for the Maintenance, All Adalimumab ew, and All Adalimumab Analysis Sets, with respect to the subgroups analyzed.

Extrinsic Factors

The number and percentage of TEAEs, overall, by primary SOC and PT, as well as AESI overall, were assessed by subgroups of nicotine use and prior antibiotic use. The subgroup categories were analyzed to

evaluate if there was any impact of extrinsic factors on the overall safety profile of adalimumab in subjects with moderate to severe HS.

In the Placebo-Controlled Analysis Set, a smaller percentage of subjects in the adalimumab total group who never used nicotine (non-users) reported TEAEs overall, TEAEs at least possibly related to study drug, and infections than subjects who had used nicotine (ex-users) and subjects who currently use nicotine (users). Similar results were observed for the placebo group; however, the percentages of subjects who reported these events were small across subgroups. The clinical significance of these differences was deemed unclear.

In the Placebo-Controlled Analysis Set, a statistically significant treatment by antibiotic use interaction was observed overall for TESAEs (P = 0.015) with more TESAEs reported in subjects concomitantly using antibiotics and adalimumab. No clinically meaningful differences were observed for the Maintenance, All Adalimumab ew, and All Adalimumab Analysis Sets, with respect to the subgroups analyzed.

Pregnancy and Lactation
In the HS clinical development program, female subjects were required to be either not of childbearing potential or of childbearing potential and practicing an approved method of birth control throughout the study and for 150 days after the last dose of study drug. A lactating or pregnant female was not eligible to participate in the studies. The results of the serum pregnancy test performed during the screening period and urine pregnancy test performed at the baseline visit must have been negative. A subject who became pregnant during participation in the clinical studies was to be discontinued from study drug. Pregnancy in a study subject was not considered an AE. However, the medical outcome of an elective or spontaneous abortion was considered an SAE and was to be reported to AbbVie within 24 hours of the site becoming aware of the event.
Thirteen pregnancies were reported in the HS clinical development program:

- Two pregnancies occurred in Study M10-467: 1 woman (adalimumab eow group) delivered a stillborn infant due to gestational hypertension (this subject had a relevant history of pregnancy-induced hypertension during a prior pregnancy that produced an infant without complications) and 1 woman (adalimumab ew group) delivered a premature infant by emergency cesarean because of an event of pre-clampsia.

- Three pregnancies occurred in Study M11-810: 2 women (adalimumab ew/eow and adalimumab ew [subject discontinued in Period A] groups) delivered live infants with no noted birth defects; the third woman had an elective abortion.

- Five pregnancies occurred in Study M11-313: 2 women (both in the placebo/ew group) delivered live infants (no further information is available); 1 subject (placebo/ew group) had an ectopic pregnancy that was non-viable; and the other 2 women (adalimumab ew/ew and ew/eow groups) had an ectopic pregnancy and elective abortion, respectively.

- Three pregnancies occurred in Study M12-555: 1 woman (placebo/placebo/ew group) had a spontaneous abortion and the other 2 had delivery dates of September 2014 and November 2014.

Elderly
With respect to percentage of subjects experiencing TEAEs sub-group analyses were only performed based on the age categories < 40 years of age ("younger") and subjects ⩾ 40 years ("older") as it is acknowledged that HS patients are often in the range 30-40 years with a minority of patients being elderly. However, the CHMP requested an analysis of all, fatal and serious AEs observed in elderly patients as well as all AEs leading to treatment withdrawal or related to falling, infections, cardiovascular, cerebrovascular and CNS events.
The MAH provided this information which is summarized in**Table 74**.

Table 15: Analysis of AE in the elderly population included in the HS studies

	Age < 65 yrs N = 717	65 – 74 yrs N = 10	75 – 84 yrs N = 0	85 + N = 0
Total	564 (78.7)	8 (80.0)	0	0
Fatal	2 (0.3)	0	0	0
Serious	76 (10.6)	2 (20.0)	0	0
Withdrawal	67 (9.3)	3 (30.0)	0	0
CNS (confusion/extrapyramidal)	140 (19.5)	1 (10.0)	0	0
AE related to falling	5 (0.7)	0	0	0
CV events	4 (0.7)	0	0	0
Cerebrovascular events	2 (0.3)	0	0	0
Infections	370 (51.6)	7 (70.0)	0	0

The CHMP considered that the available data, whilst limited do not raise any specific concerns in this indication for elderly patients.

Immunological events

Immunogenicity of adalimumab in the HS population is discussed in the PK section of this AR, in relation to the effect of adalimumab antibodies on pharmacokinetics.

Immunogenicity of adalimumab was assessed in Studies M10-467, M11-313 and M11-810 using a double antigen sandwich enzyme -linked immunosorbent assay (ELISA) method. A sample was classified as AAA+ if the AAA concentration in serum was > 20 ng/mL and the serum sample was collected within 30 days after an adalimumab dose.

In the Phase 2 Study M10-467, five subjects were AAA positive (4.9%) during the DB period (Weeks 0-16): 2 subjects in the 40 mg ew group (3.9%) and 3 subjects in the 40 mg eow group (5.8%). Another 11 (7.1%) new subjects became AAA+ in the OL period (Weeks 17 52). The percentage of subjects with AAA+ samples was 10.4% (16/154) during the entire study period (Week 0 to Week 52).

In the two Phase 3 Studies, the percentage of subjects with AAA+ samples following 12 weeks of adalimumab 40 mg ew treatment in Period A was 3.2% (10/316). For subjects who continued to receive adalimumab 40 mg ew treatment in Period B, the percent of subjects testing positive for AAA was 10.1% (10/99). In all subjects who received at least one dose of adalimumab in the studies, the percent of subjects testing positive for AAA was 6.5% (30/461 subjects). The AAA+ rate was comparable between ew/ew and ew/eow subjects in Period B.

Concerning the impact of immunogenicity on safety, the rate of any AEs and the rate of infectious AEs were comparable between AAA+ and AAA– subjects. For the remaining AEs (e.g., serious AEs, serious infection AEs, diverticulitis, allergic reactions, worsening/new onset of psoriasis and hematologic disorders etc.), the numbers of AAA+ and/or AAA– subjects who reported these AEs were too small to make a definitive conclusion.

Safety related to drug-drug interactions and other interactions

Drug-drug interactions have not been specifically evaluated in the HS clinical development program. Concomitant use of biologic DMARDS, other TNF blockers, or MTX were not allowed in Studies M11-810 and M11-313. Antibiotics were used in a sub-set of patients in study M11-810, as stipulated in the protocol.

Discontinuation due to adverse events

In the *Placebo-Controlled Analysis Set*, TEAEs leading to discontinuation were reported in 2.1% of subjects in the adalimumab total group and 2.7% of subjects in the placebo group. TEAEs leading to discontinuation in 4 subjects in the adalimumab total group and 3 subjects in the placebo group were considered by the investigator as at least possibly related to study drug. All TEAEs leading to discontinuation were reported in 1 subject each in the adalimumab total and placebo groups, except for hidradenitis (3 subjects in the adalimumab total group and 2 subjects in the placebo group).

In the *All Adalimumab Analysis Set*, 70 (9.6%) subjects reported TEAEs leading to discontinuation. Of the subjects who reported TEAEs leading to discontinuation, 60% reported events that were considered by the investigator as at least possibly related to study drug.

TEAEs leading to discontinuation that were reported in ≥ 2 subjects included hidradenitis in 23 subjects (3.2%); pustular psoriasis in 6 subjects (0.8%); psoriasis in 3 subjects (0.4%); and weight increased, rash pustular, paresthesia, and drug eruption in 2 subjects each (0.3%). All other TEAEs leading to discontinuation were reported in 1 subject each (0.1%).

Post marketing experience

There is no post marketing experience from use of Humira in the HS indication.

Adalimumab was first approved for treatment of RA on 31 December 2002 (international birth date). As of 31 December 2013, adalimumab has been evaluated in more than 42,000 subjects with different conditions, e.g. RA, other arthritis conditions, CD, paediatric CD, psoriasis, paediatric psoriasis, ulcerative colitis and uveitis. The estimated cumulative post-marketing patient exposure since the IBD through 31 December 2013 is 2.9 million PYs. Potential new safety signals are monitored through post-marketing safety surveillance e.g. by reports from clinical studies, all reports from spontaneous sources, the literature, regulatory agencies, post-marketing studies and registries. Eight AbbVie-sponsored adalimumab safety registries are ongoing.

2.5.1. Discussion on clinical safety

The proposed posology for Humira in adult patients with moderate to severe HS is an initial dose of adalimumab 160 mg on Day 1, followed by a dose of adalimumab 80 mg on Day 15, and then dosing of adalimumab 40 mg every week (ew) starting on Day 29. The CHMP noted that the proposed dosing schedule for Humira in HS is quite intense, with high initial loading doses followed by 40 mg every week (ew) from week 4. This is a higher dose compared with the approved posologies of Humira in rheumatoid arthritis, other arthritis conditions and psoriasis. The HS posology is, however, rather similar to the posology approved in ulcerative colitis and Crohn´s disease (in CD a high loading dose recommended if a rapid response is desirable) except that for both these indications, the maintenance dose is 40 mg every other week, with a possibility to increase the dose to 40 mg every week if needed.

The documentation provided by the MAH, included some information from studies in other indications in which adalimumab 40 mg ew and 40 mg eow were compared. Approximately 400 subjects have been exposed to adalimumab 40 mg ew in 5 clinical studies in non-HS indications, with the duration of exposure to this dose of adalimumab ranging between 4 and 52 weeks. No consistent trends were observed in incidence rates of Adverse Events of Special Interest (AESI) in the ew versus eow groups across the CD and UC open-label studies. Some increases in the incidence rates of events with adalimumab 40 mg ew, as compared to adalimumab 40 mg eow were observed, particularly in the UC studies; however, these increases may be related to increased inflammatory bowel disease activity in the subjects who required dose escalation to adalimumab ew dosing. In order to collect further information on the long-term safety of adalimumab with the new dosing regime in the HS indication the MAH was requested to provide the results of the ongoing study M12-555 and this safety concern was also included in the RMP for Humira.

In the HS studies, the percentages of subjects reporting adverse events were comparable between the placebo and total adalimumab (eow and ew) groups during the placebo-controlled period of the Phase 2 and 3 studies. SAEs were also experienced by similar proportions of subjects in the total adalimumab (ew and eow) and placebo groups. AEs led to study drug discontinuation in 2.1% and 2.7% of subjects in the total adalimumab and placebo groups, respectively.

Safety data for Period B (Weeks 12 to 36 in the HS studies) revealed few differences in the safety profiles between the different dosing regimens. Overall, the safety profiles were comparable for the adalimumab ew and eow groups.

The most frequently reported TEAEs for adalimumab in the All Adalimumab Analysis Set were hidradenitis, nasopharyngitis, headache, upper respiratory tract infection, nausea, urinary tract infection and arthralgia. The percentage of subjects who reported hidradenitis as an AE was significantly lower in the adalimumab ew/ew group, as compared to the adalimumab ew/eow and ew/placebo groups. Thus, apart from the hidradenitis AEs which is related to the patient population within this indication, the pattern of TEAEs does not appear different from what has previously been observed with adalimumab.

The number and type of AEs leading to discontinuation were not of great concern. In the All Adalimumab Analysis Set, 10% of subjects reported TEAEs leading to discontinuation. Except hidradenitis, 3.2%, pustular psoriasis or psoriasis were quite common reasons for discontinuation.

A number of AESI were identified from the clinical trials conducted in HS. In the Placebo-Controlled Analysis Set, the most frequently reported AESI in both the adalimumab total and placebo groups were injection site reaction, allergic reaction (mostly urticaria and pruritus generalized; 1 event of drug sensitivity), and hematologic disorder (mostly anaemia).

Similarly, in the Maintenance Analysis Set and All Adalimumab Analysis Set, the most frequently reported AESI were injection site reaction, allergic reactions and hematologic disorders (mainly anaemia; 2 subjects each reported events of neutropenia and lymphopenia) and events of worsening/new onset psoriasis were also reported.

Subjects who reported AESI that were serious and considered by the investigator as at least possibly related to study drug included 10 subjects who reported serious infections (purulent discharge/rash pustular, cellulitis, pneumonia chlamydial, pneumonia, septic shock, pyelonephritis, infection, sepsis, pneumonia viral) and 1 subject each who reported events of malignancy (seminoma), acute MI, pustular psoriasis and anaemia.

Adalimumab affects the immune system and it is well known that it causes an overall increased infection risk. In both the Placebo-Controlled Analysis and Maintenance Analysis Sets, around 30% of subjects across all groups reported treatment-emergent infections, the most common being nasopharyngitis, upper respiratory tract infection, urinary tract infection and bronchitis.

With respect to treatment-emergent serious infections, such infections were reported in 2.9% of subjects in the All Adalimumab Analysis Set. Some of the infections reported were pilonidal cyst, pneumonia, cellulitis and pyelonephritis. Extensive warnings in relation to the risk of infections with adalimubab use are already included in the SmPC for Humira. In addition, the Humira Risk Management Plan includes a number of additional risk minimisation measures to minimise such risks.

Since HS is a condition with skin lesions that may become infected, it was considered important to perform a post-hoc adjudication for identification of potential SSTIs. Cases of SSTIs occurred both in adalimumab- and placebo-treated subjects and a fairly large portion was reported as hidradenitis. Some of those who developed SSTIs had other relevant risk factors, e.g. diabetes or prior history of SSTIs.

The rate or severity of infections, including SSTIs, with Humira in HS does not give cause for concern as it does not differ markedly with the experience from the other licensed indications of Humira. However, an

increased risk for infections should always be considered, especially in vulnerable patients. This is adequately addressed in the currently approved SmPC. One issue to be considered in this respect is the required use of topical antiseptics in the pivotal phase 3 studies and which was a request also in study M12-555 as this could potentially have reduced the overall rate of SSTIs of HS lesions. The product information now states that all subjects in the main clinical studies were required to use topical antiseptics. This was agreed by the CHMP.

With respect to AESI other than infections, no new or unexpected findings were overall observed in the HS studies. One observation is, however, made in relation to events of worsening/new onset psoriasis. Six events of pustular psoriasis were reported (0.8% in the All Adalimumab Analysis Set). In the Humira product information, worsening or new onset of psoriasis (including palmoplantar pustular psoriasis) are included as common ADRs. However, pustular psoriasis (generalised) is currently not included in the Humira SmPC. However, the MAH clarified that these were cases of pustular psoriasis mainly affecting the palms or the scalp and therefore the CHMP concluded that it is not warranted to add generalised pustular psoriasis in the ADR table in section 4.8 of the SmPC.

Serious AEs were reported in 11% of subjects in the All Adalimumab Analysis Set, with anaemia, cellulitis, ectopic pregnancy, hidradenitis, non-cardiac chest pain, palpitations, pilonidal cyst, pneumonia, postoperative wound infection, sepsis, and septic shock reported in ≥ 2 subjects each. 2.8% of subjects reported TESAEs that were considered at least possibly related to study drug, of these, pneumonia was reported in 2 subjects. With the exception of hidradenitis which is an indication specific adverse event and is not considered to be causally associated with Humira treatment, the observed events are consistent with the known safety profile of Humira with appropriate warnings and risk minimisation measures already included in the SmPC and RMP respectively.

A total of two deaths on adalimumab have been reported in the HS clinical studies; one due to cardio-respiratory arrest and the other due to septic shock following severe autoimmune pancreatitis. None of these events were considered related to adalimumab by the investigators. Even though this was considered plausible, cardiac disorders, e.g. myocardial infarction and cardiac arrest, are labelled uncommon or rare ADRs in the Humira SmPC.

With respect to laboratory findings and vital signs, no new concerns were identified in the HS population, compared with previous indications for adalimumab.

Concerning safety in special populations, for intrinsic factors (sex, age, race, baseline BMI, baseline Hurley Stage, and prior HS surgery), there were a few statistically significant differences in the Placebo-controlled Analysis Set, but no clinically meaningful differences were observed. In many cases, the sample sizes were too small to make firm conclusions. No clinically meaningful differences between sub-groups were observed for the other analysis sets either.

For extrinsic factors, analyses were made for subgroups of nicotine use and prior antibiotic use. In the Placebo-Controlled Analysis Set, a smaller percentage of subjects in the adalimumab total group who never used nicotine (non-users) reported TEAEs overall, TEAEs possibly related to study drug, and infections compared with nicotine users and ex-users. Similar results were observed for the placebo group. In the Placebo-Controlled Analysis Set, a statistically significant treatment by antibiotic use interaction was observed with more TESAEs reported in subjects concomitantly using antibiotics and adalimumab.

Concerning immunological events, some allergic reactions and TEAEs related to hypersensitivity have been reported, however, the data do not give cause for concern in relation to what is known for adalimumab in other indications. Immunogenicity of adalimumab in the HS population was discussed both related to the effect of adalimumab antibodies on pharmacokinetics, efficacy and safety. The number of subjects being AAA+ was overall low (approximately 10%) and, as for efficacy, firm conclusions are difficult to make. However, immunogenicity did not have an apparent impact on the safety of adalimumab in HS subjects.

2.5.2. Conclusions on clinical safety

The safety profile of adalimumab in HS does not appear different from what that previously observed with adalimumab in other indications, except for rather frequent reporting of hidradenitis as an AE.

The rate or severity of infections, including SSTIs, with Humira in HS does not give cause for concern in comparison with the experience in other indications. The required use of topical antiseptics in the pivotal studies could potentially have reduced the overall rate of SSTIs of HS lesions and it is now mentioned in the product information that all subjects in the main clinical studies were required to use topical antiseptics. For AESI other than infections, no new or unexpected findings were overall observed in the HS studies.

Serious AEs were reported in 11% of subjects, with anaemia, cellulitis, ectopic pregnancy, hidradenitis, non-cardiac chest pain, palpitations, pilonidal cyst, pneumonia, postoperative wound infection, sepsis, and septic shock being the most common. Several events of worsening/new onset psoriasis were reported, including cases of pustular psoriasis. It was clarified that these cases had mainly palmo-plantar involvement but were not to be regarded as generalised pustular psoriasis.

With the exception of hidradenitis which is related to the target population in this indication and is not considered to be causally associated with Humira treatment, the observed events are consistent with the known safety profile of Humira with appropriate warnings and risk minimisation measures already included in the SmPC and RMP respectively.

The CHMP considered that the available data with the adalimumab 40 mg ew dosing regimen in the HS population are relatively limited compared to the information available with the dosing regimens in the other approved Humira indications. Therefore and in order to further characterise the long-term safety in adult patients treated with Humira for HS, the CHMP requested that this information should be collected through the ongoing study M12-555. Consequently, the MAH has included in the RMP as missing information, long term safety in HS and will provide the final study report from study M12-555 as outlined in the RMP.

2.5.3. PSUR cycle

The PSUR cycle remains unchanged.

2.6. Risk management plan

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the risk management plan version 11.3 could be acceptable if the MAH implements the changes to the RMP as described in the PRAC endorsed PRAC Rapporteur assessment report.

The MAH implemented the requested changes in the Risk Management Plan version: 11.3.1

2.7. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC have been updated as detailed in the appended product information. The package leaflet has been updated accordingly.

3. Benefit-Risk Balance

Benefits

Beneficial effects

The primary end-point, HiSCR, was met in both studies, albeit with some differences in the size of the effect of adalimumab vs. placebo between the studies. In study M11-313, 42% of the adalimumab-treated subjects reached HiSCR (26% on placebo) while in Study M11-810, 59% of adalimumab-treated subjects reached HiSCR (28% on placebo). Baseline Hurley stage and baseline concomitant antibiotic use (Study M11-810 only) were stratification factors in the Period A randomization for both studies. A significantly higher HiSCR rate in the adalimumab ew group compared to the placebo group was observed in every subgroup. The treatment difference between adalimumab and placebo were greater among subjects with Hurley Stage III than those with Hurley Stage II and among subjects who received concomitant antibiotics compared to those who did not.

For the three, ranked secondary end-points (proportion of subjects who achieved AN count of 0, 1, or 2 in Hurley Stage II subjects; pain reduction assessed by NRS30 in subjects with baseline skin pain NRS ≥ 3 and Change in modified Sartorius score; all assessed at week 12), Study M11-810 met all these endpoints with statistically significant differences between adalimumab 40 mg ew and placebo. In Study M11-313 all outcomes except one were numerically in favour of adalimumab ew, however, none of these three end-points achieved statistical significance. *Post-hoc* analyses for the same end-points performed on data from the phase 2 Study M10-467 showed statistically significant differences between adalimumab ew and placebo, in favour of adalimumab.

Other secondary end-points generally mirrored the results of the primary and ranked secondary end-points. With respect to lesion counts, the percent change from baseline in different lesion counts at Week 12 showed decreases in the range 10-55% for adalimumab ew vs. maximally 25% decreases for placebo across the two studies. A small number of subjects (10% in study M11-313 and 15% in M11-810) achieved complete elimination of AN (AN = 0) with adalimumab ew treatment. The occurrence of flare was experienced by 11% (Study M11-810) and 14% (Study M11-313) of subjects in the adalimumab ew group and approximately 35% of subjects in the placebo group ($P < 0.001$, in both studies).

With respect to reduction in skin pain (NRS30; a ranked secondary end-point), in study M11-313, a greater proportion of subjects achieved NRS30 in the adalimumab ew group compared with the placebo group during Period A for all visits.

Outcomes related to patient-reported Quality of Life showed an effect of adalimumab vs. placebo was shown for both DLQI and TSQM.

Regarding maintenance treatment, results from part B of the pivotal studies as well as interim results from the OLE study M12-555 showed that the response rates at most time points were highest with the ew/ew treatment in all analysis populations. AEs of "hidradenitis" (i.e. worsening of disease) were more common for ew/pbo (20%) and for ew/eow (18%) compared with ew/ew (5%). For a range of secondary end-points, the ew/ew treatment generally also showed better results compared with the ew/eow and ew/pbo groups in the ITT_B_PRR Population.

In the *post-hoc* analyses of the sub-group of AN25 responders (partial responders), it was found that among the group of HiSCR non-responders, this sub-group was able to reach HiSCR, in particular with adalimumab 40 mg ew/ew. Based on this, continued therapy beyond 12 weeks is recommended except in those patients without any improvement for whom continued therapy should be reconsidered.

Uncertainty in the knowledge about the beneficial effects

Whilst both pivotal studies met the primary end-point, HiSCR, there was a difference in the size of the effect of adalimumab vs. placebo between these studies. The difference between adalimumab and placebo was 16% in study M11-313 and 31.5% in study M11-810. While in study M11-810, roughly 30% more patients in the ADA ew group met the primary endpoint compared to the placebo-treated group, in study M11-313 the gain in the number of responders was lower (almost half; 15%).

The treatment differences were statistically significantly higher for adalimumab at all-time points, except at Week 12, which was the time point for assessment as a ranked secondary end-point. Thus, the treatment effect seemed to decrease over time, which was also observed to some extent in Study M11-810, although the difference vs. placebo was overall larger and a significant difference was observed at all-time points. Therefore, continued therapy beyond 12 weeks should be carefully reconsidered in a patient with no improvement within this time period. The benefit and risk of continued long-term treatment should be periodically evaluated

For the three, ranked secondary end-points, none of these achieved statistical significance in Study M11-313, however, all outcomes except one were numerically in favour of adalimumab ew.

Possible reasons for the difference between the two studies and the failure to achieve statistical significance for the ranked secondary end-points in study M11-313 provided by the Applicant were between-study differences in baseline characteristics (body weight, factors indicating HS severity such as draining fistula count, AN count, mean pain score and modified Sartorius scores, proportion of black subjects). In addition to between-study differences, there were also some within-study differences in baseline characteristics between the adalimumab and placebo groups, e.g. body weight in study M11-810 (mean 96 kg in the placebo group and 90 kg in the adalimumab group).

Risks

Unfavourable effects

The safety profile of adalimumab in HS does not appear different from what that previously observed with adalimumab in other indications, except for rather frequent reporting of hidradenitis as an AE and which is not necessarily causally associated with adalimumab.

It is well known that adalimumab causes an overall increased infection risk. In both the Placebo-Controlled Analysis and Maintenance Analysis Sets, around 30% of subjects across all groups reported treatment-emergent infections, the most common being nasopharyngitis, upper respiratory tract infection, urinary tract infection and bronchitis. The rate or severity of infections, including SSTIs, with Humira in HS did not give cause for concern in comparison with the experience in other indications.

Serious AEs were reported in 11% of subjects in the All Adalimumab Analysis Set, with anemia, cellulitis, ectopic pregnancy, hidradenitis, non-cardiac chest pain, palpitations, pilonidal cyst, pneumonia, postoperative wound infection, sepsis, and septic shock being most common. 2.8% of subjects reported TESAEs that were considered at least possibly related to study drug, of these, pneumonia was reported in 2 subjects.

A total of two deaths on adalimumab have been reported in the HS clinical studies; one due to cardio-respiratory arrest and the other due to septic shock following severe autoimmune pancreatitis. None of these events were considered related to adalimumab by the investigators.

With respect to laboratory findings and vital signs, no new concerns were identified in the HS population, compared with previous indications for adalimumab.

Concerning immunological events, some allergic reactions and TEAEs related to hypersensitivity have been reported, however, the data do not give cause for concern in relation to what is known for adalimumab in other indications. The number of subjects with adalimumab antibodies was overall low (approximately 10%), however, immunogenicity did not have an apparent impact on the safety of adalimumab in HS subjects.

Uncertainty in the knowledge about the unfavourable effects

The overall observed incidence of infections, specifically SSTIs, might have been influenced by the required use of topical antiseptics in the pivotal phase 3 studies and also in study M12-555. This could potentially have reduced the overall rate of SSTIs of HS lesions. Hence, the use of a topical antiseptic wash on the HS lesions is recommended in the SmPC.

In addition, given the relatively limited experience with the dosing regimen in HS, compared to the other approved indications of Humira, further information on the long term safety of Humira with the new dosing regimen will be collected through the ongoing open label study which is included in the RMP.

Benefit-Risk Balance

Importance of favourable and unfavourable effects

HS can be a severe and debilitating condition, in particular in moderate to severe cases. There are currently no approved medicinal products for the treatment of HS and there are few randomized, controlled trials to provide firm support for HS treatments. Thus, there is an unmet medical need in this condition.

An extensive program has been performed for Humira in HS, with development of a new score, the HiSCR, to assess efficacy in the two pivotal studies. Both pivotal studies met this primary efficacy end-point, albeit with different size of the effect vs. placebo.

The effect observed for the primary end-point HiSCR, for the ranked secondary end-points (in Study M11-810) and other end-points is deemed clinically relevant. The HiSCR outcome in Study M11-313 can also be considered clinically meaningful, and is supported by significant improvement in quality of life endpoints. In addtion, the *post-hoc* analysis of HiSCR and ranked secondary end-points (corresponding to phase 3 end-points) in the phase 2 study M10-467, however, provide further support for efficacy.

Adalimumab has been approved for more than 10 years and is used in a range of conditions with autoimmune origin. Its safety profile is considered well characterized at this stage, with infections and risks related to malignancies being well-known risks. The proposed dosing schedule for Humira in HS is quite intense, more frequent than the ones commonly used in the other approved indications of Humira. However, the safety profile of adalimumab in HS does not appear different from what that previously observed with adalimumab in other indications, except for rather frequent reporting of hidradenitis as an AE. This includes the rate and severity of infections, including SSTIs.

Benefit-risk balance

Discussion on the Benefit-Risk Balance

The efficacy of adalimumab in HS as shown in the two pivotal studies and supported by the phase 2 study is deemed clinically relevant, including the positive outcomes related to patient-reported QoL. The dosing schedule in HS is the most intensive one so far recommended for Humira, however, the safety profile of adalimumab in HS did not appear significantly different from what has previously been observed with adalimumab in other indications.

Furthermore, the clinical need for the higher maintenance dose in this indication is justified. Therefore, and given that the cumulative experience and available safety information with the use of Humira, with this high maintenance dose is reassuring, a continuous maintenance dose regimen of 40 mg ew is accepted.

At the same time it is acknowledged that the safety profile of adalimumab is complex and not entirely benign. Thus, a continuous or life-long, treatment of HS may not be justified in all cases. This is clearly reflected in the SmPC with clear recommendations to healthcare professionals that the benefit-risk of long-term Humira should be periodically re-evaluated. In addition in cases of patients with no improvement continued therapy beyond 12 weeks should be carefully reconsidered.

The benefit-risk balance of adalimumab for the treatment of active moderate to severe hidradenitis suppurativa (acne inversa) in adult patients with an inadequate response to conventional systemic HS therapy is considered positive.

4. Recommendations

☒ The application for Humira in the treatment in the treatment of active moderate to severe hidradenitis suppurativa is approvable since other concerns and major objections have all been resolved.

Final Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends the variation to the terms of the Marketing Authorisation, concerning the following change:

Variation(s) accepted		**Type**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II

Extension of Indication to include the treatment of active moderate to severe hidradenitis suppurativa (acne inversa) in adult patients with an inadequate response to conventional systemic HS therapy.

As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC are updated and the Package Leaflet is being updated accordingly. In addition, the MAH proposed minor editorial changes in the SmPC and Package Leaflet.

The requested variation proposed amendments to the SmPC and Package Leaflet.

- **Periodic Safety Update Reports**

The marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list)) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.>

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk management plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the

RMP.

When the submission of a PSUR and the update of a RMP coincide, they should be submitted at the same time.

In addition, an updated RMP should be submitted:

At the request of the European Medicines Agency;

Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.