2.0 Synopsis

AbbVie Inc.	**Individual Study Table Referring to Part of Dossier:** **Volume:** **Page:**	**(For National Authority Use Only)**
Name of Study Drug: Adalimumab		
Name of Active Ingredient: Adalimumab		
Title of Study: A Phase 3 Multicenter Study of the Safety and Efficacy of Adalimumab in Subjects with Moderate to Severe Hidradenitis Suppurativa – PIONEER II		
Investigator: Gregor Jemec, MD, DMSc [redacted] Denmark		
Study Sites: 53		
Publications: None		
Studied Period (Years): First Subject First Visit: 28 December 2011 Last Subject Last Visit: 28 April 2014	**Phase of Development:** 3	
Objective: The primary objective of this study was to determine the clinical safety and efficacy of adalimumab, as compared to placebo, in subjects with moderate to severe HS after 12 weeks of treatment.		

Methodology:

The study duration 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.

Period A: 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 or matching placebo for an evaluation of safety and efficacy. The randomization was to be stratified by baseline Hurley Stage (II versus III) and baseline concomitant antibiotic use (yes versus no). A subject's Hurley Stage was determined by the worst Hurley Stage across all affected anatomic regions.

Period B: 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 to be re-randomized in a 1:1:1 ratio to receive adalimumab 40 mg every week (ew), adalimumab 40 mg every other week (eow), or matching placebo. Subjects randomized to placebo in Period A were to be assigned (using re-randomization numbers) to continue on placebo.

Number of Subjects (Planned and Analyzed):

Planned: 300 subjects

Analyzed: 326 subjects

Diagnosis and Main Criteria for Inclusion:

Subjects were to have a diagnosis of hidradenitis suppurativa (HS) for at least 1 year prior to Baseline; stable HS for at least 2 months prior to Screening and at Baseline; HS lesions present in at least 2 distinct anatomic areas (e.g., left and right axilla; or left axilla and left inguino-crural fold), 1 of which was Hurley Stage II or Hurley Stage III; and 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). Subjects were also to have a total inflammatory nodules (AN) count of greater than or equal to 3 at Baseline. Subjects must have had a negative tuberculosis (TB) screening assessment (including a purified protein derivative [PPD] test or QuantiFERON-TB Gold test, or equivalent) and a negative chest x-ray (posterior-anterior and lateral views) 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.

Subjects with any other active skin disease or condition (e.g., bacterial, fungal or viral infection) that could interfere with assessment of HS and subjects with a draining fistula count of greater than 20 at Baseline were excluded. 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 were also excluded, as were subjects who received prescription topical therapies for the treatment of HS within 14 days prior to Baseline, systemic nonbiologic therapies with potential therapeutic impact for HS < 28 days prior to Baseline, or oral concomitant analgesics (including opioids) for HS-related pain within 14 days prior to Baseline. Subjects who had previous exposure to adalimumab or other anti-tumor necrosis factor (anti-TNF) therapy were also excluded.

Test Product, Dose/Strength/Concentration, Mode of Administration and Lot Number:

Adalimumab 40 mg/0.8 mL subcutaneous (SC) injection (bulk lot numbers: 10-005762, 11-003870, 11-005882, 13-000648) or matching placebo (bulk lot numbers: 08-018846, 11-004399, 12-007038).

Duration of Treatment:

36 weeks (12 weeks in Period A, 24 weeks in Period B)

Reference Therapy, Dose/Strength/Concentration and Mode of Administration and Lot Number:

None

Criteria for Evaluation

Efficacy:

The primary efficacy variable was the proportion of subjects who achieved hidradenitis suppurativa complete response (HiSCR) at Week 12.

The ranked secondary efficacy variables were as follows:

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 were:

- Proportion of subjects who achieved HiSCR.
- Proportion of subjects who achieved AN count of 0, 1, or 2, among subjects with Hurley Stage II at Baseline.
- Proportion of subjects who achieved NRS30 – at worst, among subjects with baseline Patient's Global Assessment of Skin Pain NRS ≥ 3.
- Proportion of subjects who achieved NRS30 – 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, among subjects who had any abscess at Baseline.
- Percentage change from Baseline in number of abscesses, among subjects who had at least 1 abscess at Baseline.
- Change from Baseline in number of abscesses.
- Proportion of subjects who achieved complete elimination of draining fistulas at each visit, among subjects who had any draining fistulas at Baseline.
- Percentage change from Baseline in number of draining fistulas, among subjects who had at least 1 draining fistula at Baseline.
- Change from Baseline in number of draining fistulas.
- Percentage change from Baseline in number of inflammatory nodules, among subjects who had at least 1 inflammatory nodule at Baseline.
- Proportion of subjects who achieved complete elimination of inflammatory nodules at each visit, among subjects who had any inflammatory nodules at Baseline.
- Change from Baseline in number of inflammatory nodules.
- Number of protocol-allowed interventions during Period A.

Criteria for Evaluation (Continued)

Efficacy (Continued):

- Proportion of subjects with Dermatology Life Quality Index (DLQI) = 0.
- Proportion of subjects with DLQI = 0 or 1.
- Change from Baseline in DLQI.
- Change from Baseline in Work Productivity and Activity Impairment Questionnaire: Specific Health Problem (WPAI:SHP).
- Percentage change from Baseline in Patient's Global Assessment of Skin Pain NRS – at worst, among subjects who had baseline NRS ≥ 3.
- Percentage change from Baseline in Patient's Global Assessment of Skin Pain NRS – on average, among subjects who had baseline NRS ≥ 3.
- Change from Baseline in Patient's Global Assessment of Skin Pain NRS – at worst.
- Change from Baseline in Patient's Global Assessment of Skin Pain NRS – on average.
- Proportion of subjects who achieved at least 50% reduction in the AN count relative to Baseline (AN50).
- Proportion of subjects who achieved at least 75% reduction in the AN count relative to Baseline (AN75).
- Proportion of subjects who achieved 100% reduction in the AN count relative to Baseline (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 by at least 1 Hurley Stage in at least 1 affected anatomic region.
- Proportion of subjects who experienced improvement by at least 1 Hurley Stage in at least 1 affected anatomic region.
- Change from Baseline in Treatment Satisfaction Questionnaire with Medicine (TSQM).
- Change from Baseline in European Quality of Life-5 Dimensions (EQ-5D) index.
- Change from Baseline in EQ-5D visual analog scale (VAS).
- Proportion of subjects who experienced flare, defined as an at least 25% increase in AN counts with a minimum increase of 2 relative to Baseline.
- Number of days on flare, calculated from the day when flare was observed to the day prior to the observation that flare was no long present. There could have been multiple periods in which flares were observed, in which case, the total days from the multiple periods were to be used.
- 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.

Criteria for Evaluation (Continued)

Efficacy (Continued):

- Change from Baseline in c-reactive protein (CRP).
- Percentage change from Baseline in CRP.

In addition, progression of representative lesions were to be evaluated as follows:

- The sign of deterioration in a lesion was defined as deterioration to a more severe lesion type or an increase in severity score in at least 2 categories (erythema, tenderness, and size) within the same lesion type.
- The sign of improvement in a lesion was defined as improvement to a less severe lesion type or a decrease in severity score in at least 2 categories (among erythema, tenderness, and size) within the same lesion type.
- The overall lesion progression for a subject was defined as the total number of lesions showing signs of improvement – the total number of lesions showing signs of deterioration, where a positive result denoted an overall improvement and a negative result denoted as overall deterioration.
- Proportion of subjects achieving overall improvement in representative lesions and proportion of subjects experiencing overall deterioration in representative lesions were to be analyzed.
- The average change in each category (erythema, tenderness, and size) for each representative lesion type was to be analyzed as well.

Other secondary efficacy variables in Period B were:

- The secondary efficacy variables were to be summarized for each subpopulation in the Intent-to-Treat (ITT) Population. The treatment comparisons were to be performed in subjects who were randomized to adalimumab in Period A and who achieved HiSCR at Week 12. In addition, change from re-randomization was to be analyzed for continuous variables for subjects who achieved HiSCR.
- Time to LOR was to be analyzed for subjects who achieved HiSCR.
- Time to the second incidence of 2-consecutive visits with AN count ≥ Baseline. AN count was to be summarized for subjects who were randomized to adalimumab in Period A and who did not achieve HiSCR.

Safety:

Adverse events (AEs), laboratory data, physical examinations, and vital signs were assessed throughout the study.

Statistical Methods

Efficacy:

The primary analysis was the comparison of the adalimumab treatment group versus the placebo treatment group 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 group and the difference in response rates (adalimumab – placebo) was compared and the 95% confidence interval computed using Cochran Mantel-Haenszel (CMH) test, stratified by baseline Hurley Stage (II versus III) and concomitant use of oral antibiotics (Y/N). In Period B, the analyses of each adalimumab group versus placebo, and between the 2 adalimumab groups, were performed. Categorical variables were analyzed by the CMH test, adjusting for baseline Hurley Stage (II versus III). Continuous variables were analyzed by analysis of covariance (ANCOVA) with baseline Hurley Stage (II versus III) and the corresponding baseline value in the model. Key efficacy results were also analyzed by demographics and baseline characteristics.

Safety:

All AEs, serious AEs (SAEs), and AEs leading to discontinuation were collected during the study and up to approximately 70 days after the last dose of study drug (for subjects who did not participate in the open-label study, Study [redacted]). For subjects who participated in the open-label extension (OLE), the 70-day safety evaluation was completed as part of the OLE. Safety analyses were carried out using the safety population in each period (Safety_A Population and Safety_B Population) and the Cross-Period Safety Population. Pretreatment AEs were also summarized. The analysis of the safety population in Period B was provided overall and by Week 12 HiSCR status. A treatment-emergent AE was defined as an event with onset or worsening after the first study drug injection and within approximately 70 days after the last study drug injection. The number and percent of subjects experiencing treatment-emergent AEs were tabulated using the Medical Dictionary for Drug Regulatory Activities version 16.1 system organ class and preferred term. Comparisons of the percentages of subjects experiencing an AE in the adalimumab group versus the placebo group were performed using Fisher's exact tests for data collected in Period A. Comparisons of the percentages of subjects experiencing an AE in each of the adalimumab groups versus the placebo group were performed using Fisher's exact tests for data collected in Period B for the ITT_B_R population. Summaries (including percentages and events per 100 patient-years [PYs]) of SAEs; deaths; AEs leading to discontinuation from the study; and AEs of special interest (AESIs), according to the most updated Humira® risk management plan, were provided as well. Mean change in laboratory variables and vital sign variables were summarized at each visit. The comparison of the adalimumab treatment group and the placebo group in Period A was performed using a 1-way ANOVA. The comparison of each adalimumab group versus placebo was performed using a 1-way ANOVA for the ITT_B_R Population. The last evaluation prior to the first dose of study drug was used as baseline for all analyses. For selected parameters, a listing of all subjects with any laboratory determination meeting common toxicity criteria (CTC) of Grade 2 or higher was provided. Shift tables for changes from Baseline according to the normal range were also provided.

Summary/Conclusions

This study evaluated the clinical safety and efficacy of adalimumab, as compared to placebo, in adult subjects with moderate to severe HS. In Period A, a total of 326 subjects were randomized 1:1 to either placebo or adalimumab 40 mg ew and comprise the ITT_A Population. Subjects were stratified by baseline Hurley Stage and baseline concomitant antibiotic use. The majority of subjects in the ITT_A population were white, female, considered obese or morbidly obese, and were users of nicotine and alcohol. The mean age was 35.5 years. Baseline demographics and disease characteristics were generally balanced among subjects in the adalimumab ew and placebo treatment groups. The median duration of HS for subjects randomized in Period A was 9.31 years. All randomized subjects in Period A received at least 1 dose of study drug. Of the 326 subjects randomized in the study, 306 subjects completed Period A and continued to Period B, where subjects initially randomized to adalimumab were re-randomized to receive either adalimumab ew, adalimumab eow, or placebo. Subjects initially randomized in Period A to placebo continued to receive placebo in Period B in a blinded fashion. Re-randomization was stratified by HiSCR at Week 12 (responder versus nonresponder) and baseline Hurley Stage (II versus III). All re-randomized subjects received at least 1 dose of study drug. Of the 306 subjects who were re-randomized in Period B, 116 subjects completed Period B and 190 subjects discontinued from the study. The most frequently reported primary reason for discontinuation was LOR or WOAI. A higher proportion of subjects who continued to receive placebo and who were re-randomized to placebo in Period B discontinued from the study per IXRS instruction (55.6% and 49.0%, respectively), as compared to subjects who were re-randomized to adalimumab eow and ew (41.5% and 39.2%, respectively).

This study met its primary and all ranked secondary efficacy endpoints.

Period A Efficacy Results:

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

- Among subjects with baseline Hurley Stage II HS, a statistically significantly higher proportion of subjects treated with adalimumab ew achieved an AN count of 0, 1, or 2 at Week 12 than subjects treated with placebo (first ranked secondary efficacy endpoint).
- Among subjects with baseline skin pain NRS ≥ 3, a statistically significantly higher proportion of subjects who were treated with adalimumab ew achieved at least a 30% reduction and a 1-unit reduction from Baseline in Patient's Global Assessment of Skin Pain (NRS30) – at worst at Week 12 than subjects who were treated with placebo (second ranked efficacy endpoint).
- Statistically significantly greater mean decreases in the modified Sartorius score were observed at Week 12 for subjects treated with adalimumab ew than for subjects treated with placebo (third ranked efficacy endpoint).

Summary/Conclusions (Continued)

Period A Efficacy Results (Continued):

- The abscess, inflammatory nodule, draining fistula, and total fistula counts were decreased more in subjects treated with adalimumab ew than with placebo. The severity of these representative abscesses, inflammatory nodules, or draining fistulas were reduced more in subjects treated with adalimumab ew than with placebo.
- The risk of disease worsening (i.e., a 25% increase with at least a 2 count increase in inflammatory lesion count) was lower and the duration of disease flare was shorter for subjects treated with adalimumab ew than for subjects treated with placebo.
- A greater reduction in HS-related Patient's Global Assessment of Skin Pain (NRS30) was observed for subjects treated with adalimumab than for subjects treated with placebo.
- A greater improvement in the DLQI score was observed for subjects treated with adalimumab ew than for subjects treated with placebo.
- Improvement in TSQM scores was greater for subjects treated with adalimumab ew than subjects treated with placebo.

Period B Efficacy Results:

Efficacy assessments from subjects who were randomized to adalimumab ew in Period A and re-randomized to adalimumab ew (ew/ew group) in Period B showed generally better treatment outcomes than subjects who reduced dosing frequency to eow (ew/eow group) or who were re-randomized to placebo (ew/placebo) for both HiSCR responders (ITT_B_R Population) and HiSCR nonresponders (ITT_B_NR Population). Further, analyses revealed clear efficacy benefits associated with adalimumab ew among subjects in the ITT_B_NR Population who achieved at least a 25% reduction in AN count relative to Baseline at Week 12 (i.e., AN25 responders, or partial responders). Subjects who were randomized to placebo in Period A and continued on placebo in Period B (ITT_B_PBO Population) showed a consistently low level of HiSCR, which decreased from Week 12 to Week 36.

ITT_B_R Population

- Among HiSCR responders at Week 12, HiSCR was maintained for more subjects re-randomized to adalimumab (ew or eow) than re-randomized to placebo.
- Among HiSCR responders at Week 12, subjects in the ew/placebo group demonstrated a numerical trend toward a more rapid LOR.
- Across a number of secondary efficacy endpoints in Period B (AN count of 0, 1, or 2; AN50; AN75; NRS30; modified Sartorius score; lesion counts; and DLQI), subjects who received adalimumab ew had better outcomes than those who reduced their dose to adalimumab eow or placebo.

Summary/Conclusions (Continued)

Period B Efficacy Results (Continued):

ITT_B_NR Population

- The proportion of subjects in the ITT_B_NR Population who achieved HiSCR in Period B was greater for subjects re-randomized to adalimumab ew than for subjects re-randomized to adalimumab eow or placebo.
- A greater proportion of AN25 responders in the ITT_B_NR Population who continued adalimumab ew after Week 12 were able to achieve HiSCR than those who were re-randomized to adalimumab eow or placebo.
- Across a number of secondary efficacy endpoints in Period B (AN count of 0 , 1, or 2; AN50; AN75; NRS30; modified Sartorius score; lesion counts; and DLQI), subjects in the ITT_B_NR Population who were re-randomized to adalimumab ew showed greater efficacy than subjects re-randomized to adalimumab eow or placebo.

Efficacy assessments from subjects in the combined ITT_B_R and ITT_B_NR Populations also showed higher HiSCR rates at Week 36 among those who continued adalimumab ew treatment, as compared to subjects who reduced dosing frequency to adalimumab eow or who received placebo.

Based on the above results, the ITT_B_PRR Population, which was identified post-hoc and included Week 12 HiSCR responders and partial responders (achieved an AN25 response), showed better treatment outcomes among those continuing adalimumab ew treatment, than among subjects who reduced dosing frequency to adalimumab eow or who received placebo. The ITT_B_PRR Population is likely to be the most clinically relevant subpopulation for comparison of treatment outcomes among the ew/ew, ew/eow, and ew/placebo groups because it includes subjects who have either demonstrated a clinical response to adalimumab or have demonstrated the potential for a clinical response to adalimumab.

Safety Results:

No new adalimumab-related safety risks were identified in Study M11-810. Adalimumab was generally safe and well tolerated, as determined through evaluations of treatment-emergent AEs (TEAEs), laboratory values, and vital signs values. The proportion of subjects in the Cross-Period Population who reported TEAEs was similar between subjects who received only placebo and subjects who received at least 1 dose of adalimumab. TEAEs reported by subjects who received at least 1 dose of adalimumab were diarrhea, gastroenteritis, headache, hidradenitis (considered to be an exacerbation of underlying disease), nasopharyngitis, nausea, and upper respiratory tract infection. The AEs of gastroenteritis, hidradenitis, nasopharyngitis, and upper respiratory tract infection were reported more frequently by subjects who received placebo than by subjects who received adalimumab. The AEs of diarrhea, headache, and nausea were reported more frequently by subjects who received adalimumab than by subjects who received placebo. The majority of TEAEs were mild or moderate in severity. The rates of discontinuation from study drug due to AEs were low. The AEs that led to discontinuation from adalimumab were worsening of atrial fibrillation, rash pustular, drug eruption, and parapsoriasis (pityriasis lichenoides), rash, and acute myocardial infarction. One death due to cardio respiratory arrest occurred 42 days after the last dose of adalimumab in a subject who had a family history of coronary heart disease and other cardiac risk factors. The incidence of infectious AEs was similar between subjects who received placebo and subjects who received at least 1 dose of adalimumab. The majority of infectious events were nonserious and mild in severity. Two subjects receiving adalimumab reported serious infections (infection and pneumonia). One subject receiving adalimumab had an event of non-melanoma skin cancer (NMSC) (squamous cell carcinoma of the right nasal slope). No clinically meaningful changes in laboratory parameters or vital signs were noted in subjects who received adalimumab. Three pregnancies were reported in this study. One subject in the placebo/placebo group had an elective abortion and the other 2 subjects in the ew/eow group and adalimumab ew groups each gave birth to a healthy infant.

Overall, the safety profile of adalimumab treatment observed in this study is consistent with that expected for the study population of moderate to severe HS.

Conclusions:

Adalimumab 40 mg ew was superior to placebo in the treatment of abscesses and inflammatory nodules, reduction of skin pain, and health-related quality of life impairments for adult patients with moderate to severe HS. Continuous adalimumab ew therapy is more effective than step-down to adalimumab eow therapy or treatment interruption. Benefit was also demonstrated for patients with at least a partial response at Week 12 who continued on adalimumab ew. The clinical data support the assertion that the benefits in treating moderate to severe HS with adalimumab outweigh the known risks of adalimumab treatment, as administered in this study.