2.0 Synopsis

AbbVie Inc.	Individual Study Table Referring to Part of Dossier:	(For National Authority Use Only)
Name of Study Drug: Adalimumab	**Volume:** **Page:**	
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 I

Investigator:

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Study Sites: 48

Publications: None

Studied Period (Years):
    First Subject First Visit: 29 November 2011
    Last Subject Last Visit: 28 January 2014
	Phase of Development: 3

Objective:

The primary objective of this study 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.

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 every week (ew) or matching placebo 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.

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 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 receive adalimumab 40 mg ew.

| **Number of Subjects (Planned and Analyzed):** |
| Planned: 300 subjects |
| Analyzed: 307 subjects |

Diagnosis and Main Criteria for Inclusion:

Subjects were to have a diagnosis of HS for at least 1 year prior to Baseline; stable HS for at least 2 months prior to screening; HS lesions 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; 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 abscesses and 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 T-Spot TB test) and 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 must also not have received any oral antibiotic treatment for HS within 28 days prior to Baseline, prescription topical therapies for the treatment of HS within 14 days prior to Baseline, systemic non-biologic 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-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, 10-005763, 11-003870, 11-005882, 13-000648) or matching placebo (bulk lot numbers 08-018846, 11-004339, 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 achieving hidradenitis suppurativa complete response (HiSCR) at Week 12.

The following secondary efficacy variables were to be analyzed according to the rank order 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 (numeric rating scale [NRS] 30) – at worst at Week 12 among subjects with Baseline Skin Pain NRS   3

3. Change in modified Sartorius score from Baseline to Week 12

Secondary efficacy variables 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

*   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)

Criteria for Evaluation (Continued)

Efficacy (Continued):

- 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 one Hurley Stage in at least 1 affected anatomic region
- Proportion of subjects who experienced improvement by at least one Hurley Stage in at least 1 affected anatomic region
- Absolute and percentage change from Baseline in SF-36
- Change from Baseline in Hospital Anxiety and Depression Scale (HADS)
- Change from Baseline in Treatment Satisfaction Questionnaire with Medicine (TSQM)
- 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. Of note, 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
- Proportion of subjects who started oral antibiotic rescue therapy
- Change from Baseline in c-reactive protein (CRP)
- Percentage change from Baseline in CRP

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 arm and the difference in response rates (adalimumab – placebo) was compared using Cochran-Mantel-Haenszel (CMH) test, stratified by Baseline Hurley Stage (II versus III). In Period B, the analyses of each adalimumab arm versus placebo, and between the 2 adalimumab arms, were performed for the ITT_B Population. Categorical variables were analyzed by CMH adjusting for Baseline Hurley Stage (II/III). Continuous variables were analyzed by analysis of covariance (ANCOVA) with Baseline value and Baseline Hurley Stage (II versus III) 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 70 days after the last dose of the study drug. 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 and the all adalimumab treated population. Pretreatment AEs were also summarized. The analysis for 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 (MedDRA®) 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 the adalimumab group 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 event 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 adalimumab treatment group and placebo group in Period A was performed using a one-way ANOVA. The comparison of each adalimumab group versus placebo was performed using a one-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

Period A Efficacy Results:

In Period A, a statistically significantly higher percentage of subjects in the adalimumab ew group achieved HiSCR at Week 12 (primary efficacy endpoint) compared with subjects in the placebo group (41.8% [64/153] versus 26.0% [40/154]; $P = 0.003$). Furthermore, a greater proportion of subjects in the adalimumab group achieved HiSCR at each visit in Period A compared with subjects in the placebo group (P 0.05 at all visits).

Summary/Conclusions (Continued)

Period A Efficacy Results (Continued):

The study's ranked secondary endpoints did not achieve statistical significance. Additional secondary endpoints, although not considered confirmatory in nature, further substantiated the results of the primary endpoint:

- By Week 12, a higher proportion of subjects in the adalimumab ew group achieved AN50/75/100 compared with subjects in the placebo group. Improvement (both mean change and mean percent change) in AN count was higher for subjects in the adalimumab ew group compared with subjects in the placebo group.

- 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 inflammatory lesions were reduced more in subjects treated with adalimumab ew than with placebo.

- The risk of disease worsening (i.e., increase in inflammatory lesion count) was lower for subjects on adalimumab ew than for subjects on placebo and the length of time that the disease flare lasted was shorter for subjects on adalimumab ew than on placebo.

- A greater reduction in HS-related Patient's Global Assessment of Skin Pain was observed for subjects in the adalimumab group than for subjects in the placebo group. The proportion of subjects achieving NRS30 was numerically higher in the adalimumab ew group than in the placebo group.

- A greater improvement in the DLQI score was observed for subjects treated with adalimumab ew than with placebo.

Period B Efficacy Results:

ITT_B_R Population

Efficacy assessments from subjects who were randomized to adalimumab ew in Period A and re-randomized to Period B as HiSCR responders (ITT_B_R Population) showed generally better treatment outcomes among those continuing adalimumab ew treatment (ew/ew group) compared with subjects who reduced dosing frequency to eow or to placebo groups through 36 weeks. In addition, subjects who re-randomized to eow group showed generally better treatment outcomes than those to placebo.

Key results are as follows:

- Among HiSCR responders at Week 12, HiSCR was maintained for more subjects re-randomized to adalimumab than to placebo.

- Among HiSCR responders at Week 12, subjects in the ew/placebo group demonstrated a numerical trend toward a more rapid loss of response (LOR). Additionally, LOR was experienced most frequently in the ew/placebo group, and with similar frequency between the ew/ew and ew/eow groups.

- Across a number of secondary endpoints in Period B (AN count of 0, 1, or 2; AN50; AN75; NRS30; change in HS-related Patient's Global Assessment of Skin Pain; modified Sartorius score; lesion counts; and DLQI), subjects who received adalimumab ew had better outcomes than those who reduced their dose to eow or placebo.

Summary/Conclusions (Continued)

Period B Efficacy Results (Continued):

ITT_B_NR Population

Efficacy assessments from subjects who were randomized to adalimumab ew in Period A and re-randomized to Period B as HiSCR non-responders (ITT_B_NR Population) showed better treatment outcomes among those continuing adalimumab ew treatment (ew/ew group) compared with subjects in the ew/eow or ew/placebo groups.

Key results are as follows:

- The proportion of subjects who achieved HiSCR was higher for subjects in the ew/ew group compared to subjects in the ew/eow and ew/placebo groups.
- A lower proportion of subjects in the ew/ew group experienced WOAI compared with subjects in the ew/eow and ew/placebo groups.
- Across a number of secondary endpoints (AN count of 0, 1, or 2; AN50; AN75; NRS30; modified Sartorius score; lesion counts; and DLQI), subjects who were re-randomized to ew/ew showed greater efficacy than subjects re-randomized to the ew/eow or ew/placebo groups.
- All subjects who achieved AN25 at the end of Period A and continued to adalimumab ew in Period B were able to achieve HiSCR at Week 36.

Combined ITT_B_R and ITT_B_NR Populations and ITT_B_PRR Population

Efficacy assessments from subjects in the ITT_B_PRR Population (i.e., subjects in the ITT_B_R Population who achieved HiSCR at the end of Period A and subjects who achieved a partial response [AN25] at the end of Period A in the ITT_B_NR Population), which was identified post hoc, showed better treatment outcomes among those continuing adalimumab ew treatment, as compared to subjects who reduced dosing frequency to adalimumab eow or who received placebo.

When efficacy in Period B was analyzed for all subjects from the Period A adalimumab ew group together (Combined ITT_B_R and ITT_B_NR Populations), the HiSCR rate was maintained among subjects continuously treated with weekly adalimumab, while the HiSCR rates were reduced for those in the ew/eow and ew/placebo group. Across a number of secondary endpoints in Period B; including AN count of 0/1/2, AN50, AN75, NRS30, and changes in modified Sartorius score, lesion counts, and DLQI; subjects who received adalimumab ew generally achieved greater efficacy than those who received adalimumab eow; subjects in both adalimumab dose groups generally achieved better improvement than placebo-treated subjects.

ITT_EW Population

The results from subjects who received placebo in Period A and were re-randomized to adalimumab ew in Period B (ITT_B_EW Population) confirmed the efficacy of adalimumab ew that was observed in Period A.

Summary/Conclusions (Continued)

Safety Results:

In Study M11-313, adalimumab was generally safe and well tolerated as evaluated by TEAEs, laboratory values, and vital signs values. During Period A, the proportions of subjects with any adverse event, including SAEs, were comparable between adalimumab and placebo treatment groups. Furthermore, in Period B, the safety profile associated with adalimumab ew dosing was comparable to that of adalimumab eow dosing. The most common AEs among adalimumab-treated subjects across both periods; including hidradenitis (considered to be exacerbation of underlying disease), nasopharyngitis, headache, and upper respiratory tract infection; are expected for this population of subjects with moderate to severe HS and are comparable to the proportions of subjects who have been noted to experience these adverse events in other adalimumab clinical trials. Of note, during Period B, events of hidradenitis were reported by a lower proportion of subjects in the ew/ew group than the ew/placebo group and the ew/eow group. The majority of TEAEs were mild or moderate in intensity. The rates of discontinuation due to AEs were relatively balanced across treatment groups in both Periods A and B. No deaths were reported in this study. The only malignancy reported in this study was in the placebo group of Period A. One infectious SAE was reported in the adalimumab ew group in Period A; 2 infectious SAEs were reported in Period B (1 event of pneumonia in the placebo/ew group, 1 event of pyelonephritis in the ew/placebo group).

No clinically meaningful changes in laboratory parameters or vital signs were noted in adalimumab-treated subjects. There were 5 pregnancies reported in this study, the outcomes of 3 of which were reported as SAEs (1 ectopic pregnancy that was considered possibly related to study drug, 1 ectopic pregnancy that was considered not related to study drug, and 1 induced abortion that was considered not related to study drug).

Overall, the safety profile of adalimumab treatment observed in this study is expected given the population of moderate to severe HS and is consistent with the experience in other adalimumab clinical trials.

Conclusions:

In this clinical study of adalimumab in subjects with moderate to severe HS, adalimumab was efficacious, generally safe, and well tolerated. Adalimumab more effectively reduced the inflammatory lesions of moderate to severe HS (acne inversa) than placebo. Further, the numbers of abscesses, inflammatory nodules, and draining fistulas decreased more in subjects in the adalimumab group than in the placebo group, and higher reduction in skin pain and improvement in DLQI were observed in subjects in the adalimumab group compared to the placebo group. Subjects who had received adalimumab ew in Period A and continued on adalimumab ew dosing in Period B generally had better outcomes across a number of secondary endpoints in Period B; including AN count of 0/1/2, AN50, AN75, NRS30, and changes in modified Sartorius score, HS-related Patient's Global Assessment of Skin Pain, lesion counts, and DLQI compared with subjects who were re-randomized to adalimumab eow or placebo in Period B. Efficacy generally was greater for subjects in Period B who continued on adalimumab ew, even if they failed to achieve HiSCR by Week 12, compared with such subjects who were re-randomized to adalimumab eow or placebo. In this study, the rates of TEAEs, laboratory values, and vital signs values were comparable between adalimumab and placebo treatment groups. Based on the experience of 36 weeks of adalimumab treatment, the safety profile of adalimumab was as expected for the population of subjects with moderate to severe HS and is consistent with the experience of previous other adalimumab clinical studies, and the benefit-risk balance for adalimumab weekly dosing for treatment of moderate to severe HS appears favorable.