Synopsis

Abbott Laboratories	**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 2 Multicenter Study of the Safety and Efficacy of Adalimumab in Subjects with Moderate to Severe Chronic Hidradenitis Suppurativa

Coordinating Investigator: Alexa Boer Kimball, MD, Massachusetts General Hospital, Boston, MA 02114

Study Sites: 26 sites in the US, Netherlands, Denmark, and Germany

Publications: None

Studied Period (Years):	**Phase of Development:** 2
First Subject First Visit: 22 April 2009	
Last Subject Last Visit: 09 November 2010	

Objectives:

The primary objective of this study was to determine the efficacy and safety of adalimumab in subjects with moderate to severe chronic hidradenitis suppurativa (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 pharmacokinetics (PK) and immunogenicity of adalimumab following subcutaneous (SC) injection were also assessed.

Methodology:

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. Approximately 150 adult subjects with moderate to severe chronic HS were planned to be enrolled. The study included a 30-day Screening period, a 16-week placebo-controlled period, a 36-week OL period, and a 70-day follow-up period (phone call).

Subjects were to return to the site for the Baseline visit within 30 days from the date of the Screening visit. Study visits were to occur at Baseline and at Weeks 2, 4, 8, 12, 16, 20, 24, 28, 31, 39, 45, and 52 or Early Termination (ET). Additionally, all subjects were to be contacted via telephone at Weeks 6, 10, 14, and 22 to monitor signs or symptoms of infection at or near an HS lesion. If any signs or symptoms were reported at the time of the call, an unscheduled study visit was to be conducted to assess whether a secondary infection was present. Each subject was to be given an information card with information on signs and symptoms of infections at or near an HS lesion with instructions to contact the site immediately if any signs or symptoms of such an infection developed.

Methodology (Continued):

Subjects may have discontinued from the study at any time. Subjects who prematurely discontinued from the study prior to Week 52 were to have an ET visit. All subjects were to have a follow-up phone call 70 days after the last administration of study drug to determine the status of any adverse events (AEs) or the occurrence of any serious adverse events (SAEs).

In the DB period, subjects were randomized in a 1:1:1 ratio at Week 0 to receive adalimumab (40 mg every week [ew; same as qwk in the protocol] or 40 mg every other week [eow]) or matching placebo. Randomization was to be stratified by Hurley stage (Stage III versus Stage I or II) for HS. Enrolled subjects with Hurley Stage III were not to exceed 50%.

Subjects randomized to adalimumab 40 mg ew were to receive a loading dose of adalimumab 160 mg at Week 0 and adalimumab 80 mg at Week 2, followed by adalimumab 40 mg ew starting at Week 4 through Week 15. Subjects randomized to adalimumab 40 mg eow were to receive a loading dose of adalimumab 80 mg at Week 0, followed by adalimumab 40 mg eow starting at Week 1 through Week 15. Subjects randomized to placebo were to receive matching placebo, administered ew, starting at Week 0 through Week 15. In order to maintain the blind in the DB period, all subjects received 4 injections at Week 0; 1 injection at Week 1; 2 injections at Week 2; 1 injection ew from Week 3 through Week 15; and 2 injections at Week 16 in a blinded fashion.

All subjects enrolled in the study who completed the DB period were eligible to participate in the OL period. In the OL period, subjects were to receive OL adalimumab 40 mg eow with the option to escalate to ew dosing. Subjects from the placebo arm in the DB treatment period were to receive a blinded dose of 80 mg adalimumab at Week 16 in the OL treatment period. All subjects were to be treated with 40 mg eow starting at Week 17 through Week 28. At Week 28 or 31, if a subject had a Physician's Global Assessment (PGA) of moderate disease or worse (score of ≥ 3), the principal investigator, and the subject were to evaluate the risk/benefit of having the subject dose escalate to ew adalimumab. If the subject dose escalated to ew adalimumab, the subject was to remain on ew adalimumab for the remainder of the study. Subjects who did not dose escalate at Week 28 or Week 31 were to remain on eow adalimumab through Week 51.

Number of Subjects (Planned and Analyzed):

Planned: 150 subjects

Analyzed: 154 subjects

Diagnosis and Main Criteria for Inclusion:

- Males and females ≥ 18 years of age.
- Diagnosis of HS for at least 6 consecutive months that involves ≥ 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.

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

Adalimumab 40 mg/0.8 mL, pre-filled SC syringes

Bulk Product Lot Numbers: 07-012406, 08-019941, 09-025414

Duration of Treatment: 52 weeks including a 30-day Screening period, 16 weeks of placebo-controlled treatment, 36 weeks of OL 40 mg adalimumab eow treatment, and a 70-day follow-up phone call.

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

Placebo

Bulk Product Lot Numbers: 08-018846

Criteria for Evaluation

Efficacy:

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.

Secondary efficacy variables for the intent-to-treat (ITT) populations included:

- Proportion of subjects who achieved a clinical response at each visit (other than at Week 16)
- Proportion of subjects who achieved PGA of clear, clear/minimal, clear/minimal/mild, and ≥ 1 grade and ≥ 2 grades of improvement relative to Baseline
- Proportion of subjects achieving complete clearance of abscesses, complete clearance of draining fistulas, complete clearance of abscesses and draining fistulas, and complete clearance of inflammatory nodules
- Proportion of subjects achieving an AN (abscesses and inflammatory nodules) 50/60/75/90/100 (50%/60%/75%/90%/100% reduction in total AN count relative to Baseline)
- Proportion of subjects achieving an AN50 with no increase in abscess count and no increase in draining fistula count relative to Baseline
- Proportion of subjects with Dermatology Life Quality Index (DLQI)=0 and DLQI=0/1
- Proportion of subjects achieving 30% reduction and at least 10 mm reduction from Baseline in Patient's Global Assessment of skin pain (visual analogue scale [VAS])
- Proportion of subjects who achieved "complete or good disease control" in the Patient's Global Assessment of disease activity

Criteria for Evaluation (Continued)

Efficacy (Continued):

- Absolute and percent change from Baseline in number of each type of lesions and in total count of AN
- Absolute and percent change from Baseline in Patient's Global Assessment of skin pain (VAS)
- Change from Baseline in
    - Sartorius scale
    - DLQI
    - Patient Health Questionnaire-9 (PHQ-9)
    - European Quality of Life – 5 Dimensions questionnaire (EQ-5D)
    - Work Productivity and Activity Impairment Questionnaire – Specific Health Problem (WPAI-SHP): Specific Health Problem
    - Number of ER/acute care visits per 4-weeks
    - Average number of minutes per day to get ready in the past 7 days
- Number of interventions during Period 1

In addition, time to PGA of 3 or worse among subjects who had PGA < 3 at entry of Period 2 was analyzed in the ITT-2 population.

Key efficacy variables were summarized in the Dose Escalation population at Week 52.

Pharmacokinetic: Summary statistics for adalimumab serum concentration at each time of scheduled sampling were to be calculated. In addition, PK model-based analyses were to be performed with the focus on apparent clearance (CL/F) and volume of distribution (V/F). The PK variables assessed in this study are described in a separate report R&D/11/528.

Safety: AE, physical examination, vital signs, and laboratory data were assessed throughout the study.

Statistical Methods

Efficacy:

All statistical tests were 2-tailed with the significance level 0.05. All *P* values were rounded to 3 decimal places. Descriptive statistics were provided that included the number of observations, mean, and standard deviation for continuous variables, and counts and percentages for discrete variables. The following populations were used to analyze efficacy and safety.

Statistical Methods (Continued)

Efficacy (Continued):

The ITT population in each period and the ITT population for integrated analysis across Period 1 and Period 2 were used for the efficacy analyses.

- The ITT Population in Period 1 (ITT-1) included all subjects who were randomized 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.
- 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. ITT-Int was used to evaluate the efficacy of 2 dosing strategies, adalimumab 40 mg ew followed by 40 mg eow (step-down) versus continued adalimumab 40 mg eow. The ITT-Int population was analyzed in 2 ways, with and without the option of dose escalation.

Safety was analyzed in the following safety populations.

- The Safety population for each period and the Safety population for the integrated analysis across periods included all subjects who were in the corresponding ITT populations and received ≥ 1 dose of study drug in the corresponding period.
- All Adalimumab Treated population included subjects who received ≥ 1 dose of adalimumab in the study.
- The Eow population included all subjects who received adalimuamb 40 mg eow in Period 1 and subjects who switched from placebo in Period 1 to adalimumab 40 mg eow in Period 2. If a subject dose escalated, the evaluations after the start of dose escalation were excluded from the analysis in the Eow population.

In addition, safety and efficacy analyses were summarized in the Dose Escalation population, defined as all subjects who dose escalated from 40 mg eow to 40 mg ew.

Statistical Methods (Continued)

Efficacy (Continued):

The primary analysis was the comparison between each of the adalimumab treatment groups and the placebo treatment group in the proportion of subjects achieving a clinical response as defined by achieving a PGA of clear, minimal, or mild, with a minimum of 2 grades improvement (reduction) from Baseline on the PGA at Week 16. The Cochran-Mantel-Haenszel (CMH) test with factors of treatment and Baseline Hurley staging was used for the analysis. An initial overall comparison of the 3 treatment groups was tested. If this was significant, pairwise comparison of each adalimumab dose group versus placebo was performed. If the homogeneity was rejected (at the alpha level of 0.05), the analysis was performed separately for each stratum.

The primary analysis was carried out in the ITT population in Period 1. Non-responder imputation (NRI), where subjects missing the Week 12 visit were counted as non-responders, was used as the primary approach to impute the missing values.

The CMH test and analysis of covariance (ANCOVA) with factors of treatment and Hurley stage were used to assess the treatment differences for discrete variables and continuous variables, respectively. Missing values were imputed by NRI (primary approach) and last observation carried forward (LOCF, sensitivity analysis) for categorical variables, and by LOCF (primary approach) and as observed (sensitivity analysis) for continuous variables.

Pharmacokinetics:

PK methods are described in a separate report R&D/11/528.

Safety:

Safety analyses were carried out using the safety population in each period, the All Adalimumab population, the EOW population, and the Dose Escalation population. All pairwise comparisons were performed on the Safety population in Period 1. The comparison of eow/eow and ew/eow groups was performed using data from Week 0 to Week 52, excluding the dose escalation period. Pretreatment AEs were summarized as well. A treatment-emergent AE (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. The number and percent of subjects experiencing TEAEs were tabulated using the MedDRA® system organ class (SOC) and preferred term (PT).

Summaries (including percentages and event per 100 patient-years [PYs]) of SAEs, deaths, AEs leading to discontinuation from the study, and pre-specified AEs of special interest were provided as well.

Statistical Methods (Continued)

Safety (Continued):

Mean change in laboratory and vital signs parameters at each visit were summarized for all treated subjects, and compared between each adalimumab treatment group and placebo group using a one-way ANOVA in the first period. The last evaluation prior to the first dose of study drug in Period 1 was to be used as Baseline for all analyses.

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

Summary/Conclusions

Efficacy Results:

This Phase 2 study was designed to evaluate the efficacy and safety of adalimumab in subjects with moderate to severe chronic HS. The 16-week DB placebo-controlled period assessed adalimumab at 2 dosing regimens (40 mg ew after a 160/80 mg loading dose or 40 mg eow after an 80 mg loading dose). In the 36-week OL period, all subjects started with OL adalimumab 40 mg eow and were permitted to dose escalate at Week 28 or Week 31 to 40 mg ew if the subject failed to achieve PGA < 3 through Week 51.

The study enrolled subjects with a diagnosis of moderate to severe HS (PGA ≥ 3) for at least 6 months prior to Baseline that involved ≥ 2 distinct anatomic areas. Subjects must have been unresponsive or intolerant to oral antibiotics for treatment for their HS. Randomization was stratified by Hurley staging (Stage III versus Stage I or II) for HS.

A total of 154 subjects were randomized: 51 to placebo, 52 to adalimumab eow, and 51 to adalimumab ew. All randomized subjects received ≥1 dose of study drug. No subjects received the wrong treatment in any study period. Baseline demographics were generally well balanced across treatment arms. The majority of all enrolled subjects were female (71.4%), white (71.4%), < 40 years old (63.6%), nicotine users (55.2%), and Hurley Stage II (55.2%). Mean weight for all enrolled subjects was 97.2 kg.

The primary endpoint for this study was the proportion of subjects achieving clinical response at Week 16, defined as a PGA score of clear (0), minimal (1), or mild (2), with a minimum of 2 grades improvement (reduction) from Baseline on the PGA at Week 16. A statistically significantly higher proportion of subjects in the adalimumab ew treatment group achieved clinical response, compared with subjects in the placebo group at Week 16 (17.6% versus 3.9%, $P = 0.025$) as well as at Week 12 (21.6% versus 5.9%, $P = 0.020$). The proportion of subjects in the adalimumab eow treatment group at Weeks 12 and 16 (7.7% and 9.6%, respectively) was not statistically significantly different from placebo. All responders were Hurley Stage I or II with the exception of 1 subject in the adalimumab ew group who was Hurley Stage III.

Summary/Conclusions (Continued)

Efficacy Results (Continued):

Treatment with adalimumab ew was superior to placebo in the majority of secondary endpoints evaluated, with statistically significant differences observed most often at Week 12 or Week 16. For most Period 1 secondary efficacy endpoints, ew treatment was more effective than eow treatment at Weeks 12 and 16, and notably fewer statistically significant differences were observed for comparisons between the adalimumab eow and placebo treatment groups. Specifically, a numerical trend for better efficacy with adalimumab ew compared with adalimumab eow was noted for the proportion of subjects experiencing improvement in PGA of ≥ 1 or ≥ 2 grades; the proportion of subjects achieving PGA scores of clear, minimal, or mild; the proportion of subjects achieving complete clearance of draining fistulas; mean percent improvement in the number of inflammatory nodules; mean percent reduction in pain VAS scores; proportion of subjects achieving ≥ 30% reduction in pain; mean decrease in DLQI; and mean decrease in PHQ-9 depression severity score.

The proportion of subjects achieving an AN50 response (≥ 50% reduction in the total number of inflammatory abscesses and nodules relative to Baseline), with no increase in abscess count and no increase in draining fistula count relative to Baseline, among subjects with > 2 inflammatory abscesses and/or nodules and ≤ 20 draining fistulas at Baseline was statistically significantly greater in the adalimumab ew group compared with the placebo group at Week 16 (54.5% versus 25.6%, $P = 0.007$).

Maintenance of response was assessed in subjects who had a PGA < 3 at entry into Period 2. During OL adalimumab eow treatment in Period 2, two-thirds of all subjects treated with adalimumab in Period 1 were unable to maintain this level of response or required dose escalation.

Among the 89 subjects who dose escalated, 14.6% achieved a clinical response at Week 52. Discounting the contribution of dose escalation at Weeks 28 or 31, the proportion of subjects achieving clinical response was low at Week 52, regardless whether subjects had initiated therapy with eow dosing or ew dosing.

Pharmacokinetic Results:

Pharmacokinetic results and conclusions are presented in a separate PK report (R&D/11/528).

Summary/Conclusions (Continued)

Safety:

Results from Study M10-467 demonstrated that adalimumab is generally safe and well tolerated for up to 52 weeks of treatment (16-week DB period and 36-week OL period) in subjects with moderate to severe chronic HS.

No statistically significant differences were observed between either of the adalimumab treatment groups compared to placebo or between the adalimumab treatment groups in the DB period.

Among subjects who received ≥ 1 dose of adalimumab at any time during the study:

- No subjects died.
- A total of 79.9% of subjects who received 1 dose of adalimumab at any time during the study experienced ≥ 1 TEAE. About half of subjects had TEAEs that were considered by the investigator to be possibly or probably related to study drug. The majority of subjects reported TEAEs that were mild to moderate in severity.
- Fifteen subjects reported ≥ 1 treatment-emergent SAE; 6 prematurely discontinued as a result. The majority of subjects had SAEs that were considered not related or probably not related to study drug by the investigator.

The safety and tolerability of adalimumab for up to 52 weeks was also demonstrated by evaluation of TNF-inhibitor-related events of interest. There were no reports of TB, lymphoma, NMSC, HSTCL, leukemia, melanoma, lupus-like syndrome, cutaneous or non-cutaneous vasculitis, demyelinating disorder, CHF, myocardial infarction, pulmonary embolism, diverticulitis, intestinal perforation, intestinal stricture, elevated ALT level TEAEs, adalimumab-related medication error TEAEs, Stevens-Johnson Syndrome, erythema multiforme, interstitial lung disease, pancreatitis, sarcoidosis, progressive multifocal leukoencephaolopathy, reversible posterior leukoencephalopathy syndrome, or ALS in any subject who received adalimumab during the study.

For those TEAEs of special interest that were reported, few subjects reported such events with the exception of infections:

- Fourteen subjects prematurely discontinued from the study due to a TEAE. Most subjects had events that were considered by the investigator as possibly or probably related to study drug; most subjects had events that were mild to moderate in severity.
- Infections were reported by 56.4% of subjects (84 subjects) who received ≥ 1 dose of adalimumab during the study. The most frequently reported infections were nasopharyngitis and upper respiratory tract infection. Six subjects had serious infections; 2 discontinued from the study as a result of their serious infection. One subject reported an opportunistic infection (cutaneous coccidioidomycosis; probably related) and 2 subjects reported parasitic infections (acarodermatitis and trichomoniasis; both probably not related).
- Twelve subjects reported ≥ 1 injection site-related TEAE. The most frequently reported injection site-related reaction among subjects who received ≥ 1 dose of adalimumab at any time during the study was injection site reaction. All other injection site-related reaction TEAEs were reported by ≤ 2% of subjects each. None were serious, severe, or led to premature discontinuation of the study. All were considered at least possibly related to study drug by the investigator.

Summary/Conclusions (Continued)

Safety (Continued):

- One subject reported a treatment-emergent malignancy (vocal cord neoplasm; serious; moderate in severity; probably not related). The subject eventually prematurely discontinued from the study as a result of the TEAE.
- Four subjects reported treatment-emergent allergic reactions during the study. All were non-serious, mild to moderate in severity, all resolved, and all of the subjects remained on the study.
- Five subjects reported hematological disorder TEAEs. Two subjects reported serious events (anemia; severe and possibly related and moderate in severity and probably not related).
- One subject reported non-serious mild increased ALT (possibly related) and AST (probably not related). The subject continued on study.
- One subject reported a CVA TEAE of non-serious transient ischemic attack (moderate; not related). The subject continued on study.
- Three subjects reported ≥ 1 new or worsening psoriatic condition. All were mild or moderate in severity and non-serious. The event in 1 subject was considered by the investigator as possibly related to study drug and those in the other 2 subjects were considered probably not related. Two of these subjects had a history of Ps.

The rates of TEAEs in the Eow population (538.8 events/100 PY) were higher than the rates in the Dose Escalation population (332.6 events/100 PY) and were similar to the rates of the All Adalimumab treated population (528.9 events/100 PY).

No safety concerns were identified in the analysis of clinical laboratory and vital signs parameters.

Conclusions:

Adalimumab therapy with dose escalation for suboptimal responders was effective for improvement of moderate to severe HS for up to 52 weeks, with most subjects requiring dose escalation to weekly dosing after de-escalation. Additionally, adalimumab was generally safe and well tolerated; the safety profile observed throughout the study was consistent with previous clinical trials for adalimumab, and no new safety signals were observed.

Date of Report: 29Sep2011