2.0 Synopsis

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

Title of Study:
A Controlled Study of HUMIRA® in Subjects with Chronic Plaque Psoriasis of the Hands and/or Feet

Coordinating Investigator:
Craig Leonardi, MD
[redacted]

Study Sites:
17 study sites in Canada and the United States

Publications: 2

Studied Period (Years): First Subject First Visit: 14 August 2008 Last Subject Last Visit: 30 July 2009	**Phase of Development:** 4

Objectives:
The objectives of this study were to evaluate the efficacy and safety of a 16-week course of subcutaneous (SC) HUMIRA® 40 mg every other week (eow) compared with placebo in adults with moderate to severe chronic plaque psoriasis (Ps) involving hands and/or feet and to examine the sustainability of that response for an additional 12 weeks of open-label (OL) treatment.

Methodology:
This study was a 2 period study with a placebo-controlled double-blind (DB) period and an OL period.

Period 1 (Week 0 – 16; DB): At Week 0, subjects were randomized in a 2:1 ratio to receive either active adalimumab (Arm A) or matching placebo (Arm B). Subjects in Arm A received a loading dose of 80 mg (two 40 mg injections) adalimumab at Week 0 followed by 40 mg eow adalimumab from Week 1 until Week 15. Subjects in Arm B received 2 placebo injections SC at Week 0 followed by 1 placebo injection SC eow from Week 1 to Week 15. At Week 16, subjects were evaluated for the primary endpoint of Physician's Global Assessment (PGA) of hands and/or feet.

Period 2 (Week 17 – 28; OL): At Week 16, subjects in Arm B switched from placebo to adalimumab. All subjects (Arm A and Arm B) received 2 injections at Week 16 to maintain the blind, with subjects in Arm A receiving placebo injections and subjects in Arm B receiving adalimumab (loading dose of two 40 mg injections). All subjects then received adalimumab 40 mg eow from Week 17 to Week 27.

Number of Subjects (Planned and Analyzed):

Planned: 75 subjects

Analyzed: A total of 81 subjects (27 placebo and 54 adalimumab) were randomized. Of these 81 subjects, 72 were included in the efficacy and safety analysis sets (23 placebo and 49 adalimumab). Nine subjects from one site were excluded from the main analyses due to investigator noncompliance.

Diagnosis and Main Criteria for Inclusion:

Subjects were to have been diagnosed with chronic plaque Ps of the hands/feet with a PGA of Ps ≥ 3 (according to the modified scale for Ps on the hands and/or feet), have had a diagnosis of moderate to severe plaque Ps for at least 6 months, and be considered by the investigator as candidates for systemic therapy.

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

Adalimumab 40 mg/0.8 mL SC injection

Lot numbers:

Adalimumab: 07-011702 and 07-014216

Placebo: 06-009051

Duration of Treatment:

Up to 28 weeks.

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 a PGA of 0 (representing no signs of plaque Ps) or PGA 1 (representing just perceptible erythema and scaling) using the PGA scale for Ps Involving the Hands and/or Feet at Week 16.

Secondary efficacy variables were:

- Change in erythema, scaling, induration, and fissuring (ESIF) from Baseline
- Proportion of subjects achieving at least moderate improvement (reduction in ESIF from Baseline > 50%)
- Proportion of subjects achieving marked improvement (reduction in ESIF from Baseline > 75%)
- Change in Nail Psoriasis Severity Index (NAPSI) of target nail from Baseline
- Change in Dermatology Life Quality Index (DLQI) from Baseline
- Proportion of subjects achieving a DLQI score of 0
- Proportion of subjects with PGA 0 or 1 or 2
- Proportion of subjects with PGA 0 or 1 (in addition to Week 16)
- Proportion of subjects with PGA 0
- Change in Work Productivity and Activity Impairment Questionnaire: Psoriasis (WPAI:PSO) from Baseline
- Change in Patient Health Questionnaire (PHQ-9) depression severity score from Baseline
- Proportion of subjects with difficulties according to PHQ-9

Criteria for Evaluation (Continued)

Efficacy (Continued):

- Change in visual analogue scale (VAS) Ps/psoriatic arthritis (PsA) pain
- Proportion of subjects with Psoriasis Area Severity Index (PASI) 50/75/90/100 response

Safety:

Adverse events (AEs) were monitored throughout the study. Standard laboratory evaluations, vital signs determinations, physical examinations, electrocardiogram, and chest x-ray were performed at specified time points throughout the study. Treatment-emergent adverse events (TEAEs) were defined as any AE with an onset date on or after the first adalimumab dose up to 70 days after the last adalimumab dose. For subjects who continued adalimumab therapy (commercial Humira®) after the discontinuation of study treatment, AEs that occurred within 70 days of the last study dose but after the first dose of non-study provided adalimumab were not to be reported in Study M10-405. Events for all subjects that were reported during Study M10-405 and were ongoing as of termination were to be followed up and any updated information or end date was to be captured in the study database.

Statistical Methods

Efficacy:

The primary and secondary efficacy variables were described by statistical characteristics. Categorical data were described by frequency and percentage, quantitative data by mean, standard deviation, minimum, first quartile, median, third quartile, and maximum. The number of nonmissing values was given. For quantitative "change from Baseline" efficacy variables, the change, as well as visit and Baseline values, were included in the descriptive analysis for those subjects who had both visit and Baseline values.

Descriptive analyses in Period 1 were presented by randomized treatment group as well as overall. Descriptive analyses in Period 2 were reported stratified by the treatment the subject was randomized to in Period 1 and overall. All statistical tests were 2-tailed.

All analyses of the OL Period 2 were descriptive.

Safety:

AEs, including special events of interest, were analyzed separately for Period 1 and Period 2, as well as for both periods together. For the analysis of Period 1, comparisons between treatment groups of the percentage of subjects experiencing an AE were performed using Fisher's exact tests. AEs that started prior to the first injection of study drug in Period 2 were analyzed for Period 1; AEs that started on or after the date of the first injection of study drug in Period 2 were analyzed for Period 2.

TEAEs are defined as any event with an onset date after the first dose of study drug and with an onset date no more than 70 days after the last dose of study drug, or until the subject received commercial Humira, if applicable.

AE data were summarized and presented using primary Medical Dictionary for Regulatory Activities (MedDRA) system organ classes (SOCs) and preferred terms (PTs) according to the most current implemented MedDRA version. Subjects reporting > 1 AE for a given MedDRA PT were counted only once for that PT (most severe incident for the severity tables and most related incident for the relationship tables). Subjects reporting more than one type of AE within a SOC were counted only once for that SOC. Subjects reporting more than one type of AE were counted only once in the overall total.

Statistical Methods (Continued)

Safety (Continued):

The number and percentage of AEs rated as at least possibly related to study drug (probably related or possibly related) were summarized using the same conventions described above.

AEs were summarized by maximum severity. If a subject had an AE with unknown severity, then the subject was counted in the severity category of "unknown," even if the subject had another occurrence of the same event with a severity present. The only exception was if the subject had another occurrence of the same AE with the most extreme severity. In this case the subject was counted in the severe category.

AEs were summarized by maximum relationship, as assessed by the investigator. If a subject had an AE with unknown relationship, then the subject was counted in the relationship category of "unknown," even if the subject had another occurrence of the same event with a relationship present. The only exception was if the subject had another occurrence of the same AE with a relationship assessment of "probably related" or "possibly related." In this case, the subject was counted under the "probably related" or "possibly related" category, as applicable.

Summary/Conclusions

Efficacy Results:

This study was conducted to evaluate the efficacy and safety of a 16-week course of adalimumab 40 mg eow compared with placebo in adults with moderate to severe chronic plaque Ps involving hands and/or feet and to examine the sustainability of that response for an additional 12 weeks of OL treatment.

The efficacy results of this study showed that 16 weeks of adalimumab compared to placebo was efficacious in the treatment of adults with moderate to severe chronic plaque Ps involving the hands and/or feet, and that the response for many endpoints at Week 16 was sustained at Week 28 following 12 additional weeks of OL adalimumab.

The primary efficacy variable was the proportion of subjects achieving a PGA 0 (clear) or PGA 1 (almost clear) using the PGA scale for Ps for the hands and/or feet at Week 16. Subjects who did not have PGA assessments at Week 16 were imputed as non-responders. At Week 16, a statistically significantly greater proportion of subjects who received adalimumab achieved PGA 0 or 1 for the hands and/or feet compared to subjects who received placebo (30.6% versus 4.3%, respectively; $P = 0.014$).

Statistically significant differences between the placebo and adalimumab groups at Week 16 were observed for the following endpoints in favor of adalimumab:

- Mean change from Baseline in total ESIF score (–10.92 adalimumab versus –5.04 placebo; $P = 0.037$)
- Mean change from Baseline in ESIF score for the palms (–5.80 adalimumab versus –2.65 placebo; $P = 0.038$)
- Proportion of subjects achieving at least moderate improvement in ESIF (> 50 % reduction from Baseline) (42.9% adalimumab versus 17.4% placebo; $P = 0.038$)
- Proportion of subjects achieving marked improvement in ESIF (> 75% reduction from Baseline) (28.6% adalimumab versus 4.3% placebo; $P = 0.027$)
- Mean change from Baseline in NAPSI (–1.67 adalimumab versus –0.13 placebo; $P = 0.017$)
- Proportion of subjects achieving a PASI 90 response (0 placebo versus 20.4% adalimumab; $P = 0.025$)

Summary/Conclusions (Continued)

Efficacy Results (Continued):

- Statistically significant differences between the placebo and adalimumab groups at Week 16 were observed in favor of adalimumab, and, for subjects who had been randomized to adalimumab at Week 0, Week 28 values met or exceeded Week 16 values for the following endpoints:
- Mean change from Baseline in total ESIF (Week 28 = –11.96, Week 16 = –0.92)
- Mean change from Baseline in ESIF of the palms (Week 28 = –6.59, Week 16 = –5.80)
- Mean change from Baseline in NAPSI (Week 28 = –2.00, Week 16 = –1.67)
- Proportion of subjects who achieved a PASI 90 (Week 28 = 20.4%, Week 16 = 20.4%)

Safety Results:

Adalimumab was generally safe and well tolerated as evaluated by TEAEs including deaths and serious adverse events (SAEs), TEAEs of special interest, laboratory values, and vital signs values.

No statistically significant differences were observed between groups for the proportions of subjects experiencing TEAEs during Period 1. In the 2 periods combined, > 79% of subjects in either group experienced at least one TEAE. The most frequently reported TEAE was nasopharyngitis (22.2%) followed by headache (11.1%). The majority of subjects reported TEAEs that were nonserious and mild or moderate in severity; 7 subjects experienced at least one TEAE that was severe. Most subjects experienced events that were probably not related or not related to study drug, as assessed by the investigator.

There were no deaths in this study. Serious TEAEs were reported by 1 subject who received placebo only and 2 subjects who received adalimumab from study start, 1 subject experiencing the event after treatment discontinuation. All serious TEAEs were considered severe. All serious TEAEs were considered by the investigator to be not related or probably not related to study drug, with the exception of 2 events, which occurred in one subject (breast mass and breast cancer; possibly related; received placebo only).

A total of 17.4% (4/23) of subjects randomized to placebo and 6.1% (3/49) of subjects randomized to adalimumab experienced a TEAE that led to premature discontinuation from the study. Just over half of subjects experienced at least 1 treatment-emergent infection; all were nonserious. One opportunistic infection was reported in a subject randomized to the adalimumab group (oral candidiasis; not related). No cases of tuberculosis were reported. One subject reported a malignancy (breast cancer) during the study. The subject was randomized to the placebo group and received placebo only. One subject experienced congestive heart failure. The subject was randomized to the adalimumab group and experienced pulmonary edema 43 days after treatment discontinuation. The investigator considered the event not related to study drug. No subject reported a serious treatment-emergent hepatic event.
One subject reported a treatment-emergent hepatic event that led to permanent discontinuation. The subject, who was randomized to the adalimumab group, permanently discontinued the study because of increased alanine and aspartate aminotransferase on Day 55 (5 days after treatment discontinuation). The events were severe and considered possibly related to study drug by the investigator.

No cases of lymphoma, nonmelanoma skin cancer, demyelinating disease, lupus/lupus-like reaction, or hematologic events (serious or leading to permanent discontinuation) occurred during the study.

No clinically meaningful changes in mean laboratory values were observed. Shifts to high or low values were generally infrequent. Changes in vital signs were clinically unremarkable.

Conclusions:

Adalimumab was efficacious, safe, and well-tolerated up to 28 weeks in adult subjects with moderate to severe chronic Ps involving the hands and/or feet. The significant efficacy noted for adalimumab-treated subjects at Week 16 in the primary endpoint was supported by significant improvements from Baseline noted with other hand/foot Ps efficacy measures (ESIF Palms) and with nail Ps measures (NAPSI). Among hfPGA responders, improvements relative to Baseline in DLQI and certain work productivity measures were substantial and clinically relevant. The safety profile of adalimumab-treated subjects was consistent with what has been observed in other adalimumab Ps clinical trials.