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, Randomized, Double-Blind, Placebo-Controlled, Multicenter Study to Assess the Safety and Efficacy of Adalimumab (Humira®) in Chinese Subjects with Moderate to Severe Plaque Psoriasis (Ps)

Investigator:

Jianzhong Zhang

[redacted]

Study Sites: 16

Publications: None

Studied Period (Years): First Subject First Visit: 14 August 2012 Last Subject Last Visit: 21 December 2013	**Phase of Development:** 3

Objective:

The primary objective of this study was to evaluate the safety and efficacy of adalimumab in Chinese subjects with moderate to severe plaque Ps.

Methodology:

The study consisted of a 30-day screening period, an initial 12-week double-blind treatment period (Period A), and a subsequent 12-week open-label treatment period (Period B), plus a 70-day follow-up visit after the last dose of study drug administration.

Period A: A 12-week double-blind, placebo-controlled treatment period during which subjects were to be randomized at Week 0 (Day 1) in a 4:1 ratio to receive either adalimumab every other week (eow; starting at Week 1 through Week 11, after 80 mg at Week 0 for the initial dose), or matching placebo.

Period B: A 12-week open-label treatment period. All subjects continuing to Period B regardless of the treatment in Period A were to receive adalimumab 40 mg eow starting at Week 13 through Week 23. At Week 12, subjects from the placebo arm in Period A were to receive a blinded dose of adalimumab 80 mg, while subjects from the adalimumab arm in Period A were to receive matching placebo.

Number of Subjects (Planned and Analyzed):

Planned: 420 subjects

Analyzed: 425 subjects

Diagnosis and Main Criteria for Inclusion:

Subjects were to have a clinical diagnosis of Ps for at least 6 months as determined by subject interview of his/her medical history and confirmation of diagnosis through physical examination by the investigator, stable plaque Ps for at least 2 months before Screening and Baseline visits as determined by subject interview of his or her medical history, and moderate to severe plaque Ps (defined by ≥ 10% Body Surface Area (BSA) involvement and Physician's Global Assessment of Ps (PGA) score of 'Moderate' at the Baseline visit). Subjects were also to have a Ps Area and Severity Index (PASI) score of ≥ 10 at the Baseline visit. Subjects must have had a negative tuberculosis (TB) screening assessment (including a 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 diagnoses of erythrodermic Ps, pustular Ps, medication-induced or medication-exacerbated Ps or new onset of guttate Ps were excluded, as were subjects who had a diagnosis of other active skin diseases or skin infections (bacterial, fungal, or viral) that may have interfered with the evaluation of Ps or subjects who could not discontinue topical therapies for the treatment of Ps. Subjects who had previous exposure to biologic therapy were also excluded.

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

Adalimumab 40 mg/0.8 mL SC injection (bulk lot number [redacted]) or matching placebo (bulk lot number [redacted])

Duration of Treatment:

24 weeks (12 weeks per study period)

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

None

Criteria for Evaluation

Efficacy:

The primary efficacy endpoint was the proportion of subjects achieving at least a 75% reduction in PASI score (PASI 75) at Week 12 relative to the baseline PASI score.

Secondary efficacy variables were:

- Proportion of subjects achieving PASI 75 response (except at Week 12, which is the primary endpoint)
- Percent change from baseline in PASI
- Change from baseline in PASI
- Proportion of subjects achieving PASI 50/90/100 response
- Proportion of subjects achieving PGA of 'clear'
- Proportion of subjects achieving PGA of 'clear or minimal'
- Proportion of subjects achieving DLQI of 0
- Proportion of subjects achieving DLQI of 0 or 1
- Change from baseline in DLQI
- Change from Baseline in the SF-36 Physical Component Score (PCS) and Mental Component Score (MCS) and the 8 sub-domains.

Criteria for Evaluation (Continued)

Safety:

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

Statistical Methods

Efficacy:

The primary analysis compared the adalimumab treatment group versus the placebo treatment group based on the proportion of subjects achieving PASI 75 at Week 12. The comparison was based on Pearson's chi-square test. All discrete secondary efficacy variables were analyzed by Pearson's chi-square test; in instances where 25% or more of the cells have expected counts of less than 5, a Fisher's exact test was used. All continuous secondary efficacy variables were analyzed using an analysis of covariance (ANCOVA) that included the baseline score as a covariate. The efficacy variables were summarized in Period B, where treatment groups were not compared. Key efficacy results were also analyzed by demographics and baseline characteristics.

Safety:

All 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 do not participate in Period B). Safety analyses were carried out using the safety population in each period and the All Adalimumab Treated population. Pretreatment AEs were also summarized. 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 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. 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 according to the most updated adalimumab risk management plan were also provided. Mean change in laboratory variables and vital sign variables were summarized at each visit. The comparisons of the adalimumab treatment group and placebo group in Period A were performed using a one-way ANOVA. 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 Terminology Criteria (CTC) of Grade 3 or higher was provided. Shift tables for changes from baseline according to the normal range were also provided.

Summary/Conclusions

Period A Efficacy Results:

Significantly more adalimumab-treated subjects achieved the primary endpoint, compared with subjects treated with placebo. The PASI 75 response rate at Week 12 was 77.8% for the 338 subjects randomized to adalimumab eow, compared with 11.5% for the 87 subjects randomized to placebo ($P < 0.001$). The results for the primary endpoint were supported by all secondary efficacy variables:

- Statistically significantly more subjects treated with adalimumab than placebo achieved PASI 50 and PASI 75 response at Weeks 3, 7, and 12; achieved PASI 90 response at Weeks 7 and 12; and achieved PASI 100 response by Week 12. Mean percentage improvement in PASI scores was statistically significantly greater for adalimumab eow versus placebo at Weeks 3, 7, and 12.
- Significantly more subjects treated with adalimumab than placebo achieved PGA 'clear' or 'minimal' at Weeks 3, 7, and 12, and achieved PGA of 'clear' at Weeks 7 and 12.
- Mean improvement in DLQI scores was significantly greater for adalimumab-treated subjects compared with placebo-treated subjects at Week 12. At Week 12, significantly more subjects treated with adalimumab than placebo in achieved a DLQI value of either '0' or '1.'
- Significant improvement in PCS, MCS, and the 8 domains of SF-36 were observed at Week 12.

Period B Efficacy Results:

- Clinically meaningful efficacy was sustained up to 24 weeks in the subsequent open-label Period B.

Safety Results:

In this study, adalimumab was generally safe and well tolerated as evaluated by TEAEs, laboratory values, and vital signs values. Comparing the adverse event profile of subjects treated with adalimumab eow versus placebo in Period A, the proportion of subjects with any adverse event, any serious adverse event, or any infectious adverse events were similar. The most common adverse events in Period A, upper respiratory tract infection and nasopharyngitis, were also similar between these groups and comparable to the proportions of subjects who have been noted to experience these adverse events in other adalimumab clinical trials. The majority of TEAEs were mild or moderate in intensity. The rates of discontinuation due to AEs were relatively balanced between adalimumab and placebo in Period A.

Period B was noteworthy for a [redacted] year-old subject (Subject [redacted]) who experienced a fatal AE of congestive cardiac failure, associated with myocarditis, lung infection, and arrhythmia. Congestive heart failure has been an AE noted in other adalimumab clinical trials, making this not a novel safety signal. Two cases of TB were noted, which has also been reported in other adalimumab clinical trials and post-marketing surveillance. Two cases of malignancy (gastric cancer and endometrial cancer) were detected, both of which have been noted in prior adalimumab clinical trials.

No clinically relevant changes in laboratory parameters or vital signs were noted in adalimumab-treated patients.

Overall, the safety profile of 24 weeks of adalimumab treatment in this study is consistent with the experience in other adalimumab clinical trials in subjects with Ps.

Summary/Conclusions (Continued)

Conclusions:

In this study of 12 weeks of double-blind treatment and 12 weeks of open-label treatment in subjects with moderate to severe plaque Ps in China, adalimumab was efficacious, generally safe and well tolerated. The large majority of subjects in this study achieved treatment success, as exemplified by PASI 75 response at Week 12 in adalimumab-treated subjects compared with placebo. Similar clinically relevant and statistically significant efficacy was also observed in all secondary efficacy endpoints. This considerable efficacy was sustained up to an additional 12 weeks. The safety profile of 24 total weeks of adalimumab treatment in this study is consistent with the experience in other adalimumab clinical trials in subjects with Ps.