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 Multicenter Study of the Efficacy and Safety of the Human Anti-TNF Monoclonal Antibody Adalimumab in Subjects with Peripheral Spondyloarthritis

Coordinating Investigator:

Philip Mease, MD

[redacted]

Study Sites:

28 study sites located in Australia, Belgium, Canada, the Czech Republic, France, Germany, Greece, Hungary, Ireland Spain, and the US.

Publications:

9 articles

Studied Period (Years): First Subject First Visit: 15 March 2010 Last Subject Last Visit: 12 May 2014	**Phase of Development:** 3

Objective:

The objective of this study was to evaluate the efficacy and safety of adalimumab 40 mg administered every other week (eow) subcutaneously (SC) compared to placebo for 12-weeks followed by OL safety and efficacy assessments in subjects with non-AS, non-PsA active peripheral SpA who have had an inadequate response to ≥ 2 non-steroidal anti-inflammatory drugs (NSAIDs), or are intolerant to, or have a contraindication for, NSAIDs.

Methodology:

This was a Phase 3, placebo-controlled, double-blind (DB), randomized study with an OL period conducted in the US, Canada, Europe, and Australia in subjects with non-AS, non-PsA peripheral SpA. The study included a 30-day Screening period, a 12-week DB placebo-controlled treatment period, a 144 week OL 40 mg adalimumab eow treatment period, and a 70-day follow-up phone call.

At Baseline (Day 1), subjects were randomized in a 1:1 ratio to receive either adalimumab or matching placebo. During the 12-week DB period, subjects were to visit the study site on Weeks 2, 4, 8, and 12. Upon completion of the DB period (Week 12), all subjects entered the OL period during which all subjects received adalimumab 40 mg SC eow for up to an additional 144 weeks.

Number of Subjects (Planned and Analyzed):

Approximately 154 subjects planned; 165 subjects analyzed.

Diagnosis and Main Criteria for Inclusion:

The subject was to be at least 18 years of age, was to have had an inadequate response to ≥ 2 non-steroidal anti-inflammatory drugs (NSAIDs), or be intolerant to, or have a contraindication for, NSAIDs. In addition, the subject was required to have current arthritis and/or enthesitis, and/or dactylitis and a) one or more of the following parameters: either anterior uveitis, Crohn's Disease (CD) or ulcerative colitis (UC), evidence of preceding infection, positive human leukocyte antigen (HLA)-B27, sacroiliitis on imaging OR b) at least 2 of the following spondyloarthritis (SpA) features: arthritis, enthesitis, dactylitis, inflammatory back pain in the past, or family history of SpA. In addition, the subject was not to have a history of psoriasis (Ps) or psoriatic arthritis (PsA), a diagnosis of ankylosing spondylitis (AS) at or before Screening, the presence of back pain ≥ 20 mm on a total back pain VAS at Screening or Baseline, an extra-articular manifestation (e.g., uveitis) that was not clinically stable for at least 28 days prior to Baseline, or a medical history of inflammatory arthritis of a different etiology other the peripheral SpA.

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

Adalimumab 40 mg/0.8 mL in prefilled syringes self-administered subcutaneously (SC). Lot numbers include the following: 08-019941, 09-025414, 10-001959, 11-003870, 11-005882.

Duration of Treatment: Up to 156 weeks of adalimumab exposure.

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

Placebo for adalimumab – 0.8 mL in prefilled syringes self-administered SC. Lot numbers include the following: 08-018846, 08-017132, 08-020877.

Criteria for Evaluation

Efficacy:

The primary efficacy endpoint was the proportion of subjects achieving the following composite Peripheral SpA Response criteria (PSpARC) response at Week 12: ≥ 40% improvement from Baseline in Patient's Global Assessment (PTGA) of disease activity, ≥ 40% improvement (minimum 20 mm absolute improvement) from Baseline in PTGA of pain, and ≥ 40% improvement from Baseline in at least 1 of the following 3 criteria: SJC (76 joints) and TJC (78 joints), enthesitis count, or dactylitis count. Ranked secondary efficacy variables that were analyzed at Week 12 included PGA of disease activity (VAS), BASDAI score, HAQ-S (total score), and SF-36™ v2 physical component (change from Baseline).

Safety:

Treatment-emergent adverse events (TEAEs), laboratory measures, and vital signs were summarized and reported.

Statistical Methods

Efficacy:

Improvement in the primary efficacy endpoint (PSpARC40 response) was assessed from the Baseline measurement (last measurement prior to first DB dose). The response rate observed in the group randomized to adalimumab 40 mg eow was compared to that in the placebo group. The response rates were tested using a 2-sided Pearson's Chi-square test with $\alpha = 0.05$. Subjects with missing primary endpoint responses at Week 12 were treated as non-responders according to non-responder imputation (NRI) criterion. Unless otherwise stated, all statistical comparisons of secondary efficacy variables were conducted between the adalimumab group and placebo group at Week 12 at the 2-sided $\alpha = 0.05$ significance level using a stepwise testing procedure. Testing for secondary endpoints was performed only if the primary efficacy endpoint was significant. Discrete variables were summarized using count and percentages, and were compared between adalimumab and placebo groups using Pearson's Chi-square or Fisher's exact test (if ≥ 25% of the cells had expected counts less than 5). Continuous efficacy variables were summarized by summary statistics (number of subjects, mean, 95% confidence interval, standard deviation, first quartile, median, third quartile, minimum, and maximum) at Week 12. Change from Baseline at Week 12 in the continuous variables was compared between adalimumab and placebo groups using an analysis of covariance (ANCOVA) method adjusting for the Baseline score. The OL extension data (post Week 12) was summarized descriptively. No statistical comparison was conducted based on the randomized treatment group.

Safety:

Safety analyses were carried out using the safety population, which included all subjects who received ≥ 1 dose of DB study drug. Treatment emergent AEs were summarized and reported. TEAEs were defined as AEs that began either on or after the first dose of the study drug, and within 70 days after the last dose of the study drug if subjects terminated from the study. The number and percent of subjects experiencing AEs were tabulated by body system and Medical Dictionary for Drug Regulatory Activities (MedDRA® version 17.0) preferred term (PT). In addition, summary of AEs by severity and relationship to study drug were presented. AEs, which were serious, severe, or life-threatening, which led to premature study discontinuation were listed and described in detail.

Mean change in laboratory variables and vital signs variables at each visit was summarized for all treated subjects, and compared between treatment groups 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 Toxicity Criteria (CTC) ≥ Grade 3 was provided. Shift tables for changes from Baseline according to the normal range were also provided for laboratory variables.

Summary/Conclusions

Efficacy Results:

A statistically significantly greater proportion of subjects in the adalimumab treatment group achieved PSpARC40 responses at Week 12 compared with placebo (ITT using the NRI analyses method; 39.3% versus 19.8%, $P = 0.006$). Similar results were observed using the PP population (42.1% versus 21.6%, $P = 0.007$). Sensitivity analyses were performed for the primary endpoint using the ITT population. Results similar to the primary efficacy analysis using NRI analysis were observed when using sensitivity analyses, which included OC, LOCF, Completer Cases, and Multiple Imputations analyses methods.

Ranked secondary efficacy variables that were analyzed at Week 12 included PGA of disease activity (VAS), BASDAI score, HAQ-S (total score), and SF-36v2 physical component (change from Baseline). The Week 12 analysis shows that that there was a statistically significant difference in favor of adalimumab 40 mg eow versus placebo for the first 2 ranked secondary efficacy endpoints. Ranked secondary endpoint 3 did not achieve statistical significance ($P = 0.051$). Therefore, although ranked secondary endpoint 4 was statistically significant ($P < 0.001$), this could not be claimed as further analysis could not be done beyond ranked secondary endpoint 3. To assess the impact of missing data from the efficacy analyses, sensitivity analyses were performed for the ranked secondary endpoints using the ITT population and the OC, Complete Cases, and Multiple Imputation methods. Results from all imputation methods were similar to the primary analyses performed for each of the ranked secondary efficacy endpoints.

Additional endpoints assessed at Week 12 through Week 156 provided supportive evidence for the robustness and durability of responses to adalimumab in this peripheral SpA subject population. Variables demonstrating a reduction in signs and symptoms of peripheral SpA (e.g., PSpARC20/50/70, ASDAS assessments, BASDAI50, and changes from Baseline in BASDAI total score, hs-CRP, and SPARCC enthesitis index score) achieved statistically significant results at Week 12 in favor of adalimumab. Responses were sustained or continued to improve at Week 24 (after 12 weeks of OL adalimumab treatment) and through Week 156.

Safety Results:

Safety results from this study for up to 156 weeks of adalimumab treatment in subjects with peripheral SpA were consistent with the known safety profile of adalimumab in other indications. Overall, 93.3% of subjects who received at least 1 dose of adalimumab during the study reported 1 or more TEAEs. One subject died (car accident) 56 days following discontinuation of OL adalimumab treatment. The event was considered not related to study drug by the investigator. Another subject died (pulmonary embolism) 5 days after completion of OL adalimumab treatment. The event was considered probably not related to study drug by the investigator. The investigator provided an alternative etiology of obesity. Throughout the study, all serious adverse events (SAEs) and TEAEs leading to premature discontinuation from the study, by specific PT, were reported by 1 subject each in the Any Adalimumab Safety Set (except for spondyloarthropathy, which was reported by 3 subjects). The majority of SAEs were considered not related or probably not related to study drug by the investigator. During the DB period, the most frequently reported TEAE that was possibly or probably related to study drug by the investigator was nasopharyngitis (4.8% for adalimumab subjects versus 13.6% for placebo subjects; Safety Analysis Set). Among subjects who received adalimumab at any time during the study, the most frequently reported possibly or probably related TEAEs were upper respiratory tract infection (10.3%), nasopharyngitis (7.9%), sinusitis (6.7%), bronchitis (5.5%), injection site reaction (4.8%), headache (3.6%), and oropharyngeal pain (3.6%).

Summary/Conclusions (Continued)

Safety Results (Continued)

The safety and tolerability of adalimumab for up to 156 weeks in this study was also demonstrated by the TNF-inhibitor-related events of special interest examined. No cases of legionella infection, oral candidiasis, active TB, reactivation of hepatitis B, progressive multifocal leukoencephalopathy (PML), lupus-like reactions and systemic lupus erythematosus (SLE), demyelinating disorder, cutaneous vasculitis, intestinal perforation related events, intestinal stricture related events, cardiovascular events (including myocardial infarction [MI] and CHF), interstitial lung disease, Stevens-Johnson Syndrome, pancreatitis, sarcoidosis, reversible posterior leukoencephalopathy syndrome (RPLS), amyotrophic lateral sclerosis (ALS), or adalimumab administration-related medication errors were reported during the study.

Conclusions:

In summary, the efficacy results of this study demonstrated that adalimumab is an effective treatment for reducing the signs and symptoms in active peripheral SpA subjects who had an inadequate response to ≥ 2 NSAIDs, or had intolerance to, or a contraindication for, NSAIDs. This was evidenced by the consistently significant improvements observed compared with placebo in various efficacy outcome measures that reflect the different aspects of the disease. Treatment response was maintained with continued adalimumab therapy of up to 156 weeks. Additionally, the safety results from this study for up to 156 weeks of adalimumab treatment in subjects with peripheral SpA were consistent with the known safety profile of adalimumab, and no new safety signals were observed.