

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 Multicenter, Randomized, Double-Dummy, Double-Blind Study Evaluating Two Doses of Adalimumab versus Methotrexate (MTX) in Pediatric Subjects with Chronic Plaque Psoriasis (Ps)			
Investigator: Kim Papp, MD K. Papp Clinical Research Inc. 135 Union Street East Waterloo, Ontario N2J 1C4			
Study Sites: 38 sites in Belgium, Canada, Chile, Czech Republic, Germany, Hungary, Italy, Mexico, Netherlands, Poland, Spain, Switzerland, and Turkey			
Publications: None			
Studied Period (Years): First Subject First Visit: 14 December 2010 Last Subject Last Visit: 03 February 2015 (date of last 70-day follow-up call)	Phase of Development: 3		
Objectives: The objectives of this study were to determine the safety and efficacy of 2 doses of adalimumab versus MTX in pediatric subjects with severe chronic plaque Ps, to determine the time to loss of disease control, the ability to regain response upon re-treatment, and to examine the pharmacokinetics (PK) and immunogenicity of adalimumab following subcutaneous (SC) administration in this subject population.			

Methodology:

This multicenter, randomized, double-blind, double-dummy study had a 30-day screening period and a multiperiod study design.

Period A – Primary treatment phase (16-week duration): Subjects were randomized to receive adalimumab 0.8 mg/kg, adalimumab 0.4 mg/kg, or MTX in 1:1:1 ratio.

Period B – Withdrawal phase (up to a 36-week duration): Responders were withdrawn from active treatment and monitored for loss of disease control (i.e., worsening of PGA in comparison to Week 16_A by at least 2 grades).

Period C – Retreatment phase (16-week duration): Subjects who had experienced loss of disease control were re-treated with adalimumab. Subjects who were initially randomized to adalimumab in Period A were to receive blinded re-treatment, according to their initial dose assignment (adalimumab 0.4 mg/kg or adalimumab 0.8 mg/kg). Subjects who were initially randomized to MTX were to receive adalimumab 0.8 mg/kg; however, subjects were blinded as to the dose of adalimumab that they were receiving.

Period D – Long-term follow-up phase (52-week duration): Subjects continued to receive adalimumab 0.8 mg/kg or adalimumab 0.4 mg/kg. Subjects who did not experience loss of disease control in Period B continued to be observed off study drug.

Number of Subjects (Planned and Analyzed):

111 subjects planned

114 subjects randomized and analyzed

Diagnosis and Main Criteria for Inclusion:

Subjects were to be children (from 4 to 11 years of age) and adolescents (from 12 through 17 years of age) with a clinical diagnosis of Ps for at least 6 months, as determined by the subject's medical history and confirmation of diagnosis through physical examination by the investigator. Eligible subjects must have failed topical therapy and required systemic therapy to control their disease with at least 1 of the following:

- Physician's Global Assessment (PGA) ≥ 4
- Body surface area (BSA) involved $> 20\%$
- Ps Area and Severity Index (PASI) > 20
- PASI > 10 and at least 1 of the following: active psoriatic arthritis unresponsive to nonsteroidal anti-inflammatory drugs (NSAIDs), clinically relevant facial involvement, clinically relevant genital involvement, clinically relevant hand and/or foot involvement, or Children's Dermatology Life Quality Index (CDLQI) > 10 .

Subjects who had prior biologic use other than prior treatment with etanercept, treatment with etanercept therapy within 4 weeks prior to the baseline visit, or MTX use within the past year or prior MTX use at any time where the subject did not adequately respond or did not tolerate MTX, were excluded. Subjects with infection(s) requiring treatment with intravenous (IV) anti-infectives within 30 days prior to the baseline visit or oral anti-infectives within 14 days prior to the baseline visit were also excluded.

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

Adalimumab 40 mg/0.8 mL for SC injection (bulk lot numbers: 9-022029, 10-005219, 11-005881, 13-001150).

Adalimumab 20 mg/0.8 mL for SC injection (bulk lot numbers: 09-024591, 11-000653, 13-003440).

Matching placebo for adalimumab (bulk lot numbers: 09-024593, 11-000422).

Duration of Treatment:

The total duration of the study varied for individual subjects, depending on their response to treatment and the time that a subject entered Period D. The total duration of study participation depended on a subject's length of duration in the different study periods. The minimum time in the study was to be 56 weeks (based on a minimum duration of 4 weeks in Period A and a maximum of 52 weeks in Period D) and the maximum time in the study was to be 120 weeks (based upon a subject losing control of disease at the Week 36_B visit and completing all other study periods). On completion of the study, each subject was to be treated according to the principal investigator's best clinical judgment.

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

MTX 2.5 mg tablets (bulk lot numbers: 10-002986, 11-001060).

MTX 10 mg tablets (bulk lot numbers: 10-002987, 10-003605, 11-001061).

Matching placebo for MTX 2.5 mg (bulk lot numbers: 10-003149, 12-001654) and 10 mg (bulk lot numbers: 10-003150, 12-001655).

Folic acid 0.4 mg tablets (bulk lot number: 10-004138) (sites in Czech Republic and Hungary only).

Criteria for Evaluation

Efficacy:

The primary efficacy endpoints were:

- The proportion of subjects achieving a \geq PASI 75 response at Week 16_A, adalimumab 0.8 mg/kg versus MTX.
- The proportion of subjects achieving a PGA 0,1 (cleared or minimal) at Week 16_A, adalimumab 0.8 mg/kg versus MTX.

The a priori defined order of the statistical hypotheses was:

1. Superiority of adalimumab 0.8 mg/kg versus MTX, regarding the proportion of subjects achieving a PASI 75 response at Week 16_A;
2. Superiority of adalimumab 0.8 mg/kg versus MTX, regarding the proportion of subjects achieving a PGA 0,1 (clear or minimal) at Week 16_A.

Criteria for Evaluation (Continued)

Efficacy (Continued):

The following secondary variables were evaluated per the ranking order as listed below:

1. The proportion of subjects achieving a PASI 90 at Week 16_A, adalimumab 0.8 mg/kg versus MTX;
2. The proportion of subjects achieving a PASI 100 at Week 16_A, adalimumab 0.8 mg/kg versus MTX;
3. Absolute change from baseline in the CDLQI scores at Week 16_A, adalimumab 0.8 mg/kg versus MTX;
4. Absolute change from baseline in the Pediatric Quality of Life Inventory (PedsQL) scores at Week 16_A, adalimumab 0.8 mg/kg versus MTX;
5. The proportion of subjects achieving PGA 0,1 (cleared or minimal) upon completion of re-treatment (Period C), according to the initial randomized group assignment in Period A (adalimumab 0.8 mg/kg versus adalimumab 0.4 mg/kg);
6. Time to loss of disease control (Period B), according to the initial randomized group assignment in Period A (adalimumab 0.8 mg/kg versus MTX);
7. Time to loss of disease control (Period B), according to the initial randomized group assignment in Period A (adalimumab 0.8 mg/kg versus adalimumab 0.4 mg/kg).

In addition to the primary and ranked secondary endpoints, the following efficacy endpoints were to be assessed at the different time points throughout the study:

- Proportion of subjects achieving a PGA 0,1 (cleared or minimal).
- Proportion of subjects achieving a PGA 0 (cleared).
- Proportion of subjects achieving \geq PASI 50/75/90/100.
- Mean % improvement in PASI score relative to baseline (Week 0_A).
- Change from baseline in CDLQI.
- Proportion of subjects with CDLQI = 0.
- Time to PASI 50/75/90/100 response.
- Change from baseline in PedsQL.
- Change from baseline in the Children's Depression Inventory: Short (CDI:S).

Safety:

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

Statistical Methods

Efficacy:

All efficacy analyses were to be based on the ITT population.

As the strict a priori order of hypotheses was to be adhered to for confirmatory statistical testing (step down procedure, including the ranked primary and ranked secondary endpoints), all statistical tests were to be done at a level of significance of 5% and the overall type I error level was still preserved.

Due to the expected small number of subjects per group with prior etanercept treatment, the primary confirmatory analysis was to be done using a chi-square test or Fisher's exact test, if the expected cell count was less than 5 at an alpha level of 5%. Analysis using a Cochran-Mantel-Haenszel test stratified for prior etanercept use was to be done as a sensitivity analysis. Subjects who did not have PGA or PASI assessments at Week 16_A were to be imputed as nonresponders in the primary analysis. Subjects who "early escaped" to OL adalimumab (Period D) during the initial 16-week Period A were also to be imputed as nonresponders for Week 16_A efficacy analyses.

Efficacy parameters were to be summarized using descriptive statistics.

The statistical comparisons for the ranked secondary endpoints were to be carried out in the hierarchical order described above. All statistical tests were to be 2-sided with a significance level of 5%.

Statistically significant results (P value ≤ 0.05) must have been achieved for a comparison in the higher rank, including the ranked primary endpoints, in order to initiate the next comparison in the lower rank.

Subjects with missing data were to be imputed as nonresponders for categorical variables and as LOCF for continuous variables for the primary analyses. Subjects who "early escaped" to OL adalimumab (Period D) during the initial 16-week Period A were also to be imputed as nonresponders for Week 16_A efficacy analyses.

For secondary endpoints and other efficacy endpoints, the chi-square test or Fisher's exact test, if expected cell count is less than 5; the 1-way ANOVA; and the log rank test were to be used to assess the treatment difference for discrete variables, continuous variables, and time to event variables, respectively.

Safety:

All safety analyses were to be based on the safety population, which includes all subjects who received at least 1 dose of study drug.

Treatment-emergent AEs were to be defined as events with an onset date after the first study drug until 70 days following the last study drug administration or until a subject initiates adalimumab therapy not supplied in the context of the clinical trial after the end of study participation, whichever is earlier.

Serious adverse events (SAEs) with onset after informed consent, but before the first study drug administration were to be considered as pre-treatment SAEs and reported separately.

Adverse events were to be tabulated using the most current Medical Dictionary for Regulatory Activities (MedDRA) by primary system organ class and preferred term. Summaries by severity and relationship to study drug were also to be done. Serious AES, severe AEs, and AEs leading to discontinuation were to be listed and described in detail. AEs of special interest for treatment with biologics were to be defined in the SAP and analyzed separately.

In all AE summaries, the number of subjects in a particular treatment group represents the number of subjects in the treatment group for which subjects were initially randomized (i.e., in Period A), whether or not it was the treatment being received when the event occurred.

Statistical Methods (Continued)

Safety (Continued):

AEs were to be summarized by frequency and percentage and presented for each initial randomized treatment group, as well as for the overall study. As by study design, subjects remained in the study for a variable length of time, so results for Period A, Period C, Period D, and for the overall study were also to be presented as events/100 patient years (E/100PYs). In addition, treatment emergent AEs reported from the first dose of adalimumab 0.8 mg/kg were also analyzed.

Comparisons of the percentages of subjects experiencing an AE between the dose groups were to be performed using Fisher's exact tests.

Other safety variables, such as laboratory data and vital signs, were to be described by descriptive statistics for each treatment group. Treatment comparisons were to be performed by 1-way ANOVA. In addition, shift tables and listings were to be provided for abnormal values, whereby the normal range of the analyzing laboratory was to be used.

Summary/Conclusions

After all subjects had completed Period C or discontinued from the study (cut-off date 02 December 2013), the study was unblinded and a pre-planned interim analysis was conducted. Results for Periods A, B and C as well as for the ongoing Period D were reported in an interim report

██████████. The current report includes the original analyses of Periods A, B, and C as reported in interim report ██████████ as well as final data from Period D, which is now complete. Unless otherwise specified, the data presented in this report for Periods A through C are from the interim report tables and data for Period D and overall are from the final report tables. Any important differences in data from Periods A, B, and C between the interim and final analyses are described. Both the interim report tables and final report tables are provided.

Efficacy Results:

Results of this study demonstrate that adalimumab 0.8 mg/kg reduces the severity of plaque Ps when administered for 16 weeks as initial treatment and retreatment after treatment withdrawal. Results also demonstrated that adalimumab 0.8 mg/kg was better at reducing the severity of plaque Ps than MTX or adalimumab 0.4 mg/kg. This is supported by the following:

- A statistically significantly higher proportion of subjects treated with adalimumab 0.8 mg/kg achieved a PASI 75 response after 16 weeks of treatment than subjects treated with MTX (57.9% versus 32.4%, respectively, $P = 0.027$).
- A 20% higher proportion of subjects treated with adalimumab 0.8 mg/kg achieved a PGA 0,1 (cleared, minimal) response after 16 weeks of treatment than subjects treated with MTX, although no statistical significance was observed.
- Approximately 80% of subjects who were nonresponders after 16 weeks of MTX treatment achieved a PGA 0,1 (cleared, minimal) response after being treated with adalimumab 0.8 mg/kg for 16 weeks in Period D.
- Subjects treated with adalimumab 0.8 mg/kg achieved PASI 75 and PGA 0,1 (cleared, minimal) responses earlier (as early as Week 4_A) than subjects treated with MTX. At Week 4_A, 23.7% of subjects treated with adalimumab 0.8 mg/kg achieved a PASI 75 response versus 0% of subjects treated with MTX ($P = 0.002$), and 28.9% of subjects treated with adalimumab 0.8 mg/kg achieved a PGA 0,1 (cleared, minimal) response versus 8.1% of subjects treated with MTX ($P = 0.021$).

Summary/Conclusions (Continued)

Efficacy Results (Continued):

- Approximately 90% of subjects originally treated with MTX who were nonresponders in Period A achieved a PASI 75 response with adalimumab 0.8 mg/kg after 16 weeks of treatment in Period D and sustained this response to the end of the study (Week 52_D).
- Approximately 50% to 60% of subjects regained a PGA 0,1 (cleared, minimal) response after re-treatment with adalimumab 0.8 mg/kg in Period C. A difference in response rates of 28.3% between subjects re-treated with adalimumab 0.8 mg/kg (i.e., subjects from the randomized adalimumab 0.8 mg/kg and MTX groups) and subjects re-treated with adalimumab 0.4 mg/kg was not statistically significant but was considered clinically relevant. A 10% higher proportion of subjects originally randomized to MTX achieved a PGA 0,1 (cleared, minimal) response than subjects originally randomized to adalimumab 0.8 mg/kg.
- The majority of subjects (78.9%) who were nonresponders with MTX in Period A and continued directly to Period D achieved a PGA 0,1 (cleared, minimal) response with adalimumab 0.8 mg/kg after 16 weeks in Period D, and the majority sustained this response to Week 52_D.
- Although the results were not statistically significant, subjects treated with adalimumab 0.8 mg/kg scored lower in CDLQI than subjects treated with MTX, indicating a more comprehensive improvement in skin-related quality of life.

Safety Results:

Safety data were consistent with the known safety profile of adalimumab in adult patients with Ps and pediatric patients with other conditions. No new safety risks were identified in the pediatric Ps study, as compared to adult Ps and as delineated in the current Humira[®] label, including a similar infection profile. No drug-related deaths or malignancies were observed in the clinical trial and no new autoimmune diseases were reported.

The frequency of SAEs in this long-term study was low; the total rate of SAEs 5.9 E/100 PYs for all subjects ever treated with adalimumab 0.8 mg/kg from the first dose of adalimumab 0.8 mg/kg and 7.4 E/100 PYs for all subjects treated with adalimumab (0.4 mg/kg and 0.8 mg/kg) from the first dose of adalimumab 0.8 mg/kg. One death due to an accidental fall occurred 11 days after the last dose of adalimumab 0.8 mg/kg in Period D, but before the last scheduled Period D visit. A total of 9 SAEs were reported in 8 subjects. SAEs that occurred during Period A were hand fracture, gastrointestinal infection due to food poisoning, and agitation, all of which occurred in subjects receiving adalimumab 0.4 mg/kg. One SAE of hemorrhagic ovarian cyst occurred in Period B in a subject who had been initially randomized to adalimumab 0.8 mg/kg. Five SAEs occurred during Period D, including the 1 death due to an accidental fall; tendon injury in a subject receiving adalimumab 0.4 mg/kg; rash maculo-papular in a subject receiving adalimumab 0.8 mg/kg; chest pain in a subject randomized to MTX, but receiving adalimumab 0.8 mg/kg; and eye nevus in a subject receiving adalimumab 0.8 mg/kg. All of the SAEs were considered by the investigator to be not related or probably not related to study drug with the exception of eye nevus, which was assessed as possibly related to study drug. The number of SAEs in subjects treated with adalimumab 0.8 mg/kg was not higher than the number of SAEs in subjects treated with adalimumab 0.4 mg/kg.

Summary/Conclusions (Continued)

Safety Results (Continued):

In addition to the 1 subject who had an accidental fall that resulted in death (discussed above), there were 2 subjects who discontinued because of an AE. One subject randomized to adalimumab 0.4 mg/kg discontinued due to a moderate event of Ps flare, and 1 subject initially randomized to MTX, but receiving adalimumab 0.8 mg/kg at the time of the event, discontinued due to an event of severe urticaria.

The most common AEs of special interest were infections (rate of all infections reported by subjects receiving adalimumab 0.8 mg/kg was 170.4 E/100 PYs). One event of serious gastrointestinal infection from food poisoning was reported in Period A by a subject receiving adalimumab 0.4 mg/kg. Most of the events of infection were nonserious respiratory infections that occurred in subjects randomized to adalimumab. Two subjects randomized to adalimumab reported mild or moderate events of herpes zoster in Period A that were considered by the investigator to be probably related to adalimumab and 1 subject had a moderate event of herpes zoster in Period D that was considered by the investigator to be possibly related to adalimumab. Overall, a higher rate of allergic reaction-related AEs (i.e., urticaria, pruritus, bronchospasm, and asthma) was seen in subjects initially randomized to MTX (18.2 E/100 PYs) than subjects initially randomized to adalimumab (4.5 E/100 PYs); all allergic reaction-related AEs were nonserious.

Subjects initially randomized to MTX experienced a slightly higher number of events of abdominal pain and/or nausea in Period A than subjects initially randomized to adalimumab and these events were qualitatively worse for subjects treated with MTX. The majority of subjects who reported injection site reaction-related AEs were randomized to adalimumab 0.8 mg/kg.

Assessing the safety profile of long-term treatment with adalimumab 0.8 mg/kg (exposure from first dose was 100.93 PYs in 98 subjects) confirmed the presence of no new identified safety risks. Results are similar to what has been observed in the adult Ps population and other pediatric populations, such as JIA and pediatric CD.

Two subjects had CTC \geq Grade 3 hematology values and 3 subjects had CTC \geq Grade 3 clinical chemistry values that were considered potentially clinically significant. The laboratory values decreased to $<$ Grade 3 for all but 1 subject, who had \geq Grade 3 hyponatremia (sodium value was 158 mmol/L on Post-treatment Day 5; all other sodium values were within normal range). Three subjects had potentially clinically significant values for liver function tests. Liver enzyme values returned to normal range for 1 subject, and 2 subjects still had elevated ALT/AST values (post-study follow-ups were planned, but no further information on results of retesting is available) or elevated bilirubin values (bilirubin values were high throughout the study, including during screening) at the last visit.

Three pregnancies were reported; 2 subjects discontinued early from the study because of the pregnancy and 1 subject's pregnancy was reported during the study follow-up. Each of the 3 subjects delivered a healthy infant. No significant complications during pregnancy, labor, or delivery and no birth defects were noted.

Conclusions:

There are limited treatment options for pediatric patients with severe chronic plaque Ps. Adalimumab 0.8 mg/kg eow reduces the severity of chronic plaque Ps and in many cases, clears the condition. Adalimumab was generally well tolerated and the safety profile was similar to that of MTX and consistent with previous clinical trial experience with adalimumab. Adalimumab 0.8 mg/kg eow has demonstrated statistically significant and clinically meaningful efficacy over MTX, which supports a favorable benefit-risk profile for pediatric patients from 4 to 17 years of age with severe chronic plaque Ps.

Date of Report: 05May2015