



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 Multicenter, Randomized, Double-Period, Double-Blind Study to Determine the Optimal Protocol for Treatment Initiation with Methotrexate and Adalimumab Combination Therapy in Patients with Early Rheumatoid Arthritis (OPTIMA)		
Coordinating Investigator: Prof. Dr. JS Smolen, Vienna General Hospital, Institute of Rheumatology, Clinic for Internal Medicine III, Währinger Gürtel 18-20, 1090 Vienna Austria		
Study Sites: 171 sites in Argentina, Australia, Austria, Belgium, Canada, Czech Republic, France, Germany, Hungary, Mexico, Netherlands, New Zealand, Norway, Poland, Puerto Rico, Slovakia, South Africa, Spain, Sweden, the United Kingdom, and the United States		
Publications: 6		
Studied Period (Years): First Subject First Visit: 28 December 2006 Last Subject Last Visit: 01 July 2010	Phase of Development: 4	
Objectives: The objective of this study was to compare the proportion of subjects who achieved low disease activity as defined by both a clinical response ($DAS28 < 3.2$) and no radiographic progression ($\Delta mTSS \leq 0.5$) at Week 78 (among those subjects who responded at Week 22 and 26, i.e., $DAS28 < 3.2$) in subjects treated with adalimumab (ADA) plus methotrexate (MTX; combination therapy) for 78 weeks (Arm 2) and subjects treated with placebo (PBO) plus MTX (monotherapy) for 78 weeks (Arm 4). Subjects who did not achieve a clinical response ($DAS28 < 3.2$) at Week 22 or Week 26 were not allowed to continue on their current treatment and were given open-label combination therapy (ADA+MTX) for the remainder of the study under ethical consideration. This study was also designed to evaluate the maintenance of clinical response in a population of subjects initially treated with combination therapy but subsequently with MTX monotherapy (by discontinuing adalimumab).		



Methodology:

This was a 78-week, multicenter, randomized, double-blind, double-treatment period study designed to compare the safety and efficacy of adalimumab and MTX compared to placebo and MTX in subjects with early RA. Subjects were randomized to receive adalimumab 40 mg eow or placebo injections in combination with MTX for 26 weeks (Period 1). All subjects in all arms received open-label MTX weekly throughout the study (both Period 1 and Period 2). Subjects achieving clinical response (defined as DAS28 < 3.2) at Week 22 and Week 26 in the combination arm at the end of Period 1 were randomized to receive placebo (MTX monotherapy) or combination therapy (adalimumab and MTX) in a 1:1 ratio for the duration of Period 2 (52 weeks). Subjects achieving clinical response at Week 22 and Week 26 in the placebo arm (MTX monotherapy) at the end of Period 1 continued to receive MTX monotherapy and placebo injections in a blinded fashion for the duration of Period 2. Subjects failing to achieve clinical response at Week 22 and Week 26 at the end of Period 1 received open-label combination therapy during Period 2 regardless of treatment assignment in Period 1. Period 2 treatment arms were as follows: ADA+MTX/PBO+MTX (Arm 1), ADA+MTX/ADA+MTX (Arm 2), ADA+MTX/OL ADA+MTX (Arm 3), PBO+MTX/PBO+MTX (Arm 4), and PBO+MTX/OL ADA+MTX (Arm 5).

Number of Subjects (Planned and Analyzed): 1,000 planned, 1,032 enrolled and analyzed

Diagnosis and Main Criteria for Inclusion:

Subjects were aged ≥ 18 years with diagnosis of RA as defined by 1987-revised ACR classification criteria and disease duration of < 1 year from diagnosis. Disease severity criteria included DAS28 > 3.2, ≥ 6 swollen joints, ≥ 8 tender joints, and ESR ≥ 28 mm/h or CRP ≥ 15 mg/L. Subjects must have been naïve to anti-TNF- α therapy and have previously been treated with > 2 DMARDs or MTX.

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

Adalimumab 40 mg/0.8 mL, administered eow as a SC injection solution in 1-mL, pre-filled syringe. Lot numbers were 06-007039, 07-010526, 07-011930, 07-011196, 08-017131, 08-015939, and 08-019941.

Methotrexate 2.5 mg tablets, administered orally. Lot numbers were 06-005610, 06-006012, 06-006014, 07-013273, 07-013318, 07-013275, 08-016506, 08-020605, and HM7112 (vendor lot number).

Duration of Treatment: Total study duration was up to 82 weeks and included a screening period of up to 28 days. The treatment period was 78 weeks, including 26 weeks in Period 1 and 52 weeks in Period 2. All subjects were to have a follow-up contact approximately 70 days after the last administration of the study drug to obtain information on any new or ongoing adverse events (AEs) except for subjects that continued on commercial adalimumab therapy after the end of their study participation.

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

Placebo matching adalimumab, administered eow as a SC injection solution in 1-mL, pre-filled syringe (DB period only). Lot numbers were 06-006518, 06-009051, and 08-018846.



Criteria for Evaluation

Efficacy:

The primary efficacy variable was the composite response at Week 78 defined by low disease activity (DAS28 < 3.2) and no radiographic progression from Baseline (Δ mTSS \leq 0.5). The primary efficacy variable was to be compared between subjects treated with combination therapy (both adalimumab and MTX) in a blinded fashion for 78 weeks and subjects treated with MTX monotherapy in a blinded fashion for 78 weeks (Arm 2 versus Arm 4).

Secondary efficacy variables were as follows:

- Composite response at Week 78 defined by DAS28 < 3.2 and Δ mTSS \leq 0.5 (comparison between Arm 1 and Arm 2)
- Response defined by DAS28 Low Disease Activity (DAS28 < 3.2) at Week 78
- Response defined by DAS28 Remission (DAS28 < 2.6) at Week 78
- Response defined by no radiographic progression (Δ mTSS \leq 0.5) at Week 78
- Response defined by ACR20 criteria at Week 78
- Response defined by ACR50 criteria at Week 78
- Response defined by ACR70 criteria at Week 78
- Response defined by ACR90 criteria at Week 78
- Response defined by ACR100 criteria at Week 78
- Change in DAS28 at Week 78
- Response defined by CDAI \leq 10 at Week 78
- Response defined by SDAI \leq 11 at Week 78
- Response defined by CDAI remission (\leq 2.8) at Week 78
- Response defined by SDAI remission (\leq 3.3) at Week 78
- Change in Clinical Disease Activity Index (CDAI) at Week 78
- Change in Simplified Disease Activity Index (SDAI) at Week 78
- Change in synovitis score according to the RA MRI Scoring System (RAMRIS) at Week 78 (for subjects enrolled in High-Field MRI substudy)
- Composite response defined by (Δ mTSS \leq 0.5 and HAQ < 0.5) at Week 78
- Composite response defined by (Δ mTSS \leq 0.5 and HAQ < 0.5 and ACR70) at Week 78
- Composite response defined by (Δ mTSS \leq 0.5 and HAQ < 0.5 and DAS28 < 2.6) at Week 78

The secondary efficacy variables 1 through 20 are not ranked in the sense that no statistical multiplicity adjustment was to be done. Secondary variables 2 through 20 were to be compared among Arms 1 and 2 as well as Arms 2 and 4.

Safety: Adverse events (including serious adverse events [SAEs] and AEs of special interest for adalimumab), clinical laboratory tests (hematology, chemistry, urinalysis, and liver function tests), and vital signs were assessed.



Statistical Methods

Efficacy: The primary efficacy variable, the composite response at Week 78 defined by low disease activity ($\text{DAS28} < 3.2$) and no radiographic progression from Baseline ($\Delta\text{mTSS} \leq 0.5$), was compared for Arm 2 (blinded combination therapy) versus Arm 4 (blinded MTX monotherapy). The null hypothesis associated with the above comparison states that there is no difference between Arm 2 and Arm 4; the alternative hypothesis is that there is a difference in the percentage of responders between the 2 groups. This hypothesis was tested at the 2-sided $\alpha = 0.05$ level of significance using Pearson's chi-square test. This analysis was based on the imputed response derived using the non responder imputation approach. Secondary efficacy variables were performed at the 2-sided $\alpha = 0.05$ significance level, without using a stepwise testing procedure or any alpha adjustment. Percentage of responders was compared among treatment groups where subjects with missing responses were imputed using the non-responder imputation approach. Changes in CDAI or SDAI were compared among treatment groups using an analysis of covariance adjusting for Baseline (ANCOVA). For each item in the ACR criteria, summary statistics of variation or percentage change from Baseline were calculated.

Safety:

The number and percentages of subjects experiencing treatment-emergent adverse events (TEAEs) were tabulated using the Medical Dictionary for Regulatory Activities (MedDRA[®]) version 13.1 system organ class (SOC) and preferred term (PT). Summaries by severity and relationship to study drug were provided. Serious, severe, or life-threatening TEAEs, TEAEs leading to discontinuation, and TEAEs of interest were listed and described in detail.

Other safety variables, such as clinical laboratory and vital sign data, were described by descriptive statistics. Shift tables and listings were provided for abnormal values based on the normal range of the analyzing laboratory or criteria pre-specified by the sponsor.

Summary/Conclusions

Efficacy Results:

This randomized, double-blind, double-treatment period study was designed to compare the proportion of subjects who achieved low disease activity, as defined by both $\text{DAS28} < 3.2$ and no radiographic progression ($\Delta\text{mTSS} \leq 0.5$) at Week 78 (among those subjects who responded at Week 22 and Week 26, i.e., $\text{DAS28} < 3.2$) in subjects treated with ADA+MTX (combination therapy) for 78 weeks (Arm 2) and subjects treated with PBO+MTX (monotherapy) for 78 weeks (Arm 4). The maintenance of clinical response in a population of subjects initially treated with combination therapy but subsequently with MTX monotherapy (by discontinuing adalimumab) was also evaluated.

Adult subjects with early RA (disease duration < 1 year) and naive to MTX were enrolled if they met all of the following disease severity criteria: $\text{DAS28} > 3.2$, $\text{SJC} \geq 6$, $\text{TJC} \geq 8$, and $\text{ESR} \geq 28$ mm/h or $\text{CRP} \geq 1.5$ mg/dL, and at least 1 of the following: > 1 erosion, RF positive, or anti-CCP antibody positive. A total of 1,032 subjects were enrolled, received at least 1 dose of study drug (ITT population), and were included in the efficacy analyses.



Summary/Conclusions

Efficacy Results (Continued):

At Baseline, the study population was similar between treatment groups. No significant differences in demographics, presenting Baseline disease conditions, ECG, CXR, and prior and concomitant medications were observed between treatment groups. Clinical response (defined as DAS28 low disease activity, DAS28 < 3.2) was achieved at Week 22 and Week 26 for 207 of 515 (40.2%) subjects in the ADA+MTX group and for 112 of 517 (21.7%) subjects in the PBO+MTX group. The 207 subjects from the ADA+MTX group were re-randomized to receive either ADA+MTX (N = 105) or PBO+MTX (N = 102), while the 112 subjects in the PBO+MTX group continued to receive PBO+MTX. The remaining 607 subjects who did not achieve a clinical response at Week 22 or Week 26 were given open-label combination therapy (OL ADA+MTX) for the remainder of the study.

In Period 1, approximately twice as many subjects with early RA that were treated with ADA+MTX achieved the stable low disease activity target at Weeks 22 and 26 compared to subjects treated with PBO+MTX.

All primary and secondary efficacy endpoints were at Week 78, the end of Period 2. The primary efficacy endpoint was low disease activity (DAS28 < 3.2) and no radiographic progression ($\Delta mTSS \leq 0.5$). A significantly greater percentage of subjects in the sustained combination therapy arm (ADA+MTX/ADA+MTX) compared to the sustained MTX monotherapy arm (PBO+MTX/PBO+MTX group) achieved this composite response at Week 78 (69.5% versus 54.5%, $P = 0.023$).

Of the 19 unranked secondary efficacy endpoints that compared sustained combination therapy (ADA+MTX/ADA+MTX) versus sustained MTX monotherapy (PBO+MTX/PBO+MTX group), 6 were statistically significant in favor of combination therapy, as follows: DAS28 remission (73.3% versus 58.9%, $P = 0.026$), ACR90 response (45.7% versus 31.3%, $P = 0.029$), change in DAS28 (-3.71 versus -3.04 , $P = 0.004$), change in CDAI (-33.29 versus -27.63 , $P = 0.030$), change in SDAI (-35.61 versus -29.30 , $P = 0.036$), and the composite response of no radiographic progression, normal function, and ACR70 (53.3% versus 38.4%, $P = 0.028$). Thus, among subjects who achieved clinical response (DAS28 low disease activity) at Week 22 and Week 26 and received either sustained ADA+MTX (Arm 2) or sustained PBO+MTX (Arm 4), results at Week 78 suggest a continuing benefit of combination therapy.

Of the 20 unranked secondary efficacy endpoints that compared sustained combination therapy (ADA+MTX/ADA+MTX) versus withdrawal of adalimumab following clinical response (ADA+MTX/PBO+MTX), 6 were statistically significant in favor of sustained combination therapy, as follows: DAS28 remission (73.3% versus 55.9%, $P = 0.009$), ACR70 response (69.5% versus 55.9%, $P = 0.043$), ACR90 response (45.7% versus 23.5%, $P < 0.001$), change in DAS28 (-3.71 versus -3.54 , $P = 0.048$), change in synovitis score in the HF MRI substudy (-3.38 versus 2.00 , $P < 0.001$), and the composite response of no radiographic progression, normal function, and ACR70 (53.3% versus 36.3%, $P = 0.014$). Thus, subjects who responded to combination therapy in Period 1 and were withdrawn from adalimumab in Period 2 evidenced a lower degree of response in both clinical and radiographic measures of disease over time compared with subjects who continued to receive combination therapy.



Summary/Conclusions

Efficacy Results (Continued):

Subjects who failed to achieve clinical response at Week 22 and Week 26 while receiving MTX monotherapy showed improvement in a number of efficacy measures after being switched to open-label combination therapy. For example, the proportion of subjects in the PBO+MTX/OL ADA+MTX arm who achieved DAS28 low disease activity increased from 10.1% at Weeks 26 to 53.2% at Week 78. By contrast, the proportion of subjects in the ADA+MTX/OL ADA+MTX who achieved DAS28 low disease activity increased from 18.5% at Weeks 26 to 41.7% at Week 78. Thus, in general, subjects who failed to achieve clinical response at Week 22 and Week 26 while receiving double-blind combination therapy did not show the same extent of improvement after being switched to open-label combination therapy as did subjects who had failed to respond while treated with double-blind MTX monotherapy.

Results from the low-field and high-field MRI substudies are reported separately (R&D/11/146).

Safety Results:

In Period 1, similar incidences of TEAEs, AEs at least possibly related to study drug, severe AEs, serious AEs, AEs leading to discontinuation of study drug, and SAEs at least possibly drug-related were observed in the ADA+MTX and PBO+MTX groups. In Period 2, the proportion of subjects with TEAEs, AEs at least possibly drug related, and severe AEs was slightly higher in the PBO+MTX/PBO+MTX (Arm 4) and ADA+MTX/PBO+MTX (Arm 1) groups than the ADA+MTX/ADA+MTX (Arm 2) group. In these 3 groups, the incidence of serious AEs was similar, and the number of subjects who discontinued due to AEs was small.

In total, there were 10 deaths in the study, 9 of which were treatment emergent. In Period 1, 1 subject in the PBO+MTX group and 5 subjects in the ADA+MTX group experienced fatal TEAEs; in Period 2, 1 subject in the ADA+MTX/OL ADA+MTX (Arm 3) group and 2 subjects in the PBO+MTX/OL ADA+MTX (Arm 5) group, respectively, had AEs that were fatal. All of these fatal AEs occurred posttreatment. In addition, there was 1 non-treatment emergent death reported in the ADA+MTX group in Period 1. Five fatal AEs were pulmonary events (Period 1: acute respiratory distress syndrome and interstitial lung disease [2 cases]; Period 2: bronchopulmonary aspergillosis and pneumonia). Six of the 9 fatalities in subjects treated with ADA+MTX were related to or occurred in close proximity with serious infections; 3 of the 6 subjects with infections were older than 70 years.

In Period 1, the PBO+MTX group alone had 1 subject with a parasitic infection other than opportunistic infection and 2 subjects with MI-related AEs; the ADA+MTX group alone had reports of interstitial lung disease AEs (4 subjects), malignancies (2 subjects), a lupus-like syndrome, a hematologic AE, a non-cutaneous vasculitis AE, an intestinal perforation related AE, a cerebrovascular accident related AE, and a tuberculosis AE. A smaller proportion of subjects in the PBO+MTX group than the ADA+MTX group reported injection site reaction related TEAEs, a reflection of the SC placebo versus adalimumab injections. The proportion of subjects reporting TEAEs in other AE categories was generally similar between treatment groups.

In Period 2, in several AE categories of special interest, no TEAEs were reported by subjects in the PBO+MTX/PBO+MTX (Arm 4), ADA+MTX/ADA+MTX (Arm 2), and ADA+MTX/PBO+MTX (Arm 1), including NMSC AEs, non-cutaneous vasculitis AEs, diverticulitis AEs, cerebrovascular accident-related AEs, psoriatic condition or worsening AEs, and CHF-related AEs.



Safety Results (Continued):

No subjects in any arm in Period 2 reported AEs in the following categories: lymphoma AEs, HSTCL AEs, leukemia AEs, melanoma AEs, lupus-like syndrome AEs, demyelinating disease AEs, cutaneous vasculitis AEs, intestinal perforation-related AEs, intestinal structure-related AEs, medication error-related AEs, Stevens-Johnson syndrome AEs, erythema multiforme-related AEs, sarcoidosis AEs, progressive multifocal leukoencephalopathy AEs, reversible posterior leukoencephalopathy syndrome AEs, and ALS AEs.

Similar proportions of subjects in Arm 4 and Arm 1 compared with Arm 2 reported infections (41.1% and 38.2%, respectively, versus 39.0%) with a slightly smaller proportion of subjects in Arm 4 (1.8%) and a similar proportion of subjects in Arm 1 (3.9%) versus Arm 2 (5.7%) reporting serious infections. Opportunistic infections other than TB were few overall: no subject in Arm 2; 1 subject, 2 subjects, 1 subject, and 4 subjects in Arm 1, Arm 3, Arm 4, and Arm 5, respectively. One subject in Arm 1 and 2 subjects in Arm 5 had TB AEs (an additional subject who had a positive PPD test during the study developed TB 4 months posttreatment). Event rates for AEs of special interest followed the same pattern.

Changes from Baseline observed in hematology and clinical chemistry parameters were not clinically relevant. Few statistically significant differences between groups in Period 1 and among arms in Period 2 were observed. Mean increases from Baseline to the end of Period 2 that were observed for cholesterol in each treatment arm and for ALT and AST in Arm 3 and Arm 5 were associated with substantial numbers of subjects changing from normal at Baseline to high at the final value. Small percentages of subjects in each treatment arm had at least 1 post Baseline AST or ALT value $\geq 3 \times$ ULN in Period 1 and Period 2. No subject in any group/arm had values for ALT and AST $\geq 3 \times$ ULN accompanied by a total bilirubin value $\geq 2 \times$ ULN in Period 1 or Period 2. The majority of subjects with potentially clinically significant (CTC grade ≥ 3) hematology and clinical chemistry values had isolated or transient values that were not associated with any AEs.

No clinically meaningful differences from Baseline to the final value were observed in mean vital sign values between the PBO+MTX and ADA+MTX groups in Period 1 or between any treatment arm and Arm 2 in Period 2.

Conclusions:

The benefit of ADA+MTX combination therapy in the early RA population has been demonstrated in this study. Among subjects who were clinical responders (DAS28 low disease activity) at Week 22 and Week 26, the proportion of subjects who also had no radiographic progression at Week 78 was greater in the ADA+MTX (combination therapy) arm than in the PBO+MTX (MTX monotherapy) arm. Subjects who responded to combination therapy in Period 1 and were withdrawn from adalimumab in Period 2 evidenced a lower degree of response in both clinical and radiographic measures of disease over time compared with subjects who continued to receive combination therapy. The risk/benefit ratio of adalimumab continues to be favorable.

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