2.0 Synopsis

<table>
<tr><td>AbbVie Inc.</td><td rowspan="3">Individual Study Table Referring to Part of Dossier:
Volume:
Page:</td><td rowspan="3">(For National Authority Use Only)</td></tr>
<tr><td>Name of Study Drug:
Adalimumab (Humira®)</td></tr>
<tr><td>Name of Active Ingredient:
Adalimumab</td></tr>
<tr><td colspan="3">Title of Study: A Double-Blind, Randomized, Parallel-Arm, Multicenter Study to Determine the Dose Response of Methotrexate (MTX) in Combination Therapy with Adalimumab in Subjects with Early Rheumatoid Arthritis (CONCERTO)</td></tr>
<tr><td colspan="3">Coordinating Investigator: Professor Gerd R. Burmester, MD
Professor of Medicine, Department of Rheumatology and Clinical Immunology, Berlin, Germany</td></tr>
<tr><td colspan="3">Study Sites: 64 study sites (US, Canada, Argentina, Austria, Belgium, the Czech Republic, Germany, Spain, Puerto Rico, and Poland)</td></tr>
<tr><td colspan="3">Publications: 3</td></tr>
<tr><td colspan="2">Studied Period (Years):
First Subject First Visit: 29 October 2010
Last Subject Last Visit: 11 September 2012</td><td>Phase of Development: 3</td></tr>
<tr><td colspan="3">Objectives: The objective of this study was to assess and compare the proportion of subjects who achieved low disease activity, as defined by a clinical response (Disease Activity Score based on C-reactive protein, [DAS28(CRP)] < 3.2) at Week 26 with 4 different regimens of methotrexate (MTX) in combination with adalimumab in order to determine the dose-response pattern of MTX in subjects with early rheumatoid arthritis (RA). The study was also designed to evaluate the PK and safety of 4 different regimens of MTX in combination with adalimumab in subjects with early RA.</td></tr>
<tr><td colspan="3">Methodology: This study was a double-blind, randomized, parallel-arm, multi-country, multicenter study to determine the dose-response pattern of MTX in combination therapy with adalimumab in approximately 380 adult subjects with early RA.

At least 3 days, but not greater than 28 days, prior to Day 1 (first injection), subjects were provided written informed consent and underwent screening procedures. The subject was to meet all inclusion and none of the exclusion criteria in order to qualify for the study. Subjects were randomized in a ratio of 1:1:1:1 to receive 1 of 4 different regimens of MTX (2.5 mg, 5 mg, 10 mg, or 20 mg) weekly and all subjects were to receive adalimumab (40 mg/0.8 mL) every other week (eow) throughout the study. For subjects completing the Week 26 study, the last MTX dose was to be administered at Week 25 and the last adalimumab injection was to be administered at Week 24. No study drug was to be administered or injected at the final visit. A follow-up call was made 70 days following the last dose of adalimumab to inquire about new and update ongoing adverse events (AEs).</td></tr>
</table>

Number of Subjects (Planned and Analyzed):
Intent to treat (ITT) population: (380 planned, 395 analyzed) The ITT population consisted of all randomized subjects who received at least 1 dose of study drug and was used for the analysis of primary and secondary efficacy variables.

Per-protocol (PP) population: (380 planned, 348 analyzed) The per-protocol population, which consisted of all ITT subjects who completed the study and did not have major protocol violations, was used to evaluate the impact of major protocol violations on the primary variable. The exclusion of subjects were determined by classification prior to database lock.

Safety population: (380 planned, 395 analyzed) The safety analysis set, which included all randomized subjects who took at least one dose of study drug, was used to determine the safety of the combination therapy. No randomized subjects were excluded from the safety population.

Diagnosis and Main Criteria for Inclusion: This study was to enroll adult subjects who were naïve to systemic biologic therapy (including adalimumab) or had not been exposed to > 1 disease modifying antirheumatic drug, including MTX, and who did not have significant co-morbidities that would place the subject at risk or affect the ability to assess safety and efficacy. Male and female adults were required to be ≥ 18 years of age and have a diagnosis of RA, as defined by either the 1987-revised American College of Rheumatology (ACR) classification criteria or the new ACR/European League Against Rheumatism diagnostic criteria for RA 2010, for < 1 year. Inclusion criteria included Baseline DAS28(CRP) ≥ 3.2, at least 6 swollen joints of 66 joints assessed and 8 tender joints of 68 joints assessed at Baseline and Screening, and CRP ≥ 1.5 mg/dL at Screening or ESR ≥ 28 mm/1h at Screening and Baseline. Additional inclusion criteria were either a positive test for rheumatoid factor, at least 1 bony erosion, or a positive test for anti-cyclic citrullinated peptide antibody.

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

Test Product	Dose/Strength/Concentration	Mode of Administration	Bulk Lot Number
Adalimumab	40 mg/0.8 mL prefilled syringe	SC injection	10-000765, 11-001131
MTX	2.5 mg gelatin capsule	Oral	10-002515, 10-002583, 12-000786
MTX	7.5 mg gelatin capsule	Oral	10-002548, 10-002584, 12-000787
MTX	10 mg gelatin capsule	Oral	10-002585, 10-002618, 12-000788

Duration of Treatment:
Last adalimumab dose: Week 24
Last MTX dose: Week 25
Last visit: Week 26

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

Reference Therapy	Dose/Strength/Concentration	Mode of Administration	Lot Number
Placebo for MTX	Matching capsule	Oral	10-002613, 09-022074

Criteria for Evaluation

Efficacy:

Primary Endpoint:

Proportion of subjects achieving low disease activity, as defined by (DAS28[CRP] < 3.2), at Week 26. Component measurements include tender joint count (TJC), swollen joint count (SJC), CRP, Health Assessment Questionnaire – Disability Index (HAQ-DI), and Physician's/Patient's Global Assessment of Disease Activity (visual analog scale [VAS]).

Secondary Endpoints:

- Response defined by ACR 20/50/70/90/100 criteria at Week 26; component measurements include TJC, SJC, CRP, and VAS.
- Change in modified Total Sharp Score (ΔmTSS) at Week 26; component x-ray measurements include joint erosion and joint space narrowing.
- Proportion of subjects with no radiographic progression (ΔmTSS ≤ 0.5) at Week 26; component x-ray measurements include joint erosion and joint space narrowing.
- DAS28(CRP) < 2.6 at Week 26; component measurements include TJC, SJC, CRP, HAQ-DI, and VAS.
- Change in HAQ-DI at Week 26
- Proportion of subjects with ΔHAQ-DI ≥ – 0.22 at Week 26

Pharmacokinetic: Concentrations of MTX polyglutamates and serum concentrations of adalimumab and anti-adalimumab antibodies were to be measured in samples that had been obtained prior to dosing at Baseline and at Weeks 2, 4, 8, 12, 16, 20, and 26/early termination (ET). Results will be provided in a separate report after analysis (R&D/12/841).

Pharmacogenetic: DNA samples were to be analyzed for genetic factors contributing to the subject's response to study treatment in terms of PK, pharmacodynamics, efficacy, tolerability, and safety. Results will be provided in a separate report after analysis.

Biomarkers: Biomarker analyses were to be performed on samples that had been collected at Baseline and at Weeks 4, 12, and 26/ET visits. Results will be provided in a separate report after analysis.

Safety: AEs were to be assessed at every visit from Baseline through Week 26/ET (serious adverse events [SAEs] were collected from Screening) and MTX toxicity-related AEs were to be assessed at every study visit starting at Week 2 through Week 26/ET. All subjects also were to be contacted 70 days following their last dose of adalimumab to monitor new and update ongoing AEs/SAEs, except those subjects that continued on commercial adalimumab therapy after the end of study participation.

Vital sign determinations of sitting blood pressure, heart rate, respiratory rate, body temperature, and weight were to be obtained at each visit. Blood specimens for hematology and chemistry were to be obtained at Screening, all subsequent study visits, and if applicable, the ET visit and any unscheduled visits, if appropriate. Urine samples were to be obtained for urinalysis testing at all visits.

Statistical Methods

Efficacy: Categorical data were summarized using frequencies and percentages and comparisons between treatment groups were made using the Cochran-Armitage trend test or an appropriate exact test (if $\geq$ 25% of the cells have expected counts less than 5). Continuous data were summarized by mean, standard deviation, median, minimum, and maximum values. Changes from baseline in continuous variables were compared among treatment groups using analysis of covariance, adjusting for baseline (ANCOVA). All statistical tests were conducted at an $\alpha = 0.05$ level (two-sided), unless otherwise stated. Categorical responses were presented by observed and nonresponder imputation (NRI) approaches and continuous responses were presented by observed and last observation carried forward (LOCF) approaches, where deemed appropriate. All data were summarized as "observed" or "imputed."

Demographics, baseline characteristics, and all efficacy variables were analyzed using the ITT population. The primary endpoint was analyzed using the PP population, in addition to the ITT population.

Safety: Treatment-emergent AEs (TEAEs) were summarized using the Medical Dictionary for Drug Regulatory Activities (MedDRA) version 15.0. TEAEs were defined as adverse events that occurred on or after the first dose of study drug and no more than 70 days after the last dose of study drug. A subject who reported more than 1 AE in different system organ classes (SOCs) was counted only once in the overall total. A subject who reported 2 or more different preferred terms (PTs) within the same SOC was counted only once in the SOC total. A subject who reported more than 1 AE with the same PT was counted only once using the most extreme event.

TEAEs were summarized as number and percentage or per 100 patient years and select TEAEs were analyzed by maximum severity and maximum relationship to study drug. A chi square test or an appropriate exact test was used to analyze treatment group differences for qualitative categorical variables.

Mean changes from baseline in all continuous laboratory parameters and vital sign variables at each visit were summarized and compared between treatment groups using a 1-way analysis of variance (ANOVA). The baseline, minimum, maximum, and final value means were presented for subjects who had both baseline and postbaseline values.

Summary/Conclusions

Efficacy Results: This study evaluated the dose-response effect of MTX, in combination with adalimumab, over 26 weeks in subjects with early RA. The majority of subjects were female and white, with a mean age of 51.9 years. No statistically significant differences in demographics, duration of RA, or other baseline disease measures were observed between dose groups, with the exception of TJC28, ESR, DAS28, and CDAI. The mean for TJC28, ESR, DAS28, and CDAI was highest in the 5 mg dose group.

Summary/Conclusions (Continued)

Efficacy Results (Continued): Results of the primary endpoint, low disease activity (DAS28[CRP] < 3.2) at Week 26, demonstrated that the proportions of subjects who achieved low disease activity increased with increasing MTX dose (as observed, $P = 0.004$; NRI, $P = 0.005$). Odds Ratios were > 1 and numerically increased with increasing MTX dose, which is consistent with the trend test. These results were consistent with results for the following secondary endpoints at Week 26: change from Baseline in DAS28(CRP) (as observed and LOCF); disease remission, defined as DAS28(CRP) < 2.6 (as observed and NRI); ACR20/50/70 responses (as observed and NRI); change in mTSS ≤ 0.5 (as observed and NRI); and change from Baseline in HAQ-DI ≤ – 0.22 (NRI only). No notable trends were observed across dose groups for the subject-reported health-related quality of life measures, SF-36v2 physical and mental components, CQR, TSQM, or MOS-Sleep.

Exploratory analyses in which 1) proportions of subjects with DAS28(CRP) low disease activity and no radiographic progression (as observed and NRI), 2) proportions of subjects with DAS28(CRP) remission and no radiographic progression (as observed and NRI), or 3) proportions of subjects with DAS28(CRP) low disease activity and no radiographic progression and HAQ-DI < 0.5 (NRI only) were assessed also demonstrated that response at Week 26 increased with each increase in MTX dose.

Pharmacokinetic Results: Results will be provided in a separate pharmacokinetic report (R&D/12/841).

Safety Results: No deaths occurred during the study. Two-thirds of all subjects reported at least 1 TEAE. Nine subjects prematurely discontinued from the study due to an AE. In general, the event rate was low and scattered across the 4 MTX dose groups. Few TEAEs (upper respiratory tract infection and alopecia) showed a trend in which frequencies increased with an increase in MTX dose. The TEAEs that were most frequently reported by at least 5% of subjects in any treatment group were nausea, nasopharyngitis, headache, and alopecia and the proportion of subjects who reported these TEAEs was highest in the 10 mg or 20 mg MTX dose group. The majority of TEAEs were considered by the investigator to be mild to moderate in severity. A total of 16 subjects reported severe TEAEs and include anemia, abdominal pain, nausea, vomiting, and upper respiratory tract infection. The majority of these severe events were reported by subjects in the 10 mg and 20 mg MTX dose groups. Most TEAEs reported by subjects were considered by the investigator to be not related to adalimumab or MTX. Approximately 22% of all subjects reported a TEAE that was considered by the investigator to be at least possibly related to adalimumab, with a greater proportion of subjects in the 2 highest MTX groups, as compared to the 2 lowest MTX groups. Thirty-three percent of all subjects reported a TEAE that was considered by the investigator to be at least possibly related to MTX, with a greater proportion of subjects in the 2 highest MTX groups, as compared to the 2 lowest MTX groups. There were no trends observed across treatment groups in the types of at least possibly related AEs.

Summary/Conclusions (Continued)

Safety Results (Continued):

A total of 17 subjects experienced at least 1 SAE during the study (RA flare; anemia; abdominal pain; acute coronary syndrome; appendicitis; asthenia; chest pain; colitis, ulcerative; hypertension; inguinal hernia; intervertebral disc degeneration; osteoarthritis; and sepsis) and 3 subjects had SAEs that were considered by the investigator to be at least possibly related to adalimumab (RA flare and worsening anemia) or MTX (worsening anemia and asthenia). SAEs that were mild or moderate in severity were reported in 9 subjects and SAEs that were severe (RA flare, anemia, abdominal pain, acute coronary syndrome, asthenia, intervertebral disc degenerative, and sepsis) were reported in 8 subjects. A total of 9 subjects experienced at least 1 TEAE that led to discontinuation from study drug (fatigue, RA flare, anemia, arthritis, asthma, hepatic enzyme increased, liver function test abnormal, myalgia, nausea, pigmentation disorder, pneumonitis, rash, upper respiratory infection, urticaria, and vomiting).

MTX-related toxicity was assessed from a listing of 18 common AEs associated with MTX. The AEs most frequently reported by subjects in any treatment group were infection, nausea and/or vomiting, stomach pain/discomfort, and abnormal hair loss. A greater proportion of subjects reporting at least 1 AE were in the 2 highest MTX groups, as compared to the 2 lowest MTX groups. An increasing incidence of abnormal hair loss and infection was observed with an increase in MTX dose; however, no other trends were observed. MTX is known to reduce adalimumab clearance and inhibit AAA formation, leading to an increase in adalimumab exposure, as compared to adalimumab monotherapy. The increase in AEs with MTX dose; therefore, may be a result of increased adalimumab exposure. Overall, the frequency of AEs was low and MTX was well tolerated.

Of the special interest AEs that were examined, 24% of subjects reported at least 1 treatment-emergent infection during the study. The proportion of subjects who reported these AEs was highest in the 10 mg or 20 mg MTX dose group. Serious infections occurred in 2 subjects, 1 with sepsis that was considered by the investigator to be severe and probably not related to adalimumab or MTX and 1 with appendicitis that was moderate in severity and not related to adalimumab or MTX. Both subjects were in the 5 mg MTX dose group. One subject had an event of oral candidiasis that was considered by the investigator to be moderate in severity and probably not related to adalimumab, but probably related to MTX. Six subjects reported at least 1 treatment-emergent allergic reaction. No trends were observed across dose groups in the proportion of subjects who experienced these events. Two events (skin rash [hives] and pruritus) were intermittent, mild to moderate in severity, and considered by the investigator to be possibly related to adalimumab and/or MTX. The subject that had moderate pruritus discontinued from the study. Two subjects (1 subject in the 5 mg dose group temporarily discontinued from study drug) reported a treatment-emergent worsening of psoriasis that was mild to moderate in severity and considered by the investigator to be probably related to adalimumab, but not or probably not related to MTX. A total of 7 subjects reported treatment-emergent anemia or worsening anemia that was mild to severe during the study. Two events of anemia were considered by the investigator to be serious and 1 subject discontinued from study drug. One event of anemia was considered by the investigator to be moderate in severity and probably not related to adalimumab or MTX and the other event of anemia was considered by the investigator to be severe and possibly related to adalimumab and MTX.

A total of 14 subjects reported at least 1 treatment-emergent injection site reaction. There were no trends in the types of events that occurred across dose groups. Eleven of these events were considered by the investigator to be probably related to adalimumab and 1 event was considered to be possibly related to adalimumab. None of these events were considered serious.

Summary/Conclusions (Continued)

Safety Results (Continued):

Results from hematology, chemistry, and urinalysis laboratory parameters were clinically unremarkable and no trends across MTX dose were indicated. The majority of subjects did not experience a shift in alanine transaminase (ALT), aspartate transaminase (AST), alkaline phosphatase, or bilirubin values and for those subjects that experienced a shift, the shift was small. A total of 11 subjects had clinically significant abnormalities, as defined by the investigator in consultation with the AbbVie medical monitor, in their liver function tests and 3 of these subjects discontinued early from the study, 2 of whom discontinued because of their abnormal liver function test. Fifteen subjects had a small increase (from $< 1.5 \times$ ULN to $\geq 1.5 - < 3.0 \times$ ULN) in ALT and 10 subjects had a small increase in AST (from $< 1.5 \times$ ULN to $\geq 1.5 - > 3.0 \times$ ULN). No trends across MTX dose groups were observed. No subjects met the criteria for Hy's Law. There were no shifts in final ANA values and 3 subjects had a shift in final anti-dsDNA values, which were in the higher MTX dose groups.

Conclusions:

The primary objective for this study was met. The data presented in this clinical study report indicate that combination therapy of adalimumab + MTX improves the signs and symptoms of RA and inhibits radiographic progression of the disease when administered over 26 weeks in subjects with early RA. Trends were observed for a number of validated endpoint measurements in which higher MTX dose (10 mg and 20 mg) led to greater increases in response. In general, the adverse event rate was low and scattered across the 4 MTX dose groups. Subjects in the higher MTX dose groups reported a greater number of AEs and a greater number of AEs that were severe. Increases in ALT and AST were small and no trends across MTX dose groups were observed.

In conclusion, results of this study show that all doses of MTX (2.5 mg, 5 mg, 10 mg, and 20 mg) in combination with adalimumab 40 mg eow were efficacious and generally safe and well-tolerated.

Date of Report: 16Jul2013