

## 2.0 Synopsis

<b>AbbVie Inc.</b>	<b>Individual Study Table Referring to Part of Dossier:</b>  <b>Volume:</b>  <b>Page:</b>	<b>(For National Authority Use Only)</b>
<b>Name of Study Drug:</b> Adalimumab and Methotrexate		
<b>Name of Active Ingredient:</b> Adalimumab and Methotrexate		
<b>Title of Study:</b> A Multicenter, Double-Blind, Randomized, Parallel-Arm Study to Determine the Effect of Methotrexate Dose on Clinical Outcome and Ultrasonographic Signs in Subjects with Moderately to Severely Active Rheumatoid Arthritis Treated With Adalimumab (MUSICA)		
<b>Coordinating Investigator:</b> Gurjit Kaeley, MBBS		
<b>Study Sites:</b> 47 sites in the US and Puerto Rico		
<b>Publications:</b> None		
<b>Studied Period (Years):</b> First Subject First Visit: 13 September 2010 Last Subject Last Visit: 31 January 2013	<b>Phase of Development:</b> 4	
<p><b>Objectives:</b> To test for non-inferiority of low dose methotrexate (MTX) plus adalimumab (ADA) as compared to high dose MTX plus ADA, with respect to clinical efficacy, using the mean Disease Activity Score for 28 joints based on C-reactive protein (DAS28[CRP]) in each arm at Week 24 as the primary endpoint.</p> <p>The study was also designed to evaluate the pharmacokinetic and safety of ADA in combination with 2 dosing regimens of MTX in subjects with active rheumatoid arthritis (RA).</p>		
<p><b>Methodology:</b> This was a Phase 4, multicenter, double-blind, randomized, parallel-arm study design. Subjects who met eligibility criteria were to be randomized in a 1:1 ratio to 1 of the following 2 treatment arms in a double-blind manner.</p> <ul style="list-style-type: none"> <li>• Arm 1 = open-label ADA 40 mg subcutaneous (SC) every other week (eow) + blinded high dose weekly oral MTX (20 mg per week)</li> <li>• Arm 2 = open-label ADA 40 mg SC eow + blinded low dose weekly oral MTX (7.5 mg per week).</li> </ul> <p>Randomization was to be stratified based on the subject's MTX dose (15, 17.5, or 20 mg/week) prior to the Baseline visit and the subject's consent to participate in the optional pharmacogenetic analysis.</p>		
<p><b>Number of Subjects (Planned and Analyzed):</b> Three hundred subjects were planned to be randomized equally to 2 treatment groups. A total of 309 subjects were randomized (154 subjects in the ADA + 7.5 mg MTX treatment group and 155 subjects in the ADA + 20 mg MTX treatment group) and analyzed in the intent-to-treat (ITT) and safety populations. Three hundred subjects (148 subjects in the ADA + 7.5 mg MTX treatment group and 152 subjects in the ADA + 20 mg MTX treatment group) were analyzed in the per protocol (PP) population.</p>		

**Diagnosis and Main Criteria for Inclusion:** Males or females (non-childbearing potential or of childbearing potential practicing approved methods of birth control)  $\geq 18$  years of age. Subjects were to have a diagnosis of RA as defined by the 1987 revised ACR classification criteria, a DAS28(CRP) score  $\geq 3.2$  at Screening, at least 5 tender joints out of 68, and 5 swollen joints out of 66 at Baseline. Subjects must have been treated with an MTX dose (oral and/or injectable) of 15 mg or more per week for at least 12 weeks prior to Screening. Subjects were to be in good general health as determined by the study Investigator. Subjects must have had a negative chest x-ray and negative tuberculosis (TB) test at Screening. Subjects with a positive TB test must have completed a minimum of 2 weeks of an ongoing course of anti-TB therapy.

Subjects were to be excluded from the study if they had previous exposure to ADA (Humira<sup>®</sup>), rituximab (Rituxan<sup>®</sup>), natalizumab (Tysabri<sup>®</sup>), or efalizumab (Raptiva<sup>®</sup>); had a history of allergic reaction or significant sensitivity to any constituents of the study drugs (ADA or MTX); contraindications/significant intolerance to oral MTX; moderate to severe congestive heart failure or recent cerebrovascular accident; evidence of dysplasia; a history of malignancy, listeriosis, or histoplasmosis; clinically significant hematologic, renal, hepatic or demyelinating disease (including myelitis); neurologic symptoms suggestive of demyelinating disease; or chronic or active hepatitis B or hepatitis C infection, human immunodeficiency virus (HIV) infection, immunodeficiency syndrome, or chronic recurring infections (non-viral).

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

Drug	Mode of Administration	Manufacturer	Formulation	Bulk Lot Numbers
ADA	Subcutaneous Injection	[REDACTED]	40 mg/0.8 mL solution for injection ADA/mannitol, citric acid monohydrate, sodium citrate, disodium phosphate dihydrate, sodium dihydrogen phosphate dihydrate, sodium chloride, polysorbate 80, water for injections, sodium hydroxide added as necessary to adjust pH	10-001960 11-003870
MTX	Oral	MTX tablets: [REDACTED]	2.5 mg tablets over-encapsulated into hard gelatin capsule	N/A
		Over-encapsulated MTX capsules: [REDACTED]	7.5 mg MTX capsule (contains three, 2.5 mg tablets and microcrystalline cellulose)	10-002548 12-002876
			10 mg MTX capsule (contains four, 2.5 mg tablets and microcrystalline cellulose)	10-002618 12-002875
Matching placebo for MTX	Oral	Hard gelatin capsule containing microcrystalline cellulose.	[REDACTED]	10-002613

**Duration of Treatment:** This study consisted of a 3 to 28 day Screening period; Baseline visit (Day 1), and a 24 Week Treatment period (Weeks 4, 8, 12, 16, 20, and 24). Subjects who completed Week 24 were to be considered as having completed the study.

All subjects were to have a follow-up phone call 70 days after the last injection of ADA to obtain information on any new or ongoing AEs.

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

Not applicable.

**Criteria for Evaluation**

**Efficacy:**

The primary endpoint of this study was to examine the non-inferiority of low dose MTX + ADA compared to high dose MTX + ADA, based on the mean DAS28(CRP) score of each arm at Week 24, with non-inferiority margin as 15% of the mean DAS28(CRP) of the high dose MTX arm.

Secondary variables were to include non-inferiority comparisons of the low dose MTX arm to the high dose MTX arm based on the percentage of subjects with the following variables:

- Power Doppler Score (ultrasound disease activity score) improvement of at least 30% at Week 24, with non-inferiority margin as 15% absolute difference between the high dose and low dose MTX arms.
- American College of Rheumatology (ACR)50 at Week 24, with non-inferiority margin as 15% absolute difference between the high dose and low dose MTX arms.
- ACR70 at Week 24, with non-inferiority margin as 15% absolute difference between the high dose and low dose MTX arms.
- Health Assessment Questionnaire – Disability Index (HAQ-DI) change from Baseline at least –0.22 at Week 24, with non inferiority margin as 15% absolute difference between the high dose and low dose MTX arms.
- Mean percentage change in Medical Outcomes Study (MOS) (Sleep Index II) score at Week 24, with non inferiority margin as 15% of the mean percentage change in MOS score of the high dose MTX arm.

**Pharmacokinetic:**

Serum concentrations of ADA anti- adalimumab antibody (AAA) were to be obtained prior to dosing at Baseline, Weeks 4, 8, 12, 16, 20, and 24/ET study visits.

**Safety:**

Safety was to be assessed by the incidence of AEs, including those related to the administration of MTX and AEs of special interest, immunological assessments of AAA and antibodies to double stranded DNA, and changes in vital sign results and clinical and laboratory data during the entire study.

## **Statistical Methods**

### **Efficacy:**

The primary and secondary efficacy variables were to be analyzed for the intent-to-treat (ITT) population, defined as all subjects who were randomized and received at least one dose of study medication. In order to evaluate the impact of major protocol violations on the results of the trial, additional analysis of the primary efficacy variable was to be conducted on the per protocol (PP) population, which consisted of all ITT subjects who were not major protocol violators. The non-inferiority was to be assessed using an Analysis of Covariance (ANCOVA, only main effects) model with treatment, Baseline DAS28(CRP), and strata (the subject's prescribed MTX dose prior to the Baseline visit). The 2-sided 95% confidence interval of the difference between the high dose and the low dose arm based on the Least Squared (LS) means from the ANCOVA was to be used to assess the non-inferiority. To account for missing DAS28(CRP) score, a last observation carried forward (LOCF) approach was to be used for primary endpoint analysis. Unless otherwise stated, all comparisons of secondary efficacy variables were to be performed at the 2-sided  $\alpha = 0.05$  significance level, without using a stepwise testing procedure or any alpha adjustment. All statistical comparisons for the primary and secondary endpoints were to be done at Week 24 unless otherwise stated. Demographic and Baseline characteristics were to be summarized and compared between treatment groups adjusting for the strata of prior MTX dose levels. The number of observations, means, standard deviations, medians, minimums and maximums were to be summarized for continuous variables. The number and percent were to be summarized for categorical variables.

### **Pharmacokinetic:**

Descriptive statistics for ADA and MTX polyglutamates concentration were to be provided and stratified by study visit and treatment Arm. The number and percentage of subjects who develop AAA were to be determined if data permitted, ADA concentration data may be analyzed using a nonlinear mixed effects model (population PK analysis). The relationship between MTX dose and/or MTX glutamate exposure and ADA PK parameters may have been evaluated by using the nonlinear mixed effect model. The relationship of response (primary efficacy variables and other responses of interest) with study drug exposure must have been explored.

### **Safety:**

The safety population consisted of all subjects who received at least one dose of study medication. Treatment-emergent and pre-treatment AEs were to be summarized and reported. The number and percent of subjects experiencing AEs by Medical Dictionary for Regulatory Activities (MedDRA) system organ class and preferred term, summary of AEs by severity and relationship to study drug, serious AEs, and AEs that resulted in premature discontinuation of study drug were summarized.

Mean change in laboratory variables and vital signs variables at each visit were to be summarized for all subjects and compared between treatment groups using a one way Analysis of Variance (ANOVA). The last evaluation prior to the first dose of study drug was to be used as Baseline for all analyses. For selected parameters, a listing of all subjects with any laboratory determination meeting common toxicology criteria (CTC) of Grade 3 or higher was to be provided. Shift tables for changes from Baseline according to the normal range were to be provided for laboratory variables.

## Summary/Conclusions

### Efficacy Results:

The majority of subjects were female (231/309; 74.8%) and white (253/309; 81.9%), with a mean age of 54.8 years. Overall, Baseline disease characteristics were typical of a subject population with RA. A statistically significant difference was not observed between treatment groups in the ITT population for any of the Baseline disease characteristics, health-related quality of life measures, or vital signs (blood pressure, pulse, respiratory rate, or temperature). The most frequently reported co-morbidities in this RA population were hypertension, hyperlipidemia, gastroesophageal reflux disease, osteoarthritis, and depression.

More subjects reported taking at least 1 systemic NSAID than systemic corticosteroids or synthetic DMARDs during the study. Most subjects were compliant with study drug (MTX and ADA) throughout the study. The mean compliance was > 96%.

Most subjects (88.7%) completed the study. The number of subjects who discontinued early from the study was similar between the 7.5 mg MTX treatment group (19/154; 12.3%) and the 20 mg MTX treatment group (16/155; 10.3%). Adverse events were the most reported primary reason for discontinuation in both treatment groups.

Non-inferiority was not demonstrated for the primary endpoint (DAS28[CRP]) comparing the low dose (7.5 mg) MTX + ADA with the high dose (20 mg) MTX + ADA at Week 24. For the secondary endpoints, only the HAQ-DI with a change from Baseline at least -0.22 demonstrated non-inferiority when comparing the low dose MTX + ADA treatment group with the high dose MTX + ADA treatment group at Week 24. For the subgroup subjects who had previous MTX of 15 mg/week, the low dose (7.5 mg) MTX treatment group (n = 76) was demonstrated to be non-inferior to the high dose (20 mg) MTX treatment group (n = 75) for the primary endpoint (DAS28[CRP]) at Week 24.

There was no statistically significant difference between the 2 treatment groups with regards to ultrasonographic synovial hypertrophy, synovial vascularity, and bony erosion.

### Pharmacokinetic Results:

PK results and conclusions are presented in a separate report (R&D/13/273).

### Safety Results:

No deaths were reported during the study. A total of 195 (63.1%) of all subjects reported as least 1 TEAE, and 72 subjects (23.3%) and 85 subjects (27.5%) of all subjects reported a TEAE that was considered by the Investigator as at least possibly related to ADA or MTX, respectively. A total of 17 subjects experienced at least 1 SAE during the study; no SAE was reported by more than 1 subject. Six subjects had SAEs that were considered by the Investigator to be at least possibly ADA related, and 5 subjects had SAEs that were considered by the Investigator to be at least possibly MTX related. Twelve subjects had AEs that were severe. Thirteen subjects experienced at least 1 AE that was the primary reason for discontinuation from study. The TEAEs most frequently reported by at least 5% of all subjects were nausea, upper respiratory tract infection, urinary tract infection, dizziness, headache, and fatigue. Twenty-three percent of subjects reported at least 1 MTX toxicity-related AE. The MTX toxicity-related AEs most frequently reported by at least 3% of all subjects were infection, nausea and/or vomiting, abnormal hair loss, and stomach pain/discomfort.

**Summary/Conclusions (Continued)****Safety Results (Continued):**

Of the special interest AEs that were examined, 99 subjects (32%) reported at least 1 treatment-emergent infection, 2 subjects (1 serious and 1 non-serious) reported malignancy, 3 subjects reported at least 1 treatment-emergent non-serious allergic reaction, 1 subject reported non-serious moderate diverticulitis, 1 subject experienced a serious severe myocardial infarction, 2 subjects reported a treatment-emergent non-serious worsening of psoriasis during the study, 4 subjects (1 serious) reported a treatment-emergent hematologic disorder, 1 subject experienced a serious transient ischemic attack, and 1 subject experienced a non-serious mild hepatic steatosis.

A total of 9 subjects (2.9%) reported at least 1 treatment-emergent injection site reaction with the greater proportion of subjects in the 7.5 mg MTX treatment group than in the 20 mg MTX treatment group. All of these events were considered by the Investigator to be possibly or probably related to ADA. None of the events were considered serious, severe, or resulted in discontinuation from study drug.

Mean change from Baseline to Week 24 in hematology, chemistry, and urinalysis laboratory parameters was clinically unremarkable. There were few shifts in hematology, chemistry, and urinalysis laboratory parameter values. A total of 12 subjects had at least 1 clinically significant (common toxicology criteria [CTC] Grade 3) abnormality in their hematology laboratory values, and 30 subjects had at least 1 clinically significant abnormality in their chemistry laboratory values. A total of 10 subjects had clinically significant abnormalities in their liver function tests. The majority of subjects did not experience a shift in ALT, AST, alkaline phosphatase, or bilirubin.

Mean change from Baseline in vital signs (systolic BP, diastolic blood pressure, heart rate, respiratory rate, and weight) was clinically unremarkable from Baseline to Week 24 with no statistical significance demonstrated between the 7.5 mg MTX and 20 mg MTX treatment groups. However, a statistically significant difference between the 7.5 mg and 20 mg MTX treatment groups was demonstrated in the mean change from Baseline in body temperature at Weeks 4 and 16 (a relatively large mean increase and mean decrease in body temperature was observed in the 7.5 mg MTX treatment group and 20 mg MTX treatment group at both visits, respectively). However, the statistically significant difference in body temperature was not clinically meaningful. No other statistically significant or clinically remarkable differences in vital signs were observed.

**Conclusions:**

The data presented in this study indicate that non-inferiority was not demonstrated for the primary endpoint (DAS28[CRP]) and that a statistically significant difference was demonstrated when comparing the low dose (7.5 mg) MTX treatment group with the high dose (20 mg) MTX treatment group for selected parameters. Only the HAQ-DI with a change from Baseline at least -0.22 demonstrated non-inferiority when comparing the low dose MTX treatment group with the high dose MTX treatment group; all other secondary endpoints as well as ultrasonographic changes in RA were inconclusive. No new safety findings were observed in this study.