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: Radiographic, Clinical and Patient outcomes in a multicenter, open-label phase IV randomized trial of earlier Adalimumab introduction therapy versus later introduction as per standard of care after initial Methotrexate failure in Early Rheumatoid Arthritis patients (RADAR)</td></tr>
<tr><td colspan="3">Coordinating Investigator: Dr. Edward Keystone</td></tr>
<tr><td colspan="3">Publications: None</td></tr>
<tr><td colspan="2">Studied Period (Years):
First Subject First Visit: 22 September 2010
Last Subject Last Visit: 27 July 2015</td><td>Phase of Development: Phase 4</td></tr>
<tr><td colspan="3">Objectives:
Primary Objective:
To compare the effectiveness of EARLY versus SOC in reducing joint damage in the hands and/or feet at 24 months as determined by the proportion of subjects with no radiographic progression
Due to the early termination of the study, the preliminary endpoint was re-defined at Month 12.

Secondary Objectives:
1. To compare the effectiveness of EARLY versus SOC in reducing joint damage in the hands and/or feet at 12 months as determined by the proportion of subjects with no radiographic progression.
2. To compare the effectiveness of EARLY versus SOC in reducing joint damage in the hands and/or feet at 12 and 24 months as determined by the change in mTSS.
3. To compare the effectiveness of EARLY versus SOC in achieving a therapeutic response as measured by the ACR 20 / 50 / 70 at 24 months.
4. To compare the effectiveness of EARLY versus SOC in achieving DAS28 Remission (DAS28<2.6) at 24 months.</td></tr>
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Secondary Objectives: (Cont'd)

5. To compare the effectiveness of EARLY versus SOC in improving functional status as measured by the change in Health Assessment Questionnaire (HAQ) at 24 months.

6. To compare the effectiveness of EARLY versus SOC in improving work related productivity as measured by the Work Limitation Questionnaire (WLQ) at 24 months.

7. To compare the effectiveness of EARLY versus SOC in improving Quality of Life as measured by the EuroQol (EQ-5D) at 24 months.

8. To compare the effectiveness of EARLY versus SOC in reducing fatigue as measured by the change in Functional Assessment of Chronic Illness Therapy- (FACIT)-Fatigue Scale at 24 months.

9. To compare the effectiveness of EARLY versus SOC with respect to the incidence of flare-ups after remission as defined in subject that have had at least 3 months or two consecutive visits with DAS28≥2.6 at 24 months.

Other Objectives:

1. To compare the effectiveness of EARLY versus SOC in reducing Swollen Joint Count (SJC) and Tender Joint Count (TJC) at 24 months.

2. To compare the effectiveness of EARLY versus SOC in achieving a therapeutic response as measured by the EULAR response (Moderate and good response) at 24 months.

3. To compare the effectiveness of EARLY versus SOC in achieving DAS28 Low disease activity (DAS28<3.2) at 24 months.

4. To compare the effectiveness of EARLY versus SOC in reducing disease activity as measured by the change in DAS28 at 24 months.

5. To compare the effectiveness of EARLY versus SOC in reducing the proportion of subjects experiencing rapid radiographic progression defined by a change in mTSS of 5 units at 12 months.

6. To compare the effectiveness of EARLY versus SOC in improving functional status as measured by the percentage of subjects achieving Minimal Clinical Important Difference (MCID) defined as a 0.22 unit decrease in HAQ.

7. To compare the effectiveness of EARLY versus SOC in improving functional status as measured by the percentage of subjects achieving a HAQ< 0.5.

8. To compare the effectiveness of EARLY versus SOC in reducing fatigue as measured by the percentage of subjects achieving MCID defined as a 3.56 unit decrease in FACIT-F.

9. To compare the effectiveness of EARLY versus SOC in terms of healthcare resources utilization as measured by the Health Care Resource Questionnaire (HCR) at 24 months.

10. To compare the subject satisfaction of EARLY versus SOC using Likert Scale for patient's satisfaction with care at 24 months.

11. To compare the effectiveness of EARLY versus SOC in improving depression by the Beck Depression Inventory (BDI-II) at 24 months.

Methodology:

This was a multi-center, randomized, open-label, controlled, parallel group trial conducted in Canada, designed to assess the effectiveness of EARLY versus SOC in subjects with early RA, who have had an inadequate response to MTX therapy after a minimum of 3 months.

Subjects in the EARLY group were initiated on combination treatment of MTX with adalimumab 40 mg every other week (EOW) at the baseline visit. For subjects in the SOC group, treatment with adalimumab was allowed after six months and was initiated according to sequential stepwise algorithm representing the current SOC in Canada and regional formulary / reimbursement policies.

Adjustment of treatment in both groups was up to the discretion of the treating physician. This included addition of any other medication or dose adjustment of existing medications, including adalimumab. All RA related treatment changes along with justification / clinical reasoning were recorded in the study eCRFs. Any adalimumab adjustment therapy was done following the recommended dose as per the current HUMIRA® Product Monograph.

Number of Subjects (Planned and Analyzed):

A total of 240 subjects were to be randomized. The study was terminated earlier because of recruitment issues. Therefore, a total of 77 subjects were randomized (37 subjects in the SOC group and 40 subjects in the EARLY group), representing approximately a third of the expected randomized subjects.

Diagnosis and Main Criteria for Inclusion:

Inclusion Criteria:

- Subject has a diagnosis of rheumatoid arthritis as defined by the 1987-revised American College of Rheumatology-classification criteria and has disease duration of less than 2 years from diagnosis.

- Subject must have been on a dose of MTX therapy either subcutaneously or orally administered (15-25 mg /week) for at least 3 months prior to baseline visit and has had an inadequate response to treatment defined as having a Disease Activity Score DAS28 > 3.2 (at screening visit).

- Subject must also meet the following three criteria (at screening visit): At least 4 swollen joints out of 66 assessed; at least 4 tender joints out of 68 assessed; subject must have an elevated erythrocyte sedimentation rate (ESR) >= 20 mm/1h or C-reactive protein (CRP) >upper limit of normal (ULN).

- Subject must fulfill at least one of the following three criteria: History of rheumatoid factor (RF) positive; history of at least one erosion on X-ray or magnetic resonance imaging (MRI); history of anti-CCP (anti-citrullinated Protein) antibody positive.

Diagnosis and Main Criteria for Inclusion: (Cont'd)

Exclusion Criteria:

- Subject has previous exposure to any biologic therapy including adalimumab.
- Prior disease-modifying antirheumatic drugs (DMARD) triple therapy with MTX.
- Subject has been treated with intra-articular or parenteral administration of corticosteroids in the preceding 4 weeks prior to baseline visit. Inhaled corticosteroids for stable medical conditions are allowed.
- Subject has undergone joint surgery within the preceding two months (at joints to be assessed within the study) of baseline.
- Subject has a poorly controlled medical condition, such as uncontrolled diabetes, unstable heart disease, congestive heart failure, recent cerebrovascular accidents and any other condition which, in the opinion of the Investigator, would put the subject at risk by participating in the study.

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

Adalimumab (Humira®) was provided to subjects via prescription as per current HUMIRA® Product Monograph. The participating subjects eligible to receive Humira® were enrolled by the site personnel in PROGRESS (Humira® Patient support program). No by-subject listing of study drug administration is available.

Duration of Treatment:

The study duration was 24 months. Assessments were conducted at screening and baseline visits with follow-up visits at 3, 6, 9, 12, 18, and 24 months for a total of eight (8) visits. Approximately 320 subjects meeting entry criteria were to be enrolled at approximately 35 sites located across Canada. Subjects were randomized in a 1:1 ratio to the EARLY or SOC groups.

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

Not applicable.

Criteria for Evaluation

Efficacy:

Primary Variable: The primary efficacy variable was the proportion of subjects without radiographic progression, defined as $\Delta mTSS \leq 0.5$, at Month 12. The primary endpoint is defined at Month 12 instead of Month 24 due to the early termination of the study.

Criteria for Evaluation (Cont'd)

Secondary Variables:

- Proportion of subjects without radiographic progression, defined as ΔmTSS ≤ 0.5, at Month 6 and Month 24.
- Change from baseline in mTSS or Δ mTSS (at Month 6, 12 and 24).
- Proportion of subjects experiencing rapid radiographic progression, defined as ΔmTSS ≥ 5 at Month 12.
- ACR20/50/70 Response.
- SJC (66 and 28) and TJC (68 and 28).
- Physician's Global Assessment of Disease Activity Visual Analog Scale (VAS)
- Patient's Global Assessment of Disease Activity Visual Analog Scale (VAS)
- Patient's Global Assessment of Pain (VAS)
- CRP [mg/L]
- DAS28(CRP).
- DAS28(CRP) Remission, defined as DAS28(CRP) < 2.6.
- DAS28(CRP) Low Disease Activity, defined as DAS28(CRP) < 3.2.
- European League Againt Rheumatism (EULAR) good response (defined in Section 10.2.3).
- EULAR moderate response (defined in Section 10.2.3).
- Incidence of flare-up after remission by Month 24 defined as subjects who have reached remission (DAS28 < 2.6) but later had two consecutive visits with DAS28 ≥ 2.6 (based on observed cases only).
- HAQ-DI.
- Proportion of subjects achieving MCID in HAQ, defined as a 0.22 unit decrease in HAQ.
- Proportion of subjects achieving HAQ < 0.5.
- FACIT-Fatigue Scale.
- Proportion of subjects achieving MCID in FACIT-F, defined as a 3.56 unit decrease in FACIT-F.
- WLQ.
- EuroQol (EQ-5D).
- BDI-II.
- Likert Scale for patient's satisfaction with care.
- HCR (Only descriptive summaries of observed values will be provided for this variable; statistical analysis does not apply).

Safety:

Safety was assessed by reporting AEs and changes in physical examination. All AEs were coded according to the Medical Dictionary for Regulatory Activities (MedDRA) (Version 18.0) dictionary of terms and were classified according to causal association to adalimumab (HUMIRA®). All events were reported by body system using MedDRA preferred terms. The incidence rates of AEs were described as the proportion of subjects experiencing at least one event and as the number of events per subject.

Statistical Methods

Efficacy:

Primary Analysis of Primary Efficacy Variable:

The primary efficacy variable for this study was the proportion of subjects without any radiographic progression (ΔmTSS<=0.5 unit) at Month 12. The null hypothesis to be tested was that there was no difference between two groups against the alternative hypothesis that proportions were different. Between group differences were tested using a 2-sided Chi-Square test at a level of significance of 5%. Subjects with missing sharp score at Month 12 were treated as 'progressor' i.e. their ΔmTSS were assumed to be >0.5. The primary analysis was repeated for Month 24 as a secondary analysis.

Sensitivity Analysis for Primary Efficacy Variable:

A logistic regression was performed to compare the proportion of radiographic progression between two groups adjusting for those baseline mTSS. A repeated measures model for mTSS change from baseline was fitted to use all longitudinally collected sharp scores.

Secondary Efficacy Variables:

Percentage of binary responses were compared between two groups using Pearson's Chi-square test or Fisher's exact test (if expected cell count < 5), with analysis conducted for both observed and LOCF data, as well as NRI data. This was applicable for ACR response, radiographic non-progression (based on 0.5 cut-off), radiographic rapid progression (based on 5 cut-off), DAS28<2.6 or <3.2, disease flare (DAS28>2.6 at two consecutive visits), etc.

Change from Baseline was compared between two groups using an analysis of covariance method adjusting for the Baseline score using LOCF imputed values. This was applicable for changes in the mTSS at 6, 12 and 24 months, SJC, TJC, DAS28, HAQ, WLQ, EuroQol, FACIT, BDI, HCR, and subject satisfaction at 3, 6, 9, 12, 18, and 24 months. For mTSS, a linear extrapolation method was also implemented to impute for missing sharp score.

Safety:

Safety analyses were carried out using safety population, which includes all subjects that received at least one dose of study medication.

Treatment-emergent (TEAEs) and pre-treatment SAEs were summarized and reported. TEAEs are defined as AEs that begun either on or after the first dose of the study medication, and up to within 70 days after the last dose of the study medication if subjects terminated the study. The number and percentage of subjects experiencing AEs were tabulated by body system and MedDRA® preferred term. In addition, summary of AEs by severity and relationship to study drug were presented. AEs that are serious, severe, life threatening, or lead to premature study drug discontinuation were listed and described in detail.

Safety: (Cont'd)

Mean change in laboratories variable and vital signs variables at each visit were 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) of Grade 3 or higher was provided. Shift tables for changes from Baseline according to the normal range were also provided for lab variables.

Summary/Conclusions

Efficacy Results:

The majority of subjects were female (50 subjects, 67.6%), White (68 subjects, 91.9%), and the mean age (± SD) was 52.8 ± 11.01 years (range: 28 - 80 years). At baseline, a slightly higher proportion of subjects were in the category overweight (≥ 25 BMI < 30 kg/m^2) in the SOC group than in the EARLY group, although this difference was not detected as statistically significant (P-value=0.095). Total JSN and CRP at baseline showed slightly higher values in the SOC group, although these values were not detected as statistically significant (P-value ≥ 0.05). RA disease duration, was slightly lower in the EARLY group, although not shown to be statistically significant (P-value=0.200).

No clinically meaningful nor statistically significant differences were observed between the two treatment groups for the primary efficacy variable; the proportion difference between the groups for subjects with no radiographic progression at Month 12 was -1.3% (95% CI: -24.3 and 20.8; P-value=0.907). Results from the sensitivity analysis, as well as from the subgroups analysis, were consistent with this finding. The repeated measures analysis of change from baseline in mTSS suggest less radiographic progression for the EARLY group than for the SOC group (Month 6 P-value = 0.030; Month 12 P-value = 0.031; Month 24 P-value = 0.044).

Clinically meaningful results from secondary variables are summarized as follows:

- No Radiographic Progression: A slightly higher proportion of subjects showing no progression was measured in the EARLY group than in the SOC group at Month 24 (proportion difference = 21.4%; 95% CI: -1.8 and 44.6), although this difference was not detected as statistically significant (P-value = 0.093).
- Change from Baseline in mTSS: Significant difference between the SOC group and the EARLY group at Month 6 (LS mean difference ± SE: -0.86 ± 0.382; P-Value = 0.027) and Month 12 (LS mean difference ± SE: -1.46 ± 0.667; P-Value = 0.033).
- Rapid Radiographic Progression at Month 12: The number of subjects was lower in the EARLY group than in the SOC group, with a proportion difference ranging from -13.7% and -11.5% for the NRI, observed, LOCF, and linear extrapolated imputations, although this difference was not detected as statistically significantly (P>0.05).
- Change from Baseline in Swollen Joint Count and Tender Joint Count: Highest significant difference between the SOC group and the EARLY group detected at Month 6 (SJC66: LS mean difference ± SE: -4.2 ± 1.16; P-value < 0.001 and TJC68: LS mean difference ± SE: -6.9 ± 2.02; P-value < 0.001).

Efficacy Results: (Cont'd)

- Change from Baseline in Physician's Global Assessment of Disease Activity: Significant difference between the SOC group and the EARLY group at Month 3, Month 6, and Month 9 with the highest significance detected at Month 6 (VAS: LS mean difference ± SE: -25.2 ± 6.11; P-value < 0.001).
- Change from Baseline in DAS28(CRP): Significant difference between the SOC group and the EARLY group at Month 6 (LS mean difference ± SE: -0.8 ± 0.30; P-value = 0.007).

None of the patient reported outcomes (PROs) showed clinically meaningful differences between the treatment groups.

Safety Results:

No deaths were reported during the study.

Almost all subjects (97.3%) reported at least one TEAE, and 40 subjects (54.1%) reported a TEAE that was considered by the investigator to be at least possibly related to adalimumab. Of the 7 subjects (9.5%) who experienced a SAE, 1 subject (1.4%) developed herpes zoster that was considered by the investigator to be at least possibly related to adalimumab. Eleven subjects (14.9%) experienced a severe TEAE. The number of subjects were similar between treatment groups, except for TEAEs considered by the investigator to be at least possibly related to adalimumab (15 subjects [42.9%] in the SOC group and 25 subjects [64.1%] in the EARLY group).

TEAEs that were most frequently reported (≥ 10%) were: RA, nasopharyngitis, alanine aminotransferase increased, rash, aspartate aminotransferase increased, depression, headache, and injection site reaction.

The most commonly reported TEAEs that were at least possibly related to adalimumab were: injection site reaction, blood cholesterol increased, nasopharyngitis, sinusitis, and herpes zoster.

Eleven subjects reported severe TEAEs. Each severe TEAEs were reported in no more than 1 subject of any treatment groups, and no trends were observed between treatment groups.

Leading to study discontinuation, four subjects experienced events that were at least possibly related to adalimumab: 1 subject (2.9%) in the SOC group (drug hypersensitivity) and 3 subjects (7.7%) in the EARLY group (herpes zoster, hypoaesthesia, pustular psoriasis and rash papular).

Of all the TEAEs of special interest assessed in this study, there were no reports of the following: legionella infection, diverticulitis, opportunistic infection excluding oral andidiasis, TB (active or latent), parasitic infection, reactivation of hepatitis B, progressive multifocal leukoencephalopathy, hepatosplenic T-cell Lymphoma, lupus-like reactions and systemic lupus erythematosus, sarcoidosis, autoimmune hepatitis, myocardial infarction related AE, cerebrovascular accident related AE, congestive heart failure related AE, pulmonary embolism related AE, interstitial lung disease, intestinal perforation, pancreatitis, Stevens-Johnson syndrome, erythema multiforme related AE, demyelinating disorder, amyotrophic lateral sclerosis, reversible posterior leukoencephalopathy syndrome, and liver failure and other liver event AE.

Safety Results: (Cont'd)

Results for other TEAEs of special interest are summarized as follows:

- One subject (1.4%) in the EARLY group experienced herpes zoster infection that was serious and severe, and was considered by the investigator to be probably related to adalimumab:
- Two subjects (2.7%) in the EARLY group developed an oral candidiasis, and one event was considered to be probably related to adalimumab.
- Of the 3 malignancy events reported (3 subjects, 4.1%), two events were a malignancy other than lymphoma, HSTCL, leukaemia, NMSC or melanoma, and none were at least possibly related to adalimumab. No trends were detected across treatment groups.
- Two subjects (2.7%) in the SOC group developed allergic reactions (drug hypersensitivity and uricaria) that were considered at least possibly related to adalimumab.
- One subject (1.4%) in the EARLY group developed cutaneous vasculitis. It was considered to be probably not related to adalimumab.
- In the EARLY group, 1 subject (1.4%) developed psoriasis and 1 subject (1.4%) developed pustular psoriasis that were considered to be at least probably related to adalimumab.

- In the EARLY group, 1 subject (1.4%) developed aneamia and 1 subject (1.4%) developed leukopenia that were considered to be at least probably related to adalimumab.
- One subject (1.4%) in the EARLY group experienced a Humira administration related medication error, which was considered to be not related to the drug.
- Of the ten subjects (13.5%) who reported at least 1 injection site reaction, seven subjects (9.4%) were in the EARLY group. All of the events were considered by the investigator to be probably related to adalimumab and none were considered serious.

Mean change from baseline to final value in hematology and chemistry laboratory variables was clinically unremarkable and did not indicate any trends across the two treatment groups. Similarly, no shift trends were detected in hematology or chemistry during the study.

Conclusions:

This study, terminated earlier because of recruitment issues, did not meet the primary endpoint, which was revised to be the proportion of subjects with no radiographic progression at Month 12. Few secondary endpoints suggest adalimumab may improve signs and symptoms of early RA compared to MTX alone (change from baseline in mTSS, change from baseline in SJC and TJC, change from baseline in VAS, and change from baseline in DAS28(CRP)). None of the patient reported outcomes showed clinically meaningful differences between treatment groups. Adalimumab, assessed in this study as an earlier therapy versus a later therapy in early RA patients, was generally safe and well tolerated. No new safety signals were detected for adalimumab.