2.0 Synopsis

AbbVie Inc.	**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 pilot study of the feasibility of discontinuation of adalimumab in stable RA patients in clinical remission (ADMIRE)

Investigator:

Dr Ronald van Vollenhoven, [redacted] Sweden redacted information - 09Jun2014

Study Sites:

Multicenter, 8 sites in Sweden

Publications:

1 poster, 2 abstracts

Studied Period (Years): First Subject First Visit: 28 January 2009 Last Subject Last Visit: 19 September, 2012	**Phase of Development:** 4

Objectives:

Treatments with adalimumab (Humira®) and other TNF blockers, once started as therapy for Rheumatoid Arthritis (RA), are usually continued indefinitely. Information, concerning the possibility to discontinue anti-TNF therapy in RA patients who are in remission, is limited.

The objective of this pilot study was to assess the proportion of patients, with established RA in stable remission (DAS28 < 2.6) after treatment with adalimumab in combination with methotrexate, in whom it is possible to discontinue adalimumab.

A possibility to discontinue treatment in patients who are in clinical remission would release financial means in the community for more patients to gain disease control through anti-TNF treatment.

Methodology:

This was a multi-centre, randomized, open-label pilot study of rheumatoid arthritis patients in stable remission (DAS28 < 2.6) treated with adalimumab + MTX that were randomized in a 1:1 ratio to continue with adalimumab treatment or discontinue adalimumab treatment for the following 52 weeks.

Methodology (Continued):

After Week 52 an observational extension was conducted to observe patients treated at the discretion of the investigator. The observational extension period lasted until Weeks 105 – 156 (average Week 125). One follow-up visit was scheduled at study Weeks 104 – 156, ending the observational extension period. All patients in both arms received MTX weekly throughout the randomized phase of the study.

Number of Subjects (Planned and Analyzed):

Planned: 50

Included: 33

Analyzed: 33

Inclusion of study patients was stopped when 33 patients had been included. This decision was made as inclusion of additional study patients within a reasonable time period was regarded as not possible. Prior to stop of inclusion, the inclusion period had been repeatedly extended. The participating study sites had systematically evaluated their RA patient cohorts for suitable study patients. Furthermore, no more suitable study sites were available in Sweden.

As the number of included and analyzed patients was reduced, cf. the number planned, the power to detect differences between the two treatment arms decreased.

Diagnosis and Main Criteria for Inclusion:

Stable RA patients in clinical remission.

Main criteria for inclusion included: age ≥ 18 years, diagnosis of RA as defined by the 1987-revised ACR-classification and has a documented positive RF test or erosion on radiograph of hands or feet, currently treated with adalimumab and MTX (at least 10 mg/week; orally or subcutaneously) and has received both for at least 6 months (MTX dose stable for at least 2 months), in remission as defined by DAS28 < 2.6 for at least the 3 past months (based on assessments at baseline and on at least one more occasion 3 to 6 months prior to baseline), concomitant DMARD or oral corticosteroid therapy stable for at least 3 months at study entry.

Main criteria for exclusion included: Patient treated with intra-articular or parenteral administration of corticosteroids in the preceding 4 weeks (inhaled corticosteroids for stable medical conditions were allowed), oral prednisone or prednisone equivalent > 10 mg/day, joint surgery within the preceding 2 months (at joints to be assessed within the study), history of acute inflammatory joint disease of different origin other than RA (e.g., mixed connective tissue disease, seronegative spondyloarthritis, psoriatic arthritis, Reiter's syndrome, fibromyalgia, systemic lupus erythematosus or any arthritis with onset prior to age 17 years).

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

Humira/Adalimumab, 40 mg eow, s.c. injection

Duration of Treatment:

Treatment according to randomization until study Week 52. Treatment during the observational extension phase was at the discretion of the investigator.

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

Not applicable.

Criteria for Evaluation

Efficacy:

Primary Variable

- The proportions of RA patients in remission defined as DAS28 < 2.6 at Week 28 in Arm 1 (adalimumab and MTX continued) and Arm 2 (adalimumab discontinued, MTX continued).

Secondary Variable(s):

- The proportions of RA patients in remission defined as DAS28 < 2.6 at Week 52 in Arm 1 (adalimumab and MTX continued) and Arm 2 (adalimumab discontinued, MTX continued).
- The incidence of flare (defined as DAS28 ≥ 2.6 or DAS28 increase > 1.2 units) at Weeks 4, 8, 12, 20, 28, 36, 44 and 52.
- The response rate, defined as return to baseline DAS28 + 10% after reinstitution of adalimumab (after flare), evaluated at 4, 8 and 12 weeks after adalimumab reinstitution.
- The response rate, defined as DAS28 < 2.6 or DAS28 decrease > 1.2 units, after reinstitution of adalimumab (after flare), evaluated at 4, 8 and 12 weeks after adalimumab reinstitution.
- The physical function, evaluated by HAQ at Weeks 4, 8, 12, 20, 28, 36, 44, 52 and 104 – 156.
- The quality of life, evaluated by EuroQOL EQ-5D, at Weeks 4, 8, 12, 20, 28, 36, 44, 52 and 104 – 156.
- The degree of fatigue, evaluated by FACIT, at Weeks 4, 8, 12, 20, 28, 36, 44, 52 and 104 – 156.
- The impact of work capacity and activity, evaluated by WIS and WPAI, at Weeks 12, 28, 52 and 104 – 156.
- The change in radiological (modified Sharp/van der Heijde) score at Weeks 52 and 104 – 156.

Pharmacokinetic:

Not applicable.

Safety:

Safety was assessed by adverse events, physical examination, vital signs and laboratory data.

Statistical Methods

Efficacy:

The aim of this pilot study was to gather information about the effect of discontinuation of adalimumab treatment in patients in clinical remission. Efficacy analysis was conducted in the intent-to-treat population. As specified in the statistical analytical plan, analysis performed on FAS was considered as main. The analysis of baseline, efficacy and safety data are of descriptive nature. In addition to descriptive statistics, 95% confidence intervals for remission rates, response rates and flare rates are calculated within each group and Fisher's exact test is used to compare the remission rates between the two treatment groups.

Pharmacokinetic:

Not applicable.

Statistical Methods (Continued)

Safety:

The analysis of safety data is of descriptive nature. All adverse events, whether in response to a query, observed by site personnel, or reported spontaneously by the patient was to be reported.

The analysis of safety was performed on Safety analysis set, e.g., all patients randomized. AEs are displayed as per randomization arm. For patients in the MTX arm who entered rescue, AEs are displayed separately when appropriate.

Summary/Conclusions

Thirty-three patients were included in the analysis, 17 in Arm 1 (adalimumab + MTX) and 16 in Arm 2 (MTX). Mean disease durations were 10 and 13 years, and baseline DAS28 scores were 1.98 and 1.73 for Arm 1 (adalimumab + MTX) and 2 (MTX), respectively. At Week 28, there was a higher proportion of RA patients in remission in the Arm 1 (adalimumab + MTX) compared to Arm 2 (MTX). This difference was statistical significant.

The average DAS28 score was relatively stable over time from baseline to Week 52 in treatment Arm 1 (adalimumab + MTX) and for patients in treatment Arm 2 (MTX) who never reinstituted adalimumab (MTX, rescue arm excluded). For patients in the rescue arm the average DAS28 score increased after baseline.

The response rate in patients who reinstituted adalimumab after flare in Arm 2 (MTX rescue arm) was highest between 1 to 4 weeks after reinstitution for both definitions of response (return to baseline DAS28 + 10% or less/DAS28 < 2.6 or DAS28 decrease > 1.2 units).

No differences between treatment arms could be shown for physical function (measured by HAQ) or quality of life, including degree of fatigue. The impact of work capacity and activity, measured by WIS and WPAI, showed no obvious differences between the treatment groups.

Both the physician's and the patient's global assessment of disease activity showed a somewhat higher activity for the MTX rescue arm compared to the adalimumab + MTX arm and the MTX arm, rescue arm excluded. Similar results were seen for the patient's assessment of pain.

The safety evaluation showed that both study medications were well tolerated with 82.4% of the patients in Arm 1 (adalimumab + MTX) who reported at least one adverse event and 87.5% of patients in Arm 2 (MTX) during the randomized phase. Most of the adverse events were of mild to moderate intensity.

Thirty-one patients (16 from Arm 1 [adalimumab + MTX] and 15 from Arm 2 [MTX]) were evaluated at the observatory extension visit (Weeks 104 – 156). Twenty-two patients were receiving adalimumab and 9 were not. Ten of the 16 patients from Arm 1 (adalimumab + MTX) were treated with adalimumab and methotrexate and 6 study patients had stopped adalimumab.

Of the 15 patients from Arm 2 (MTX) who participated in the extension phase and stopped adalimumab (in accordance to the protocol), 12 had restarted adalimumab, 9 of these patients had restarted adalimumab rescue during the randomized phase and 3 more patients started adalimumab during the extension phase. In total, only 3 patients originally randomized to Arm 2 (MTX) were still not receiving adalimumab at the observatory visit at Weeks 104 – 156.

The overall conclusion of this study is that patients on adalimumab and MTX were more likely to remain in remission longer than patients in whom adalimumab was discontinued. Only 3 patients in Arm 2 (MTX) completed the study without reinstitution of adalimumab. Both adalimumab and MTX were safe and well tolerated.

Summary/Conclusions (Continued)

Efficacy Results:

There was a higher proportion of RA patients in remission in Arm 1 (adalimumab + MTX) compared to Arm 2 (MTX) at Week 28. This difference was statistically significant (p = 0.021), when analyzed as prespecified in the protocol. This difference persisted at Week 52 (p = 0.14).

However, the calculations above do not take the presence of the rescue option for patients in Arm 2 (MTX) in account. Patients in Arm 2 (MTX) were considered not to be in remission if DAS28 were 2.6 or more on any visit before or at Week 28 (and thus allocated to the rescue treatment option), whereas patients in Arm 1 (adalimumab + MTX) could have had DAS28 of 2.6 or more on visits before Week 28 but were still considered as in remission at Week 28 if DAS28 at Week 28 was then less than 2.6.

To account for the impact of the rescue treatment option in Arm 2 (MTX) a post-hoc modified comparison between the two arms was performed. In this analysis study patients in Arm 1 (adalimumab + MTX) who fulfilled the definition for flare before Week 28 were handled the same way as study patients in Arm 2 (MTX) (see above) in the calculations. When applying this post-hoc modification, there was still a higher proportion of patients in remission at Week 28 in treatment Arm 1 (adalimumab + MTX) (50.0%) compared to treatment Arm 2 (MTX) (18.8%), but the difference was reduced and was not statistically significant at the 5% level (p-value of 0.13). The average DAS28 score was relatively stable over time from baseline to Week 52 in treatment Arm 1 (adalimumab + MTX) and patients in treatment Arm 2 (MTX) who never reinstituted adalimumab (MTX, rescue arm excluded). For patients in the rescue arm the average DAS28 score increased after baseline.

Pharmacokinetic Results:

Not applicable.

Safety Results:

The safety evaluation showed that both study medications were well tolerated with 82.4% of the patients in Arm 1 (adalimumab + MTX) who reported at least one adverse event and 87.5% of patients in Arm 2 (MTX) during the randomized phase. Most of the adverse events were of mild to moderate intensity.

Conclusions:

Patients on adalimumab and MTX stayed in remission longer than patients with adalimumab discontinued although this difference was not shown to be statistically significant when the same definition of remission was used for the treatment arms. Only 3 patients in Arm 2 (MTX) completed the study without reinstitution of adalimumab, indicating that permanent discontinuation of adalimumab is only possible in a minor proportion of the RA patient population represented in this study. Both adalimumab and MTX were safe and well tolerated.