

2.0 Synopsis

AbbVie	Individual Study Table Referring to Part of Dossier:	(For National Authority Use Only)
Name of Study Drug: HUMIRA 40 mg/0.8 ml for subcutaneous injection	Volume:	
Name of Active Ingredient: Adalimumab	Page:	
Title of Study: Humira 40 mg/0.8 mL Syringe for Subcutaneous Injection - Special Investigation (Follow-up Survey of the Study of Adalimumab (D2E7) for Prevention of Joint Destruction in Patients With Rheumatoid Arthritis in Japan (M06-859))		
Investigator:		
Study Site(s): 77 sites in Japan		
Publications: No publications provided		
Studied Period (Years): 2 years First Subject First Visit: 24 Mar 2010 Last Subject Last Visit: 19 Oct 2012	Phase of Development: Post Marketing Surveillance	
Objective(s): The present survey will be conducted to assess the risk and benefit of continuing or discontinuing biological therapy according to clinical practice during the 52-week period following completion of the treatment period in the M06-859 study in patients who have continued treatment with adalimumab for 52 weeks.		
Methodology: <ol style="list-style-type: none"> 1) A central registration system was used. 2) The investigators registered patients in this survey after they had obtained informed consent for ① participation in this follow-up survey and ② usage of data obtained during the M06-859 study in the present follow-up survey. Due to the observational study, continuation or discontinuation of treatment with adalimumab was judged at the investigator's discretion. 3) Patients were followed for 52 weeks after completion of the treatment period in Study M06-859. 4) The investigators completed case report forms for their patients after 52-week follow-up period, sign and seal the forms, and provide the forms to medical representatives. 		

Number of Subjects (Planned and Analyzed):

Planned: 300 patients at maximum. The target sample size is 300 patients in Study M06-859. The target sample size for the present survey was therefore set at 300 patients, as all patients enrolled in the M06-859 study can continue treatment with adalimumab until the end of the treatment period.

Enrolled and analyzed: 220

Diagnosis and Main Criteria for Inclusion:

The participants are patients who have continued treatment with adalimumab until the end of the treatment period in the M06-859 study, provided informed consent to participate in the present follow-up survey. The participants may or may not continue treatment with adalimumab during the present follow-up survey. Patients who use biological agents other than adalimumab after the period of treatment in Study M06-859 will be excluded from the present follow-up study.

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

Marketed product of Humira, 40 mg/0.8 ml for subcutaneous injection

Duration of Treatment:

52 weeks

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

Not applicable

Criteria for Evaluation

Demographics and Baseline Characteristics:

Age, Sex, Body weight, RA duration, Prior DMARDs use (except for MTX), Glucocorticoids use, Rheumatoid factor, HAQ-DI, DAS28-ESR, mTSS, mTSS change during Study M06-859 and MMP-3 were summarized at baseline. These data were collected from Study M06-859.

Outcome Measures:

- Improvement rating based on Disease Activity Score 28 [Time Frame: at Week 26, 52]
- Matrix metalloprotease-3 [Time Frame: at Week 26, 52]
- X-ray findings for hands and feet [Time Frame: at Week 52]
- Health Assessment Questionnaire [Time Frame: at Week 26, 52]
- Evaluation of adverse events [Time Frame: at Week 52]

Effectiveness:

Effectiveness was assessed using DAS28-4 (ESR) (28-joint Disease Activity Score based on erythrocyte sedimentation rate), Matrix metalloprotease-3 (MMP-3), X-ray findings for hands and feet (modified total sharp score; mTSS) and Health Assessment Questionnaire Disability Index (HAQ-DI).

Missing data for DAS28-4 (ESR), MMP-3 and HAQ-DI were processed using the last observation carried forward method. Missing data for mTSS was processed using the linear extrapolation method.

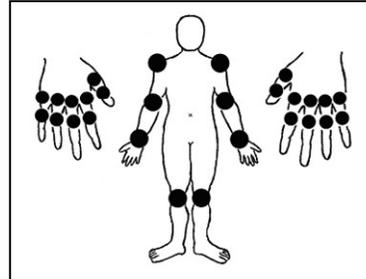
28-Joint Disease Activity Score 28 (DAS28)

Method for calculating absolute activity of disease

<Efficacy variables>

(A) Number of tender joints

(R/L shoulder joint, elbow joint, wrist joint, metacarpophalangeal joint [MCP], proximal interphalangeal joint, [PIP] and knee joint; total of 28 joints)



(B) Number of swollen joints

(R/L shoulder joint, elbow joint, wrist joint, metacarpophalangeal joint [MCP], proximal interphalangeal joint, [PIP] and knee joint; total of 28 joints)

(C) 1-h value of ESR

(D) Overall activity of the disease (VAS) (mm)

(Patient assesses current status of overall rheumatoid arthritis activity by him-/her-self, using 10-cm horizontal line.)

(E) C-reactive protein (CRP) (mg/dL)

<Equation using ESR>

$$\text{DAS28-4 (ESR)} = 0.56 \times \sqrt{A} + 0.28 \times \sqrt{B} + 0.70 \times \ln(C) + 0.014 \times (D)$$

$$\text{DAS28-3 (ESR)} = [0.56 \times \sqrt{A} + 0.28 \times \sqrt{B} + 0.70 \times \ln(C)] \times 1.08 + 0.16$$

<Equation using CRP>

$$\text{DAS28-4 (CRP)} = 0.56 \times \sqrt{A} + 0.28 \times \sqrt{B} + 0.36 \times \ln(E + 1) + 0.014 \times (D) + 0.96$$

$$\text{DAS28-3 (CRP)} = [0.56 \times \sqrt{A} + 0.28 \times \sqrt{B} + 0.36 \times \ln(E + 1)] \times 1.10 + 1.15$$

Modified Total Sharp Score (mTSS)

Modified Total Sharp Score (mTSS) is a measure of radiographs, used in evaluation of inhibition of joint destruction of disease. Digitized X-rays of hands and feet were obtained then scored in a blinded manner: for erosion (0 [no damage] to 5 [complete collapse or total destruction of joint]) and for joint space narrowing (0 [no damage] to 4 [complete luxation of joint]). Sum of scores was giving as total mTSS (0 [normal] to 380 [maximal disease]). Large positive change in mTSS indicates disease progression; small positive/no change indicates slowing/halting of disease progression.

Health Assessment Questionnaire Disability Index (HAQ-DI)

Subjects assessed their ability to perform the following tasks: 1) dress/groom; 2) arise; 3) eat; 4) walk; 5) reach; 6) grip; 7) maintain hygiene; and 8) maintain daily activity. Subjects assessed their ability to do these tasks over the past week by marking their response on a questionnaire. Possible responses/scores included the following: without any difficulty (0); with some difficulty (1); with much difficulty (2); and unable to do (3). Negative mean changes from baseline in the disability index of the HAQ-DI indicated improvement.

Safety:

Adverse events (AEs) were coded with the Medical Dictionary for Regulatory Activities (MedDRA/J Version 15.1). The frequency of AEs was analyzed by System Organ Class (SOC) and Preferred Terms (PTs). The incidence of AEs was expressed as number and percentage, and these were further expressed as serious adverse events (SAEs) and non-SAEs. Laboratory data were collected when patients experienced AEs.

When a patient experienced more than one episode of AEs coded to a single PT of MedDRA, the episodes were counted as one case of the relevant PTs.

Statistical Methods

Demographics and Baseline characteristics and effectiveness measurements of the study patients were summarized for adalimumab continued patients and discontinued patients, respectively. Continuous variables were presented by the number of non-missing values, mean, standard deviation, minimum, 1st quartile, median, 3rd quartile, and maximum. Categorical variables were described by frequency and percentage. Statistical comparisons were conducted between adalimumab continued patients and discontinued patients. Wilcoxon rank sum test was used in continuous variables, for example, DAS28-4 (ESR), mTSS and HAQ-DI. Fisher's exact test was used in categorical variables, for example, MMP-3. Level of significance was set at 0.05. Missing data were not imputed and excluded from summaries and analyses.

The analysis was performed using SAS[®] (SAS Institute Inc., Cary, NC, USA).

Summary/Conclusions

Patients Characteristics:

Among 278 patients completing the 52-week study M06-859, 220 patients were registered in Study P12-069. Of these, 106 patients continued treatment with adalimumab (ADA continuation group), while 114 patients discontinued treatment with adalimumab (ADA discontinuation group). Patient background (e.g., age, sex, body weight, RA duration, prior DMARDs use, glucocorticoids use and rheumatoid factor), DAS28-4 (ESR), MMP-3, mTSS and HAQ-DI were comparable in both groups. The mean age was 56.0 years in the ADA continuation group and 54.7 years in the ADA discontinuation group, respectively. More than 80% of the patients were female and the mean RA duration was 1.3 years in the both group. The mean DAS28-4 (ESR) was 2.89 in the ADA continuation group and 2.74 in the ADA discontinuation group, respectively.

Reasons for Withdrawal from Study P12-069:

The total number of withdrawal patients before the 52-week observation period in the ADA continuation and ADA discontinuation groups were 41 (41/106, 38.7%) and 22 (22/114, 19.3%), respectively. In the ADA continuation group, lack of efficacy (9/106, 8.5%) and sufficient response to adalimumab (9/106, 8.5%) were the most common reasons for discontinuation. In the ADA discontinuation group, initiation of biological therapy (15/114, 13.2%) was the most common reason for discontinuation.

Effectiveness Results:

Effectiveness of adalimumab treatment was assessed for 198 of 220 patients; 22 patients were excluded due to lack of assessable data.

DAS28-4 (ESR) was assessed at Weeks 26 and 52. The mean DAS28-4 (ESR) at Weeks 0, 26 and 52 in the ADA continuation group were 2.93, 2.72 and 2.70, respectively. The mean DAS28-4 (ESR) at Weeks 0, 26 and 52 in the ADA discontinuation group were 2.73, 3.17 and 3.20, respectively. At Weeks 26 and 52, the mean DAS28-4 (ESR) was significantly higher in the ADA discontinuation group than in the ADA continuation group. The median DAS28-4 (ESR) in the ADA discontinuation group at Week 52 was 2.87, and more than 50% of ADA discontinuation group patients achieved DAS28-4 (ESR) < 3.2, which means low disease activity, for 52 weeks.

MMP-3 was assessed at Weeks 26 and 52. A cut-off point of 121.0 ng/ml (male) and 59.7 ng/ml (female) was used for MMP-3 positive/negative categorization due to gender difference. At Weeks 0, 26 and 52, 38.7%, 36.6% and 22.6% of ADA continuation group patients were MMP-3 positive, respectively. At Weeks 0, 26 and 52, 31.3%, 36.5% and 44.8% of ADA discontinuation group patients were MMP-3 positive, respectively. At Week 52, the proportion of MMP-3-positive patients was significantly higher in the ADA discontinuation group than in the ADA continuation group.

mTSS was assessed at Week 52. The mean changes in mTSS from Week 0 to Week 52 were 0.8 and 0.6 in the ADA continuation group and the ADA discontinuation group, respectively. There were no significant differences in the mean changes in mTSS from Week 0 to Week 52 in both groups.

HAQ-DI was assessed at Weeks 26 and 52. Mean HAQ-DI at Weeks 0, 26 and 52 in the ADA continuation group, was 0.27, 0.20 and 0.20, respectively. Mean HAQ-DI at Weeks 0, 26 and 52 in the ADA discontinuation group was 0.24, 0.24 and 0.26, respectively. There were no significant differences in mean HAQ-DI at Weeks 26 and 52 in both groups.

Safety Results:

Safety analysis was performed in 220 patients.

Total number of patients with AEs in the ADA continuation group and the ADA discontinuation group were 51 patients (48.1%) and 38 patients (33.3%), respectively. The incidence of SAEs and non-SAEs in the ADA continuation group was 4.7% (n = 5) and 43.4% (n = 46). The incidence of SAEs and non-SAEs in ADA discontinuation group was 2.6% (n = 3) and 30.7% (n = 35). The most frequent AE in both groups was nasopharyngitis (12.3%, n = 13 and 7.0%, n = 8 in the ADA continuation and ADA discontinuation groups, respectively). No overall safety profile changes in adalimumab were observed and life threatening AEs were not detected.

Conclusions:

At 26 and 52 weeks patients who continued adalimumab achieved a significantly lower DAS-28-4 (ESR) and MMP-3 than those that discontinued ADA, while HAQ-DI and changes in mTSS were similar in both groups at Week 52. More than 50% of the ADA discontinued patients sustained low disease activity (DAS-28-4 [ESR] < 3.2) for 1 year. ADA therapy after M06-859 was generally safe.

Date of Report: 25Jun2013