2.0 Synopsis

Abbott Laboratories **Eisai Co., Ltd**	**Individual Study Table Referring to Part of Dossier:** **Volume:** **Page:**	**(For National Authority Use Only)**
Name of Study Drug: Humira 40 mg/ 0.8 mL		
Name of Active Ingredient: Adalimumab		

Title of Study:

A Phase 3 Multicenter, Randomized, Double-Blind, Parallel Group, Placebo-Controlled Study Comparing Adalimumab and Placebo in Adult Japanese Subjects with Rheumatoid Arthritis

Investigator:

Tatsuya Atsumi and others

Study Sites:

Hokkaido University Hospital and 93 other study sites

Publications:

None

Studied Period (Years):	**Phase of Development:** III
First Subject First Visit: 28 Mar 2009 (Subject 011901, 011902) Last Subject Last Visit: 1 Aug 2011 (Subject 012709)	

Objectives:

The primary objective of this study was to evaluate the inhibition of radiographic progression in joint destruction of adalimumab 40 mg given every other week (eow) subcutaneously (sc) compared to placebo in adult Japanese subjects with RA.

Methodology:

This study was a phase 3 multicenter, randomized, double-blind, parallel group, placebo-controlled study designed to evaluate the inhibition of radiographic progression by adalimumab compared to placebo in adult Japanese MTX- or leflunomide-naive subjects with early RA. Approximately, 300 Japanese subjects with early RA were to be enrolled into this study. The study included a Screening period, a 52-week (26-week double-blind + 26-week open-label) administration period of study drug, and a safety follow-up period after the subject either completed or early terminated from the study. Subjects were enrolled in this study at the time when informed consent was obtained. Screening assessments were conducted during the period from the subject enrollment to the first administration of the study drug. All subjects received weekly MTX (6 – 8 mg) as a basal treatment during the administration of the study drug.

The subjects were assessed for eligibility by means of inclusion and exclusion criteria during Screening and Baseline. As a general rule, the eligibility at Screening was to be assessed within 14 days after the enrollment, and performed at Screening visit unless in exceptional circumstances. DMARDs that subjects had received prior to the study enrollment were to be washed out 28 days prior to the

administration of the study drug. Subjects with a latent TB infection detected by purified protein derivative (PPD) skin test, chest X-ray and/or medical history at Screening, could participate in the study under the condition that ongoing isoniazid treatment for latent TB had been initiated at least 21 days prior to administration of study drug.

The eligibility was also assessed at Baseline visit, and the subjects who met all of the inclusion criteria and none of the exclusion criteria began administration of adalimumab. As a general rule, the Screening period was to be more than 14 days for subjects who had not received any DMARDs before obtaining consent. All subjects including those who received DMARDs had to have their Baseline visit no later than 42 days from the date of the Screening visit. Subjects who met all inclusion criteria and none of the exclusion criteria were randomized in a 1:1 ratio to receive either a subcutaneous injection of 40 mg adalimumab or matching placebo eow for 26 weeks. All subjects who completed the 26-week double-blind treatment period were to be eligible to enter the 26-week open-label period where they were to receive 40 mg adalimumab sc eow.

Efficacy and safety were to be assessed at Weeks 2, 4, 8, 12, 16, 20, 26, 30, 34, 38, 42, 46 and 52, or at the early termination (ET) visit, if applicable. Blood samples for evaluation of serum adalimumab and anti-adalimumab antibody (AAA) concentration were to be collected at Baseline and Weeks 2, 4, 8, 12, 16, 20, 26, 30, 34, 38, 42, 46 and 52, or at the ET and the follow-up visit, if applicable.

In the double-blind treatment period, subjects who experienced an increase in disease activity of more than a 20% increase in tender joint counts (TJC) and swollen joint counts (SJC) compared to Baseline at Week 12, 16 or 20 (in their original group assignment) were considered for open-label rescue treatment. In that case, the subjects were to be stopped receiving adalimumab/placebo in the double-blind period, and were to receive open label adalimumab 40 mg eow as rescue treatment. The subjects who completed rescue treatment until Week 26 were to be entered in the open-label period.

The primary endpoint was defined as the change from Baseline in modified Total Sharp Score (TSS) at Week 26. Secondarily, the change from Baseline in mTSS at Week 52 was to be assessed, and the results of 52 weeks treatment with adalimumab (adalimumab group) were to be compared with the results of the 26 weeks MTX treatment + 26 weeks adalimumab treatment (placebo group).

The similarity between the data obtained from this study and those from study [redacted] in Western subjects with early RA was to be compared. Subjects who completed the study or who prematurely terminated from the study were to have a 28-day follow-up after the completion or discontinuation from the study, and a 70-day follow-up after the last dose of adalimumab administration to evaluate safety.

Number of Subjects (Planned and Analyzed):

Planned: 300 subjects (150 subjects per group)

Obtained informed consent: 406

Randomized: MTX (Placebo): 163, Adalimumab + MTX: 171, Total: 334

Subjects completed Week 52: MTX (Placebo): 120, Adalimumab + MTX: 132, Total: 252

Subjects received rescue treatment: MTX (Placebo): 28, Adalimumab + MTX: 14, Total: 42

Rescue subjects completed Week 52: MTX (Placebo): 21, Adalimumab + MTX: 5, Total: 26

Diagnosis and Main Criteria for Inclusion:

Japanese subjects who met all of the inclusion criteria and none of the exclusion criteria were enrolled in this study.

<Inclusion Criteria>

1. Male or female subject aged 20 or older at the time of informed consent.
2. Subject who met the definition of RA based on the ACR criteria. The disease duration was less than

or equal to 2 years from diagnosis at the time of informed consent.

3. Subject who had at least 10 tender joint counts (TJC) out of 68 joints and at least 8 swollen joint counts (SJC) out of 66 joints at Screening and at Baseline.
4. Subject who was MTX or leflunomide naive.
5. Subject who had not previously received more than two other DMARDs (except MTX and leflunomide).
6. Subject who had laboratory analysis of C-reactive protein (CRP) ≥ 1.5 mg/dL or ESR ≥ 28 mm/h at Screening.
7. Subject who had at least one joint erosion or RF positivity at Screening.
8. Subject who could discontinue DMARDs therapy for 28 days prior to study drug administration if the subject had received DMARDs (except MTX and leflunomide) at the time of informed consent.
9. Subject who could decrease the dose of the corticosteroid (predonizone equivalents > 10 mg/day) for 28 days prior to study drug administration if the subject had received corticosteroid (prednisone equivalents ≤ 10 mg/day) at the time of informed consent.
10. If female, subject was either not of childbearing potential, defined as postmenopausal for at least one year or surgically sterile (bilateral tubal ligation, bilateral oophorectomy or hysterectomy) at the time of informed consent. If female subject was of childbearing potential or male subject was with procreative capacity, practicing one of the following methods of birth control throughout the study and for 150 days after last dose of study medication:
    - Condoms, sponge, foams, jellies, diaphragm or intrauterine device (IUD)
    - Contraceptives (oral, transdermal patch or parenteral) for three months prior to study drug administration
    - Vasectomized partner
11. If female of child bearing potential, the result of a pregnancy test performed at Screening and Baseline was negative.
12. Subject was able and willing to give written informed consent and to comply with the requirements of the study protocol.

<Exclusion Criteria>

1. Subject who had a history of, or current, acute inflammatory joint disease of different origin from RA (e.g., mixed connective tissue disease, rheumatoid factor (RF) negative spondyloarthropathy, progressive systemic sclerosis (scleroderma), psoriatic arthritis, Reiter's syndrome, systemic lupus erythematosus, or any arthritis with onset prior to age 16 years).
2. Subject who had a history of cancer, lymphoma, leukemia or lymphoproliferative disease, other than a successfully treated non-metastatic cutaneous squamous cell or basal cell carcinoma and/or localized carcinoma in situ of the cervix for 5 years at the time of informed consent.
3. Subject was known to have immune deficiency or a history of HIV.
4. Subject who had a history of listeriosis, histoplasmosis, active TB or persistent chronic infections.
5. Subject who had a recent active infections requiring hospitalization or treatment with intravenous (iv) anti-infectives within 28 days or oral anti-infectives within 14 days prior to the time of informed consent.
6. Subject who had a history of, or current, neurologic symptoms suggestive of central nervous system (CNS) demyelinating disease.
7. Subject who had symptoms of interstitial pneumonia thereby will be considered by the investigator to be unsuitable candidate (Subject will not able to use MTX or subject has an active interstitial pneumonia.)

8. Subject who had a congestive heart failure, bone marrow suppression, pleural effusion or ascites.
9. Subject with a history of clinically significant drug or alcohol abuse.
10. Subject who had a poorly controlled medical condition such as follows;
    - Uncontrolled diabetes
    - Unstable ischemic heart disease, congestive heart failure
    - Recent cerebrovascular accidents, recent stroke (within 1 year at the time of informed consent)
11. Subject who had positive serology for anti-HIV antibody (HIV Ab), Hepatitis B surface antigen (HBsAg), anti-hepatitis C antibody (HCV Ab), in the Screening laboratory analysis.
12. Screening laboratory analysis showed any of the following abnormal results;
    - Hemoglobin < 9.0 g/dL for male, or < 8.5 g/dL for female;
    - Total white blood cell (WBC) count < 3,000/mm^3;
    - Platelet count < 150,000/mm^3;
    - Aspartate transaminase (AST) or alanine transaminase (ALT) > 2 × the upper limit of the reference range;
    - Total bilirubin ≥ 3 mg/dL;
    - Serum creatinine > 1.5 mg/dL
13. Subjects who revealed any findings, which shows a history of TB infection (calcified nodules or granulomas and/or fibrotic scar, apical or basilar thickening) by chest X-ray examination at Screening.
14. Subjects who were judged as "strongly positive" or PPD ≥ 5 mm of induration in a purified protein derivative (PPD) skin test for the detection of latent TB infection at Screening.
    - "Strongly positive" was defined as induration and erythema (≥10 mm of diameter) with either bulla, necrosis or double redness.
    - Subjects who demonstrated evidence of latent TB infection (either PPD ≥ 5 mm of induration, irrespective of BCG vaccination status, and negative chest X-ray findings for active TB) but was not evaluated as "strongly positive" would be included to participate in the study under the condition that the prophylactic treatment (isoniazid 300 mg/day or 5 mg/kg in the case of low body weight for 9 months) for latent TB must be initiated 21 days prior to study drug administration, however the course of prophylaxis need not be completed prior to the onset of study.

    The liver enzymes (ALT and AST) were to be measured about 1 week prior to study drug administration in each clinical site and the subject was to discontinue from the study as defined by laboratory abnormal results (> 2 × the upper limit of the reference range and/or the investigator's best clinical judgment).

    Subject who had documented and completed prophylactic treatment for TB did not need to repeat this treatment. However, the investigator considered re-prophylactic treatment if the subject who had received prophylaxis in the past also had contact with people with active TB or TB like symptoms.
15. Subject who had previously received anti-TNF-α therapy (e.g. adalimumab, infliximab, etanercept or investigational products in anti-TNF-α trial), anti-IL-6 receptor antibody (tocilizumab), CTLA4-Ig or anti-CD20 antibody.
16. Subject who had previously received cyclophosphamide, cyclosporine, azathioprine or tacrolimus.
17. Subject who had received any investigational chemical agent in the past 28 days or 5 half-lives prior to Baseline (whichever is longer).

18. Subject who had received any other biological or investigational biological agents in the past 24 weeks or 5 half-lives prior to Baseline (whichever is longer).
19. Subject had a history of an allergic reaction or significant sensitivity to constituents of study drug.
20. Subject was administered a live vaccine within 12 weeks prior to Screening or plans to receive a live vaccine during the study.
21. Subject had received intra-articular joint injection(s), intra-muscular injection or intravenous injection with corticosteroids, or intra-articular joint injection(s) with hyaluronate sodium within 28 days prior to Baseline.
22. Subject who needed to receive concomitant therapy of DMARDs (except MTX and leflunomide) or corticosteroid (prednisone equivalents > 10 mg/day) during the administration period of the study drug.
23. Subject had received joint surgery involving joints to be assessed within 8 weeks prior to Screening.
24. Subject that was wheelchair-bound or bedridden ("Class IV" in Classification of Functional Status in Rheumatoid Arthritis).
25. Female subject who was pregnant or breast-feeding.
26. Subject who was considered by the investigator, for any reason, to be an unsuitable candidate for the study.

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

Study Drug: Injection form packaged in pre-filled syringes containing 40 mg adalimumab/0.8 mL

Dose/Strength/Concentration: Adalimumab 40 mg

Mode of Administration: Subcutaneous

Duration of Treatment:

52 weeks (26-week double-blind phase and 26-week open-label phase)

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

Study Drug: Injection form packaged in pre-filled syringes containing placebo/0.8 mL

Dose/Strength/Concentration: Placebo

Mode of Administration: Subcutaneous

Criteria for Evaluation

Efficacy:

Primary Efficacy Variable

Primary efficacy endpoint was the change from Baseline in mTSS at Week 26 of 40 mg adalimumab eow + MTX compared to placebo + MTX.

Secondary Efficacy Variable

1. ACR20, ACR50, ACR70 and ACR90 response at Week 2, 4, 8, 12, 16, 20, 26, 30, 34, 38, 42, 46 and 52.
2. Proportion of subjects who achieved a major clinical response defined as an ACR70 response for any 6 continuous months prior to and including Week 52.
3. Numeric ACR (ACR-N) at Week 2, 4, 8, 12, 16, 20, 26, 30, 34, 38, 42, 46 and 52.
4. Change from Baseline in HAQ at Week 2, 4, 8, 12, 16, 20, 26, 30, 34, 38, 42, 46 and 52.
5. Change from Baseline in DAS28 at Week 2, 4, 8, 12, 16, 20, 26, 30, 34, 38, 42, 46 and 52.
6. Remission defined by DAS28 (< 2.6) at Week 26 and 52.
7. Change from Baseline in the physical and mental component of SF-36 at Weeks 26 and 52.

8. Change from Baseline in mTSS at Week 52.
9. Change in mTSS from Week 26 to Week 52.
10. Change from Baseline in erosion score at Weeks 26 and 52.
11. Change in erosion score from Week 26 to Weeks 52.
12. Change from Baseline in joint space narrowing (JSN) score at Weeks 26 and 52.
13. Change in JSN score from Week 26 to Weeks 52.
14. No worsening in mTSS, erosion score and JSN at Week 26 and 52 (change from Baseline in mTSS, erosion score and JSN ≤ 0 and ≤ 0.5).
15. No worsening in mTSS, erosion score and JSN at Week 52 (change from Week 26 in mTSS, erosion score and JSN ≤ 0 and ≤ 0.5).
16. Subjects with no erosions at Baseline and no new erosions at Week 26 and 52.
17. Subjects with no erosions at Week 26 and no new erosions at Week 52.
18. Subjects with non-involved joints at Baseline and no newly involved joints at Week 26 and 52.
19. Subjects with non-involved joints at Week 26 and no newly involved joints at Week 52.

Pharmacokinetic:

Serum adalimumab concentration and serum AAA concentration have been measured as well as pharmacokinetic model based analyses have been performed [redacted]

Safety:

Adverse event, vital signs and laboratory values.

Statistical Methods

All statistical tests were two-tailed with the significance level 0.05. All p-values were rounded to three decimal places. 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.

The analysis was performed using SAS® [redacted] No adjustment was made for multiple centers because the number of subjects per center was limited.

Analysis Populations:

The analysis population was described below.

- Full-analysis set (FAS) was defined as all subjects who received at least one double-blind study drug, and had at least one assessment of efficacy under double-blind study treatment.
- Per-protocol set (PPS) population was defined as the FAS but excluded all subjects with major protocol deviations.
- Safety analysis population was the same as the FAS population in this study.

The analysis for open label period was done using data from subjects who received at least one open-label study drug in or after Week 26 in FAS.

Demographics and Baseline Characteristics:

Demographics and Baseline characteristics of the study subjects were summarized for each treatment group. Descriptive statistics were presented. These variables were analyzed to assess the comparability of the two treatment groups provided by randomization; in general, continuous variables were analyzed using Wilcoxon rank sum test, whereas categorical valuables were analyzed using Fisher's Exact test. The Baseline value was to be determined by the last non-missing measurement recorded on or before the date that the first dose of study drug (during double-blind phase) was received.

Efficacy:

The primary analysis was the comparison of the adalimumab group vs. the placebo group regarding the change of Baseline in mTSS at Week 26 using Wilcoxon rank sum test for observed data.

In addition, supportive analysis was performed using the Linear Extrapolation (LE) and the Last Observation Carried Forward (LOCF) approach to impute missing values. Subjects who switched to rescue phase before having Week 26 X-ray, were to be excluded from this analysis.

Secondary variables were analyzed as secondary analyses. The Fisher's exact test and Wilcoxon rank sum test were used to assess potential treatment differences of the adalimumab group vs. the placebo group for discrete variables and continuous variables, respectively.

OC was used for the primary analysis of X-ray data. For binary variables such as ACR response and clinical remission (DAS 28), NRI (Non-Responder Imputation) was used for the primary analysis, and LOCF approach was used, if needed in the double-blind analyses. OC was used for the primary analysis in the open-label analyses. . For continuous variables such as ACR-N, DAS 28, HAQ, SF-36, LOCF was used for primary analysis in the double-blind analyses, and OC was used for the primary analysis in the open-label analyses. The baseline value of the double-blind analyses was to be determined by the last non-missing measurement recorded on or before the date that the first dose of study drug (during double-blind phase) was received. The baseline value of the open-label-analyses was to be determined by the last non-missing measurement recorded on or before the first dose date of adalimumab. Statistical plans were changed after the SAP was approved. [redacted]

Pharmacokinetic:

Adalimumab concentrations were summarized at each time point using descriptive statistics including number of subjects, number of non-missing observations (n_{nmiss}), mean, median, standard deviation, coefficient of variation, minimum and maximum. Individual subject concentrations vs time plots and mean concentrations vs time plots were provided. Population pharmacokinetic analysis was performed to estimate the apparent clearance (CL/F) and apparent volume of distribution (V/F) of adalimumab in subjects with RA. Serum AAA concentrations were listed for each collection time ([redacted]

Safety:

Adverse Events

In the double-blind analyses, a treatment emergent adverse event (TEAE) was defined as an event with onset or worsening after the first study drug injection and within 70 days after the last study drug injection. TEAEs were defined based on the following:

- Double-Blind Phase: TEAEs were defined as any event with an onset date that was on or after the first dose of study drug in the double-blind period till Week 26 for Week 26 completers. For early terminated subjects, TEAEs were defined as any event with an onset date no more than 70 days after the last dose of study drug in the double-blind period for early terminated subjects; TEAEs reported during rescue period were excluded from this presentation. Actual treatment received during the

double-blind period was used for this presentation.

- Rescue period: TEAEs were defined as any event with an onset date during rescue period; for early terminated subjects in rescue period, TEAEs were reported with an onset date no more than 70 days after last dose of study drug.
- Any Adalimumab Exposure: TEAEs were defined as any event with an onset date that was on or after the first dose of adalimumab and with an onset date no more than 70 days after the last dose of adalimumab.

In the open-label analyses, a TEAE was defined as any event with an onset date that is on or after the first dose of adalimumab and with an onset date no more than 70 days after the last dose of adalimumab.

The number and percentages of subjects experiencing TEAEs were tabulated by system organ classes (SOCs) and Medical Dictionary for Drug Regulatory Affairs (MedDRA) preferred terms as defined by MedDRA. MedDRA version 13.1 was used for this clinical study report. In addition, a summary of adverse events by severity and relationship to study drug was presented. TEAEs that were judged by the investigator to be probably related, possibly related, or probably not related to the study drug were also tabulated. A summary of serious and severe adverse events, deaths, and adverse events leading to discontinuation were also provided. In addition, comparisons of the percentages of subjects experiencing an adverse event in each of the adalimumab group vs. the placebo group were performed by Fisher's exact test.

Laboratory Data and Vital Signs

Descriptive statistics as well as changes in laboratory and vital sign variables at each visit were summarized for all treated subjects. The comparison of each of the adalimumab groups vs. the placebo group was performed using Wilcoxon rank sum test for data collected during double-blind period. The last evaluation prior to the first dose of study drug in the double-blind period was used as Baseline. Laboratory data collected during the rescue period was excluded from the data of the double-blind period.

Summary/Conclusions

Efficacy Results:

Based on the results of study M06-859, adalimumab + MTX combination therapy for 26 weeks was found to be statistically superior to MTX monotherapy in inhibition of radiographic progression, improvement of clinical signs and symptoms, physical function, disease activity, and physical aspect of QOL in Japanese subjects with RA. In addition, adalimumab + MTX combination therapy for 52 weeks was effective compared to 26 week MTX monotherapy followed by 26-week adalimumab + MTX combination therapy in inhibition of radiographic progression in Japanese subjects with RA, and this results demonstrated that timing of initiation of adalimumab therapy in combination with MTX affected the inhibition of radiographic progression. In the adalimumab + MTX group, the improvements of clinical signs and symptoms, physical function, disease activity, and QOL seen at Week 26 were maintained for up to Week 52.

- As already reported in 26-week CSR [redacted] following 26 weeks of treatment, adalimumab + MTX combination therapy was statistically superior to MTX monotherapy in inhibition of radiographic progression in subjects with RA ($p<0.001$), as demonstrated by the primary efficacy variable: the mean change from Baseline in mTSS at Week 26.
- As already reported in 26-week CSR [redacted] adalimumab + MTX combination therapy was found to be statistically superior to MTX monotherapy in inhibition of radiographic progression, improvement of clinical signs and symptoms, physical function, disease activity, and physical aspect of QOL in Japanese subjects with RA.
- The mean change from Baseline in mTSS and erosion score at Week 52 in the adalimumab + MTX / OL group was smaller compared to the MTX / OL group. The number of subjects with no worsening

in mTSS, erosion score and JSN score, subjects with no erosions at Baseline and no new erosions at Week 52, and subjects with non-involved joints at Baseline and no newly involved joints at Week 52 were higher in the adalimumab + MTX / OL group compared to the MTX / OL group. Therefore, adalimumab + MTX combination therapy for 52 weeks was effective compared to 26 week MTX monotherapy followed by 26-week adalimumab + MTX combination therapy in inhibition of radiographic progression in Japanese subjects with RA. Meanwhile, there was no difference in change from Week 26 to Week 52 in these X-ray image variables between the adalimumab + MTX / OL group and the MTX / OL group.

- The ACR 20, ACR 50, ACR 70, ACR 90 response rates and ACR-N seen at Week 26 were maintained or further improved through Week 52 in the adalimumab + MTX / OL group. These results demonstrated the sustained effectiveness of adalimumab + MTX combination therapy in improvement of clinical signs and symptoms of RA for up to 52 weeks. In the MTX / OL group, further improvement was seen after Week 26, and ACR 20, ACR 50, ACR 70, ACR 90 response rates and ACR-N at Week 52 was comparable to the adalimumab + MTX / OL group. The number of subjects who achieved a major clinical response defined as an ACR70 response for any 6 continuous months prior to and including Week 52 was higher in the adalimumab + MTX / OL group compared to the MTX / OL group.
- The HAQ score seen at Week 26 were maintained through Week 52 in the adalimumab + MTX / OL group. This result demonstrated the sustained effectiveness of adalimumab + MTX combination therapy in improvement of physical function of RA for up to 52 weeks. In the MTX / OL group, the HAQ score seen at Week 26 were maintained through Week 52, and HAQ score at Week 52 was comparable to the adalimumab + MTX / OL group.
- The DAS 28 and the number of subjects who achieved clinical remission, as defined by DAS 28 (ESR) < 2.6 seen at Week 26 were maintained or further improved through Week 52 in the adalimumab + MTX / OL group. This result demonstrated the sustained effectiveness of adalimumab + MTX combination therapy in improvement of disease activity of RA for up to 52 weeks. In the MTX / OL group, further improvement was seen after Week 26, and DAS 28 and the number of subjects who achieved clinical remission at Week 52 was comparable to the adalimumab + MTX / OL group.
- The SF-36 PCS and MCS seen at Week 26 were maintained or further improved through Week 52 in the adalimumab + MTX / OL group. This result demonstrated the sustained effectiveness of adalimumab + MTX combination therapy in improvement of QOL of RA for up to 52 weeks. In the MTX / OL group, SF-36 PCS and MCS seen at Week 26 were maintained or further improved through Week 52, and SF-36 PCS and MCS at Week 52 was comparable to the adalimumab + MTX / OL group.

Safety Results:

The safety conclusions are summarized below:

- The overall incidence of AEs was 88.7% (289/326), and the number of AEs overall per 100 patient year (PYs) was 507.5 events/100PYs in all adalimumab subjects. The most frequently reported treatment-emergent AE reported in ≥ 10% of subjects in all adalimumab subjects by MedDRA preferred term (PT) was nasopharyngitis (29.8%, 97/326).
- More than three-fourths (928/1180 events) of AEs were considered not related or probably not related to the study drug, and most of AEs (1078/1180 events) were mild.
- There was no significant difference in overall incidence of AEs between subgroups by sex and age.
- No deaths were reported in all adalimumab subjects.
- In all adalimumab subjects, 21 subjects (6.4%) reported 27 SAEs, and 8 subjects reported 9 serious infections. The SAEs which occurred in at least 2 subjects were pneumonia (4 subjects), cataract (2

subjects) and gastroenteritis (2 subjects).

- In all adalimumab subjects, 15 subjects (4.6%) reported 17 AEs leading to discontinuation. The AEs leading to discontinuation which occurred in at least 2 subjects were interstitial lung disease and toxic skin eruption (2 subjects, respectively).
- In all adalimumab subjects, 169 subjects (51.8%) reported 305 infectious AEs. The infectious AEs reported for ≥ 5% of subjects were nasopharyngitis (29.8%, 97/326). Eight (8) subjects reported 9 serious infectious AEs.
- In all adalimumab subjects, 16 subjects (4.9%) reported 16 hepatic related AEs. No hepatic related AEs reported for ≥ 5% of subjects in all adalimumab subjects. No serious hepatic related AEs were observed. In all adalimumab subjects, 64 subjects (19.6%) reported 95 elevated LFT levels related AEs. The elevated LFT levels related AEs reported for ≥ 5% of subjects were alanine aminotransferase increased (8.6%, 28/326), hepatic function abnormal (7.4%, 24/326) and aspartate aminotransferase increased (6.7%, 22/326). No serious elevated LFT levels related AEs were observed.
- In all adalimumab subjects, 41 subjects (12.6%) reported 52 injection site reaction related AEs. The injection site reaction related AEs reported for ≥ 5% of subjects were injection site reaction (8.6%, 28/326). No injection site reaction related AEs were observed.
- In all adalimumab subjects, 17 subjects (5.2%) reported 22 hematologic event AEs. No hematologic event AEs reported for ≥ 5% of subjects in all adalimumab subjects. No serious hematologic event AEs were observed.
- No tuberculosis was observed in all adalimumab subjects. One subject (0.3%) reported 1 opportunistic infection related AEs (excluding tuberculosis). No serious opportunistic infection related AEs were observed.
- In all adalimumab subjects, 1 subject (0.3%) reported 1 lupus-like syndrome AEs. No serious lupus-like syndrome AEs were observed.
- In all adalimumab subjects, 10 subjects (3.1%) reported 10 allergic reaction related AEs in all adalimumab subjects. No serious allergic reaction related AEs were observed.
- In all adalimumab subjects, 1 subject (0.3%) reported 1 psoriatic condition and worsening AEs. No serious psoriatic condition and worsening AEs were observed.
- In all adalimumab subjects, 3 subjects (0.9%) reported 3 interstitial lung disease AEs. One interstitial lung disease and 1 organising pneumonia were serious.
- In all adalimumab subjects, 1 subject (0.3%) reported 1 pancreatitis AE. This AE (pancreatitis acute) was serious.
- No malignancies, tuberculosis, demyelinating disease, myocardial infarction or congestive heart failure were observed in all adalimumab subjects.
- No AEs related to extended exposure to adalimumab were observed.
- No clinically significant changes were observed in laboratory parameters and vital signs.

The results demonstrated that adalimumab 40 mg eow with MTX combination therapy for 52 weeks was generally safe and well tolerated in Japanese patients with RA.

Conclusions:

The results of study M06-859 demonstrated that adalimumab 40 mg eow + MTX combination therapy for 52 weeks was more effective than 26-week MTX monotherapy followed by 26-week adalimumab 40 mg eow + MTX combination therapy in inhibiting radiographic progression in Japanese patients with RA. Adalimumab therapy for 52 weeks was generally safe in combination with MTX, and both adalimumab + MTX combination therapy and MTX monotherapy were well tolerated.

The results demonstrate that administration of adalimumab in combination with MTX is beneficial for RA patients with high disease activity and poor prognostic factors (i.e. RF positive or with erosion) even if the patients are MTX-naïve.