



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 (To be determined for 20 mg product) Humira 20 mg/ 0.4 mL (To be determined for 20 mg product)		
Name of Active Ingredient: Adalimumab		
Title of Study: A Multicenter, Open-label Study of the Safety, Efficacy, and Pharmacokinetics of the Human Anti-TNF Monoclonal Antibody Adalimumab in Children With Polyarticular Juvenile Rheumatoid Arthritis		
Investigator: Hiroaki Umabayashi and 14 other investigators. [REDACTED]		
Study Sites: Miyagi children's hospital and 13 other study sites. [REDACTED]		
Publications: None		
Studied Period (Years): First Subject First Visit: 19 May 2008 (Subject00201) Last Subject Last Visit: 05 Sep 2011 (Subject 00904)	Phase of Development: III	
Objectives: The primary objective of this study was to evaluate the safety, efficacy and pharmacokinetics including immunogenicity (measured as anti-adalimumab antibody (AAA) of fixed dose adalimumab eow in Japanese subjects with polyarticular JRA. The secondary objective of this study was to confirm the similarity between the data obtained from this study and those from study [REDACTED] conducted in western subjects with JRA.		
Methodology: Study M10-240 was single arm, open-label, multicenter study to evaluate efficacy, safety and pharmacokinetics of adlimumab eow in Japanese polyarticular JRA subjects. The subject had to satisfy the inclusion and exclusion criteria at enrollment, and the joint evaluation and pregnancy test were to be conducted at Week 0 (pre-dose). The first study drug was to be administered within 4 weeks. Subjects weighing less than 30 kg (the weight at Week 0) were to be dosed with 20 mg of adalimumab eow. Subjects weighing 30 kg or more were to be dosed with 40 mg of adalimumab eow. The duration of the study was to be up to obtaining the approval from Ministry of Health, Labour and Welfare (MHLW).		



The primary efficacy variable was to be evaluated at Week 16, and the study data for 24 weeks was to be summarized to apply the approval from MHLW. And the study data at Week 60 are to be submitted to MHLW. After Week 60, the data was to be collected suitably according to MHLW's instruction.

Number of Subjects (Planned and Analyzed):

Planned: MTX 20, non-MTX 5, Total 25

Obtained informed consent: 28

Enrolled: MTX 20, non-MTX 5, Total 25

Complete: MTX 14, non-MTX 2, Total 16

Diagnosis and Main Criteria for Inclusion:

The study population was polyarticular JRA patients who filled all of each following inclusion criterion, and did not conflict with exclusion criteria.

<Inclusion Criteria>

1. Subjects were to have a diagnosis of Polyarticular JRA by the ACR criteria. Disease onset might have been systemic, polyarticular, or pauciarticular. If the disease was systemic onset, then the subjects were to be free of any systemic JRA manifestations for at least 12 weeks before the time of qualification.
2. Subjects who could not control disease activity by NSAIDs or MTX etc. (Insufficient efficacy*, impossible continuation of the medication for adverse events or impossible doing of standard therapy for medical history or complication)

* Subjects were to have the following number of active joints even if MTX 8 to 10 mg/m² was administered for 3 months or more: MTX 8 to 10 mg/m² was defined as the dose to be equal to 8 to 10 mg per 1 m² body surface area per week with MTX prescribed by the clinical site.

3. At the time of study screening, the subject was to have continuing active disease defined as ≥ 5 swollen joints (not due to deformity) and ≥ 3 joints with limitation of passive motion (LOM) with pain by passive motion or/and pain by pressure (tenderness). These joints were not mutually exclusive.
4. Subjects were to be age 4 to 17 at the enrollment.
5. Dose of MTX was to be stable for at least 12 weeks prior to the screening visit. Non-MTX was to have discontinued at least 14 days prior to the baseline (Day1) visit.
6. Disease-modifying antirheumatic drugs (DMARDs) other than MTX, was to have been discontinued 28 days before screening.
7. Post-pubertal females were to have a negative urine pregnancy test at screening and Week 0 (pre-dose).
8. All sexually active male and female study participants were to have been practicing adequate contraception until 150 days after last administration.
9. Parent or legal guardian (when the subject was married, he/she could sign by him/herself.) was to have voluntarily signed and dated an informed consent form, approved by an Institutional Review Board (IRB). Subjects were to comply with the study protocol.

<Exclusion Criteria>

1. Subjects who had a history or combination of inflammatory joint disease difference from JRA like psoriatic arthritis, arthritis related to enthesopathy, and systematic lupus erythematosus, etc.
2. Functional class IV by ACR criteria.



3. Demonstration of significant cardiac disease in 12-ECG or Echo Cardiography.
4. Demonstration of clinically significant deviations in any of the following laboratory parameters:
 - Total white cell count < 4000 cells/mm³
 - Hematocrit < 24%
 - Platelet count < 100,000/mm³
 - Neutrophils < 1,000 cells/mm³
 - Total Serum Bililubin > 2.0 mg/dL
 - AST > 80 U/L
 - ALT > 90 U/L
 - Glomerular filtration rate (GFR) of < 90 mL/min/1.73 m² BSA
[GFR (mL/min/1.73 m² BSA) = 0.55 x height (cm)/plasma creatinine (mg/dL)]
5. Subjects with the difficulty to secure the vein for collecting blood.
6. Subjects who had positive serology for anti-HIV antibody, hepatitis B surface antigen or hepatitis C antibody.
7. Subjects who had prior exposure to alkylating agents such as cyclophosphamide.
8. Subjects who had previous treatment with anti-TNF (Infliximab and etanercept), IL-1, IL-6 or other investigative biological agent.
9. Subjects who had been administered a live vaccine within 12 weeks prior to study drug administration or had the plan to be administered a live vaccine within study period.
10. Subjects who had joint surgery within 8 weeks prior to the screening evaluation or plan to join surgery within 16 weeks from first dose.
11. Subjects who had any ongoing chronic or active infection or any major episode of infection requiring hospitalization or treatment with iv antibiotics within 28 days or oral antibiotics within 14 days prior to the screening evaluation.
12. Subjects who had intra-articular, im or iv administration of corticosteroids and hyaluronic acid within 28 days prior to enrollment.
13. Subjects who had treatment with any other investigational agent within 28 days or 5 half-lives of the agent, whichever is longer, prior to the screening evaluation.
14. Subjects who has a history of a CNS neoplasm, active CNS infection, demyelinating disease, degenerative neurological disease or any progressive CNS disease.
15. Subjects who had a disease, for instance severe or poorly controlled diabetes mellitus or hypertension, which could be adversely affected by study participation.
16. Subjects who had a history of listeria infection.
17. Subject to whom tuberculosis was confirmed by chest X-ray or chest CT at screening or admitted to history of the past of tuberculosis, and was diagnosed by other inspections (PPD skin test or QuantiFERON, etc.) as tuberculosis. The patient not finally diagnosed with tuberculosis or latent tuberculosis can enroll.
18. 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.



19. Pregnant or nursing female.
20. Subjects who had a history of/or current psychiatric illness that would interfere with ability to comply with protocol requirements or give informed consent.
21. Subject who had a recent history of alcohol or drug abuse.
22. Subjects who were considered by the investigator or sub-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 20 mg/ 0.4 mL or 40 mg/0.8 mL

Dose/Strength/Concentration: Adalimumab 20 mg or 40 mg

Mode of Administration: Subcutaneous

Study Drug	Lot No. / Product No.	Production No.	Adalimumab concentration	Manufacturing Date	Expiry Date
Adalimumab (D2E7) 20 mg	08-015214/17102572	RV3B	50 mg/mL	Dec. 2007	Jun. 2010
	09-021496/D0800687	RW9A	50 mg/mL	Mar. 2009	Mar. 2011
	10-003496/D0800687	RY1B	50 mg/mL	Mar. 2010	Sep. 2012
Adalimumab (D2E7) 40 mg	07-014216/17102473	RV3A	50 mg/mL	Nov. 2007	May 2010
	08-019941/17102472	RW7A	50 mg/mL	Nov. 2008	May. 2011
	10-001959/D1000030	RY1A	50 mg/mL	Feb. 2010	Aug. 2012

Duration of Treatment:

From Feb 2008 until the approval of adalimumab for JIA indication in Japan. Study drug administration was to be completed on the approval day, and the study was to be completed after 70 days follow-up period.

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

None

Criteria for Evaluation

Efficacy:

Primary variable:

ACR Pedi 30 response rate at Week 16

Secondary variables:

1. ACR Pedi 50, ACR Pedi 70 and ACR Pedi 90 response rates at Week 16, and ACR Pedi 30, ACR Pedi 50, ACR Pedi 70 and ACR Pedi 90 response rates at Week 2, 4, 8, 24 and every 12 weeks after Week 24.
2. Tender Joint Count (TJC)
3. Swollen Joint Count (SJC)
4. Pain on Passive Motion Joint Count (POM)
5. Limitation of Passive Motion Joint Count (LOM)
6. Active Joint Count (AJC)



7. CRP
8. CHAQ
9. Physician's global assessment of disease activity
10. Patient's global assessment of overall well-being
11. DAS28 ESR
12. Anti-CCP antibody
13. MMP-3
14. TNF α
15. BAP
16. CTX
17. NTX

ACR Pedi 30 response rate at Week 16 in study M10-240 was to be compared to that in open-label lead-in phase of study [REDACTED] visually [REDACTED].

Pharmacokinetic:

Serum adalimumab concentration and serum AAA concentration were assessed at the time point according to the protocol [REDACTED].

Safety:

Adverse event, vital signs and laboratory values.

Statistical Methods

The analysis population was described below.

- Full analysis set (FAS) population: All subjects who received at least one dose of study drug
- Per-protocol set (PPS): FAS excluding all subjects with major protocol deviations.
- Safety analysis set: All subjects who received at least one dose of study drug.

Because no major protocol deviation was observed and PPS was same as FAS, PPS population was not used for any analyses.

Demographic and baseline characteristics were to be summarized for the FAS. The descriptive statistics were to be summarized for the continuous data. The categorical data was to be calculated the counts and percentages.

Efficacy:

Clinical efficacy parameters were to be evaluated at Week 2, 4, 8, 16, 24 and every 12 weeks after Week 24. The primary efficacy variable was to be analyzed at Week 16, and ACR Pedi 30 in study M10-240 and study [REDACTED] were to be compared visually [REDACTED].

ACR Pedi 30, 50, 70 and 90 response rates were to be calculated the counts and percentages. The descriptive statistics were to be summarized for ACR Pedi components and DAS 28 components at each visit. In addition, the mean changes and percent changes from baseline for ACR Pedi components were to be summarized with the descriptive statistics.

Missing data of ACR Pedi responses was to be imputed using observed and NRI imputation methods. The primary analysis of ACR Pedi responses was NRI. No adjustment was made for multiple centers



because the number of subjects per a center was limited.

Pharmacokinetic:

Adalimumab concentrations were to be summarized at each time point using descriptive statistics. Individual subject concentration vs time plots and mean concentration vs time plots were to be provided. Population pharmacokinetics analysis was to be performed to estimate adalimumab apparent clearance (CL/F) and apparent volume of distribution (V/F) in subjects with JRA. Serum AAA concentrations were to be summarized at each collection time using descriptive statistics [REDACTED]

Safety:

Adverse Events

Treatment-emergent adverse events (TEAEs) was defined as any event with an onset or worsening date was on or after the first dose of study drug and no more than 70 days after the last dose of study drug. TEAEs were to be tabulated for any adalimumab exposure. In addition, pre-treatment serious adverse events (SAEs) were to be summarized as well. The number and percentages of subjects experienced TEAEs were to be tabulated by Medical Dictionary for Drug Regulatory Affairs (MedDRA) system organ class and MedDRA preferred term according to Version 11.0 of MedDRA coding dictionary. In addition, TEAEs were also to be summarized by maximum severity and maximum relationship to study drug. Any AEs at least possibly related (probably, or possibly) to the study drug, and any AEs at least probably not related (probably, or possibly related or probably not related) to the study drug were to be summarized. Any SAEs, any severe AEs, deaths, and any AEs leading to discontinuation of study drug were also to be summarized.

Laboratory data and Vital signs

Mean changes from Baseline were to be summarized with the visit mean and change from baseline mean for all laboratory and vital sign parameters at each visit. The baseline value was determined by the last non-missing measurement recorded before the first dose of study drug was received. For selected laboratory parameters, a listing of all subjects with any laboratory determination during each period meeting CTCAE of Grade 3 or higher was to be provided. The laboratory data was to be categorized based on the normal ranges of the laboratory used in this study, and the shift table was to be tabulated.

Summary/Conclusions

Efficacy Results:

This interim study report assessed the efficacy of adalimumab at SC doses of 20 mg or 40 mg eow in subjects with polyarticular JRA for 60 weeks. The results of efficacy analysis are described below.

- The primary efficacy variable; ACR Pedi 30 response rate at Week 16 was 90.0% (18/20) in the MTX stratum, 100% (5/5) in the non-MTX stratum, and 92.0% (23/25) in total. It demonstrated that adalimumab was effective in Japanese subjects with JRA [REDACTED]
- In the MTX stratum, the improvements in ACR Pedi 30, ACR Pedi 50, and ACR Pedi 70 response rates; TJC 75; SJC 66; POM 75; LOM 69; AJC 73; CRP; CHAQ; PhGA of Disease Activity; PGA of Disease Activity; and DAS 28 seen at Week 24 were maintained for up to 120 weeks. In addition, further improvement in ACR Pedi 90 response rate was observed after Week 24 and maintained through Week 120. In the non-MTX stratum, the improvements in ACR Pedi 30, ACR Pedi 50, ACR Pedi 70, and ACR Pedi 90 response rates; LOM 69; CHAQ; PhGA of Disease Activity; PGA of Disease Activity; and DAS 28 seen at Week 24 were maintained for up to 96 weeks. In addition, further improvements in TJC 75, SJC 66, POM 75, AJC 73 and CRP were observed after Week 24. This was because great improvements in these variables were seen in one subject in the non-MTX stratum. The improvements were maintained



for up to 96 weeks in the remaining 4 subjects. The results demonstrated that adalimumab was effective in reducing the disease activity in subjects with JRA, and these improvements were subsequently maintained for at least 120 weeks in the MTX stratum and for 96 weeks in the non-MTX stratum.

- In other secondary variables, an improving trend was observed in MMP-3 through Week 120 and in BAP through Week 108 in the MTX stratum. In the non-MTX stratum, an improving trend was observed in MMP-3 and BAP through Week 96.

These results demonstrated that adalimumab 20 mg (subjects weighing < 30 kg) or 40 mg (subjects weighing \geq 30 kg) eow was effective in reducing the disease activity in subjects with JRA, and these improvements were subsequently maintained for at least 120 weeks in the MTX stratum and for 96 weeks in the non-MTX stratum.

Safety Results:

- The overall incidences of AEs in the safety analysis set were 100% in the MTX stratum, the non-MTX stratum, and total. The number of AEs per 100 patient years (PYs) was 590.0 events/100PYs in the MTX stratum, 936.2 events/100PYs in the non-MTX stratum, and 655.9 events/100PYs in total. The treatment-emergent AEs (by MedDRA PT) reported in \geq 24.0% of subjects (6 subjects) in total were upper respiratory tract infection (56.0%, 14/25 subjects), nasopharyngitis (56.0%, 14/25 subjects), pharyngitis (36.0%, 9/25 subjects), influenza (32.0%, 8/25 subjects), pyrexia (28.0%, 7/25 subjects), urticaria and gastroenteritis (24.0%, 6/25 subjects, respectively).
- Almost half (158/324 events) of the AEs reported in the safety analysis set were considered not related or probably not related to the study drug. The majority of AEs (311/324 events) were mild in severity.
- There was no significant difference in overall incidence of AEs between subgroups by sex, age, body weight, CRP at baseline and the duration of JRA.
- No deaths were reported.
- Six subjects (24.0%) reported 11 SAEs (all subjects were in the MTX stratum). The SAEs were pyrexia (2 events), hepatitis B, herpes zoster, pharyngitis, pneumonia, dehydration, arthralgia, juvenile arthritis, amnesia and pharyngolaryngeal pain (1 event, respectively), and herpes zoster and amnesia (Subject [REDACTED] respectively) were reported after Week 60. Four subjects reported 4 serious infectious AEs. Seven SAEs were moderate and 4 SAEs were mild in severity. Seven SAEs were assessed as at least possibly related to the study drug, and 6 of them were moderate in severity. All SAEs were resolved as of the final visit with the exception of 2 events (Subject [REDACTED] hepatitis B, Subject [REDACTED] amnesia).
- One subject (4.0%) reported 1 AE leading to discontinuation of study drug through Week 60. Subject [REDACTED] reported hepatitis B. This event was considered mild in severity and possibly related to the study drug, and reported as a SAE. The subject discontinued the study due to the lack of efficacy and this SAE (hepatitis B). Hepatitis B was ongoing as of the 70 day follow-up, however, it was confirmed the subject was resolved in further contact after 70 day follow-up. No AEs leading to discontinuation of the study drug were reported after Week 60.
- Twenty-four subjects (96.0%) reported infectious AEs (19 subjects [95.0%] in the MTX stratum, and 5 subjects [100%] in the non-MTX stratum). The infectious AEs (by MedDRA PT) reported in \geq 10% of subjects in total were nasopharyngitis (56.0%, 14 subjects), upper respiratory tract infection (56.0%, 14 subjects), pharyngitis (36.0%, 9 subjects), influenza (32.0%, 8 subjects), gastroenteritis (24.0%, 6 subjects), hordeolum (20.0%, 5 subjects), impetigo (12.0%, 3 subjects) and oral herpes (12.0%, 3 subjects). Four subjects (16.0%) reported 4 serious infectious AEs ([REDACTED] pneumonia, [REDACTED] hepatitis B, [REDACTED] pharyngitis [REDACTED]; herpes zoster). Six events (Subject [REDACTED]: pneumonia, [REDACTED]



pharyngitis, [REDACTED] bronchitis/influenza, [REDACTED]; oral herpes, [REDACTED]; herpes zoster) were moderate and the remaining 130 events were mild in severity, so most of them were mild. Eighty-three events were considered to be at least “possibly related” to the study drug. Four of them (Subject [REDACTED]: pneumonia, [REDACTED]: pharyngitis, [REDACTED]: oral herpes, [REDACTED]: herpes zoster) were assessed moderate; however, no severe infectious AEs were reported. Two events (hepatitis B, oral herpes) were unresolved as of the final visit. Hepatitis B (Subject [REDACTED]) was ongoing as of the 70 day follow-up after the final administration of the study drug; however, it was confirmed resolved in further contact. Oral herpes (Subject [REDACTED]) was judged by the principal investigator not to require following up.

- Three subjects (12.0%) reported 3 hepatic related AEs through Week 60. The hepatic related AEs reported during 60 weeks by PT were hepatic function abnormal (8.0%, 2 events) and blood alkaline phosphatase increased (4.0%, 1 event). All of them were mild in severity and considered to be at least possibly related to the study drug. These two hepatic function abnormalities were resolved and blood alkaline phosphatase increased was ongoing as of Week 60. There were no serious hepatic related AEs (Hepatitis B is not classified to Hepatic AEs according to the classification for AE Categories of Special). No hepatic related AEs were reported after Week 60.
- Six subjects (24.0%) reported 8 injection site reaction related AEs through Week 60. The injection site reaction AEs by MedDRA PT were injection site erythema (16.0%, 4 events), injection site reaction (8.0%, 2 events), injection site swelling and injection site warmth (4.0%, 1 event, respectively). All injection site reaction related AEs were considered to be related to the study drug, however, the severity was mild and the subjects took no treatments. Seven of them were resolved, and the remaining 1 event (Subject [REDACTED]: injection site reaction) was ongoing sporadically as of Week 60. No injection site reaction related AEs were reported after Week 60.
- No malignant AEs, opportunistic infection related AEs including TB, congestive heart failure related AEs, demyelinating disease related AEs, allergic reaction related AEs, Lupus-like syndrome AEs, hematologic related AEs were reported.
- No AE related to extended exposure to adalimumab was observed.
- No clinically significant changes were observed in laboratory parameters and vital signs.
- There were 20 (80.0%) subjects switched to self-injection. No subjects discontinued the study due to AEs which were considered to be related to self-injection. There were no safety concerns in administering the study drug by self-injection.

The results demonstrated that adalimumab treatment with 20 mg (subjects weighing < 30 kg) or 40 mg (subjects weighing ≥ 30 kg) eow for approximately 2 years (for at least 120 weeks in the MTX stratum and for at least 96 weeks in the non-MTX stratum) was generally safe and tolerated in Japanese patients with JRA.

Conclusions:

In the study M10-240, adalimumab 20 mg or 40 mg eow was effective in reducing the disease activity in Japanese subjects with JRA, and this demonstrated the sustained benefit and effectiveness observed for approximately 2 years (for at least 120 weeks in the MTX stratum and for at least 96 weeks in the non-MTX stratum) of long-term treatment with adalimumab. Additionally, adalimumab treatment was generally safe and well tolerated.