



2.0 Synopsis

Name of sponsor: Abbott Japan Co., Ltd. and Eisai Co., Ltd	Tabular format Applicable part of the dossier Volume no:	(For National Authority Use Only)
Name of finished product: Humira	Page:	
Name of Active Ingredient: adalimumab (JAN)		
Study Title: Long-term continuously repeated dose study of adalimumab (D2E7) in patients with rheumatoid arthritis (Phase I/II study)		
Investigator: [REDACTED] total 10 personnel		
Institutions Performing the Study: [REDACTED] Total 9 facilities		
Publications: (reporting documents of this study): (Private)		
Study Period: May 2003 – January 2009 (Date of initial consent by the subject dosed with the study drug) May/26/2003 (subject identification codes: [REDACTED]) (Date of final observation and examination for the subjects dosed with the study drug) January/9/2009 (subject identification codes: [REDACTED])	Development Stage: Phase I/II	
Objectives: The primary objectives of this study are to evaluate the long-term safety and tolerability of repeated subcutaneous (sc) administration of adalimumab in adult Japanese subjects with rheumatoid arthritis (RA) in an open-label study. The secondary objectives of this study are to determine efficacy in terms of magnitude and duration of maintenance of ACR 20/50/70 response after repeated sc administration of adalimumab.		

redacted information 23Sep2014



Study Method:

This study is the none-blind, long-term repeated administration study of adalimumab to follow for a long term the subjects with RA who completed former continuous repeated administration study of adalimumab (Protocol DE035X/D2E7-J081-003). The eligibility of enrolment of a subject into this study will be determined based on the results of preceding adalimumab study and the assessments of the observation period of the present study.

In the present study, adalimumab will be repeated until the investigational drug is approved in our country in order to investigate safety of the long-term repeated administration of adalimumab in RA patients. After approval for RA indication, this study will be conducted as the post-marketing clinical study. In that case, the post-marketing clinical study will continue until 6 months after launch in maximum. All patients will receive the same 40 mg dose subcutaneously biweekly. The efficacy will be evaluated every 6 weeks after initial administration and every 12 weeks after 24 weeks from the initial administration in accordance with the ACR criteria until the final administration was completed or the treatment was discontinued.

Chest x-ray examination and 12-lead ECG will be performed periodically during the observation period of this study and every 24 weeks from the initial administration.

Number of Cases (at the time of planning and analysis):

At the time of planning: Target number of subjects: 36

Number of cases entered the study: 25 subjects

Population for safety analysis: 25 subjects

Population for efficacy analysis: 25 subjects

Diagnosis and Primary Inclusion Criteria:

Target disease: Rheumatoid arthritis

Inclusion Criteria:

1. An RA patient who completed proceeding continuous repeated administration study of adalimumab (Protocol DE035X/D2E7-J081-003).
2. Body weight less than 100 kg.
3. Subjects who wish to continue study drug administration.
4. A female who is never childbearing (postmenopausal for at least 1 year or surgically sterile) or a female with pregnancy test negative who will ensure to practice contraception during the study period and also for 90 days after completion of the study.
5. Subjects must be able and willing to give written informed consent and to comply with the requirements of this study protocol.

Exclusion Criteria:

1. A subject who experienced the inflammatory joint disease different from RA during the period of preceding adalimumab study, such as mixed connective tissue disease, RF-negative spondyloarthropathy, psoriatic arthritis, Reiter's syndrome, systemic lupus erythematosus, progressive systematic sclerosis (scleroderma), and the arthritis occurred prior to the age of 16 years, but not including Sjögren's syndrome.



Exclusion Criteria (Continued):

2. A subject who experienced any of the following status during the preceding adalimumab study:
 - Severe or uncontrollable diabetes
 - Intra-articular, intramuscular or intravenous treatment with corticosteroids required
 - Joint surgery conducted (on the joint to be assessed in the present study)
3. A subject who was prescribed the inhibited concomitant drug(s) during the preceding adalimumab study.
4. A subject with a history of:
 - Drug or alcohol abuse
 - Intravenous drug abuse
 - Active infection with *Listeria* or tuberculosis
 - Lymphoma or leukaemia
 - Any malignancy with the exception of completely respected basal-cell carcinoma without metastasis
5. A subject who experienced the following laboratory test abnormalities during the observation period of this study:
 - Haemoglobin < 9.5 g/dL for males and 9.0 g/dL for females
 - White blood cell (WBC) < 3000/mm³
 - Platelet < 150,000/mm³
 - AST or ALT > 2 × the upper limit of the reference range
 - Total bilirubin ≥ 3 mg/dL
 - Serum creatinine > 1.5 mg/dL
6. A subject who received a live vaccine within 3 months prior to the observation period of this study or is to be treated with a live vaccine during the period of this study.
7. A subject who experienced chronic or active infection or any major episode of infection requiring hospitalization or treatment with intravenous antibiotics within 30 days of entry into study or chronic use of oral antibiotics within 14 days of entry into study.
8. A subject who showed the evidence of past tuberculosis (calcified node and pleural scar) on chest x-ray examination.
9. A subject with past or present central nervous system (CNS) demyelinating disorders.
10. A subject wheelchair-bound or bedridden (Classification of Functional Status in Rheumatoid Arthritis).
11. Pregnant or lactating women.
12. A subject who was doubted HIV infection.
13. A subject that the investigator considers ineligible for study participation.



Investigational Product, Dosage and Administration, Lot Number:

Investigational Product:

Aqueous injection containing 50 mg/mL of adalimumab. As additives, D-mannitol and polysorbate 80 are contained.

Lot Number:

Study Drug	Lot/Product Number	Production Number	Concentration of a Final Product	Date of Manufacture
Adalimumab (D2E7) 40 mg, vial	██████████	RQ4A	50 mg/mL	██████████
	██████████	RR4A		██████████
Adalimumab (D2E7) 40 mg, syringe	██████████	RT4A	50 mg/mL	██████████
	██████████	RU7B		██████████

Study Period: redacted information 23Sep2014
 From May 2003 to 6 months after launch.

Evaluation Criteria

Safety:

The number of injections with frequency and percentage, AEs, general laboratory tests and vital signs.

Efficacy:

The responder rates of ACR20, ACR50 and ACR70 relative to the baseline (Day 1 of DE035) every 6 weeks for 24 weeks from the initial administration and every 12 weeks thereafter. Individual component of ACR efficacy criteria, morning stiffness and ACR20 AUC were assessed as secondary efficacy endpoints.

Statistical Procedures

Analysis of Safety Endpoint:

The number of injections planned versus those performed was summarized with frequency and percentage. Summary statistics (number of data, mean, standard deviation, the 1st semi-interquartile value, median, the 3rd semi-interquartile value, minimum) was calculated.

A percent of the subjects who had at least 1 event of adverse effect relative to all subjects for safety analysis is calculated as frequency (%) of AEs under the base of subject unit.

Frequency (%) of AEs by organ (translated from the terms of MedDRA), symptom/finding (translated from the terms of MedDRA version 10.1) under event base also calculated.

Summary statistics (number of data, mean, standard deviation, the 25th percentile, median, the 75th percentile, minimum, and maximum value) of laboratory test results and vital signs by timing of assessment were calculated. Summary statistics (number of data, mean, standard deviation, the 1st semi-interquartile value, median, the 3rd semi-interquartile value, minimum) of the gain of change from the baseline by timing of assessment also was calculated. For classified data, a cross table was prepared.



Analysis of Safety Endpoint (Continued):

The analysis through early 2 study (DE035/D2E7-J081-002 and DE035X/D2E7-J081-003) and this study was added for AE. A similar analysis was added about the ratio of the number of people reported around 100 patients by dosing the study drug of one year. Overview of adverse event after the approval (16 April 2008) was also calculated.

Analysis of Efficacy Endpoint:

Efficacy endpoints were analyzed every 6 weeks for 24 weeks from initial administration, and every 12 weeks thereafter. ACR response rates (ACR20, ACR50 and ACR70) and relative ratio (%) of their components were calculated. Summary statistics (number of data, mean, 95% confidence intervals, standard deviation, the 1st semi-interquartile value, median, the 3rd semi-interquartile value, minimum) of each component consisting of ACR and ACR20 AUC were calculated. For each component consisting ACR, mean and 95% confidence intervals of the gain changed from the baseline and changing rate were calculated, respectively.

Summary statistics (number of data, mean, 95% confidence intervals, standard deviation, the 1st semi-interquartile value, median, the 3rd semi-interquartile value, minimum) of duration of morning stiffness and the gain of the duration of morning stiffness changed from the baseline were calculated.

Summary/Conclusions

Demographic:

- At Baseline, the mean duration of RA for all subjects was 7.5 years, the mean of the tender and swollen joint counts were 24.9 and 19.6, respectively; the mean CRP was 4.88 mg/dL. These characteristics were consistent with those of patients with moderate to severe RA.

Safety

- All 25 subjects (100%) reported at least one treatment-emergent AE during the study. Overall, the most commonly reported treatment-emergent AEs were nasopharyngitis (15/25 subjects, 60.0%), diarrhea, pruritus, adverse drug reaction, hepatic function abnormal, cystitis, contusion, back pain, rheumatoid arthritis (aggravated), insomnia, rhinorrhoea, upper respiratory tract inflammation, eczema, rash (4/25 subjects, 16.0%). A total of 92.0% of treatment-emergent AEs was considered as at least probably not related to study drug, and 56.0% of treatment-emergent AEs was considered as at least possibly related to study drug.
- Most of the AEs were mild. Pyelonephritis, sepsis, rheumatoid arthritis (aggravated), and non-Hodgkin's lymphoma which was observed in 1 subject, respectively, was considered as severe.
- There were 21 SAEs in 10 subjects in the study. None of the SAE was judged by the investigator as probably related to study drug. SAEs which were considered to be possibly related to study drug were pyelonephritis, sepsis (2 events in 1 subject, respectively), lymphadenitis, metastases to lymph nodes, non-Hodgkin's lymphoma, rectal cancer, and upper respiratory tract inflammation (1 events in 1 subject, respectively).
- Four subjects were discontinued the study due to AE (██████ rheumatoid arthritis (aggravated), ██████: arthralgia, ██████: rectal cancer, and ██████ non-Hodgkin's lymphoma). All of them were serious.

redacted information 23Sep2014



Safety Continued)

- A total of 17 subjects (68.0%) experienced infectious treatment-emergent AEs. Frequently observed infection was nasopharyngitis (60.0%), cystitis (16.0%) and gastroenteritis (12.0%). Probably drug related infection was bronchitis, nasopharyngitis, subcutaneous abscess, and tinea infection in 1 subject, respectively. One subject experienced pyelonephritis and sepsis both of which were serious and possibly related to the study drug.
- Injection site reactions were observed in 2 subjects. Both of them were considered as mild and probably related to the study drug.
- Three malignant (non-Hodgkin's lymphoma, rectal cancer and metastases to lymph nodes) were observed in 2 subjects. Both of them were considered as possibly related to the study drug.
- There were no reports of deaths, opportunistic infection, or immunologic reactions.
- No clinically relevant physical examination results, vital signs, or laboratory values were observed.
- The content and the occurrence rate of the AEs (including those reported in 3 subjects from whom the results till Week 60 was obtained) were almost similar to preceded study in Western and two studies (DE035/D2E7-J081-002 and DE035X/D2E7-J081-003) in Japan. In this study, the content and the occurrence rate of AE were similar to those observed in preceding dose study of adalimumab in Japan and Western.

Efficacy Results:

ACR 20/50/70 in the efficacy analysis set were following,

	ACR 20	ACR 50	ACR 70
	% (n/N)		
Week 0	0.0 (0/10)	28.0 (7/25)	20.0 (5/25)
Week 36	50.0 (4/8)	50.0 (10/20)	30.0 (6/20)
Week 48	66.6 (2/3)	66.6 (10/15)	33.3 (5/15)
Week 108	100 (3/3)	83.3 (10/12)	50.0 (6/12)
Week 156	100 (3/3)	72.7 (8/11)	36.3 (4/11)
Week 204	100 (3/3)	80.0 (8/10)	40.0 (4/10)
Week 264	100 (1/1)	50.0 (1/2)	50.0 (1/2)
Final Visit	20.0 (2/10)	44.0 (11/25)	32.0 (8/25)

Overall, though the number of subjects are small, it was confirmed that the effect of the improvement of the RA symptom are maintained by 40 mg eow sc dosing of adalimumab.



Conclusions:

In this long term study where all subjects who previously received 20 mg, 40 mg, or 80 mg of adalimumab sc eow in study DE035X were switched to 40 mg eow, remarkable long term improvements and maintenance of efficacy were observed.

In addition, this study demonstrated that a repeated biweekly 40 mg sc dose of adalimumab was generally well tolerated and safe in long term therapy. With longer term exposure, the type and frequency of AEs observed remained similar. No clinically relevant physical examination results, vital signs, or laboratory values were observed during the course of the study.