2.0 Synopsis

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Name of Study Drug: Humira		
Name of Active Ingredient: adalimumab (JAN)		

Title of Study:

A Non-Randomized, Open-Label, Roll-Over Study With Self Injection of Adalimumab in Adult Japanese Subjects With Rheumatoid Arthritis

Investigator:

[redacted] total 38 personnel

Study Sites:

[redacted] Total 38 sites in Japan

Publications: redacted information 19Nov2014

(N/A)

Studied Period (Years): Jan 2006 to Dec 2008 First Subject First Visit: 30 Mar 2006 Last Subject Last Visit: 30 Dec 2008	**Phase of Development:** 2/3

Objectives:

The primary objectives of this study are to evaluate the long-term safety and tolerability of repeated subcutaneous (sc) self-injections (by the subject or a subject's family member) of adalimumab in adult Japanese subjects with RA in an open-label study.The secondary objective of this study is to determine efficacy after repeated sc, self-injection of adalimumab.

Methodology:

This is a multi-center; open-label, continuation study of M03-651 in which subjects will receive repeated sc self-injections of adalimumab. This study will be used to assess the safety profile of self-injected adalimumab in adult Japanese subjects. Subjects will be evaluated for entry into Study M05-775 at or after their Week 36 visit in the M03-651 study. The treatment of the study drug was completed on time when marketing product (Humira) was available in each site. The investigator or sub-investigator ("investigator") explained the contents of the self-injection study to the subjects using the explanatory material, guidebook, guide video, and etc. After the explanation by the investigator the subject was allowed to practice an injection with a placebo syringe and skin model.

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Subjects who wished to participate in the self-injection study, could give written informed consent, and were judged by the investigator to be eligible for the study were allowed to participate in the M05-775 study. At the start of the M05-775 study the subject was considered as completing the M03-651 study. Subjects who completed M03-651 had to complete the evaluations and tests that were specified on the last day of treatment in the M03-651 before proceeding to the M05-775 study. The screening visit of the M05-775 study was designated as week 0.

At Week 0, subjects received a self-injection under the supervision of investigator. The subject continued to perform the self-injections every other week (eow) in the presence of investigator until the investigator felt that the subject could perform the self-inject of adalimumab safely and without the supervision of the investigator. When the investigator and subject agreed that the self-injection could be performed safely without the need of supervision of the investigator the investigator and subject signed a Confirmation Form of Self Injection, and thereafter the self-injections could be performed without the supervision of investigator.

The subject continued to receive the same dose (40 mg or 80 mg eow) that the subject had received in the M03-651 study. Whether the injection was performed in or away from the medical site the investigational product should be injected by the subject; however, there maybe times that it was acceptable for the investigator to perform the inject. In addition, after enrolling in the M05-775 study, if the subject wished to receive adalimumab injections from the investigator instead of self-injection or if the investigator judged that the subjects couldn't safely administer the self-injection the subject was allowed to continue in the M05-775 study by receiving injections from the investigator. The type of injection (self-injection or investigator administered injection) was recorded in the subject's case report form.

After the start of M05-775 an efficacy evaluation with the ACR criteria was performed every 4 weeks up to week 24 and every 12 weeks after week 24. A safety evaluation with laboratory tests was performed every 4 weeks up to week 24 and every 12 weeks after week 24 until the last administration of study drug. Efficacy evaluation was performed every 4 weeks up to week 24 and every 12 weeks after week 24 until the last administration of study drug. Subjects who discontinued the self-injections, but remained in the M05-775 study received the same safety and efficacy evaluations as those subjects administering the self-injection.

Blood samples for measurement of serum adalimumab and anti-adalimumab antibody concentrations were collected at every 24 weeks.

If the investigator judged that sufficient efficacy was not obtained for the subject receiving 40 mg eow dosing the investigator was allowed to escalate the dose up to 80 mg eow with the exception of those subjects that were receiving concomitant DMARDs (M02-575 rescue subjects). The criterion for dose escalation was the same as that of the M03-651 study. The criterion for other concomitant therapies was also the same as that noted in the M03-651 study

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Number of Subjects (Planned and Analyzed):

Planned: 312 subjects (as maximum number),

Consented: 88 subjects

Diagnosis and Main Criteria for Inclusion:

Among the subjects who completed the preceding dose-response study, or the subjects who were shifted to the rescue arm and completed 24 weeks in that study, those who wished to continue administration of study drug, met the inclusion criteria, and did not violate the exclusion criteria, were eligible for this study.

Inclusion criteria

1. Subjects that completed Week 36 of the M03-651 study and wish to participate in a self-injection study and willing to give written informed consent and to comply with the requirements of this study protocol.

2. Females must be postmenopausal for at least 1 year, surgically sterile, or practicing birth control throughout the study and for 150 days after study completion. Female subjects currently using oral contraceptives should also use a barrier method during the study and for 150 days after study completion.

3. Subjects or subjects with family members judged by the investigator, as capable of safely self-injecting the study drug in compliance with the study protocol and willing to complete a subject diary.

Exclusion criteria

1. Subjects who develop serious adverse events (AEs) at the time of confirmation of eligibility for this study.

2. Subjects who develop severe infections requiring hospitalization or intravenous injection of antibiotics within 28 days before confirmation of eligibility for this study, or infections required for oral administration of antibiotics within 14 days before confirmation of eligibility for this study.

3. The investigator considers, for any reason, the subject to be unacceptable to participate in the study.

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

Test Product: Aqueous injection containing 50 mg/mL adalimumab (pre-filled syringe)

Dose/Strength/concentration: 40 mg eow (the dosage could be increased to 80 mg eow in the subjects assessed to be insufficiently responsive to the treatment as defined in the protocol)

Mode of administration: subcutaneous administration

Lot number: [redacted] redacted information 19Nov2014

Duration of Treatment:

Until marketing product (Humira) was available in each site.

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

N/A

Criteria for Evaluation

Efficacy:

- During the study, ACR20, ACR50, and ACR70 response were evaluated every 4 weeks until Week 24 and every 12 weeks thereafter.
- Individual component of ACR efficacy criteria and duration of morning stiffness were evaluated every 4 weeks until Week 24 and every 12 weeks thereafter.

Pharmacokinetic:

- Serum AAA and adalimumab concentrations were performed at Week 0, every 24th week, and termination (or discontinuation) and during the follow-up (for 28 days after the termination or discontinuation).

Safety:

- Vital signs, physical findings (including subjective findings), and general laboratory tests (hematology, blood biochemistry, general urinalysis) were performed every 4 weeks until 24 weeks after start of treatment, thereafter every 12 weeks in this study.
- Chest-X ray examination and ECG were performed on week 24, thereafter every 24 weeks in this study.
- Adverse events were investigated from obtaining consent until 70 days after the last day of treatment.

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Statistical Methods

Efficacy:

Baseline values were obtained at Week 0 (immediately before the administration) in the M02-575 study, but baselines for subjects transferred from the rescue treatment group of M02-575 study were obtained at Week 0 (immediately before the administration) in the M03-651 study. Efficacy analysis was performed in full analysis set (FAS, subject who was treated with study drug) and the Self-Injection Set 1 (subject who did the self-injection at least once). Descriptive statistics were calculated focused on analysis for efficacy. Since the number of subjects per site was small, site adjusted analysis was not planned. Efficacy endpoints were analyzed every 4 weeks until Week 24, and every 12 weeks thereafter.

1. 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 first semi-interquartile value, median, the third semi-interquartile value, minimum, and maximum) for each parameter of ACR was calculated.

2. For each parameter of ACR, mean of the changes and the changing rates from baseline.

3. Summary statistics (number of data, mean, 95% confidence intervals, standard deviation, the first semi-interquartile value, median, the third semi-interquartile value, minimum, and maximum) of duration of morning stiffness and changes from baseline.

Pharmacokinetic:

1. A listing of serum adalimumab concentration was to be provided.

2. The percentage of subjects who are AAA positive was reported by treatment groups. Samples were considered to be AAA positive on treatment if the following criteria were met: the measured AAA concentration was >20 ng/mL; [redacted]

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Safety:

In safety analysis, values obtained at Week 0 (immediately before 1st adalimumab administration) were used as baseline values. Baselines for subjects administered adalimumab in the M02-575 study were measurements obtained immediately before administration of adalimumab in the M02-575 study. For subjects administered placebo in the M02-575 study baselines were obtained at Week 0 (immediately before the administration) in the M03-651 study.

As Safety Analysis Set, in addition to the Safety Analysis Set including all subjects administered at least one dose of the study drug, a group of subjects performing self injection once or more (Self-Injection Set 1) and a group of subjects performing self injection outside the hospital once or more (Self-Injection Set 2) were set.

1. Exposure to Study Drug: The number of injections planned and those performed were summarized with frequency and percentage. Summary statistics were calculated for the duration of study drug treatment.

2. Adverse Events Percentage of the subjects who had at least one adverse event of in the safety analysis set of subjects was calculated as frequency (%) of AEs. Frequency (%) of AEs by organ classified by MedDRA (version 10.1) System Organ Class (SOC), and by symptom/finding classified by MedDRA Preferred Term (PT) were also calculated. Summarization by intensity and relationship to study drug was performed. For serious AEs, and severe/life-threatening AEs, the details were described. A listing of all adverse events was prepared. For adverse events, the number rate of emergent adverse events found in every 100 patients during a year of study drug administration was to be calculated For adverse events, both data from a group of subjects that performed at least one self injection (Self-Injection Set 1) in this study and that obtained at conclusion in the M03-651 study performed in the same subjects (before the transfer to this study) were shown to be compared to consider the difference between the injection by medical staff and self-injection.

(3) For laboratory test and vital signs, a listing of subjects with abnormal results (under or above the standards) was prepared. Summary statistics were calculated by visit. Summary statistics of the change from the initial state (before the first administration) were also calculated. With regard to clinical examination values, analysis on CTC grade was calculated. Analysis of laboratory test results and vital signs was calcutated in Safety Analysis Set.

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Summary/Conclusions

Efficacy Results:

- Observed ACR20 response rate in Self-Injection Set 1 was 77.4% (65/84 subjects) at Week 0 (just before the first self-injection), 74.7% (62/83 subjects) at Week 4, 71.9% (46/64 subjects) at Week 24, 78.1% (57/73 subjects) at Week 48, 82.3% (51/62 subjects) at Week 108, and 71.4% (60/84 subjects) at the final visit. Observed ACR50 response rate in Self-Injection Set 1 was 56.0% (47/84 subjects) at Week 0 (just before the first self-injection), 50.6% (42/83 subjects) at Week 4, 53.1% (34/64 subjects) at Week 24, 58.9% (43/73 subjects) at Week 48, 71.0% (44/62 subjects) at Week 108, and 57.1% (48/84 subjects) at the final visit. Observed ACR70 response rate in Self-Injection Set 1 was 32.1% (27/84 subjects) at Week 0 (just before the first self-injection), 34.9% (29/83 subjects) at Week 4, 31.3% (20/64 subjects) at Week 24, 34.2% (25/73 subjects) at Week 48, 46.8% (29/62 subjects) at Week 108, and 41.7% (35/84 subjects) at the final visit. ACR20/50/70 was maintained for a longtime. Similar results were shown in FAS.
- In all ACR evaluation items in Self-Injection Set 1, significant improvement in changes from the baseline which was found at Week 0 (just before the first self-injection) was sustained during the study.

As described above, virtually constant efficacy was sustained from the initial self injection to the final evaluation even under self injection by subject his/herself or his/her family.

Pharmacokinetic Results:

[redacted] Serum adalimumab concentration in the subjects who were AAA positive were lower than subjects who were AAA negative.

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Safety Results:

Safety results for Self-Injection Set 1 are follows;

- Adverse events were reported with an incidence of 98.8% (85/86 subjects).
- Adverse events reported with an incidence of >=10% included nasopharyngitis (61.6%, 53 subjects), adverse drug reactions (29.1%, 25 subjects), antinuclear antibody positive (16.3%, 14 subjects), constipation, bronchitis (14.0%, 12 subjects), contusion (12.8%, 11 subjects), dental caries (11.6%, 10 subjects), rheumatoid arthritis, cough, upper respiratory tract infection, upper respiratory tract inflammation, pruritus, and rash (10.5%, 9 subjects).
- The proportion of subjects who reported at least probably not drug related AE was 90.7% (78/86 subjects). At least probably not drug related AE with the incidence of >=10% included nasopharyngitis (50.0%, 43 subjects), antinuclear antibody positive (15.1%, 13 subjects), bronchitis (11.6%, 10 subjects), and upper respiratory tract inflammation (10.5%, 9 subjects).
- The proportion of subjects who reported at least possibly drug related AE was 69.8% (60/86 subjects). At least probably not drug related AE with the incidence of >=10% included nasopharyngitis (22.1%, 19 subjects) and antinuclear antibody positive (15.1%, 13 subjects).
- Five subjects (5.8%) reported 7 severe AE (joint dislocation, joint destruction, malignant ascites, ovarian cancer, acute renal failure, anaemia, and bronchopneumonia). Relationship to the study drug of these severe AEs were "possibly related" for acute renal failure, "probably not related" for joint destruction, malignant ascites, ovarian cancer, and "note related" for anaemia, bronchopneumonia, and joint dislocation.
- Seventy-two subjects (83.7%) reported 222 infections. Common reported infection was nasopharyngitis (61.6%, 53 subjects), bronchitis (14.0%, 12 subjects), upper respiratory tract inflammation (10.5%, 9 subjects), pharyngitis and tiena infection (5.8%, 5 subjects, each). 7 subjects reported 7 serious infections (2 urinary tract infection and cellulitis, 1 bronchopneumonia, enteritis infectious, herpes zoster).
- Ten subjects (11.6%) reported 13 injection site reactions, and 12 subjects (14.0%) reported 19 hepatic events. All of them were mild and managed without any other treatment.
- One subject reported 2 malignant. Subject [redacted] reported malignant ascites and ovarian cancer, which causality were probably not drug related (steroids, immunomodulators, and female in nature were the alternative etiologies). These were severe and serious, and subject was discontinued. These AEs were ongoing on 151 days after the onset.

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- Two subjects reported oral candidiasis.
- One subject died for ileus which was onset 4 months after the final adalimumab treatment. This was not counted as treatment emergent death.
- Twenty-two subjects (25.6%) reported 34 serious AEs. Of these SAEs, 3 subjects were discontinued the study due to the SAE (bronchopneumonia, malignant ascites and ovarian cancer, and cardiac failure. The causality of these SAEs were "probably related" for 1 event (1 subject), possibly related for 6 events (5 subjects), probably not related for 7 events (5 subjects), and "not related for 20 events (15 subjects). 5 SAEs in 4 subjects were ongoing at the timing of study completion.
- There was no tendency which suggested the increase of AEs after the self-injection.
- There was no tendency which suggested the difference of onset by time period.
- No clinically meaningful findings were observed for laboratory test and vital signs.

Conclusions:

In this study, subjects having completed the M03-651 study who wished to receive a further continued treatment were enrolled. The long term safety and efficacy of adalimumab treated by self-injection were evaluated. As results, with the adequate explanation by investigators, efficacy and safety of adalimumab self injection performed by the subjects or his/her family showed no differences to those injected by the investigators for a long time. Log term self-injection did not cause the unknown adverse event, and did not increase the onset of adverse event. In conclusion, treatment of adalimumab by self injection does not affect efficacy and safety, and is a beneficial safe and effective method of treatment for the patients.