1. Study Synopsis

| Name of sponsor: | Abbott Japan Co., Ltd.  
|                 | Eisai Co., Ltd.        |
| Name of finished product: | (Undecidedness) |
| Name of active ingredient: | adalimumab (INN) |

Study title:  
A Multicenter, Randomized, Double-Blind, Parallel Group, Placebo-Controlled, Dose-Ranging Study of Subcutaneously Administered adalimumab (D2E7) in Adult Japanese Subjects with Rheumatoid Arthritis

Investigator: Total 68 personnel  
Institutions performing the study: Total 68 sites  
Publications (reporting documents of this study): (Private)

Study period: 3 February 2004~9 June 2005  
Development stage: Phase II/III

Objectives:  
The primary objective of this study was to evaluate the efficacy, safety and pharmacokinetics of sc doses of 20 mg adalimumab eow, 40 mg adalimumab eow, and 80 mg adalimumab eow and placebo eow in adult Japanese subjects with Rheumatoid Arthritis (RA).  
The secondary objective of this study was to compare the data obtained from this study M02-575/D2E7-J081-011 to those from Study DE011 conducted in Western subjects with RA in Europe, Australia and Canada.

Study method:  
This study was a multicenter, Phase II/III, randomized, double-blind, parallel group, placebo-controlled, dose ranging and safety study in which subjects received repeated sc doses of adalimumab for 24 weeks.  
Subjects were randomly assigned to one of the four treatment groups in a [1:1:1:1] ratio: 20 mg adalimumab eow, 40 mg adalimumab eow, 80 mg adalimumab eow or placebo eow. Subjects who successfully participated and completed the requirements of this study were given the option to enter into an open-label rollover study, M03-651/D2E7-J081-012. Subjects received sc dose of 40 mg adalimumab eow, in an open-label rollover study as a rule. Subjects taking DMARD, etc. were washed out 4 weeks (28 days) prior to randomization.  
In this study, screening period was from consent form signed to immediately prior to dosing, and double blind period was from first dose to visit at Week 24. Study period was from consent form signed to the follow-up visit. Subjects who were entered into an open-label rollover study were tested for the time. Subjects were enrolled into an open-label rollover study after visit at Week 24. Subjects were evaluated eligibility two times at registration of patient and at Week 0 (Pre-dose), and then administrated study drug.  
Measures of disease activity (TJC, SJC) and Laboratory tests were performed at screening, Week 0 (Pre-dose), and Weeks 2, 4, 8, 12, 16, 20, and 24 (or premature discontinuation, if applicable). For subjects who chose not to rollover into next study, clinical and safety assessments were performed 28 days after completion or discontinuation of the study. Serum was collected at screening, Weeks 12 and 24 (or premature discontinuation, if applicable) for testing RF, antinuclear antibodies (ANA) and anti- double stranded DNA (anti-dsDNA). Blood samples for serum adalimumab concentrations were collected at Week 0 (immediately prior to dosing), Weeks 2, 4, 8, 12, 16, 20, and 24 (or premature discontinuation, if applicable), and follow-up visit. Blood samples for anti-adalimumab antibody (AAA) concentrations were collected at Week 0 (immediately prior to dosing), Weeks 4, 8, 12, 16, 20, and 24 (or premature discontinuation, if applicable), and follow-up visit. Subjects who had less than 10% reduction in TJC and SJC compared to Week 0 (Pre-dose) after at least 8 weeks on treatment in their originally assigned group were shifted to open-label rescue treatment. Administration of study drug was stopped and, at the discretion of the treating physician, higher doses of steroids, NSAID, or a conventional DMARD were
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<td>adalimumab (INN)</td>
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prescribed till the end of the 24 weeks study. After the completion of the rescue part, subjects were allowed to enter the open-label rollover study.

Number of subjects (at the time of planning and analysis)
- Planned: 320 subjects
- Acquired consent: 482 subjects
- Received Treatment: 352 subjects
- Completed: 318 subjects

PK, efficacy and safety analyzed: 352 subjects (87 subjects of placebo group, 87 subjects of 20 mg group, 91 subjects of 40 mg group and 87 subjects of 80 mg group)
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|———  
| Abbott Japan Co., Ltd.  
| Eisai Co., Ltd.  
| Name of finished product:  
| — Undecidenedness  
| Name of active ingredient:  
| adalimumab (INN)  
| Target disease:  
| Subjects were adult male and female Japanese who have moderate to severe RA.  
| [Inclusion criteria]  
| (1) Meet ACR criteria for diagnosis of active RA and have at both screening and baseline visits ≥10 swollen joints, ≥12 tender joints. (Distal interphalangeal joints [DIPs] are not to be included in joint count for inclusion.) The baseline visit must occur at least 28 days after the last DMARD therapy for those subjects receiving DMARD at screening.  
| (2) Subjects must have failed prior treatment with one or more DMARD.  
| (3) C-reactive protein (CRP) ≥2 mg/dL.  
| (4) Age 20 years and older.  
| (5) Body weight less than or equal to 100 kg.  
| (6) A negative (serum) pregnancy test for all female subjects of child-bearing potential at screening and a negative (urine) pregnancy test prior to study drug administration.  
| (7) Females must be postmenopausal for at least 1 year or surgically sterile or practicing birth control throughout the study and for 90 days after the last study drug administration.  
| (8) 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 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). (excluding Sjogren’s Syndrome)  
| (2) History of:  
| • clinically significant drug or alcohol abuse in the previous year.  
| • intravenous (iv) drug abuse.  
| • active infection with Listeria or tuberculosis (TB).  
| • lymphoma or leukemia.  
| • any malignancy with the exception of successfully treated non-metastatic basal-cell carcinoma of the skin.  
| (3) Requirement for any excluded medication, with the following stipulations:  
| • If the subject is on a DMARD (including MTX), they must discontinue it for at least 28 days prior to initial study drug administration and return for baseline visit within 42 days.  
| • DMARD (except biological drugs) will be available for the subjects who shifted to rescue treatment after at least 8 weeks on treatment in their original group assignment.  
| (4) Subjects may not have been administered a live vaccine within three months prior to study drug administration or during the study.  
| (5) Treatment with any other investigational agent within 28 days or 5 half-lives of the agent, whichever is longer, prior to the screening evaluation.  
| (6) Treatment with any investigational biologic agent, including anti-CD4 antibody, within 6 months prior to the screening evaluation.  
| (7) Prior treatment with any TNFα antagonist (Infliximab, Etanercept, etc.), including adalimumab.  
| (8) Prior exposure to alkylating agents such as cyclophosphamide.  
| (9) Wheelchair-bound or bedridden. (Class IV based on Classification of Functional Status in Rheumatoid Arthritis).  
| (10) Pregnant or breast-feeding.
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(11) Known positive human immunodeficiency virus (HIV) status.
(12) Positive serology for HIV antibody (HIV Ab), Hepatitis B surface antigen (HBs Ag), or Hepatitis C antibody (HCV Ab).
(13) 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.
(14) Advanced or poorly controlled diabetes.
(15) Preexisting or recent onset of central nervous system (CNS) demyelinating disorders.
(16) Intra-articular, intramuscular or iv administration of corticosteroids or hyaluronic acid within 28 days prior to screening evaluation.
(17) Joint surgery involving joints to be assessed within this study, within 2 months prior to the screening evaluation.
(18) Unstable ischemic heart disease, active inflammatory bowel disease, active peptic ulcer disease, recent stroke (within 3 months of the screening evaluation) or any poorly controlled medical condition.
(19) Demonstration of clinically significant deviations in any of the following laboratory parameters:
   - Hemoglobin <9.0 g/dL for males and <8.5 g/dL for females;
   - Total white blood cell (WBC) count <3000/mm³;
   - Platelet count <150,000/mm³;
   - AST or ALT >2 x the upper limit of the reference range;
   - Total bilirubin>3 mg/dL;
   - Serum creatinine >1.5 mg/dL.
(20) Chest X-ray finding with a history of pneumonia (calcified nodules and/or pleural scarring).
(21) Subjects with positive tuberculin skin test defined as:
   - Subjects who have induration and ≥10 mm diameter of erythema with bullae/necrosis/double redness and are determined as severely (strong) positive.
   - Subjects who have skin reaction with ≥5 mm diameter of induration.
   - Subjects who have skin reaction with ≥5 mm diameter of induration [not severely (strong) positive] may be enrolled if INH prophylaxis is initiated at least 3 weeks prior to study drug dosing and continued for a total of 9 months at a dose of 300 mg/day.
(22) The investigator considers the subject, for any reason, to be unacceptable for study participation.
Test Product, Dose/Strength/Concentration and Mode of Administration, Lot Number:
Test Product: Placebo, Aqueous injection containing 25 or 50 mg/mL adalimumab (Vial)
Dose/Strength/concentration: placebo, 20 mg, 40 mg and 80 mg
Mode of administration: subcutaneous administration

Lot number:

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<tr>
<th>Study Drug</th>
<th>Lot No./ Product No.</th>
<th>Production No.</th>
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<td>RQZA</td>
<td>25 mg/mL</td>
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<td></td>
<td>11171HK/17102422</td>
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Duration of Treatment: 24 weeks

Evaluation criteria

(1) Efficacy
   - Primary efficacy variables
     ACR20 response rate at Week 24 compared to Week 0 (immediately prior to dosing).
   - Secondary efficacy variables
     ACR20 response rate, ACR50 response rate, ACR70 response rate, individual components of the ACR response (including TJC and SJC), and morning stiffness at Weeks 0 (Pre-dose), 2, 4, 8, 12, 16, 20, and 24 for all treatment groups.
     RF at Weeks 0 (Pre-dose), 12, and 24
     ACR20 AUC over the 24-week study period.

(2) Safety
   - Primary Safety Variables
     Treatment-emergent adverse events.
   - Secondary Safety Variables
     Laboratory values, vital signs, and physical examinations.
     Comparisons of changes from Week 0 (Pre-dose) during treatment for all treatment groups.
     The occurrence of marked laboratory abnormalities.

(3) PK Variables
   - Individual serum adalimumab concentration and serum AAA concentrations at each time of scheduled sampling.

Statistical procedures

Comparability of Populations

Demographic and baseline characteristics among the four treatment groups (placebo group, 20 mg group, 40 mg group, and 80 mg group) were compared.
Continuous variables were compared using the one-way ANOVA test. Summary statistics for continuous variables included the number of observations, mean, standard deviation, 1st quartile, median, 3rd quartile, minimum, and maximum. Discrete variables were compared using the $\chi^2$-test. Frequencies and relative frequencies (percent) were given.
Demographic data, key efficacy and safety results were presented by sex, age, weight,
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When statistical deviation was seen about demographics and other baseline characteristics among the four treatment groups, sensitivity analysis was performed using the logistic regression analysis that made the item, which deviation was regarded, as covariates.

**Efficacy Analysis**

Unless otherwise specified, all statistical tests were conducted against a two-sided alternative hypothesis, employing a significance level of 0.05. Usually the effect of study centers was analyzed. However, since there were not enough subjects per treatment per center, study center was not adjusted in the statistical analyses.

Similarity between M02-575 and DE011 was assessed by visually.

(1) **Primary Efficacy Analysis**

- The comparisons of the ACR20 response rates of the placebo group against that of the 40 mg and 80 mg cow adalimumab groups, using Pearson’s $\chi^2$-test at week 24. While testing hypothesis for the 2 dose arms (40 and 80 mg cow) at Week 24 endpoint, Hochberg procedure were applied to control for multiplicity. If both $p$-values were smaller than 0.05, then the individual null hypotheses (no treatment difference between adalimumab and the placebo) were rejected. If one $p$-value did not show significance at 0.05, then the other hypothesis was tested against an adjusted at the 0.025 level. If the test was significant at adjusted 0.025, then the null hypothesis was rejected.
- In an effort to assess the impact of subjects who dropout of the trial, data were analyzed as observed as well as last observation carried forward (LOCF) post baseline. The last non-missing visit up to and including the Week 24 assessment for each subject was summarized as the ‘Endpoint’ visit.

(2) **Secondary Efficacy Analysis**

- Analysis for ACR20 between 20 mg adalimumab dose groups and placebo at week 24 were secondary and the results were supportive for the primary analyses. Pearson’s $\chi^2$-test was used to compare the ACR20 response rate between 20 adalimumab dose groups and the placebo.
- For ACR50 and ACR70 at Weeks 12 and 24, number of responder and response rate was presented in each group.
- For ACR20 at Week 12, number of responder and response rate was presented in each group.
- For individual components of the ACR response at Week 0 (Pre-dose), Weeks 12 and 24, summary statistics (the number of observations, mean, confidence Intervals (95%), standard deviation, 1st quartile, median, 3rd quartile, minimum, and maximum) by treatment group were presented. This applies to the original values as well as to changes and percentage changes from Week 0 (Pre-dose) at each time point. ANCOVA that adjust the baseline as covariates was performed, and the placebo group was compared with each adalimumab group.
- For ACR20 AUC, summary statistics (the number of observations, mean, confidence Intervals (95%), standard deviation, 1st quartile, median, 3rd quartile, minimum, and maximum) by treatment group were presented.
- In an effort to assess the impact of subjects who dropout of the trial, data were analyzed as observed as well as last observation carried forward (LOCF) post baseline for five analysis (ACR 20 response rate at Week 24, ACR 50 and ACR 70 at Weeks 12 and 24, ACR 20 at Week 12, Individual components of the ACR response at Week 0 (Pre-dose), Weeks 12 and 24, and ACR20 AUC) mentioned above. The last non-missing visit up
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to and including the Week 24 assessment for each subject was summarized as the 'Endpoint' visit.

**Safety Analyses**

- **Adverse Events:**
  - Frequency (%) of adverse events by organ (translated from system organ class of MedDRA) and symptom/finding (translated from preferred terms of MedDRA) under event base was calculated. AE was also displayed by severity and the investigator’s assessment of relationship to study drug.
  - Treatment emergent adverse events which were serious, severe or life threatening were described in detail. All AEs were presented in the data listing.
- **Laboratory Parameters and Vital Signs:**
  - All laboratory and vital signs values beyond the normal ranges with showing L (Low level) and H (High level) were listed. Summary statistics were calculated by each treatment group at each evaluation time. Moreover, the summary statistics was calculated also about the amount of change from Week 0 (Pre-dose).

**Pharmacokinetic Analyses**

- Summary statistics about the serum trough concentrations of adalimumab were calculated by each treatment group at each time point. In addition, the mean serum trough concentrations of adalimumab observed in Japanese subjects at each time point in Study M02-575/D2E7-J081-011 were compared to those in the Western RA subjects for the respective dose group in Study DE011.

**Summary · Conclusion**

**Result of efficacy analysis**

The Efficacy Conclusions obtained by this study is shown below.

- **ACR20 response rates at Week 24 in the adalimumab treated groups showed dose-dependent improvement, with statistical significance (p<0.05) compared to placebo:**
  - 28.7% (25/87 subjects) in the 20 mg group, 44.0% (40/91 subjects) in the 40 mg group, 50.6% (44/87 subjects) in the 80 mg group, and 13.8% (12/87 subjects) in the placebo group.
- **Similarly, the ACR20, ACR50 and ACR70 response rates at Week 24 for each of the adalimumab treatment groups were statistically significantly superior (p<0.05) compared to the placebo group with the exception of ACR50 response rate in the 20 mg group. The increase of the response rates was time-dependent.**
- **Subjects in all three of adalimumab groups reported statistically significant (by 95% CI) improvements in all individual ACR components at Week 24 compared to baseline with the exception of CRP in the 20mg group.** For the 20 mg group, there was only significant improvement in SJC compared to the placebo group at Week 24. On the other hand, for both 40 mg and 80 mg groups, all individual ACR components showed statistically significant improvement compared to the placebo group (p<0.05) at Week 24, with the exception of subject's assessment of pain for the 80 mg group and disability index of HAQ for the 40 mg and 80 mg group.
- **Results of subgroup analyses showed there was a difference for the ACR response rate in the adalimumab treated groups. However, the difference was not clinically significant.**

In general, administration of 20, 40 and 80 mg of adalimumab every other week demonstrated the statistically significant improvement of the signs and symptoms of RA compared to placebo. Especially doses of 40 mg and 80 mg showed a remarkable improvement. Thus, the results confirmed the efficacy of 40 mg or 80 mg adalimumab administered every other week in Japanese RA subjects.
### Result of safety analysis

The conclusion of the safety obtained by this study is shown below.

- The occurrence rates of adverse events were higher in all three adalimumab groups (92.0% [80/87 subjects] in the 20 mg group, 98.9% [90/91 subjects] in the 40 mg group, and 93.1% [81/87 subjects] in the 80 mg group) compared to placebo (81.6%, 71/87 subjects).
- The most commonly reported treatment-emergent AEs across all treatment groups were nasopharyngitis, injection site erythema, anti-DNA antibody positive, and anti-nuclear antibody positive. Nasopharyngitis occurred at similar rates in each of the adalimumab groups as well as the placebo group.
- Overall, the majority of the reported AEs were mild or moderate in intensity and the number of subjects reporting severe AEs in each of the adalimumab treatment group was similar to that of the placebo group.
- Similar rates of infectious AEs were reported in each of the adalimumab treatment group, as well as the placebo group. The majorities of the reported infectious AEs were mild or moderate in intensity.
- Injection site reaction was reported by a higher percentage of subjects in each of the adalimumab treatment group compared to placebo, while most of them were mild in intensity. Injection site reaction led to the early withdrawal of 3 adalimumab-treated subjects.
- The occurrence rate of SAEs was comparable between the placebo (9.2%, 8/87 subjects) and the 20 mg (11.5%, 10/87 subjects) and 80 mg (9.2%, 8/87 subjects) adalimumab treatment groups, but was slightly higher in the 40 mg group (18.7%, 17/91 subjects). The higher rate of SAEs in the 40 mg group is in part due to 5 subjects reporting RA-related SAEs.
- Three SAEs in 2 subjects resulted in death in the study. One subject in the 40 mg group (Subject No.: 061-30) died from lung infection and interstitial lung disease, and another subject in the 80 mg group (Subject No.: 070-24) died from cerebral haemorrhage. Of these 3 SAEs, only one (lung infection) was judged as possibly related to the study drug.
- Neither malignancies nor opportunistic infections including TB was reported by adalimumab-treated subjects in the study. Two placebo-treated subjects experienced malignancy during the study.
- Although higher number of subjects in the adalimumab group shifted from negative to positive ANA compared to placebo, there was no dose-dependent trend for this shift amongst the adalimumab groups. Far fewer subjects shifted from negative to positive anti-dsDNA, which is a more specific test. In addition, none of the subjects reported clinical manifestations of systemic lupus erythematosus.
- None of the laboratory findings observed in the study were considered clinically relevant. There was no clinically relevant vital sign and physical exam findings observed in the study.

As a conclusion, repeated sc doses of 20 mg, 40 mg, and 80 mg of adalimumab eow for 24 weeks were generally well tolerated in Japanese subjects with moderate to severe RA.

### Result of Pharmacokinetics analysis

- When 20 mg, 40 mg, and 80 mg adalimumab eow was sc dosed in adult Japanese subjects with RA, serum trough concentrations of adalimumab remained relatively constant from Week 8 to Week 24, as previously observed in DE011.
- Steady-state serum concentrations of adalimumab were lower in M02-575 compared to DE011 at 40 mg eow dose, and slightly lower at 20 mg eow dose.
- From the start of the study drug treatment to 30 days after completion or withdrawal, 35/87
Comparison of M02-575 study and DE011 study

The two populations in the studies M02-575 and DE011 are well comparable to each other.
In efficacy evaluation, the ACR20 response rates across the 3 treatment groups being compared in the two studies were quite similar, with similar dose response effects.
In safety evaluation, similar safety profiles of adalimumab in both the Japanese population (M02-575) and the Western population (DE011) were obtained. While there should be additional integrated analyses with safety profiles from other studies, it can be concluded that the safety information collected in M02-575 and DE011 can be bridged.
In pharmacokinetics, though steady-state serum concentration of adalimumab was lower in M02-575 compared to DE011 in the 40 mg eow group, serum trough concentrations of adalimumab in M02-575 remained relatively constant out to 24 weeks, as observed in DE011. Overall, all observations lead to the conclusion that the bridging between M02-575 and DE011 study is established, and it is possible to take in overseas data to Japan.

Conclusion
In efficacy, 20 mg, 40 mg and 80 mg adalimumab administered subcutaneously every other week leads to satisfactory significant improvements compared to placebo in signs and symptoms of rheumatoid arthritis in Japanese subjects. Especially 40 mg and 80 mg showed a high effect of the improvement.
In safety, repeated eow sc doses of 20 mg, 40 mg, and 80 mg of adalimumab in Japanese subjects with RA for 24 weeks were generally well tolerated.
In pharmacokinetics, although steady-state serum concentrations of adalimumab were lower in M02-575 compared to DE011 at 40 mg eow dose, remained relatively constant out to 24 weeks, as previously observed in DE011.
As a conclusion, as well as comparison with DE011, the similar profiles of adalimumab for efficacy, safety, and PK are obtained from both Japanese and Western subjects. All observations lead to the conclusion that 40 mg and 80 mg adalimumab administered subcutaneously every other week provides clinical usefulness for rheumatoid arthritis in Japanese subjects.

Date of preparation of report:

5/June/2007