2.0 Synopsis

Abbott Laboratories	**Individual Study Table Referring to Part of Dossier:**	**(For National Authority Use Only)**
Name of Study Drug: **Adalimumab**	**Volume:**	
Name of Active Ingredient: **Adalimumab**	**Page:**	

Title of Study:

A Multi-center Continuation Study of the Human Anti-TNF Antibody D2E7 Administered as a Subcutaneous Injection in Patients with Rheumatoid Arthritis

Investigator:

Charles Birbara, MD; [redacted]

Study Sites:

85 sites in the US and Canada.

Publications:

None

Studied Period (Years): First Subject First Visit: 12 Jul 2000 Last Subject Last Visit: 09 May 2006	**Phase of Development:** 3

Objectives:

To evaluate the long-term safety, tolerability, and clinical efficacy following repeated administration of adalimumab in subjects with rheumatoid arthritis (RA). Safety was evaluated by monitoring adverse events (AEs) and changes in clinical laboratory parameters and vital signs. Long-term efficacy of adalimumab was assessed by evaluating its effects on: (1) the signs and symptoms of RA; (2) physical function; (3) rates of clinical remission; and (4) patient-reported outcome (PRO) measures.

Methodology:

Study DE020 was designed to evaluate long-term efficacy and safety following administration of 40 mg adalimumab for 5 years in subjects with RA. Subjects with RA who completed a Phase 1, 2, or 3 adalimumab study in the US or Canada (i.e., feeder Studies [redacted] and had a favorable safety, tolerability, and efficacy profile when treated with adalimumab were enrolled.

All eligible subjects underwent a Screening visit and a Study Entry Visit. Subjects then received their first open-label dose of 40 mg adalimumab. Subsequent doses of study drug were administered either every other week (eow) or monthly. Subjects who received monthly dosing in a feeder study began the continuation study on a monthly dosing schedule. All other subjects began the continuation study at eow dosing intervals. Subjects who were receiving adalimumab eow and maintained an ACR50 response for two consecutive visits could have their dosing interval lengthened to a monthly dosing schedule.

Number of Subjects (Planned and Analyzed):

Planned: 1000

Analyzed: 846

Diagnosis and Main Criteria for Inclusion:

Eligible subjects included males and females over 18 years of age with RA who had participated in a prior adalimumab study and who had a favorable safety, tolerability, and efficacy profile when treated with adalimumab.

Subjects were not to have any abnormal laboratory value that, in the opinion of the Investigator, indicated that the subject might have been at risk by further participation in the study. Female subjects were not to be pregnant or breast-feeding. Subjects who had known human immunodeficiency virus or a history of tuberculosis (TB) or listeriosis, even if inaction, could not participate in the study. Subjects were not to have any ongoing chronic or active infection or any major episode of infection requiring hospitalization or treatment with intravenous antibiotics within 30 days of entry into the study or chronic use of oral antibiotics. Subjects were not to have any underlying cardiac, pulmonary, metabolic, renal or gastrointestinal conditions, chronic or latent infectious diseases, immune deficiency, or history of malignancy that, in the opinion of the Investigator, placed the subject at an unacceptable risk for participation in this study.

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

Open-label adalimumab was administered as a 40 mg subcutaneous (SC) injection (0.8 mL/injection or 1.6 mL/injection) eow. The dosing frequency was to be increased to adalimumab 40 mg weekly in response to an increase in disease activity. All subjects received 40 mg of adalimumab as a total dose per injection. Multiple lot numbers were used. [redacted]

Duration of Treatment:

At least five years.

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

None

Criteria for Evaluation

Efficacy:

Assessments for Signs and Symptoms of RA

ACR20/50/70/100 and European League Against Rheumatism (EULAR) Response, their components, along with C-reactive protein (CRP) and rheumatoid factor (RF) were examined to assess the long-term efficacy of adalimumab in maintaining a reduction in the signs and symptoms of RA.

ACR20/50/70/100: A subject was considered an ACR20/50/70/100 responder if the following three criteria were met:

- ≥ 20% (or ≥ 50, 70, or 100%) improvement in Tender Joint Count, and
- ≥ 20% (or ≥ 50, 70, or 100%) improvement in Swollen Joint Count, and
- ≥ 20% (or ≥ 50, 70, or 100%) improvement in 3 of following 5:
    - Patient's Assessment of Pain

- Patient's Global Assessment of Disease Activity
- Physician's Global Assessment of Disease Activity
- Health Assessment Questionnaire (HAQ-DI)
- Acute phase reactant (CRP)

An improvement at a particular visit of ≥ 20% was defined as a percent change from Baseline -20. The percent change was calculated by 100 x (Value – Baseline)/Baseline. If the percent change in TJC or SJC was not missing and percent change in at least three out of the remaining five ACR components was present, then the ACR20 response was calculated. If 20% improvement criteria were not met as specified above (i.e., an ACR20 score could be calculated, but a 20% response was not achieved), then the ACR20 score was considered as "non-responder." If the percent change in TJC or SJC was missing, then the ACR20 response was considered as "missing." If the percent change in TJC or SJC was not missing and percent change in at least three out of the remaining five ACR components was missing, then the ACR20 response was considered as "missing."

The percent improvement of the different items was assessed at each visit compared to Baseline and rounded to 0.1%. In this study, CRP values were used as "acute−phase reactant" for calculation of ACR20.

EULAR Response: Good EULAR response [yes, no] or at least moderate EULAR response [yes, no] based on the EULAR response criteria using DAS28 based on CRP, as defined below:

	Change in DAS28 From Baseline[a]		
DAS28 at current visit	**≤−1.2**	**−1.2 to 0.6**	**≥ −0.6**
≤ 3.2	Good	Moderate	None
> 3.2 to ≤ 5.1	Moderate	Moderate	None
> 5.1	None	Moderate	None

a. Baseline values were those prior to the first dose of study drug (either adalimumab or placebo) in the respective lead-in study.

TJC: An assessment of 28 joints (68 joints or regions for Studies [redacted]) was done by pressure or joint manipulation on physical examination.

SJC: An assessment of 28 joints (66 joints or regions for Studies [redacted]) was done by physical examination. The joints examined for swelling were the same as those examined for tenderness, except the hip joints were excluded.

Patient Assessment of Pain: An assessment of the subject's level of pain within the last 24 hours before the evaluation was made, using a 100 mm horizontal visual analogue scale (VAS). The left end of the VAS (0 mm) was for no pain and the right end of the VAS (100 mm) was for unbearable pain.

Patient Global Assessment of Disease Activity: The subject's overall assessment of arthritic activity within the last 24 hours (prior to the evaluation) was made, using a 100 mm horizontal VAS. The left end of the VAS (0 mm) indicated absence of symptoms and the right end of the VAS (100 mm) indicated very strong disease activity.

Physician Global Assessment of Disease Activity: An assessment of the subject's current disease activity was made by the physician using a 100 mm horizontal VAS. The left end of the VAS (0 mm) indicated absence of disease activity and the right end of the VAS (100 mm) indicated extreme disease activity.

Duration/Presence of Morning Stiffness: Duration of morning stiffness was measured in minutes; the presence of morning stiffness was a categorical variable (yes/no). Morning stiffness was not assessed in Study [redacted]

CRP: A laboratory measure for evaluation of the acute−phase reactant.

ESR: A laboratory measure for evaluation of the acute−phase reactant.

RF: A laboratory measure (immunoglobulin) for the evaluation of RA.

Assessments for Improvement in Physical Function

HAQ-DI was examined to assess the long-term efficacy of adalimumab in maintaining improvement in physical function.

HAQ-DI: The HAQ-DI is a measure of disability that has a range from 0 to 3 with a higher score indicating a greater extent of functional limitations ([redacted] The subject was to assess his/her physical function during the past week by measuring his/her ability to perform the following: (1) dress/groom; (2) arise; (3) eat; (4) walk; (5) reach; (6) grip; (7) maintain hygiene; and (8) maintain daily activity.

HAQ-DI Response: Subjects were classified as a "responder" if an improvement of 0.22; the minimally clinically important difference was achieved. The analysis was repeated defining "responder" as an improvement of 0.50, 0.75, and 1.00.

Assessments for Clinical Remission

The following variables were examined to assess the long-term efficacy of adalimumab in maintaining rates of clinical remission: clinical remission itself and major clinical response.

Clinical Remission: Clinical remission was assessed using the following criteria based on CRP.

DAS28: Proportion of subjects who met the pre-defined DAS28 criteria of clinical remission (i.e., DAS28 <2.6) based on CRP where DAS28 = 0.56*sqrt (TJC28) + 0.28*sqrt (SJC28) + 0.36*log (CRP*10+1)
+ 0.014*(Patient's Global Assessment of Disease Activity) + 0.96

Clinical remission was also measured based on ESR. The same criteria applied with the exception of the DAS28 which was determined as the proportion of subjects who met the pre-defined DAS28 criteria of clinical remission (i.e., DAS28 <2.6) based on ESR where DAS28 = 0.555*sqrt(TJC28) + 0.284*sqrt(SJC28) + 0.70*ln(ESR [mm/1h]) + 0.0142*(Patient's Global Assessment of Disease Activity).

Major Clinical Response: Subjects who maintained an ACR70 response for at least 6 months following the first injection of adalimumab.

Assessments for Improvement in Patient-reported Quality of Life

The SF-36 was examined to assess the long-term efficacy of adalimumab in maintaining improvement in patient-reported quality of life.

The SF-36 assesses: (1) limitations in physical functioning because of health problems; (2) limitations in usual role because of physical health problems; (3) bodily pain; (4) general health perceptions; (5) vitality; (6) limitations in social functioning because of physical or emotional problems; (7) limitations in usual role because of emotional problems; and (8) general mental health. In addition to these eight components, physical and mental component summaries were also derived using the following steps. First, the eight SF-36 scales were standardized using means and standard deviations from the general US population. Second, they were aggregated using weights (factor score coefficients) from the general US population. Finally, aggregate physical and mental component summary scores were standardized using a linear T-score transformation to have a mean of 50 and a standard deviation of 10 in the general US population.

Safety:

Safety assessments included AE assessment, physical exam results, vital sign measurements, and clinical laboratory results.

Statistical Methods

Analyses of clinical assessment were carried out in the Full Analysis Set as well as for other sets or subgroups. Appropriate stratification for studies and centers were done. The data from former studies e.g., Studies [redacted] were included in the analysis as well. Demographic and Baseline variables were done descriptively.

Efficacy:

The analysis of efficacy was done descriptively. All subjects who received at least one dose of study medication were included irrespective of possible protocol deviations. No confirmatory analysis was done. The analysis focused mainly on the maintenance of efficacy. Both the Baseline visit and the last visit of the original study were included in the analysis. All efficacy variables were described per visit and treatment received (statistical characteristics, frequency and percentage, confidence intervals). In order to assess a possible bias caused by dropouts, different approaches were used, e.g. all observed, LOCF, and completers only. In order to assess possible study or center effects, by-study and by-center tables were done for the most important efficacy parameters.

The analysis of dropouts vs. subjects continuing in Study DE020 per year for ACR20 response was added after database lock to the analyses described in the SAP.

Safety:

All patients who received at least one injection of adalimumab were included in the safety analysis. Adverse events were presented by frequency and percentage. In addition, AEs of special interest, e.g., serious adverse events (SAEs), or AEs leading to premature study discontinuation, were listed and narratives are provided. Vital signs and laboratory data were described by statistical characteristics and frequency of abnormal values. The frequency of abnormal laboratory values was presented based on normal ranges.

Summary/Conclusions

Efficacy Results:

Adalimumab was found to maintain efficacy through 5 years of exposure to adalimumab as supported by results from signs and symptoms endpoints, physical function endpoints, clinical remission endpoints, and PRO endpoints with no clinically meaningful differences between subgroups:

Signs and Symptoms Endpoints

- ACR20/50/70/100 and EULAR response rates were maintained through 5 years of adalimumab exposure.
- Results from the other efficacy endpoints (TJC68 and TJC28, SJC66 and SJC28, Patient Assessment of Pain, Patient Global Assessment of Disease Activity, Physician Global Assessment of Disease Activity, Duration/Presence of Morning Stiffness, and CRP levels) support the conclusion that the reductions in the signs and symptoms of RA were maintained through 5 years of adalimumab exposure.

Physical Function Endpoints

- Mean changes from Baseline in HAQ-DI demonstrate that improvements in physical function was maintained through 5 years of adalimumab exposure.
- Results from HAQ-DI 0.22/0.50/0.75/1.0 response rates provide supportive evidence that the improvements in physical function were maintained through 5 years of adalimumab exposure.

Clinical Remission Endpoints

- The rates of clinical remission were maintained through 5 years of adalimumab exposure.
- Over the 5−year period of adalimumab treatment, 28.5% of subjects achieved a major clinical response.

Patient-Reported Quality of Life Endpoints

Quality of life measures, as measured by the FACIT-Fatigue score and the HUI were maintained through 144 weeks of treatment with adalimumab. Data beyond 144 weeks were not captured.

Pharmacokinetic Results:

Pharmacokinetic results were reported in a separate report [redacted]

Safety Results:

Adalimumab was generally safe and well tolerated following long-term administration as evaluated by the incidence of AEs, severe AEs, and study drug-related AEs.

- A total of 808 subjects (95.5%) reported at least one treatment-emergent AE during the study. No new or clinically meaningful trends in treatment-emergent AE rates were observed following 5 years of exposure to 40 mg adalimumab (all doses) based on age, body weight, weight group, Baseline RF status, and duration of RA at Baseline. A total of 329 subjects (38.9%) reported severe treatment-emergent AEs (i.e., severe or life-threatening/intractable). A total of 511 subjects (60.4%) reported AEs considered by the Investigator to be at least possibly related to study drug (i.e., possibly, probably, or definitely related to study drug)

In general, the majority of the most common treatment-emergent AEs, severe AEs and at least possibly study drug-related AEs are either consistent with the safety profile described in the currently approved prescribing information for adalimumab or are associated with the disease of interest. Therefore, no new safety findings were observed during this long-term continuation study of adalimumab.

Adalimumab was generally safe and well-tolerated following long-term administration as evaluated by the incidence of deaths, SAEs, AEs leading to withdrawals, AEs leading to dose reductions, and AEs leading to study drug dose interruptions.

- Sixteen subjects died (1.9%) following 5 years of exposure to adalimumab. Ten of these subjects died during the open-label treatment period and six subjects died during the post-study period (i.e., >70 days post the last dose of study drug). All 10 treatment-emergent deaths were considered by the Investigator to be unrelated (i.e., unlikely related or unrelated) to study drug.
- A total of 322 subjects (38.1%) reported treatment-emergent SAEs.
- There were 109 subjects (12.9%) who reported treatment-emergent AEs that led to withdrawal from the study. Nine subjects (1.1%) reported treatment-emergent AEs leading to a dose reduction and 381 subjects (45.0%) reported treatment-emergent AEs leading to a study drug dose interruption.

In conclusion, most of the commonly reported treatment-emergent SAEs, AEs leading to withdrawal, AEs leading to a dose reduction, and AEs leading study drug dose interruptions are consistent with the safety profile described in the currently approved prescribing information for adalimumab, are associated with the disease of interest, or are common in a middle-aged population following a long-term assessment of safety.

Adalimumab was generally safe and well tolerated following long −term administration as evaluated by TNF inhibitor-related and other special AEs of interest.

- A total of 657 subjects (77.7%) reported infectious treatment-emergent AEs. There were 82 subjects (9.7%) who had serious infections.
- Forty subjects (4.7%) reported treatment-emergent malignant AEs (excluding non-melanoma skin cancers) and 36 subjects (4.3%) reported non-melanoma skin cancers.
- Seven subjects (0.8%) reported two specific allergic reaction AEs (drug hypersensitivity and general hypersensitivity).
- A total of 113 subjects (13.4%) reported 15 specific injection site reaction AEs.
- Nineteen subjects (2.2%) reported five specific opportunistic infection AEs.
- There were two cases of treatment-emergent TB reported during the study.
- Fourteen subjects (1.7%) reported three specific AEs associated with CHF. One subject died due to an AE associated with CHF (ventricular cardiomyopathy). The Investigator considered the death to be unrelated to study drug.
- Two subjects (0.2%) reported two specific lupus-like syndromes.
- A total of 96 subjects (11.3%) reported a hepatic-related AE.
- Two subjects (0.2%) reported serious blood dyscrasias.
- There were no reports of treatment-emergent demyelinating disorders.

Overall, the number and severity of TNF inhibitor-related and other special AEs of interest are also consistent with the safety profile described in the currently approved prescribing information for adalimumab. No new safety findings were observed during this long-term continuation study of adalimumab.

Adalimumab was generally safe and well tolerated following long −term administration as evaluated by clinical laboratory results and vital signs.

- Mean changes from Baseline suggest that treatment with adalimumab is associated with small mean increases from Baseline in hemoglobin, hematocrit, and RBC and decreases from Baseline in platelet counts. Mean changes from Baseline also suggest that treatment with adalimumab is associated with small mean decreases in WBC and neutrophil counts, and small mean increases from Baseline in lymphocyte counts. The mean changes for these hematology parameters were all small, and were similar to those reported in adalimumab-treated subjects with RA or other primary conditions.
- The low number of subjects with changes of potential clinical significance in hematology parameters demonstrates that clinically important changes are uncommon following treatment with adalimumab.
- Mean changes from Baseline suggest that treatment with adalimumab is associated with increases in liver function tests (ALT, AST, and total bilirubin) and serum triglycerides and decreases in alkaline phosphatase and BUN. The mean changes from Baseline for these parameters were generally small. Changes in values for triglycerides were similar to those reported for adalimumab-treated subjects with RA or other primary conditions.
- Only nine subjects had elevations in ALT that met the potentially clinically significant criteria, five of whom also had AST elevations of potential clinical significance at the same timepoints as their ALT elevations. These elevations were generally transient; AST and/or ALT values returned to normal and/or remained slightly elevated during continued treatment with adalimumab in eight of the nine subjects. Eight of the nine subjects also experienced a hepatic-related AE(s).

Mean changes from Baseline in systolic and diastolic blood pressure and pulse rate were all small and not clinically meaningful.

Conclusions:

Efficacy results from this open-label continuation study demonstrate that long-term administration of adalimumab results in: (1) maintained reduction of the signs and symptoms of RA; (2) maintained improvement in physical function; (3) maintained rates of clinical remission; and (4) maintained improvement in patient−reported quality of life. Safety results from Study DE020 demonstrate that long-term administration of adalimumab is generally safe and well tolerated; no new safety findings were observed during this long-term continuation study of adalimumab. Overall, the findings from this analysis suggest that there is no change to the risk benefit profile of long-term use of adalimumab.