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 Multicenter Study of the Safety and Efficacy of Human Anti-TNF Monoclonal Antibody Adalimumab (D2E7) in Patients with Active Rheumatoid Arthritis

Investigator:

Alfred Cividino, MD

Study Site(s):

Multicenter study with a total of 69 sites in Canada.

Publications:

Cividino A on behalf of the CanACT Investigators. Efficacy and safety of adalimumab (HUMIRA[®]) in Canadian Clinical Practice. A comparison of the Canadian and the European Practice: The CanACT and the ReACT trials. Presented at the Canadian Rheumatology Association meeting, 2005.

Studied Period (Years):	Phase of Development:
First Subject First Visit (Screening): 11 Nov 2003	Phase 3b/4
Last Subject Last Visit: 23 Dec 2004	

Objective(s):

The primary objective of this study was to assess the safety (by collecting adverse events [AEs] and serious adverse events [SAEs]) of adalimumab administered every other week (eow) to subjects with moderately to severely active rheumatoid arthritis (RA) who had failed prior disease-modifying antirheumatic drugs (DMARDs).

The secondary objectives of the study were to assess the clinical efficacy, as well as the impact on quality of life, productivity, and specific direct medical and indirect resource utilization in subjects with moderately to severely RA who had failed prior DMARDs and were treated with adalimumab eow.

Methodology:

This was an open-label, noncomparative access study (part of the Adalimumab Access Program) that was designed to evaluate the safety of adalimumab in subjects with active RA and to establish adalimumab as an effective therapy in subjects suffering from moderately to severely active RA despite standard anti-rheumatic therapies. The time period considered to be optimal for demonstration of effectiveness was 12 weeks. This study also was designed to evaluate the health-related quality of life of the subjects who received adalimumab.

Number of Subjects (Planned and Analyzed):

Planned: 750 subjects.
Enrolled: 879 subjects. Completed: 769 subjects (87.5%).
Analyzed: total of 879 subjects -- 879 subjects who received adalimumab eow, and 42 of these who increased to adalimumab weekly (ew).

Diagnosis and Main Criteria for Inclusion:

Subjects with RA who had completed (*i.e.,* not dropped out of) another study with adalimumab, such as Study DE013, OR fulfilled all of the following inclusion criteria:

Subject was ≥ 18 years of age; if female, subject was either not of childbearing potential (defined as postmenopausal for at least 1 year or surgically sterile [bilateral tubal ligation, bilateral oophorectomy or hysterectomy]), or was of childbearing potential and practicing an accepted method of birth control (negative serum pregnancy test performed at Screening); subject had a confirmed diagnosis of RA defined by ≥ 5 swollen joints and one additional criterion of positive rheumatoid factor (RF), one or more joint erosions on x-ray, or Health Assessment Questionnaire (HAQ) score > 1; subject had met the American College of Rheumatology (ACR) criteria for diagnosis of RA for at least 3 months; subject had an unsatisfactory response or intolerance to prior standard therapy, as required by local provincial guidelines prior to initiating biologic therapy; subject had an evaluation for latent tuberculosis (TB) that was negative or, if there was evidence of prior TB infection, subject was given prophylactic treatment in accordance with Centers for Disease Control and Prevention (CDC) guidelines; subject who was taking prednisone had a dose ≤ 10 mg/day; subject met ACR Functional Class I, II or III (1992 criteria); and subject signed the informed consent and agreed to the guidelines on prior and concomitant therapy.

Subject was excluded if he/she:

had failed ≥ 2 biologics; had prior treatment with cyclophosphamide or chlorambucil; had been previously treated with total lymphoid irradiation or anti-CD4 or CAMPATH 1H monoclonal antibodies, resulting in persistent CD4 lymphopenia; had prior treatment with an intravenous (iv) immunoglobulin or any investigational agent (except for adalimumab) within 30 days or 5 half-lives of the agent; had a persistent or severe infection(s) requiring hospitalization or treatment with iv antibiotics within 30 days, or oral antibiotics within 14 days, prior to enrollment; had a positive serology for Hepatitis B or Hepatitis C indicating active infection; had a history of or current acute inflammatory joint disease of origin other than RA, *e.g.*, mixed connective tissue disease, systemic lupus erythematosus; had a history of cancer within the past 10 years other than a successfully treated, non-metastatic cutaneous squamous cell or basal cell carcinoma and/or localized carcinoma *in situ* of the cervix; or had a history of any of the following: malignant lymphoma or leukemia, neurologic symptoms suggestive of central nervous system demyelinating disease (*e.g.,* multiple sclerosis), uncontrolled diabetes, unstable ischemic heart disease, active inflammatory bowel disease, active peptic ulcer disease, recent stroke (within 3 months), active TB or listeriosis (or other infections suggestive of significant or profound immunosuppression), or positive human immunodeficient virus (HIV) status.

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

Adalimumab 40 mg administered subcutaneously (sc) eow or ew; adalimumab as 40 mg/0.8 mL formulation from four lots: 04203HT, 14317HT, 14318HT, and 08274HT.

Duration of Treatment:

Subjects were exposed to adalimumab for a mean (±SD) of 180.7 (±76.89) days (range: 15 to 405 days). Because the study ended as planned, when marketing authorization was granted in Canada, subjects who were considered to have completed the study received adalimumab for at least 12 weeks, but could have received adalimumab for a longer time period.

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

None.

Criteria for Evaluation

Efficacy: Because this study was designed to establish whether subjects with moderately to severely active RA would show response when adalimumab was added to the pre-existing inadequate standard anti-rheumatic therapy, response was formally evaluated by the change in disease activity score (DAS28) (resulting from 28 tender joint count [TJC] and swollen joint count [SJC], erythrocyte sedimentation rate [ESR], and visual analog scale [VAS] for the Patient Global Assessment of Disease Activity [PGAD]) at each visit compared with Baseline. The change in DAS28 at Week 12 was the primary efficacy variable (changed from Patient General Health section of DAS28 *via* Amendment #3) assessed in this study. The formula for calculation of the DAS28 is as follows:

$$\text{DAS28} = 0.56\sqrt{TJC} + 0.28\sqrt{SJC} + 0.70 \ln(\text{ESR 1}^{\text{st}}\text{ hour}) + 0.014\,(\text{PGAD})$$

where TJC is the tender joint count; SJC is the swollen joint count; ESR is the erythrocyte sedimentation rate; and PGAD is the Patient Global Assessment of Disease Activity.

An array of secondary variables were also assessed, including the rate of change in DAS28 score from Baseline; ACR20, ACR50, and ACR70 responses; EULAR responses of "moderate or better" and "good;" TJC change from Baseline; SJC change from Baseline; C-reactive protein (CRP) change from Screening; ESR change from Baseline; Physician Global Assessment of Disease Activity change from Baseline; PGAD change from Baseline; patient self-assessed disability index of the HAQ change from Baseline; and the HUI2/3 (Health Utility Index Mark 2 and Mark 3) multi-attribute utility score change from Baseline.

Safety: Safety was assessed through AEs, SAEs, physical examinations, clinical laboratory results, and vital signs.

Quality of Life: Changes from Baseline in HUI2/3, measuring quality of life, and HAQ, measuring functional status, were assessed as secondary efficacy variables. Additional health economic assessments included RAQoL (quality of life), Health and Labour Questionnaire (HLQ; productivity), and Direct Medical and Indirect Resource Utilization (DMIRU; medical care).

Statistical Methods

Efficacy: The analyses were performed using the intent-to-treat (ITT) population, which was defined as all enrolled subjects who received at least one dose of study drug (879 subjects). No subject from another adalimumab study was enrolled, so that all subjects were adalimumab-naive. For continuous variables, frequency distributions, measures of central tendency (mean and median), and measures of

dispersion (variance, standard deviation) were calculated. For categorical variables, frequency distributions were reported. For primary sample estimates, 95% confidence intervals were calculated in order to provide an assessment of the precision of the estimate and to allow for inference to the parent population.

Specifically, for each subject, the change from baseline in the DAS28 was calculated for each visit at which data was collected. The hypothesis tested was: no mean change in the DAS28 score from Baseline using the paired Student's t-test. The primary analysis included the change at the 12-week, 24 week, and the final visit. The rate of change in DAS28 at each visit (secondary efficacy variable) was calculated using linear regression analysis.

Safety: The primary objective of the study was to assess the safety of adalimumab 40 mg sc adalimumab eow. In order to address this objective, the incidence of AEs was described in terms of the proportion of subjects experiencing the event and as the number of events per person-time of follow-up. AEs were described by body system, preferred term, severity, and relationship to the study drug. AEs were analyzed at three timepoints: through Week 12 (Days 1-87), Beyond Week 12 (Days 88 and later), and Overall.

Summary/Conclusions

Efficacy Results: The primary efficacy analysis of the mean change in DAS28 showed clinical improvement at Week 12 compared with Baseline (mean ± SD: 6.13 ± 1.177); the mean decrease (mean [95% C.I.]: -1.95 [-2.04, -1.84]) was statistically significant ($p < 0.001$). When analyzed by subgroup, the mean decrease in DAS28 at Week 12 was statistically significant ($p < 0.001$) for all age groups; for all weight groups; for both males and females; for race groups with more than five subjects (*i.e.,* Whites; Asians; Other); for subjects who received adalimumab with concomitant medications (including one or more DMARDs; methotrexate [MTX]; antimalarials; leflunomide); and for subjects who had or had not previously received biologics (*e.g.,* infliximab, etanercept, anakinra). MTX was the most frequently used previous (90.9% of subjects) and concomitant (60.8% of subjects) medication.

The analyses for the secondary efficacy variables showed that:

- At Baseline, mean TJC was 14.9; mean SJC was 13.2; mean ESR was 30.3 mm/1h; mean Physician Global Assessment of Disease Activity was 63.4 mm on VAS; mean PGAD was 65.1 mm on VAS; and mean Patient Assessment of Pain was 66.2 mm on VAS. Mean changes from Baseline at Week 12 for TJC (-8.1), SJC (-6.8) ESR (-10.1 mm/1h), Physician Global Assessment of Disease Activity (-34.3), PGAD (-27.7), Patient Assessment of Pain (-28.2), and the disability index of the HAQ score (-0.51) showed clinical improvement compared with Baseline; all of these mean decreases were statistically significant ($p < 0.001$).

- At Baseline, mean CRP was 21.2 mg/L. The mean change in CRP (-10.36 mg/L) showed clinical improvement at the end of study (final visit) compared with Baseline; the mean decrease was statistically significant ($p < 0.001$).

- At Baseline, the mean disability index of the HAQ score was 1.55. The mean change in the disability index of the HAQ (-0.51) score showed clinical improvement at Week 12 compared with Baseline, and the mean decrease was statistically significant ($p < 0.001$).

- At Baseline, the mean multi-attribute utility scores of the HUI2 and HUI3 scores were 0.597 and 0.382, respectively. The mean changes in the HUI2 (0.156) and HUI3 (0.232) showed clinical improvement at Week 12 compared with Baseline and were statistically significant ($p < 0.001$).

- ACR20 response at Week 12 was achieved by 51.3% of subjects, while ACR50 and ACR70 responses were achieved by 26.8% and 11.1% of subjects, respectively.
- Moderate or better EULAR response at Week 12 was achieved by 66.0% of subjects; good EULAR response at Week 12 was achieved by 28.2% of responders.

Safety Results: Through Week 12, 624 subjects (71.0%) who received adalimumab eow reported an AE. Most AEs were mild or moderate in severity. The most frequently reported ($\geq$ 3% of subjects) treatment-emergent AEs at Week 12 were injection site reaction not otherwise specified (NOS) (79 subjects, 9.0%), headache (71 subjects, 8.1%), and RA (50 subjects, 5.7%). Injection site reaction NOS and headache were the most frequently reported AEs considered by the Investigator to be possibly or probably related to study drug.

Overall, AEs were reported by 80.4% of all subjects. AEs reported overall were similar to those reported through Week 12 in number and frequency. The most frequently reported ($\geq$ 3% of subjects) treatment-emergent AEs overall were injection site reaction NOS (91 subjects, 10.4%), headache (89 subjects, 10.1%), and RA (90 subjects, 10.2%).

Sixty-seven (67) subjects (7.6%) overall experienced SAEs; most of the SAEs were severe. Two subjects (0.22%) died due to two severe SAEs each (pneumonia aggravated and lung cancer metastatic; staphylococcal sepsis and acute myocardial infarction). Three of these four SAEs were considered to be not or probably not related to study drug; staphylococcal sepsis was considered by the Investigator to be possibly related to adalimumab treatment. Of all SAEs, one SAE (pleural effusion) was considered by the Investigator to be probably related to adalimumab treatment; almost 40% were considered to be possibly drug-related.

Sixteen (16) subjects (1.8%) reported infectious SAEs overall (nine subjects through Week 12). Pneumonia, cellulitis, post procedural site wound infection, postoperative infection, and pyelonephritis were the only AEs reported by more than one subject (2 subjects each, 0.2%). Most of the infectious SAEs were considered by the Investigator to be possibly related to study drug.

Four subjects (0.5%) reported malignancies: breast cyst, lung cancer metastatic, basal cell carcinoma, and adenocarcinoma of the cervix. The latter three malignancies were serious; breast cyst was not serious. Adenocarcinoma of the cervix was considered to be possibly related to adalimumab treatment.

No immunologic SAEs were reported during the study, no abnormal laboratory value was considered an SAE, and no clinically relevant changes in mean laboratory parameters occurred. Changes in mean vital signs values were very small and clinically unremarkable. Analysis of the mean change in RF (-40.7 IU/mL for adalimumab eow and -114.6 IU/mL for adalimumab ew) showed clinical improvement compared with Baseline.

A small number of subjects (66 [7.5%]) had AEs leading to discontinuation of adalimumab: about 25% of the AEs were severe, and almost 65% were considered by the Investigator to be at least possibly related to study drug. Eight subjects discontinued adalimumab due to SAEs categorized as infections and infestations.

Health Economics Results: Analyses of the health economic assessments of RAQoL (quality of life), HLQ (productivity), and DMIRU (medical care) were performed by the CHEOS Group under the direction of Principal Investigator Aslam H. Anis, PhD, Professor of Economics and Director, Health Administration Program, in the Department of Health Care and Epidemiology at the University of British Columbia, Vancouver, BC, Canada. The results of these analyses are contained in a separate report.

Conclusions:

In summary, the efficacy data from this study further demonstrate and confirm the previously demonstrated efficacy of adalimumab (40 mg sc) in the treatment of subjects with active RA who have failed prior DMARDs. Safety data from this study further demonstrate and confirm that adalimumab is safe and well tolerated in subjects with active RA. No significant or unexpected safety issues emerged during the study.

Date of Report: 26Sep2006