



2.0 Synopsis

Abbott Laboratories	Individual Study Table Referring to Part of Dossier: Volume: Page:	(For National Authority Use Only)
Name of Study Drug: Adalimumab		
Name of Active Ingredient: Adalimumab		
Title of Study: An Open-Label Study to Assess the Efficacy and Safety of the Fully Human Anti-TNF- α Monoclonal Antibody Adalimumab (D2E7) in Patients with Active Rheumatoid Arthritis who have Failed Previous Treatment with Infliximab (Remicade [®])		
Coordinating Investigator: Prof. Dr. Ferdinand Chr. Breedveld LUMC Leids Universitair Medisch Centrum, Department of Rheumatology, C-04-R, Albinusdreef 2, NL-2333 ZA Leiden, The Netherlands		
Study Sites: Multicenter: two sites in Germany and one site in the Netherlands		
Publications: Van der Bijl AE, Breedveld FC, Antoni C, Kalden JR, Kary S, Burmester GR, <i>et al.</i> Infliximab failures in rheumatoid arthritis can be successfully treated with adalimumab (HUMIRA [®]). <i>Ann Rheum Dis</i> 2004;63(suppl I):264 (poster FRI0055). Van der Bijl AE, Breedveld FC, Antoni C, Kalden JR, Kary S, Burmester GR, <i>et al.</i> Adalimumab (HUMIRA [®]) is effective in treating patients with rheumatoid arthritis who previously failed infliximab treatment. <i>Ann Rheum Dis</i> 2005;64(suppl III):428-429 (poster SAT0062).		
Studied Period (Years): First Subject Visit: 19 Mar 2003 Last Subject Visit: 21 Dec 2004	Phase of Development: 3b	
Objectives: Efficacy: To explore the efficacy of adalimumab in subjects who had been previously treated with infliximab and failed infliximab treatment due to lack of efficacy or intolerance. Safety: To explore the safety of adalimumab in subjects who received prior treatment with infliximab.		
Methodology: This study included a screening period of at least three days depending upon the availability of all results and the local guidelines for assessment of the tuberculin skin test with purified protein derivative (PPD). There was a 16-week study treatment period (adalimumab 40 mg every other week [eow] subcutaneously [sc]) followed by maintenance therapy up to Week 56. During the maintenance therapy visits were performed every eight weeks. Approximately 40 subjects with rheumatoid arthritis (RA) were to be enrolled in at least three study sites. All subjects received adalimumab. Study medication (40 mg) was self-administered by sc injection eow. Switching to weekly dosing was requested for a few patients by the Investigator during the course of treatment. A waiver was granted by the Sponsor. Efficacy and safety measurements were performed throughout the study.		



<p>Number of Subjects (Planned and Analyzed): Planned: 40 Analyzed: 41</p>
<p>Diagnosis and Main Criteria for Inclusion: Eligible subjects included males and females ≥ 18 years of age with American College of Rheumatology (ACR) criteria for diagnosis of RA for at least 6 months, active RA as defined by the Disease Activity Score 28 (DAS28) ≥ 3.2 at study entry, and unsatisfactory response, loss of response or intolerance to prior infliximab treatment. The subject should have received infliximab at least 4 times. Women of childbearing potential had to have a negative pregnancy test (serum human chorionic gonadotropin) prior to start of study treatment and had to use a reliable method of contraception. Male subjects with procreative capacity were to also ensure that effective contraception was used during the study and for 70 days after study completion. Subjects had to be able and willing to self-administer sc injections or have available a suitable person(s) to administer sc injections. Subjects had to be able and willing to give written informed consent and to comply with the requirements of the study protocol.</p>
<p>Test Product, Dose/Strength/Concentration, Mode of Administration and Lot Number: Adalimumab (40 mg adalimumab in 0.8 mL) for sc self-injection every other week. Lot numbers: 94121HT and 05220HT (bulk 90015HK).</p> <p>Duration of Treatment: Primary study period: 16 weeks Maintenance period: up to 56 weeks</p>
<p>Reference Therapy, Dose/Strength/Concentration and Mode of Administration and Lot Number: Not applicable.</p>
<p>Criteria for Evaluation:</p> <p>Efficacy: Efficacy analyses were conducted on the main study period through Week 16 and through Week 56 of the study. Change in DAS28 compared with study entry, tender joint count (TJC), swollen joint count (SJC), European League Against Rheumatism (EULAR) response, ACR20/50/70 response, Physician Global Assessment of Disease Activity, Patient Global Assessment of Disease Activity, Patient Assessment of Pain, Disability Index of the Health Assessment Questionnaire (HAQ-DI), C-Reactive Protein (CRP), and erythrocyte sedimentation rate (ESR) were assessed. Subgroup analyses were conducted on each efficacy parameter according to concomitant disease-modifying antirheumatic drug (DMARD) use (yes or no), reason for stopping prior infliximab treatment (unsatisfactory response, loss of efficacy, intolerance) and human anti-chimeric antibody (HACA) status at Baseline (positive or negative).</p> <p>Pharmacokinetic: Serum concentrations of adalimumab and anti-adalimumab antibody (AAA) were determined at Study Entry Visit I (Baseline, Week 0) and Week 16, Week 40 and Week 56. Serum infliximab and HACA samples were analyzed only at Study Entry Visit I (Baseline, Week 0) and Week 16. Pharmacokinetic results are presented in a separate pharmacokinetic report R&D/05/263.</p> <p>Safety: Safety was determined by the evaluation of treatment-emergent adverse events (AEs) (incidence, relationship to study drug, severity), laboratory data, and vital signs.</p>



Statistical Methods:

Efficacy: The analysis was done descriptively by presenting summary statistics and confidence intervals. Both the observed and the last observation carried forward (LOCF) approach were applied. The values at all visits as well as changes from Baseline were summarized.

Safety: Safety variables were evaluated using descriptive statistics. AEs were tabulated by primary system organ class and preferred term, whereby the Medical Dictionary for Drug Regulatory Activities (MedDRA) dictionary version 7.1 was used. The number and percentage of subjects experiencing AEs was presented. Also summaries by severity and relationship to study drug were done. All AEs that led to premature withdrawal were listed and described in detail.

Summary/Conclusions:

Efficacy Results: A total of 41 subjects were enrolled in the study and comprised the intent-to-treat data set. The mean period of prior infliximab infusions was 17.3 ± 15.1 months with a mean single dose of infliximab of 262.4 ± 87.6 mg. The mean period between the last infliximab infusions and the first adalimumab administrations was 13.0 ± 5.3 weeks. The majority of subjects discontinued treatment with infliximab due to loss of efficacy over time (51.2%).

By Week 16 of treatment, the mean change from Baseline in TJC and SWC was $> -42\%$ and -55% , respectively. For DAS28, the mean change from Baseline at Week 16 was -1.60 (mean percent change $> -25\%$). Evaluation of those subjects who experienced at least a moderate EULAR response indicated that the percent of subjects with at least a moderate response increased at each time point measurement through Week 16, attaining $> 60\%$ response rate through the last observation. Similarly, measurements of good EULAR response indicated an increasing trend, attaining $> 24\%$ at the last observation. Measurements of ACR response indicated that results for ACR20 response held steady through Week 16 at $\sim 45\%$ to 50% . An increasing proportion of responders was noted for ACR50 and ACR70 over time, attaining $\sim 28\%$ and 18% at the last observation, respectively.

Analysis of the mean change from Baseline in Physician's and Patient's Global Assessment of Disease Activity and Patient's Assessment of Pain indicated that scores declined from Baseline levels at all measurement timepoints during treatment with adalimumab. This trend is also reflected in the positive outcome of the HAQ-DI.

Overall, results observed during the 16-week treatment period of the study indicated that subjects who had previously discontinued treatment with infliximab, regardless of the reason for discontinuation of such treatment, appeared to experience clinically meaningful improvements in all efficacy endpoints.

Although the primary efficacy evaluation was conducted through 16 weeks of treatment, subjects were followed through 56 weeks of adalimumab treatment. Results through the end of the study correlated well with improvements observed through Week 16. For the efficacy variables TJC, SJC, DAS28, EULAR response (at least moderate and good), ACR20/50/70 responses, Physician's Global Assessment of Disease Activity, Patient's Global Assessment, Patient's Assessment of Pain, and HAQ-DI, efficacy results were maintained through Week 56.

Safety Results: The mean duration of exposure for all treated subjects was 46.7 ± 18.2 weeks. The mean number of injections for all treated subjects was 25.1 ± 11.1 . Total subject exposure to study drug was equal to 36.7 patient years.



Almost all subjects, 97.6% (40/41), reported one or more treatment-emergent AEs during treatment with adalimumab. The most commonly reported treatment-emergent AEs were RA, nasopharyngitis, and diarrhea (the event term RA was considered exacerbation of the subject's underlying condition). A total of 11/41 subjects reported one or more treatment-emergent AEs that were considered severe in intensity. Except for two occurrences of RA, all of the severe AEs were reported as single occurrences. A total of 82.9% (34/41) of subjects reported a total of 43 events that were considered at least possibly related to study drug administration. The most commonly occurring treatment-emergent AEs that were considered at least possibly related to study drug administration were nasopharyngitis, influenza, antinuclear antibody positive, RA, and pruritus.

A total of 5 subjects (experiencing 6 AEs) were withdrawn from the study due to the occurrence of an AE, with 4 of these 6 events considered to have been either possibly or probably related to study drug administration. A total of 22 subjects experiencing 28 AEs that led to change in study medication, of which 9 events in 9 subjects were considered to have had any relationship to study drug administration. The events led in 21 subjects to temporary discontinuation of study drug, and in 1 subject to an increase in study drug (RA flare).

A total of 16 subjects experienced 25 serious adverse events (SAEs) during the study; all but two of which were considered to have been unrelated or probably unrelated to study drug administration.

Serious infections: one subject developed pulmonary tuberculosis during the study period. The Investigator considered the event probably related to adalimumab. The Sponsor considered the event possibly related to study drug administration on the basis of temporal relationship, although the diagnosis was not confirmed by culture results and despite pre-existence of the symptoms. One case of cellulitis was observed. No opportunistic infections were reported.

Three subjects reported the development of malignancies during the study including one case of B-cell lymphoma, one case of T-cell lymphoma, and one basal cell carcinoma. All three events were considered either unrelated or probably unrelated to study drug administration due to the short exposure to adalimumab.

No other significant AEs of special interest were noted, such as events associated with congestive heart failure, demyelinating diseases, or other autoimmune disorders including lupus-like reactions. One subject with a history of hypertension died during the study as a result of intracerebral bleeding; the death was considered to have been probably unrelated to study drug administration.

No clinically meaningful changes from Baseline or trends of clinical concern were observed with regard to hematology, blood chemistry, or urinalysis result. Similarly, no meaningful changes from Baseline were observed in vital signs or electrocardiogram results.

Conclusions: In general, the study demonstrated clinically meaningful improvements in response to treatment with adalimumab in a patient population that had previously failed infliximab therapy. No new or concerning safety signals were observed in this population, suggesting that previous TNF antagonist treatment (specifically infliximab) would not interfere with adalimumab therapy.

Date of Report: 20Mar2006