



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: A Multi-center, Randomized, Double-blind, Placebo-controlled Study Comparing 80 mg of Adalimumab with Placebo, and Demonstrating the Non-inferiority of Monthly 80 mg Adalimumab Dosing Compared With 40 mg Adalimumab Every Other Week Dosing		
Coordinating Investigators: There were 2 Coordinating Investigators: 1 for the US and 1 for Europe and Australia. Alan Kivitz, MD Altoona Center for Clinical Research, 1125 Old Route, 220 North, Duncansville, PA 16635, USA Prof Hans-Peter Tony Universität Würzburg, Medizinische Klinik und Poliklinik II Schwerpunkt Rheumatologie/ Klinische Immunologie, Klinikstr.8, 97070 Würzburg, Germany		
Study Sites: Seventy-two (72) sites in the United States (US), Canada, Puerto Rico, Germany, the United Kingdom, and Australia		
Publications: Not applicable.		
Studied Period (Years): First Subject First Visit: 31 Dec 2007 Last Subject Last Visit: 14 Apr 2009	Phase of Development: 3b	
Objectives: The objectives of this study were to demonstrate the superiority of adalimumab 80 mg monthly dosing compared with placebo and to demonstrate the non-inferiority of adalimumab 80 mg monthly compared with 40 mg every other week (eow) dosing after 12 weeks of therapy using American College of Rheumatology (ACR) 20 responder rates. Both objectives were important in considering a recommendation for treatment with 80 mg monthly dosing.		



Methodology: The study consisted of a Screening period (maximum of 33 days), followed by a Baseline visit, and 24 weeks of treatment. Treatment consisted of Period 1, a 12-week placebo-controlled period, and Period 2, a 12-week period, in which subjects randomly assigned to the placebo group were switched to adalimumab 40 mg eow.

A total of 432 rheumatoid arthritis (RA) subjects were randomized (4:3:1 ratio), in a blinded manner, at the 72 study sites and received over the course of 24 weeks 80 mg adalimumab monthly, 40 mg adalimumab eow, or placebo (12 weeks) followed by 40 mg adalimumab eow (12 weeks).

At scheduled site visits (Weeks 2, 4, 8, 12, 16, 20, and 24), efficacy and quality of life assessments were completed. The primary and secondary endpoint evaluations occurred at Week 12. Monitoring of adverse events (AEs), physical examinations, 12-lead electrocardiograms (ECGs), vital signs, and laboratory testing were performed throughout the study. Pharmacokinetic (PK) analysis, including an intensive PK sampling on a subset of methotrexate (MTX) and non-MTX subjects, and immunogenicity assessments were also performed.

Number of Subjects (Planned and Analyzed):

Planned: 424

Analyzed: 432

Diagnosis and Main Criteria for Inclusion: Eligible subjects included males and females ≥ 18 years of age with 1987-revised American College of Rheumatology classification criteria for diagnosis of RA for a minimum of 3 months, and subjects had to meet the following criteria: at least 6 swollen joints out of the 66 assessed and at least 6 tender joints out of the 68 assessed. Subjects on disease modifying anti-rheumatic drugs (DMARDs) other than leflunomide or MTX had to discontinue the DMARD for at least 28 days before the Baseline visit (wash-out period). Subjects on leflunomide were to have had a 3 month washout period, although the subject may have been treated with cholestyramine to shorten this period. Subjects may have been MTX-naïve or may have been currently on MTX. Subjects on MTX had to be on a stable dose of MTX between 15 mg and 25 mg, with the route of administration maintained for at least 6 weeks prior to Baseline. Subjects previously treated with MTX had to have had MTX withdrawn at least 28 days prior to Baseline. 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. Subjects had to be in good general health, and were evaluated for latent tuberculosis (TB) infection with a purified protein derivative test and chest x-ray. Subjects with evidence of latent TB were allowed to enter the study provided that they began prophylactic treatment before receiving study drug, provided documentation of TB prophylactic treatment, or had no evidence of active TB.

In Germany, all subjects had to be on MTX to be enrolled; subjects with latent or active TB were not allowed to be enrolled.



Test Product, Dose/Strength/Concentration, Mode of Administration and Lot Number:
For Adalimumab 80 mg and 40 mg: <ul style="list-style-type: none">• Adalimumab 40 mg/0.8 mL (2 × 1 mL pre-filled syringes of adalimumab 40 mg/0.8 mL and 2 × 1 mL pre-filled syringes of placebo for adalimumab dosing); subcutaneous (SC) injection• Lot numbers: US sites (06-006938, 06-007039, and 08-015939); Ex-US sites (06-006938 and 08-015939)
Duration of Treatment: 24 weeks
Reference Therapy, Dose/Strength/Concentration and Mode of Administration and Lot Number: Placebo for Adalimumab 0.8 mL (4 x 1 mL pre-filled syringes of placebo for placebo dosing); SC Lot numbers: US sites (06-009051); Ex-US sites (06-009051)
Criteria for Evaluation <p>Efficacy: The primary efficacy endpoint was a hierarchically-ranked comparison of the ACR20 response rates at Week 12 (in descending order of importance): adalimumab 80 mg monthly versus placebo and adalimumab 80 mg monthly versus adalimumab 40 mg eow. Secondary efficacy endpoints focused on the comparison between the adalimumab 80 mg and placebo groups at Week 12 in the Health Assessment Questionnaire (HAQ), Short Form 36v2™ (SF-36), and Work Productivity and Activity Impairment. Other variables included changes from Baseline in several quality of life questionnaires.</p> <p>Pharmacokinetic: Blood samples for anti-adalimumab antibody assay and adalimumab concentration measurement were collected just before dosing at Baseline and Weeks 2, 12, and 24/ET (maximum of 4 blood samples planned per subject; approximate total of 1696 samples for the entire study). For intensive PK analysis, a total of 56 MTX and 24 non-MTX subjects provided blood samples on Week 20 (Day 0); Week 20, (Day 2); Week 20, (Day 4); Week 21 (Day 7); Week 22 (Day 14); Week 23 (Day 21); and Week 24 (Day 28). PK analyses are presented in R&D/09/996.</p> <p>Safety: Safety assessments performed during the study were as follows: AEs, laboratory tests, vital signs, physical examinations, and ECGs.</p>



Statistical Methods

Efficacy:

The populations included in the efficacy analyses were the intent-to-treat (ITT, all randomized subjects who received at least one dose of study drug), full analysis set (FAS, a subset of ITT subjects excluding Dr. Kellner's site [27010]), and per-protocol (PP, a subset of ITT subjects who did not have any major protocol violations). Abbott identified Investigator noncompliance with the protocol requirements at Dr. Kellner's site and made the decision to exclude the data from Dr. Kellner's site from all efficacy analyses.

All statistical comparisons for the primary and secondary endpoints were performed at Week 12. The first ranked primary efficacy endpoint comparison (superiority of adalimumab 80 mg versus placebo in proportion of ACR20 responders at Week 12), was tested using a two-sided Pearson's Chi-square test with $\alpha = 0.05$. The second ranked primary efficacy endpoint comparison (non-inferiority of adalimumab 80 mg versus adalimumab 40 mg at Week 12) was tested using a one-sided test statistic following the normal approximation with $\alpha = 0.05$. Because of the hierarchical nature of these two hypotheses, the second comparison was to be performed only if the null hypothesis from the first comparison was rejected. To account for the missing data for the primary endpoint (ACR20), a non-responder imputation (NRI) approach was used, i.e., subjects with missing ACR20 responses were imputed as non-responders. The last observation carried forward (LOCF) rule was used to impute missing continuous efficacy data at Week 12. A sensitivity analysis was also performed for the non-inferiority comparison. For the secondary efficacy analyses, a fixed sequence testing approach was used.

Pharmacokinetics:

PK analyses are presented in a separate report (R&D/09/996).

Safety:

Subjects included in the safety analyses were in the FAS and safety (all subjects who received at least one dose of study drug) populations. Treatment-emergent AEs (TEAEs) were summarized and presented using primary Medical Dictionary for Regulatory Activities (MedDRA) system organ classes (SOCs) and preferred terms (PTs) according to Version 12.0, or later, of the MedDRA coding dictionary. TEAEs were also summarized by maximum severity (mild, moderate, or severe) and by maximum relationship to study drug, as assessed by the Investigator. All serious adverse events (SAEs), deaths, and AEs leading to discontinuation of study drug were listed. Special TEAEs were summarized and presented using primary MedDRA SOCs and PTs and TEAEs were summarized by event rate per 100 patient years.

For hematology, clinical chemistry, and urinalysis laboratory parameters, mean changes from Baseline to post-baseline visits (Period 1, Period 2); were summarized shifts in hematology, clinical chemistry, and urinalysis values from Baseline to Final Value, and subjects with individually clinically significant abnormalities according to Common Toxicity Criteria (Version 3.0) were identified. The number and percent of subjects with specified shifts from Baseline to maximum values in liver function tests were summarized. The number of subjects with shifts in anti-nuclear antibody and double-stranded deoxyribonucleic acid were summarized. Mean changes in vital signs from Baseline were summarized (Period 1, Period 2).



Summary/Conclusions

Efficacy Results:

The primary efficacy endpoint, the difference in ACR20 response rates between the adalimumab 80 mg and placebo groups using the FAS of subjects and NRI, was not statistically significant (47.3% versus 33.9%, respectively; $P = 0.074$); thus, superiority of adalimumab 80 mg compared with placebo could not be claimed. Treatment effect was preserved at 81.7%, and non-inferiority of adalimumab 80 mg monthly compared with 40 mg eow could not be tested because the null hypothesis of the first comparison was not rejected. However, using the ITT and PP populations, the superiority of adalimumab 80 mg monthly versus placebo could be demonstrated based on achieving statistical significance ($P = 0.05$ for each population). Non-inferiority of adalimumab 80 mg monthly versus 40 mg eow was not demonstrated ($P = 0.109$ and $P = 0.121$, respectively). Secondary efficacy endpoints were ranked controlling for multiplicity, and analysis stopped after secondary endpoint 1, the change from Baseline in HAQ at Week 12. Based on the Disability Index of the HAQ using the FAS set of subjects, using LOCF imputation, the adalimumab 80-mg monthly group showed a 22.78% improvement in physical function compared with an 8.90% improvement at Week 12 and a between-group mean decrease (0.21) that was statistically significant ($P = 0.005$) in favor of adalimumab 80 mg monthly. Similar results were demonstrated using the FAS set of subjects and values as observed.

Pharmacokinetic Results:

PK results are presented in a separate report (R&D/09/996).

Safety Results:

Adalimumab was generally safe and well tolerated in subjects with RA who received treatment with adalimumab 80 mg monthly or 40 mg eow.

The proportions of subjects who received any adalimumab with AEs, SAEs, and other significant AEs of interest were consistent with previous adalimumab studies. No new safety signal was observed.

Treatment-emergent AEs were predominately mild to moderate in severity; the majority were not considered by the Investigator to be probably or possibly related to study drug. The most frequently reported SAEs considered by the Investigator to be related to study drug were pneumonia and cellulitis. The most frequently reported AEs leading to discontinuation of study drug were pneumonia, worsening RA, and cellulitis.

No TB, lymphoma, demyelinating disease AEs, or lupus-like syndromes AEs were reported by any subject who received adalimumab. AEs of special interest AEs in categories of opportunistic infections excluding TB, malignant AEs, congestive heart failure-related AEs, hepatic-related AEs, allergic-reaction-related AEs, hematologic-related AEs, and blood dyscrasias-related AEs were reported by a small percentage of subjects (< 3.1%). Overall, the AEs of special interest reported during the study for subjects who received any adalimumab were consistent with the known safety profile of adalimumab. No new safety findings were observed in terms of these AEs. Safety information collected in this study is similar to that reported in other adalimumab clinical studies.

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Conclusions:

Using the FAS of subjects to evaluate efficacy, the superiority of adalimumab 80 mg monthly versus placebo was not proven for the primary endpoint of the difference in the proportion of ACR20 responders between the adalimumab 80 mg monthly and placebo groups. Safety results demonstrated that adalimumab was generally safe and well tolerated with a safety profile similar to that reported in other adalimumab clinical studies.