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: HUMIRA Efficacy Response Optimization Study in Subjects with Active Rheumatoid Arthritis (HERO)		
Coordinating Investigator: Dr. Alan Kivitz (Altoona Center For Clinical Research, PC, 1125 Old Route 220 North, Duncansville, PA 16635)		
Study Sites: Multicenter; 207 sites in the US		
Publications: 6 abstracts/posters		
Studied Period (Years): First Subject First Visit: 02 Aug 2004 Last Subject Last Visit: 03 Feb 2006	**Phase of Development:** 4	
Objectives: The primary objective of this study was to evaluate the efficacy of adalimumab 40 mg, given subcutaneously (SC) every other week (eow), compared to placebo in subjects with active rheumatoid arthritis (RA), with particular emphasis on subject-reported outcomes and early response. Secondary objectives included: ● Evaluation of subject reported assessments vs. physician reported assessments of disease activity. ● Evaluation of potential diurnal variation of disease activity in RA subjects using electronic diaries. ● Evaluation of serious adverse events (SAE) and other safety parameters in RA subjects treated with adalimumab 40 mg SC eow in a Phase 4 study.		
Methodology: This was a randomized, double-blind (DB) (first dose), placebo-controlled, multi-center, Phase 4 study of adalimumab in the US, designed to demonstrate the early efficacy, safety, and tolerability of adalimumab in the treatment of subjects with active RA. All subjects received a blinded single dose of study medication (either placebo or adalimumab 40 mg eow), administered at the Baseline visit, followed by 10 weeks of open-label (OL) adalimumab 40 mg SC eow beginning at Week 2. With the exception of biologic disease-modifying antirheumatic drugs (DMARDs), subjects were permitted to continue their current regimen of anti-rheumatic therapies and thus the trial evaluated adalimumab in a more real-life clinical practice setting.		
Number of Subjects (Planned and Analyzed): Planned: 2500, Randomized and received study drug: 1936, Analyzed for efficacy: 1936, Analyzed for safety (DB period and All Adalimumab treatment period): 1936 and 1911, respectively		

Diagnosis and Main Criteria for Inclusion: Subjects were male or female subjects aged 18 years or older and, in the Investigator's opinion must have had the potential to receive benefit from adalimumab therapy due to moderately to severely active RA. Concomitant oral prednisone, if used, must have been ≤ 10 mg qd (equivalent dose for other corticosteroids) and must have been stable for at least 30 days prior to the Screening visit. If the subject was using any traditional DMARDs (hydroxychloroquine, leflunomide, methotrexate (MTX), gold, sulfasalazine, cyclosporine, or azathioprine), doses must have been stable for at least 60 days prior to the Screening visit. Subjects were not to have previously received any biologic DMARDs, including adalimumab, etanercept, and infliximab or have received intra-articular and/or intramuscular injection(s) with corticosteroids within 4 weeks prior to Baseline. Additionally, the subject must not have received any investigational therapy within 6 weeks prior to Baseline. Subjects were excluded if they failed to complete 80% or greater of e-diary based assessments during the Screening period. Subjects must have completed a minimum of two days of the e-diary assessments to assess the 80% compliance requirement.

Test Product, Dose/Strength/Concentration, Mode of Administration and Lot Number: Test product was provided as an SC injection solution in 1 mL pre-filled syringes containing adalimumab 40 mg/0.8 mL (bulk drug product lot number: 90-018HK).

Duration of Treatment: The study continued for 12 weeks. All subjects received a blinded single dose of study medication, administered at the Baseline visit, followed by 10 weeks of OL adalimumab 40 mg SC eow beginning at Week 2.

Reference Therapy, Dose/Strength/Concentration and Mode of Administration and Lot Number: The reference product, placebo, was provided as an SC injection solution in 1 mL pre-filled syringes containing matching placebo for adalimumab (bulk drug product lot number: 90-014HK).

Criteria for Evaluation

Efficacy: The primary efficacy variable was percent change from Baseline to Week 2 visit in Subject's Global Assessment of Disease Activity as captured using the e-diary. The secondary efficacy variables included the following:

- Percent change in Physician's Global Assessment of Disease Activity from Baseline to Weeks 2, 4, and 12.
- Change from Baseline in swollen joint count (SJC), tender joint count (TJC), and limited motion or deformity at Weeks 2, 4, and 12.
- Change from Baseline in C-reactive protein (CRP) to Weeks 2, 4, and 12.
- Percent change from Baseline was calculated for each of the following efficacy variables:
  - Subject's Global Assessment of Disease Activity (to Week 1, 4, and 12).
  - Subject's Global Assessment of Pain (to Weeks 1, 2, 4, and 12).
  - Subject's Global Assessment of Function (to Weeks 1, 2, 4, and 12).
  - Subject's Global Assessment of Fatigue (to Weeks 1, 2, 4, and 12).
  - Subject's Global Assessment of Morning Stiffness (to Weeks 1, 2, 4, and 12).
- Change from Baseline in SF-36 Health Status Survey to Weeks 2, 4, and 12.
- Change from Baseline in the Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F) to Weeks 2, 4, and 12.

- Change from Baseline in the Health Assessment Questionnaire (HAQ) to Weeks 2, 4, and 12.
- ACR20, ACR50, and ACR70 Response Rate to Weeks 2, 4, and 12.
- Time to significant outcome.
- Diurnal variation in diary based assessments.

Safety: Safety was assessed by SAE monitoring, physical examination, vital signs, and laboratory data.

Statistical Methods

Efficacy/Safety:

Two sets of statistical analyses were performed: efficacy and safety of the first dose of adalimumab 40 mg SC compared to placebo was performed using data in the DB period (Baseline – Week 2 visit), and cumulative efficacy and safety of adalimumab were summarized throughout the study.

The primary objective for the statistical analysis was to compare adalimumab 40 mg SC eow to placebo in % change from Baseline of daily Subject's Global Assessment of Disease Activity score to Week 2 visit in the intent-to-treat subject population.

All statistical tests were two-tailed with the significance level 0.05. All p-values were rounded to four decimal places. Descriptive statistics were provided. These included the number of observations, mean, and standard deviation for continuous variables; and counts and percentages for discrete variables.

Last observation carried forward (LOCF) analysis was conducted when appropriate. LOCF analysis of binary variables was supportive. LOCF analysis of continuous variables was primary.

Summary/Conclusions

Efficacy Results:

Subjects who received adalimumab, compared to subjects who received placebo, had statistically significantly greater improvement in health as early as Week 2:

- Subjects treated with adalimumab reported a statistically significantly greater percent decrease in Subject's Global Assessment of Disease Activity, the primary endpoint, at Week 2 than did subjects treated with placebo (-17.22% vs. 0.27%, respectively; $p < 0.001$).

Results of assessment of disease activity as done by both the physician and the subject similarly demonstrated improvement by Week 2:

- Subjects treated with adalimumab had a statistically significantly greater percent decrease in Physician's Global Assessment of Disease Activity at Week 2 than did subjects treated with placebo (-22.76% vs. –3.98%; $p < 0.001$).

Results from subject assessments (e-diary) further demonstrated improvement in health, specifically that:

- Improvement occurs as early as one day after initiating adalimumab therapy: At Day 2, statistically significant improvements were observed in Subject's Global Assessment of Disease Activity, Pain, Function, Fatigue, and Morning Stiffness for subjects who received adalimumab.
- Subjects who continued on adalimumab from the DB period to the OL period showed continuous improvement in all assessments.
- Subjects who began adalimumab treatment in the OL period showed considerable reduction in all assessments through Week 12.

- Overall, adalimumab-treated subjects are more likely to achieve a 20%, 50%, or 70% reduction in disease activity during the first two weeks of treatment compared to placebo-treated subjects.
- Minimal diurnal variation was observed.

Data from physician assessments demonstrated similar results that support that adalimumab treatment results in health improvement. In general, subjects treated with adalimumab showed statistically significant and clinically meaningful improvements at Week 2. These improvements continued during the OL period for subjects randomized to adalimumab while subjects who were originally randomized to placebo showed considerable improvement upon starting adalimumab in the OL period.

- At Week 2, subjects treated with adalimumab reported a statistically significantly greater decrease ($p < 0.001$) compared to subjects treated with placebo in SJC (-2.62 vs. -1.43, respectively), TJC (-3.37 vs. -1.84, respectively), and limited motion or deformity (-0.71 vs. -0.18, respectively).
- Subjects treated with adalimumab reported a statistically significantly greater decrease compared to subjects treated with placebo in CRP (-0.86 vs. 0.03, respectively; $p < 0.001$) at Week 2, indicating a decrease in inflammation.
- At Week 2, subjects who received adalimumab reported statistically significantly greater improvements in the following SF-36 domains compared to subjects who received placebo: Role – Physical (3.24 vs.9.86, respectively, $p < 0.001$); Bodily Pain (7.05 vs. 1.99, respectively, $p < 0.001$); Social Functioning (5.70 vs. 2.51, respectively, $p < 0.001$); and Role – Emotional (6.06 vs. -0.90, respectively, $p < 0.001$). Subjects in both treatment groups had worsening of symptoms in the following domains: Mental Health (-2.85 vs. -1.49, respectively, $p = 0.017$), Physical Functioning (-3.51 vs. -1.72, respectively, $p < 0.001$), and Vitality (-2.19 vs. -6.12, respectively, $p < 0.001$). There were no differences between treatment groups in General Health, Physical Component Summary, and Mental Component Summary at Week 2. At Week 4, differences in improvements in the adalimumab group compared to the placebo group continued for Role – Physical ($p = 0.043$) only. There were no differences between treatment groups in any SF-36 domain at Week 12.
- Subjects treated with adalimumab reported a statistically significantly greater decrease in FACIT-F at Week 2 than did subjects treated with placebo (-4.35 vs. -1.70, respectively; $p < 0.001$).
- At Week 2, subjects treated with adalimumab reported a statistically significantly greater decrease compared to subjects treated with placebo in the HAQ (-0.18 vs. -0.06, respectively; $p < 0.001$) and HAQII (-0.20 vs. -0.06, respectively; $p < 0.001$).
- A statistically significantly greater proportion of subjects in the adalimumab treatment group achieved ACR20/50/70 responses at Week 2 ($p <0.001$) compared to subjects in the placebo treatment group.

Overall, subjects in the adalimumab treatment group who continued to receive adalimumab in the OL period showed continuous improvement in their disease activity and health based on several measures, while placebo-treated subjects who received adalimumab for the first time in the OL period showed considerable improvement as well.

Safety Results:

Adalimumab was generally safe and well tolerated following eow administration for 10 or 12 weeks as evaluated by the assessment of SAEs, laboratory parameters, and vital signs.

- No deaths were reported during this study.
- In general, the incidence of SAEs was low, as no individual, unique SAE was reported by ≥ 3 subjects. SAEs were reported by just six subjects in the DB period (three treated with placebo and three treated with adalimumab) and by 59 subjects (3.1%) irrespective of DB or OL treatment (any adalimumab).
- The majority of events were mild to moderate in severity and were considered at least probably not related or not related to study medication.
- A total of 20 subjects discontinued from the study prematurely due to a treatment-emergent SAE. No trends were observed in the types of treatment-emergent SAEs that led to study discontinuation.
- Less than 1% of subjects reported at least one treatment-emergent serious infection during the study.
- Six subjects reported treatment-emergent serious malignancies, all of which were considered not related or probably not related to study medication.
- No central nervous system demyelinating disease events or treatment-emergent lupus-like reactions were reported during this study.
- One hypersensitivity/injection site reaction was reported during the study; the event was moderate in severity, considered probably related to study drug, and was the cause of this subject's discontinuation from the study.
- No clinically significant changes in laboratory parameters or vital signs were observed.

Conclusions: This study demonstrated that subjects with RA treated with adalimumab 40 mg eow have a rapid response as early as one day after the initial adalimumab injection, as captured by e-diary-based assessments. Both the Physician's Global Assessment of Disease Activity and Subject's Global Assessment of Disease Activity also documented this early response observed by Week 2. Electronic diary assessment results showed minimal diurnal variation in subject assessments. Safety results demonstrated that adalimumab is generally safe and well-tolerated in adults with active RA.