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 Five-Year, Post-Marketing Observational Study to Follow-up Patients with Rheumatoid Arthritis Formerly Treated in Study M02-497 (ReAct) and Subsequently Prescribed HUMIRA®

Coordinating Investigator: Gerd R. Burmester, MD

Study Sites: Patients were enrolled at 414 sites in 11 countries, including 10 European countries (Austria, Belgium, France, Germany, Greece, Italy, Portugal, Spain, the Netherlands, United Kingdom) and Australia.

Publications: 4 abstracts

Studied Period (Years):	**Phase of Development:**
First Subject First Visit: 17 August 2003 Last Subject Last Visit: 15 July 2010	Post-marketing observational study

Objectives: The objectives of this post-marketing observational study were to observe and assess the long-term use, safety, and efficacy of adalimumab, as prescribed by the rheumatologist in a normal clinical setting and in accordance with the terms of the European marketing authorization.

Methodology: The study design was a non-interventional, observational design to assess the frequency and percentage of adverse events (AEs), serious adverse events (SAEs), and AEs of special interest in adult rheumatoid arthritis (RA) patients treated with adalimumab in accordance with the local marketing authorization per routine clinical practice. In addition, patients' disease activity scores (DAS28) and American College of Rheumatology (ACR) and European League against Rheumatism (EULAR) responses were calculated to evaluate the effectiveness of adalimumab treatment. No control group was used, as this was a postmarketing observational study (PMOS) during which patients received adalimumab as prescribed by the rheumatologist in a normal clinical setting. Patients were followed for up to 5 years from study entry.

Number of Subjects (Planned and Analyzed): Up to 4,000 patients were planned to be enrolled; 3,440 patients were enrolled and 3,435 patients were analyzed (5 patients were excluded from the analysis population because they did not receive adalimumab treatment).

Diagnosis and Main Criteria for Inclusion:
Inclusion: Patients with ongoing adalimumab treatment who completed at least Month 3 (Visit 5) of Study M02-497 (ReAct) and who had subsequently been prescribed adalimumab according to the European Summary of Product Characteristics (SmPC). Patients must have been willing to consent to data being collected and provided to Abbott.

Exclusion: Contraindications according to the SmPC.

Test Product, Dose/Strength/Concentration, Mode of Administration and Lot Number: This was a postmarketing observational study. Patients were treated with commercially available adalimumab in normal clinical practice and in accordance with the terms of the local marketing authorization.

Duration of Treatment: Patients were followed for up to 5 years from study entry.

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

None

Criteria for Evaluation

Efficacy: Patients' DAS28, EULAR and ACR responses were evaluated. Data on the following individual parameters were collected if assessed as part of clinical practice at each site:

- 28 joint count of swelling and tenderness
- Physician's global assessment of disease activity (on visual analog scale [VAS])
- Patient's global assessment of disease activity (on VAS)
- Patient's assessment of pain (on VAS); erythrocyte sedimentation rate (ESR) (1^{st} hour), C-reactive protein (CRP)

Patient-Reported Outcomes: All sites used the Health Assessment Questionnaire (HAQ). For French sites, the Arthritis Impact Measurement Scales-2 Short Form (AIMS-2 SF) was also used.

Safety: AEs and SAEs were collected throughout the study. Pregnancy, if it occurred, was reported to Abbott and monitored but not collected in the database.

Statistical Methods

Efficacy:

The efficacy analysis of continuous variables was done descriptively by presenting summary statistics (n, mean, standard deviation, minimum, 1^{st} quartile, median, 3^{rd} quartile, and maximum) and confidence intervals. For categorical data, absolute and relative frequencies were calculated. Summaries include an endpoint visit defined as the last value observed during the study period, as appropriate.

The primary focus was on the analysis of data from Study M03-634 alone. Furthermore, as requested by the European Medicines Agency's (EMA) Committee for Medicinal Products for Human Use (CHMP), an integrated analysis of data from Study M02-497 and Study M03-634 was done for the Study M03-634 study population.

Safety: AEs were analyzed by presenting frequency and percentage as well as number of events and events per 100 patient years. Besides fatal AEs, SAEs, AEs leading to withdrawal, severe AEs, also AEs of special interest for treatment with biologics were reported in detail.

The primary focus was on the analysis of data from Study M03-634 alone. Furthermore, at the request of the EMA/CHMP, an integrated analysis of AEs from Study M02-497 and Study M03-634 was done for the Study M03-634 study population. This analysis was also broken down into time periods (up to 1 year, > 1 year up to 3 years; > 3 years up to 5 years; and > 5 years) calculated from the date of first injection in Study M02-497.

Summary/Conclusions

Efficacy Results:

Of the 3,435 patients who enrolled, 1,805 (52.5%) completed the study. Reasons for discontinuation included loss of efficacy (16.2% of patients), adverse events (12.5%), loss to follow-up (8.5%), withdrawn consent (4.5%), or death (1.0%).

Mean DAS28 scores showed that disease activity remained at a stable (low) level from the final value in Study M02-497. The change from Baseline and the percent change from Baseline (observed values) showed reductions at all time points over the 60 months of treatment in Study M03-634. Results from other efficacy and patient-reported outcomes assessments were consistent with the DAS28 results.

Clinical response to adalimumab treatment was sustained through 5 years of observation in patients with long-standing RA seen in normal clinical practice.

Safety Results:

A total of 67.9% of patients experienced one or more treatment-emergent AEs during the treatment period in Study M03-634, for an overall AE rate of 80.2 events per 100 patient-years (E/100 PY). In 37.4% of patients, the AEs were considered by the Investigator to be at least possibly related to adalimumab. A total of 22.0% of patients experienced one or more treatment-emergent SAEs during the treatment period in Study M03-634, for an overall SAE rate of 10.3 E/100 PY, including 8.7% of patients with SAEs considered at least possibly related to adalimumab.

The most common AEs were viral and bacterial infections, with 3,235 events (26.1 E/100 PY) observed in 1,436 patients (41.8%), which is consistent with the AE profile of other anti-TNF agents. Respiratory tract infections (bronchitis, nasopharyngitis and influenza) and urinary tract infections were the most frequently observed events and were also most frequently considered by the investigator to be at least possibly related to the study drug. The most frequent severe AEs and SAEs were pneumonia and myocardial infarction.

Forty-nine patients (1.4% [31 female, 18 male]) died during this study. The age-adjusted standardized mortality ratio (SMR) was calculated using the 2001 WHOSIS data for each country in which the study was conducted. The observed deaths in female and male patients were, in all countries, clearly below the number of expected deaths (49 observed deaths versus 104.2 expected deaths), with an overall SMR of 0.47 (95% CI = 0.35–0.62).

The incidence rate of serious infections was 2.2 E/100 PY, which was lower than previously observed rates in earlier studies with adalimumab. Eleven patients were diagnosed with active or reactivated TB during this study (0.1 E/100 PY). Three patients (0.1%) died of serious infections (2 sepsis, 1 septic shock; 0.0 E/100 PY). In 4 further patients a fatal event occurred secondary to serious infections.

Safety Results (Continued):

Treatment-emergent malignancies (first primary cancer) occurred at frequencies that remained lower than expected for an age-, sex- and race-matched general population, with an SIR = 0.67 (95% CI = 0.54–0.83). The SIR for melanoma was not elevated (SIR = 0.94, 95% CI = 0.25–2.41), while the SIR for all non-melanoma skin cancers (0.46, 95% CI = 0.31–0.65) and for BCC (SIR = 0.32, 95% CI = 0.19–0.50) were significantly fewer than expected in age/sex matched population. However, the SIR for all lymphomas was significantly elevated to 2.46 (95% CI = 1.31–4.22) with an excess of non-Hodgkin's lymphoma (SIR = 2.04; 95% CI = 0.98–3.76) and Hodgkin's lymphoma (SIR = 7.87, 95% CI = 1.58–22.99).

Myocardial infarction was reported in 35 patients (1.0%; 0.3 E/100 PY)). Thirty-one patients (0.9%) reported 38 (0.3 E/100 PY) serious and non-serious AEs of heart failure. In 21 patients (0.2 E/100 PY), heart failure or congestive heart failure was serious resulting in death in 6 patients. In addition to the increased risk of heart failure in RA, almost all patients had a history of multiple traditional risk factors. Thirty-eight patients (0.1%; 0.3 E/100 PY) reported cerebrovascular accidents.

Among other adverse events of interest, vasculitis was reported in 20 patients (0.6%; 0.2 E/100 PY), lupus-like syndrome was reported in 21 patients (0.6%; 0.2 E/100 PY), interstitial lung disease was reported in 6 patients (0.2%; 0.0 E/100 PY). Twenty-three patients reported treatment-emergent psoriatic conditions that the investigator considered to be possibly or probably related to adalimumab.

In the integrated safety analysis of Study M02-497 and Study M03-634 by period, the incidence of any AE was highest in the period up to 1 year (72.7% of patients) and declined in the subsequent periods. The number and incidence of fatal AEs was lower in the period up to 1 year (1 death, 0.0% of patients) than in the 3 later periods (21, 17, and 10 deaths, respectively; 0.3 to 0.4/100 PYs). No increase in incidence was seen in the periods after 1 year. Serious AEs were most frequent in the period > 1 year to 3 years (430 patients, 12.7%; 13.5 E/100 PY); during the periods after 3 years, no overall increase in the incidence of SAEs per 100 PYs was observed (9.2 and 8.6 E/100 PY respectively). During the entire observation period, treatment was discontinued in 499 patients (14.5%) due to 565 AEs (3.5 E/100 PY). The highest withdrawal rate due to AEs was observed during the period > 1 to 3 years, with 284 events (4.7 E/100 PY) observed in 7.6% of patients. Irrespective of the first year of the observation, no time dependent increase of withdrawal rate due to AEs could be observed up to a period of > 5 years. It should be noted that AEs were more closely monitored during Study M02-497 than during Study M03-634, thus the difference in the rates of AEs may be due to reporting bias. In addition, patients who withdrew during Study M02-497 and some patients who had SAEs during Study M02-497 did not enter Study M03-634 and are thus not included in the integrated analysis.

In this long-term observational study, adalimumab appeared to be generally well-tolerated in patients with moderate to severe RA who are receiving concomitant anti-rheumatic therapy. No trends of clinical concern were established with regard to the incidence of deaths, SAEs, including AEs of special interest, like serious infections and malignancies. No previously unrecognized safety concerns or risk factors were identified throughout this study. No AE/SAE reporting rate increase or change was observed during this study. Safety data were comparable to those observed in previous adalimumab trials, and similar to what has been observed in trials with other TNF inhibitors.

Conclusions: In this 5-year, multicenter, uncontrolled PMOS of patients with RA, adalimumab was generally safe and well tolerated over 16,274.1 PYs of exposure (Study M02-497 + Study M03-634). No new safety signals were observed.