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:

An Open-Label, Multicenter Study to Assess the Safety and Efficacy of the Fully Human Anti-TNFα Monoclonal Antibody Adalimumab (D2E7) when Added to Inadequate Standard Anti-Rheumatic Therapy in Patients with Active Rheumatoid Arthritis

Coordinating Investigator:

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Study Sites:

Multicenter: 448 sites in 11 European countries and Australia

Publications:

11 abstracts (posters)

Bombardieri S, Moutsopoulos HM, McKenna F, Michel B, Webber DG, Kupper H. Rapid response to adalimumab (Humira®) after first dose: The REACT Trial. Ann Rheum Dis 2004;63(Suppl I):261 (Poster FRI0042).

Bombardieri S, Tzioufas AG, McKenna F, Michel BA, Webber DG, Kupper H. Efficacy evaluation of adalimumab (Humira®) in patients with single and multiple prior biologics in the REACT Trial. Arthritis Rheum 2004;50(9)(Suppl):S187-8. Poster Presentation 365 at the 2004 Annual Scientific Meeting of the American College of Rheumatology, 16-21 October 2004, San Antonio, Texas.

Bombardieri S, Tzioufas AG, McKenna F, Beat MA, Spencer-Green GT, Kupper H. Efficacy evaluation of adalimumab (Humira®) by dose and administration route of concomitant methotrexate in widespread clinical practice (REACT Trial). Ann Rheum Dis 2005;64(Suppl III):428 (Poster SAT0061).

Bombardieri S, Tzioufas AG, McKenna F, Ozer U, Kupper H. Adalimumab (Humira®) is effective in treating patients with rheumatoid arthritis who previously failed etanercept and/or infliximab in real-life clinical settings. Arthritis Rheum 2005;52(9)(Suppl):S144. Poster Presentation 294 at the 2005 Annual Scientific Meeting of the American College of Rheumatology, November 12-17, 2005, San Diego, California.

Burmester GR, Alten R, Tony H, Liman W, Gromnica-Ihle E, Stierle HE et al. Safety and efficacy of adalimumab (Humira®) in patients with rheumatoid arthritis in Germany: REACT Study. Ann Rheum Dis 2004;63(Suppl I):266 (Poster FRI0061).

Burmester GR, Monteagudo Saez I, Malaise MG, Canas da Silva J, Webber DG, Kupper H. Adalimumab (Humira®) is effective in patients who have previously been treated with TNF-antagonists (etanercept and/or infliximab) in widespread clinical practice: 12-week outcomes in the REACT Trial. Ann Rheum Dis 2005;64(Suppl III):423-4 (Poster SAT0047).

Burmester GR, Monteagudo Saez I, Malaise MG, Kary S, Kupper H. Adalimumab (Humira®) is effective and safe in treating rheumatoid arthritis (RA) in real-life clinical practice: 1-Year results of the REACT study. Arthritis Rheum 2005;52(9)(Suppl):S541. Poster Presentation 1436 at the 2005 Annual Scientific Meeting of the American College of Rheumatology, November 12-17, 2005, San Diego, California.

Burmester GR, Monteagudo Sáaz I, Malaise M, Canas da Silva J, Webber DG, Kupper H. Efficacy and safety of adalimumab (Humira®) in European clinical practice: The REACT Trial. Ann Rheum Dis 2004;63(Suppl I):90 (Oral Presentation FRIOP0105).

Mariette XL, Bijlsma JWJ, Herold M, Eiselstein J, Spencer-Green GT, Kupper H. Adalimumab (Humira®) is as effective when used in combination with other DMARDs as with methotrexate in treating rheumatoid arthritis: The REACT Study. Arthritis Rheum 2004;50(9)(Suppl):S183. Poster Presentation 354 at the 2004 Annual Scientific Meeting of the American College of Rheumatology, 16-21 October 2004, San Antonio, Texas.

Mariette X, Bijlsma JWJ, Herold M, Unnebrink K, Kupper H. Adalimumab (Humira®) is as effective when used with other concomitant DMARDs as when used with methotrexate in treating rheumatoid arthritis in widespread clinical practice: The REACT Study. Ann Rheum Dis 2005;64(Suppl III):424 (Poster SAT0048).

Mariette X, Bijlsma JWJ, Herold M, Eiselstein J, Spencer-Green GT, Kupper H. Efficacy evaluation of adalimumab (Humira®) in combination with single and multiple disease-modifying antirheumatic drugs in the REACT Trial. Ann Rheum Dis 2004;63(Suppl I):278 (Poster FRI0099).

Studied Period (Years):	**Phase of Development:** 3b
First Subject's First Visit: 25 Sep 2002	
Last Subject's Last Visit: 20 Nov 2004	

Objectives:

The primary objective of this study was to evaluate the safety of adalimumab in subjects receiving concomitant anti-rheumatic therapy. The secondary objective was to evaluate the efficacy of adalimumab when added to preexisting inadequate standard antirheumatic therapy in subjects with moderate to severely active rheumatoid arthritis (RA).

Methodology:

This study included a Screening period followed by a 12-week study treatment period. Thereafter, a supply of adalimumab was provided until regulatory approval of adalimumab was secured and the product became generally available. During this time, continuation visits were to be performed every eight weeks. Standard efficacy and safety measurements were performed throughout the study.

All subjects were to have received the same dose of adalimumab, 40 mg eow. However, subjects without concomitant disease-modifying anti-rheumatic drug (DMARD) use may derive clinical benefit from dose escalation to 40 mg weekly; therefore, these subjects had the option to be dose escalated if adequate EULAR response was not achieved at Week 12.

Number of Subjects (Planned and Analyzed):

Planned: 4000 subjects

Analyzed: 6610 for safety and efficacy

Diagnosis and Main Criteria for Inclusion:

Subjects were to be males or females ≥ 18 years of age with an American College of Rheumatology (ACR) criteria for diagnosis of RA for at least 3 months, active RA as defined by Disease Activity Score (28 joints) (DAS28) ≥ 3.2 at study entry, and an unsatisfactory response or intolerance to prior DMARDs. Subjects were not to have had prior treatment with alkylating agents such as cyclophosphamide or chlorambucil; prior treatment with intravenous (iv) immunoglobulin or any investigational agent within 30 days, or 5 half lives of the product, whichever was longer; or prior treatment with investigational biologic therapy (*e.g.*, anti CD4). Subjects were not to have been treated 2 months prior to study entry with approved biologic therapy (*e.g.*, etanercept, infliximab, anakinra).

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

Adalimumab 40 mg/0.8 mL injection solution sc

Lot Numbers:. 82-001-9A-02, 95135HT, 04198HT, 95139HT, 07237HT, 07250HT, 040209A/HT1, 08271HT, 82-001-9A-03, 95134HT, 95137HT, 95141HT, 01173HT, 04200HT, 07239HT, 07252HT, 040209A/HT3, 08273HT, 14316HT, 16340HT, 82-001-9A-04, 95136HT, 95140HT, 04199HT, 04200HT01, 07238HT, 07251HT, 08272HT, 90016HK/02, 70841, 95135HS, 110649A03, 011724HT, 040209A/HT2, 90016HK, and 040209/HT2

Duration of Treatment:

This study included a 12-week study treatment period. Thereafter, adalimumab was provided until regulatory approval of adalimumab was secured and the product became generally available. The mean duration of the study was ~7 months, with some subjects treated for up to 2 years.

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

Not applicable. This was an open-label study in which all subjects received investigational product (adalimumab).

Criteria for Evaluation

Efficacy:

The following efficacy variables were evaluated:

- DAS28 change from Baseline
- ACR20/50/70 response
- European League Against Rheumatism (EULAR) response
- Tender Joint Count (TJC) and Swollen Joint Count (SJC) (28 joints) change from Baseline
- Erythrocyte Sedimentation Rate (ESR) change from Baseline
- C-Reactive Protein (CRP) change from Baseline
- Physician Assessment of Disease Activity (Visual Analogue Scale [VAS]) change from Baseline
- Patient Assessment of Disease Activity (VAS) change from Baseline
- Patient Assessment of Pain change from Baseline (VAS)

- Disability index of the HAQ change from Baseline
- Arthritis Impact Measurement Scales 2 – Short Form (AIMS2–SF) change from Baseline (France only)

Safety:

Adverse events (AEs) were monitored throughout the study. Standard laboratory evaluations, vital signs determinations, and physical examinations were performed at specified timepoints throughout the study. Electrocardiogram (ECG), chest x-ray, tuberculin (purified protein derivative) test, and hepatitis test were performed at Screening. Measurements for antinuclear antibodies (ANAs) was performed throughout the study; measurement of anti-dsDNA was to be performed automatically if the ANA results were positive.

Statistical Methods

Efficacy and safety analyses were performed on the set of subjects who received at least one injection of adalimumab (N=6610). Since this was not a confirmatory study, no per−protocol analysis was planned or performed. All analyses were descriptive.

Demographics and Baseline Characteristics:

Demographic and Baseline variables were described by summary statistics. For continuous data, n, mean, standard deviation, minimum, 1st quartile, median, 3rd quartile, and maximum were presented. For categorical data, absolute and relative frequency were calculated.

Efficacy:

Efficacy results were presented descriptively by summary statistics. Both the "as observed" approach and the last observation carried forward (LOCF) approach were applied. The values at all visits as well as changes from Baseline were summarized.

Safety:

Treatment-emergent AEs were summarized. Treatment-emergent AEs were defined as events with an onset date after the first adalimumab injection and up to 70 days after the last adalimumab injection. AEs were tabulated by primary system organ class (SOC) and preferred term (PT) (Medical Dictionary for Regulatory Activities [MedDRA] Version 8.0). Summaries by severity and relationship to study drug were performed. Certain AEs, like those that were serious, severe, or leading to premature withdrawal, e.g., malignancies and serious infections, were listed and described in detail. Other safety variables, like laboratory data, were described by statistical characteristics as mentioned above. In addition, shift tables were provided for abnormal values, whereby the normal range of the analyzing laboratory was used.

Summary

A total of 6610 subjects were enrolled in the study and comprised the analysis set. The majority of subjects were white and female. Subjects had a mean age of 53.7 years. All subjects had RA diagnosis documented by medical history. Mean duration of RA for all treated subjects was 129.7 months (10.8 years). Subjects had previously taken a mean of 3 DMARDs prior to enrollment in the study. At study entry, subjects had high disease activity with a mean DAS28 of 6.0, despite treatment with anti-rheumatic drugs. Overall, 75.4% of subjects received one or more concomitant DMARD medications during the study, and 74.8% and 70.1% of subjects received concomitant steroids or NSAID medications, respectively, during the study. A total of 6235 (94.3%) of subjects were observed up to the

Week 12 visit, the mean duration of treatment with adalimumab was 232.6 ± 124.2 days. Total subject exposure was 4210.1 years. A total of 7.1% of subjects (470/6610) withdrew from the study through Week 12. Of these subjects, the main reason for study discontinuation was occurrence of one or more AEs followed by lack of efficacy and withdrawal of consent.

Efficacy Results:

Adalimumab was effective in the treatment of subjects with moderate to severely active RA when added to preexisting inadequate standard antirheumatic therapy as demonstrated by ACR and EULAR responses, and changes from Baseline in DAS28, SJC, TJC, HAQ-DI, Patient and Physician Assessment of Disease Activity, Patient Assessment of Pain, ESR, CRP, and AIMS2-SF scores (France only).

Mean improvements observed through the main study period (Week 12) were maintained for all efficacy endpoints throughout the study. No decrease in efficacy parameters was observed for any endpoint at any time during the study.

Efficacy results are presented below:

ACR and EULAR Response:

	Adalimumab N = 6610				
	Responders n (%)				
Timepoint	**ACR20**	**ACR50**	**ACR70**	**EULAR At Least Moderate Response**	**EULAR Good Response**
Week 2	2640 (41.7)	775 (12.0)	205 (3.2)	4102 (66.4)	748 (12.1)
Missing	284	170	111	433	433
Week 6	3548 (59.0)	1704 (28.0)	621 (10.1)	4601 (77.2)	1432 (24.0)
Missing	593	525	480	652	652
Week 12	4151 (68.9)	2447 (40.2)	1121 (18.2)	5011 (82.8)	2008 (33.2)
Missing	582	517	463	560	560
Last observation	4367 (67.3)	2943 (45.0)	1610 (24.6)	5281 (81.5)	2516 (38.9)
Missing	117	77	62	134	134

Change from Baseline to Week 12 in key efficacy variables:		
	Mean± SD	**Mean % ± SD**
DAS28	-2.1 ± 1.4	-22.9 ± 17.4
TJC	-8.5 ± 7.0	-60.9 ± 48.5
SJC	-6.7 ± 5.5	-62.7 ± 44.6
HAQ	-0.54 ± 0.61	-34.0 ± 46.2
Physician Assessment of Disease Activity	-33.4 ± 22.0	-53.3 ± 96.9
Patient Assessment of Disease Activity	-28.3 ± 27.3	-39.9 ± 98.1
Patient Assessment of Pain	-30.5 ± 28.1	-42.4 ± 61.6
CRP	-12.4 ± 27.5	-17.6 ± 136.3
ESR	-11.6 ± 19.9	-21.3 ± 77.2

Change from Baseline in AIMS2-SF: AIMS2-SF (France only) values decreased from Baseline to Week 12 for the following domains: physical, symptom, affect, and work. Little or no difference from Baseline was observed for the social domain. Improvements from Baseline values were maintained throughout the study, as the mean decrease seen at the last observed value at Week 28 was comparable to the values observed at Week 12.

Subgroup Analysis

Analyses were performed for DAS28, ACR20/50/70 responses, and EULAR response by the following subgroups:

- Duration of RA (< 2 years, ≥ 2 years)
- RF status at Baseline (positive, negative)
- Concomitant DMARDs – subjects with 0 DMARDs at Baseline, subjects with 1 or more DMARDs at Baseline, subjects with MTX (only DMARD) at Baseline, subjects with leflunomide (only DMARD) at Baseline, subjects with sulfasalazine (only DMARD) at Baseline, subjects with antimalarial (only DMARD) at Baseline, subjects with MTX and leflunomide (exclusively) at Baseline, subjects with 1 DMARD at Baseline, subjects with 2 DMARDs at Baseline, subjects with 3 or more DMARDs at Baseline.
- Previous anti-TNF treatment (infliximab and/or etanercept) (yes/no)

Subgroup analyses of ACR20/50/70 and EULAR responses demonstrated that concomitant DMARD use is better than monotherapy, the number of concomitant DMARDs has no major impact on efficacy, and subjects who had failed TNF-antagonists responded well, but their response was somewhat inferior to that observed for anti-TNF-naïve subjects.

Dose Escalation

Subjects without concomitant DMARD use were permitted to dose escalate to adalimumab 40 mg weekly if they did not demonstrate adequate response. A total of 414 subjects underwent dose escalation. Mean time to dose escalation was 139 days. Examination of ACR responses and change from Baseline in DAS28 (based on ESR) at 8- and 16-weeks post dose escalation demonstrated positive benefit for subjects who dose escalated.

Safety Results:

Adalimumab was generally safe and well-tolerated in subjects with moderate to severe RA who were receiving concomitant anti-rheumatic therapy. No new safety signals were observed with regard to the incidence of deaths, serious adverse events (SAEs), or other significant AEs including specifically, serious infections, malignancies, or immunologic reactions, and no unexpected safety concerns were seen throughout 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.

Since the mean duration of the study was ~ 7 months, with some subjects receiving treatment for up to 2 years, safety data through the end of the study (entire Treatment Period) is presented. It is important to note that RA was the underlying condition for all subjects enrolled in the study. Occurrences of "rheumatoid arthritis" as indicated within any AE analyses represent primarily joint surgeries or an exacerbation or flare of the subjects' current conditions.

A total of 72.4% (4783/6610) of subjects experienced one or more treatment-emergent AEs during the entire treatment period. A total of 42.7% (2824/6610) of subjects reported one or more AEs that were considered by the Investigator to have been at least possibly related to study drug administration during the entire treatment period. A total of 9% (595/6610) of subjects reported events that were severe.

Treatment-Emergent AEs Reported by > 2% of subjects are presented by MedDRA Preferred Term for the Entire Treatment Period:

	Adalimumab
	N = 6610
MedDRA 8.0 Preferred Term	**n (%)**
Subjects with one or more adverse events	4783 (72.4)
Rheumatoid arthritis	641 (9.7)
Headache	317 (4.8)
Nasopharyngitis	293 (4.4)
Injection site reaction	277 (4.2)
Antinuclear antibody positive	266 (4.0)
Hypertension	198 (3.0)
Urinary tract infection	187 (2.8)
Influenza	182 (2.8)
Upper respiratory tract infection	173 (2.6)
Diarrhea	159 (2.4)
Bronchitis	154 (2.3)
Nausea	143 (2.2)
Asthenia	143 (2.2)
Hypercholesterolemia	145 (2.2)
Cough	139 (2.1)

Few deaths occurred during the study (35/6610; 0.5%). Furthermore, analysis of mortality rates indicated that subjects treated with adalimumab experienced slightly lower mortality rates than expected based on comparison with a age and sex-matched standardized population, which was 41.2 deaths. The number of subjects who reported treatment-emergent SAEs was generally low (882/6610; 13.3%).

Examination of other AEs of interest revealed that:

- The overall incidence rate of serious infections was low throughout the course of treatment with 3.1% (202/6610) of subjects reporting serious infection. The serious infection incidence rate (5.5 events per 100-PYs) is within the range of infections reported in RA populations (range of 3.0 to 9.0 events per 100-PYs). The rates of serious infectious AEs observed in the present clinical trial are comparable to the rates seen in subjects with long-standing RA.
- Reports of TB (21 subjects) and other serious opportunistic infections were infrequent.
- Treatment-emergent malignancies occurred at frequencies at or below those expected from a general population with 0.7% (43/6610) reporting malignancy. Two lymphomas were reported.
- Treatment-emergent AEs leading to study discontinuation and temporary dose reductions or withdrawal were infrequent (670/6610; 10.1% and 963/6610; 14.6%, respectively).
- Drug hypersensitivity reactions, immunologic reactions, demyelinating events, and lupus and lupus-like syndromes were few.

No clinically meaningful changes in mean laboratory values were observed. Shifts to high or low were generally infrequent. Changes in vital signs were clinically unremarkable.

Conclusions:

Adalimumab was well tolerated by subjects receiving a broad spectrum of different concomitant anti-rheumatic therapy. No new safety signals were observed for any safety parameter. Efficacy assessments were similar to those observed in other investigations of adalimumab and provided insight into the beneficial effects of adalimumab in subjects with RA who were receiving concomitant anti-rheumatic therapy. Subgroup analyses indicated that use of concomitant DMARD(s) may be predictive of additional efficacy benefits. Subjects who had failed prior TNF-antagonists have a good chance to respond well to adalimumab.