2.0 Synopsis

Abbott Laboratories	**Individual Study Table Referring to Part of Dossier:**	**(For National Authority Use Only)**
Name of Study Drug: **Humira®**	**Volume:**	
Name of Active Ingredient: **Adalimumab**	**Page:**	

Title of Study: A multicenter randomized double-blind placebo-controlled study of the human anti-TNF monoclonal antibody D2E7 in rheumatoid arthritis patients currently receiving treatment with methotrexate

Investigator:

[redacted]

Study Sites:

There are 83 sites in the US, Canada and the EU.

Publications:

None

Studied Period (Years): First Subject First Visit: 09 Feb 2000 Last Subject Last Visit: 25 Aug 2005	**Phase of Development:** 3

Purpose for Amendment:

The reasons for this amendment were that some sections did not accurately depict the Baseline timepoint of Week 0, the fact that some of the numbers in the safety narratives did not match the subject data listings accurately, and the necessity for a few minor administrative changes. This amendment has led to slight numerical changes in the report of the safety narratives and in-text tables. However, the overall conclusions about the safety and efficacy of long-term adalimumab use for this subset of subjects are unchanged.

Objective: To evaluate the long-term safety and maintenance of efficacy following repeated administration of adalimumab in subjects with rheumatoid arthritis (RA) receiving concurrent methotrexate (MTX) therapy.

Methodology: The open label extension phase of Study DE019 was conducted in subjects with RA receiving concurrent MTX who were previously enrolled in and completed the placebo controlled portion of the study. Subjects who participated in Study DE019 were randomized to receive weekly placebo or one of two adalimumab doses (20 mg weekly or 40 mg every other week [eow]) for 52 weeks. Data collected during the 52-week, double-blind, placebo-controlled portion of the study have been presented in a previous CSR (R&D/01/744). Following the placebo-controlled portion of the study, subjects were given the option to initiate open label treatment with biweekly doses of 40 mg adalimumab for an additional 52 weeks. Data collected during the first year of the open label extension phase have been presented in a previous CSR (R&D/03/528). Following 1 year of open label treatment,

subjects first had the option to extend the open label treatment for up to 156 weeks (3 years total) and then to 260 weeks (5 years total) for evaluation of the long term efficacy and safety of adalimumab. This report summarizes the results after the first 5 years after randomization.

Number of Subjects (Planned and Analyzed):

Up to 600 subjects (the planned population of the DE019 study) were eligible for inclusion in the open−label extension phase. A total of 553 subjects were analyzed.

Diagnosis and Main Criteria for Inclusion:

Subjects must have completed the placebo-controlled portion of Study DE019. Subjects also must have met the ACR criteria for diagnosis of active RA and had at both the Screening and DE019 Week 0 Visits ≥ 6 swollen joints, ≥ 9 tender joints, and a C-reactive protein (CRP) ≥ 1 mg/dL, despite a minimum of three months of treatment with MTX.

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

Adalimumab, 40 mg subcutaneous (SC) eow. Lot numbers DEE-02001, 81-002-S2, 80-904-S2, 90039HT, S6693H0, 96-045-S2, 06-570-S2, 12-114-S2, 16-363-S2, 21-781-S2, and 05-002778.

Duration of Treatment:

Up to five years of adalimumab exposure for subjects randomized to adalimumab during the randomized period. Subjects randomized to placebo during the first year could have up to four years of adalimumab exposure.

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

Not applicable; this was an open-label study.

Criteria for Evaluation

Efficacy:

The long-term efficacy of adalimumab was assessed by evaluating its effects on:

(1) the signs and symptoms of RA; as measured by
- ACR50/70/90/100;
- tender joint count (TJC);
- swollen joint count (SJC);
- Patient's Assessment of Pain;
- Patient's Global Assessment of Disease Activity;
- Physician's Global Assessment of Disease Activity;
- Duration of Morning Stiffness;
- Presence of Morning Stiffness;
- CRP,

(2) physical function as measured by
- HAQ 0.22/0.50/0.75/1.0 Response Rates.

(3) structural damage;
- Modified Total Shape Score

Erosion Score;
- Joint Space Narrowing Score; and
- Radiographic Progression, defined as a change from Baseline of >0.5 in mTSS.

(4) rates of clinical remission;

- Proportion of subjects who met the pre defined DAS28 criteria of clinical remission (*i.e.*, DAS28 <2.6), where DAS28 = 0.56*sqrt(TJC out of 28 joints) + 0.28*sqrt(SJC out of 28 joints) + 0.36*log(CRP*10+1) + 0.014*(Patients Global Assessment VAS) + 0.96;
- Modified criteria for clinical remission (*i.e.*, DAS28 <2.6, TJC ≤1 and SJC ≤ 1); and
- "Good" EULAR response using DAS28 defined as:

	Change in DAS28 From Baseline[a]		
DAS28 at current visit	**<-1.2**	**-1.2 to -0.6**	**> -0.6**
≤ 3.2	Good	Moderate	None
> 3.2 to < 5.1	Moderate	Moderate	None
> 5.1	Moderate	None	None

a. Baseline is the last visit prior to the first dose of adalimumab.

- Plus the Major clinical response where Subjects who maintained an ACR70 response for at least six months following the first injection of adalimumab through Year 5.

and (5) patient reported outcome measures for the SF-36 and FACIT Fatigue scale

Pharmacokinetic:

Not applicable.

Safety:

Adverse events (AEs) were monitored throughout the study. Standard laboratory parameters, vital signs, and physical examinations were measured at each study visit. Serum anti-dsDNA antibodies, Serum IgG, hepatitis serologies chest x-rays and purified protein derivative were taken at the study entry screen visit.

Statistical Methods

Efficacy:

The analysis of efficacy variables was based on "observed" data using descriptive statistics. No statistical comparisons were done. Efficacy variables, excluding radiographic measurements, were presented by adalimumab exposure. Radiographic measurements were presented at Baseline, Week 52, Week 156 and Week 260 by original randomized treatment group and overall. The Baseline value was considered to be the last non missing value prior to taking the first injection of adalimumab (*i.e.*, prior to the first blinded injection of study drug for subjects randomized to receive adalimumab in Study DE019 or prior to the first open label injection of adalimumab for subjects randomized to receive placebo in Study DE019).

No statistical hypothesis was tested. Observed values were presented by adalimumab exposure. No imputation was performed.

Pharmacokinetic:

Not applicable.

Safety:

Treatment emergent AEs were defined as any AE with an onset date on or after the date of the first adalimumab injection. If the Investigator provided a final diagnosis for multiple symptoms, only the final diagnosis was counted, once for the subject. For any one AE (*i.e.* preferred terms), each preferred term was counted only once per subject, and if different categories (*e.g.* for severity or relationship to

study drug) occurred, the worst one (the most severe and the most highly related, respectively) was taken. AEs were coded using MedDRA dictionary Version 8.1.

Summary/Conclusions

Key Demographic and Baseline Characteristics

Characteristic		**N=553**
Age (years)		
	Mean ± SD	55.71 ± 12.02
	Range	21 - 86
Sex, n (%)		
	Female	413 (74.7)
	Male	140 (25.3)
Race, n (%)		
	Asian	9 (1.6)
	Black	34 (6.1)
	Caucasian	467 (84.4)
	Hispanic	36 (6.5)
	Other	7 (1.3)

Efficacy Results:

Maintained Reduction of the Signs and Symptoms of RA

- ACR20 results show that the reductions in the signs and symptoms of RA achieved following 1 year of adalimumab exposure are sustained through 5 years of exposure.

	Number of Responders	**Total Number of Subjects**	**% Responders**
Week 2	124	412	30.1
Week 52	234	332	70.5
Week 104	253	385	65.7
Week 156	232	345	67.2
Week 208	219	313	70.0
Week 260	165	219	75.3

- Results from the other efficacy measurements assessed in the 5 year, open label extension portion of Study DE019 (ACR50/70/90/100 response rates, TJC, SJC, Patient's Assessment of Pain, Patient's Global Assessment of Disease Activity, Physician's Global Assessment of Disease Activity, Duration/Presence of Morning Stiffness, and CRP levels) provide supportive evidence that the reductions in the signs and symptoms of RA achieved following 1 year of adalimumab exposure are sustained through 5 years of exposure.

Maintained Improvement in Physical Function

- Mean changes from Baseline in HAQ DI show that improvements in physical function achieved following 1 year of adalimumab exposure are sustained through 5 years of exposure.

	n	Mean ± SD
Week 2		
Baseline Value	416	1.44 ± 0.63
Week 2 Value	416	1.16 ± 0.68
Change from Baseline	416	-0.28 ± 0.40
Week 52		
Baseline Value	335	1.40 ± 0.64
Week 52 Value	335	0.79 ± 0.68
Change from Baseline	335	-0.62 ± 0.58
Week 104		
Baseline Value	399	1.32 ± 0.66
Week 104 Value	399	0.79 ± 0.69
Change from Baseline	399	-0.53 ± 0.58
Week 156		
Baseline Value	359	1.30 ± 0.67
Week 156 Value	359	0.75 ± 0.67
Change from Baseline	359	-0.55 ± 0.59
Week 208		
Baseline Value	324	1.30 ± 0.66
Week 208 Value	324	0.75 ± 0.70
Change from Baseline	324	-0.55 ± 0.60
Week 260		
Baseline Value	221	1.37 ± 0.61
Week 260 Value	221	0.70 ± 0.71
Change from Baseline	221	-0.67 ± 0.64

- Results from other efficacy measurements assessed in the 5 year, open label extension portion of Study DE019 (HAQ 0.22/0.50/0.75/1.0 response rates) provide supportive evidence that the improvements in physical function achieved following 1 year of adalimumab exposure are sustained through 5 years of exposure.

Inhibition of Structural Damage

- Mean changes from Baseline in mTSS show that exposure to adalimumab 40 mg eow for 1 year results in improvement in structural damage, and exposure to adalimumab 40 mg eow for up to 5 years results in minimal radiographic progression.

	Placebo Mean ± SD	20 mg weekly Mean ± SD	40 mg eow Mean ± SD
Week 52	N=92	N=114	N=120
Baseline Value	55.859 ± 40.108	69.193 ± 61.475	68.221 ± 59.416
Week 52 Value	58.364 ± 40.916	69.496 ± 61.616	67.592 ± 59.002
Change from Baseline	2.505 ± 7.657	0.303 ± 6.622	-0.629 ± 5.833
Week 156	N=92	N=114	N=120
Baseline Value	55.859 ± 40.108	69.193 ± 61.475	68.221 ± 59.416
Week 156 Value	59.592 ± 41.082	70.221 ± 60.691	68.232 ± 59.225
Change from Baseline	3.734 ± 9.157	1.029 ± 9.220	0.011 ± 9.534
Week 260	N=86	N=107	N=113
Baseline Value	56.017 ± 40.447	68.636 ± 59.728	68.588 ± 59.695
Week 260 Value	59.959 ± 41.077	71.276 ± 60.447	69.420 ± 59.543
Change from Baseline	3.942 ± 9.784	2.640 ± 9.596	0.832 ± 10.622

- Efficacy results from erosion and joint space narrowing scores provide supportive evidence that exposure to adalimumab 40 mg eow for 1 year results in improvement in structural damage, and exposure to adalimumab 40 mg eow for up to 5 years results in minimal radiographic progression. Additional support is provided by the demonstration that 73.3% of subjects had no radiographic progression following exposure to adalimumab 40 mg eow for 1 year, and a majority of subjects originally randomized to adalimumab 40 mg eow (58.4%) still had no radiographic progression (as defined as <= 0.5 mTSS) following 5 years of adalimumab exposure.

Maintained Rates of Clinical Remission

- Multiple definitions of clinical remission (DAS28 criteria, modified criteria, or the "Good" EULAR response criteria) showed that the rates of clinical remission achieved following 1 year of adalimumab exposure are sustained through 5 years of exposure.
- Over the 5 year period of adalimumab exposure, 115 of 534 subjects (21.5%) achieved a major clinical response.

Maintained Improvement in Patient Reported Quality of Life

- Beginning at Week 12, each individual domain and both summary component scores of the SF-36 demonstrated clinically meaningful improvements; these improvements were sustained at each time point through Week 156.
- Improvements in FACIT Fatigue scale scores seen following 1 year of adalimumab exposure are sustained through 3 years of exposure.

Impact of Changes in MTX and Oral Corticosteroid Dosing on Adalimumab Efficacy

- In those subjects whose MTX or corticosteroid dose was reduced, ACR, HAQ DI and clinical remission response rates at the final visit were notably higher compared to subjects whose MTX or oral corticosteroid dose was unchanged or increased. Therefore, treatment with adalimumab may result in a MTX and oral corticosteroid sparing effect, a clinically relevant finding given the side effects associated with these two agents.

Pharmacokinetic Results:

Not applicable.

Safety Results:

Adalimumab was generally safe and well tolerated through 260 weeks of treatment as evaluated by the incidence of AEs overall, severe AEs, and drug-related AEs.

- Overall, 537 (97.1%) of the 553 subjects comprising the study analysis set reported a treatment emergent AE. Two hundred seventy one subjects (49.0%) reported a severe treatment emergent AE, and 381 subjects (68.9%) reported an AE judged by the Investigator to be at least possibly drug related (*i.e.*, treatment related).

- In general, the majority of the most commonly reported AEs, severe AEs and treatment related AEs are either consistent with the safety profile described in the currently approved prescribing information for adalimumab (*e.g.*, upper respiratory and urinary tract infections), are associated with the disease of interest (*e.g.*, rheumatoid arthritis and arthralgia), or are common in a middle aged population that has been evaluated for up to a 5 year period (*e.g.*, hypertension). Therefore, no new safety findings were observed during this long term extension study of adalimumab.

Adalimumab was generally safe and well tolerated through 260 weeks of treatment as evaluated by the incidence of deaths, SAEs, and discontinuations due to AEs.

- Sixteen (16) treatment emergent AEs resulted in 11 deaths following up to 5 years of adalimumab exposure in Study DE019; 6 of the 11 subjects died from AE(s) judged by the Investigator to be at least possibly drug related.
- Overall, 224 subjects (40.5%) experienced an SAE(s), and 99 subjects (17.9%) experienced an AE(s) that resulted in discontinuation of study drug.
- In general, the majority of the most commonly reported SAEs and AEs that resulted in discontinuation of study drug are either consistent with the safety profile described in the currently approved prescribing information for adalimumab, are associated with the disease of interest, or are common in a middle aged population that has been evaluated for up to a 5 year period. Therefore, no new safety findings were observed during this long term extension study of adalimumab.

Adalimumab was generally safe and well tolerated as evaluated by TNF inhibitor-related and other special AEs of interest.

- Overall, 434 subjects (78.5%) experienced an infectious AE(s); however only 59 subjects (10.7%) experienced a serious infectious AE(s).
- Twenty-four subjects (4.3%) experienced a malignant AE(s); 12 of these AEs were judged by the Investigator to be at least possibly drug related, and 2 were fatal (B cell lymphoma and malignant lung neoplasm). Additionally, 19 subjects experienced non-melanoma skin cancers; 2 of these, squamous cell carcinoma and skin neoplasm, were considered to be study drug-related.
- Four (4) serious opportunistic infections developed in 4 subjects. All 4 events were judged by the Investigator to be at least possibly drug related.
- Four (4) subjects experienced AEs related to congestive heart failure, only one of which was considered by the Investigator to be at least possibly drug related.
- Two (2) subjects developed lupus like reactions (*i.e.*, "cutaneous lupus erythematosus). One of these subjects had similar rashes prior to entry into and during placebo treatment during the double blind portion of Study DE019.

- Fifty four subjects (9.8%) experienced an hepatic related AEs reported during the study.
- Overall, the number and severity of TNF inhibitor related and other special AEs of interest are consistent with the safety profile described in the currently approved prescribing information for adalimumab. Therefore, no new safety findings were observed during this long term extension study of adalimumab.

Adalimumab was generally safe and well tolerated as evaluated by clinical laboratory results and vital signs.

AEs (by MedDRA preferred term) reported by ≥ 5% of subjects for the DB phase are shown below.

Conclusions:

Efficacy results from the 5 year, open label extension portion of Study DE019 demonstrate that administration of adalimumab for up to 5 years results in: (1) maintained reduction of the signs and symptoms of RA; (2) maintained improvement in physical function; (3) inhibition of structural damage; (4) maintained rates of clinical remission; and (5) maintained improvement in patient reported quality of life. Safety results from the 5 year, open label extension portion of Study DE019 demonstrate that administration of adalimumab for up to 5 years is generally safe and well tolerated; no new safety findings were observed during this long term extension study of adalimumab.