CENTER FOR DRUG EVALUATION AND RESEARCH AND CENTER FOR BIOLOGICS EVALUATION AND RESEARCH

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STATISTICAL REVIEW(S)

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CENTER FOR BIOLOGICS EVALUATION AND RESEARCH

Office of Biostatistics and Epidemiology
Division of Biostatistics (HFM-215)

Statistical Review

FDA NUMBER: 125057.0

TASK TYPE: BLA

SPONSOR: *Abbott Lab.*

SUBJECT: *Original BLA for adalimumab (HUMIRA) in the treatment of rheumatoid arthritis*

DATE: 11/12/2002

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BACKGROUND

Abbott Laboratories submitted this original BLA for adalimumab (HUMIRA, D2E7) in the treatment of rheumatoid arthritis. The sponsor states that adalimumab is the first fully human monoclonal antibody engineered by gene technology that uses phage display technology to enhance its binding efficiency to TNF. It does not contain non-human or artificial protein sequences. Adalimumab is subcutaneously injected by the patient every other week and will be supplied in a pre-filled single-use syringe that has been adapted for use by RA patients who may have decreased manual dexterity. As a fully human antibody, adalimumab may offer improvements over existing TNF antagonists by providing decreased immunogenicity, fewer allergic reactions, longer half-life, and the ability to be given both with and without methotrexate (MTX). The recommended dose of adalimumab for adult patients with RA is 40 mg administered every other week as a SC injection.

Recent clinical trials using agents that block TNF activity demonstrate the central role for the cytokine in the pathogenesis of RA and other autoimmune diseases. Etanercept, a soluble TNF receptor, and infliximab, a mouse chimeric monoclonal antibody against TNF, are the only currently available TNF antagonists for the treatment of RA. The recommended dose of etanercept for adult patients is 25 mg given twice weekly as a subcutaneous (SC) injection. Infliximab must be given by a prolonged intravenous infusion in a physician office-based setting. The recommended dose of infliximab is 3mg/kg given as an intravenous infusion followed with additional similar doses at 2 and 6 weeks after the first infusion then every 8 weeks thereafter.

To date, the adalimumab clinical development program includes 23 studies, 17 of which were conducted in RA patients under IND 7627 (originally conducted by Knoll Pharmaceutical Company) and are therefore included in the integrated efficacy database. Four of these studies (DE009, DE011, DE019, and DE031) represent adequate and well-controlled trials demonstrating substantial evidence of the effectiveness of adalimumab. DE009 was a dose-finding study. DE011 was the only monotherapy trial for this agent. DE019 and DE031 were the most important studies and are the primary focus of this review.

Financial interests and arrangements of Clinical Investigators are not included because no clinical investigator participated in financial arrangements or holds financial interests per 21 CFR 54. The sponsor certifies that they have not entered into any financial arrangement with the list clinical investigators whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a).

PROTOCOL DE019

DE019 was a multicenter, double-blind, randomized, placebo-controlled, parallel group, Phase III study in which patients were assigned to one of two adalimumab dose groups (weekly dose of 20 mg adalimumab or 40 mg adalimumab every other week [eow]) or placebo. Adalimumab solution for injection and placebo were administered as a sc injection. This study was composed of three parts: 1) a washout period during which all previous DMARDs (except MTX) were discontinued. All patients were to be on a stable dose of MTX for at least 4 weeks prior to the screening visit; 2) a 52-week double-blind placebo controlled period; and 3) a 52-week open-label period. Adalimumab or placebo was administered as a single sc injection (1.6 mL/injection) weekly for up to 52 weeks during the double-blind placebo-controlled period. All concomitant therapies for RA, including MTX and corticosteroids, were to be kept unchanged in dose and route of administration during the study. At or after the Week 16 visit, DMARDs (except TNF antagonists) could be added for non-responding patients. The decision to prescribe another DMARD was left to the discretion of the investigator, but consultation with the Knoll medical monitor could be sought, if necessary.

There were three primary efficacy endpoints: ACR20 at Week 24; modified total Sharp x-ray score change at Week 52; and disability index of the HAQ change at Week 52. The three primary efficacy variables were considered in a hierarchical order. The ACR20 response was tested for statistical significance first. Testing for statistical significance in radiographic progression (change in modified total Sharp x-ray score) at Week 52 was carried out only if the result of ACR20 response at Week 24 was statistically significant. Testing for statistical significance in the change from baseline of the disability index of the HAQ total score at Week 52 was done only if the test for change in modified total Sharp x-ray score was significant. All statistical tests were conducted with a two-sided significance level of 0.05.

The American College of Rheumatology (ACR) response criteria were used to measure clinical response. A patient was considered as an ACR20 responder if he/she had at least 20% improvement from the baseline according the ACR response criteria. Modified total Sharp x-ray score - a measure of the change in joint health obtained from scoring x-ray results. Radiographs of the hands/wrists and feet of each patient were obtained at screening and at Weeks 24, 52, and last visit for those who terminated early. Digitized images of each radiograph were scored by two physicians. The assessors were blinded to study treatment and the chronological order of the images. The modified total Sharp x-ray scoring method required 16 joints of each hand/wrist and 6 joints of each forefoot to be scored for erosions on a scale from 0 (no damage) to 5. Fifteen joints of each hand/wrist and 5 joints of each forefoot were also scored for joint space narrowing on a scale of 0 (no damage) to 4. The erosion score and the narrowing score were added and the sum scores of the two physicians were averaged to obtain the modified total Sharp x-ray score. Disability index of the HAQ (Health Assessment Questionnaire) assessed disability by measuring the patient's ability to perform the following: 1) dress/groom; 2) arise; 3) eat; 4) walk; 5) reach; 6) grip; 7) maintain hygiene; and 8) maintain daily activity on a score of 0 to 3 (worst).

The planned sample size was 600 randomized patients with RA who had been treated concomitantly with MTX for a minimum of 3 months, prior to study entry. A total of 619 patients (full analysis set) were randomized and treated in the double-blind, placebo-controlled period of this study at 89 sites, as follows: 212 (34.2%) patients were randomized to the 20 mg weekly group, 207 (33.4%) patients adalimumab the 40 mg eow group, and 200 (32.3%) patients were randomized to placebo.

A total of 467 (75.4%) of 619 patients completed the study: 168 (79.2%) in the 20 mg weekly group, 159 (76.8%) in the 40 mg eow group, and 140 (70.0%) of 200 patients in the placebo group. The majority of patients withdrew because of adverse events (55 [8.9%] of 619 patients: 42 [10.0%] of 419 adalimumab treated patients and 13 [6.5%] of 200 placebo-treated patients), followed by lack of efficacy and/or progression of study disease (12 [2.9%] of 419 adalimumab-treated patients and 23 [11.5%] of 200 placebo-treated patients), and withdrawal of consent (19 [4.5%] of 419 adalimumab-treated patients and 15 [7.5%] of 200 placebo-treated patients).

Overall, the mean age of the patients from the all adalimumab group was 56.7 years while patients randomized to placebo had a mean age of 56.1 years. There were more female (464 [75.0%] of 619) than male (155 [25.0%] of 619) patients, and the majority of the patients were Caucasian (520 [84.0%] of 619), with Hispanic, Black, Asian, and other races accounting for a total of 99 (16.0%) of 619 patients. Overall, the treatment groups were comparable with regard to all baseline measures of disease activity. The duration of RA for the study population was very broad. Patients randomized to adalimumab 20 mg weekly ranged in their duration of disease from 0.2 to 52.1 years (mean: 11.0, median: 8.3), patients randomized to adalimumab 40 mg biweekly ranged in their duration of disease from 0.2 to 46.8 years (mean: 11.0, median: 8.0), and patients randomized to placebo ranged in their duration of disease from 0.5 to 46.0 years (mean: 10.9, median: 8.7). No meaningful differences were observed among the adalimumab and placebo treatment groups at baseline.

1.0 ACR20 Index

Comparison among the two adalimumab treatment groups and placebo of the ACR20 response rates at Week 24 was the highest hierarchical primary efficacy outcome. Patients who received additional DMARDs after Week 16 or patients who terminated the study before Week 24 were classified as 'non-responders'. Adjustments for multiple comparisons were done following the closure principle. An initial assessment over all three-treatment groups was carried out. If significant, pairwise comparisons between each adalimumab dose group and the placebo group were performed. The ACR20 response rate at Week 24 was assessed using Pearson's Chi-square test. After 24 weeks of treatment, each adalimumab treatment group (20 mg weekly and 40 mg eow) was associated with a statistically significant ($p<0.001$) improvement in observed ACR20 response compared to placebo (Table 22). In addition, the last observation carried forward (LOCF) approach was used to impute missing values as the secondary analysis. LOCF data demonstrated similar results.

Table 22 **ACR20 response at Week 24: Number (%) of patients responding by randomized treatment group (full analysis set)**

Time point	Adalimumab 20 mg weekly (N=212)	Adalimumab 40 mg eow (N=207)	Placebo (N=200)
Week 24			
Observed Week 24	129 (60.8)[a]	131 (63.3)[a]	59 (29.5)
LOCF Week 24	133 (62.7)[a]	136 (65.7)[a]	62 (31.0)

[a] Statistically significantly different from placebo ($p \leq 0.001$).

Data source: Section 9, Table 9.2.1.a, 9.2.3a, and 9.2.4a

Observed ACR20 responses are displayed graphically for the full analysis set of patients in Figure 3. Overall, the adalimumab treatment groups had a higher response at each time point compared to placebo. There was separation between adalimumab- and placebo-treated patients as early as Week 2. The separation was established by Week 4 and maintained through Week 52.

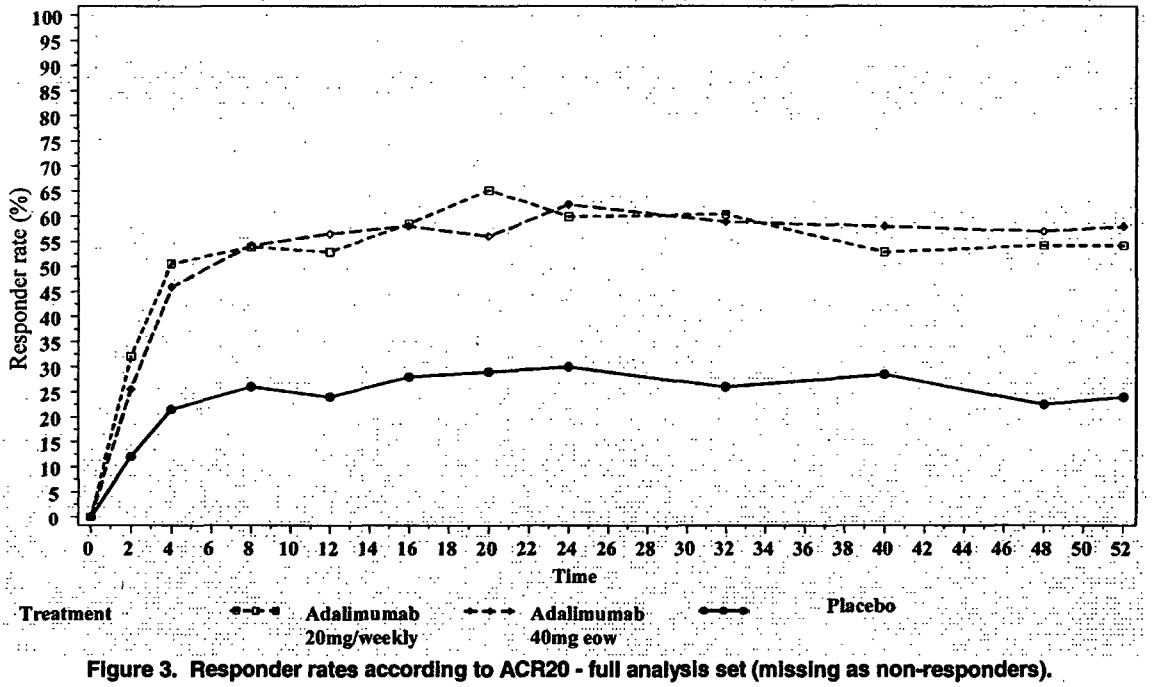


Figure 3. Responder rates according to ACR20 - full analysis set (missing as non-responders).

Subgroup analysis for ACR20 at Week 24 was performed. The subgroups were based on gender (male, female), age (<65, ≥65), race (white, black, Asian, Hispanic, other), body weight (>70 kg, ≥70 kg), RF status at baseline (positive and negative), and corticosteroid use at baseline (yes and no). In each of the subgroups, patients treated with adalimumab consistently had larger changes in their ACR20 response, as compared to those who received placebo. In a few instances, the number of patients within a specific subgroup was too small to allow for a valid comparison. In general, adalimumab's effectiveness was not affected by these subgroups. ACR20 results for Week 52 were similar to Week 24 results for all treatments.

ACR50 and ACR70 response rates at Week 24 were 39% and 20.8% in the 40 mg group, compared to 10% and 2.5% in the placebo group, respectively. The results for Week 52 were similar to those at Week 24 for all treatments. Observed major clinical response was defined as a continuous ACR70 response over a 6-month period. After 52 weeks of treatment, each adalimumab treatment group had a higher major clinical response rate compared to placebo (9.4% and 8.7 % in the 20 mg and 40 mg groups vs. 1.5% in the placebo group). As shown in Table 32, after 24 and 52 weeks of treatment, each adalimumab treatment group was associated with a statistically significant ($p<0.001$) improvement in observed ACR-N values compared to placebo.

Table 32 **Numeric ACR at Weeks 24 and 52 by randomized treatment group (full analysis set)**

	Adalimumab					
	20 mg weekly		40 mg eow		Placebo	
Time point	N	Mean ± SD	N	Mean ± SD	N	Mean ± SD
Week 24						
Observed Week 24	184	38.1± 39.2[a]	175	38.8 ± 40.4[a]	155	3.5 ± 50.2
LOCF Week 24	212	34.4 ± 40.8[a]	205	33.4 ± 44.0[a]	199	-6.4 ± 58.3
Week 52						
Observed Week 52	169	40.2 ± 38.9[a]	160	41.9 ± 44.9[a]	141	2.6 ± 53.2
LOCF Week 52	212	32.1 ± 48.6[a]	205	35.0 ± 48.1[a]	199	-7.0 ± 60.5

[a] Statistically significantly different from placebo ($p\leq0.001$).

Data source: Tables 9.2.26a and 9.2.27a

1.1 Comments

a. This reviewer has checked the sponsor's analysis and found that the results agree with what the sponsor has presented.

b. **Missing data/Worst case analysis**: Twenty-eight (13%) patients in the 20 mg weekly group, 32 (15%) in the 40 mg eow group, and 45 (23%) patients in the placebo group did not have complete ACR assessments at Week 24. They were considered as non-responders in the primary analysis. This reviewer performed the worst case analyses for the ACR20 primary endpoints in which subjects with missing data were treated as non-responders if they received adalimumab treatment or considered as responders if they were in the placebo group. Although this is the most conservative analysis, statistically and clinically significant results still hold for the comparison between the 40 mg eow group and the placebo group (ACR20 response rate at Week 24: 63% vs. 52%, $p=0.0212$). The ACR20 response rate in the 20 mg weekly group (61%) was also numerically higher than that in the placebo group (52%) ($p=0.0701$).

c. **Study site**: A total of 619 patients were treated in the double-blind, placebo-controlled period of this study at 89 sites. The number of patients enrolled per site ranged from one to 23. There were seven sites with at least 10 patients enrolled in adalimumab 40 mg eow or placebo arms that may allow for a meaningful comparison. Subgroup analysis for these sites showed that patients treated with adalimumab 40 mg eow consistently had a higher ACR20 response rate, as compared to those who received placebo.

d. **Correlation between baseline Sharp score and ACR20 response**: Comparisons between the placebo and adalimumab groups in ACR20 at Week 24 by different baseline TSS subgroups are shown in the following table. Although patients treated with adalimumab had higher ACR20 response rates than those treated with placebo across all subgroups, the difference in ACR20 between the placebo and adalimumab groups in patients with good baseline TSS (25.5 ≥ TSS) was not statistically significant.

ACR20 Response by Patients with Different Baseline Total Sharp Score

	20 mg weekly		40 mg eow		Placebo		
Baseline TSS	N	Responders (%)	N	Responders (%)	N	Responders (%)	P-value
Missing	11	2 (18%)	13	0 (0%)	16	0 (0%)	0.071
25.5 ≥ TSS	52	28 (54%)	51	34 (67%)	41	22 (54%)	0.324
54.5 ≥ TSS>25.4	54	38 (70%)	47	33 (70%)	45	17 (38%)	0.001
98.0 ≥ TSS>54.5	49	32 (65%)	47	32 (68%)	49	12 (24%)	<0.001
98.0 < TSS	46	29 (63%)	49	32 (65%)	49	8 (16%)	<0.001

2.0 Modified Sharp score

Comparison of the modified total Sharp x-ray score changes at Week 52 was the second hierarchical primary efficacy outcome. Missing values were imputed using a linear extrapolation method. A secondary analysis was performed following the LOCF approach to impute missing values. Endpoint data were ranked with van der Waerden method prior to performing the analysis. The difference among all treatment groups was to be assessed using analysis of covariance (ANCOVA) with the baseline erosion scores as the covariate. If this was significant ($p \leq 0.05$), pairwise comparisons between each active treatment group and placebo were to be evaluated using the same method.

An overall comparison of the change from baseline in modified total Sharp x-ray scores (extrapolated) to Week 52 revealed a statistically significant difference ($p<0.001$) across the treatment groups, and permitted pairwise comparisons. The magnitude of the change associated with each of the adalimumab treatment groups was smaller and was statistically significantly different ($p<0.001$ for both) from placebo (Table 24). The smaller changes observed in patients treated with adalimumab were indicative of a slowing of the disease progression. Similar results were observed when repeating the analyses using the LOCF data set and evaluable data set.

The subgroup analysis for the change from baseline in modified total Sharp x-ray scores to Week 52 was performed. The subgroups were based on gender (male, female), age (<65, ≥65), race (white, black, Asian, Hispanic, other), body weight (>70 kg, ≥70 kg), RF status at baseline (positive and negative), corticosteroid use at baseline (yes and no), Duration of RA (0 – 2, >2-5, >5-10, >10), Number of prior DMARDS (1, 2-4, >4), and Baseline Sharp score (<30, 30-90, >90). In each of the subgroups, patients treated with

adalimumab consistently had smaller changes in their modified total Sharp x-ray scores, as compared to those who received placebo. In a few instances, the number of patients within a specific subgroup was too small to allow for a valid comparison. In general, adalimumab's effectiveness was not affected by these subgroups.

Table 24 Modified total Sharp x-ray score changes (extrapolated) at Week 52 by randomized treatment group (full analysis set)

	Adalimumab							
	20 mg weekly				40 mg eow			
Time point	N	Mean ± SD	Median	Range	N	Mean ± SD	Median	Range
Baseline	201	66.4 ± 56.3	48.5		194	72.1 ± 60.7	54.5	
Change at Week 52	196	0.8 ± 4.9 [a]	0.0		183	0.1 ± 4.8 [a]	0.0	

	Placebo			
Time point	N	Mean ± SD	Median	Range
Baseline	184	66.4 ± 47.4	55.5	
Change at Week 52	172	2.7 ± 6.8	1.0	

Note: an overall comparison of the treatment groups demonstrated a statistically significant difference ($p \leq 0.001$) (see Section 9, Table 9.2.8c).

Analyses on the two components of the total Sharp score also demonstrated similar results. The mean changes from baseline in erosion and joints space narrowing were 0 and 0.1 units in the 40 mg adalimumab group, respectively, compared to 1.7 and 1.1 units in patients treated with placebo.

2.1 Comments

a. This reviewer has checked the sponsor's analysis and found that the results agree with what the sponsor has presented.

b. 68 out of 619 patients (11%) did not have x-ray data for the radiographic primary endpoint analysis. The sponsor just simply excluded these patients in the analysis. In order to use all randomized patients (ITT principle), this reviewer conducted a variety of sensitivity analyses with different imputation approaches. The changes in the adalimumab 40 mg group were statistically significantly different ($p<0.01$) from placebo in the first three sensitivity analyses. In the worst case analysis where the worst change was assigned patients treated with Adalimumab if missing and the best change was assigned to patients treated with placebo, the 25th percentile, median, and the 75th percentile changes in the adalimumab 40 mg group were still numerically smaller than those in the placebo group.

Sensitivity Analysis I
Assigning the worst change (50.5) to all patients with missing values

Group	n	mean	std	median	q1	q3	min	max	P-value*
20 MG WEEKLY	212	4.54	13.99	0.5	-0.5	2.00			<0.0001
40 MG BIWEEKLY	207	5.93	16.79	0.0	-1.0	2.00			<0.0001
PLACEBO	200	9.37	17.78	1.5	0.0	8.25			

*: Adalimumab group vs. placebo group using The Wilcoxon rank sum test.

Sensitivity Analysis II
Assigning the median change (0.5) to all patients with missing values

Group	n	mean	std	median	q1	q3	min	max	P-value*
20 MG WEEKLY	212	0.76	4.75	0.5	-0.5	1.00			<0.0001
40 MG BIWEEKLY	207	0.13	4.48	0.0	-1.0	1.00			<0.0001
PLACEBO	200	2.37	6.31	0.5	0.0	3.25			

*: Adalimumab group vs. placebo group using The Wilcoxon rank sum test.

Sensitivity Analysis III
Assigning the 75th percentile change (2.0) to patients treated with Adalimumab
Assigning the 25th percentile change (-.5) to patients treated with placebo

Group	n	mean	std	median	q1	q3	min	max	P-value*
20 MG WEEKLY	212	0.88	4.76	0.5	-0.5	2.00			0.051
40 MG BIWEEKLY	207	0.31	4.52	0.0	-1.0	2.00			.0054
PLACEBO	200	2.23	6.36	0.5	-0.5	3.25			

*: Adalimumab group vs. placebo group using The Wilcoxon rank sum test.

Sensitivity Analysis IV
Assigning the worst change (50.5) to patients treated with Adalimumab
Assigning the best change (-37.0) to patients treated with placebo

Group	n	mean	std	median	q1	q3	min	max	P-value*
20 MG WEEKLY	212	4.54	13.99	0.5	-0.5	2.00			0.8896
40 MG BIWEEKLY	207	5.93	16.79	0.0	-1.0	2.00			0.9669
PLACEBO	200	-2.88	15.16	0.5	-0.5	3.25			

*: Adalimumab group vs. placebo group using The Wilcoxon rank sum test.

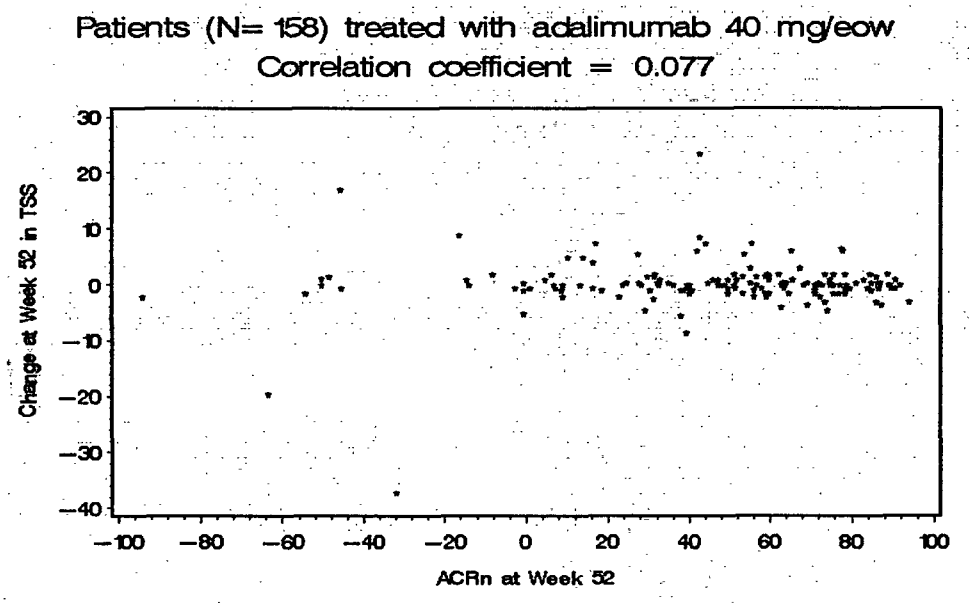
c. We define radiographic progression as having the change from baseline in TSS >0 and conducted the analyses for this endpoint. As shown in the following table, the percentages of progression in the adalimumab 40 mg groups were statistically significantly different ($p<0.01$) from placebo in the first two analyses. In the worst case analysis, where patients were treated as progression in the Adalimumab groups if missing and patients were considered as no progression in the placebo if missing, there were still fewer patients with radiographic progression in the adalimumab 40 mg group than that in the placebo group.

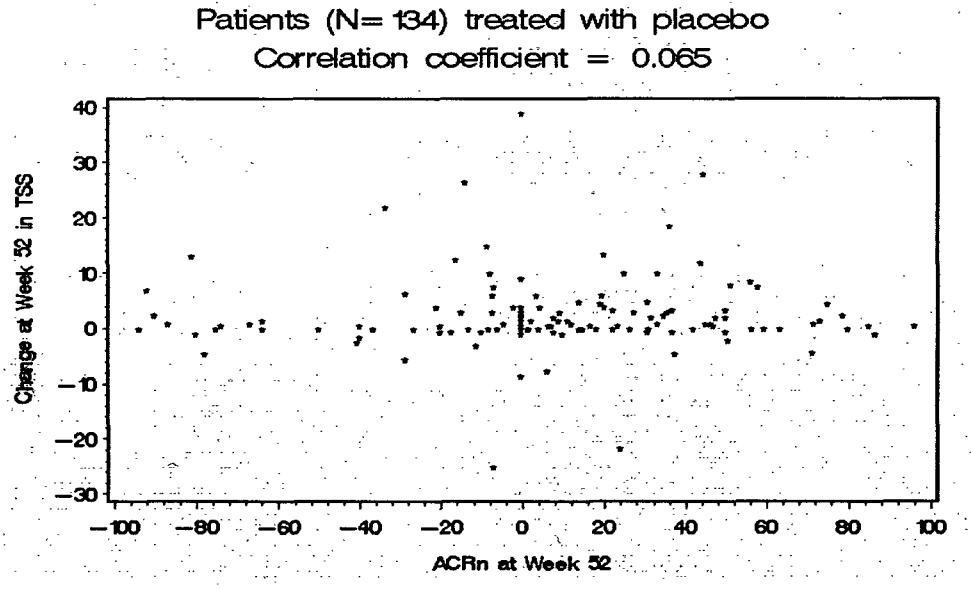
Patient's Progression Status at Month 12

	20 MG EVERY WEEK		40 MG BI-WEEKLY		PLACEBO PATIENTS	
	N	Progression(%)	N	Progression(%)	N	Progression(%)
Evaluable Patients	196	96 (49%)*	183	78 (43%)*	172	104 (60%)
Missing As Progression	212	112 (53%)*	207	102 (49%)*	200	132 (66%)
Worst Case	212	112 (53%)	207	102 (49%)	200	104 (52%)

*: P<0.05 when compared to the placebo group.

d. **Correlation between ACRn and TSS**: As shown in the following two figures, there were no correlations between ACRn and Change in TSS at Week 52.





3.0 HAQ

The third primary efficacy endpoint of disability index of the HAQ change at Week 52, was to be performed if the modified total Sharp x-ray score was significant at Week 52 ($p \leq 0.05$). Thus, the change in disability index of the HAQ total score was considered as the last tier in the hierarchy of the primary efficacy variables. If the testing of disability index of the HAQ was warranted, significance testing was to be done following the closure principle. The difference among all treatment groups was to be assessed using ANCOVA with the baseline value as the covariate. If this was significant ($p \leq 0.05$), pairwise comparisons between each active treatment group and placebo were to be evaluated using the same method.

An improvement in the disability index of the HAQ was represented by a negative mean change from baseline (i.e. decreased disease assessment). An overall comparison of the change from baseline in the disability index of the HAQ at Week 52 revealed a statistically significant difference ($p<0.001$) across the treatment groups, and permitted pairwise comparisons. After 52 weeks of treatment, each adalimumab dose group was associated with a statistically significant ($p<0.001$) improvement in observed disability index of the HAQ compared to placebo (Table 26). The response at Week 52 was comparable between the adalimumab 20 mg weekly and the 40 mg eow treatments. LOCF values demonstrated similar results.

Table 26 **Disability index of the HAQ at Week 52 by randomized treatment group (full analysis set)**

	Adalimumab					
	20 mg weekly		40 mg eow		Placebo	
Time point	N	Mean ± SD	N	Mean ± SD	N	Mean ± SD
Baseline	212	1.44 ± 0.64	206	1.45 ± 0.63	199	1.48 ± 0.59
Observed change at Week 52	168	-0.69 ± 0.55[a]	160	-0.64 ± 0.57[a]	140	-0.34 ± 0.54
LOCF change at endpoint	212	-0.61 ± 0.55[a]	204	-0.59 ± 0.57[a]	198	-0.25 ± 0.56

[a] Statistically significantly different from placebo ($p\leq0.001$).

Data source: Section 9, Tables 9.2.12a, 9.2.13a, 9.2.14a, and 9.2.15a

Subgroup analysis was conducted on the observed disability index of the HAQ at Week 52. The subgroups were based on gender (male, female), age (<65, ≥65), race (white, black, Asian, Hispanic, other), body weight (>70 kg, ≥70 kg), RF status at baseline (positive and negative), and corticosteroid use at baseline (yes and no). In each of the subgroups with at least 10 patients, patients treated with adalimumab consistently had larger improvements in their disability index of the HAQ score, as compared to those who received placebo. In a few instances, the number of patients within a specific subgroup was too small to allow for a valid comparison. In general, adalimumab's effectiveness was not affected by these subgroups.

3.1 Comments

a. This reviewer has checked the sponsor's analysis and found that the results agree with what the sponsor has presented.

b. 151 out of 619 patients (24%) did not have HAQ data for evaluation at Week 52. The sponsor excluded these patients in the primary analysis. In order to use all randomized patients (ITT principle), this reviewer conducted a variety of sensitivity analyses with different imputation approaches. As shown in the first two sensitivity analyses below, the changes from baseline in HAQ at Week 52 in the adalimumab 40 mg group were statistically significantly different ($p<0.01$) from those in the placebo group. In the third analysis, where the 75th percentile change was assigned patients treated with Adalimumab if missing and the 25th percentile change was assigned to patients treated with placebo, the improvement in the adalimumab groups was no longer better than that in the placebo

group.

Sensitivity Analysis I
Assigning the worst change (1.125) to all patients with missing values

Group	n	mean	std	median	q1	q3	min	max	P-value*
20 MG WEEKLY	212	-0.31	0.88	-0.50	-1.00	0.00			<0.0001
40 MG BIWEEKLY	207	-0.24	0.89	-0.38	-0.88	0.50			<0.0001
PLACEBO	200	0.10	0.81	0.00	-0.38	1.13			

*: Adalimumab group vs. placebo group using The Wilcoxon rank sum test.

Sensitivity Analysis II
Assigning the median change (-0.5) to all patients with missing values

Group	n	mean	std	median	q1	q3	min	max	P-value*
20 MG WEEKLY	212	-0.65	0.49	-0.5	-1.00	-0.38			<0.0001
40 MG BIWEEKLY	207	-0.61	0.50	-0.5	-0.88	-0.38			<0.0001
PLACEBO	200	-0.39	0.46	-0.5	-0.50	-0.13			

*: Adalimumab group vs. placebo group using The Wilcoxon rank sum test.

Sensitivity Analysis III
Assigning the 75th percentile change (-0.125) to Adalimumab treated patients
Assigning the 25th percentile change (-1.000) to placebo patients

Group	n	mean	std	median	q1	q3	min	max	P-value*
20 MG WEEKLY	212	-0.57	0.54	-0.50	-1.00	-0.13			0.9734
40 MG BIWEEKLY	207	-0.52	0.55	-0.38	-0.88	-0.13			0.2683
PLACEBO	200	-0.54	0.54	-0.63	-1.00	-0.13			

*: Adalimumab group vs. placebo group using The Wilcoxon rank sum test.

c. A change in HAQ of 0.25-0.35 has been shown to be clinically meaningful and corresponds to a change in functioning that a typical patient can notice. We consider improvement of 0.3-unit in HAQ from baseline at week 52 as important measurements. The analysis in the following table provides analyses on the proportion of patients that achieved an improvement from baseline in HAQ $\geq$ 0.3 at week 52 using various methodologies for handling missing data. In each of these analyses, patients in adalimumab groups demonstrated better improvement in HAQ, compared to the placebos except the worst-case analysis. We repeated this analysis using improvement of 0.3-unit in HAQ from baseline at Weeks 24 and 52 as the endpoint and obtained similar results.

Improvement from Baseline in HAQ $\geq$ 0.3 at Week 52

Methods of Handling Missing Data	Adalimumab 20 mg weekly (N=212)	Adalimumab 40 mg biweekly (N=207)	Placebo (N=200)
Missing as no improvement			
#Improvement (%)	126 (59%)	114 (55%)	66 (33%)
P-value vs. placebo	<0.001	<0.001	
Modified Worst Case*			
#Improvement (%)	126 (59%)	114 (55%)	94 (47%)
P-value vs. placebo	0.012	0.103	

The Worst Case			
#Improvement (%)	126 (59%)	114 (55%)	126 (63%)
P-value vs. placebo	0.458	0.104	

*: Placebo patients with missing data assigned individual best score, adalimumab patients with missing data assigned individual worst score.

Improvement from Baseline in HAQ ≥ 0.3 at Weeks 24 and 52

Methods of Handling Missing Data	Adalimumab 20 mg weekly (N=212)	Adalimumab 40 mg biweekly (N=207)	Placebo (N=200)
Missing as no improvement			
#Improvement (%)	115 (54%)	103 (50%)	55 (28%)
P-value vs. placebo	<0.001	<0.001	
Modified worst case*			
#Improvement (%)	115 (54%)	103 (50%)	79 (40%)
P-value vs. placebo	0.003	0.037	
The worst case			
#Improvement (%)	115 (54%)	103 (50%)	107 (54%)
P-value vs. placebo	0.879	0.450	

*: Placebo patients with missing data assigned individual best score, adalimumab patients with missing data assigned individual worst score.

4.0 Safety

The mean duration of exposure (313.2 days) for all patients who received adalimumab (316.2 days for the 20 mg weekly group and 310.0 days for the 40 mg eow group) was longer than that of patients who received placebo (286.3 days). Overall, the mean number of injections for adalimumab-treated patients was 44.8 (45.2 injections for the 20 mg weekly group and 44.4 injections for the 40 mg eow group) and was higher than placebo (40.5). Patients were exposed to a mean cumulative adalimumab dose of 895.5 mg (903.2 mg for the 20 mg weekly group and 887.6 mg for the 40 mg eow group).

An overview of patients with treatment-emergent AEs during the study is presented by treatment group for the safety set of patients in Table 53. A majority (92.4%) of the 619 randomized patients reported one or more treatment-emergent AEs. Overall, a total of 1581, 1564, and 1485 AEs were reported by the 20 mg weekly, 40 mg eow, and placebo treatment groups, respectively. With few exceptions, the percentages of patients who reported AEs were similar among the adalimumab and placebo treatment groups (i.e., there was not a ≥10% difference among the treatment groups). However, the percentage of patients with AEs considered by the investigators to be at least possibly related to study drug administration was higher (i.e., ≥10%) in the 40 mg adalimumab eow (57.5% of 207 patients) and the 20 mg adalimumab weekly (58.0% of 212 patients) treatment groups compared to the placebo treatment group (47.5% of 200 patients, $p<0.05$). Similarly, the percentage of patients who reported infectious AEs was higher in both

adalimumab treatment groups (66.5% of 212 patients in the 20 mg weekly group and 61.8% of 207 patients in the 40 mg eow group) than the placebo treatment group (50.5% of 200 patients, $p<0.05$). Although the number of adalimumab-treated patients who reported serious infectious AEs was not ≥10% higher than placebo-treated patients, the difference was statistically significant ($p<0.05$) between the 40 mg eow and placebo treatment groups.

Table 53 Overview of number (%) of patients with treatment-emergent adverse events (safety set)

	Adalimumab							
	20 mg weekly 186.7 pt-yrs (N=212)		40 mg eow 179.2 pt-yrs (N=207)		All adalimumab 365.5 pt-yrs (N=419)		Placebo 161.3 pt-yrs (N=200)	
Adverse event category[a]	N (%)	N/100 pt-yrs[b]	N (%)	N/100 pt-yrs[b]	N (%)	N/100 pt-yrs[b]	N (%)	N/100 pt-yrs[b]
Any AE	201 (94.8)	107.7	190 (91.8)	106.0	391 (93.3)	106.9	181 (90.5)	112.2
Any SAE	34 (16.0)	18.2	26 (12.6)	14.5	60 (14.3)	16.4	19 (9.5)	11.8
Any severe or life-threatening AE	55 (25.9)	29.5	42 (20.3)	23.4	97 (23.2)	26.5	37 (18.5)	22.9
Any at least possibly drug-related AE	123 (58.0)[c]	65.9	119 (57.5)[c]	66.4	242 (57.8)[c]	66.1	95 (47.5)	58.9
Any AE leading to death	1 (0.5)	0.5	2 (1.0)	1.1	3 (0.7)	0.8	0 (0.0)	0.0
Any AE leading to withdrawal	21 (9.9)	11.2	26 (12.6)	14.5	47 (11.2)	12.8	17 (8.5)	10.5
Any AE leading to dose interruption	59 (27.8)	31.6	42 (20.3)	23.4	101 (24.1)	27.6	50 (25.0)	31.0
Any infectious AE	141 (66.5)[c]	75.5	128 (61.8)[c]	71.4	269 (64.2)[c]	73.5	101 (50.5)	62.6
Any serious infectious AE	5 (2.4)	2.7	11 (5.3)[c]	6.1	16 (3.8)[c]	4.4	1 (0.5)	0.6
Any immunologic reaction	1 (0.5)	0.5	4 (1.9)	2.2	5 (1.2)	1.4	3 (1.5)	1.9
Any serious immunologic reaction	0 (0.0)	0.0	1 (0.5)	0.6	1 (0.2)	0.3	1 (0.5)	0.6
Any malignancies (including lymphoma)	5 (2.4)	2.7	3 (1.4)	1.7	8 (1.9)	2.2	1 (0.5)	0.6

[a] More than one AE category per patient possible.

[b] Statistical significance for N/100 pt-yrs data cannot be measured.

[c] Statistically significantly different from placebo ($p \leq 0.05$).

Post-study AEs (ie, occurring >30 days after withdrawal from the study) are included in the appendices and where noted in the text.

Data source: Section 9, Tables 9.3.5a and 9.3.8

SAEs were reported in 14.3% of 419 patients treated with adalimumab and in 9.5% of 200 patients treated with placebo. Severe or life-threatening AEs were reported in 23.2% of patients who received adalimumab and in 18.5% of patients who received placebo. Three adalimumab-treated patients (Patient #01705, 20 mg weekly, and Patients #01706 and #08702, both 40 mg eow) died of AEs experienced during the placebo-controlled period. Two of the deaths were judged by investigators to be possibly related to study drug: Patient #01705, a 63-year-old female in the 20 mg weekly group had a prior history of a chest mass/lump died during the post-study period following intensive chemotherapy for B-cell lymphoma and after experiencing severe pancytopenia; and Patient #08702, a 75-year-old female in the 40 mg eow group died during the placebo-controlled period following SAEs of *E. coli* urosepsis, septic shock, pancytopenia, and cardiac arrest. Patient #08702 had a prior history of anemia, urinary tract infection, obesity, cardiac dysrhythmia, cardiomyopathy, congestive heart failure, and cardiac murmurs that may have influenced the events leading to death.

A serious infectious AE was defined as any infection that resulted in patient hospitalization or treatment with iv antibiotics. A total of 19 serious infections were reported in 17 (2.7%) of 619 patients, including 16 (3.8%) of 419 adalimumab-treated patients (5 [2.4%] of 212 patients given 20 mg weekly and 11 [5.3%] of 207 patients given 40 mg eow) and 1 (0.5%) of 200 placebo-treated patients. The most frequently reported serious infectious AE (i.e., occurring in >1 patient) was pneumonia (6 [1.4%] of

419 adalimumab-treated patients and 1 [0.5%] of 200 placebo-treated patients). There were more serious infectious AEs overall in the adalimumab-treated patients than the placebo-treated patients.

PROTOCOL DE031

This was a multi-center, double-blind, randomized, placebo-controlled, parallel group, Phase III study in which adalimumab (40 mg) was subcutaneously (sc) administered every other week for up to 24 weeks to patients with RA who were not adequately treated with their current antirheumatic therapies. This study was designed to evaluate the safety and efficacy of adalimumab compared to a placebo control in patients with RA who were not adequately responding to other anti-rheumatic therapies. Patients continued to receive their pre-study dose of anti-rheumatic therapies. Anti-rheumatic therapies permitted for use during the study included DMARDs (hydroxychloroquine, leflunomide, methotrexate, parenteral gold, oral gold and sulfasalazine, or any combination of these or other DMARDs), NSAIDs and oral or intra-articular steroids. Doses of these DMARDs as well as concomitant prednisone and NSAIDs must have been stable for at least 28 days prior to screening.

A total of 600 patients were planned to be equally allocated to the two treatment groups, adalimumab 40 mg every other week and placebo. This sample size was chosen in order to increase the total number of patients exposed to adalimumab to approximately 300, thus allowing the study to be powered to show one adverse event with an incidence of 1% with at least 95% probability and with an incidence of 0.4% with at least 70% probability. Analysis of this enlarged safety database was intended for evaluation of any differences in AEs between patients treated with adalimumab *versus* standard rheumatologic care.

A total of 636 patients were randomized to double-blind treatment: 318 patients were randomized to adalimumab and 318 patients were randomized to placebo. A total of 578 (90.9%) of 636 randomized patients completed this study: 290 (91.2%) of 318 adalimumab-treated patients and 288 (90.6%) of 318 placebo treated patients. Fifty-eight (9.1%) of 636 patients were withdrawn from the study prematurely (8.8% on adalimumab and 9.4% on placebo).

Patients ranged in age from 21 to 86 years. The mean age of patients was 55.0 years in the adalimumab group and 55.8 years in the placebo group. There were more female (505 [79.4%] of 636) than male (131 [20.6%] of 636) patients. The majority (556 [87.4%] of 636 patients) were Caucasian; 80 (12.6%) of 636 patients were Black, Hispanic, Asian, or other races. The demographic characteristics of the study population were generally reflective of the overall RA population and were not significantly different between the treatment groups. The duration of RA for the study population was very broad. Patients randomized to adalimumab ranged in their duration of disease from 0.1 to 52 years (mean: 9.3, median: 6.7) and patients randomized to placebo ranged in their duration of disease from 0.2 to 59.1 years (mean: 11.5, median: 8.6).

1.0 Efficacy Endpoints

The ACR20 response at Week 24 was defined as the primary efficacy variable. All patients with missing visits or who withdrew from the study prematurely were counted as non-responders at the missing visits or from the time point of premature discontinuation

onwards in the primary analysis. ACR20 response rates of the adalimumab and placebo groups were compared using Pearson's chi-square test with a two-sided significance level of 0.05. After the completion of this study, Knoll learned that an investigator (Dr. — Site #7) was undergoing proceedings to be debarred. The sponsor decided to exclude patients in Site #7 (6 patients) from the primary efficacy analysis.

As shown in Table 34, The ACR20 response rate at Week 24 was 167 (53.0%) of 315 patients for the adalimumab group and 110 (34.9%) of 315 patients for the placebo group ($p<0.001$). When repeating the analysis with the data from all 636 patients (i.e., including Dr. — patients, ITT), the results are consistent with the primary analysis as indicated in Table 3.1.1a.

Table 34 ACR20 response rate: number (%) of patients responding over time by randomized treatment group (full analysis set, excluding Site #7)

Time point	Adalimumab (N=315) N (%)	Placebo (N=315) N (%)
Week 2	104 (33.0)[a]	27 (8.6)
Week 4	124 (39.4)[a]	55 (17.5)
Week 8	159 (50.5)[a]	76 (24.1)
Week 12	163 (51.7)[a]	93 (29.5)
Week 16	165 (52.4)[a]	100 (31.7)
Week 20	177 (56.2)[a]	107 (34.0)
Week 24	167 (53.0)[a]	110 (34.9)
LOCF Week 24	172 (54.6)	112 (35.6)

[a] Statistically significantly different from placebo ($p<0.001$).

Patients with an initiation of a new DMARD were counted as non-responders after initiation of DMARD.

Data source: Section 9, Table 9.3.1a, Appendix 1.9.2a

Table 3.3.1a Summary of response according to ACR20. Full analysis set patients

Analysis (1)	Visit	Adalimumab (N=318) N	(%)	Placebo (N=318) N	(%)	Adalimumab-Placebo (%)	95% conf. int.
Observed	Week 2	104	(32.7)	29	(9.1)	(23.6)	[17.5; 29.6]
	Week 4	125	(39.3)	57	(17.9)	(21.4)	[14.6; 28.2]
	Week 8	161	(50.6)	77	(24.2)	(26.4)	[19.2; 33.7]
	Week 12	164	(51.6)	94	(29.6)	(22.0)	[14.6; 29.5]
	Week 16	166	(52.2)	102	(32.1)	(20.1)	[12.6; 27.6]
	Week 20	177	(55.7)	108	(34.0)	(21.7)	[14.2; 29.2]
	Week 24	168	(52.8)	111	(34.9)	(17.9)	[10.3; 25.5]
LOCF	Week 2	106	(33.3)	29	(9.1)	(24.2)	[18.1; 30.3]
	Week 4	126	(39.6)	57	(17.9)	(21.7)	[14.9; 28.5]
	Week 8	163	(51.3)	78	(24.5)	(26.7)	[19.5; 34.0]
	Week 12	166	(52.2)	95	(29.9)	(22.3)	[14.9; 29.8]
	Week 16	171	(53.8)	103	(32.4)	(21.4)	[13.9; 28.9]
	Week 20	182	(57.2)	109	(34.3)	(23.0)	[15.4; 30.5]
	Week 24	174	(54.7)	113	(35.5)	(19.2)	[11.6; 26.8]

Subgroup analyses for potential factors influencing the ACR20 response rate were conducted for gender, age, ethnicity, and concomitant treatment with MTX, antimalarial drugs, leflunomide, sulfasalazine, concomitant DMARDs (i.e., 0, 1, 2, or >3), and other DMARDs (see Table 35). In each of the demographics subgroups, patients treated with adalimumab consistently had larger changes in their ACR20 response, as compared to those who received placebo when there were at least 10 patients within a specific subgroup.

Table 35 Subgroup analysis at Week 24 for ACR20 (full analysis set, excluding Site #7)

	ACR20			
	Adalimumab		Placebo	
Concomitant medication	Total N	% Response	Total N	% Response
Methotrexate	178	56.7	199	35.2
Antimalarial	75	50.7	82	32.9
Leflunomide	42	33.3	46	37.0
Sulfasalazine	29	58.6	33	24.2
Other DMARDs	25	52.0	25	44.0
No DMARD	54	50.0	45	33.3
One DMARD	184	55.4	172	37.8
Two DMARDs	66	50.0	84	29.8
Three or more DMARDs	11	45.5	14	35.7

Antimalarial (eg, HCG, chloroquine)

Data source: Section 9, Tables 9.3.1e-f

As shown in Table 35, adalimumab patients taking concomitant MTX, antimalarial treatments, or sulfasalazine or other DMARDs demonstrated a higher ACR20 response rate compared to placebo patients. Adalimumab patients taking concomitant leflunomide had a similar ACR20 response rate to placebo at Week 24 (33.3% and 37.0%, respectively). The lower response rate at Week 24 for adalimumab patients treated with leflunomide may have been influenced by the higher number of patient withdrawals in the adalimumab plus concomitant leflunomide group. Of the patients receiving concomitant leflunomide, 7 of 42 (16.7%) adalimumab-treated patients but only 3 of 46 (6.5%) placebo-treated patients were withdrawn from the study prematurely. There was no pattern of reasons for withdrawal in either group. Of note, three of the adalimumab-treated early withdrawal patients had demonstrated ACR20 responses prior to being withdrawn, compared to one of the placebo-treated early withdrawal patients. In addition, there was no difference in the incidence of "clinical flare reaction" AEs in the adalimumab-treated patients compared to the placebo-treated patients (7.1% vs. 6.5%, respectively). The placebo plus concomitant leflunomide group had an increase in ACR20 response from Week 12 to 24, which may have been due to the greater use of rescue steroids in this group. Among patients taking concomitant leflunomide, 5 of 46 (10.9%) placebo patients but only 1 of 42 (2.4%) adalimumab patients received rescue steroid treatment before reaching ACR20 criteria. Therefore, the early withdrawals may have decreased the overall adalimumab-treated patient response while rescue steroid use may have increased the placebo-treated patient response.

1.1 Comments

a. The benefit of treating patients with RA in this trial appears to be similar to that in Study DE019. This reviewer has checked the sponsor's analysis and found that the results agree with what the sponsor has presented.

b. **Characteristics of patients who used concomitant leflunomide**: This reviewer compared some characteristic of patients treated with concomitant leflunomide between the two groups. It appears that patients treated with adalimumab had more number of tender joints at baseline, shorter duration of exposed to the study drug, and a higher rate of injection site reaction, as compared to the controls. These factors may have decreased the response rate in the adalimumab group.

Some Characters of Patients Who Used Concomitant Leflunomide

Variables	40 mg eow (N= 42)		Placebo (N = 46)		P-value*
	n	%	n	%	
Use of MTX at baseline	10	24%	18	39%	0.123
Rheumatoid Factor +	31	74%	37	80%	0.459
Injection Site Reaction	4	10%	0	0%	0.048
	Mean	SD	Mean	SD	
CRP at baseline	20	32	16	16	0.904
Swollen Joints at baseline	22	13	24	12	0.452
Tender Joints at baseline	30	12	25	13	0.048
Days of exposed to Drug	157	38	165	22	0.0285
Duration of RA	127	77	145	92	0.452

*: Chi-square test for dichotomous variables and Wilcoxon Rank Sum test for continuous variables.

2.0 Safety

The mean duration (23.2 weeks *vs.* 23.0 weeks) and total number of injections of study drug (12.0 *vs.* 12.0) were comparable in patients who received adalimumab or placebo. The mean total dose of adalimumab administered during the study was 481.4 mg. Table 17 shows that comparable percentages of patients in the adalimumab (86.5% of 318 patients) and placebo (82.7% of 318 patients) treatment groups reported one or more treatment-emergent AEs during the study. The percentage of patients with AEs considered to be at least possibly related to study drug according to the investigator's assessment was higher in the adalimumab group (46.2%) than in the placebo group (34.9%); this difference was statistically significant. This statistical significance was maintained when AEs at least possibly related to study drug were analyzed without injection site reaction. Injection site reaction was statistically significantly greater in patients receiving adalimumab than in patients receiving placebo.

In contrast, the incidence of both SAEs and severe or life-threatening AEs was higher in the placebo-treated group than the adalimumab-treated group (6.9% vs. 5.3% and 15.4% vs. 11.9%, respectively), although these differences did not reach statistical significance. One death due to an AE was reported during the study. Patient #15106, treated with adalimumab, died following SAEs of herpes zoster, followed by streptococcal superinfection (necrotizing fasciitis). There were no significant differences in the incidences of severe or life-threatening AEs, SAEs, or deaths between the two treatment groups.

Table 17 Overview of patients with treatment-emergent AEs (safety set)

	Adalimumab (N = 318) (141.2 pt-yrs)		Placebo (N = 318) (139.9 pt-yrs)		Adalimumab *vs.* Placebo
Patients with any[a]	N (%)	N/100 pt-yrs[b]	N (%)	N/100 pt-yrs[b]	p<0.05[c]
AE	275 (86.5)	194.8	263 (82.7)	188.0	-
AE leading to death	1 (0.3)	0.7	0 (0.0)	0.0	-
SAE	17 (5.3)	12.0	22 (6.9)	15.7	-
AE resulting in withdrawal	9 (2.8)	6.4	7 (2.2)	5.0	-
AE resulting in dose interruption	38 (11.9)	26.9	27 (8.5)	19.3	-
Severe or life-threatening AE	38 (11.9)	26.9	49 (15.4)	35.0	-
At least possibly drug-related AE	147 (46.2)	104.1	111 (34.9)	79.3	Yes
Infection	166 (52.2)	117.6	157 (49.4)	112.2	-
Serious infection	4 (1.3)	2.8	6 (1.9)	4.3	-
Malignancy	4 (1.3)	2.8	0 (0.0)	0.0	Yes
Immunologic reaction	1 (0.3)	0.7	1 (0.3)	0.7	-
AE except injection site reaction	270 (84.9)	191.2	258 (81.1)	184.4	-
At least possibly drug-related AE except injection site reaction	117 (36.8)	82.9	89 (28.0)	63.6	Yes

[a] More than one AE per patient possible.

[b] Number of patients with AEs per 100 patient-years.

[c] Pearson's χ^2 test.

Data source: Section 9, Table 9.2.4a

Similar rates of infections were observed in the two treatment groups. A total of 166 (52.2%) of 318 adalimumab-treated and 157 (49.4%) of 318 placebo treated patients reported infections during the study. Infections were considered to be serious in 4 (1.3%) patients receiving adalimumab and in 6 (1.9%) patients receiving placebo. Malignancies were reported in 4 (1.3%) adalimumab-treated patients (3 cases of basal cell carcinoma of the skin and one case of T-cell lymphoma) and in no placebo-treated patients (see Section 5.3.4.3 for details). An immunologic reaction (fixed eruption) was reported in one adalimumab-treated patient (Patient #9003). The incidence of infections was similar for patients in the adalimumab and placebo treatment groups.

PROTOCOL DE009

DE009 was a multicenter, double-blind, randomized, placebo-controlled study designed to compare the effects of adalimumab at several dose levels over 24 weeks in patients with RA on stable treatment with MTX. A washout period was chosen so all patients would be on a standard DMARD regimen prior to receiving study drug. This was done to assure comparability of the treatment groups. Patients were prohibited from taking any concomitant anti-heumatic/ anti-inflammatory drugs except MTX and corticosteroids.

This study was designed to determine if there was a significantly higher ACR20 response rate for three doses of adalimumab (20, 40, or 80 mg every other week, sc) compared to placebo. The primary efficacy endpoint of this study was the ACR20 response at Week 24.

A total of 271 patients (full analysis set) were randomized into the double-blind, placebo-controlled period of the study at 35 sites, as follows: 209 (77.1%) of 271 patients were randomized to adalimumab (69 [25.5%] patients in the 20 mg group, 67 [24.7%] patients in the 40 mg group, and 73 [26.9%] patients in the 80 mg group) and 62 (22.9%) of 271 patients were randomized to placebo.

1.0 Efficacy Endpoint

The primary efficacy endpoint of this study was ACR20 at Week 24. Patients who withdrew from the study prior to Week 24 due to AEs were counted as non-responders. Patients who rolled over into open label study, DE009, at Week 16 or 20 were considered non-responders for the Week 24 analysis. The primary efficacy analysis was a comparison of the ACR20 response rates at Week 24 between each of the adalimumab treatment groups and placebo on the intent-to-treat population using a Pearson's Chi-square test.

After 24 weeks of treatment, each adalimumab treatment group (20, 40, and 80 mg) was statistically significantly superior ($p<0.05$) to placebo for the ACR20 response (Table 21). The response at Week 24 was comparable between the 40 and 80 mg doses and was slightly lower for the 20 mg dose. In comparison, fewer placebo-treated patients showed improvement at Week 24. Week 24 LOCF data demonstrated similar values between adalimumab and placebo relative to observed values.

Table 21 ACR20 response: Number (%) of patients responding over time by randomized treatment group (full analysis set, excluding Site #7)

	Adalimumab			
Time point	20 mg (N=67)	40 mg (N=63)	80 mg (N=70)	Placebo (N=60)
Week 24 (observed)	32 (47.8)[a]	42 (66.7)[a]	46 (65.7)[a]	8 (13.3)
LOCF Week 24	34 (50.7)[a]	42 (66.7)[a]	46 (65.7)[a]	8 (13.3)

[a] Statistically significantly different from placebo ($p \leq 0.05$).

Data source: Section 9, Tables 9.2.1.a, 9.2.24a, and 9.2.35a, Appendix 2.6.4

1.1 Comments

This reviewer has checked the sponsor's analysis and found that 41 patients in the 40 mg group reached an ACR20 response instead of 42 patients as presented in Table 21. This discrepancy would not have an impact on drawing a conclusion. In addition, the sponsor used 41 patients (65.1%), the correct number, in the proposed Package Insert.

2.0 Safety Evaluation

Patients receiving adalimumab had a longer mean duration of treatment (151.9 days) than patients receiving placebo (124.0 days). The mean duration of treatment was similar among adalimumab groups and each adalimumab treatment group had greater duration than placebo. An overview of patients with treatment-emergent AEs is presented in Table 29.

Table 29 Overview of number (%) of patients with treatment-emergent adverse events (safety set)

	Adalimumab								Placebo	
	20 mg eow 27.4 pt years (N=69		40 mg eow 28.2 pt years (N=67)		80 mg eow 31.4 pt years (N=73)		All adalimumab 87.0 pt years (N=209)		21.0 pt years (N=62)	
AE category	N (%)	N/100 pt years	N (%)	N/100 pt years	N (%)	N/100 pt years	N (%)	N/100 pt years	N (%)	N/100 pt years
Any adverse event (AE)	65 (94.2)	237.1	59 (88.1)	209.4	64 (87.7)	204.2	188 (90.0)	216.2	49 (79.0)	232.9
Any serious AE	2 (2.9)[b]	7.3	3 (4.5)	10.7	6 (8.2)[b]	19.1	11 (5.3)	12.7	1 (1.6)	4.8
Any severe AE	13 (18.8)	47.4	5 (7.5)	17.8	6 (8.2)	19.1	24 (11.5)	27.6	2 (3.2)	9.5
Any life threatening AE	0 (0.0)	0.0	0 (0.0)	0.0	1 (1.4)	3.2	1 (0.5)	1.2	0 (0.0)	0.0
Any at least possibly drug-related AE	38 (55.1)	138.6	34 (50.7)	120.7	35 (47.9)	111.6	107 (51.2)	123.1	22 (35.5)	104.6
Any AE leading to death	0 (0.0)	0.0	0 (0.0)	0.0	0 (0.0)	0.0	0 (0.0)	0.0	0 (0.0)	0.0
Any AE leading to withdrawal	4 (5.8)	14.6	0 (0.0)	0.0	1 (1.4)	3.2	5 (2.4)	5.8	2 (3.2)	9.5
Any AE resulting in dose reduction	0 (0.0)	0.0	0 (0.0)	0.0	0 (0.0)	0.0	0 (0.0)	0.0	0 (0.0)	0.0
Any AE resulting in additional concurrent medication	55 (79.7)	200.7	44 (65.7)	156.2	55 (75.3)	175.4	154 (73.7)	177.1	38 (61.3)	180.6
Any AE resulting in dose increase	0 (0.0)	0.0	0 (0.0)	0.0	0 (0.0)	0.0	0 (0.0)	0.0	0 (0.0)	0.0
Any AE leading to dose interruption	2 (2.9)	7.3	7 (10.4)	24.9	14 (19.2)	44.7	23 (11)	26.5	3 (4.8)	14.3
Any infectious AE	45 (65.2)	164.2	40 (59.7)	142.0	50 (68.5)	159.5	135 (64.6)	155.3	29 (46.8)	137.8
Any serious infectious AE	0 (0.0)	0.0	1 (1.5)	3.6	1 (1.4)	3.2	2 (1.0)	2.3	0 (0.0)	0.0
Any malignancy	0 (0.0)	0.0	0 (0.0)	0.0	1 (1.4)	3.2	1 (0.5)	1.2	0 (0.0)	0.0
Any immunologic reaction	0 (0.0)	0.0	1 (1.5)	3.6	0 (0.0)	0.0	1 (0.5)	1.2	1 (1.6)	4.8

[a] No statistically significant difference among treatment groups by chi-square test (p>0.05, Section 9, Table 9.3.54a).
[b] Two events, arthralgia (20 mg adalimumab) and clinical flare reaction (80 mg adalimumab), resulted in elective total joint replacement surgeries that were performed during the continuation study, DE009X. Since the symptoms leading to the surgeries started during this study, the SAEs are counted here.
Data source: Section 9, Table 9.3.5 and Table 9.3.5h

No patients died during the placebo-controlled treatment period. SAEs were reported in 11 (5.3%) adalimumab-treated patients and 1 (1.6%) placebo- treated patient. Severe or life-threatening AEs were reported in 25 (12.0%) of 209 adalimumab-treated patients and 2 (3.2%) of 62 placebo-treated patients. Upon examination of exposure-adjusted data, differences were clinically significant for SAEs (i.e., 12.7 *vs.* 4.8 patients/100 pt-yrs in the all adalimumab and placebo treatment groups, respectively) and severe AEs (27.6 *vs.* 9.5 patients/100 pt-yrs in the all adalimumab and placebo treatment groups, respectively). A total of 2 (1.0%) of 209 adalimumab-treated patients (1 [1.5%] of 67 patients given 40 mg and 1 [1.4%] of 73 patients given 80 mg) and no placebo-treated patients experienced SAEs of an infectious nature. Overall, 135 (64.6%) of 209 adalimumab-treated patients and 29 (46.8%) of 62 placebo-treated patients reported one or more non-serious infectious AEs after study drug administration.

PROTOCOL DE011

DE011 was a multicenter, double-blind, placebo-controlled study in Europe for assessing the effects of adalimumab at 20 and 40 mg given every week or every other week sc for 26 weeks in patients with RA. This study was designed to confirm the effectiveness of every week and every other week dosing of adalimumab at 20 and 40 mg (monotherapy), compared to placebo in patients not taking MTX.

Patients were assessed for study entry (screen visit) and qualified patients entered the washout period. A washout period was chosen to eliminate other DMARDs/SAARDs that might interact with adalimumab or obscure the effect of adalimumab. A total of 544 patients entered the double-blind placebo-controlled period. Of the patients randomized to double-blind treatment, 434 patients were randomized to adalimumab (106 patients to the 20 mg every other week [eow] dose group, 112 to the 20 mg weekly dose group, 113 to the 40 mg eow group, 103 to the 40 mg weekly group) and 110 were randomized to placebo.

The study design consisted of four parts or periods. Eligible patients began the study by entering, at maximum, a 4-week **washout period** in which DMARDs and slow acting anti-rheumatic drugs (SAARDs) were withdrawn. Patients who had been off DMARDs for more than 3 weeks at the study entry visit had only a 1-week washout period. NSAIDs and corticosteroids equivalent to a maximum of 10 mg prednisolone per day were allowed to be continued but were required to remain unchanged in dose until the end of the study. Patients returned to the site after the washout period for the baseline visit.

The baseline visit signified the beginning of the double-blind **placebo-controlled treatment period**. At this visit patients were randomized to one of five cohorts of approximately 100 patients each. Four cohorts received sc injections of either 20 or 40 mg adalimumab every week or every other week and one cohort received placebo. Each dose of study drug was self administered (or given by a qualified person) in a single injection of 1.6 mL, every week for up to 26 weeks; patients randomized to receive adalimumab every other week received a placebo injection on alternate weeks.

Patients who experienced an increase in disease activity or had less than 10% reduction in SJC and TJC compared to baseline, after at least 8 weeks of treatment, had the option to enter the **rescue part** of the study. Adalimumab/placebo treatment was stopped and, at the discretion of the treating physician, these patients could receive higher doses of NSAIDs, corticosteroids, or DMARDs through the remainder of the 26-week placebo controlled treatment period.

At the end of the 26-week placebo-controlled treatment period these patients were eligible to rollover into continuation Study DE018 and receive open-label adalimumab treatment. Patients who permanently withdrew from Study DE011 at any time entered the **post-study period** and were examined at 1, 2, 3, and 6 months after their last injection of adalimumab/placebo in order to evaluate the long-term safety profile of adalimumab. If during the post-study period, patients participated in a consecutive trial with another investigational agent (which started at least

2 months after their last injection of adalimumab/placebo) then no further post-study documentation was collected.

1.0 Efficacy Endpoints

The primary efficacy endpoint was the ACR20 response. The primary efficacy analysis was a comparison of the response rates at visit 10 (26 weeks after first injection) according to ACR20 between the four active treatment groups and placebo. Patients who did not complete the 6-month placebo-controlled period in their original group assignment (drop-outs or patients who entered the rescue part) or patients with missing data were counted as non-responders. Each of the four active treatment groups was tested for difference *vs.* placebo using a two-sided Pearson's Chi-square test with a two-sided overall significance level of 0.05. Due to the multiple testing, a p-value from each test was judged using the Bonferroni-Holm procedure for statistical significance.

After 26 weeks of treatment, every adalimumab treatment group (every week or eow treatment with 20 or 40 mg) was statistically significantly superior ($p<0.05$) to placebo for the ACR20 response (20 mg eow: $p=0.006$; 20 mg weekly: $p<0.001$; 40 mg eow: $p<0.001$; 40 mg weekly: $p<0.001$; these p-values are significant when judged against the Bonferroni-Holm procedure).

Table 20 ACR20 response: Number (%) of patients responding by randomized treatment group (full analysis set)

	Adalimumab				
Time point	20 mg eow (N=106)	20 mg weekly (N=112)	40 mg eow (N=113)	40 mg weekly (N=103)	Placebo (N=110)
Observed Week 26	38 (35.8)[a, b]	44 (39.3)[a, b]	52 (46.0)[a, b]	55 (53.4)[a, b, c]	21 (19.1)
LOCF Week 26	40 (37.7)[a]	48 (42.9)[a]	53 (46.9)[a]	56 (54.4)[a]	23 (20.9)

[a] Statistically significantly different from placebo based on 98.75% confidence intervals ($p\leq0.05$).
[b] Statistically significantly different from placebo based on Pearson's χ^2 test ($p\leq0.05$).
[c] Statistically significantly different from 20 mg eow and 20 mg weekly based on Pearson's χ^2 test ($p\leq0.05$).

Data source: Section 9, Table 9.2.1.a, Section 10, Appendix 1.9.2a and Appendix 2.6.6.

Secondary endpoints included ACR50, ACR70, changes in each individual component of the ACR measures at Week 26, etc. Similarly, ACR50 and ACR70 response rates were also statistically significantly greater than placebo at all doses tested ($p<0.05$). In addition to the composite ACR responses, individual components of the ACR measures were also statistically significantly improved in adalimumab treated patients as compared to placebo-treated patients at all adalimumab doses, with the exception of the 20 mg eow dose, which demonstrated a slightly lower degree of efficacy.

1.1 Comments

a. This is the only randomized trial without concomitant MTX. The results show that adalimumab is effective in treating RA patients when used alone.

b. This reviewer has checked the sponsor's analysis and found that the results agree with what the sponsor has presented.

2.0 Safety Evaluation

The mean duration of exposure for patients receiving adalimumab (162.0 days) was longer than that of patients receiving placebo (133.9 days). Similarly, within the adalimumab dose groups, the group with the longest duration of treatment (172.4 days for the 40 mg weekly group) was slightly longer than that of the group with the shortest duration (152.4 days for the 20 mg eow group). This ordering reflects the relative numbers of patients entering the rescue period.

An overview of patients with treatment-emergent AEs during the study is presented by treatment group in Table 33. Of the 14 AE parameters, three showed a statistically significantly ($p \leq 0.05$ by Pearson's Chi-square test) higher percentage in the all adalimumab patient group than in patients who received placebo: AEs, AEs at least possibly related to study drug, and AEs leading to temporary withdrawal. AEs leading to switching to the rescue period occurred at a statistically significantly higher percentage in placebo-treated patients than in patients who received adalimumab.

Table 33 Overview of number (%) of patients with treatment-emergent AEs (safety set)

	Adalimumab										Placebo	
	20 mg eow 44.24 pt-yrs (N=106)		20 mg weekly 49.58 pt-yrs (N=112)		40 mg eow 50.07 pt-yrs (N=113)		40 mg weekly 48.61 pt-yrs (N=103)		All adalimumab 192.5 pt-yrs (N=434)		40.34 pt-yrs (N=110)	
Patients with any *	N (%)	N/100 pt-yrs	N (%)	N/100 pt-yrs	N (%)	N/100 pt-yrs	N (%)	N/100 pt-yrs	N (%)	N/100 pt-yrs	N (%)	N/100 pt-yrs
AE	105 (99.1)	237.4	110 (98.2)	221.9	112 (99.1)	223.7	102 (99.0)	209.9	429 (98.8)*	222.9	105 (95.5)	260.3
Serious AE (SAE)	11 (10.4)	24.9	18 (16.1)	36.3	13 (11.5)	26.0	11 (10.7)	22.6	53 (12.2)	27.5	16 (14.5)	39.7
Severe or life-threatening/intractable AE	30 (28.3)	67.8	28 (25.0)	56.5	27 (23.9)	53.9	21 (20.4)	43.2	106 (24.4)	55.1	25 (22.7)	62.0
At least possibly drug- related AE	73 (68.9)	165.0	73 (65.2)	147.2	74 (65.5)	147.8	69 (67.0)	142.0	289 (66.6)*	150.1	49 (44.5)	121.5
AE leading to death	0 (0.0)	0.0	0 (0.0)	0.0	2 (1.8)	4.0	1 (1.0)	2.1	3 (0.7)	1.6	1 (0.9)	2.5
AE leading to permanent withdrawal	5 (4.7)	11.3	6 (5.4)	12.1	7 (6.2)	14.0	5 (4.9)	10.3	23 (5.3)	11.9	3 (2.7)	7.4
AE leading to temporary withdrawal	13 (12.3)	29.4	14 (12.5)	28.2	15 (13.3)	30.0	15 (14.6)	30.9	57 (13.1)*	29.6	4 (3.6)	9.9
AE leading to dose reduction	0 (0.0)	0.0	1 (0.9)	2.0	0 (0.0)	0.0	0 (0.0)	0.0	1 (0.2)	0.5	0 (0.0)	0.0
AE leading to dose increase	0 (0.0)	0.0	0 (0.0)	0.0	0 (0.0)	0.0	0 (0.0)	0.0	0 (0.0)	0.0	0 (0.0)	0.0
AE leading to switch to rescue period	7 (6.6)	15.8	7 (6.3)	14.1	4 (3.5)	8.0	0 (0.0)	0.0	18 (4.1)*	9.4	11 (10.0)	27.3
Infection	48 (45.3)	108.5	51 (45.5)	102.9	56 (49.6)	111.8	50 (48.5)	102.9	205 (47.2)	106.5	43 (39.1)	106.6
Serious infection	2 (1.9)	4.5	5 (4.5)	10.1	1 (0.9)	2.0	2 (1.9)	4.1	10 (2.3)	5.2	0 (0.0)	0.0
Malignancy	1 (0.9)	2.3	0 (0.0)	0.0	2 (1.8)	4.0	1 (1.0)	2.1	4 (0.9)	2.1	1 (0.9)	2.5
Immunologic reaction	1 (0.9)	2.3	1 (0.9)	2.0	1 (0.9)	2.0	1 (1.0)	2.1	4 (0.9)	2.1	0 (0.0)	0.0

* More than one AE per patient possible.
* Comparison *versus* placebo (Pearson's χ^2 test): $p \leq 0.05$.
Data source: Section 9, Table 9.3.1.4a

SAEs were reported in 12.2% (27.5 patients/100 pt-yrs) of patients treated with adalimumab and in 14.5% (39.7 patients/100 pt-yrs) of patients treated with placebo. Severe or life-threatening/intractable AEs were reported in 24.4% (55.1 patients/100 pt-yrs) of patients receiving adalimumab and in 22.7% (62.0 patients/100 pt-yrs) of patients receiving placebo. Four patients died during the placebo-controlled period of the study; 3 (0.7%; 1.6 patients/100 pt-yrs) of 434 of these patients were receiving adalimumab and 1 (0.9%; 2.5 patients/100 pt-yrs) of 110 patients was receiving placebo.

3.0 HAHA issues

A patient was defined as Human anti-human antibodies (HAHA) positive if there was a HAHA value of >20 ng/mL during the placebo-controlled period. HAHAs were examined in Studies DE009, DE011, and DE019. A total of 1062 patients treated with adalimumab and 372 patients treated with placebo had serum samples analyzed for

HAHAs in these three adequate and well-controlled studies. In Studies DE009 and DE019, only 4 (0.6%) of 628 patients treated with adalimumab were HAHA(+) on at least one occasion during the active treatment phase of the studies due to the concomitant use of MTX. In Study DE011, in which adalimumab was given as monotherapy, 54 (12.4%) of 434 patients treated with adalimumab were HAHA(+) on at least one occasion during the active treatment phase of the study, 378 were HAHA(-), and two did not HAHA data. Since use of MTX can suppress the expression of HAHA and only a few patients with HAHA(+) in Studies DE009 and DE019, we used HAHA data from the study without MTX, i.e., Study DE011, for further analyses.

3.1 **Relationship between HAHA and ACR20 response at Week 26:** The ACR20 response rate among the patients who were HAHA positive was lower than those who did not develop HAHA as shown in the following table. This raises a concern that the development of HAHA may have a negative impact on the efficacy of adalimumab.

Relationship between HAHA and ACR20 Response at Week 26—Study DE011

	HAHA Positive		HAHA Negative		P-value
	N	ACR20 (%)	N	ACR20 (%)	
Adalimumab patients	54	14 (26%)	378	175 (46%)	0.0048
20 mg biweekly	19	7 (37%)	87	31 (35%)	0.921
20 mg weekly	11	1 (9%)	101	43 (43%)	0.048
40 mg biweekly	20	6 (30%)	92	46 (50%)	0.104
40 mg weekly	4	0 (0%)	98	55 (56%)	0.042
Placebo	0	0 (0%)	110	21 (19%)	----

3.2 **Relationship between HAHA development and adalimumab administration:** The following table shows the apparent greater immunogenicity (HAHA) observed with biweekly administration of adalimumab compared to the weekly administration. It appears that HAHA development may depend on the frequency of administration.

Relationship between HAHA and Adalimumab—Study DE011

	N	HAHA + (%)	P-value
All patients			
Weekly	214	15 (7%)	0.0006
Biweekly	218	39 (18%)	
Subgroup			
20 mg weekly	112	11 (10%)	0.0816
40 mg biweekly	112	20 (18%)	

CONCLUSIONS

1. The data from the four controlled studies consistently showed the efficacy of adalimumab on the primary clinical endpoint of ACR20 at Weeks 24 or 26. Adalimumab is effective in reducing signs and symptoms in adult patients with moderately to severely active RA.

2. In Study DE019, the magnitude of change from baseline to Week 52 in modified total Sharp x-ray score, joint space narrowing score, and erosion score associated with adalimumab was smaller and was statistically significantly different from placebo. Adalimumab is effective in inhibiting the progression of structural damage in RA patients.

3. It appears that adalimumab treatment was associated with slightly higher incidences of infections (both serious and non-serious) and malignancies.