Table 19 : Study DE019 : Maintenance of ACR20 Response at Week 52 For Patients Who Were Responders At Week 24 By Treatment Group

	Responders		
	Adalimumab		
	20 mg weekly (N=212)	40 mg q2w (N=207)	Placebo (N=200)
	N (%)	N (%)	N (%)
ACR20 Response at Week 24 (Based on all randomized patients)	**129 (61%)**	**131(63%)**	**59 (30%)**
ACR20 Response at Week 52 (Based on all randomized patients)			
Total	116 (55%)	122 (59%)	48 (25%)
Maintained from Week 24	107 (51%)	117 (57%)	37 (19%)
Not maintained from Week 24	9 (4%)	5 (2%)	11 (6%)
Percentage of Responders Maintained from Week 24 Through Week 52	**107/129 (83%)**	**117/131 (89%)**	**37/59 (63%)**

The percentage of ACR20 responses by treatment subsets among 40 mg q2w adalimumab-treated patients at Week 24 was uniformly greater than among placebo-treated patients with a few exceptions, i.e. among Blacks and Hispanics. Among the adequate and well-controlled groups, the ACR20 response for Blacks at Week 24 (36%, 11/31) resembled that for placebo (34%, 11/32). However, ACR20 responses among Blacks were higher than for placebo at six time-points earlier than Week 24 (Week 2 [39% vs. 13%], Week 4 [42% vs. 19%], Week 8 [52% vs. 28%], Week 12 [45% vs. 25%], Week 16 [48% vs. 31%], and Week 20 [39% vs. 31%]). In addition, comparison of the change in TSS (radiologic progression) between adalimumab- and placebo-treated patients revealed the highest rate of progression among Black placebo-treated patients (7.7u/yr) and a markedly reduced rate of progression among Black adalimumab-treated patients (0.4 u/yr) [Table 22]. Therefore, the data indicate that Black patients did have a response to adalimumab treatment. Patients subsetted based on weight, RF positivity, and corticosteroid use had similar responses to adalimumab (approximately 60%) as the study population as a whole (Table 20).

Table 20 : Study DE019 : ACR20 Responders at Week 24 by Treatment Subsets

	Adalimumab 40 mg Q2w		Placebo	
	N	%	N	%
Males	35	71	18	33
Females	96	61	41	28
Age				
< 65 years	93	66	48	31
≥ 65 years	42	65	13	29
Race				
White	111	64	39	24
Black	5	36	5	39
Asian	4	80	1	50
Hispanic	3	23	6	40
Other	1	50	1	25
Weight				
≤ 70 kg	56	62	14	18
≥ 70 kg	75	64	45	37
RF positive	110	66	54	30
RF negative	26	67	7	33
Corticosteroid use +	56	62	31	31

b. Modified Total Sharp X-ray Score Changes at Week 52

The rate of radiographic progression was evaluated by calculating the change in modified total Sharp x-ray scores (TSS)(relative to baseline) at Weeks 24 and 52. Missing data were imputed by linear extrapolation to week 52. An overall comparison of the change from baseline in modified total Sharp x-ray scores to Week 52 revealed a statistically significant difference ($p \leq 0.001$) across the treatment groups, and permitted pair-wise comparisons. Significance testing was to be done following the closure principle. The difference among all treatment groups was to be assessed using analysis of covariance (ANCOVA) with the baseline value as the covariate. Comparisons rates were performed using Pearson's x^2 test. The magnitude of the change associated with each of the adalimumab treatment groups was smaller and was statistically significantly different ($p \leq 0.001$ for both) from placebo (Table 21) indicating that adalimumab use was associated with a reduced rate of progression of structural damage.

Observed and LOCF (use of linear extrapolation to impute missing data) data demonstrated similar results. Similar results were observed when the data were analyzed using the per protocol set of patients. An overall comparison of the change from baseline in modified total Sharp x-ray scores to Week 52 for the per-protocol set revealed a statistically significant difference ($p \leq 0.001$) across the treatment groups, and permitted pair-wise comparisons. The magnitude of the change associated with each of the adalimumab treatment groups was smaller and was statistically significantly different ($p \leq 0.001$ for both) from placebo. The mean modified total Sharp score for the proposed adalimumab dose of 40 mg q2w at Week 52 was 0.1 compared to 0.8 for 20 mg qw and 2.7 for the placebo-treated patients.

Normality was evaluated by applying the Shapiro-Wilk test procedure to the residuals from the parametric model. The resulting p-value was ≤ 0.05 indicating the normality assumption was violated. Therefore, the final analysis was performed following a non-parametric approach, ranking the results prior to fitting the model. Missing values were imputed using linear extrapolation from baseline and the last during-study evaluation.

Table 21 : Study DE019 : Modified Total Sharp X-Ray Score Changes (Extrapolated) At Weeks 24 and 52 By Treatment Group (full set analysis)

	Adalimumab											
	20 mg weekly				40 mg eow				Placebo			
Time point	N	Mean ± SD	Median	Range	N	Mean ± SD	Median	Range	N	Mean ± SD	Median	Range
Baseline	201	66.4 ± 56.3	46.5	(2.0-280.0)	194	72.1 ± 60.7	54.5	(1.5-308.5)	184	66.4 ± 47.4	55.5	(0.5-230.5)
Change at Week 24	196	0.6 ± 4.9 [a]	0.0	(-27.5-50.5)	183	0.3 ± 4.5 [b]	0.0	(-18.0-46.0)	172	1.3 ± 3.7	0.5	(-22.5-15.0)
Change at Week 52	196	0.8 ± 4.9 [b]	0.0	(-14.5-50.5)	183	0.1 ± 4.8 [b]	0.0	(-37.0-23.5)	172	2.7 ± 6.8	1.0	(-25.0-39.0)

[a] Statistically significantly different from placebo ($p \leq 0.01$) based on median values.
[b] Statistically significantly different from placebo ($p \leq 0.01$) based on median values

Modified total Sharp x-ray score changes are presented by subgroups in Table 22. Comparison of the changes between adalimumab-treated patients and placebo-treated patients demonstrates a smaller increase in modified total Sharp x-ray scores with adalimumab compared to placebo in each of the subgroup analyses with the exception of patients >65 years of age. Among patients > 65 years of age receiving 20 mg weekly, the 12-month change in TSS was similar to placebo (2.7 vs. 3.2 u/yr). However, in the group receiving 40 mg q2w, the 12-month change in TSS was reduced compared to placebo (1.6 vs. 3.2 u/yr).

Of note, the largest increase in radiographic progression occurred among Blacks taking placebo. However, the rate of progression was reduced to a similar level among Black patients receiving adalimumab as for other groups. Rheumatoid factor positivity or negativity did not seem to influence the effect of adalimumab on radiographic progression.

Table 22: Study DE019 : Modified Sharp X-Ray Score (Observed) Changes At Week 52 By Age, Gender, Body Weight, Race, and RF Status

Treatment	Adalimumab			Placebo
	20 mg Weekly N=212	40 mg Q2W N=207	All Adalimumab N=419	N=200
Completed study	168 (79%)	159 (77%)	327 (78%)	140 (70%)
Subgroup at Week 52	N / Mean ± SD			
Age				
< 65 years	138 0.3 ± 2.6	116 0.5 ± 4.8	254	128 2.7 ± 7.1
≥ 65 years	45 2.7 ± 8.8	49 1.6 ± 4.8		33 3.2 ± 5.5
Gender (female) N= Change at week 52	138 1.0 ± 4.9	127 0.3 ± 4.7	265	116 2.9 ± 6.4
Body Weight				
≤ 70 Kg at Baseline N= Change at 52 weeks	62 0.8 ± 2.3	69 0.2 ± 6.0	131	59 3.8 ± 6.4
≥ 70 Kg at Baseline N= Change at 52 weeks	121 1.0 ± 5.9	96 0.1 ± 3.9	217	102 2.1 ± 6.9
Race (%)				
Caucasian	156 1.0 ± 5.4	143 0.1 ± 5.1	299	138 2.6 ± 6.9
Hispanic	11 0.0 ± 1.9	6 0.0 ± 0.8	17	10 0.9 ± 1.4
Black	11 0.7 ± 1.6	11 0.4 ± 4.0	22	8 7.7 ± 7.6
Asian	2 1.8 ± 1.1	4 0.3 ± 0.3	6	2 3.8 ± 5.3
Other	3 0.0 ± 0.0	1 -1.0	4	3 3.5 ± 4.1
Rheumatoid Factor (positive)				
Baseline N=	165	158	323	165
	68 ± 55.6	77.6 ± 61.3		68.5 ± 47.5
Change at Week 52 N=	149	135	282	145
	0.9 ± 5.2	0.0 ± 5.3		2.7 ± 6.4
Rheumatoid Factor (negative)				
Baseline N=	36	36	72	19
	58.9 ± 59.6	48.0 ± 52.6		48.2 ± 43.3
Change at Week 52 N=	34	30	64	16
	1.1 ± 4.1	0.5 ± 1.9		3.3 ± 9.8

As expected, the baseline TSSs were progressively higher in patients with increasing duration of RA. The overall therapeutic effect of adalimumab was similar at all stages of the disease (Table 23)

Table 23 : Study DE019 : Modified Total Sharp X-Ray Score (Observed) Changes At Week 52 By Duration of RA

Treatment	Adalimumab			
	20 mg Weekly N=212	40 mg Q2W N=207	All Adalimumab N=419	Placebo N=200
Completed study (52 weeks)	168 (79%)	159 (77%)	327 (78%)	140 (70%)
Withdrew early	44 (21%)	48 (23%)	92 (22%)	60 (30%)
Duration of RA				
0 –2 years				
Baseline N=	28	24	52	18
	21.7 ± 14.5	28.3 ± 27.4		25.9 ± 18.4
Change at Week 52 N=	24	24	48	15
	-0.0 ± 1.2	0.4 ± 4.1		4.7 ± 6.3
>2 – 5 years				
Baseline N=	37	42	79	43
	44.5 ± 38.1	36.3 ± 31.5		44.3 ± 37.1
Change at Week 52 N=	34	36	70	38
	1.5 ± 9.1	1.1 ± 2.4		3.9 ± 8.3
>5 – 10 years				
Baseline N=	48	42	90	41
	61.3 ± 44.9	51.9 ± 36.7		55.3 ± 39.0
Change at Week 52 N=	41	31	72	35
	-0.3 ± 3.4	-0.3 ± 3.9		2.3 ± 5.9
> 10 years				
Baseline N=	87	86	173	82
	93.3 ± 63.1	111.6 ± 63.9		92.4 ± 46.5
Change at Week 52 N=	83	74	157	73
	1.6 ± 3.9	-0.3 ± 6.2		2.0 ± 6.3

Source of Data: Sponsor's Table 25

The magnitude of the baseline TSSs did not have any apparent influence on the decrease in rate of progression of adalimumab-treated patients at the proposed dose compared to placebo-treated patients (Table 24).

Table 24 : Study DE019 : Modified Total Sharp X-Ray Score (Observed) Changes At Week 52 (Continued)

Treatment	Adalimumab			
	20 mg Weekly N=212	40 mg Q2W N=207	All Adalimumab N=419	Placebo N=200
Completed study (52 weeks)	168 (79%)	159 (77%)	327 (78%)	140 (70%)
Withdrew early	44 (21%)	48 (23%)	92 (22%)	60 (30%)
Baseline Sharp score				
Baseline score <30 N=	59	59	118	51
	16.0 ± 7.5	15.9 ± 7.0		16.4 ± 8.3
Change at Week 52 N=	52	53	105	44
	-0.0 ± 1.4	-0.5 ± 2.9		-1.5 ± 3.3
Baseline score 30 – 90 N=	91	81	172	75
	55.3 ± 16.9	58.7 ± 18.9		54.5 ± 16.5
Change at Week 52 N=	82	65	147	68
	1.2 ± 3.5	-0.2 ± 5.4		-4.1 ± 7.6
Baseline score > 90 N=	51	54	105	58
	144.4 ± 51.6	153.6 ± 47.8		125.7 ± 28.2
Change at Week 52 N=	49	47	96	49
	-1.5 ± 8.4	-0.1 ± 5.9		-2.1 ± 7.6

We performed analyses to determine what fraction of patients experienced no x-ray progression. At week 24, similar proportions of adalimumab-treated patients and placebo-treated patients manifested no new erosions. However at Week 52, 60% of the 40 mg q2w adalimumab-treated patients had no new erosions compared to baseline vs. 46% of placebo-treated patients (Table 25).

Table 25 : Study DE019 : Erosion Score: Patients with No New Erosions and Lower Erosion Scores at Weeks 24 and 52 by Randomized Treatment Group (full analysis set)

TimePoint	Adalimumab				Placebo	
	20 mg weekly		40 mg Q2w			
	N	%	N	%	N	%
Patients with no new erosions (=0 and <0)						
Week 24	117	62	108	**61**	99	**60**
LOCF Week 24	119	62	119	**62**	103	**58**
Week 52	106	58[a]	102	**62**[b]	74	**46**
LOCF Week 52	119	59[a]	122	**63**[c]	85	**46**
Patients with lower erosion scores (<0)[d]						
Week 24	59	31	65	**37**[a]	41	**25**
LOCF Week 24	60	31	69	**36**[a]	41	**23**
Week 52	54	30[a]	63	**38**[c]	31	**19**
LOCF Week 52	57	28[a]	72	**37**[c]	35	**19**

a Statistically significantly different from placebo ($p \leq 0.05$).
b Statistically significantly different from placebo ($p \leq 0.01$).
c Statistically significantly different from placebo ($p \leq 0.001$).
d Comparison was done across three categories: <0, 0 and >0.

Erosion score changes were greater for placebo-treated patients than for 40 mg biweekly adalimumab-treated patients at both Week 24 and Week 52, and changes for 20 mg weekly adalimumab-treated patients were intermediate. LOCF data demonstrated similar results (Table 26).

Table 26 : Study DE019 : Erosion Score at Weeks 24 and Week 52 By Randomized Treatment Group – (full analysis set)

	Adalimumab				Placebo	
	20 mg weekly		40 mg eow			
Time point	N	Mean ± SD	N	Mean ± SD	N	Mean ± SD
Baseline	201	36.7 ± 31.4	194	41.4 ± 33.4	184	37.2 ± 25.8
Week 24						
Change at Week 24	189	0.3 ± 2.3	178	0.2 ± 2.9	166	0.7 ± 2.4
LOCF Week 24	193	0.3 ± 2.3	191	0.2 ± 2.8[a]	179	0.7 ± 2.4
Week 52						
Change at Week 52	183	0.4 ± 2.6[b]	165	0.0 ± 3.0[b]	161	1.7 ± 4.6
LOCF Week 52	201	0.4 ± 2.5[b]	194	0.0 ± 2.8[b]	184	1.6 ± 4.4

[a] Statistically significantly different from placebo (p≤0.05).

[b] Statistically significantly different from placebo (p≤0.001).

Adalimumab-treated patients demonstrated less of an increase in JSN scores than placebo at Weeks 24 and 52 (Table 27). The nominal p-values for these comparisons were <0.005.

Table 27 : Study DE019 : Joint Space Narrowing: Change in Joint Space Narrowing and Joint Space Narrowing Scores at Weeks 24 and 52 by Randomized Treatment Group (full analysis set)

	Adalimumab				Placebo	
	20 mg weekly		40 mg eow			
Time point	N	Mean ± SD	N	Mean ± SD	N	Mean ± SD
Change in joint space narrowing score						
Baseline	201	29.7 ± 26.9	194	30.7 ± 29.2	184	29.2 ± 24.5
Week 24						
Change at Week 24	189	0.4 ± 2.9	178	0.1 ± 2.2	166	0.6 ± 2.0
LOCF change at Week 24	193	0.4 ± 2.9	191	0.1 ± 2.2	179	0.5 ± 2.0
Week 52						
Change at Week 52	183	0.5 ± 2.9	165	0.1 ± 2.4[b]	161	1.1 ± 3.1
LOCF change at Week 52	201	0.5 ± 2.8	194	0.1 ± 2.3[b]	184	1.0 ± 3.0
Patients with joint space narrowing scores (=0 and <0 versus >0)[c]						
Week 24						
Week 24	130	68.8[a]	129	72.5[b]	96	57.8
LOCF Week 24	132	68.4[a]	138	72.3[b]	103	57.5
Week 52						
Week 52	124	67.8[b]	113	68.5[b]	84	52.2
LOCF Week 52	138	68.7[b]	135	69.6[b]	100	54.3

[a] Statistically significantly different from placebo (p≤0.05).

[b] Statistically significantly different from placebo (p≤0.01).

[c] Comparison was done across two categories: (<0 and =0) and >0.

Table 28 presents the changes in TSS by quartiles and the $10^{th}/90^{th}$ percentiles. The 90^{th} percentile for changes in TSS was 3 units for adalimumab-treated patients compared to 10 units for placebo.

Table 28: Study DE019 : Change from baseline at Week 52 in TSS*

--Repeat Sponsor's primary analysis with additional quartiles of information

Group	n	mean	std	median	q1	q3	p10	p90	min	max
20 MG WEEKLY	196	0.79	4.94	0	-0.5	1.08	-2.0	3	-14.5	50.5
40 MG BIWEEKLY	183	0.09	4.77	0	-1.0	1.08	-2.5	3	-37.0	23.5
PLACEBO	172	2.67	6.76	1	0.0	4.00	-1.0	10	-25.0	39.0

*: Patients without baseline score or one score after baseline were excluded.
For patients without score at Week 52, their values were estimated using linear extrapolation method.

An analysis was performed to assess whether a linear imputation method or LOCF would be the best imputation technique for handling missing data. Table 29 demonstrates that similar results are seen for the 12-month change in TSS using the two imputation techniques. This is not surprising given the small amount of missing data in the trial.

Table 29 : Study DE019 : Comparison of Statistical Inference Conclusions Based on Change from Baseline at Week 52 in TSS* Using Different Imputation Methods

Imputation Method	40 MG BIWEEKLY (n=183)			PLACEBO (n=172)		
	Mean	SD	Median	Mean	SD	Median
Linear Extrapolation	0.09	4.77	0	2.67	6.76	1
LOCF	0.13	4.70	0	2.63	6.61	1

*: Patients without baseline score or one score after baseline were excluded.

Table 30 uses data for patients who had baseline, Week 24 and Week 52 x-ray assessments, and displays the difference between the actual Week-52 value and that obtained by imputing Week-52 values from Week-24 values using linear extrapolation or LOCF. For untreated patients, linear extrapolation closely approximated Week-52 values (mean difference = 0.05), while LOCF values differed markedly (mean difference = 1.48). This analysis suggests that linear extrapolation is a more accurate imputation technique.

Table 30 : Study DE019 : Difference Between the Real and the Imputed Values at Week 52 in TSS*

Imputation Method	40 MG BIWEEKLY (n=183)			PLACEBO (n=172)		
	Mean	SD	Median	Mean	SD	Median
Linear Extrapolation	-0.53	9.21	0	0.05	6.96	0
LOCF	-0.15	5.22	0	1.48	5.48	0.5

*: Patients without complete TSS score were excluded.

Table 31 presents additional sensitivity analyses to support the statistical findings of the primary analysis. Statistically significant differences between adalimumab and placebo remain when worse scores (75th percentile) are imputed for missing values with adalimumab and better scores (25th percentile) for placebo (Sensitivity Analysis III). A worse case scenario (Sensitivity Analysis IV) abrogates the treatment effect.

Table 31 : Study DE019 : Sensitivity Analyses Total Sharp Score

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	-14.5	50.5	<0.0001
40 MG BIWEEKLY	207	5.93	16.79	0.0	-1.0	2.00	-37.0	50.5	<0.0001
PLACEBO	200	9.37	17.78	1.5	0.0	8.25	-25.0	50.5	

*: Adalimumab group vs. placebo group using 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	-14.5	50.5	<0.0001
40 MG BIWEEKLY	207	0.13	4.48	0.0	-1.0	1.00	-37.0	23.5	<0.0001
PLACEBO	200	2.37	6.31	0.5	0.0	3.25	-25.0	39.0	

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

Sensitivity Analysis III

Assigning the 75th percentile change (2.0) to patients with missing values treated with Adalimumab Assigning the 25th percentile change (-.5) to patients with missing values 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	-14.5	50.5	0.051
40 MG BIWEEKLY	207	0.31	4.52	0.0	-1.0	2.00	-37.0	23.5	0.0054
PLACEBO	200	2.23	6.36	0.5	-0.5	3.25	-25.0	39.0	

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

Sensitivity Analysis IV

Assigning the worst change (50.5) to patients with missing values treated with Adalimumab Assigning the best change (-37.0) to patients with missing values 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	-14.5	50.5	0.8896
40 MG BIWEEKLY	207	5.93	16.79	0.0	-1.0	2.00	-37.0	50.5	0.9669
PLACEBO	200	-2.88	15.16	0.5	-0.5	3.25	-37.0	39.0	

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

c. Disability Index of the HAQ at Week 52

An improvement in the disability index of the HAQ was represented by a negative mean change from baseline (i.e., assessed decrease in disease). After 52 weeks of treatment, both adalimumab dose groups (20 mg weekly and 40 mg q2w) were associated with statistically significant ($p \leq 0.001$) improvements in observed disability index (HAQ) compared to placebo (Table 32).

The change in disability index of the HAQ scores at Week 52 for the adalimumab treatment groups in the per-protocol set were also statistically significantly superior ($p<0.001$) to placebo. The scores at Week 52 were comparable between 20 mg weekly and 40 mg eow treatment groups

Normality was evaluated by applying the Shapiro-Wilk test procedure to the residuals from the parametric model. The resulting p-value was >0.05 indicating the normality assumption was not violated. The final analysis was therefore performed following a parametric approach. ANCOVA statistical analyses was utilized for change in modified change in disability index of the HAQ.

Table 32 : DE019 : Disability index of the HAQ at Week 52 by Randomized Treatment Group (full analysis set)

	Adalimumab				Placebo	
	20 mg weekly		40 mg eow			
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≤0.001).

Among adalimumab-treated patients treated with 40 mg biweekly, 60% achieved HAQ (improvement) score reductions of ≥ 0.22 and 46% achieved HAQ score reductions of ≥ 0.50 units at 52 weeks. Among placebo-treated patients 41% achieved HAQ score reductions of ≥ 0.22 and 25% achieved HAQ score reductions of ≥ 0.50 units.

2. Secondary Efficacy Endpoints

A substantial number of adalimumab-treated patients demonstrated ACR50 responses (40%) at both Week 24 and Week 52 compared to placebo (10%) (Table 33). [Continuous secondary efficacy variables were to be analyzed using ANCOVA, with baseline and treatment group as covariates. Pearson's x^2 test was to be used for discrete data]

Table 33 : Study DE019 : ACR50 Response At Weeks 24 and 52: Number (%) of Patients Responding By Randomized Treatment Group

	Adalimumab		
Time point	20 mg weekly (N=212)	40 mg q2w (N=207)	Placebo (N=200)
Week 24	87 (41)[a]	81 (39)[a]	19 (10)
Week 52	80 (38)[a]	86 (42)[a]	19 (10)

[a] Statistically significantly different from placebo (p ≤0.001)

Over 20% of the 40 mg biweekly adalimumab-treated patients demonstrated ACR70 responses at both Week 24 and Week 52 (Table 34).

Table 34 : Study DE019 :ACR70 Response At Weeks 24 and 52: Numbers (%) of Patients Responding By Randomized Treatment Group

Time point	Adalimumab 20 mg weekly (N=212)	Adalimumab 40 mg q2w (N=207)	Placebo (N=200)
Week 24	37 (18) [a]	43 (21) [a]	5 (3)
Week 52	44 (21) [a]	48 (23) [a]	9 (5)

[a] Statistically significantly different from placebo ($p \leq 0.001$)
Source: sponsor's Table 30

A significantly greater proportion of adalimumab-treated patients than placebo experienced a major clinical response at Week 52, a unique achievement for a RA therapeutic agent in a 1-year study. (Table 35)

Table 35 : Study DE019 : Major Clinical Response at Week 52 by Treatment Group

Major clinical response[a]	Adalimumab 20 mg weekly (N=212)	Adalimumab 40 mg q2w (N=207)	Placebo (N=200)
Yes	20 (9.4)[b]	18 (8.7)[b]	3 (1.5)

[a] Defined as a continuous ACR70 over a 6 month period

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

The percentages of ACR50, ACR70 , and major clinical responses for adalimumab, all demonstrated statistical significance.

Table 36 demonstrates the higher number and percentage of placebo-treated patients compared to adalimumab-treated patients who were non-responders and required additional DMARDs.

Table 36 : Study DE019 : Number of Patients Using Additional DMARDs

Enrolled in study	N = 619

Treatment	Adalimumab			
	20 mg Weekly N=212	40 mg Q2W N=207	All Adalimumab N=419	Placebo N=200
Completed study	168 (79%)	159 (77%)	327 (78%)	140 (70%)
Withdrew early	44 (21%)	48 (23%)	92 (22%)	60 (30%)
Number of patients using additional DMARDs				
Week 24				
ACR20 responder	0	2 (1%)	2 (1%)	1 (1%)
ACR20 non-responder	6 (3%)	7 (3%)	13 (3%)	31 (16%)
Week 52				
ACR20 responder	0	0	0	0
ACR20 non-responder	6 (3%)	8 (4%)	14 (3%)	30 (15%)

3. Summary of Efficacy Data

In this trial, there were three primary efficacy endpoints: the ACR20 response rate at Week 24 was the highest hierarchical primary efficacy outcome, followed by comparisons of the modified total Sharp x-ray score changes at Week 52, and the third primary efficacy endpoint was the disability index of the HAQ change at Week 52. The ACR20 response at Week 24 for both adalimumab-treatment groups (20 mg weekly [61%] and 40 mg q2w [63%], the proposed approval dosage) was statistically superior to the placebo-treated group (30%). The separation between adalimumab- and placebo-treated patients occurred as early as Week 2, was established by Week 4, and maintained through Week 52. All subsets of patients examined demonstrated a treatment effect of adalimumab.

Comparison of the change from baseline in modified total Sharp x-ray scores to Week 52 revealed a statistically significant difference between adalimumab-treatment groups and the placebo-treated group. The smaller changes observed in patients treated with adalimumab was consistent with a slowing of the rate of progressions of structural damage.

The study demonstrated a greater degree of improvement in the HAQ scores from baseline to Week 52 for both adalimumab doses compared to placebo. While these data are consistent with an important clinical benefit, they do not meet the criteria outlined in the guidance document for a claim of improvement in physical function/prevention of disability. Demonstration of sustained improvement for 2 years is required for this claim.

V. Study DE031 - Adalimumab Plus Stable Dose DMARD

A. Clinical Trial Design

Study DE031 is a multicenter, randomized, double-blind, placebo-controlled, phase III 24 week trial in which adalimumab 40 mg is self-administered subcutaneously (sc) every other week to patients with RA whose disease was not adequately treated with their current anti-rheumatic therapies. The primary objective is to contrast the safety profile of adalimumab with placebo when both are administered with pre-existing rheumatologic care in patients with active RA. The secondary objective is to determine and compare the efficacy of adalimumab with placebo when both are administered with pre-existing rheumatologic care. Efficacy is measured by ACR20 response criteria and improvement in physical function and health-related quality of life as measured by the HAQ and SF-36.

Patients had a confirmed diagnosis of RA (as defined by the 1987-revised ACR criteria) for at least 3 months and were in ACR functional class I, II, or III. Patients were inadequately treated with their current anti-rheumatic therapies and had active RA. Doses of DMARDs, as well as concomitant prednisone (≤10 mg daily) and NSAIDs, were required to be stable for at least 28 days prior to screening. At the baseline visit, patients were randomized to adalimumab or placebo (randomly assigned in a 1:1 ratio) and this signified the start of the 24-week placebo-controlled period. Patients were examined at Weeks 2, 4, 8, 12, 16, 20 and 24 of the study. Patients who failed to meet or maintain an ACR20 response were allowed a single increase in dosage of their DMARD and/or steroid therapy, treatment with another DMARD after 3 months of study participation, or further dose adjustments following consultation with the medical monitor. Patients who prematurely withdrew for lack of efficacy received usual medical care. All patients who completed the placebo-controlled period were eligible for enrollment into the open label continuation Study DE031X .

Planned enrollment for this study was 400 patients. However, based on changes made in Amendment B, the planned sample size was increased to 600 patients (Figure 11). Ultimately, 636 patients were analyzed, 318 in each treatment group, the adalimumab-treatment group and the placebo-treated group .

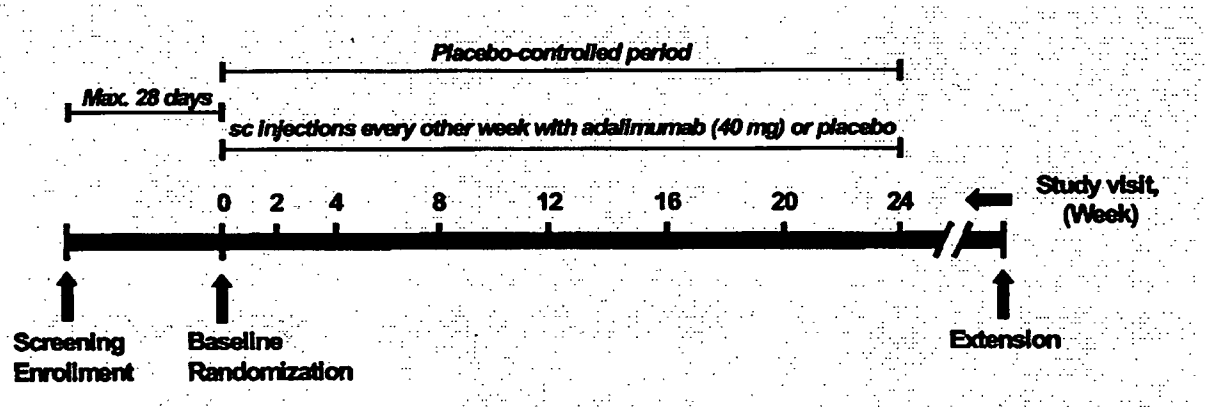

Figure 11: Study DE031 : Study Design

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 and reflect the safety and efficacy that will be experienced post approval within usual current clinical practice. The study design reflected standard clinical practice, and therefore allowed adjunctive treatments and dose adjustments. A washout period for azathioprine and cyclosporine was chosen to decrease the potential for immunosuppression during the study.

Clinical adverse events (AEs), infections, immune reactions, malignancies, injection site reactions, changes in physical examinations, laboratory evaluations and vital signs were monitored. Chest x-rays and electrocardiograms (ECG) were done at study entry; an additional chest x-ray was performed at Week 12 in patients with positive tuberculin purified protein derivative (PPD) skin tests.

Eligibility consisted of RA patients with:
Inclusion criteria – major criteria for patients

- Patients were 18 years of age or older. Female patients of child-bearing potential had negative pregnancy test at screen.
- ACR criteria of active RA for at least 3 months (≥ 6 swollen joints and ≥9 tender joints)
- Receiving glucocorticoids equivalent to ≥10 mg of prednisone daily
- DMARD dose was required to remain unchanged for at least 28 days
- All males and females of reproductive potential used a reliable method of contraception.

Exclusion criteria – major criteria for patients

- Who had received previous treatment with total lymphoid irradiation, monoclonal antibodies, alkylating agents, any TNF antagonist, intravenous (iv) immunoglobulin or any investigational agent
- History of cancer, lymphoproliferative disease, or positive HIV status.
- History of or current acute inflammatory joint disease other than RA
- History of unstable, persistent, or chronic medical conditions, infection, active tuberculosis or listeriosis, iv antibiotics within 30 days, or oral antibiotics within 14 days prior to screening
- Pregnant or breast-feeding.

- History of clinically significant drug or alcohol abuse, drug abuse, having received intra-articular, intramuscular, or iv administration of corticosteroids within 4 weeks evaluation,
- Joint surgery within 2 months prior to the screening evaluation.
- Abnormal laboratory values: hematological, hepatic or renal

Concomitant therapy

All concomitant therapies, including over-the-counter preparations, taken by the patient during the study were recorded on the CRF. Patients were allowed to continue drug therapies including antirheumatic therapies during the study except for azathioprine and/or cyclosporine. 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 (≤10 mg daily) and NSAIDs must have been stable for at least 28 days prior to screening. All efforts were made to keep the patient in the study during the 24-week placebo-controlled period.

Since this protocol was designed to reflect current clinical practice, the following adjunctive treatments and dose adjustments were allowed:

- Maximum of three intra-articular steroid injections were permitted during the first 3 months of the study (injected joint(s) were not assessed during joint examinations for 28 days following each injection).
- Dose of background DMARD, steroid, or NSAID therapies could be adjusted once during the study; further dose adjustments were instituted only after consultation with the medical monitor.

Secondary efficacy assessment - ACR20 response

The efficacy analysis was performed on the "full analysis set" of patients defined by the intent-to-treat principle. The full analysis set was defined as all patients who were randomized and received at least one injection of study drug and had at least one post-dose efficacy assessment. The ACR20 response at Week 24 (change from baseline) (using CRP as the acute phase reactant) was defined as the 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.

ACR20 response rates of the adalimumab and placebo-treated groups were compared using Pearson's χ^2 test with a two-sided level of significance of α=0.05. All other efficacy variables were summarized descriptively (statistical characteristics, frequencies, percentages, confidence intervals) and analyzed by exploratory two-sided statistical tests. For categorical data, Pearson's χ^2 test was used. For continuous data, an analysis of covariance (ANCOVA) model was used that included the treatment group as a factor and the respective baseline value as a covariate. In case of baseline imbalances between the treatment groups, further covariates could be added to the model.

A total of 400 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.

B. Study Conduct

Planned enrollment for this study was increased to 600 patients. Over 700 patients enrolled, 318 patients were randomized to each of the two treatment arms (adalimumab and placebo), and 91% of patients randomized to each treatment arm completed the study (Table 37). Dropouts occurred equally in both groups (9%). However, the number of dropouts due to lack of efficacy and/or progression of disease was higher in the placebo-treated group than in the adalimumab-treatment group. No increased incidence of withdrawals due to AEs was observed in the adalimumab-treatment group compared to the placebo-treated group.

A summary of patient disposition (all randomized patients) is presented in Figure 12 and Table 37. Due to the fact that one of the investigators (Dr. — Site #7) was undergoing proceedings to be debarred, patients enrolled at his site (6 patients) were removed from the efficacy analysis. All randomized patients are included in the demographic and safety analyses.

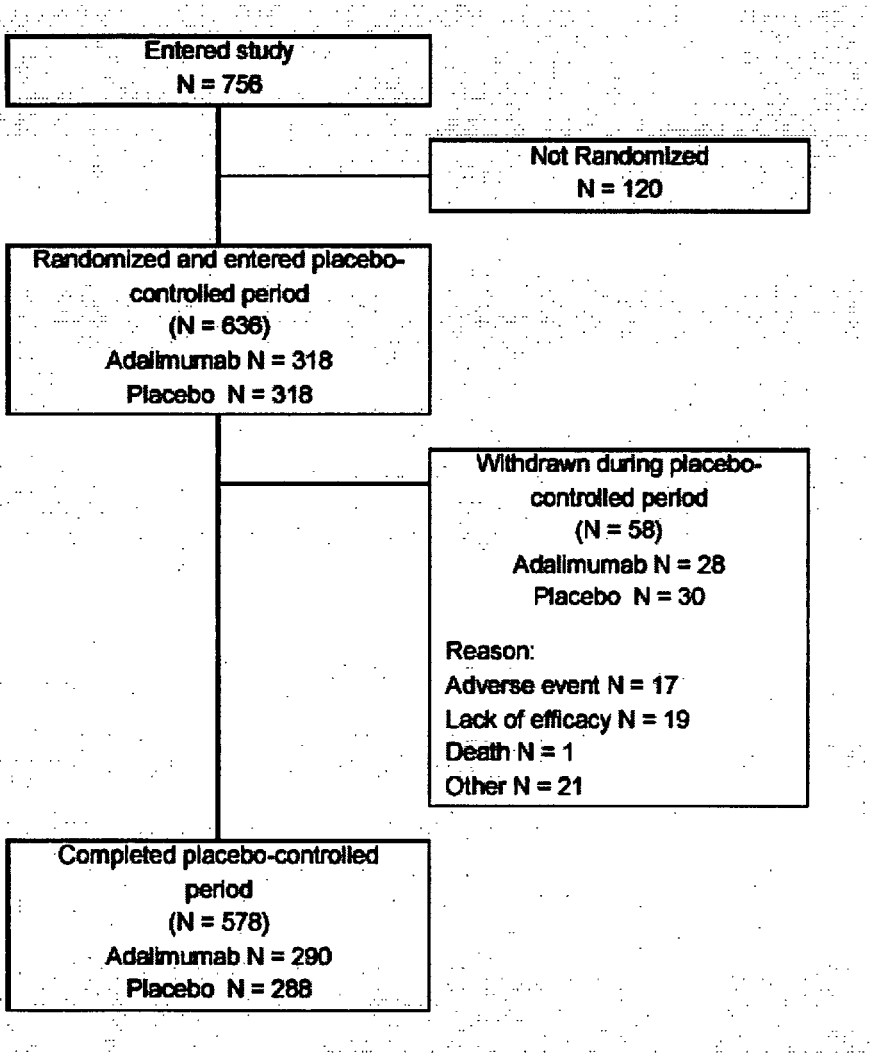

Figure 12 : StudyDE031 : Patient Disposition

Table 37 : Study DE031 : Patient Disposition (Number [%] of Patients) by Randomized Treatment Group (all randomized patients)

Result	Treatment group Adalimumab (N=318)	Placebo (N=318)	Total (N=636)
Completed study	290 (91)	288 (91)	578 (91)
Early discontinuation	28 (9)	30 (9)	58 (9)
Early withdrawals due to:			
Adverse event	9 (3)	8 (3)	17 (3)
Lost to follow-up	2 (1)	0 (0)	2 (0)
Protocol deviations	5 (2)	3 (1)	8 (1)
Death	1 (0)	0 (0)	1 (0)
Lack of efficacy and/or progression of disease	5 (2)	14 (4)	19 (3)
Administrative reasons	6 (2)	5 (2)	11 (2)

Table 38 : Study DE031 : Demographic characteristics at baseline by randomized treatment group (all randomized patients)

Demographic characteristic	Adalimumab (N=318)	Placebo (N=318)
Mean Age (years)	55	56
Female (%)	80	79
Ethnicity		
Caucasian (%)	89	86
Black (%)	4	6
Hispanic (%)	5	6
Mean Weight (kg)	78	76
Mean RA duration (years)	9	12
Rheumatoid Factor positive (%)	63	62
RA-relevant previous disease (at least one) (%)	56	59
Tender joint count (median)	25	25
Swollen joint count (median)	18	19
Patient global assessment of disease activity (mm on VAS)	53	52
Patient assessment of pain (mm on VAS)	57	58
Disability index (HAQ)	1.38	1.38
CRP (mg/dL) (mean)	1.5	1.5
FACIT Fatigue scale (median)	30	30
DMARD therapy		
DMARD discontinued prior (%)	56	56
Concomitant RA-specific DMARD therapy (%)	82	85
Concomitant RA-specific non-DMARD therapy (%)	99	96
Increase in DMARD dose (%)	2	4
Initiation of DMARD (%)	1	3
Increase in steroid dose (%)	4	6
Tuberculin PPD at baseline (N/%)		
PPD Positive	7/2	4/1
PPD Positive-on prophylaxis	4/1	3/1
PPD not stated-on prophylaxis	1/0	1/0

C. Safety Analysis

Comparable percentages of patients in the adalimumab and placebo 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 than in the placebo group. Injection site reaction was significantly greater in patients receiving adalimumab than in patients receiving placebo. Neither the incidence of SAEs nor severe or life-threatening AEs was higher in the adalimumab-treated group. One death due to an AE was reported during the study. Patient #15106, treated with adalimumab, died following a SAE of herpes zoster, complicated by streptococcal superinfection (necrotizing fasciitis). No significant differences in the incidences of severe or life-threatening AEs, SAEs, or deaths were observed between the two treatment groups (Table 39). Summarization of all safety issues will be provide in the Integrated Safety Analysis.

Table 39 : Study DE031 : 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 (87)	194.8	263 (83)	188.0	-
AE leading to death	1 (0)	0.7	0 (0)	0.0	-
SAE	17 (5)	12.0	22 (7)	15.7	-
AE resulting in withdrawal	9 (3)	6.4	7 (2)	5.0	-
AE resulting in dose interruption	38 (12)	26.9	27 (9)	19.3	-
Severe or life-threatening AE	38 (12)	26.9	49 (15)	35.0	-
At least possibly drug-related AE	147 (46)	104.1	111 (35)	79.3	Yes
Infection	166 (52)	117.6	157 (49)	112.2	-
Serious infection	4 (1)	2.8	6 (2)	4.3	-
Malignancy	4 (1)	2.8	0 (0)	0.0	Yes
Immunologic reaction	1 (0)	0.7	1 (0)	0.7	-
AE except injection site reaction	270 (85)	191.2	258 (81)	184.4	-
At least possibly drug-related AE except injection site reaction	117 (37)	82.9	89 (28)	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.

The numbers of patients reporting serious infections, malignancies, or immunologic reactions during this study were very small. The incidence of infections was similar for patients in the adalimumab and placebo treatment groups. A higher proportion of serious infections were reported in patients in the placebo-treated group (6 cases, 2%) compared

to the adalimumab-treated group (4 cases, 1%). A higher proportion of patients in the adalimumab-treated group experienced malignancies (4 cases, 1%) compared to the placebo-treated patients (0 cases). The malignancies observed in the adalimumab-treated patients were 3 cases of basal cell carcinoma of the skin and one case of T-cell lymphoma. Patient 11601 was noted to have enlarged lymph nodes after three doses of study drug, was subsequently biopsied, and diagnosed with a T-cell lymphoma. The nominal p-value for the incidence of malignancies was <0.05. However, this does not take into account the multiple comparisons.

The mean duration and total number of injections of study drug were comparable in patients who received adalimumab or placebo. The mean total dose of adalimumab administered during the study was 481.4 mg.

A total of 9 (3%) of 318 adalimumab-treated patients and 7 (2%) of 318 placebo-treated patients withdrew from the study due to one or more treatment-emergent AEs. A summary of all patients who experienced AEs resulting in withdrawal is provided in Table 40. There were two cases of rashes and two cases of infections (infected foot and herpes zoster) among the adalimumab-treated patients leading to discontinuation from the study.

Table 40 : Study DE031 Patients Withdrawn Due to Treatment-Emergent AEs (safety set)

Pt. No.	Age, gender	Treatment	Adverse event (HARTS term)	Day on drug at onset	Duration (days)	Serious	Severity[a]	Relationship[b]	Outcome
3504	53, F	Adalimumab	Rash	104	–	No	Grade 1	Possible	Not resolved
10311	65, F	Placebo	Congestive heart failure	34	9	Yes	Grade 2	Unrelated	Resolved
10410	68, F	Adalimumab	Rash	16	9	No	Grade 1	Possible	Resolved
11601	64, M	Adalimumab	Neoplasm	58	–	Yes	Grade 3	Unlikely	Not resolved
11613	61, M	Adalimumab	Infection[c]	82	45	Yes	Grade 2	Unrelated	Resolved
11614	62, M	Placebo	Pneumonia	93	5	Yes	Grade 2	Possible	Resolved
12102	55, F	Adalimumab	Laboratory test abnormal	1	–	No	Grade 1	Unrelated	Not resolved
12115	70, F	Adalimumab	Hypertensive encephalopathy	15	7	Yes	Grade 3	Possible	Resolved
13203	61, F	Placebo	Abdominal pain	29	45	No	Grade 3	Possible	Resolved
13309	38, M	Adalimumab	Bursitis	53	–	No	Grade 3	Unlikely	Not resolved
13403	63, F	Adalimumab	Laboratory test abnormal	140	–	Yes	Grade 2	Probable	Not resolved
13601	52, F	Placebo	Dyspnea	57	1	No	Grade 3	Unlikely	Resolved
15006	58, F	Placebo	Abscess	73	–	Yes	Grade 3	Unrelated	Resolving
15106[d]	70, M	Adalimumab	Herpes zoster	7	–	No[d]	Grade 2	Possible	Not resolved
15712	52, F	Placebo	Cellulitis	85	–	No	Grade 2	Possible	Not resolved
15901	71, F	Placebo	Pneumonia	31	74	No	Grade 2	Possible	Resolved

[a] Grade 1 = mild; Grade 2 = moderate; Grade 3 = severe; Grade 4 = life-threatening.

[b] Relationship to study drug as determined by the investigator.

[c] Infection of right foot.

[d] At the time of withdrawal, the herpes zoster AE in Patient #15106 was not an SAE. Entries in this table reflect the status at the time of study withdrawal. The patient ultimately died due to this AE (see Section 5.3.2).

F: female; M: male

Comparison of the AEs subsetted by concomitant DMARD subgroups is summarized in Table 41. A higher rate of certain categories of associated AEs with certain concomitant DMARDs was seen. AEs resulted in a higher incidence of dose interruption when leflunomide was combined with adalimumab (8 cases, 19%) compared to placebo (1

case, 2%). In addition, AEs at least possibly adalimumab-related were more frequent when adalimumab was given concomitantly with MTX, leflunomide, and other DMARDs, but not with antimalarials and sulfasalazine. A higher rate of SAEs was seen among placebo-treated patients than adalimumab-treated patients when given concomitantly with MTX and antimalarials.

Comparison of the number (percentage) of patients with the most frequently reported treatment-related AEs subsetted by number of concomitant DMARDs, shows a higher incidence of AEs that were considered drug-related when adalimumab is given alone or with one additional DMARD compared to placebo. There was no clear pattern of an increase in AEs overall among patients receiving adalimumab along with two or three additional DMARDs (Table 42).

Comparison of the number (percentage) of patients with the most frequently reported treatment-related AEs by concomitant DMARD therapy does not demonstrate a higher frequency of adalimumab-related AEs (Table 43). Comparison of the number (percentage) of patients with the most frequently reported treatment-related AEs corrected for frequency per 100 patient years reveals that rash, injection site reaction, and back pain were seen more frequently among adalimumab-treated patients \than placebo-treated patients with a nominal p value of < 0.05.

Table 41 : Study DE031 : Overview of Treatment-Emergent AEs by Concomitant DMARD Therapy[a] (safety set)

	Methotrexate		Antimalarials		Leflunomide		Sulfasalazine		Other DMARDs	
	Adalimumab	Placebo	Adalimumab	Placebo	Adalimumab	Placebo	Adalimumab	Placebo	Adalimumab	Placebo
Patients with any[a]	(N=178) N (%)	(N=199) N (%)	(N=75) N (%)	(N=82) N (%)	(N=42) N (%)	(N=46) N (%)	(N=29) N (%)	(N=33) N (%)	(N=25) N (%)	(N=25) N (%)
Adverse Event	153 (86)	161 (81)	63 (84)	74 (90)	39 (93)	39 (85)	23 (80)	28 (85)	23 (92)	19 (76)
AE leading to death	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
SAE	8 (5)	17 (9)	4 (5)	7 (9)	3 (7)	2 (4)	2 (7)	1 (3)	0 (0)	0 (0)
AE resulting in withdrawal	5 (3)	4 (2)	0 (0)	2 (2)	2 (5)	1 (2)	0 (0)	0 (0)	0 (0)	0 (0)
AE resulting in dose interruption	16 (9)	13 (7)	7 (9)	6 (7)	8 (19)	1 (2)	2 (7)	4 (12)	1 (4)	3 (12)
Severe or life-threatening AE	19 (11)	28 (14)	7 (9)	13 (16)	8 (19)	8 (17)	5 (17)	5 (15)	1 (4)	2 (8)
At least possibly drug-related AE	78 (44)	67 (34)	37 (49)	40 (49)	23 (55)	18 (39)	14 (48)	14 (42)	14 (56)	9 (36)
Infection	100 (56)	96 (48)	34 (45)	48 (59)	24 (57)	21 (46)	13 (45)	15 (46)	14 (56)	15 (60)
Serious infection	4 (2)	4 (2)	1 (1)	3 (4)	0 (0)	2 (4)	1 (3)	0 (0)	0 (0)	0 (0)
Malignancy	2 (1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Immunologic reaction	0 (0)	1 (1)	0 (0)	1 (1)	0 (0)	0 (0)	1 (3)	0 (0)	0 (0)	0 (0)

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

Table 42 : Study DE031 : Overview of Treatment-Emergent AEs by Number of Concomitant DMARD Therapies (safety set)

Number of concomitant DMARDs	0		1		2		3	
	Adalimumab	Placebo	Adalimumab	Placebo	Adalimumab	Placebo	Adalimumab	Placebo
Patients with any[a]	(N=57) N (%)	(N=48) N (%)	(N=184) N (%)	(N=172) N (%)	(N=66) N (%)	(N=84) N (%)	(N=11) N (%)	(N=14) N (%)
AE	46 (81)	36 (75)	166 (90)	145 (84)	54 (82)	72 (86)	9 (82)	10 (71)
AE leading to death	0 (0)	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
SAE	3 (5)	2 (4)	12 (7)	13 (8)	1 (2)	7 (8)	1 (9)	0 (0)
AE resulting in withdrawal	2 (4)	1 (2)	7 (4)	5 (3)	0 (0)	1 (1)	0 (0)	0 (0)
AE resulting in dose interruption	10 (18)	4 (8)	22 (12)	19 (11)	6 (9)	4 (5)	0 (0)	0 (0)
Severe or life-threatening AE	7 (12)	7 (15)	23 (13)	30 (17)	7 (11)	10 (12)	1 (9)	2 (14)
At least possibly drug-related AE	22 (39)	11 (23)	90 (49)	60 (35)	29 (44)	33 (39)	6 (55)	7 (50)
Infection	28 (49)	17 (35)	99 (54)	93 (54)	31 (47)	41 (49)	8 (73)	6 (43)
Serious infection	0 (0)	0 (0)	3 (2)	3 (2)	0 (0)	3 (4)	1 (9)	0 (0)
Malignancy	2 (4)	0 (0)	2 (1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Immunologic reaction	0 (0)	0 (0)	1 (1)	0 (0)	0 (0)	1 (1)	0 (0)	0 (0)

[a] More than one AE per patient possible.

Table 43: Study DE031: Number (%) of Patients with The Most Frequently Reported Treatment-Emergent AEs by Concomitant DMARD Therapy (safety set)

AEs[c]	Methotrexate		Antimalarials		Leflunomide		Sulfasalazine		Other	
	Adalimumab (N=178) N (%)	Placebo (N=199) N (%)	Adalimumab (N=75) N (%)	Placebo (N=82) N (%)	Adalimumab (N=42) N (%)	Placebo (N=46) N (%)	Adalimumab (N=29) N (%)	Placebo (N=33) N (%)	Adalimumab (N=25) N (%)	Placebo (N=25) N (%)
Upper respiratory infection	32 (18)	28 (14)	16 (21)	18 (22)	7 (17)	8 (17)	6 (21)	5 (15)	9 (36)	5 (20)
Injection site pain	20 (11)	22 (11)	10 (13)	12 (15)	6 (14)	7 (15)	2 (7)	2 (6)	3 (12)	1 (4)
Rash	16 (9)	8 (4)	3 (4)	4 (5)	5 (12)	3 (7)	3 (10)	2 (6)	2 (8)	3 (12)
Injection site reaction	13 (7)	2 (1)	8 (11)	2 (24)	4 (10)	0 (0)	3 (10)	1 (3)	2 (8)	0 (0)
Nausea	16 (9)	11 (6)	10 (13)	4 (5)	6 (14)	3 (7)	3 (10)	2 (6)	1 (4)	0 (0)
Urinary tract infection	21 (12)	10 (5)	6 (8)	7 (9)	5 (12)	1 (2)	0 (0)	2 (6)	1 (4)	2 (8)
Headache	13 (7)	13 (7)	12 (16)	9 (11)	3 (7)	2 (4)	3 (10)	3 (9)	0 (0)	1 (4)
Sinusitis	16 (9)	13 (7)	9 (12)	9 (11)	2 (5)	2 (4)	0 (0)	2 (6)	0 (0)	4 (16)
Flu syndrome	13 (7)	7 (4)	5 (7)	3 (4)	2 (5)	2 (4)	2 (7)	1 (3)	2 (8)	3 (12)
Accidental injury	16 (9)	11 (6)	6 (8)	9 (11)	3 (7)	4 (9)	3 (10)	3 (9)	1 (4)	2 (8)
Abdominal pain	9 (5)	9 (5)	2 (3)	5 (6)	2 (5)	1 (2)	3 (10)	1 (3)	0 (0)	0 (0)
Rhinitis	17 (10)	24 (12)	5 (7)	9 (11)	2 (5)	6 (13)	3 (10)	3 (9)	2 (8)	1 (4)
Diarrhea	14 (8)	12 (6)	6 (8)	7 (9)	3 (7)	7 (15)	1 (3)	2 (6)	1 (4)	0 (0)
Clinical flare reaction	8 (5)	10 (5)	3 (4)	5 (6)	3 (7)	3 (7)	4 (14)	2 (6)	1 (4)	2 (8)
Back pain	11 (6)	3 (2)	2 (3)	1 (1)	4 (10)	1 (2)	3 (10)	2 (6)	4 (16)	0 (0)
Surgery	8 (5)	6 (3)	5 (7)	3 (4)	3 (7)	0 (0)	0 (0)	1 (3)	1 (4)	0 (0)

[a] Occurring in ≥5% of patients in any treatment group.
[b] MTX = methotrexate; Antimal = antimalarials (eg, HCG, chloroquine); Leflu = leflunomide; Sulfasal = sulfasalazine; Other = other DMARDs.
[c] More than one AE per patient possible.

Table 44 lists all the patients in Trial DE031 with SAEs. Eighteen occurred among adalimumab-treated patients and 22 occurred among placebo-treated patients. There was no clear pattern of SAEs among adalimumab-treated patients.

Table 44 : Study DE031 : Patients with SAEs (safety set)

Treatment/ Pt. No.	Age, gender	Adverse event (HARTS term)	Day on drug at onset	Duration (days)	Severity[a]	Relationship[b]
Adalimumab						
13403	63, F	Laboratory test abnormal	140	-	Grade 2	Probable
12115	70, F	Hypertensive encephalopathy	15	7	Grade 3	Possible
15106	70, M	Skin disorder, Herpes zoster[c]	12	16	Grade 3, 4[c]	Possible
9708	67, F	Asthma	91	43	Grade 2	Unlikely
10203	81, M	Gastrointestinal hemorrhage	152	4	Grade 2	Unlikely
11601	64, M	Neoplasm [T-cell lymphoma]	58	-	Grade 3	Unlikely
12603	23, M	Gastrointestinal disorder	4	2	Grade 3	Unlikely
13502	75, F	Congestive heart failure	13	3	Grade 2	Unlikely
2706	45, F	Bone fracture [not spontaneous]	38	76	Grade 3	Unrelated
10506	52, F	Skin carcinoma [basal cell carcinoma]	15	21	Grade 2	Unrelated
11110	61, F	Chest pain	-16	3	Grade 3	Unrelated
11613	61, M	Infection	82	45	Grade 2	Unrelated
11703	69, M	Myocardial infarction	95	4	Grade 4	Unrelated
11914	44, F	Tachycardia, arrhythmia	173	6	Grade 3	Unrelated
12001	43, F	Gastrointestinal disorder	35	5	Grade 3	Unrelated
12112	74, F	Surgery	65	11	Grade 2	Unrelated
12905	46, F	Pelvic pain	22	34	Grade 3	Unrelated
15713	58, M	Kidney calculus	86	7	Grade 3	Unrelated
Placebo						
15714	44, F	Pneumonia	85	10	Grade 3	Possible
16006	46, F	Gastrointestinal disorder [torsion of appendiceal fat]	22	8	Grade 3	Possible
13601	52, F	Asthma	57	2	Grade 4	Possible
10712	72, F	Bronchitis	184	4	Grade 3	Possible
11614	62, M	Pneumonia	93	5	Grade 2	Possible
10708	78, F	Bronchitis	6	5	Grade 2	Unlikely
10711	66, F	Colitis	117	4	Grade 3	Unlikely
11604	69, F	Thrombosis leg	170	8	Grade 2	Unlikely
11607	58, F	Lung disorder, abdominal pain	51	4	Grade 2	Unlikely
11611	74, F	Atrial fibrillation	95	4	Grade 3	Unlikely
15107	60, F	Chest pain	99	2	Grade 3	Unlikely
10311	65, F	Congestive heart failure	34	9	Grade 2	Unrelated
11106	57, F	Myocardial infarction	48	4	Grade 3	Unrelated
11114	46, F	Vaginal hemorrhage	4	3	Grade 3	Unrelated
11616	56, F	Pulmonary embolus	70	8	Grade 3	Unrelated
12502	59, M	Surgery	84	4	Grade 2	Unrelated
13103	53, M	Neck pain	170	2	Grade 3	Unrelated
13408	42, F	Psychosis	148	3	Grade 3	Unrelated
13602	55, F	Cardiomyopathy	141	5	Grade 3	Unrelated
14903	35, F	Anaphylactic reaction	79	1	Grade 2	Unrelated
15006	58, F	Abscess	73	-	Grade 3	Unrelated
15305	68, F	Adenoma	84	7	Grade 3	Unrelated

[a] Grade 1 = mild; Grade 2 = moderate; Grade 3 = severe; Grade 4 = life-threatening.

[b] Relationship to study drug as determined by the investigator.

[c] Herpes zoster infection began as a skin disorder of moderate severity and progressed to streptococcal superinfection (necrotizing fasciitis) and sepsis.

F: female; M: male

One adalimumab-treated patient (Patient #15106) died during the study (Table 45). This patient developed herpes zoster 12 days after the first injection of adalimumab, which then progressed into a streptococcal group A superinfection at the site of the herpes lesions. This progressed to necrotizing fasciitis and sepsis. The patient was admitted to the hospital and underwent surgical debridement of the lesion. The patient never recovered and died 16 days after the appearance of the herpetic lesions. This adalimumab-treated patient was also taking prednisone and methotrexate for control of RA.

Table 45 : Study DE031 Patient with fatal AE (safety set)

Patient number	Age Gender	Treatment	Adverse event (HARTS term)	Day on drug at onset	Duration (days)	Severity	Relationship[a]
15106	70 Male	Adalimumab	Skin disorder Herpes zoster[b]	12	16	Grade 3, 4[b]	Possible

[a] Relationship to study drug as determined by the investigator.
[b] Herpes zoster infection began as a skin disorder of moderate severity and progressed to streptococcal superinfection (necrotizing fasciitis) and sepsis.

Serious infectious AEs were reported in ten study patients, 4 (1.3% of 318) adalimumab-treated patients and 6 (1.9% of 318) placebo-treated patients (Table 46). Among the adalimumab-treated patients, there were 2 cases of gastrointestinal disorder (appendicitis), 1 case of herpes zoster, and 1 case of foot infection. Approximately 50% of both adalimumab-treated and placebo-treated patients reported one or more non-serious infectious AEs after study drug administration.

Table 46 : Study DE031 : Patients with serious infections (safety set)

Pt. No.	Age, gender	Treatment	Adverse event (HARTS term)	Day on drug at onset	Duration (days)	Severity[a]	Relationship[b]	Outcome
10708	78, F	Placebo	Bronchitis	6	5	Grade 2	Unlikely	Resolved
10711	68, F	Placebo	Colitis[c]	117	4	Grade 3	Unlikely	Resolved
10712	72, F	Placebo	Bronchitis	164	4	Grade 3	Possible	Resolved
11613	61, M	Adalimumab	Infection[d]	82	45	Grade 2	Unrelated	Resolved
11614	62, M	Placebo	Pneumonia	93	5	Grade 2	Possible	Resolved
12001	43, F	Adalimumab	Gastrointestinal disorder[e]	35	5	Grade 3	Unrelated	Resolved
12803	23, M	Adalimumab	Gastrointestinal disorder[e]	4	2	Grade 3	Unlikely	Resolved
15006	58, F	Placebo	Abscess	73	--	Grade 3	Unrelated	Resolving
15106	70, M	Adalimumab	Skin disorder, Herpes zoster	12	16	Grade 3, 4	Possible	Fatal
15714	44, F	Placebo	Pneumonia	85	10	Grade 3	Possible	Resolved

[a] Grade 1 = mild; Grade 2 = moderate; Grade 3 = severe; Grade 4 = life-threatening.
[b] Relationship to study drug as determined by the investigator.
[c] Clostrium difficile.
[d] Infection of right foot.
[e] Appendicitis.
[f] Herpes zoster infection began as a skin disorder of moderate severity and progressed to streptococcal superinfection (necrotizing fasciitis) and sepsis.
F: female; M: male

The six most frequently reported infectious AEs (upper respiratory infection, rhinitis, sinusitis, urinary tract infection, flu syndrome, and cough increased) are presented by concomitant DMARDs subgroups (with and without methotrexate, antimalarials, leflunomide, sulfasalazine, or other DMARDs) in Table 47 and summarized by the number of concomitant DMARDs in Table 48. There was no clear pattern of an increase in any particular type of infection beyond the fluctuations expected when large numbers of comparisons are considered.

Although there were individual subgroups where the incidence of particular infections was somewhat higher in adalimumab-treated patients than in controls, there was no overall pattern of more frequent infections associated with concomitant use of higher numbers of DMARDs (Table 48).

Table 47: Study DE031 Frequent infectious adverse events by concomitant DMARD therapy (safety set)

	Methotrexate		Antimalarials		Leflunomide		Sulfasalazine		Other DMARDs	
AEs	Adalimumab (N=178) N (%)	Placebo (N=199) N (%)	Adalimumab (N=75) N (%)	Placebo (N=82) N (%)	Adalimumab (N=42) N (%)	Placebo (N=46) N (%)	Adalimumab (N=29) N (%)	Placebo (N=33) N (%)	Adalimumab (N=25) N (%)	Placebo (N=25) N (%)
Upper respiratory infection	32 (18.0)	28 (14.1)	16 (21.3)	18 (22.0)	7 (16.7)	8 (17.4)	6 (20.7)	5 (15.2)	9 (36.0)	5 (20.0)
Rhinitis	17 (9.6)	24 (12.1)	4 (5.3)	9 (11.0)	2 (4.8)	6 (13.0)	2 (6.9)	3 (9.1)	2 (8.0)	1 (4.0)
Sinusitis	16 (9.0)	13 (6.5)	9 (12.0)	9 (11.0)	2 (4.8)	2 (4.3)	0 (0.0)	2 (6.1)	0 (0.0)	4 (16.0)
Urinary tract infection	21 (11.8)	10 (5.0)	6 (8.0)	7 (8.5)	5 (11.9)	1 (2.2)	0 (0.0)	2 (6.1)	1 (4.0)	2 (8.0)
Flu syndrome	13 (7.3)	7 (3.5)	5 (6.7)	3 (3.7)	2 (4.8)	2 (4.3)	2 (6.9)	1 (3.0)	2 (8.0)	3 (12.0)
Cough increased	6 (3.4)	8 (4.0)	2 (2.7)	1 (1.2)	0 (0.0)	1 (2.2)	2 (6.9)	1 (3.0)	0 (0.0)	2 (8.0)

Table 48: Study DE031:Frequency of the most commonly reported infectious adverse events by number of concomitant DMARD therapies (safety set)

Number of concomitant DMARDs	0		1		2		≥3	
AEs	Adalimumab (N=57) N (%)	Placebo (N=48) N (%)	Adalimumab (N=184) N (%)	Placebo (N=172) N (%)	Adalimumab (N=66) N (%)	Placebo (N=64) N (%)	Adalimumab (N=11) N (%)	Placebo (N=14) N (%)
Upper respiratory infection	11 (19.3)	9 (18.8)	38 (20.7)	19 (11.0)	10 (15.2)	16 (19.0)	4 (36.4)	4 (28.6)
Rhinitis	3 (5.3)	2 (4.2)	10 (5.4)	21 (12.2)	7 (10.6)	9 (10.7)	1 (9.1)	1 (7.1)
Sinusitis	4 (7.0)	3 (6.3)	14 (7.6)	21 (12.2)	5 (7.6)	3 (3.6)	1 (9.1)	1 (7.1)
Urinary tract infection	2 (3.5)	2 (4.2)	21 (11.4)	10 (5.8)	6 (9.1)	6 (7.1)	0 (0.0)	0 (0.0)
Flu syndrome	6 (10.5)	3 (6.3)	10 (5.4)	10 (5.8)	7 (10.6)	3 (3.6)	0 (0.0)	0 (0.0)
Cough increased	8 (14.0)	1 (2.1)	5 (2.7)	9 (5.2)	1 (1.5)	2 (2.4)	1 (9.1)	0 (0.0)

Similar numbers of adalimumab-treated patients and placebo-treated patients withdrew from the study due to one or more treatment-emergent AEs.

A higher percentage of adalimumab-treated patients converted from negative to positive ANA than placebo-treated patients during this trial. The percentage was notably higher at Week 24 than at Week 12 (Table 49).

Table 49 : Study DE031 : Patients who changed from positive to negative or negative to positive ANA until Week 12 or Week 24 [a] (safety set)

ANA titer change	Treatment	
	Adalimumab (N=318)	Placebo (N=318)
Baseline negative, Week 12 positive	31	24
Baseline positive, Week 12 negative	14	10
Baseline negative, Week 24 positive	66	39
Baseline positive, Week 24 negative	6	5

[a] Positive titer is ≥1:80.

Likewise, a higher percentage of adalimumab-treated patients converted from negative to positive anti-dsDNA than placebo-treated patients during this trial. The percentage was much higher at Week 24 (Table 50). One patient with rising ANA and anti-dsDNA titers was discontinued from the study. No clinical manifestations of lupus-like syndrome were observed among patients who became positive for autoantibodies.

Table 50: Study DE031 : Patients who changed from positive to negative or negative to positive anti-dsDNA until Week 12 or Week 24 [a] (safety set)

Anti-dsDNA titer change	Treatment	
	Adalimumab (N=318)	Placebo (N=318)
Baseline negative, Week 12 positive	2	0
Baseline positive, Week 12 negative	0	0
Baseline negative, Week 24 positive	36	3
Baseline positive, Week 24 negative	3	0

[a] Positive values are >3.5 IU/mL

D. Efficacy Analysis

Clinical trial DE031 was designed to study the safety and efficacy of adding adalimumab to DMARD regimens encountered in a typical clinical practice. Adalimumab was given alone or in combination with other DMARDs that patients were already receiving. The study assessed the efficacy of adalimumab (40 mg) administered subcutaneously every other week for up to 24 weeks in patients with RA whose disease was not adequately treated with their current antirheumatic therapies. The efficacy assessment was a comparison of the ACR20 response rates (using CRP as the acute phase reactant) between adalimumab and placebo treatments. Adalimumab demonstrated a greater degree of improvement (53%) than placebo (35%) for the observed ACR20 response rate at Week 24 (Table 51).

Table 51 : Study DE031 :ACR20 response rate: number (%) of patients responding over time by randomized treatment group (full analysis set)

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.

Since this study was designed to approximate usual clinical practice, use of intra-articular injections and the ability to adjustment of DMARD and corticosteroid doses were permitted. The frequency of increases in DMARD and corticosteroid dosing was higher in the placebo group (Table 53) which would tend to increase the placebo response rate disproportionately. This may have contributed to the relatively high 35% ACR20 response rate at Week 24 (the highest ACR20 placebo response observed in the clinical development program, when compared to the placebo responses in trials DE009 [13%], DE011 [19%], and DE019 [30%]).

ACR20 response rates are displayed graphically over the 24 week time course for adalimumab-treated patients and placebo-treated patients in Figure 13. The onset of this response was rapid and sustained.

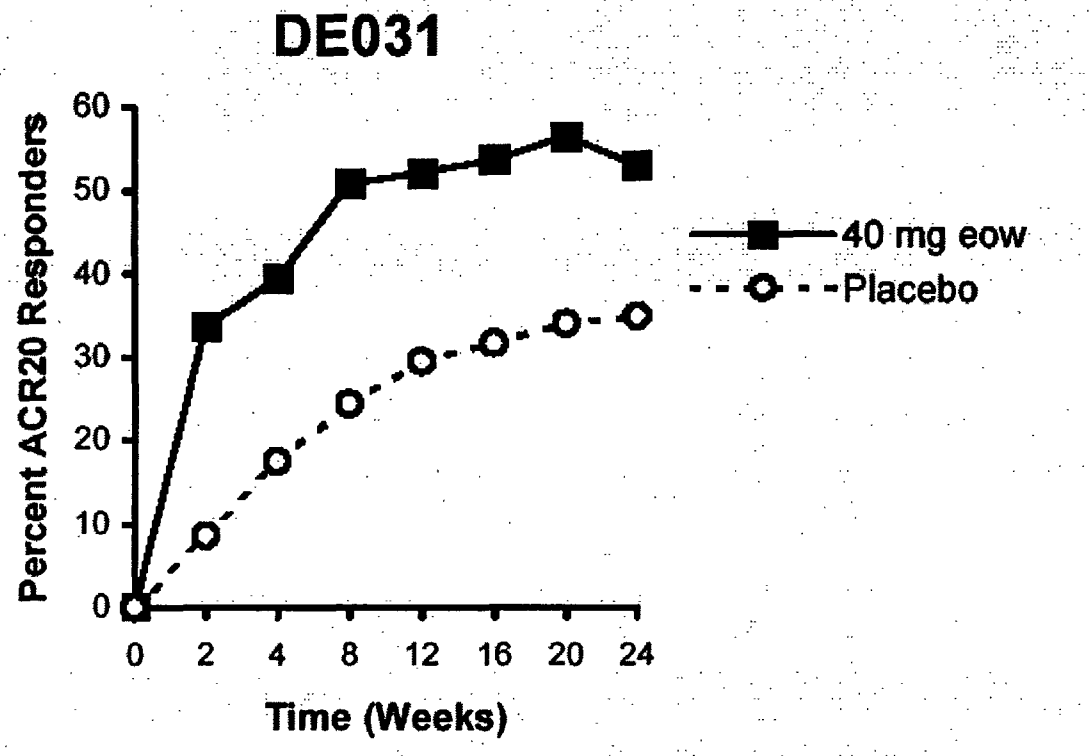

Figure 13 : Study DE031 :Time course of ACR20 responses by randomized treatment group

Adalimumab-treated patients taking concomitant methotrexate, antimalarial treatments, or sulfasalazine demonstrated a higher ACR20 response rate than placebo patients taking similar DMARDs. However, adalimumab patients taking concomitant leflunomide had a similar ACR20 response rate to placebo at Week 24 (33% and 37%, respectively) (Table 52). The patients receiving concomitant leflunomide were examined in more detail to determine whether there was a reduced treatment effect of adalimumab when added to leflunomide. First, earlier responses than Week 24 were examined. At Week 12, the ACR20 response rate for the adalimumab patients taking concomitant leflunomide was 41%, and for placebo plus leflunomide was 17%.

The lower response rate at Week 24 for adalimumab patients treated with leflunomide may have been influenced by a number of factors:

1). The higher number of patient withdrawals in the adalimumab plus concomitant leflunomide group. Of the patients receiving concomitant leflunomide, 7 of 42 (17%) adalimumab-treated patients but only 3 of 46 (7%) 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.

2). Patients treated with placebo plus concomitant leflunomide had an increase in ACR20 response from Week 12 to 24 probably due to the greater use of rescue steroids in this group (30%) compared to adalimumab plus concomitant leflunomide (14%). Among patients taking concomitant leflunomide, 5 of 46 (11%) placebo patients but only 1 of 42 (2%) adalimumab-treated patients received rescue steroid treatment before reaching ACR20 criteria.

Furthermore, thirty-five of the placebo plus leflunomide patients in this study rolled over into DE020, an open-label adalimumab 40 mg biweekly study. Their ACR20 response rate increased from 23% at study entry to 54% at Week 12.

Thus, the early withdrawals may have decreased the overall adalimumab-treated patient response, and the higher ACR20 response rate demonstrated by the placebo-treated patients in this study could be attributed to the greater rescue initiation of DMARDs, increased dosages of DMARDs and steroids, and intra-articular injections (Table 53). Data detailing the frequency and medications utilized for intra-articular injections were not provided.

Table 52: Study DE031 : Concomitant Medication at Week 24 for ACR20

	ACR 20			
	Adalimumab		Placebo	
Concomitant medication	Total N	% Response	Total N	% Response
Methotrexate	178	57	199	35
Antimalarial	75	51	82	33
Leflunomide	42	33	46	37
Sulfasalazine	29	59	33	24
Other DMARDs	25	52	25	44
No DMARD	54	50	45	33
One DMARD	184	55	172	38
Two DMARDs	66	50	84	30
Three or more DMARDs	11	46	14	36

Antimalarial (e.g., HCG, chloroquine)

Table 53: Study DE031 : Incidence of DMARD or Steroid Therapy Change

Therapy change	Adalimumab (N=315) N (%)	Placebo (N=315) N (%)
Increase in dose of DMARD therapy	6 (1.9)	14 (4.4)
Increase in dose of steroid therapy	14 (4.4)	20 (6.3)
Initiation of DMARD	3 (1.0)	8 (2.5)
Total	23 (7.3)	42 (13.3)

E. Summary of Analyses for Study DE031

This trial was designed to mimic typical clinical practice where adalimumab would be given alone or in combination with other DMARDs. The study assessed the efficacy of adalimumab administered 40 mg subcutaneously every other week for up to 24 weeks to patients with RA whose disease was not adequately treated with their current antirheumatic therapies. The efficacy assessment, a comparison of the ACR20 responses, demonstrated a greater degree of improvement in the adalimumab-treated patients (53%) than placebo (35%) at 24 weeks. Similar efficacy was seen for adalimumab regardless of the background DMARD regimen

Comparable percentages of patients in the adalimumab and placebo treatment groups reported one or more treatment-emergent AEs during the study. However AEs considered to be at least possibly related to study drug were more frequent in the adalimumab group than in the placebo group. Injection site reaction was seen more frequently in patients receiving adalimumab than in patients receiving placebo. The incidence of infections was similar for patients in the adalimumab and placebo treatment groups. The proportion of adalimumab-treated patients experiencing serious infections was similar to placebo-treated controls. However, there was one death in the adalimumab-treatment group in a patient with herpes zoster complicated by streptococcal superinfection (necrotizing fasciitis). No pattern of an increase in AEs or SAEs was seen when adalimumab was combined with any specific DMARD or combination of DMARDs.

A higher proportion of patients in the adalimumab-treated group experienced malignancies compared to the placebo–treated patients. The malignancies observed in the adalimumab-treated patients were three cases of basal cell carcinoma and one case of T-cell lymphoma. The rate of malignancies in patients receiving adalimumab will be considered further in the Integrated Safety Analysis

A higher percentage of adalimumab-treated patients converted from negative to positive ANA and positive anti-dsDNA than placebo-treated patients during this trial. No clinical autoimmune disease was observed. The evidence of auto antibodies and autoimmune disease will be discussed further in the Integrated Safety Analysis.

VI. Integrated Safety Analysis

A. Safety Database

Safety data from all US and non-US (Europe, Australia, and Canada) sources that were available as of August 31, 2001 were integrated within this integrated summary of safety information (hereafter referred to as the 'ISS') to provide a comprehensive safety profile for adalimumab in this patient population. Safety data related to deaths, malignancies, serious adverse events, and serious infections were up-dated as of August 31, 2002. A total of 20 clinical trials completed during the adalimumab clinical development program are included in the integrated safety database (Table 54).

Table 54: ISS : Studies contributing safety information to the adalimumab integrated safety database

Study category	Study	Location	Study characteristics	Dose(s) of adalimumab and route	Duration of study	Number enrolled
Clinical pharmacology studies in healthy volunteers	DE015	NA	Bioequivalence study in healthy volunteers	40 mg subcutaneous or intravenous	Single dose	61
	DE024C	EU	Pharmacokinetic/bioequivalence study in healthy volunteers	0.1, 0.3, 1.0 mg/kg subcutaneous; 1.0 mg/kg intravenous	Single dose	80
	DE029	NA	Bioequivalence study in healthy volunteers	40 mg subcutaneous	Single dose	120
Clinical pharmacology studies in RA patients	DE001/DE003 (pbo-ctrl)	EU	Multi-center, placebo-controlled	0.5, 1.0, 3.0, 5.0, or 10.0 mg/kg, intravenous	≥6 weeks	120
	DE004 (pbo-ctrl)	EU	Multicenter, placebo-controlled	0.5 mg/kg weekly, subcutaneous	12 weeks	24
	DE005/DE005X (pbo-ctrl)	NA	Multicenter, placebo-controlled, with concomitant MTX	0.25, 0.5, 1.0, 3.0, or 5.0 mg/kg, intravenous	≥6 weeks	60
	DE007 (pbo-ctrl)	EU	Multicenter, placebo-controlled	20, 40 or 80 mg weekly, subcutaneous	12 weeks	284
	DE010 (pbo-ctrl)	EU	Multicenter, placebo-controlled, with concomitant MTX	1.0 mg/kg, intravenous or subcutaneous	≥6 weeks	54
Adequate and well-controlled studies	DE009	NA	Multicenter, placebo-controlled, in patients concomitantly treated with MTX	20, 40, or 80 mg every other week, subcutaneous	24 weeks	271
	DE011	EU, AUS, CAN	Multicenter, placebo-controlled, with no concomitant DMARDs	20 or 40 mg, weekly or every other week, subcutaneous	26 weeks	544
	DE019	NA	Multicenter, placebo-controlled, with MTX, investigates joint erosion	20 mg weekly or 40 mg every other week, subcutaneous	52 weeks	619
	DE031	NA	Multicenter, placebo-controlled, with DMARDs, NSAIDs, or steroids	40 mg every other week, subcutaneous	24 weeks	636
Open-label continuation studies or phases	DE003	EU	Continuation of DE001/DE003 (pbo-ctrl)	0.5, 1.0, 3.0, 5.0, or 10.0 mg/kg every other week, intravenous	24 months	117
	DE004	EU	Continuation of DE004 (pbo-ctrl)	0.5 or 1.0 mg/kg weekly, subcutaneous	2.5 years	22
	DE005X	NA	Continuation of DE005 in RA patients concomitantly treated with MTX	All patients transition to 40 mg every other week, subcutaneous	28 months	58
	DE007 (2 yr)[a]	EU	Open-label continuation of DE007 (1 yr), with 3 dose levels in RA patients	20, 40 or 80 mg weekly, subcutaneous	2 years	271
	DE009X	NA	Continuation of DE009, in patients concomitantly treated with MTX	40 mg every other week, subcutaneous	8 months	250
	DE010	EU	Continuation of DE010 (pbo-ctrl), in RA patients with concomitant MTX	1.0 mg/kg every other week, subcutaneous	2.5 years	53
	DE018	EU, AUS, CAN	Continuation for European studies DE003, DE004, DE007, DE010, DE011	40 mg every other or 40 mg weekly, subcutaneous	96 weeks	794
	DE020	NA	Continuation for North American studies DE005X, DE009X, and DE031	40 mg every other week, subcutaneous	Open-ended	810

Source of data: sponsor's ISS Table 1
AUS: Australia ; EU: Europe ; NA : North America (including U.S. and Canada) ; CAN : Canada
MTX = methotrexate ; pbo-ctrl = placebo-controlled
[a] Includes a 9-month blinded continuation period that followed DE017

The overall body of adalimumab safety data presented in this section evaluates safety concerns related to:

- The short- and long-term safety and tolerability of adalimumab.
- Safety of adalimumab when used alone or in combination with methotrexate or other DMARDs.
- Safety of adalimumab when administered subcutaneously at the recommended dose of 40 mg every other week, and at the higher dose of 40 mg weekly.
- Adverse events (AEs) experienced by RA patients treated with adalimumab, frequency and severity.

- Incidences and types of serious infections, malignancies, autoimmune disorders, and deaths associated with adalimumab treatment, particularly in patients exposed to higher than recommended doses.
- Incidence and effects of elevated anti-nuclear antibodies (ANAs), anti-double stranded deoxyribonucleic acid (anti-dsDNA) titers, and human anti-human antibodies (HAHAs) observed in some RA patients treated with adalimumab.
- Any apparent effect on the safety profile of adalimumab by the development of HAHAs or by prolonged dose interruptions.

Overall, the mean age of the patients treated with adalimumab was 55 years. Most adalimumab-treated patients (77%) were female, and the majority of adalimumab-treated patients (91%) were Caucasian. The mean duration of RA was 131 months and 80% of subjects were RF positive at baseline. Many of the patients were receiving DMARDs at baseline and during the studies. Concomitant medications included MTX in 49% of all patients and corticosteroids in 57%. With regard to co-morbid conditions among patients, hypertension was reported in 27%, diabetes in 6%, COPD in 4%, and CHF in 1% of patients.

A total of approximately 1600 patients received treatment with adalimumab at the proposed dosage of 40 mg biweekly for ≥ 6 months and approximately 800 patients received treatment at that dose for ≥ 12 months (Table 55). The supplemental safety update provided safety data for approximately 2400 adalimumab-treated patients.

Table 55: ISS : Summary of the Duration of Exposure to Adalimumab by Treatment Received in all RA Patients

	Adalimumab						
Duration of exposure[a]	20 mg Q2w sc (N=175) N (%)	20 mg wk sc (N=397) N (%)	**40 mg Q2w sc (N=1903) N (%)**	40 mg wk sc (N=466) N (%)	All sc doses[b] (N=2263) N (%)	All iv doses[c] (N=197) N (%)	All adalimumab (N=2334) N (%)
<3 month	23 (13)	39 (10)	**117 (6)**	55 (12)	95 (4)	31 (16)	109 (5)
3-<6 months	41 (23)	49 (12)	**193 (10)**	78 (17)	139 (6)	17 (9)	152 (7)
6-<12 months	111 (63)	108 (27)	**798 (42)**	151 (32)	593 (26)	14 (7)	576 (25)
12-<18 months	0 (0)	200 (50)	**669 (35)**	88 (19)	945 (42)	46 (23)	908 (39)
18-<24 months	0 (0)	0 (0)	**122 (6)**	48 (10)	214 (10)	9 (5)	195 (8)
24-<36 months	0 (0)	1 (0)	**4 (0)**	46 (10)	195 (9)	32 (16)	241 (10)
36-<48 months	0 (0)	0 (0)	**0 (0)**	0 (0)	82 (4)	48 (24)	108 (5)
≥48 months	0 (0)	0 (0)	**0 (0)**	0 (0)	0 (0)	0 (0)	45 (2)

wk = weekly Q2w = every other week sc = subcutaneous iv = intravenous
[a] The duration intervals are defined as follows: <3 months = 1-90 days; 3-<6 months = 91-163 days; 6-<12 months = 164-344 days; 12-<18 months = 345-527 days; 18-<24 months = 528-709 days; 24-<36 months = 710-1074 days; 36-<48 months = 1075-1439 days; ≥48 months = ≥1440 days.
[b] includes 80 (1.0 mg/kg) eow or wk.
[c] 0.25, 0.50, 1.0, 3.0, 5.0, 10.0 mg/kg eow or wk.

B. Treatment-Emergent Adverse Events

Table 56 presents an overview of adverse events observed during the adequate and well-controlled trials. Because patients receiving different regimens had widely varying duration of exposure, rates are calculated as events per 100 patient-years to provide a common metric. Four categories of events of special interest were observed to occur among patients at a higher frequency per 100 patient-years in the adalimumab-treatment groups compared to placebo: deaths, drug-related AEs, deaths, malignancies, and infections (serious and non-serious). These will be described in more detail.

Table 56 : ISS : Overview of number (number/100 patient years) of patients with treatment-emergent AEs during the placebo-controlled period, by randomized treatment – adequate and well-controlled studies (safety set)

	Adalimumab													
	20 mg Q2w sc (N=175)		20 mg wk sc (N=324)		**40 mg Q2w sc (N=705)**		40 mg wk sc (N=103)		80 mg Q2w sc (N=73)		All adalimumab (N=1380)		**Placebo (N=690)**	
Patients with any [a]	N (N/100PY)		N (N/100PY)		**N (N/100PY)**		N (N/100PY)		N (N/100PY)		N (N/100PY)		**N (N/100PY)**	
AE	170	(238)	312	(132)	**638**	**(160)**	102	(211)	64	(205)	1286	(164)	**598**	**(165)**
Clinical AE	165	(231)	298	(126)	**620**	**(156)**	97	(201)	64	(205)	1244	(158)	**573**	**(158)**
Laboratory AE	106	(148)	152	(64)	**216**	**(54)**	89	(184)	6	(19)	569	(72)	**178**	**(49)**
Fatal AE	0	(0.0)	1	(0.4)	**5**	**(1.3)**	1	(2.1)	0	(0)	7	(0.9)	**1**	**(0.3)**
SAE	17	(24)	53	(23)	**61**	**(15)**	14	(29)	6	(19)	151	(19)	**60**	**(17)**
AE leading to withdrawal	11	(15)	27	(11)	**45**	**(11)**	5	(10)	3	(10)	91	(12)	**29**	**(8)**
AE leading to dose interruption	16	(22)	74	(31)	**103**	**(26)**	17	(35)	14	(45)	224	(29)	**86**	**(24)**
AE leading to dose reduction	0	(0.0)	1	(0)	**0**	**(0)**	0	(0)	0	(0)	1	(0)	**0**	**(0)**
Severe or life-threatening/intractable AE	45	(63)	83	(35)	**113**	**(28)**	22	(46)	7	(22)	270	(34)	**114**	**(32)**
At least possibly drug-related AE	112	(156.7)	198	(84.0)	**376**	**(94)**	71	(146.9)	35	(112.0)	792	(100.8)	**280**	**(77)**
Infection (serious and non-serious)	93	(130.1)	196	(83.1)	**398**	**(100)**	51	(105.5)	45	(144.1)	783	(99.7)	**334**	**(92)**
Serious infection	2	(2.8)	10	(4.2)	**18**	**(4.5)**	3	(6.2)	1	(3.2)	34	(4.3)	**7**	**(1.9)**
Malignancy	2	(2.8)	5	(2.1)	**10**	**(2.5)**	1	(2.1)	1	(3.2)	19	(2.4)	**2**	**(<1)**
Immunologic reaction	1	(1.4)	2	(0.8)	**6**	**(1.5)**	1	(2.1)	0	(0)	10	(1.3)	**4**	**(1.1)**

wk = weekly Q2w = every other week sc = subcutaneous

[a] More than one AE per patient possible.